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Heart Disease

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

6th EDITION

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Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Copyright © 2001 W. B. Saunders Company

Publisher's Note

We are proud to announce that two distinguished cardiologists, Drs. Douglas P. Zipes and Peter Libby, have joined Dr. Braunwald as editors of the sixth edition. Dr. Zipes is a world-renowned arrhythmologist and clinical electrophysiologist, and Dr. Libby is a leading expert in vascular biology and vascular disease. Both new editors head important Divisions of Cardiology with strong academic and clinical programs.

Preface

The accelerating advances in cardiology since the publication of the fifth edition of *Heart Disease* have required the most extensive changes yet made in any revision. This edition, the first in the new millennium, contains 30 chapters that are new (the most for any revision to date), and the remaining 42 have been extensively revised and updated. The editors warmly welcome 56 authors who are new to this edition.

Cardiovascular disease is now, more than ever, a global problem with enormous economic consequences. The various forms of heart disease in different economies and cultures are presented in the new opening chapter by Gaziano, and principles of cost-effective practice are described in a new chapter by Hlatky and Mark. Part II, The Examination of the Patient, begins with the clinical examination and moves

progressively from simple to more sophisticated noninvasive and invasive techniques. All of these approaches are described in detail with many new illustrations. The new chapter "Relative Merits of Cardiovascular Diagnostic Techniques," by Beller, provides a rational approach to the selection among several methods available to image the heart.

Heart failure is becoming an increasingly prevalent problem. Bristow has prepared two new chapters on the treatment of this condition, with emphasis on new treatment options based on pathophysiological considerations. There also has been enormous progress in cardiac electrophysiology and arrhythmology. Zipes has enlisted a cadre of talented authors to help update this section, always one of the strongest in *Heart Disease.*

The section on atherosclerosis is entirely new, reflecting greatly expanded information in this field and Libby's expertise in the area. The risk factors for the development of atherosclerosis and methods for its prevention are presented in new chapters. In view of the increasing importance of diabetes as a risk factor for vascular disease, a new chapter on diabetes mellitus and cardiovascular disease has been added. The cardiologist is called upon increasingly to deal with patients with extracardiac vascular disease. In new chapters on this subject, Creager and Libby describe the diagnosis and management of these conditions, and Dake and Samuels describe the extracardiac vascular interventions.

The acute coronary syndromes are, by far, the most common diagnoses for cardiovascular patients admitted to the hospital. In a new chapter on unstable angina, Cannon and Braunwald describe the many new diagnostic techniques and therapeutic measures available to care for these patients, and Antman and Braunwald provide a detailed contemporary description of the clinical manifestations and management of acute myocardial infarction. Interventional cardiology has progressed rapidly since the mid-1990s, and Popma and Kuntz have prepared an excellent new chapter on this important subspecialty of cardiology.

The sixth edition also focuses on the different manifestations in various populations, with new chapters on acquired heart disease in infancy, congenital heart disease in adults, and heart disease in athletes, in diabetics, in the elderly, and in patients with HIV infection and neoplastic disease, and an updated chapter on coronary artery disease in women.

The impact of molecular biology and genetics on cardiovascular disease is growing rapidly. A new chapter, "Principles of Cardiovascular Molecular Biology and Genetics," by Leiden joins the updated chapter "Genetics and Cardiovascular Disease" by Pyeritz in providing clear explanations of this important area. Many cardiovascular diseases result, in part, from coagulation disorders. Schafer and colleagues have prepared an excellent new chapter on hemostasis, thrombosis, and fibrinolysis to equip the cardiologist with the information required to deal effectively with these disorders. Other important new chapters include "Echocardiography," by Armstrong and Feigenbaum, and "Hypotension and Syncope," by Calkins and Zipes.

Practice guidelines are increasingly influencing the diagnosis and therapy of heart

disease. Lee provides useful summaries of the most important guidelines developed by authoritative groups and skillfully places them into the perspective of modern patient care.

Considerable revisions were made both in galley proofs and page proofs to include information about the most recent advances in the field. Particular emphasis has been placed on ensuring a comprehensive and up-to-date bibliography of more than 18,000 pertinent references, including hundreds of publications that appeared in 2000. Many of the 1700 figures and 546 tables are new to this edition.

In order to allow the reader to keep pace with the enormous expansion of cardiovascular knowledge, *Heart Disease* is supplemented by a number of companion volumes. These include *Cardiac Imaging, Cardiovascular Therapeutics, Molecular Basis of Heart Disease,* and *Clinical Trials in Cardiovascular Disease.* These books have been well received, and new editions are in preparation. Companion volumes in other important segments of cardiology are planned. In addition, a *Review and Assessment* book will again accompany this edition of *Heart Disease.* It consists of 600 questions based on material discussed in the textbook and provides the answers as well as detailed explanations. The publisher, Harcourt Health Sciences, comprising W.B. Saunders, Mosby, and Churchill Livingstone, is developing a comprehensive website in cardiology: MDConsult-Cardiology. The sixth edition of *Heart Disease* will serve as the "anchor" of this website, which will be updated continuously. This multipronged educational effort--*Heart Disease,* the growing number of companion volumes, and the *Review and Assessment* book, all appearing in print and electronic (CD-ROM) form, as well as the new website--is designed to assist the reader with the awesome task of learning and remaining current in this dynamic field.

We hope that this textbook will prove useful to those who wish to broaden their knowledge of cardiovascular medicine. To the extent that it achieves this goal and thereby aids in the care of patients afflicted with heart disease, credit must be given to the many talented and dedicated persons involved in its preparation. Our deepest appreciation goes to our fellow contributors for their professional expertise, knowledge, and devoted scholarship, which are at the very "heart" of this book. At the W.B. Saunders Company, our editor, Richard Zorab, and the production team, Lynne Gery, Frank Polizzano, and Anne Ostroff, were enormously helpful. Our editorial associates, Kathryn Saxon, Janet Hutcheson, and Karen Williams, rendered invaluable and devoted assistance.

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Adapted from the Preface to the First Edition

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous scourges--bubonic plague, yellow fever, and smallpox--cardiovascular disease not only strikes down a significant fraction of the population without warning but also causes prolonged suffering and disability in an even larger number. In the United States alone, despite recent encouraging declines, cardiovascular disease is still responsible for almost 1 million fatalities each year and more than half of all deaths; almost 5 million persons afflicted with cardiovascular disease are hospitalized each year. The cost of these diseases in terms of human suffering and of material resources is almost incalculable. Fortunately, research focusing on the causes, diagnosis, treatment, and prevention of heart disease is moving ahead rapidly.

In order to provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I chose to enlist the aid of a number of able colleagues. However, I hoped that my personal involvement in the writing of about half of the book would make it possible to minimize the fragmentation, gaps, inconsistencies, organizational difficulties, and impersonal tone that sometimes plague multiauthored texts.

Since the early part of the 20th century, clinical cardiology has had a particularly strong foundation in the basic sciences of physiology and pharmacology. More recently, the

disciplines of molecular biology, genetics, developmental biology, biophysics, biochemistry, experimental pathology, and bioengineering have also begun to provide critically important information about cardiac function and malfunction. Although *Heart Disease: A Textbook of Cardiovascular Medicine* is primarily a clinical treatise and not a textbook of fundamental cardiovascular science, an effort has been made to explain, in some detail, the scientific bases of cardiovascular diseases.

EUGENE BRAUNWALD, 1980

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the editor assumes any liability for any injury and/or damage to persons or property arising from this publication.

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Part I - GENERAL CONSIDERATIONS OF CARDIOVASCULAR DISEASE

1

Chapter 1 - Global Burden of Cardiovascular Disease

J. MICHAEL GAZIANO

THE EPIDEMIOLOGICAL TRANSITIONS

At the beginning of the 20th century, cardiovascular disease (CVD) accounted for less than 10 percent of all deaths worldwide. At its end, CVD accounted for nearly half of all deaths in the developed world and 25 percent in the developing world.[1] [2] By 2020, CVD will claim 25 million deaths annually and coronary heart disease (CHD) will surpass infectious disease as the world's number one cause of death and disability.

This global rise in CVD is the result of a dramatic shift in the health status of individuals

around the world over the course of the 20th century. Equally important, there has been an unprecedented transformation in the dominant disease profile, or the distribution of diseases responsible for the majority of death and debility. Before 1900, infectious diseases and malnutrition were the most common causes of death. These have been gradually supplanted in some (mostly developed) countries by chronic diseases such as CVD and cancer, thanks largely to improved nutrition and public health measures. As this trend spreads to and continues in developing countries, CVD will dominate as the major cause of death by 2020, accounting for at least one in every three deaths.[2]

This shift in the diseases that account for the lion's share of mortality and morbidity is known as the epidemiological transition.[3] [4] The epidemiological transition never occurs in isolation but is tightly intertwined with changes in personal and collective wealth (economic transition), social structure (social transition), and demographics (demographic transition).

Because the epidemiological transition is linked to the evolution of social and economic forces, it takes place at different rates around the world. Although changes in health status have occurred (and are occurring) in every part of the world, at the beginning of the millennium national health and disease profiles vary widely by country and by region. For example, life expectancy in Japan (80 years) is more than twice that in Sierra Leone (37.5 years).[1] In a similar vein, the Group I diseases defined by Murray and Lopez in their comprehensive analysis of the global burden of disease--communicable, infectious, maternal, perinatal, and nutritional diseases--account for just 6 percent of deaths in so-called developed countries compared with 33 percent in India.[2] The vast differences in burden of disease are readily apparent across three broad economic and geographical sectors of the world (Table 1-1) . These include the established market economies (EstME) of Western Europe, North America, Australia, New Zealand, and Japan; the emerging market economies (EmgME) of the former socialist states of Eastern Europe; and the developing economies (DevE), which can further be subdivided into six geographical regions--China, India, other Asia and islands, sub-Saharan Africa, the Middle Eastern Crescent, and Latin America and the Caribbean. Currently, CVD is responsible for 45 percent of all deaths in the EstME, 55 percent of all deaths in EmgME, and only 23 percent of the deaths in DevE.

An excellent model of the epidemiological transition has been developed by Omran.[3] He divides the transition into three basic ages--pestilence and famine, receding pandemics, and degenerative and man-made diseases (Table 1-2) . Olshansky and Ault added a fourth stage, delayed degenerative diseases.[4] Although any specific country or region enters these ages at different times, the progression from one to another tends to proceed in a predictable manner.

TABLE 1-1 -- BURDEN OF DISEASE (1990 ESTIMATES) FOR THE THREE ECONOMIC REGIONS OF THE WORLD

REGION	POPULATION (MILLIONS) (% TOTAL WORLD POPULATION)	% OF DEATHS IN THE REGION DUE TO			
		Cardiovascular Disease	Other Noncommunicable Diseases*	Communicable Diseases	Injuries
Developed					
EstME	798 (15.2)	44.6%	42.8%	6.4%	10.7%
EmgME	346 (6.6)	54.6%	29.5%	5.6%	10.3%
Developing					
DevE§	4124 (78.3)	23.0%	24.3%	46.9%	6.2%
Totals	5267	28.4%	27.4%	34.2%	10.1%

Adapted from Murray CJL, Lopez AD: The Global Burden of Disease. Cambridge, MA, Harvard School of Public Health, 1996.

*Includes cancer, diabetes, neuropsychiatric conditions, congenital anomalies, and respiratory, digestive, genitourinary, and musculoskeletal diseases.

EstME: Established market economies--United States, Canada, Western Europe, Japan, Australia, and New Zealand.

EmgME: Emerging market economies--former socialist states of Russian Federation.
§DevE: Developing market economies--China, India, other Asia and islands, sub-Saharan Africa, Middle Eastern Crescent, Latin America and the Caribbean.

The Age of Pestilence and Famine

From the epidemiological standpoint, humans evolved under conditions of pestilence and famine and have lived with them for most of recorded history. This age is characterized by the predominance of malnutrition and infectious disease and by the infrequency of CVD as a cause of death. Infant and child mortality is quite high, necessitating high fertility rates and resulting in a low mean life expectancy, on the order of 30 years or so. In the countries that eventually became today's established market economies, the transition through the age of pestilence and famine was relatively slow, beginning in the late 1700s and developing throughout the 1800s. Competing influences prolonged the transition--improvements in the food supply early in the Industrial Revolution that by themselves would have reduced mortality were offset by increases in communicable disease such as tuberculosis, cholera, dysentery, and influenza that resulted from concentration of the population in urban centers.

Although the transition through the age of pestilence and famine occurred much later in

the emerging market economies and the developing economies, it has also taken place more rapidly, driven largely by the transfer of low-cost agricultural products and technologies and well-established, lower-cost public health technologies. Much of the developing world has emerged from the age of pestilence and famine. In sub-Saharan Africa and parts of India, however, malnutrition and infectious disease remain leading causes of death.

TABLE 1-2 -- FOUR TYPICAL STAGES OF THE EPIDEMIOLOGICAL TRANSITION

STAGE	DESCRIPTION	TYPICAL PROPORTION OF DEATHS DUE TO CVD (%)	PREDOMINANT TYPES OF CVD
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease cardiomyopathies due to infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths due to malnutrition and infection; precipitous decline in infant and child mortality rates	10-35	Rheumatic valvular disease, hypertension, CHD, stroke
Degenerative and man-made diseases	Increased fat and caloric intake and decreased physical activity lead to emergence of hypertension and atherosclerosis; with increased life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious diseases	35-65	CHD, stroke

Delayed degenerative diseases	Cardiovascular diseases and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events. Age-adjusted CVD mortality declines; CVD affecting older and older individuals	50	CHD, stroke, congestive heart failure

CHD=coronary heart disease; CVD=cardiovascular disease.

Adapted from Omran AR: The epidemiologic transition: A theory of the epidemiology of population change. Milbank Mem Fund Q 49:509-538, 1971; and Olshansky SJ, Ault AB: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. Milbank Q 64:355-391, 1986.

The Age of Receding Pandemics

Rising wealth and the resultant increase in the availability of food help usher in the second phase of the epidemiological transition. Better nutrition decreases early deaths due to malnutrition and may also reduce susceptibility to infectious diseases. Increased personal and public wealth is associated with improvements in public health measures that contribute to still further declines in infectious diseases. These advances, in turn, increase the productivity of the average worker, further improving the economic situation. The change most characteristic of this phase is a precipitous decline in infant and child mortality accompanied by a substantial increase in life expectancy. Examples of countries in this phase of the epidemiological transition are the United States early in the 20th century and China today, where approximately 29 percent of deaths are due to CVD and only 16 percent are due to communicable disease.[2] Changes in nutrition and other aspects of life style that cause lower rates of communicable, maternal, perinatal, and nutritional diseases eventually lead to a greater incidence of CVD.

The Age of Degenerative and Man-Made Diseases

Continued improvements in economic circumstances combined with urbanization and radical changes in the nature of work-related activities lead to dramatic life-style changes in diet, activity levels, and behaviors such as smoking. During the age of pestilence and famine, most of the population is deficient in total caloric intake relative to daily caloric expenditure. Easier access to less expensive foods and increased fat content increases total caloric intake, whereas mechanization results in lower daily caloric expenditure. This disparity leads to higher mean body-mass index, plasma lipid level, blood pressure, and blood sugar level. These changes set the stage for the

emergence of hypertensive diseases and atherosclerosis. Cancer rates also rise rapidly during the age of degenerative and man-made diseases. As the average life expectancy increases beyond 50 years, mortality from largely chronic noncommunicable diseases--dominated by CVD--exceeds mortality from malnutrition and infectious diseases.[5] [6] Countries currently in this phase of the epidemiological transition are the emerging market economies of the former Soviet socialist states.

The Age of Delayed Degenerative Disease

In the final phase of the epidemiological transition, CVD and cancer remain the major causes of morbidity and mortality. In the industrialized nations, however, major technological advances such as coronary care units, bypass surgery, and thrombolytic therapy are available to manage the acute manifestations of CVD and preventive strategies such as smoking cessation and blood pressure management are widely implemented. As a result of better treatment and widespread primary and secondary prevention efforts, deaths are prevented among those with disease and primary events are delayed. Life expectancy continues to creep upward as age-adjusted CVD mortality tends to decline, with CVD affecting older and older individuals on average.

Changes in CVD through the Epidemiological Transitions

During the transition from the age of pestilence and famine to the age of delayed degenerative disease, both the character of CVD and total rates of CVD change.[6] During the age of pestilence and famine, CVD accounts for only 5 to 10 percent of mortality, with the major forms related to infection and malnutrition--largely rheumatic heart disease and the infectious and nutritional cardiomyopathies. Given the potentially long latent period of these diseases, they are apparent well into the age of receding pandemics, when they persist as major causes of death along with emerging hypertensive heart disease and stroke. During the age of receding pandemics, CVD accounts for 10 to 35 percent of deaths. CHD rates tend to be low relative to stroke rates. In addition, risk factors and risk behaviors that will foreshadow the next phase become more widespread. During the age of degenerative and man-made diseases, increased caloric intake (particularly from saturated animal fats and processed vegetable fats), reduced daily activity, increased smoking rates, and related changes in the prevalence of hypertension, diabetes, and hyperlipidemia result in further increases in hypertensive diseases and rapid increases in CHD and peripheral vascular disease. During this phase, 35 to 65 percent of all deaths are due to CVD. Typically, the rate of CHD deaths greatly exceeds that of stroke by a ratio of 2 to 3:1.

In the final phase of the epidemiological transition, the age of delayed degenerative diseases, age-adjusted death rates from CVD begin to fall, leveling off somewhere below 50 percent of total mortality. The decline in stroke rates tends to precede the decline for CHD; thus, the ratio of CHD to stroke deaths increases, typically to between 2:1 and 5:1 (Fig. 1-1) . The decline in CVD rates is the result of two factors: better access to health technology and adoption of healthier life styles. Improvements in health technology and better access to it decreases the likelihood of death among patients presenting with acute manifestations of atherosclerotic disease, although better survival means more and more individuals living longer with such CVDs as angina pectoris,

congestive heart failure, and cardiac arrhythmias.

Reductions in risk behaviors and factors may make even greater contributions to the decline in age-adjusted rates of death. In many cases, these are the result of concerted efforts by public health and health care communities. In other cases, secular trends also play a role. For example, the widespread availability of fresh fruits and vegetables all year long in developed countries, and thus increased consumption, may have contributed to declining mean cholesterol levels before effective drug therapy was widely available. In general, however, even though age-adjusted rates of CVD continue to decline during the final phase of the epidemiological transition, the prevalence of CVD increases as the population ages.

Economic, Social, and Demographic Transitions

As mentioned earlier, several parallel transformations accompany the epidemiological transition. These include economic, demographic, and social changes that pave the way for major shifts in a population's health and the nature of the diseases that account for most of the mortality and morbidity. The economic transition is characterized by increasing per capita income; the social transition by industrialization and the resulting urbanization, the development of a public health infrastructure, wider access to health care, and increasing application of health technologies; and the demographic transition by declining fertility and age-adjusted mortality rates, leading to increases in life expectancy and an aging population.

ECONOMIC TRANSITION.

This is measured by rising levels of personal wealth, usually measured as per capita gross domestic product (GDP) or gross national product (GNP).

SOCIAL TRANSITION.

Industrialization tends to spark a large number of social changes. It is typically accompanied by urbanization, a major social force that has a significant impact on the epidemiological transition. Urbanization affects living standards and life style and affords the opportunity to develop organized health care systems.

In virtually every region of the world there has been a shift from rural to urban life. For example, in the United States, 60 percent of the population lived in rural settings at the beginning of the 20th century compared with only 20 percent at the beginning of the 21st century. In Asia, the same shift has occurred over the second half of the 20th century (Fig. 1-2) .

Figure 1-1 Increase and decline in heart disease rates through the epidemiological transition in the United States, 1900 to 1996. Rate is per 100,000 population, standardized to the 1940 U.S. population. Diseases are classified according to International Classification of Diseases (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975. *(From Achievements in public health, 1900-1999: Decline in deaths from heart disease and stroke--United States, 1900-1999. MMWR Morbid Mortal Wkly Rep 48:649-656, 1999.)*

DEMOGRAPHIC TRANSITION.

This refers to the shifting age structure of a population. During the age of pestilence and famine, individuals age 20 and younger may account for 40 to 50 percent of the population. As child and infant mortality are reduced in the age of receding pandemics, rapid gains are seen in life expectancy and the proportion of individuals age 20 and younger decreases. Declines in mortality rates are generally followed by declining fertility rates, further flattening the shape of the population distribution curve. As population growth rates fall, the mean age of the population continues to rise slowly as individuals live longer.

RATE OF CHANGE OF THE EPIDEMIOLOGICAL TRANSITION

Several factors influence how early or how quickly the epidemiological transition occurs in a given country or region. Even within a given country, segments of the population may undergo the transition at varying rates. These factors are related to economic, social, or cultural factors.

CLASS.

Epidemiological transitions occur at different rates across economic groups, generally beginning among those with higher socioeconomic status and eventually spreading to those with lower socioeconomic status. The decline in rates of malnutrition and communicable diseases as well as the rise in coronary risk factors and behaviors occur first in the privileged classes; increases in rates of stroke and CHD soon follow. Later, as the middle class grows, the epidemiological transition spreads to a broad enough sector of the population to have a measurable impact on population rates. As more and more of the burgeoning middle class passes through the second and third phases of the transition, CVD and cancer rates become the population's dominant causes of death and disability. People in the lower socioeconomic strata tend to acquire the risk factors and behaviors last, in part because of their economic situation and in part because they tend to engage in more physical activity at work. Compared with people in the upper and middle socioeconomic strata, those in the lowest stratum are less likely to have access to advanced treatments and to acquire and apply information on modification of risk factors and behaviors. Thus, CVD mortality rates decline later among those with lower socioeconomic status. In Canada, for example, CVD mortality rates are highest among the poorest individuals (Fig. 1-3) .[7]

THE EPIDEMIOLOGICAL TRANSITION IN THE UNITED STATES

Like other established market economies, the United States has proceeded through the first three stages of the epidemiological transition and is currently in the fourth. Given the large amount of economic, social, demographic, and health data available (Table 1-3) , the United States is used as a reference point for later comparisons.

THE AGE OF PESTILENCE AND FAMINE

The United States, like virtually all other countries and regions, was born into pestilence and famine. Infectious diseases killed many of the earliest immigrants to the New World. About half of the Pilgrims arriving in the New World in November of 1620 died of infection and malnutrition by the following spring. In addition, the infectious diseases the immigrants brought with them from Europe had a devastating impact on Native American populations.

At the end of the 1800s, the U.S. economy was still largely agrarian, with more than 60 percent of the population living in rural settings. However, industrialization and urbanization were well under way. Per capita income was increasing, and the food supply was improving. Modest gains in life expectancy were apparent throughout the 19th century. By 1900, life expectancy had increased to 47.8 years for men and 50.7 years for women.[8] Infectious diseases--largely tuberculosis,

Figure 1-2 Number of people living in urban areas, 1970, 1994, and 2025. *(From Population Action International, http://www.populationaction.org/why Epop-graph21.htm)*

Figure 1-3 CVD standardized mortality ratios by neighborhood income for Canadians of European ancestry, ages 35 to 74, in 1986 and 1991. *(From Sheth T, Nair C, Nargundjar M, et al: Cardiovascular and cancer mortality among Canadians of European, south Asian, and Chinese origin from 1979 to 1993: An analysis of 1.2 million deaths. Can Med Assoc J 161:132-138, 1999.)*

pneumonia, and diarrheal diseases--accounted for more deaths than any other cause.[9] CVD accounted for less than 10 percent of all deaths. Tobacco products were out of the economic reach of a large segment of the population.

THE AGE OF RECEDING PANDEMICS

Early in the 20th century, the pace of industrialization accelerated. The shift from a rural, agricultural-based economy to an urban, industrial-based economy had a number of

consequences on cardiovascular risk behaviors and factors. Not only had food supplies become abundant, but there was also a dramatic shift in dietary staples. The railway network in place at the turn of the century was capable of moving foodstuffs from the farm to the city. But because the trains were not refrigerated, perishable foodstuffs such as fresh fruits and vegetables could not readily be transported whereas cereal grains and livestock could. Large slaughter houses and meat-packing plants were established in or near urban areas. As a result, consumption of fresh fruits and vegetables declined and consumption of meat and grains increased, resulting in diets that were higher in fat and processed carbohydrates.[10] In addition, the manufacture of factory-rolled

TABLE 1-3 -- TRENDS IN THE UNITED STATES DURING THE 20TH CENTURY

	1900	**1930**	**1960**	**1990**
Population (millions)	76	123	180	249
Per Capita Income (in 1997 dollars)	NA	$11,852 (1947)	$13,154	$17,662
Age-Adjusted CVD Mortality/100,000	325	390	390	180
Age-Adjusted CHD Mortality/100,000	NA	NA	210	100
Age-Adjusted Stroke Mortality/100,000	140	100	80	25
Urbanization	39.6%	56.1%	69.9%	75.2%
Life Expectancy	49.2	59.3	69.9	75.4
Smoking				
Cigarettes per capita	54	1185	4171	3000
% **Smokers**	NA	NA	42.4% (1965)	25.5%
Total Caloric Intake	3500 kcal	3300 kcal	3100 kcal	3800 kcal
Fat Intake (% of total calories)	31.6%	37.3%	41.2%	37.6%
Cholesterol Level	NA	NA	220 mg/dl	203 mg/dl
% **Overweight**	NA	NA	24%	35%

NA=Not available.

Sources:
Population: US Census Bureau.
Per capita income: U.S. Bureau of the Census: Current Population Reports, P60-203, Measuring 50 Years of Economic Change Using the March Current Population Survey. Washington, DC, U.S. Government Printing Office, 1998.
CVD, CHD, stroke mortality: NHLBI Chartbook 1998, MMWR.
Urbanization: 1990 Census of Population and Housing, "Population and Housing Unit Counts," CPH-2-1.
Life expectancy: National Center for Health Statistics. US decennial life tables for 1989-1991, some trends and comparisons of United States life table data, 1900-91. Hyattsville, Maryland; 1999 (DHHS-99-1150-3).
Smoking: per capita consumption from Surgeon General 1989; % smokers from National Health Interview Surveys, 1965-1994.
Total caloric intake: Nutrient content of the US food supply, 1909-1994: a summary. USDA; 1998.
Fat intake: Nutrient content of the US food supply, 1909-1994: a summary. USDA; 1998.
Energy expenditure:

Cholesterol level: MMWR 48:649-656, 1999.

% obesity: MMWR 1999; 48;649-656, 1999.

cigarettes made them more portable and more affordable for the mass population.[11]

EMERGENCE OF A PUBLIC HEALTH INFRASTRUCTURE.

By 1900, such an infrastructure had emerged--40 states had health departments and many larger towns had major public work efforts to improve water supply and sewage systems.[9] Municipal use of chlorine to disinfect water was becoming widespread, and improvements in food handling such as pasteurization were introduced.[12] The health care system was growing but still largely comprised general practitioners providing care in the office or home; hospitals were largely for the indigent. The Flexner Report of 1910, which took a careful look at the quality of medical education in the United States and Canada, was the first step toward organized quality improvement in health care manpower that, along with other public health changes, was responsible for dramatic declines in infectious disease mortality rates throughout the century (Fig. 1-4) .

URBANIZATION.

The population of urban areas outnumbered that of rural areas for the first time by 1920, and by 1930 56 percent of the population was living in or near urban centers. Infectious disease mortality rates had fallen dramatically, from a crude death rate of approximately 800 per 100,000 population in 1900 to approximately 340 per 100,000 people.[9] Largely as a result of rapidly declining infant, childhood, and adolescent mortality from

malnutrition and infectious diseases, life expectancy had increased by 10 years between 1900 and 1930, to 57.8 years for men and 61.1 years for women. At the same time, cigarette smoking was on the rise. Age-adjusted CVD mortality rates, at approximately 390 per 100,000 people, were in the midst of their steady climb up from slightly more than 300 per 100,000 people in 1900. This increase was largely driven by rapidly rising CHD rates.

THE AGE OF DEGENERATIVE AND MAN-MADE DISEASES

By the middle of the 20th century, the United States was predominantly an urban, industrial economy. Only 36 percent of the population lived in rural settings. With continued mechanization and urbanization, activity levels declined considerably. The rise of suburbs meant that more and more people were driving to work or to shopping rather than walking or bicycling. Prevalence of smoking, one of the major contributors to premature mortality and chronic disease, hit its zenith at 55 percent of adult men in 1955 and among women 10 years later, at 34 percent.[13] Annual per capita consumption of cigarettes peaked in 1963 at 4345.[11]

GROWTH OF THE HEALTH CARE INDUSTRY

One of the most remarkable changes in the years after World War II was the growth of the health care industry. Only some of this was stimulated by rises in per capita GDP. In the private sector, the growth of labor unions propelled a major expansion in private health care insurance. In fact, by the late 1950s, more than two thirds of the working U.S. population had some form of private insurance.[14] The federal government also played an important role. Increases in federal funding (the Hill Burton Act of 1948) led to the construction of more hospitals to deal with the acute manifestations of chronic illnesses. These new hospitals drew on the great successes of the military hospitals.[15] In 1966, two key federal insurance programs, Medicare and Medicaid, provided access to medical care for the medically indigent and the elderly. The Health Professions Education Assistance Act of 1966, which provided capitation grants to medical schools, doubled medical school enrollment over the next two decades through expanded class size and establishment of new medical schools. The establishment of the National Institutes of Health, spurred largely by scientific achievements in medicine made during World War II, not only promoted health-related research but also transformed medical education by providing financial support for the establishment of full-time medical school faculty.

By 1965, per capita income had risen to approximately $10,000 (in 1997 adjusted dollars).[16] Deaths from infectious diseases had fallen to under 50 per 100,000 population per year, and life expectancy was up to almost 70 years. However, almost 52 percent of men and 34 percent of women were smokers, and fat consumption represented 41 percent of total calories. Age-adjusted CHD mortality rates were at their peak, at approximately 225 per 100,000 people. Stroke rates were also high, at 75 per 100,000.

A decline in age-adjusted CHD mortality rates began in the mid 1960s, and there have been substantial reductions in mortality from both stroke and CHD since then.[17] These reductions have occurred among both whites and blacks, among men and women, and in all age groups. Age-adjusted CHD mortality rates have fallen approximately 2 percent per year, and stroke rates have fallen 3 percent per year (see Fig. 1-1) . Table 1-4 gives a snapshot of CVD in 1997 , the last year for which complete statistics are available.

DECLINE IN CVD MORTALITY.

Two main factors have been attributed to the decline in CVD mortality rates--therapeutic advances and prevention measures targeted at those with CVD and those potentially at risk for it.[18] [19] Treatments once considered advanced, including the establishment of emergency medical systems, coronary care units, and the widespread use of new diagnostic and therapeutic technologies such as defibrillation, cardiac catheterization, echocardiography, angioplasty, pacemaker implantation, and bypass surgery, are now considered the standard of care. Advances in the pharmaceutical industry have also had a major impact on both primary and secondary prevention. Efforts to improve the acute management of myocardial infarction led to the development of life-saving drugs such as beta blockers, thrombolytics, and angiotensin-converting enzyme inhibitors (see Chap. 35) .[20] The widespread use of an "old" drug, aspirin, has also reduced the risk of dying of acute or secondary coronary events. Low-cost pharmacological treatment for hypertension (see Chap. 29) and the development of highly effective cholesterol-lowering drugs such as statins have also made major contributions

Figure 1-4 Decline in mortality due to infectious diseases in the United States, 1900 to 1996. Rate is per 100,000 population per year. Data on chlorine use is from American Water Works Association: Water chlorination principles and practices: AWWA manual M20. Denver, American Water Works Association, 1973. *(From Achievements in public health, 1900-1999: Control of infectious diseases. MMWR Morbid Mortal Wkly Rep 48:621-629, 1999. Adapted from Armstrong GL, Conn LA, Pinner RW: Trends in infectious disease mortality in the United States during the 20th century. JAMA 281:61-66, 1999.)*

TABLE 1-4 -- CARDIOVASCULAR DISEASE, UNITED STATES, 1997

TYPE	PREVALENCE* (MILLION)	CRUDE MORTALITY (THOUSAND)	PERCENTAGE OF TOTAL DEATHS	RATE/100,000

Cardiovascular disease	59.7			
Hypertension	50	29	1.3	10.8
Ischemic heart disease	12.2	466	20.1	174.2
Stroke	4.4	160	6.9	59.7
Arrhythmia	3.9	45	1.9	16.8
Congestive heart failure	4.6	49	2.1	18.3
Rheumatic heart disease	1.8	5	0.2	1.9
Valvular disease (nonrheumatic)	NA	17.6	0.8	6.6
	ANNUAL EVENTS* (THOUSAND)			
Myocardial infarction	1100			
New	650			
Recurrent	450			
Stroke	600			
New	500			
Recurrent	100			
CABG	607			
PTCA	447			
Valve surgery	78			
Total costs				
Direct	$185.8 billion			
Indirect	$140.8 billion			

CABG=coronary artery bypass grafting; NA=not available; CDC, Centers for Disease Control and Prevention; PTCA=percutaneous transluminal coronary angioplasty.

*Data from American Heart Association: 2000 Heart and Stroke Statistical Update. Dallas, TX, American Heart Association, 2000.

From CDC Wonder Compressed Mortality/Population Data.

to reducing deaths from CVD in both primary and secondary prevention (see Chaps. 32 and 33) . Such shifts are reflected in the burgeoning cost of medical care. In 1965, Americans spent approximately 5.9 percent of the GDP ($42 billion in unadjusted dollars) on health care.[21] In 1998, the last year for which complete statistics are available, we spent an astounding 13.5 percent of the GDP ($1.1 trillion in unadjusted dollars), or $4094 per capita.[22]

In concert with these advances, public health campaigns have also hammered home the message that certain behaviors increase the risk of CVD and that life-style modifications are particularly effective ways to reduce risk. One such success is with smoking cessation. In 1955, 57 percent of men smoked cigarettes,[13] whereas 40 years later only half that many men smoked. Among women, prevalence of smoking had fallen from a high of 34 percent in 1965 to a low of 22.5 percent in 1993, but there are signs that smoking among women is on the increase. Similar campaigns beginning in the 1970s resulted in dramatic improvements in the detection and treatment of hypertension.[17] This likely had a profound and immediate effect on stroke rates and a more subtle effect on CHD rates. Similar public health messages concerning saturated fat and cholesterol are largely responsible for the decline in overall fat consumption as a percentage of total calories from approximately 45 percent in 1965 to 34 percent in 1995[23] and the decline in population mean cholesterol levels from 220 mg/dl in the early 1960s to 203 mg/dl in the early 1990s.[17]

A main characteristic of the age of declining degenerative diseases is the steadily rising age at which a first CVD event occurs or at which people die of CVD (Fig. 1-5) (Figure Not Available) . Despite declines in age-adjusted mortality, the aging of the

Figure 1-5 (Figure Not Available) Estimated prevalence of cardiovascular disease in Americans aged 20 and older, 1988 to 1994. *(From American Heart Association: 2000 Heart and Stroke Statistical Update. Dallas, TX, American Heart Association, 2000.)*

population will cause CVD to remain the predominant cause of morbidity and mortality. This, in turn, leads to ever-increasing numbers of individuals with CVD as well as ever-increasing health expenditures related to its treatment. In 1997, for example, CVD was the first-listed diagnosis for more than 6.1 million inpatients.[24] Hospital discharges in 1997 included 756,000 for acute myocardial infarction; 635,000 for cardiac dysrhythmias; 957,000 for congestive heart failure; 1,194,000 for cardiac catheterizations; 607,000 for bypass surgery; 447,000 for angioplasty; and 176,000 for insertions or revision of a pacemaker or defibrillator. In addition, there were 1,018,000 hospital discharges for stroke.[24] [25] [26]

At the close of the 20th century, the nation was fully industrialized, with only 2 percent of the population involved in farming. Per capita GDP was approximately $32,400, and life expectancy was 74 years for men and 80 years for women. CVD continued to be the predominant cause of morbidity and mortality, but it afflicted an older population than it did in the middle of the century. Although age-adjusted CVD rates continue to fall, the

rate of decline began slowing in the 1990s, with virtually no change in stroke rates for the last 5-year period for which data are available. The rate of decline of CHD may also be slowing, owing in part to a slowing in the rate of decline in risk factors such as smoking and increases in other risk factors such as obesity.

CURRENT WORLDWIDE VARIATIONS IN THE GLOBAL BURDEN OF CVD

An epidemiological transition much like the one that occurred in the United States is occurring throughout the world. As in the United States, worldwide CVD rates have risen steadily throughout the 1900s. At the close of the 20th century, 28 percent of all deaths worldwide were due to CVD, whereas communicable diseases accounted for 34 percent of the total.[2] With the ongoing global transition--dominated by the transition in the developing world--CVD will be the number one cause of death by 2020, accounting for 36.3 percent of all deaths whereas communicable diseases will account for barely half that, at 15.1 percent.[2]

Looking behind the global transition reveals vast discrepancies in regional rates of change. These wide variations began to appear early in the 20th century. Although most of the world remained in the phase of pestilence and famine, economic circumstances in several relatively confined regions changed rapidly, accelerating the pace of their epidemiological transitions. Thus, the global burden of CVD is best understood by examining the differential rates of change in each economic region. In addition to variability in the rate of the transition, there are unique regional features that have modified aspects of the U.S.-style transition in various parts of the world.

In terms of economic development, the world can be divided into two broad sectors, as described in Table 1-1 : (1) the developed world, which can be further subdivided into the established market economies (EstME) and the emerging market economies (EmgME), and (2) the developing economies (DevE). Given the diversity within the DevE, it is useful to further subdivide it into six distinct economic/geographic regions: China, India, other Asian countries and Pacific islands, sub-Saharan Africa, the Middle Eastern Crescent, and Latin America and the Caribbean. In 2000, four of every five people live in countries with developing economies, and it is these countries that are driving the rates of change in the global burden of CVD.

Like the United States, the rest of the EstME are largely in the fourth phase of the epidemiological transition, with CVD accounting for 45 percent of all deaths in 1990 and communicable diseases accounting for well under 10 percent (see Table 1-1) . The EmgME are in the third phase of the transition, with CVD accounting for 54 percent of deaths. In the DevE overall, 23 percent of deaths are due to CVD, whereas communicable diseases account for 42 percent of deaths. Across the six subgroups of the DevE, however, there remains a high degree of heterogeneity with respect to the phase of the epidemiological transition, as illustrated by the dominant disease rates in each region (Table 1-5) . In sub-Saharan Africa, communicable disease rates still far exceed those of chronic diseases, placing it in the first phase (pestilence and famine). Some regions of India appear to be in the first phase, characterized by high rates of infectious and communicable disease, whereas others are in the second or even the third phase. The Middle East appears to be in the third phase of the epidemiological

transition. In this section we briefly describe the difficulties

TABLE 1-5 -- PERCENT MORTALITY AND PERCENT DISABILITY-ADJUSTED LIFE YEARS LOST BY DISEASE CATEGORY IN THE DEVELOPING WORLD

DEATHS	**REGION**						
	China	**India**	**Other Asia**	**SSA**	**MEC**	**LatAm**	**Total**
CMPN	15.8	51.0	39.6	64.8	42.7	31.3	41.9
Injury	11.5	8.6	10.1	12.5	9.9	12.9	10.7
NonCVD, nonCMPN	43.8	16.1	25.9	12.8	19.0	29.5	24.3
All CVD	28.9	24.2	24.4	9.9	28.4	26.2	23.0
Ischemic heart disease	8.6	12.5	8.3	2.5	13.4	11.6	9.0
Stroke	14.3	4.8	7.0	4.7	4.7	8.3	7.5
Rheumatic heart disease	1.8	0.7	0.2	0.2	0.5	0.3	0.7
Other CVD	3.4	5.2	7.3	1.7	8.3	5.3	4.7
DALYs							
CMPN	24.2	56.4	44.7	65.9	47.7	35.3	48.7
Injury	17.6	14.6	14.4	15.4	11.1	16.4	15.2
NonCVD, nonCMPN	47.2	20.9	30.8	14.9	28.2	40.3	27.9
All CVD	11.0	8.1	10.1	3.9	11.1	7.9	8.2
Ischemic heart disease	2.9	3.5	2.2	0.8	3.5	3.0	2.5
Stroke	5.2	1.5	2.5	1.6	1.6	2.5	2.4
Rheumatic heart disease	1.1	0.5	0.1	0.2	0.5	0.2	0.5

CMPN=communicable, maternal, perinatal, and nutritional diseases; CVD=cardiovascular disease; SSA=sub-Saharan Africa; MEC=Middle East Crescent; LatAm=Latin America.

Adapted from Murray CJL, Lopez AD: The Global Burden of Disease. Cambridge, MA, Harvard School of Public Health, 1996.

in assessing and comparing disease rates around the world and discuss the regional rates. We will highlight within-region variations as well.

Established Market Economies

At the beginning of the 21st century, approximately 840 million people (13.6 percent of the world's population) live in the established market economies of the United States,

Canada, Australia, New Zealand, Western Europe, and Japan. In these countries, CHD rates tend to be twofold to fivefold higher than stroke rates. Table 1-6 , for example, demonstrates this tendency among selected European countries. There are two notable exceptions. In Portugal, stroke rates for both men and women are higher than CHD rates. The same is true for Japan, where stroke is responsible for far more fatalities than CHD.

Rapid declines in CHD and stroke rates since the early 1970s signal that the EstME countries are in the fourth phase of the epidemiological transition, the age of delayed degenerative disease. In general, stroke rates have fallen faster than CHD rates, increasing the CHD-to-stroke ratio. In the United States, for example, stroke rates over the past three decades have fallen an average of 3 percent per year, whereas CHD rates have fallen approximately 2 percent per year.

The rates of CVD in Western Europe tend to be similar to those in the United States. However, the absolute rates vary by threefold among the countries of Western Europe with a clear north/south gradient, with higher CHD and stroke rates in the north. The highest CVD rates in the European established market economies (two to three times higher than the median rates) are in Finland, Northern Ireland, and Scotland, where CVD-related mortality exceeds 800 deaths per 100,000 for men and 500 deaths per 100,000 for women.[27] The lowest CVD rates are in the Mediterranean countries of Spain and France, where annual CVD rates are under 400 and 200 per 100,000 for men and women, respectively. Although both stroke and CHD rates are higher in northern Europe, the disparity in CHD rates is

TABLE 1-6 -- AGE-ADJUSTED, ALL-CAUSE AND CARDIOVASCULAR MORTALITY PER 100,000 MEN AND WOMEN AGED 45-75 YEARS IN EUROPEAN COUNTRIES (1990-1992)

COUNTRY	ALL CAUSES	CVD	CHD	STROKE
Established Market Economies				
Spain				
Men	1323	399	181	93
Women	578	180	52	57
France				
Men	1361	330	142	67
Women	552	122	36	35
Portugal				
Men	1673	593	207	267
Women	805	305	73	158
Finland				
Men	1691	834	631	110
Women	1718	837	587	132

Scotland				
Men	1846	886	655	139
Women	1103	441	273	107
Economies in Transition				
Russian Federation				
Men	2881	1343	767	409
Women	1223	657	288	178
Ukraine				
Men	2940	1490	749	606
Women	1379	830	342	408

CVD=cardiovascular disease; CHD=coronary heart disease.

World Heart Federation: Impending Global Pandemic of Cardiovascular Diseases. Barcelona, Prous Science, 1999.

much greater. For example, male CHD rates are 362 percent higher in Finland than in Spain, whereas stroke rates are only 49 percent higher.[27] CVD rates in Canada, New Zealand, and Australia are similar to those in the United States.

JAPAN.

This country is unique among the EstME. As its rates of communicable disease fell in the early part of the 20th century, stroke rates increased dramatically; and by the middle of the century they were the highest in the world. CHD rates, however, did not rise as sharply as they did in other industrialized nations and have remained lower than in any other industrialized country. Overall CVD rates have fallen 60 percent since the 1960s, largely due to a decrease in age-adjusted stroke rates. Japanese men and women currently have the highest life expectancies in the world--83 years for women and 77 years for men.[1] The difference between Japan and other industrialized countries may stem from genetic factors, but it is more likely that the average very low-fat diet and resultant low cholesterol levels have played a more important role. As is true for so many countries, Japanese dietary habits are undergoing substantial changes. For example, there has been an estimated 9.3-fold increase in annual per capita consumption of meat between 1955 and 1994, a 5.2-fold increase in egg consumption, a 7.4-fold increase in milk and dairy consumption, and a 5.3-fold increase in consumption of fats and oils.[28] These changes may explain possible recent increases in CHD.

Emerging Market Economies

The EmgME currently have the highest rates of CVD mortality in the world, and they are continuing to increase in several countries. This suggests that the EmgME are largely in the third phase of the epidemiological transition. In the former Soviet and Eastern Bloc

countries, CVD predominates as the leading cause of death, accounting for approximately 54 percent of deaths, whereas communicable diseases account for only 6 percent. As expected in this phase of the transition, the average age of people who develop and die of CVD is lower than that in the established market economies.

Overall rates are similar to those seen in the United States in the 1960s, when CVD was at its peak. Although CHD is more common than stroke, the CHD:stroke ratio is relatively low, approximating 1:1 in several countries. Within the EmgME, CVD mortality rates vary widely--the highest CVD mortality rates are in the Ukraine (1,490 for men and 830 for women per 100,000) and Russia (1,343 and 657), and the lowest rates are in Slovenia (692 and 313).[27] CVD rates for women are particularly high compared with rates in EstME countries.

FORMER SOVIET UNION COUNTRIES.

One major difference between the EstME and the EmgME countries is that CVD mortality rates are not falling in many of the latter. On the contrary, since the dissolution of the Soviet Union there has been a surprising increase in CVD rates in some of these countries. In the former socialist countries of the Russian Federation, Belarus, Ukraine, Estonia, Latvia, and Lithuania, there has been a remarkable increase in CVD rates since 1990. In Russia, life expectancy has fallen, from 61.7 years to 57.6 years for men and from 73.0 years to 71.0 years for women.[29] The causes of this decline in life expectancy are not entirely clear. Rapid increases in per capita alcohol consumption may represent one possible cause for the increasing CVD rates that underlie this decline. Inadequate health care infrastructure and lack of institution of preventive public health measures also may contribute to worsening CVD mortality rates.

CVD rates have been stable in Bulgaria, Romania, Hungary, and Poland. The only two emerging market economies in which age-adjusted CVD rates have been declining are

Figure 1-6 Time trends in mortality from CVD in selected European countries, 1970 to 1992, among men and women aged 45 to 74. Fin=Finland; Hun=Hungary; Rus=Russia; Cze=Czechoslovakia; Por=Portugal; Spa=Spain; Gre=Greece; Den=Denmark; E&W=England and Wales. *(From Sans S, Kesteloot H, Kromhout D: The burden of cardiovascular diseases mortality in Europe: Time trends in mortality from CVD in selected European countries. Eur Heart J 18:1231-1248, 1997.)*

the Czech Republic and Slovenia. Even so, CVD rates remain generally higher than in Western European countries (Fig. 1-6) .

Developing Economies

Approximately 80 percent of the world's inhabitants live in developing economies

(DevE). In general, communicable diseases are nearly twice as likely to cause death than CVD in the DevE. Overall, CVD mortality rates are approximately 23 percent, although this represents only 8.2 percent of total lost disability-adjusted life years (DALYs) because CVD tend to affect an older segment of the population than communicable diseases. An infant death due to malnutrition, for example, results in more lost DALYs than a CHD death in the sixth decade of life. There are vast differences within and between the regions and countries that make up the DevE--some are still in the age of pestilence and famine, whereas others are in the second or even third phase of the epidemiological transition (see Table 1-5) . The character of CVD varies greatly by region. In China, stroke rates far exceed CHD rates, whereas in India the reverse is true. Rheumatic heart disease remains a major problem in India, China, and sub-Saharan Africa but is less of a problem in other Asian countries and Latin America (Table 1-7) .

Many factors contribute to the heterogeneity both between and within regions of the DevE. First, the distinct regions are at various stages of the epidemiological transition. Second, vast differences in life style and behavioral risk factors exist. For example, per capita consumption of dairy products (and thus consumption of saturated fat) is much higher in India than it is in China. Third, racial and ethnic differences may lead to altered susceptibilities to various forms of CVD. Finally, social, cultural, political, and economic considerations result in vast disparities in the health care structure in each region.

CHINA.

The People's Republic of China accounts for one fifth of the world's population, with 69 percent residing outside urban centers. Since the 1950s, life expectancy in China has doubled from 35 years to 70 years. Over the same period, mortality from CVD increased threefold as a percentage of total deaths, from 12 to 36 percent.[30]

As in Japan, stroke is by far the leading cause of cardiovascular death. Hemorrhagic stroke predominates over ischemic stroke, and stroke rates are higher among women than men. These lower rates of CHD and high rates of stroke may be due to genetic factors; however, it has also been hypothesized that overall low serum cholesterol levels may contribute to high rates of hemorrhagic stroke.[31] There appears to be a north/south gradient, with higher CVD rates in northern China compared with southern China. As is the case in most DevE, there is also an urban/rural gradient for CHD, stroke, and hypertension with higher rates in urban centers. Regional differences exist in CVD rates, although they are not as great as those seen in India and sub-Saharan Africa. This is likely due to the system of resource distribution that results in less regional differences in the standard of

TABLE 1-7 -- RHEUMATIC HEART DISEASE, MORTALITY ESTIMATES FOR 2000

REGION	NUMBER OF DEATHS (THOUSAND)	% OF CVD MORTALITY	DALYs (THOUSAND)	% OF CVD DALYs
EstME	21	0.6	15	0.8

EmgME	26	1.0	38	2.3
DevE	338	2.8	5,697	4.8
India	80,000	2.7	1,569	5.5
China	192,000	5.8	2,384	8.7
Other Asia	13,000	0.7	159	0.8
Sub-Saharan Africa	19,000	1.8	62	4.7
Middle East Crescent	25,000	1.4	76	3.8
Latin America, Caribbean	9,000	0.8	18	1.9

CVD=cardiovascular disease; DALYs=disability-adjusted life years; EstME=established market economies; EmgME=emerging market economies; DevE=developing economies.

Adapted from Murray CJL, Lopez AD: The Global Burden of Disease. Cambridge, MA, Harvard School of Public Health, 1996.

living compared with Africa or India. In general, China appears to be in the third stage of a Japanese-style epidemiological transition, with CVD rates above 35 percent, although dominated by stroke and not CHD as they are in the EstME and EmgME. Major features of the transition in China are the rapidly rising rates of cigarette smoking and hypertension, much of which remains untreated.

INDIA.

One sixth of the world's population lives in India, with 72 percent of the approximately 1 billion people residing in rural settings. Accurate country-wide data on cause-specific mortality are not available; the most reliable data derive from urban centers. The best estimates suggest that CVD accounts for 24 percent of total deaths.[2] As expected, CVD mortality rates tend to be higher in urban areas than rural areas and CVD is much more prevalent among the upper and middle classes.

In contrast to China and much of the rest of Asia, CHD appears to be the dominant form of CVD. In 1960, CHD represented 4 percent of all CVD deaths, whereas in 1990 the proportion was over 50 percent.[32] CHD death rates are currently about three times higher than stroke rates. This is somewhat unexpected, because stroke tends to be a more dominant factor early in the epidemiological transition. This may reflect inaccuracies in cause-specific mortality estimates. However, it may suggest metabolic differences in response to the Western life style of higher-fat diets and lower levels of activity. It has been suggested that Indians may have an exaggerated insulin

insensitivity in response to this life-style pattern that may differentially increase rates of CHD and stroke. Furthermore, the proportion of calories derived from fat, much of which comes from dairy products, is significantly higher in India than in other parts of the developing world.

Although rates of communicable disease remain high, accounting for 51 percent of all deaths and 56 percent of all lost DALYs,[2] the rates are falling rapidly. Thus, India appears to be early in the second phase of the transition with the urban upper classes in the third phase. As in China, rheumatic heart disease continues to be a major cause of morbidity and mortality (see Table 1-7) . Certain remote areas, however, are still in the age of pestilence and famine, with CVD accounting for less than 10 percent of total deaths.[33]

SOUTHEAST ASIA.

The diversity of economic circumstances in the countries of Southeast Asia is reflected in the status and character of the epidemiological transition across the region. In South Korea, for example, 57 percent of the population resides in urban centers and the mean annual per capita GNP is $9,700, whereas in Cambodia only 19 percent of the population lives in urban centers and the per capita GNP is $240. Average life expectancy in Korea is 72 years, compared with 53 years in Cambodia.

The rapid economic expansion occurring in several Southeast Asian countries has been accompanied by the expected shift to urbanization and associated life-style changes. In the most industrialized countries, such as Singapore, CVD rates mirror those in the EstME and EmgME, with CVD predominating as a major cause of death with CHD mortality rates double those of stroke rates. In other less developed parts of Asia, such as Indonesia and Sri Lanka, the character of disease is similar to that of China. In still others, such as Vietnam and Cambodia, pestilence and famine still predominate.

SUB-SAHARAN AFRICA.

In spite of large regional variations, sub-Saharan Africa remains largely in the first phase of the epidemiological transition, with more than 40 percent of all deaths due to infectious and parasitic diseases (see Table 1-5) . Life expectancies, as a result, are the lowest in the world. As is the case in India, accurate county-wide data are not generally available and most data come from urban centers and sampling in rural areas. Overall, CVD in sub-Saharan Africa is responsible for approximately 10 percent of all deaths, with stroke representing the dominant form in keeping with patterns characteristic of the earlier phases of the epidemiological transition. Even in urban centers, CHD was rare in the middle part of the 20th century.[34] As expected, average daily physical activity among urban dwellers is falling and smoking rates are increasing. Hypertension has emerged as a major public health concern, and hypertensive heart disease accounts for the dominance of stroke.[33] Rheumatic heart disease and cardiomyopathies, the latter due mostly to malnutrition, various viral illnesses, and parasitic organisms, are also important causes of CVD mortality and morbidity.

LATIN AMERICA AND THE CARIBBEAN.

As a whole, Latin America appears to be in the third phase of the epidemiological transition. At the turn of the century, approximately 31 percent of all deaths are attributable to CVD, a figure that is expected to increase to 38 percent by 2020.[2] Whereas CHD rates are higher than stroke rates (although not to the degree seen in EstME), the combination of these two accounts for more than 75 percent of CVD in this region. CVD rates are beginning to decline in some countries in Latin America and the Caribbean. However, those with the lowest CVD rates are facing the steepest increases in CVD mortality rates.[35] Rheumatic heart disease appears to be declining in most countries in this region. Chagas' disease remains a major problem in Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Paraguay, Peru, Uruguay, and Venezuela, where as much as 30 percent of the population may be infected with the parasite responsible for this disease.

MIDDLE EAST CRESCENT.

In this region, increasing economic wealth has been characteristically accompanied by urbanization but uncharacteristically accompanied by increasing fertility rates as infant and childhood mortality rates declined. This has resulted in rapid population growth and a young mean age of the population (i.e., 44 percent younger than age 15). Mortality from CVD is increasing rapidly, and CVD is now the leading cause of death, ranging from 25 to 45 percent of total deaths. The adoption of a Western diet has occurred at a rapid rate. As in the established market economies, CHD is the predominant cause of CVD, with about three CHD deaths for every stroke death. Rheumatic heart disease remains a major cause of morbidity and mortality, but the number of hospitalizations for rheumatic heart disease is rapidly declining. This region is entering the third phase of the transition.

GLOBAL TRENDS IN CVD

Estimating global trends in the burden of disease, particularly CVD, is aided by examining regional trends. Because 80 percent or more of the world's population lives in the DevE, global rates of CVD are largely driven by rates in these countries. The acceleration of worldwide CVD rates, for example, is occurring as most DevE countries are entering the second and third phases of the epidemic transition. In this section, we summarize global and regional estimates for 1990 and 2020 provided by Murray and Lopez.[2]

In 1990, the world population stood at 5.3 billion. CVD accounted for more than 14.3 million deaths, or 28.5 percent of the world's 50 million deaths (Table 1-8) . Of these, 6.3 million deaths were due to CHD (44 percent of CVD deaths) and 4.4 million were due to stroke (31 percent of CVD deaths). An estimated 133 million lost DALYs, or 9.7 percent of the total DALYs, were due to CVD.

Expectations for 2020

By 2020, world population is estimated to reach 7.8 billion, with much of the growth occurring in the developing economies (see Table 1-8) . In the EstME, population growth (up 13 percent from 1990 to 905 million people) will be fueled by emigration from the DevE. Even this substantial growth, however, represents a gradually shrinking proportion of the world's population, from 15.1 percent in 1990 to 11.5 percent in 2020. In the EmgME, growth will be more modest (up only 5 percent to 365 million people) and also represents a falling world share, from 6.5 percent in 1990 to 4.6

TABLE 1-8 -- CONTRIBUTION OF VARIOUS CATEGORIES OF DISEASE TO GLOBAL MORTALI

	POPULATION (MILLIONS)	TOTAL DEATHS (MILLIONS)	CMPN	INJURY	NonCMPN, nonCVD	ALL CVD	IHD	STROKE		
1990										
World	5267	50.4								
% Total deaths			34.2	10.1	27.4	28.4	12.4	8.7		
EstME	798	7.12								
% Total deaths			6.4	6.2	42.8	44.6	23.4	11.1		
EmgME	346	3.8								
% Total deaths			5.6	10.3	29.5	54.6	27.1	16.9		
DevE	4124	39.5								
% Total deaths			41.9	10.7	24.3	23.0	9.0	7.5		
2020										
World	7844	68.3								
% Total deaths			15.1	12.3	36.4	36.3	16.3	11.3		
EstME	905	8.6								
% Total deaths			6.2	5.2	46.3	42.3	22.5	10.6		
EmgME	365	4.8								

% Total deaths			2.9	8.6	34.8	53.7	27.0	16.3	
DevE	6573	54.8							
% Total deaths			17.6	13.7	34.9	33.8	14.3	10.9	

CMPN=communicable, maternal, perinatal, and nutritional diseases; CVD=cardiovascular disease; IHD=ischemic heart disease; RHD=rheumatic heart disease; EstME=established market economies; EmgME=emerging market economies; DevE=developing economies.

Adapted from Murray CJL, Lopez AD: The Global Burden of Disease. Cambridge, MA, Harvard Schoo Public Health, 1996.

percent in 2020. Continued rapid growth in the DevE will increase their population by more than 60 percent, from 4.1 billion people in 1990 to 6.6 billion in 2020, or 84 percent of the world's people. By 2020, CVD will be responsible for an estimated 25 million deaths annually (36.3 percent of all deaths), more than double caused by the combination of communicable, maternal, perinatal, and nutritional conditions. As deaths from these conditions fall from 34.2 percent of the total to 15.1 percent, CVD takes on greater significance. In terms of lost DALYs, those due to CVD are expected to double between 1990 and 2020, from under 10 percent to over 20 percent.

In the EstME, the modest decline in CVD death rates begun in the later third of the 20th century will continue, with the proportion of total deaths falling from 44.6 to 42.3 percent. The rate of decline, however, appears to be slowing. The *absolute number* of deaths as well as the prevalence of CVD will continue to increase as the population continues to age. In terms of lost DALYs, the proportion due to CVD will remain stable at about 19 percent.

In the EmgME, there will be little change in the overall proportion of deaths due to CVD (54.6 percent in 1990 and 53.7 percent in 2020). As a reflection of the anticipated decreases in DALYs lost due to communicable, maternal, perinatal, and nutritional diseases, lost DALYs due to CVD will increase as a proportion of the total (23.2 percent in 1990 to 26 percent in 2020). The average age of those afflicted with CVD will increase.

In the DevE, an estimated 9 million persons died of CVD in 1990. By 2020, that figure will more than double to more than 18 million persons annually, accounting for approximately three fourths of all CVD deaths worldwide. What will drive this overall rapid rise in CVD mortality rates in the DevE? One major factor is the projected 60 percent increase in population between 1990 and 2020. Another is that most of the countries that make up the DevE will have entered the third phase of the epidemiological transition by 2020. Substantial declines in communicable disease rates, from 41.2 percent in 1990 to 17.6 percent in 2020, will increase the proportion of DALYs lost due to CVD by more than 50 percent (8.2 percent in 1990 to 13.8 percent in 2020). Because CVD will afflict a younger population in the DevE than in the more developed economies, more than 100 of the 133 million DALYs lost to CVD (75 percent) will occur

in the this region.

Only in China and sub-Saharan Africa will stroke rates far exceed CHD rates and remain the predominant form of CVD, accounting for about half of all CVD deaths. In the other Asian countries and Latin America, CHD rates will be only slightly greater than stroke rates, whereas the CHD-to-stroke ratio will exceed 2 in India and the Middle Eastern Crescent.

REGIONAL TRENDS IN RISK FACTORS

As indicated in the previous discussion, the global variation in CVD rates is related to temporal and regional variations in known risk behaviors and factors. Discussions of the strength of the associations of the various factors with CVD are found elsewhere in this text (see Chap. 31) . Recent ecological analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors--smoking, serum cholesterol, and hypertension.[36] These analyses suggest that much of the regional variations are based on differences in conventional risk factors. In this section, the focus is on regional differences in these risk factors that help explain regional variations in the rate and character of the epidemiological transition.

Tobacco

Smoking clearly represents an important worldwide avoidable cause of CVD and total death. In 1990, an estimated 6 percent of all deaths were attributable to tobacco. By 2020, the proportion of deaths due to tobacco will more than double as smoking rates rise in the developing economies. [37]

Currently, more than 1 billion of the world's inhabitants smoke.[1] Regionally, the highest per capita cigarette consumption rates are in Europe at 2080 per year (in 1995), followed closely by the countries of the Western Pacific with 1945 per day and the Americas with 1530; they are the lowest in Africa, where annual per capita consumption is 480 cigarettes (Fig. 1-7) . [1]

In the market economies, smoking rates are beginning to decline, with the most substantial changes in the EstME. In the United States, for example, more than 40 percent of adults smoked in 1965, whereas only 23 percent smoked in 1997.[38] Over the same period, per capita consumption declined

Figure 1-7 Tobacco use in the United States, 1900 to 1999. *(From Achievements in Public Health, 1900-1999: Tobacco Use--United States, 1900-1999. MMWR Morbid Mortal Wkly Rep 48:986-993,*

1999.)

from more than 4200 cigarettes per year to approximately 2000 (see Fig. 1-7) .[39] [40] However, although cigarette smoking is declining overall, smoking is on the increase among young men and women in the United States.[41] In the EmgME countries, smoking rates are extremely high--59 percent of men and 26 percent of women smoked in 1995--but are stable or falling.[42]

In the DevE, tobacco represents an important cash crop and source of employment, two things that are often in short supply. On average, about 48 percent of adult men smoke, and smoking rates are increasing about 3.4 percent per year.[1] In some countries included in the DevE, smoking rates among men are staggeringly high, reaching 73 percent in Vietnam[43] and even higher in parts of Nepal.[44] Throughout the developing world, women have traditionally represented only a small proportion of the number of smokers. That is certain to change. In terms of sheer numbers, the number of women living in the DevE will rise from 2.6 billion in 1990 to 3.9 billion by 2020. As women's spending power increases, tobacco companies are targeting them as customers even as woman-specific health education and quitting programs are rare.[45]

A unique feature of the DevE is that there is easy access to relatively low-cost cigarettes during early stages of the epidemiological transition. In the established market economies, cigarette smoking peaked late in the third phase of the transition. In many DevE which are in the first or second stages, however, male smoking rates already exceed peak rates in the EstME, and rates are expected to continue rising among both men and women. The impact of more widespread smoking earlier in the epidemiological transition means a more rapid increase in CVD rates as the DevE enter the third phase of the transition. In China, which is in the early stages of the epidemiological transition, the 1996 National Prevalence Survey determined that 63 percent of men (but only 3.8 percent of women) were current smokers.[46] A massive retrospective study of 1 million deaths estimated that tobacco was responsible for 13 percent (600,000 deaths) of total mortality in China in 1990 and will account for 3 million deaths a year by 2025.[47]

Hypertension

Hypertension is clearly a risk factor for CHD and stroke (see Chap. 28) . Elevated blood pressure is an early hallmark of the epidemiological transition. Rising mean population blood pressure is apparent as countries industrialize--emigration from less-developed to more developed countries, as well as emigration from rural to urban settings, results in increasing blood pressure levels among emigrants. Among urban-dwelling men and women in India, for example, the prevalence of hypertension is 25.5 percent and 29.0 percent, respectively, whereas it is just 14.0 percent and 10.8 percent, respectively, among those living in rural communities.[47A] Whereas the relative increase in mortality associated with a given increase in blood pressure is similar in various regions of the world, the absolute risk at the same blood pressure level varies greatly.[48] In addition, the overall impact of hypertension may vary depending on the proportion of individuals in a country whose hypertension goes untreated.

In the EstME, hypertension remains a major cause of CVD morbidity and mortality

despite high rates of detection and treatment. Given the relationship of increasing blood pressure with advancing age, the prevalence of hypertension is increasing in most (aging) established market economies. In most of the EstME, the proportion of the population with untreated hypertension is declining, although in the United States there has been a slight reversal of this trend.[49] In the EmgME, the prevalence of hypertension is at least as high as it is in the EstME, whereas rates of treatment are much lower. This may explain, at least in part, the higher stroke rates in these countries in relation to CHD rates.

Across the DevE countries, hypertension rates are quite variable. One major concern in these countries is the high rate of undetected, and therefore untreated, hypertension.

In northern Asian countries such as China and South Korea, hypertension is rapidly increasing,[50] [51] with higher rates in urban areas than rural areas. The high rates of hypertension throughout Asia likely contribute to the high prevalence of hemorrhagic stroke. In contrast, rates of hypertension remain relatively low in sub-Saharan Africa. However, the attributable risk of hypertension in urban centers is exceedingly high in most countries of this region owing to lack of available treatment. Data on mean blood pressure levels in the population are limited. High rates of hypertension are apparent only in urban centers, where there are a significant number of hospitalizations for hypertension, largely owing to the very low rates of detection and treatment.[33] In Latin America and the Caribbean, as well as in the Middle Eastern Crescent, hypertension rates are also quite variable but follow the general

pattern of being highest in more affluent countries and urban centers.

Fat Consumption

Although dietary habits clearly vary from country to country, intake of dietary fat tends to be low in many DevE and high in many EstME and generally increases with annual per capita income (Fig. 1-8) . For example, fat contributes under 20 percent of calories in rural China and India,[52] under 30 percent in Japan,[53] and well more than 30 percent in the United States. Caloric contributions from fat appear to be falling in the EstME. In the United States, for example, the percent of calories from fat have steadily declined over the past 30 years, from 45 percent of calories in 1965 to 34 percent in 1994, although the total amount of fat in the diet has increased slightly since 1989.[54]

Even in the DevE, which are broadly characterized by low fat intake, fat intake varies greatly, and tends to increase with industrialization and urbanization. Compare, for example, the low levels of fat intake in rural China and India with its contribution of 36 percent of calories in Taiwan.[55]

Lipid Levels

The causal association between plasma cholesterol levels and risk of CVD is indisputable. Low levels of high-density lipoproteins and elevated triglycerides are also clearly associated with excess risk of CVD, and this association holds across racial and ethnic divisions. The lipid profile appears to have a greater impact on CHD than on stroke.

As countries move through the epidemiological transition, mean population plasma cholesterol levels tend to rise. Social and individual changes that accompany urbanization clearly play a role, because plasma cholesterol levels tend be higher among urban residents than among rural residents. This shift is largely driven by greater consumption of dietary fats--primarily from animal products and processed vegetable oils--and decreased physical activity. Cross-cultural differences in mean cholesterol levels reflect this pattern. In rural Nigeria, which is early in the epidemiological transition, mean cholesterol levels are 120 mg/dl (3.1 mmol/liter),[56] whereas in the heavily industrialized United States and northern Europe, which are in the fourth phase, mean cholesterol levels are 200 mg/dl (5.2 mmol/liter) and 240 mg/dl (6.2 mmol/liter),[57] respectively. In the established market economies, mean population cholesterol levels are generally falling. Japan is something of an exception to this pattern, with only relatively recent increases in average serum cholesterol levels.[53] [58] This may help explain why CHD rates did not increase in the third phase of Japan's epidemiological transition. If plasma cholesterol levels continue to rise, however, CHD rates may follow in the coming years. In the emerging market economies, mean population cholesterol levels also tend to be high, but levels are stable or rising.

In the DevE, there is a wide variation in mean population cholesterol levels, although they all tend to be increasing rapidly. In Asia, mean levels range from 110 mg/dl (2.8 mmol/liter) in rural areas to 220 mg/dl (5.7 mmol/liter) in highly industrialized countries such as Singapore. [52] In many countries in Latin America and the Caribbean, cholesterol levels approach those of northern Europe. A population survey in Bogota, Colombia, for example, found that 46 percent of men had serum cholesterol levels greater than 250 mg/dl (6.5 mmol/L).[59] In sub-Saharan Africa, mean cholesterol levels in rural areas are similar to the low levels seen in China, whereas levels are considerably higher in urban centers.[60] Given the high level of global capacity to produce Western-style food products at low cost, developing countries can now afford to adopt a Western dietary life style earlier in the economic transition than was possible in the past.

As is true for hypertension, rates of hypercholesterolemia are increasing far faster than the resources needed for widespread detection and treatment. Thus, the impact of both of these on atherosclerosis may be far greater than they have been in developed economies.

Physical Inactivity

One byproduct of the increased mechanization that accompanies the economic transition is decreased physical activity. In the market economies, the widespread prevalence of physical inactivity produces a high population attributable risk of cardiovascular consequences. In United States, approximately 25 percent of the population does not participate in any leisure-time physical activity and only 22 percent report engaging in sustained physical activity for at least 30 minutes on 5 or more days a week (the current

Figure 1-8 Association between income and dietary intake, based on country-level sources of energy. *(From Drewnowski A, Popkin BM: The nutrition transition: New trends in the global diet. Nutr Rev 55:31-43, 1997.)*

recommendation). [61] The shift from physically demanding, agricultural-based work to largely sedentary industrial- and office-based work is occurring throughout the developing world. This is also accompanied by a switch from physically demanding transportation to mechanized transportation.

Diabetes Mellitus (See also Chap. 63)

Diabetes and impaired glucose tolerance represent strong risk factors for vascular disease, including CHD, cerebrovascular disorders, and peripheral vascular disease. As a consequence of, or in addition to, increasing body-mass index and decreasing levels of physical activity, worldwide rates of diabetes--predominantly type 2 diabetes, or non-insulin-dependent diabetes mellitus--are on the rise. According to World Health Organization models, the number of persons with diabetes will swell from 135 million people in 1995 to 300 million in 2025, a 35 percent increase in worldwide prevalence (from 4.0 to 5.4 percent).[62] The largest increases in prevalence of diabetes will be in China (up 68 percent between 1995 and 2025) and India (up 59 percent), followed by Latin America and the Caribbean (41 percent), other Asian countries and the Pacific Islands (41 percent), and the Middle Eastern Crescent (30 percent). The market economies will experience increases between 26 percent and 28 percent.

The prevalence of diabetes varies greatly by geographic region, race, and ethnic composition. There appear to be clear genetic susceptibilities of various racial and ethnic groups. For example, Pima Indians living in the southwestern United States are eight times more likely to develop diabetes as the general U.S. population.[63] Hispanic Americans also tend to have higher rates than white Americans.[64] Migration studies suggest that South Asians and Indians also tend to be at higher risk than those of European extraction.

Diabetes mellitus is associated with a number of other CVD risk factors, including high

triglyceride levels, low high-density lipoprotein levels, central obesity, and hypertension. In relative terms, the attributable risk of diabetes is higher in women than men.

Obesity

Obesity is clearly associated with increased risk of CHD. However, much of this risk may be mediated by other CVD risk factors, including hypertension, diabetes mellitus, and lipid profile imbalances. While rates of smoking and hypertension tend to increase early in the epidemiological transition, obesity tends to increase later.

In the mid 1980s, the World Health Organization's MONICA Project sampled 48 populations for cardiovascular risk factors. In all but one male population (China), and in most of the female populations, between 50 percent and 75 percent of adults aged 35 to 64 were overweight or obese.[65] A later follow-up study showed that the prevalence of obesity has continued to increase.[66]

In many EstME, mean body-mass index is rising at an alarming rate even as mean plasma cholesterol levels are falling and age-adjusted hypertension levels remain fairly stable during the fourth phase (the age of delayed degenerative diseases). In United States, this is occurring among all sectors of the population; however, rates are increasing faster among minorities and women.[67] Overweight and obesity are not limited to market economies. In many of the DevE countries, obesity appears to coexist with undernutrition and malnutrition. Although the prevalence of obesity in DevE countries is certainly less than among the market economies, it is on the rise there as well. A study in Mauritius, for example, documented rapid increases in obesity between 1987 and 1992,[68] whereas another estimated that 44 percent of African women living in the Cape Peninsula were obese.[69]

Further increases in the prevalence of overweight and obesity are to be expected if data on childhood and adolescent obesity are any indication.[70] Early obesity not only increases the likelihood of adult obesity, but it also increases the prevalence of weight-related disorders, including CVD.

FUTURE CHALLENGES

Although the concept of the epidemiological transition offers tremendous insight into how and why CVD is emerging as the predominant global cause of morbidity and mortality, it does not mandate that this must be so. As has been seen from the experience of established market economies, CVD rates rise in a predictable fashion with increasing rates of risk factors and behaviors. It is equally true that population-based and individual interventions can have an impact on both the rates and consequences of CVD. This raises the possibility of altering the epidemiological transition to blunt the increase in regional CVD rates or to hasten their decline. The transfer of lower cost health and food technologies from the EstME to the DevE have made great gains in the fight against communicable diseases and clearly helped hasten the transition out of the age of pestilence and famine. It is possible that similar

interventions could alter the course of later stages.

Given the multifactorial nature of CVD, no single solution will be generally applicable to all geographic and economic regions of the world. In this section are outlined the major challenges facing each economic region and the various strategies to address these problems are discussed. Appropriate regional strategies depend on a number of factors, including a country or region's stage in the epidemiological transition, the rate of change of the epidemiological transition, individual and collective resources, and cultural and political factors.

Three complementary strategies may be used to reduce morbidity and mortality from CVD. First, the overall burden of CVD risk factors in the entire population may be lowered through population-wide public health measures. These include detection and surveillance strategies, public education campaigns, and the institution of low-cost preventive interventions. National campaigns against cigarette smoking are an example of the public health approach. The second approach involves identifying and targeting higher-risk subgroups of the population who stand to benefit the most from moderate, cost-effective prevention interventions. Third, resources can be allocated to acute and chronic higher cost treatments and secondary prevention interventions for those with clinically manifest disease. Typically, resources are allocated simultaneously to all three strategies; however, this three-pronged approach has been implemented mostly in EstME with abundant financial resources for health care. In the following sections are outlined the major challenges and possible solutions for each region.

Established Market Economies

Although CVD mortality rates have fallen in most EstME, several important challenges remain. First, socioeconomic and racial disparities in CVD rates continue to linger. In the United States, for example, whereas rates of CVD mortality have fallen across the population, there are still wide disparities across racial and ethnic boundaries. Thus, a major goal will be to accelerate the widespread application of preventive and therapeutic technologies to all racial, ethnic, and socioeconomic groups.

Second, the rate of declining CVD mortality appears to be stagnating. Over the past 5 years in United States, age-adjusted

stroke mortality rates have not changed and the decline in CHD rates has slowed. These may be the result of troubling trends in a number of coronary risk factors--whereas older men and women continue to stop smoking, young adults and teenagers, particularly young women, are smoking at increasing rates; the rates of those appropriately treated for hypertension has decreased slightly in the past 5 years; obesity and diabetes rates are accelerating at rapid rates. Perhaps most troubling are observations of increasing rates of obesity and physical activity in children. Taken together, these trends may explain the flattening of mortality curves and may also

explain why mortality rates have fallen faster than CVD incidence rates.

In the absence of efforts to reverse these trends in risk factors, we may once again see increasing rates of CVD. More public health dollars need to be directed at antismoking efforts that target high-risk groups such as teenage girls and at broader application of guidelines for detecting and managing hypertension and hyperlipidemia. Effective strategies to increase activity and reverse trends in obesity and diabetes must be developed and implemented.

Third, the prevalence of CVD will continue to increase with the increasing mean age of a population even if that population's age-adjusted mortality rates continue to decline. In addition, incremental advances in therapeutic health technology and secondary prevention have led to increasing numbers of people surviving with CVD, which consumes increasing amounts of resources. With the institution of many life-saving strategies among those who present with acute manifestations of atherosclerotic disease, more and more individuals are surviving acute events such as myocardial infarction. For example, approximately one third of those who presented to hospitals with acute myocardial infarction in the 1950s died. Today, mortality is less than half that, despite the fact that sicker and older patients are presenting to the hospital. Furthermore, CHD is being diagnosed in increasing numbers of individuals before cardiovascular events. Thousands of pacemakers and defibrillators are implanted each year. As more and more individuals survive longer with CVD, so does the prevalence of congestive heart failure. Between 1985 and 1995 in the United States, hospitalizations for congestive heart failure increased from 1.7 million to 2.6 million (see Chap. 21) .[71] Over the same time period, mortality from congestive heart failure decreased.[71] [72] Thus, the management of congestive heart failure will consume more and more health care resources.[73] A major challenge for most established market economies will be the increasing financial burden of the management of CVD. More efficient and cost-effective strategies for treating CVD will have to be developed.

Emerging Market Economies

This region is largely in the third phase of the epidemiological transition. However, the resources available are considerably less than those available in the EstME. Annual per capita GNP in the EmgME ranges from about $1000 to $5000, less than the United States spends per capita on health care alone. This mandates making careful choices in terms of allocating health care dollars to each of the strategies outlined earlier.

In the EmgME, the two overarching goals are to manage the increasing number of people with CVD and to hasten the transition from the third to the fourth phase of the epidemiological transition. This will likely enhance overall productivity in the region because during the third phase of the epidemiological transition CVD, and particularly CHD, often afflicts those at the age of highest productivity. In terms of challenges facing the former socialist countries, the region can be divided into two categories: those countries with stable or declining rates and those countries with increasing CVD rates. For countries with stable or declining rates, the three-pronged approach used in the EstME should serve as a model. For those countries experiencing rapid rises in CVD rates, an important first step will be toward more centralized efforts at compiling data on

rates of disease and risk factors and then determining the major contributors to the rise. All countries in this economic sector need more careful tracking and assessment of risk factors in terms of population attributable risk. Better tracking of CVD rates risk factors will allow for more careful allocation of scarce preventive resources.

National guidelines that have been developed in the EstME need to be adapted for the EmgME. Governments should initiate major public health initiatives aimed at life-style factors, including lowering rates of smoking and drinking, modifying diet, and increasing physical activity. Major public health priorities should include smoking cessation and the detection and control of hypertension, both of which are highly cost effective. The targeting of higher-risk individuals for higher-cost preventive strategies such as pharmacological cholesterol lowering will initially need to be confined to areas such as urban centers, where the burden is high and the necessary laboratory-based health care infrastructure is available.

Throughout this economic sector, improvements in health care delivery systems will be needed to manage the already high rates of CVD prevalent in these countries. Careful attention must be paid to the transfer of lower-cost health technology, keeping in mind the considerably lower annual health care expenditures in the EmgME countries compared with those in the EstME. Interventions such as the more widespread and appropriate use of aspirin and beta blockers during acute myocardial infarction is an example of an extremely cost-effective life-saving therapy that should be implemented universally before extensive resources are directed at higher-cost interventions such as angioplasty. Manpower issues must also be addressed, given the general shortage of health care professionals in the EmgME.

Developing Economies

The problems facing the DevE may be the most challenging. These countries have rapidly increasing burdens of CVD early in their economic transitions. They often do not have the per capita resources needed to create the three-pronged type of public health and health care infrastructure currently available in the EstME. In many DevE, per capita health care expenditures are less than $50 per year. In addition, there are a number of competing national priorities, including the stimulation of economic growth, social and political change, and the devastation wrought by communicable diseases.

Rising CVD rates will eventually exert a drag on economic growth. Early in the epidemiological transition, CVD deaths occur among younger individuals than they do later in the transition. Thus, the economic impact on both the family and national productivity is greater in developing economies than in established market economies. The loss of the head of a household from CVD (or any other disease) has a devastating impact on the health and well-being of the entire family. In Bangladesh, for example, when there is an adult death, a child who depends on that adult has a 12-fold higher probability of death.[74] At present, the data on the economic consequences of CVD in the DevE are limited. Much more work is needed to refine estimates that would permit more thoughtful allocation of health care resources.

As mentioned earlier, the epidemiological transition has been accelerated at least in part

by an efficient translation of risk factors and risk behaviors from the EstME to the DevE early in the economic transition. The rapid spread of cigarette smoking is a prime example of this. A major challenge for developing countries is to attempt to change the natural history of the epidemiological transition. That such

alterations are possible is evidence from the experience of Japan, in which CHD rates were kept relatively low during a fairly rapid economic transition to an industrial-based economy. Although imbedded cultural practice such as diet likely played a large role, the Japanese experience illustrates that the nature of the transition is variable.

As is true for the EmgME, a critical first step in developing a comprehensive plan for many of the DevE is better assessment of cause-specific mortality and morbidity as well as the prevalence of the major preventable risk factors for CVD. This will enable better allocation of resources based on country-wide burdens of disease. Beginning first in the urban centers and then moving out to rural areas, government agencies will need to make careful assessments of, and create longitudinal surveillance of, major CVD risk factors for which low-cost strategies are available. High priorities include smoking and hypertension, for which the population attributable risks are likely to be high and the cost efficacy favorable. The strategy for the detection and management of high cholesterol must be carefully tailored for each region due to higher costs. Public health approaches aimed at educating the general population about diet and exercise may be useful, but precise estimates of cost efficacy are not available on these even for EstME countries. Drug therapy for cholesterol lowering is likely less cost effective than short-term smoking cessation programs or managing hypertension with low-cost medications.

Once these initial assessments have been made, guidelines for their management from a public health standpoint must be developed based on the population attributable risk and the available resources. These guidelines must be implemented with low-cost campaigns. Such prevention-directed efforts could blunt the rise in disease rates already apparent in many developed countries.

Given the extreme limitations in per capita health care resources in many DevE, the allocation of resources to higher-cost strategies for treating CVD may divert resources from the potentially more effective population-wide efforts. Thus, efforts targeted at interventions and high-technology therapeutics may have to be parsimoniously implemented only in those urban areas where risk is highest.

SUMMARY AND CONCLUSIONS

In the 1999 *World Health Report*, Director General Gro Harlem Brundtland states that we are "halfway through a two century transition" in which CVD will dominate as the major cause of death and disease. Although CVD rates are declining in the EstME, they

are increasing in virtually every other region of the world. From a worldwide perspective the rate of change in the global burden of CVD is accelerating, reflecting the change in the developing economies, which represent over 80 percent of the world's population, as they move rapidly through the second and third phases of the epidemiological transition. The consequences of this epidemic will be substantial on many levels--individual mortality and morbidity, family suffering, and staggering economic costs, both the direct costs of diagnosis and treatment and the indirect costs of lost productivity.

Each region of the world faces major challenges presented by the epidemic of CVD. There is no single global solution to the rising burden of CVD given the vast differences in social, cultural, and economic circumstances. The EstME must reverse unfavorable trends in CVD risk factors and behaviors and deal with the increasing prevalence of CVD in an aging population. To hasten the transition from the third to the fourth phase of the epidemiological transition, the EmgME must find ways to efficiently care for increasing numbers of individuals with CVD as well as to deploy lower cost prevention strategies. The most complex challenges are those facing the DevE. They must dedicate often minuscule resources to better assessment of rates of death, disease, and CVD risk factors. The allocation of resources to lower cost preventive strategies will likely be more cost effective than dedicating resources to high-cost management of CVD.

The EstME must continue to bear the burden of research and development into every aspect of prevention and treatment. Through further expansion of the knowledge base, particularly regarding the economic consequences of various treatment and prevention strategies, it is possible that the efficient transfer of low-cost preventive and therapeutic strategies may alter the natural course of the epidemiological transition in every part of the world and thus reduce the excess global burden of preventable CVD.

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Chapter 2 - Economics and Cardiovascular Disease

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The United States leads the world in spending on health care, whether measured as a percentage of gross domestic product or as dollars per capita. The decisions made by physicians control the bulk of these expenditures, and society has increasingly called for greater stewardship of the tremendous resources that doctors command. In this chapter some of the key economic principles that underlie clinical and health policy decision-making are discussed and important economic studies evaluating management of cardiovascular disorders are reviewed. Readers interested in more in-depth presentations of health economics can consult several excellent overviews.[1] [2] [3]

KEY ECONOMIC PRINCIPLES

ALTERNATIVE USES.

A key principle of economics is that all resources have alternative uses, so devoting resources to any particular activity makes them unavailable for different, and perhaps better, uses. Society's application of resources to medical care diminishes the resources available for alternative programs, such as public safety, assistance to the elderly or the

poor, or environmental protection. This same principle applies to the resources earmarked to health care: the resources devoted to coronary bypass surgery within a health care system might be used to meet alternative health needs, such as treatment of heart failure, prenatal care programs, or provision of vaccinations. Thus, the goal of health economics is to define the most efficient use of the resources available to provide health care to a population of patients.

LAW OF DIMINISHING RETURNS.

An economic principle of special relevance to medicine is the so-called law of diminishing returns, indicated schematically in Figure 2-1 . Because resources are initially applied to a particular end, the returns are large, but with each additional increment of resources applied, the returns become smaller and smaller to the point that there is no further gain, and perhaps even a loss, with application of even more resources. This type of response is familiar to clinicians caring for patients. In the case of acute myocardial infarction (AMI), for example, access to defibrillation and hospital monitoring provides great benefits and the addition of thrombolytic therapy further improves patient outcomes. The provision of yet more care may improve outcomes a bit further, but eventually at some point outcomes cannot be improved further (this point has been called the "flat of the curve" [4]). Beyond this point, providing yet more resources can actually harm patients (e.g., prolonged bed rest, prophylaxis with a type I antiarrhythmic agent). A key economic insight is that society is best served by medical care that operates not on the flat of the curve but at a point on the shoulder of the curve (see Fig. 2-1 , point B) because the resources that would be spent in moving up to the flat of the curve have better alternative uses. A major goal of economic analysis of cardiovascular care is to find the optimal level of resources for a given clinical problem.

SOCIETAL PERSPECTIVE.

Economic analyses most often employ the societal perspective: how will society as a whole benefit from the new clinical program and what will society have to pay for it. In contrast, clinicians are focused on individual patients. Their traditional role is to be the patient's advocate, to do what is possible for the patient before them, regardless of the value provided to society. Thus, economic analysis is really meant as a policy tool, for informing spending decisions about populations, not as a tool for assisting with bedside decision-making. As exemplified in Figure 2-1 , a key economic measure of value is the cost of adding an additional unit of medical benefit, or the slope of the curve.[2] [3] [5] [6] [7] In economic analysis, the costs and effects of an intervention are always compared with an explicitly defined alternative. Thus, cost-effectiveness analysis assesses the marginal (or incremental) costs required to produce one extra unit of outcome. The ratio is defined as:

where $cost_{new}$ is the total cost of the new program, $cost_{old}$ is the total cost of the old

program, and $effect_{new}$ and $effect_{old}$ indicate the medical effectiveness of the new and old programs, respectively. The cost of a program includes all relevant costs, including the intervention itself (e.g., streptokinase for an AMI), the cost of complications induced (e.g., bleeding, stroke) and averted (e.g., heart failure) by therapy, and the costs of concomitant treatments (e.g., mechanical coronary revascularization). The effectiveness of a medical intervention should be measured in outcomes of direct relevance to the patient, such as life-years of survival or quality of life. Economic analysis commonly measures effectiveness in "quality-adjusted life years" (QALYs) to assess both of these dimensions of improved clinical outcome on a common outcome scale. Laboratory-based outcome measures (e.g., ejection fraction, serum cholesterol) are intermediate, surrogate measures for ultimate patient benefit and therefore not used in economic analysis.

ECONOMICS OF SCALE.

Another final economic principle of relevance to medical care is that the production of goods and services is often more efficient in larger quantities due to "economies of scale." The high fixed cost of specialized equipment (e.g., an angiography suite) spread over more patients leads to lower costs per patient.[8] Also, large volume facilities can negotiate price discounts from suppliers and achieve more flexible use of personnel with

Figure 2-1 General relationship between application of health care resources (horizontal axis) and health outcomes (vertical axis). At point A, outcomes are improving rapidly with increased resources and treatment is cost effective. At point B, outcomes are still improving with increased resources, but at a rate that is less cost effective. At point C, increased resources are no longer improving outcome (i.e., "flat at the curve"), and at point D increased resources actually lead to worse outcomes, through iatrogenic complications and overtreatment.

their larger staff. In medical care, there is also evidence that higher patient volumes are associated with greater technical proficiency and better clinical outcomes.[9] [10] [11] Of course, beyond a certain scale, the clinical and cost advantages of higher volumes will be diminished and the disadvantages may increase (e.g., poorer communication, an impersonal approach to patient care). Nevertheless, there is strong empirical evidence of the value of maintaining a minimum level of clinical volume in procedures such as coronary angioplasty and coronary bypass surgery, and in the care of critically ill patients such as those with AMI.

MEDICAL COSTS

Provision of medical care requires resources: the time and energy of physicians, nurses, and other health care professionals; specialized facilities such as intensive care units, angiography suites, and operating rooms; and costly drugs and supplies. Use of these resources has a cost, even if medical care is provided to the patient "for free." In

principle, the best measure of this cost is what economists term the *opportunity cost,* or what has been lost by not applying resources to their next best use. As a practical matter, cost is measured by the prices paid in a competitive market. The overall cost of a medical program can then be measured as $Sigma_i P_i Q_i$, where P_i is the price for resource "i", Q_i is the quantity of resource "i" that is used, and the summation is over all "i" resources used in care of the patient. Modern hospital cost accounting systems facilitate such "microcosting" of medical care services. When microcosting is not feasible, an alternative measure of the cost of hospital services has been found by multiplying the charge for the service by a correction factor, the ratio of costs to charges,[12] found on the hospital's annual financial reports filed with the Health Care Financing Administration.[13] Because medical care is not provided in a classical competitive market, medical prices or charges are a very distorted (inflated) measure of the medical costs and should generally be avoided.

In medical economic studies, the cost of an intervention includes all relevant costs, regardless of who pays for them. The cost of an angioplasty might be borne in part by the insurance company, in part by the patient (e.g., prescription drugs after discharge), and in part by the hospital (e.g., costs over the contracted insurance payment amount). An expensive new therapy in the angioplasty laboratory may reduce total costs in the year after the procedure, and therefore be quite economically attractive. Nevertheless, hospitals may resist using the new therapy because the costs they pay are increased and they do not share the downstream savings. Even programs that save total medical costs can create economic winners and losers, whose incentives and disincentives can distort optimal resource allocation from a societal perspective. Thus, whereas economic analysis can adopt a number of valid perspectives or points of view, the societal one is preferred because it is the broadest.

Medical costs and benefits are typically spread over long time intervals, which leads to two related issues regarding measurement. Inflation changes the units of cost measurement, such that a dollar in 1995 does not have the same value as a dollar in 2000. To compare costs of alternative strategies within a given study, or those from different studies, it is therefore necessary to adjust all costs to a single standard value, such as 2000 dollars. A separate issue is that even if there were no cost inflation, it is still preferable to be paid today than to be paid in 5 years, and, conversely, it is preferable to repay a debt sometime in the future than to repay it immediately. To adjust for these time preferences, medical economic studies typically discount future costs and medical benefits by 3 percent per year.[6]

ANALYSIS OF SPECIFIC INTERVENTIONS

Economic analysis can be applied to treatment of acute illness (e.g., AMI), procedures (e.g., coronary bypass surgery), treatment of chronic illness (e.g., heart failure), prevention of disease (e.g., reduction of high cholesterol levels), or the use of diagnostic tests (e.g., coronary angiography). In the remainder of this chapter, the principles of economic analysis are illustrated by discussing cardiovascular management strategies drawn from each of these areas. Detailed review of the economics of all cardiovascular therapies is beyond the scope of this chapter and can be found elsewhere.[14]

Application of economic analysis to medical care can be illustrated by the use of thrombolytic therapy for AMI. As discussed in Chapter 35 , AMI most commonly results from the thrombotic occlusion of a major coronary artery at the site of a disrupted atherosclerotic plaque. After plaque rupture, there is a brief initial period of high risk in which appropriate therapy reduces mortality, and after a few weeks the patient's risk and quality of life settle at their chronic, steady state values. Clinical investigations have clearly established that timely reperfusion of the occluded coronary artery improves mortality of the patient with an AMI[15] and that this survival benefit is maintained over long-term follow-up.[16]

The value of streptokinase administration for AMI compared with the alternative of no reperfusion therapy can be analyzed using cost-effectiveness analysis.[17] For the purpose of this example, we assume that streptokinase costs $270 per treatment and that costs of medical care are otherwise equal in treated and untreated AMI patients. We further assume that hospital survival is improved from 88 to 92 percent by streptokinase treatment and that the life expectancy of MI survivors is 15 years, regardless of whether they were treated with streptokinase. Based on these assumptions, the incremental cost-effectiveness of streptokinase for the treatment of AMI can be calculated as:

Thus, the expenditure of $450 on average adds a year to the life of a patient with an AMI. To judge whether streptokinase therapy for AMI represents a good value for the money spent (i.e., is "economically attractive") requires a standard of comparison. Renal dialysis currently costs about $50,000 per patient per year in the United States. Because the cost of dialysis is covered by the federal Medicare program, it represents a good benchmark of how much society is willing to spend to add a life year. Programs that cost up to $50,000 per year of life added provide value that is comparable to that provided by renal dialysis and are generally considered economically attractive. Programs with cost-effectiveness ratios much worse than renal dialysis (i.e., more than $100,000 per year of life added) are generally considered to be economically unattractive. Based on these benchmarks, streptokinase therapy for AMI is a very economically attractive intervention.

Acute Coronary Syndromes

THROMBOLYTIC AGENTS.

Treatment of acute coronary syndromes (AMI [see Chap. 35], unstable angina [see Chap. 36]) has been the subject of intense clinical investigation since the early 1980s.

Coronary reperfusion by pharmacological or mechanical methods has been extensively investigated, as have antithrombotic and anticoagulation regimens. Although there are vast differences among these therapies clinically, they share common features from the perspective of economic evaluation. The therapies for acute coronary syndromes are typically short term in duration and expensive, and they provide benefit to patients mainly by reducing the short-term risk of hospital death and/or AMI.

Tissue plasminogen activator (t-PA) has been extensively studied for the treatment of AMI. t-PA is much more expensive than streptokinase, the first thrombolytic agent shown to be effective for AMI. The cost-effectiveness of t-PA was therefore investigated, first by the use of decision analysis[18] and subsequently using empirical data in conjunction with the randomized Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-1 (GUSTO-1) trial.[19] In GUSTO-1, the resource consumed during the first 6 months were documented in a sample of randomized patients. The cost of therapy was assessed by assigning standardized costs to each resource consumed (e.g., hospital days, cardiac angiography) and summing the costs over all resources used. This evaluation showed that, apart from the cost of the thrombolytic agents themselves, hospital and follow-up costs were quite similar in t-PA- and streptokinase-treated patients. Thus, the high cost of the t-PA ($2200 vs. $270) was not offset by cost savings elsewhere in the patient's care. The 30-day survival rate of t-PA-treated patients was improved by 1 percent in GUSTO-1; and based on long-term post-MI follow-up data collected by the Duke University data base, the life expectancy of survivors was projected to be 15.4 years. Using these data, the costeffectiveness of t-PA relative to streptokinase was calculated to be $27,100 per year of life saved, which was economically attractive by the previously described benchmarks. [19]

The use of streptokinase and t-PA for AMI provides a striking example of the economic principle of diminishing returns. The greatest gain in clinical outcome comes from using the least expensive effective thrombolytic agent (streptokinase) for AMI, which improves survival by 4 percent or more in absolute terms at a net cost of about $270 per patient. t-PA improves survival by a further 1 percent in absolute terms, but at an added cost of over $1900 per patient. Thus, the cost-effectiveness of streptokinase relative to placebo ($450 per life year added) is more favorable than the cost-effectiveness of t-PA relative to streptokinase ($27,100 per life year added). Simple and inexpensive therapies usually provide most of the potential improvement in outcomes for a given clinical condition, with smaller and smaller marginal improvements coming at greater and greater cost. This example also illustrates the comparative nature of economic evaluations--the value of a treatment can only be assessed in light of the therapeutic alternatives. This example also demonstrates that the difference in clinical benefit between two or more active therapies will generally be a fraction of the difference in clinical benefit between the least expensive effective therapy and placebo.

ANGIOPLASTY.

Primary angioplasty for AMI has been compared with thrombolytic therapy in several clinical trials, some of which also included an economic evaluation. A quantitative overview of trials showed the survival of patients with AMI treated with angioplasty is

equal to or better than that of patients treated with thrombolysis.[20] The results of economic analysis have been less consistent, with primary angioplasty being the less expensive strategy in some studies but raising costs in others.[21] [22] [23] This difference is largely due to differences in the rate of subsequent coronary angiography and revascularization in thrombolytic-treated patients. When rates of subsequent angiography are high, the primary angioplasty strategy has only a modest impact on net incremental costs, since many patients treated initially with thrombolysis subsequently undergo angioplasty or coronary artery bypass grafting (CABG) later in the same admission. When rates of subsequent angiography are low, however, primary angioplasty increases costs by adding revascularization procedures that would not otherwise have been done. A formal cost-effectiveness analysis of primary angioplasty relative to thrombolysis showed it to be cost-effective when performed in hospitals with existing cardiac angiography laboratories and minimal delay to therapy.[24] This analysis also suggested it would not be economically justified to build new catheterization laboratories solely to provide primary angioplasty.[24]

ANTICOAGULATION AND ANTIPLATELET REGIMENS.

Anticoagulant and antiplatelet regimens in the treatment of unstable angina and AMI have been investigated intensively in clinical trials. Because the newer agents of these classes tend to be more expensive than the standard alternatives (heparin, aspirin), economic evaluation is important. Economic evaluations are difficult to perform in these settings, however, because some or all of the benefit of these therapies come from reducing nonfatal MI, not hospital mortality. The economic analysis must therefore assess the long-term value of preventing a nonfatal MI, not just the value of improving short-term survival.

In one study, low-molecular-weight heparin (enoxaparin) improved clinical outcomes and lowered overall hospital costs relative to unfractionated heparin, largely because the $75 greater cost of enoxaparin was more than recouped by its greater effectiveness in reducing the need for costly revascularization procedures in patients with recurrent ischemia.[25] The combination of better clinical outcomes and lower cost, termed a *dominant* strategy because no tradeoffs between cost and outcome are involved, is clearly economically attractive. Use of eptifibatide, a glycoprotein IIb/IIIa inhibitor, in patients with acute coronary syndrome improved clinical outcomes, primarily nonfatal MI, at a net cost of $1014 per patient. The cost-effectiveness ratio for this drug appears economically attractive ($16,500 per life year added) based on the assumption that prevention of a

nonfatal MI increases life expectancy by approximately 2 years.[26]

Cardiac Procedures and Devices

CORONARY BYPASS GRAFTING.

In 1997, CABG was performed on 366,000 patients in the United States and 686,000 coronary angioplasty procedures were also performed.[27] With a total cost of roughly 20 billion dollars a year, the use of coronary revascularization procedures has spurred extensive economic evaluation.

CABG is an effective treatment for angina in symptomatic patients and extends life expectancy in patients with extensive coronary disease (see Chap. 37) . An overview of randomized clinical trials of surgery versus medical therapy[28] suggests that patients with left main disease may live more than 0.6 year longer after CABG, patients with three-vessel disease may live more than 0.5 year longer, and patients with one or two-vessel disease may live more than 0.16 year longer (life extension was estimated only over the first 10 years of follow-up). These data suggest that CABG is more economically attractive in patients with more extensive coronary disease who are at higher risk of death, because the absolute improvement in survival is greatest in these patients whereas the cost of the surgery is roughly the same. An early classic study[29] found the cost-effectiveness of CABG versus medical therapy for left main disease was $3800 per year of life added, a highly favorable ratio. More recent analyses[30] confirm that the cost-effectiveness of CABG is most favorable in patients with higher clinical risk (more extensive coronary disease, reduced left ventricular function), and greater degrees of angina.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA).

Despite the extensive use of PTCA (see Chap. 38) , there have been few randomized trials that compare it with medical therapy. The Randomised Intervention Treatment of Angina-2 (RITA-2) trial[31] found better angina relief but more cardiac events in stable angina patients treated with PTCA compared with medical therapy. The Angioplasty Compared to Medicine (ACME) trial found similar results in patients with single-vessel disease randomized to angioplasty or medical therapy,[32] as did the Atorvastatin Versus Revascularization Trial (AVERT) of aggressive lipid-lowering therapy versus PTCA for stable patients.[33] Economic analyses of these studies have not yet been reported.

PTCA and CABG have been compared directly in several randomized trials conducted in patients with multivessel disease. The clinical results of these studies were quite consistent in showing significantly less angina and a nonsignificant reduction in mortality in surgery patients.[34] [35] Economic analysis in the RITA trial,[36] Emory Angioplasty Versus Surgery Trial (EAST),[37] Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Grafting in Multivessel Disease (ERACI),[38] and Bypass Angioplasty Revascularization Investigation (BARI)[39] all documented significantly lower initial costs with PTCA, roughly one half to two thirds of the cost of CABG. These studies all showed that this initial cost advantage of PTCA was almost completely lost over the subsequent 2 years of follow-up as a result of the frequent need for repeat coronary revascularization procedures among angioplasty-treated patients. At 3 to 5 years of follow-up, the total medical costs averaged 4 to 6 percent lower in PTCA patients than in surgery

patients.[37] [39] Economic analysis suggests that CABG is more cost-effective than PTCA in patients with more extensive coronary disease (i.e., three-vessel disease), whereas PTCA has a significant cost advantage in patients with less extensive disease, albeit with somewhat less angina relief.[39]

Coronary stents have now become a standard part of percutaneous revascularization. Stents reduce the need for emergency bypass surgery after initial PTCA and significantly reduce the likelihood of restenosis and frequency of repeat revascularization over the subsequent 4 to 6 months.[40] [41] Use of stents substantially increases the cost of the revascularization procedure, and, in most studies, the higher cost of the stent is only partially offset by the subsequently lower incidence of repeat revascularization.[42] [43] Consequently, the total cost of patients treated with coronary stents remains 7 to 12 percent higher than that of patients treated with balloon PTCA at 1 year of follow-up, with an equivalent incidence of death and nonfatal MI. Formal cost-effectiveness models based on recent randomized trial results have not been reported; an older decision model suggested that stenting would be cost effective if restenosis were reduced by 25 percent or more.[44]

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD).

Some randomized trials have reported that the ICD (see Chaps. 23 and 26) reduces mortality in patients at risk for sudden death. Because implantation of the defibrillator costs $30,000 or more, several economic evaluations of the device have been performed. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT), ICD implantation reduced mortality by 54 percent.[45] In an economic substudy of the MADIT trial, the hospital costs of ICD-assigned patients were $25,700 higher than the cost of conventionally treated patients.[46] By 4 years of follow-up, the total cost of the ICD patients was still $22,000 higher, indicating that relatively little of the higher initial ICD costs was recouped by reducing the subsequent cost of treating clinical complications. Nevertheless, the cost-effectiveness ratio of the ICD in the MADIT trial was $27,000 per life year added,[46] largely because of the very strong effect of the ICD in reducing mortality in that study. In a decision model that projected lifetime costs and survival for patients with life-threatening ventricular arrhythmias, Owens and coworkers calculated that a 20 percent relative risk reduction by the ICD translates to a cost-effectiveness ratio of $54,000 per year of life added, whereas a 40 percent relative risk reduction translates into a cost-effectiveness ratio of $27,300 per year of life added.[47]

These studies illustrate several general points about the economic evaluation of procedures and devices. The initial cost of procedures and devices is often quite high, but long-term follow-up is needed to assess the total net cost of the procedure relative to alternative therapies. An expensive procedure may have some or all of its incremental costs recouped through prevention of costly adverse events, such as in the case of CABG relative to balloon angioplasty. The higher cost may be only partially offset by later savings (e.g., coronary stents) or barely recovered at all (e.g., implantable defibrillators). zNevertheless, high initial costs of procedures and devices may be justified if survival is sufficiently improved or quality of life is enhanced. These considerations emphasize the importance of a long-term perspective in the economic evaluation of devices and procedures, so that their full costs and benefits can be

assessed.

Chronic Disease

Economically efficient management of a chronic disease such as heart failure is very different from that of an acute illness or a surgical procedure. In chronic diseases, the cost of care is spread over many years instead of being concentrated at the outset of treatment. Similarly, the benefits of treatment accrue only over a period of prolonged follow-up. Most medical care for chronic disease is delivered in an ambulatory, outpatient setting, and patient adherence to prescribed regimens has a substantial

impact on the efficacy of therapy. Improvements in clinical and economic outcomes may come either from better therapies or from better ways to deliver established therapies, or both.

HEART FAILURE.

Angiotensin-converting enzyme (ACE) inhibitors have significantly improved survival of patients with heart failure in randomized trials.[48] An economic appraisal of enalapril therapy based on the Studies of Left Ventricular Dysfunction (SOLVD) trial results[49] suggested that over the 48 months of trial, the added cost of enalapril was completely offset by the cost savings from fewer hospitalizations for heart failure in the enalapril arm. Projections of lifetime costs and life expectancy performed using a model suggested that the net lifetime cost per patient was only $25 and that life expectancy was increased by 0.30 year,[49] yielding an extremely favorable cost-effectiveness ratio ($83 per life year added, or $119 per quality-adjusted life year added). An economic analysis based on the Survival and Ventricular Enlargement (SAVE) trial in patients with an ejection fraction less than 40 percent after an acute MI suggested that captopril therapy was economically attractive for this indication, with more favorable cost-effectiveness ratios in older patients than in younger patients.[50] Economic analyses of the Acute Infarction Ramipril Efficacy (AIRE) trial from Germany[51] and Sweden[52] both suggest that trandolapril is also an economically attractive agent in treatment of left ventricular dysfunction after MI.

The data from randomized trials of ACE inhibitors suggest that some of the cost of an intervention for heart failure may be offset by prevention of costly hospital (re)admissions. Epidemiological research has shown that most admissions for heart failure result from lack of patient adherence to drug or dietary regimens.[53] These observations suggest that intervention programs to improve outpatient management of this chronic disease have the potential to improve clinical outcomes and possibly economic outcomes as well. In one study, a nurse-directed multidisciplinary intervention significantly reduced hospital admissions and lowered overall health care costs in patients with heart failure.[54] Similar results have been reported in some,[55] [56] [57] but not

all,[58] disease management studies in patients with heart failure.

Disease Prevention

Disease prevention is very important from a clinical perspective. Some preventive measures are very effective and inexpensive, as exemplified by vaccination programs for common infectious diseases that cut risk by over 90 percent at the cost of only a few dollars. Most preventive measures are less effective in reducing the risk of disease and far more costly to implement. Vaccines, in particular, are relatively inexpensive because they are given only two or three times, whereas drugs to lower serum cholesterol or high blood pressure are given daily for decades. Thus, the cost-effectiveness of preventive programs varies considerably according to the intervention, its effectiveness, and its cost.

HYPERCHOLESTEROLEMIA.

Hypercholesterolemia (see Chap. 31) has long been established as a strong, consistent risk factor for coronary atherosclerosis, and recently HMG-CoA-reductase inhibitors ("statins") have been demonstrated to reduce the risk of death and nonfatal cardiovascular events.[59] The cost-effectiveness of this class of drugs has been controversial, largely because of the heterogeneity of patients considered for lipid-lowering therapy. Secondary prevention trials have shown substantial reductions in the absolute rate of cardiac events in patients treated with statins, including simvastatin in the Scandinavian Simvastatin Survival Study (4S) trial[60] and pravastatin in the Cholesterol and Recurrent Events (CARE)[61] and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)[62] trials. The efficacy of cholesterol lowering in primary prevention (i.e., subjects at high risk of heart disease but without evidence of clinical disease) has been investigated using pravastatin in the West of Scotland Coronary Prevention Study (WOSCOPS)[63] and lovastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[64]

The cost-effectiveness of HMG-CoA reductase therapy to prevent coronary heart disease varies from extremely favorable values in secondary prevention settings to quite unfavorable in some primary prevention settings.[65] The reason for this wide variation is that higher risk patients have a greater absolute benefit from treatment than lower risk patients. In the 4S trial,[60] for example, the 6-year overall mortality was 8.7 percent in the treated patients and 12.4 percent in the control patients, an absolute mortality difference of 3.7 percent that translates into 27 patients treated over 6 years to save one life. In contrast, the WOSCOPS study found overall mortality rates of 3.2 percent in the pravastatin group and 4.1 percent in the placebo group at 4.9 years,[63] an absolute mortality difference of 0.9 percent, which translates to 111 patients treated to prevent one death. The greater level of clinical efficacy in secondary prevention than primary prevention implies that lipid-lowering therapy is more economically attractive in the secondary prevention setting. Similarly, within the primary prevention setting, treatment of higher-risk patients (i.e., multiple risk factors, higher cholesterol levels) provides greater absolute risk reduction and hence is more cost effective than is the treatment of lower-risk patients. These insights are supported by more formal cost-effectiveness studies. Goldman and coworkers used a decision model and data from randomized

trials[65] to show that the economic attractiveness of lipid-lowering therapy varied from saving costs and reducing mortality when used as secondary prevention in men with cholesterol levels above 250 mg/dl to a highly unfavorable cost-effectiveness ratio of over $2 million per year of life added in young women with no other cardiac risk factors. Other analyses have confirmed the basic observations that primary prevention with HMG-CoA reductase therapy in low-risk patients is economically unattractive, whereas treatment of higher-risk patients is quite cost effective. [66] Clinical guidelines stress the importance of tailoring therapy to the patient's risk profile[67] [68] to achieve optimal results.

CIGARETTE SMOKING.

Cigarette smoking (see Chaps. 31 and 39) clearly increases the risk of coronary heart disease events, with evidence of risk reduction after quitting in numerous nonrandomized studies. Although the effectiveness of a physician's advice to stop smoking is low, it does induce some smokers to quit; and because such advice has such a low cost it has a favorable cost-effectiveness ratio of less than $1,000 per year of life added.[69] Use of the nicotine patch as part of a smoking cessation program adds to the number of patients who quit smoking and had a favorable cost-effectiveness rate of less than $10,000 per year of life saved in one study[70] and less than $5,000 in another study.[71] Hospital-based smoking cessation programs have also been shown to be cost effective.[72] Smoking cessation is a particularly attractive preventive measure because the interventions are generally short term and of relatively low cost, and smoking cessation has highly beneficial effects on both cardiac and noncardiac diseases (e.g., various cancers, emphysema) and thus adds considerably to life expectancy.

DIAGNOSTIC TESTING

Proper selection of diagnostic tests to evaluate various clinical problems has become more challenging as a result of the collision between the forces of technological innovation

that develop many new tests to examine different facets of a particular disease and the forces of economic restraint that insist on their cost-effective use. Economic evaluation of diagnostic tests begins from the premise that the test provides information that only has value if physicians use the information to change therapy in a way that actually improves clinical outcomes. Thus, the effectiveness of a test is gauged not solely by its information content but by its ultimate, indirect effects on patient outcomes.

Tests that provide clinical value do so by adding to what is already known about the patient. In practical terms, the test needs to add independent information to what is available from the clinical history, from the physical examination, and from simpler, less expensive tests. The information value of thallium scintigraphy (see Chap. 9) in the diagnosis of coronary artery disease, for example, must be judged by how much unique

diagnostic and prognostic information it adds to the clinical examination and the simpler stress electrocardiogram. The evaluation of diagnostic tests by measuring the incremental value of information they provide is analogous to the way that therapies are evaluated by documenting what they add compared with the best available alternative (e.g., how much better is t-PA than streptokinase for AMI). But the additional requirement placed on diagnostic tests is that they add enough information to modify decision-making. A test that is statistically more accurate does not provide value from an economic perspective unless the additional accuracy leads to improved clinical decisions. Demonstrations of a statistical improvement in diagnostic accuracy with new tests is common, but evaluations of the effects of this extra accuracy on clinical management are rare.

The evaluation of chest pain is a critical diagnostic problem that has been carefully analyzed in many studies. Early studies focused on the incremental information provided by noninvasive testing, most commonly the exercise electrocardiogram.[73] [74] These studies, by application of Bayes' rule, showed that the difference between pretest and posttest probability of disease was greatest among patients with an intermediate pretest probability of disease (i.e., between 15 percent and 85 percent). More recent cost-effectiveness analysis extended the earlier studies by considering the health outcomes resulting from detecting (or failing to detect) underlying coronary disease amenable to coronary revascularization.[75] [76] [77] These analyses suggested that immediate coronary angiography was reasonable in patients with very high pretest likelihood of coronary disease, such as an older man with typical exertional angina. In patients with an intermediate probability of coronary disease, noninvasive testing was generally economically attractive in comparison with no testing (cost-effectiveness ratios roughly $30,000 per quality-adjusted life years added), whereas coronary angiography without prior noninvasive testing was generally not economically attractive (cost-effectiveness ratio more than $65,000 per quality-adjusted life years added, depending on patient characteristics). Alternative noninvasive tests (exercise electrocardiography, exercise single photon emission computed tomographic perfusion imaging, stress echocardiography) are close enough in cost-effectiveness that the determining factors in choosing among them are the likelihood of an indeterminate test result and the degree of local expertise with each alternative. The cost-effectiveness of all diagnostic strategies for chest pain are more favorable when stringent, outcome-based guidelines for coronary revascularization are followed.

The use of routine coronary angiography in survivors of AMI has been controversial, in large part owing to conflicting evidence on the efficacy of routine versus selective angiography practices.[78] [79] [80] [81] Because of the uncertainty of the medical effectiveness of angiography, assessment of its cost-effectiveness is also uncertain at this point. In one recent analysis,[82] coronary angiography was quite economically attractive (cost-effectiveness ratios generally less than $30,000 per quality-adjusted life years added) in patients with postinfarction angina and an ejection fraction below 50 percent. Angiography was projected to be economically unattractive (cost-effectiveness ratios greater than $60,000 per quality-adjusted life years added) in patients without a prior MI unless an exercise test was positive.[82]

DEVELOPMENTS IN ECONOMIC ANALYSIS

Cost-effectiveness analysis has been applied to clinical medicine for just over 20 years.[5] The initial studies were based largely on decision models and related analytical methods and were of more interest to researchers than to clinicians. After considerable experience, consensus on some aspects of the methodology of economic analysis has been reached, although several areas of controversy remain.[3] [6] [7] The most important recent development in cost-effectiveness analysis has been the inclusion of economic endpoints as part of randomized trials, providing rigorous evaluation of the efficacy of therapies. As in all arenas of clinical research, the methods of economic evaluation in clinical trials have become more sophisticated, with application of economic models to extend clinical trial findings.[83] Future developments in cost-effectiveness analysis include wider application of economic evaluations in international settings, improved cost-identification methods, and continued development of statistical methods appropriate to cost and outcome data from clinical trials.[84] [85] [86]

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Part II - EXAMINATION OF THE PATIENT

Chapter 3 - The History

EUGENE BRAUNWALD

IMPORTANCE OF THE HISTORY

Specialized examinations of the cardiovascular system, presented in Chapters 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , and 13 , provide a large portion of the data base required to establish a specific anatomical diagnosis of cardiac disease and to determine the extent of functional impairment of the heart. The development and application of these methods are a triumph of modern medicine. However, their appropriate use is to *supplement* but not to *supplant* a careful clinical examination. The latter, consisting of the history and physical examination, remains the cornerstone of the assessment of the patient with known or suspected cardiovascular disease. When compared, the initial clinical evaluation is at least as accurate in predicting coronary anatomy and survival as

the exercise stress test.[1] There is a temptation in cardiology, as in many other areas of medicine, to carry out expensive, and occasionally uncomfortable or even hazardous, procedures to establish a diagnosis when a detailed and thoughtful history and a thorough physical examination are sufficient. Obviously, it is undesirable to subject patients to the unnecessary risks, discomfort, and expenses inherent in many specialized tests when a diagnosis can be made on the basis of the results of the clinical examination or when management will not be altered significantly as a result of these tests.

Intelligent selection of investigative procedures from the ever-increasing array of tests now available requires far more sophisticated decision-making than was necessary when the choices were limited to electrocardiography and chest roentgenography; some of the principles in such decision-making as they relate to cardiac imaging tests are dealt with in Chapter 13 . The clinical examination provides the critical information necessary for most of these decisions. With the increasing emphasis on the cost of medical care, it is likely that there will be a resurgence of interest in the relatively inexpensive clinical examination. On the other hand, it must be appreciated that there may be little correlation between the intensity of symptoms and the severity of heart disease; asymptomatic persons may have a life-threatening condition, whereas persons with many complaints referable to the cardiovascular system may have no or mild heart disease.

THE ROLE OF THE HISTORY.

The overreliance on laboratory tests has increased as physicians attempt to use their time more efficiently by delegating responsibility for taking the history to an assistant or nurse or even by limiting the history to a questionnaire. I consider this to be an undesirable trend for the patient with known or suspected heart disease. First, it must be appreciated that the history remains the richest source of information concerning the patient's illness[2] [3] and any practice that might diminish the quality or quantity of information provided by the history is likely ultimately to impair the quality of care. Second, the physician's attentive and thoughtful taking of a history establishes a bond with the patient that may be valuable later in securing the patient's compliance in following a complex treatment plan, undergoing hospitalization for an intensive diagnostic work-up or a hazardous operation, and, in some instances, accepting that heart disease is not present at all.

Obtaining the history also permits the physician to evaluate the results of diagnostic tests that have strong subjective components, such as the determination of exercise capacity (see Chap. 6) . Perhaps most importantly, a careful history allows the physician to evaluate the impact of the disease, or the fear of the disease, on the various aspects of the patient's life and to assess the patient's personality, affect, and emotional stability; often it provides a glimpse of the patient's responsibilities, fears, aspirations, and threshold for discomfort as well as the likelihood of compliance with one or another therapeutic regimen. Whenever possible, the physician should question not only the patient but also relatives or close friends to obtain a clearer understanding of the extent of the patient's disability and a broader perspective concerning the impact of the disease on both the patient and the family. For example, the patient's spouse is much more

likely than the patient to provide a history of Cheyne-Stokes (periodic) respiration.

The combination of the widespread fear of cardiovascular disorders and the deep-seated emotional, symbolic, and sometimes even religious connotations surrounding the heart may, on the one hand, lower the threshold for the development of symptoms that mimic those of organic heart disease in persons with normal cardiovascular systems. On the other hand, they may cause so much dread that serious symptoms are denied by patients with established heart disease. Patients with established heart disease are often frightened, anxious, and/or depressed; these symptoms may be as troubling as those resulting from the pathophysiology of their disorder. These and other psychological symptoms can be identified only by a careful history.[2]

TECHNIQUE.

Several approaches may be employed successfully in obtaining the medical history. I believe that patients should first be given the opportunity to relate their experiences and complaints in their own way. Although time consuming and likely to include much seemingly irrelevant information, this technique provides considerable insight into the patient's intelligence, emotional make-up, and attitude toward his or her complaints, as well as providing the patient with the satisfaction that he or she has been "heard" by the physician, rather than merely responding to a few questions and then subjected to a battery of laboratory examinations. After the patient has given an account of the illness, the physician should direct the discussion and obtain information concerning the onset and chronology of symptoms; their location, quality, and intensity; the precipitating, aggravating, and alleviating factors; the setting in which the symptoms occur and any associated symptoms; and the response to therapy.

Of course, a detailed general medical history including the personal past history, occupational history, nutritional history, and review of systems must be obtained.[4] Of particular interest is a history of thyroid disease, recent dental extractions or manipulations, catheterization of the bladder, as well as a report of earlier examinations that showed abnormalities of the cardiovascular system as reflected in restriction from physical activity at school and in rejection for life insurance, employment, or military service. Menstrual status in women should be ascertained, as well as changes in body weight, especially during the last 5 years. Personal habits such as exercise, cigarette smoking, alcohol intake, and parenteral use of drugs--illicit and otherwise--should be ascertained. The medications taken and the reasons given to the patient should be obtained. Adults should be routinely questioned about the presence of or history of the major risk factors for coronary artery disease (see Chap. 34) : cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, and a family history of premature coronary artery disease. The exact nature of the patient's work, including the physical and emotional stresses, should be assessed. The increasing appreciation of the importance of genetic influences in many forms of heart disease (see Chap. 56)

underscores the importance of the family history.

A wide variety of disorders including, but not limited to, the neurological (see Chap. 71) , endocrine (see Chap. 64) , rheumatic (see Chap. 67) , and hematologic/oncologic (see Chap. 69) areas may have important effects on the cardiovascular system; it is vital to ascertain the presence of these and other conditions that are not primarily cardiovascular.

Myocardial and coronary function that may be adequate at rest are often inadequate during exertion; therefore, specific attention should be directed to the influence of activity on the patient's symptoms. Thus, a history of chest discomfort and/or undue shortness of breath that appears only during activity is characteristic of heart disease, whereas the opposite pattern (i.e., the appearance of symptoms at rest and their remission during exertion) is almost never observed in patients with heart disease but is more characteristic of functional disorders. In attempting to assess the severity of functional impairment, both the *extent* of activity and the *rate* at which it is performed before symptoms develop should be determined and related to a detailed consideration of the therapeutic regimen. For example, the development of dyspnea after walking slowly up a flight of stairs in a patient receiving intensive treatment of heart failure denotes far more severe functional disability than does the same symptom occurring in an untreated patient who has run up a flight of stairs.

It is important also to assess the "tempo" of the progression of symptoms. A decline in the threshold for severe anginal discomfort across a 2-week period is much more likely to signify a high risk of an adverse outcome, such as cardiac death or myocardial infarction, than a similar decline occurring over 2 years. Similarly, the history of a "breakthrough" of symptoms despite maintenance of a previously successful regimen should be noted, because it, too, may be a harbinger of a poor outcome and may dictate a change in therapeutic strategy.

As the patient relates the history, important nonverbal clues are often provided. The physician should observe the patient's attitude, reactions, and gestures while being questioned, as well as the choice of words or emphasis. Tumulty has aptly likened obtaining a meaningful clinical history to playing a game of chess[5] : "The patient makes a statement and based upon its content, and mode of expression, the physician asks a counter-question. One answer stimulates yet another question until the clinician is convinced that he understands precisely all of the circumstances of the patient's illness."

CARDINAL SYMPTOMS OF HEART DISEASE

The cardinal symptoms of heart disease include dyspnea, chest pain or discomfort, syncope, collapse, palpitation, edema, cough, hemoptysis, and excess fatigue. Cyanosis is more often a sign than a symptom, but it may be a key feature of the history as well, particularly in patients with congenital heart disease. Without doubt, history-taking is the most valuable technique available for determining whether these symptoms are caused by heart disease. Examples of the manner in which these symptoms may serve as a guide to diagnosis are given in the following pages, and

reference is made to other portions of the book that contain more detailed information.

Dyspnea (See also Chap. 17)

Dyspnea is defined as an abnormally uncomfortable awareness of breathing; it is one of the principal symptoms of cardiac and pulmonary disease and ranges from an increased awareness of breathing to intense respiratory distress.[6] Dyspnea occurs after strenuous exertion in normal, healthy, well-conditioned subjects and after only moderate exertion in those who are normal but unaccustomed to exercise (dyspnea of deconditioning). It should therefore be regarded as abnormal only when it occurs at rest or at a level of physical activity not expected to cause this symptom. Dyspnea is associated with a wide variety of diseases of the heart and lungs, chest wall, and respiratory muscles as well as with anxiety[7] [8] [9] [10] ; the history is the most valuable means of establishing the etiology.[11] [12] [13] Among patients with cardiac dyspnea, this symptom is most commonly associated with and caused by pulmonary congestion, as occurs in left ventricular failure or mitral stenosis. The interstitial and alveolar edema stiffens the lungs and stimulates respiration by activating "J" receptors in the lung. Less frequently, cardiac dyspnea occurs secondary to a reduced cardiac output, without pulmonary engorgement, as in tetralogy of Fallot. Table 3-1 provides a list of the various

TABLE 3-1 -- DISORDERS CAUSING DYSPNEA AND LIMITING EXERCISE PERFORMANCE; PATHOPHYSIOLOGY; AND DISCRIMINATING MEASUREMENTS

DISORDERS	PATHOPHYSIOLOGY	MEASUREMENTS THAT DEVIATE FROM NORMAL
Pulmonary		
Air flow limitation	Mechanical limitation to ventilation, mismatching of V_A /Q, hypoxic stimulation to breathing	V_E max/MVV, expiratory flow pattern, V_D , V_T ; V_{O_2} max, V_E /V_{O_2} , V_E response to hyperoxia, (A-a)P_{O_2}
Restrictive	Mismatching V_A /Q, hypoxic stimulation to breathing	
Chest wall	Mechanical limitation to ventilation	V_E max/MVV, P_{ACO_2} , V_{O_2} max
Pulmonary circulation	Rise in physiological dead space as fraction of V_T , exercise hypoxemia	V_D /V_T , work-rate-related hypoxemia, V_{O_2} max, V_E /V_{O_2} , (a-ET)P_{CO_2} , O_2 -pulse
Cardiac		

Coronary	Coronary insufficiency	ECG, V_{O_2} max, anaerobic threshold V_{O_2}, V_E/V_{O_2}, O_2-pulse, BP (systolic, diastolic, pulse)
Valvular	Cardiac output limitation (decreased effective stroke volume)	
Myocardial	Cardiac output limitation (decreased ejection fraction and stroke volume)	
Anemia	Reduced O_2-carrying capacity	O_2-pulse, anaerobic threshold V_{O_2}, V_{O_2} max, V_E/V_{O_2}
Peripheral circulation	Inadequate O_2 flow to metabolically active muscle	Anaerobic threshold V_{O_2}, V_{O_2} max
Obesity	Increased work to move body; if severe, respiratory restriction and pulmonary insufficiency	V_{O_2}-work-rate relationship, P_{AO_2}, P_{ACO_2} V_{O_2} max
Psychogenic	Hyperventilation with precisely regular respiratory rate	Breathing pattern, P_{CO_2}
Malingering	Hyperventilation and hypoventilation with irregular respiratory rate	Breathing pattern, P_{CO_2}
Deconditioning	Inactivity or prolonged bed rest; loss of capability for effective redistribution of systemic blood flow	O_2-pulse, anaerobic threshold V_{O_2}, V_{O_2} max

$_A$ = alveolar ventilation;
Q = pulmonary blood flow;
$_E$ = minute ventilation; MVV = maximum voluntary ventilation; V_D/V_T = physiological dead space/tidal volume ratio; O_2 = oxygen; V_{O_2} = O_2 consumption; (A-a)P_{O_2} = alveolar-arterial P_{O_2} difference; (a-ET)P_{CO_2} = arterial-end tidal P_{CO_2} difference.

Modified from Wasserman D: Dyspnea on exertion: Is it the heart or the lungs? JAMA 248:2042, 1982. Copyright 1982, the American Medical Association.

syndromes that may cause dyspnea and the primary pathophysiological mechanisms that are responsible, whereas Table 3-2 (Table Not Available) lists the most important causes of acute and chronic dyspnea. Both Borg and Noble[14] and the American Thoracic Society (Table 3-3) (Table Not Available) [15] have developed scales that are useful in quantitating the severity of dyspnea.

TABLE 3-2 -- CAUSES OF ACUTE AND CHRONIC DYSPNEA

(Not Available)

From Fishman AP: Approach to the patient with respiratory symptoms. In Fishman's Pulmonary Diseases and Disorders, 3rd ed. New York, McGraw-Hill, 1998, pp 361-393.

The *sudden* development of dyspnea suggests pulmonary embolism, pneumothorax, acute pulmonary edema, pneumonia, or airway obstruction. In contrast, in most forms of *chronic* heart failure, dyspnea progresses slowly over weeks or months. Such a protracted course may also occur in a variety of unrelated conditions, including obesity, pregnancy, and bilateral pleural effusion. *Inspiratory dyspnea* suggests obstruction of the upper airways, whereas *expiratory dyspnea* characterizes obstruction of the lower airways. Exertional dyspnea suggests the presence of organic diseases, such as left ventricular failure (see Chap. 17) or chronic obstructive lung disease (see Chap. 54) ,

TABLE 3-3 -- AMERICAN THORACIC SOCIETY SCALE OF DYSPNEA

(Not Available)

From Fishman AP: Approach to the patient with respiratory symptoms. In Fishman's Pulmonary Diseases and Disorders, 3rd ed. New York, McGraw-Hill, 1998, pp 361-393.

whereas dyspnea developing at rest may occur in pneumothorax, pulmonary embolism (see Chap. 52) , pulmonary edema (see Chap. 17) , or anxiety neurosis. Dyspnea that occurs only at rest and is absent on exertion is almost always functional. A *functional origin* is also suggested when dyspnea, or simply a heightened awareness of breathing, is accompanied by brief stabbing pain in the region of the cardiac apex or by prolonged (more than 2 hours) dull chest pain. It is often associated with difficulty in getting enough air into the lungs, claustrophobia, and sighing respirations that are *relieved* by exertion, by taking a few deep breaths, or by sedation. Dyspnea in patients with panic attacks is usually accompanied by hyperventilation. A history of relief of dyspnea by bronchodilators and corticosteroids suggests asthma as the etiology, whereas relief of dyspnea by rest, diuretics, and digitalis suggests left ventricular failure. Dyspnea accompanied by wheezing may be secondary to left ventricular failure (*cardiac* asthma) or primary bronchial constriction (*bronchial* asthma).

In patients with *chronic heart failure,* dyspnea is a clinical expression of pulmonary venous and capillary hypertension (see Chap. 17) . It occurs either during exertion or in resting patients in the recumbent position, in whom it is relieved promptly by sitting upright or standing *(orthopnea).* Patients with left ventricular failure soon learn to sleep on two or more pillows to avoid this symptom. In patients with heart failure, dyspnea is often accompanied by edema of the lower extremities, upper abdominal pain (due to congestive hepatomegaly), and nocturia. The *sudden* occurrence of dyspnea in a patient with a history of previously stable mitral valve disease suggests the development of atrial fibrillation, rupture of chordae tendineae (as may occur in infective endocarditis),

or pulmonary embolism.

Paroxysmal nocturnal dyspnea is due to interstitial pulmonary edema and sometimes intraalveolar edema and is most commonly secondary to left ventricular failure. This condition, beginning usually 2 to 4 hours after the onset of sleep and often accompanied by cough, wheezing, and sweating, may be quite frightening. Paroxysmal nocturnal dyspnea is often ameliorated by the patient's sitting on the side of the bed or getting out of bed; relief is not instantaneous but usually requires 15 to 30 minutes. Although paroxysmal nocturnal dyspnea secondary to left ventricular failure is usually accompanied by coughing, a careful history often discloses that the dyspnea *precedes* the cough, not vice versa. In contrast, patients with *chronic pulmonary disease* may also awaken at night, but cough and expectoration usually *precede* the dyspnea. These patients also often have a long history of smoking and a chronic cough with sputum production and wheezing and may be able to breathe more easily while leaning forward. Nocturnal dyspnea associated with pulmonary disease is usually relieved after the patient rids himself or herself of secretions rather than specifically by sitting up. Details of the value and limitations of the history of dyspnea in differentiating between primary diseases of the heart and lungs[6] [16] are presented in Chapter 17 .

Patients with *pulmonary embolism* usually experience sudden dyspnea that may be associated with apprehension, palpitation, hemoptysis, or pleuritic chest pain (see Chap. 52) . The development or intensification of dyspnea, sometimes associated with a feeling of faintness, may be the only complaint of the patient with pulmonary emboli. *Pneumothorax* and *mediastinal emphysema* also cause acute dyspnea, accompanied by sharp chest pain. Dyspnea accompanying thoracic pain occurs in *acute myocardial infarction* (see Chap. 35) . Dyspnea is a common "*anginal equivalent*" (see Chap. 37) , that is, a symptom secondary to myocardial ischemia that occurs in place of typical anginal discomfort. This form of dyspnea may or may not be associated with a sensation of tightness in the chest, is present on exertion or emotional stress, is relieved by rest (more often in the sitting than in the recumbent position), is similar to angina in duration (i.e., 2 to 10 minutes), and is usually responsive to or prevented by nitroglycerin. The sudden development of severe dyspnea while sitting rather than lying, or whenever a particular position is assumed, suggests the possibility of a myxoma (see Chap. 49) or ball-valve thrombus in the left atrium. When dyspnea is relieved by squatting, it is caused most commonly by tetralogy of Fallot or a variant thereof (see Chap. 43) .

Patients with exertional dyspnea should be questioned about the duration of the symptom, whether it occurs gradually or abruptly, as well as the conditions that precipitate, intensify, and relieve it. Its severity can be judged in terms of the number of city blocks or flights of stairs that the patient is capable of walking or climbing at a normal pace.

APPROACH TO THE PATIENT.

A combination of the history and physical examination provide the key information required to elucidate the cause of dyspnea. The differentiation between cardiac and

pulmonary disease is aided by the approach shown in Figure 3-1 .

Chest Pain or Discomfort (See also Chaps. 35 , 36 , and 37)

Elucidation of the cause of chest pain is one of the key tasks of physicians, and this symptom is responsible for many cardiac consultations. The history remains the most important technique for distinguishing among the many causes of chest discomfort. Although chest pain or discomfort is one of the cardinal manifestations of heart disease, it is important to recognize that such pain may originate not only in the heart but also in (1) a variety of noncardiac intrathoracic structures, such as the aorta, pulmonary artery, bronchopulmonary tree, pleura, mediastinum, esophagus, and diaphragm; (2) the tissues of the neck or thoracic wall, including the skin, thoracic muscles, cervicodorsal spine, costochondral junctions, breasts, sensory nerves, and spinal cord; and (3) subdiaphragmatic organs such as the stomach, duodenum, pancreas, and gallbladder (Table 3-4) . Pain of functional origin or factitious pain may also occur in the chest. Although a wide variety of laboratory tests is available to aid in the differential diagnosis of chest pain, without question the history remains the most valuable mode of examination.

In obtaining the history of a patient with chest pain it is helpful to have a mental checklist and to ask the patient to describe the location, radiation, and character of the discomfort; what causes and relieves it, especially the extent and timing of relief by sublingual nitroglycerin; the duration, frequency, and pattern of recurrence of the discomfort; the setting in which it occurs; and associated symptoms. It is also particularly useful to observe the patient's gestures. Clenching the fist in front of the sternum while describing the sensation (Levine's sign) is a strong indication of an ischemic origin of the pain.

QUALITY OF DISCOMFORT.

Angina pectoris may be defined as a discomfort in the chest and/or adjacent area associated with myocardial ischemia but without myocardial necrosis.[17] [18] [19] [20] It is important to recognize that angina means *tightening,* not pain. Thus, the discomfort of angina often is described not as pain at all but rather as an unpleasant sensation; "pressing," "squeezing," "strangling," "constricting," "bursting," and "burning" are some of the adjectives commonly used to describe this sensation (Table 3-5) . "A band across the chest," "a weight in the center of the chest," and "a vise tightening around the chest" are other frequent descriptors. It is characteristic of angina pectoris that the intensity of effort required to incite it may vary from day to day and throughout the day in the same

Figure 3-1 Algorithm for the evaluation of the patient with dyspnea. The pace and completeness with which one approaches this framework depend on the intensity and acuity of the patient's symptoms. In

the patient with severe, acute dyspnea, an arterial blood gas analysis may be one of the first laboratory evaluations, for example, whereas it might not be obtained until much later in the work-up in a patient with chronic breathlessness of unclear cause. A therapeutic trial of a medication, for example, a bronchodilator, may be instituted at any point if one is fairly confident of the diagnosis based on the data available at that time. DVT = deep venous thrombosis; CHF = congestive heart failure; DL_{CO}= diffusing capacity of the lung for carbon monoxide. *(From Schwartzstein RM, Thibault GE: Approach to the patient with dyspnea. In Goldman L, Braunwald E [eds]: Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 98-111.)*

patient, but often a careful history will uncover explanations for this, such as meals ingested, weather, emotions, and the like. The anginal threshold is lower in the morning than at other times of the day; thus patients note frequently that activities that may cause angina in the morning do not do so later in the day. When the threshold for angina is quite variable, defies any pattern, and is prominent at rest, the possibility that myocardial ischemia is caused by coronary spasm should be considered.[19] [20] A history of prolonged, severe anginal chest discomfort accompanied by profound fatigue often signifies acute myocardial infarction.[21] Thus, a careful history not only may indicate the cause of the pain (i.e., myocardial ischemia) but can also provide a clue to the mechanism.

When dyspnea is an "anginal equivalent," the patient may describe the mid chest as the site of the shortness of breath, whereas true dyspnea is usually not well localized. Other anginal equivalents are discomfort limited to areas that are ordinarily sites of secondary radiation, such as the ulnar aspect of the left arm and forearm, lower jaw, teeth, neck, or shoulders, and the development of gas and belching, nausea, "indigestion," dizziness, and diaphoresis. When angina radiates to the arms it is often described as a "painful heaviness." Anginal equivalents above the mandible or below the umbilicus are quite uncommon. It is useful to determine whether the patient has symptoms or complications caused by atherosclerosis of other vascular beds (e.g., intermittent claudication, transient ischemic attacks,

TABLE 3-4 -- CARDIOVASCULAR CAUSES OF CHEST PAIN

CONDITION	LOCATION	QUALITY	DURATION	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS

Angina	Retrosternal region: radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms--left common	Pressure, burning, squeezing, heaviness, indigestion	<2-10 min	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal's) angina may be unrelated to activity, often early morning	S_4 , or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	Usually <20 min	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina, but may be pronounced. Transient cardiac failure can occur
Myocardial infarction	Substernal and may radiate like angina	Heaviness, pressure, burning, constriction	Sudden onset, 30 min or longer but variable	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting
Pericarditis	Usually begins over sternum or toward cardiac apex and may radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia	Sharp, stabbing, knifelike	Lasts many hours to days; may wax and wane	Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward	Pericardial friction rub

Aortic dissection	Anterior chest; may radiate to back	Excruciating, tearing, knifelike	Sudden onset, unrelenting	Usually occurs in setting of hypertension or predisposition such as Marfan's syndrome	Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurological deficit
Pulmonary embolism (chest pain often not present)	Substernal or over region of pulmonary infarction	Pleuritic (with pulmonary infarction) or angina-like	Sudden onset; minutes to <1 hr	May be aggravated by breathing	Dyspnea, tachypnea, tachycardia; hypotension, signs of acute right-sided heart failure, and pulmonary hypertension with large emboli; rales, pleural rub, hemoptysis with pulmonary infarction
Pulmonary hypertension	Substernal	Pressure; oppressive		Aggravated by effort	Pain usually associated with dyspnea; signs of pulmonary hypertension

From Andreoli TE, Bennett JC, Carpenter CCJ, Plum F: Evaluation of the patient with cardiovascular disease. In Cecil Essentials of Medicine, 4th ed. Philadelphia, WB Saunders, 1997, p 11.

TABLE 3-5 -- CHARACTERISTICS OF TYPICAL AND ATYPICAL ANGINA PECTORIS

Typical

Substernal

Characterized by a burning, heavy, or squeezing feeling

Precipitated by exertion or emotion

Promptly relieved by rest or nitroglycerin

Atypical

Located in the left chest, abdomen, back, or arm in the absence of mid-chest pain

Sharp or fleeting

Repeated, very prolonged

Unrelated to exercise

Not relieved by rest or nitroglycerin

Relieved by antacids

Characterized by palpitations without chest pain

From Douglas PS, Ginsburg GS: The evaluation of chest pain in women. N Engl J Med 333:1311-1315, 1996.

or stroke). In patients with suspected angina, a history of one of these manifestations of extracardiac atherosclerosis lends weight to the diagnosis of myocardial ischemia.

LOCATION.

Embryologically the heart is a midline viscus; thus, cardiac ischemia produces symptoms that are characteristically felt substernally or across both sides of the chest (Figs. 3-2 and 3-3) (Figure Not Available) . Some patients complain of discomfort only to the left or less commonly only to the right of the midline. If the pain or discomfort can be localized to the skin or superficial structures and can be reproduced by localized pressure, it usually arises from the chest wall and is not caused by myocardial ischemia. If the patient can point directly to the site of discomfort with the tip of a finger, and if that site is quite small (<3 cm in diameter), it is usually not angina pectoris. Like other symptoms arising in deeper structures, angina tends to be diffuse and eludes precise localization. Pain that is localized to the region of or under the left nipple or that radiates to the right lower chest is usually noncardiac in origin and may be functional or due to costochondritis, gaseous distention of the stomach, or the splenic flexure syndrome.[22] Although

Figure 3-2 Pain patterns with myocardial ischemia. The usual distribution is referral to all or part of the sternal region, the left side of the chest, and the neck and down the ulnar side of the left forearm and hand. With severe ischemic pain, the right chest and right arm are often involved as well, although isolated involvement of these areas is rare. Other sites sometimes involved, either alone or together with other sites, are the jaw, epigastrium, and back. *(From Horwitz LD: Chest pain. In Horwitz LD, Groves BM [eds]: Signs and Symptoms in Cardiology. Philadelphia, JB Lippincott, 1985, p 9.)*

Figure 3-3 (Figure Not Available) Differential diagnosis of chest pain according to location where pain starts. Serious intrathoracic or subdiaphragmatic diseases are usually associated with pains that begin in the left anterior chest, left shoulder, or upper arm, the interscapular region, or the epigastrium. The scheme is not all inclusive (e.g., intercostal neuralgia occurs in locations other than the left, lower anterior chest area). *(From Miller AJ: Diagnosis of Chest Pain. New York, Raven Press, 1988, p 175.)*

pain due to myocardial ischemia often radiates to the arm, especially the ulnar aspect of the left arm, wrist, epigastrium, or left shoulder, such radiation may also occur in pericarditis and disorders of the cervical spine. Radiation of pain from the chest to the neck and jaws is typical of myocardial infarction. Dissection of the aorta or enlargement of an aortic aneurysm usually produces pain in the back in addition to the front of the chest.

DURATION.

The duration of the pain is important in determining its etiology. Angina pectoris is relatively brief, usually lasting from 2 to 10 minutes. However, if the pain is very brief (i.e., a momentary, lancinating, sharp pain, or other discomfort that lasts less than 15 seconds), angina can usually be excluded; such a short duration points instead to musculoskeletal pain, pain due to hiatal hernia, or functional pain. Chest pain that is otherwise typical of angina but that lasts for more than 10 minutes or occurs at rest is typical of unstable angina.[18] Chest pain lasting for hours may be seen with acute myocardial infarction, pericarditis, aortic dissection, musculoskeletal disease, herpes zoster, and anxiety.

PRECIPITATING AND AGGRAVATING FACTORS.

Angina pectoris occurs characteristically on exertion, particularly when the patient is hurrying or walking up an incline. Thus, the development of chest discomfort or pain during walking, typically in the cold and up an incline or against a wind, especially after a heavy meal, is typical of angina pectoris. Angina may also be precipitated by strong emotion or fright, by a nightmare, by working with the arms over the head, by hurrying, by cold exposure, or by smoking a cigarette. Prinzmetal's (variant) angina characteristically occurs at rest and may or may not be affected by exertion; however, classical angina, although most often precipitated by effort, may progress to unstable angina, which is characterized by ischemic discomfort at rest (see Chap. 36) .

DIFFERENTIAL DIAGNOSIS.

Chest pain that occurs after protracted vomiting may be due to the Mallory-Weiss syndrome (i.e., a tear in the lower portion of the esophagus). Pain that occurs while the patient is bending over is often radicular and may be associated with osteoarthritis of the cervical or upper thoracic spine. Chest pain occurring on moving the neck may be due to a herniated intervertebral disc.

ESOPHAGEAL AND OTHER GASTROINTESTINAL PAIN.

Substernal and epigastric discomfort after swallowing may be due to *esophageal spasm or esophagitis*, often with acid reflux, with or without a hiatal hernia. These conditions

may also be associated with substernal or epigastric burning pain that is brought on by eating or lying down after meals and that may be relieved by antacids. Pain due to esophageal spasm has many of the features of and may be difficult to differentiate from angina pectoris.[22] [23] [24] [25] A history of acid reflux into the mouth (water brash) and/or dysphagia may be a useful diagnostic clue pointing to esophageal disease.[26] [27] The chest discomfort secondary to esophageal reflux is most common after meals and occurs in the supine position or on bending. The difficulty in distinguishing angina from esophageal disease is compounded by the frequent coexistence of these two common conditions, by the observation that esophageal reflux lowers the threshold for the development of angina,[28] and by the observation that esophageal spasm may be precipitated by ergonovine and relieved by nitroglycerin. Esophageal pain radiates to the back more frequently than does angina pectoris.[23]

The term *linked angina* refers to episodes of true angina caused by myocardial ischemia due to gastrointestinal disturbances. Chauhan and colleagues have demonstrated that the installation of hydrochloric acid into the distal esophagus significantly reduced coronary blood flow both in patients with angiographically confirmed coronary artery disease[29] as well as in patients with syndrome X.[30] Such a reduction did not occur in patients who had undergone cardiac transplantation, indicating that it was a reflex response, thus providing an explanation for "linked angina."

The discomfort produced by *peptic ulcer disease* is characteristically located in the mid epigastrium. It may also resemble angina pectoris, but its characteristic relationship to food ingestion and its relief by antacids are important differentiating features. Although the pain of *acute pancreatitis* may mimic acute myocardial infarction, with the former there is usually a history of alcoholism or biliary tract disease. The pain of pancreatitis, like that of acute myocardial infarction, may be predominantly in the epigastrium. However, unlike the pain of myocardial infarction, it is usually transmitted to the back, is position sensitive, and may be relieved in part by leaning forward.[22]

OTHER CAUSES.

The chest discomfort of *pulmonary hypertension* (see Chap. 53) may be identical to that of typical angina[31] [32] ; it is caused by right ventricular ischemia or dilation of the pulmonary arteries. The chest discomfort of *unstable angina* and *acute myocardial infarction* (see Chaps. 35 and 36) is similar in quality to that of angina pectoris in location and character; however, it usually radiates more widely than does angina, is more severe, and therefore is generally referred to by the patient as true *pain* rather than *discomfort.* The development of pain in these conditions is usually unrelated to unusual effort or emotional stress, often with the patient at rest or even sleeping. Characteristically, nitroglycerin does not provide complete or lasting relief.

Acute pericarditis (see Chap. 50) is frequently preceded by a history of a viral upper respiratory infection. The inflammation causes pain that is sharper than anginal discomfort, is more left sided than central, and is often referred to the neck, upper shoulders, and back. The pain of pericarditis lasts for hours and is little affected by effort but is often aggravated by breathing, turning in bed, swallowing, or twisting the body; unlike angina, the pain of acute pericarditis may lessen when the patient sits up and

leans forward.

Aortic dissection (see Chap. 40) is suggested by the sudden development of persistent, very severe pain with radiation to the back and into the lumbar region, often in a patient with a history of hypertension. An expanding *thoracic aortic aneurysm* may erode the vertebral bodies and cause localized, severe, boring pain that may be worse at night.

Chest-wall pain due to *costochondritis* or *myositis* is common in patients who present with fear of heart disease. It is associated with both local costochondral and muscle tenderness, which may be aggravated by moving or coughing. Chest-wall pain[33] may also accompany chest injury. In the *Tietze syndrome*, the discomfort is localized in swollen costochondral and costosternal joints, which are painful on palpation. When *herpes zoster* affects the left chest it may mimic myocardial infarction. However, its persistence, its localization to a dermatome, the extreme sensitivity of the skin to touch, and the appearance of the characteristic vesicles allow recognition of this condition. Pain in the chest wall is quite common after cardiac or thoracic surgery and may be confused with myocardial ischemia. Postsurgical pain is usually localized to the incision or the site of insertion of a chest tube.

The *preeruptive stage of herpes zoster* can mimic myocardial ischemia as a tight localized band across the chest.

The pain of *pulmonary embolism* (see Chap. 52) usually commences suddenly and in patients who are at rest. It is seen in patients at high risk for this condition (heart failure, venous disease, the postoperative state) and is accompanied by shortness of breath. It is typically described as tightness in the chest and is accompanied or followed by *pleuritic* chest pain (i.e., sharp pain in the side of the chest that is intensified by respiration or cough). Chest pain associated

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with *spontaneous pneumothorax* develops suddenly, is associated with acute dyspnea, and is located in the lateral area of the chest. The chest pain associated with *mediastinal emphysema* also commences suddenly and is accompanied by dyspnea, which is sometimes severe; it is located in the center of the chest.

Functional or *psychogenic chest* pain (see Chap. 70) may be one feature of an anxiety state called Da Costa's syndrome or neurocirculatory asthenia.[34] [35] [36] [37] It is not typical of angina pectoris; it is usually localized to the cardiac apex and consists of a dull, persistent ache that lasts for hours and is often accentuated by or alternates with attacks of sharp, lancinating stabs of inframammary pain of 1 or 2 seconds' duration. The condition may occur with emotional strain and fatigue, bears little relation to exertion, and may be accompanied by precordial tenderness. Attacks may be associated with palpitation, hyperventilation, numbness and tingling in the extremities, sighing, dizziness, dyspnea, generalized weakness, faintness, severe fatigability, and a history of panic attacks and other signs of emotional instability or depression. The pain

may not be completely relieved by any medication other than analgesics, but it is often attenuated by many types of interventions, including rest, exertion, tranquilizers, and placebos. Therefore, in contrast to ischemic discomfort, functional pain is more likely to show variable responses to interventions on different occasions. Patients with Da Costa's syndrome are usually young (<40 years), are female, and have high scores on depression and anxiety scales.[38]

Congenital absence of the pericardium (see Chap. 50) produces chest pain that is relieved by changing position in bed, is brought on by lying on the left side, and lasts a few seconds. Pain due to the *scalenus anticus (thoracic outlet) syndrome* may be confused with angina because it is often associated with paresthesias along the ulnar distribution of the arm and forearm. However, in contrast to angina, not only is it typically precipitated by abduction of the arm or lifting a weight but it is also not brought on by walking.

RELIEF OF PAIN.

Rest and sublingual nitroglycerin characteristically relieve the discomfort of angina in 1 to 5 minutes. If more than 10 minutes transpire before relief, the diagnosis of chronic stable angina becomes questionable and instead unstable angina, acute myocardial infarction, or pain not caused by myocardial ischemia at all is the cause. Although nitroglycerin commonly relieves the pain of angina pectoris, the discomfort of esophageal spasm and esophagitis may also be relieved by this drug. Angina pectoris is alleviated by quiet standing or sitting; sometimes resting in the recumbent position does not relieve angina. Chest pain secondary to *acute pericarditis* is characteristically relieved by leaning forward, whereas pain that is relieved by food or antacids may be due to *peptic ulcer disease* or esophagitis. Pain that is alleviated by holding the breath in deep expiration is commonly due to pleuritic inflammation. Some patients with upper gastrointestinal disease or anxiety report relief of symptoms after belching.

CHEST PAIN IN WOMEN (see Chap. 58) .

Chest discomfort that is atypical for angina pectoris is more common in women than in men, perhaps because of the higher prevalence of vasospastic and of microvascular angina and nonischemic causes of chest pain in women[39] (see Table 3-5) . Women with epicardial coronary artery disease more often report chest discomfort at rest, during sleep, or during mental stress than do men.

ACCOMPANYING SYMPTOMS.

The physician should always be concerned about the patient with the combination of chest discomfort and profuse sweating. This combination of symptoms frequently signals a serious disorder, most often acute myocardial infarction but also acute pulmonary embolism or aortic dissection. Severe chest pain accompanied by nausea and vomiting is also often due to myocardial infarction. The latter diagnosis, as well as pneumothorax, pulmonary embolism, or mediastinal emphysema, is suggested by pain associated with shortness of breath. Chest pain accompanied by palpitation may be due

to the acute myocardial ischemia precipitated by a tachyarrhythmia-induced increase in myocardial oxygen consumption in the presence of coronary artery disease. Chest pain accompanied by hemoptysis suggests pulmonary embolism with infarction or lung tumor, whereas pain accompanied by fever occurs in pneumonia, pleurisy, and pericarditis. Functional pain is commonly accompanied by frequent sighing, anxiety, or depression.

APPROACH TO THE PATIENT.

This is summarized in the algorithm shown in Figure 3-4 .[40] After administration of emergency treatment, if necessary, a focused history and physical examination should allow determination of a cardiac or possible cardiac cause. The 12-lead electrocardiogram is then helpful in guiding therapy (Fig. 3-5) .[40]

Cyanosis

Cyanosis, both a symptom and a physical sign, is a bluish discoloration of the skin and mucous membranes resulting from an increased quantity of reduced hemoglobin or of abnormal hemoglobin pigments in the blood perfusing these areas.[41] [42] It is more commonly described by a family member and may go unnoticed by the patient. There are two principal forms of cyanosis: (1) central cyanosis, characterized by decreased arterial oxygen saturation due to right-to-left shunting of blood or impaired pulmonary function, and (2) peripheral cyanosis, most commonly secondary to cutaneous vasoconstriction due to low cardiac output or exposure to cold air or water; if peripheral cyanosis is confined to an extremity, localized arterial or venous obstruction should be suspected. A history of cyanosis localized to the hands suggests Raynaud's phenomenon. Patients with central cyanosis due to congenital heart disease or pulmonary disease characteristically report that it worsens during exertion, whereas the resting peripheral cyanosis of congestive heart failure may be accentuated only slightly, if at all, during exertion.

Central cyanosis usually becomes apparent at a mean capillary concentration of 4 gm/dl reduced hemoglobin (or 0.5 gm/dl methemoglobin). In general, a history of cyanosis in light-skinned people is rarely elicited unless arterial saturation is 85 percent or less; in pigmented races, arterial saturation has to drop far lower before cyanosis is perceptible.

Although a history of cyanosis beginning in infancy suggests a congenital cardiac malformation with a right-to-left shunt, hereditary methemoglobinemia is another, albeit rare, cause of congenital cyanosis; the diagnosis of this condition is supported by a family history of cyanosis in the absence of heart disease.

A history of cyanosis limited to the neonatal period suggests the diagnosis of atrial septal defect with transient right-to-left shunting or, more commonly, pulmonary parenchymal disease or central nervous system depression. Cyanosis beginning at age 1 to 3 months may be reported when spontaneous closure of a patent ductus arteriosus causes a reduction of pulmonary blood flow in the presence of right-sided obstructive cardiac anomalies, most commonly tetralogy of Fallot. If cyanosis appears at age 6 months or later in childhood, it may be due to the development or progression of

obstruction to right ventricular outflow in patients with ventricular septal defect. A history of the development of cyanosis in a patient with congenital heart disease between 5 and 20 years of age suggests an Eisenmenger reaction with right-to-left shunting as a consequence of a progressive increase in pulmonary vascular resistance (see Chaps. 43 and 44) . Cyanosis secondary to a pulmonary arteriovenous fistula also usually appears first in childhood.

Figure 3-4 Diagnostic approach to the patient with new, acute, often ongoing chest pain. *(From Goldman L: Chest discomfort and palpitation. In Fauci A, Braunwald E, et al [eds]: Harrison's Principles of Internal Medicine, 14th ed. New York, McGraw-Hill, 1998, p 61.)*

Figure 3-5 Diagnostic approach to the patient with new, acute, often ongoing pain of potential cardiac cause or of uncertain cause. *(From Goldman L: Approach to the patient with chest pain. In Goldman L, Braunwald E [eds]: Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 84-97.)*

Syncope (See Chap. 27)

A loss of consciousness results most commonly from reduced perfusion of the brain. The history is extremely valuable in the differential diagnosis of syncope (Table 3-6) . Several daily attacks of loss of consciousness suggest (1) Stokes-Adams attacks (i.e., transient asystole or ventricular fibrillation in the presence of atrioventricular block); (2) other cardiac arrhythmias; or (3) a seizure disorder (i.e., petit mal epilepsy). These diagnoses are suggested when the loss of consciousness is abrupt and occurs over 1 or 2 seconds; a more gradual onset suggests vasodepressor syncope (i.e., the common faint) or syncope due to hyperventilation or, much less commonly, hypoglycemia.

CARDIAC SYNCOPE.

This condition is usually of rapid onset without aura and is usually not associated with convulsive movements, urinary incontinence, or a postictal confusional state. Syncope in aortic stenosis[43] [44] [45] is usually precipitated by effort. Patients with syncope secondary to a convulsive disorder often have a prodromal aura preceding the seizure. Injury from falling is common, as are urinary incontinence and a postictal confusional state, associated with headache and drowsiness. Unconsciousness developing gradually and lasting for a few seconds suggests vasodepressor syncope or syncope secondary to postural hypotension (see Chap. 27) , whereas a longer period suggests aortic stenosis or hyperventilation. Hysterical fainting is usually not accompanied by any

untoward display of anxiety or change in pulse, blood pressure, or skin color, and there may be a question whether any true loss of consciousness occurred. It is often associated with paresthesias of the hands or face, hyperventilation, dyspnea, chest pain, and feelings of acute anxiety.

REGAINING CONSCIOUSNESS.

Consciousness is usually regained quite promptly in syncope of cardiovascular origin but more slowly in patients with convulsive disorders. When consciousness is regained after vasodepressor syncope, the patient is often pale and diaphoretic with a slow heart rate, whereas after a Stokes-Adams attack the face is often flushed and there may be cardiac acceleration. Patients who report an injury when falling during a fainting spell usually have a convulsive disorder or occasionally syncope of cardiac origin, but patients who have unconsciousness related to emotional disturbance rarely sustain physical trauma.

DIFFERENTIAL DIAGNOSIS.

A family history of syncope or near-syncope can often be elicited in patients with hypertrophic cardiomyopathy (see Chap. 48) or ventricular tachyarrhythmias associated with QT prolongation (see Chap. 25) . A history of syncope during childhood suggests the possibility of obstruction to left ventricular outflow--valvular, supravalvular, or subvalvular aortic stenosis. In patients with hypertrophic cardiomyopathy, syncope may be posttussive and occurs characteristically in the erect position, when arising suddenly, after standing erect for long periods, and during or immediately after cessation of exertion.

Patients with syncope secondary to orthostatic hypotension may have a history of drug therapy for hypertension or of abnormalities of autonomic function, such as impotence, disturbances of sphincter function, peripheral neuropathy, and anhidrosis.[46] [47] [48]

Calkins and coworkers demonstrated the value of the clinical history in the differentiation between serious arrhythmias (ventricular tachycardia or atrioventricular block) and neurocardiogenic syncope. Features predictive of the former were male gender, age older than 54 years, two or fewer episodes of syncope, and duration of warning of 5 seconds or less. On the other hand, features of syncope not due to arrhythmia included palpitations, blurred vision, nausea, diaphoresis, or lightheadedness before syncope, and nausea, warmth, diaphoresis, or fatigue after syncope.[49]

Palpitation (See Chap. 22)

This common symptom is defined as an unpleasant awareness of the forceful or rapid beating of the heart. Patients may describe it as pounding, jumping, racing, or irregularity of the heart beat, a "flip flopping" or "rapid fluttering" in the chest, or pounding in the neck.[50] [51] It may be brought about by a variety of disorders involving changes in cardiac rhythm or rate, including all forms of tachycardia, ectopic beats,

compensatory pauses, augmented stroke volume due to valvular regurgitation, hyperkinetic (high cardiac output) states, and the sudden onset of bradycardia. In the case of premature contractions the patient is more

TABLE 3-6 -- CLUES FROM THE HISTORY IN ELUCIDATING THE CAUSE OF SYNCOPE

Preceding Events	**Mechanisms of Syncope**
Drugs:	Orthostatic hypotension (antihypertensives), hypoglycemia (insulin)
Severe pain, emotional stress:	Vasovagal syncope, hyperventilation
Movement of head and neck:	Carotid sinus hypersensitivity
Exertion:	Any form of obstruction to left ventricular outflow, Takayasu's arteritis
Upper extremity exertion:	Subclavian "steal"
Type of Onset	
Sudden:	Neurological (seizure disorder); arrhythmia (ventricular tachycardia or fibrillation, Stokes-Adams)
Rapid with premonition:	Vasovagal, neurological (aura)
Gradual:	Hyperventilation, hypoglycemia
Position at Onset	
Arising:	Orthostatic hypotension
Prolonged standing:	Vasovagal
Any position:	Arrhythmias, neurological, hypoglycemia, hyperventilation
Postsyncopal Clearing of Sensorium	
Slow:	Neurological
Rapid:	All others
Associated Events	
Incontinence, tongue biting, injury:	Neurological

Modified from Lindenfeld JA: Syncope. In Horwitz LD, Groves BM (eds): Signs and Symptoms in Cardiology. Philadelphia, JB Lippincott, 1985.

commonly aware of the postextrasystolic beat than of the premature beat itself, and it appears that it is the increased motion of the heart within the chest that is perceived. This explains why palpitation is not a characteristic feature of aortic or pulmonic stenosis or of severe systemic or pulmonary hypertension, conditions characterized by an increased force of cardiac contraction.

When episodes of palpitation last for an instant, they are described as "skipped beats" or a "flopping sensation" in the chest and most commonly are due to extrasystoles. On the other hand, the sensation that the heart has "stopped beating" often correlates with the compensatory pause after a premature contraction. When palpitation secondary to premature contraction increases during exercise, the prognosis is more ominous than when they disappear during exercise.

DIFFERENTIAL DIAGNOSIS.

Palpitation characterized by a slow heart rate may be due to atrioventricular block or sinus node disease. When palpitation begins and ends abruptly, it is often due to a paroxysmal tachycardia such as paroxysmal atrial or junctional tachycardia, atrial flutter, or atrial fibrillation, whereas a gradual onset and cessation of the attack suggest sinus tachycardia and/or an anxiety state. A history of chaotic, rapid heart action suggests the diagnosis of atrial fibrillation; fleeting and repetitive palpitation suggests multiple ectopic beats. A history of multiple paroxysms of tachycardia followed by palpitation that occurs only with effort or excitement suggests paroxysmal atrial fibrillation that has become permanent, with the palpitation being experienced only when the ventricular rate rises. A history of dizziness, presyncope, or syncope with palpitations may be due to ventricular tachycardia and may be an ominous prognostic sign.

Some patients have taken their pulse during palpitation or have asked a companion to do so. A regular rate between 100 and 140 beats/min suggests sinus tachycardia, a regular rate of approximately 150 beats/min suggests atrial flutter, and a regular rate exceeding 160 beats/min suggests paroxysmal supraventricular tachycardia. As an adjunct to the history, it may be possible to ascertain the rhythm responsible for the palpitation by tapping the finger on the patient's chest in a variety of rhythms and asking the patient to identify the pattern that most closely resembles the abnormal feeling. Alternatively, patients can be asked to reproduce the arrhythmia by tapping their fingers on a tabletop at the rate and rhythm they perceived during palpitation. These maneuvers may provide important clues to the etiology of the responsible arrhythmia.

A history of palpitation during strenuous physical activity is normal, whereas palpitation during mild exertion suggests the presence of heart failure, atrial fibrillation, anemia, or thyrotoxicosis or that the individual is severely deconditioned. When palpitation can be relieved suddenly by stooping, breath-holding, or induced gagging or vomiting (i.e., by vagal maneuvers), the diagnosis of paroxysmal supraventricular tachycardia is suggested. A history of syncope *after* an episode of palpitation suggests either asystole or severe bradycardia following the termination of a tachyarrhythmia. Palpitation followed by angina suggests that myocardial ischemia has been precipitated by increased oxygen demands induced by the rapid heart rate. Palpitations are frequently accompanied by, and are often caused by, anxiety, panic reactions, or emotionally

startling experiences. [50]

A directed history is useful in elucidating the cause of palpitation (Table 3-7) . Is there a history of cocaine or amphetamine abuse? Thyrotoxicosis? Anemia? Do the palpitations occur after heavy cigarette smoking or caffeine ingestion? Is there a family history of syncope, arrhythmia, or sudden death?

DIAGNOSTIC APPROACH TO THE PATIENT.

The diagnostic approach is shown in Figure 3-6 (Figure Not Available) . The key decision points are the determination of whether structural heart disease is present and whether the patient complains of severe symptoms, including syncope and presyncope.

Edema

LOCALIZATION.

This is helpful in elucidating the etiology of edema.[52] [53] [53A] Unilateral leg edema is most commonly due to deep venous thrombosis or cellulitis. Thus a history of edema of the legs that is most pronounced in the evening is characteristic of heart failure or bilateral chronic venous insufficiency. Inability to fit the feet into shoes is a common early complaint. In most patients, any visible edema of both lower extremities is preceded by a weight gain of at least 3 to 5 kg. Cardiac edema is generally symmetrical. As it progresses, it usually ascends to involve the legs, thighs, genitalia, and abdominal wall. In patients with heart failure who are confined largely to bed, the edematous fluid localizes in the sacral area. Edema may be generalized (anasarca) in the nephrotic syndrome, severe heart failure, and hepatic cirrhosis. These three conditions can be distinguished by consideration of the history, physical examination, and simple laboratory tests (Table 3-8) . A variety of drugs interfere with sodium excretion and may cause edema as well (Table 3-9) . A careful history regarding their recent use is indicated in patients with generalized edema.

A history of edema around the eyes and face is characteristic of the nephrotic syndrome, acute glomerulonephritis, angioneurotic edema, hypoproteinemia, and myxedema. A history of edema limited to the face, neck, and upper arms may be associated with obstruction of the superior vena cava, most commonly by carcinoma of the lung, lymphoma, or aneurysm of the aortic arch. A history of edema restricted to one extremity is usually due to venous thrombosis or lymphatic blockage of that extremity.

ACCOMPANYING SYMPTOMS.

A history of dyspnea associated with edema is most frequently due to heart failure, but it may also be observed in patients with large bilateral pleural effusions, elevation of the diaphragms due to ascites, angioneurotic edema with laryngeal involvement, and pulmonary embolism. When dyspnea precedes edema, the underlying disorder is usually left ventricular dysfunction, mitral stenosis, or chronic lung disease with cor pulmonale. A history of jaundice suggests that edema may be of hepatic origin, whereas

edema associated with a history of ulceration and pigmentation of the skin of the legs is most

TABLE 3-7 -- ITEMS TO BE COVERED IN HISTORY OF PATIENT WITH PALPITATION

DOES THE PALPITATION OCCUR:	IF SO, SUSPECT:
As isolated "jumps" or "skips"?	Extrasystoles
In attacks, known to be of abrupt beginning, with a heart rate of 120 beats/min or over, with regular or irregular rhythm?	Paroxysmal rapid heart action
Independent of exercise or excitement adequate to account for the symptom?	Atrial fibrillation, atrial flutter, thyrotoxicosis, anemia, febrile states, hypoglycemia, anxiety state
In attacks developing rapidly though not absolutely abruptly, unrelated to exertion or excitement?	Hemorrhage, hypoglycemia, tumor of the adrenal medulla
In conjunction with the taking of drugs?	Tobacco, coffee, tea, alcohol, epinephrine, ephedrine, aminophylline, atropine, thyroid extract, monoamine oxidase inhibitors
On standing?	Postural hypotension
In middle-aged women, in conjunction with flushes and sweats?	Menopausal syndrome
When the rate is known to be normal and the rhythm regular?	Anxiety state

From Goldman L, Braunwald E: Chest discomfort and palpitation. In Isselbacher KJ, Braunwald E, et al (eds): Harrison's Principles of Internal Medicine, 13th ed. New York, McGraw-Hill, 1994.

Figure 3-6 (Figure Not Available) Diagnostic approach to the patient with palpitations. *(From Hlatky MA: Approach to the patient with palpitations. In Goldman L, Braunwald E [eds]: Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 122-128.)*

commonly due to chronic venous insufficiency or postphlebitic syndrome. When cardiac edema is not associated with orthopnea, it may be due to tricuspid valve disease or constrictive pericarditis. A history of leg edema after prolonged sitting (particularly in the elderly) may be due to simple venous stasis and not be associated with disease at all.

A history of ascites *before* edema suggests cirrhosis, whereas a history of ascites *after* edema suggests cardiac or renal disease. Idiopathic cyclic edema is associated with the

menstrual cycle. A history of edema on prolonged standing is observed in patients with chronic venous insufficiency.

TABLE 3-8 -- PRINCIPAL CAUSES OF GENERALIZED EDEMA: HISTORY, PHYSICAL EXAMINATION, AND LABORATORY FINDINGS

ORGAN SYSTEM	HISTORY	PHYSICAL EXAMINATION	LABORATORY FINDINGS
Cardiac	Dyspnea with exertion prominent--often associated with orthopnea--or paroxysmal nocturnal dyspnea	Elevated jugular venous pressure, ventricular (S_3) gallop; occasionally with displaced or dyskinetic apical pulse; peripheral cyanosis, cool extremities, small pulse pressure when severe	Elevated urea nitrogen-to-creatinine ratio common; elevated uric acid; serum sodium often diminished; liver enzymes occasionally elevated with hepatic congestion
Hepatic	Dyspnea infrequent, except if associated with significant degree of ascites; most often a history of ethanol abuse	Frequently associated with ascites; jugular venous pressure usually normal or low; blood pressure typically lower than in renal or cardiac disease; one or more additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren contracture, spider angiomata, male gynecomastia or testicular atrophy, caput medusa); asterixis and other signs of encephalopathy may be present	If severe, reductions in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); liver enzymes may or may not be elevated, depending on the cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; magnesium and phosphorus often markedly reduced if associated with ongoing ethanol intake; uric acid typically low; macrocytosis from folate deficiency

Renal	Usually chronic; associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs or myoclonus; dyspnea can be present, but generally less prominent than in heart failure	Blood pressure often high; hypertensive or diabetic retinopathy in selected cases; nitrogenous fetor; periorbital edema may predominate; pericardial friction rub in advanced cases with uremia	Elevation of serum creatinine and urea nitrogen most prominent; also frequent hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)

From Chertow GM, Thibault GE: Approach to the patient with edema. In Goldman L, Braunwald E (eds): Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 112-121.

TABLE 3-9 -- DRUGS ASSOCIATED WITH EDEMA FORMATION

- Nonsteroidal antiinflammatory drugs
- Antihypertensive agents
  - Direct arterial/arteriolar vasodilators
    - Minoxidil
    - Hydralazine
    - Clonidine
    - Methyldopa
    - Guanethidine
  - Calcium channel antagonists
  - Alpha-adrenergic antagonists
- Steroid hormones
  - Corticosteroids
  - Anabolic steroids
  - Estrogens
  - Progestins

Cyclosporine

Growth hormone

Immunotherapies

Interleukin-2

OKT3 monoclonal antibody

From Chertow GM, Thibault GE: Approach to the patient with edema. In Goldman L, Braunwald E (eds): Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 112-121.

COUGH

Cough, one of the most frequent of all cardiorespiratory symptoms, may be defined as an explosive expiration that provides a means of clearing the tracheobronchial tree of secretions and foreign bodies.[54] [55] [56] It can be caused by a variety of infectious, neoplastic, or allergic disorders of the lungs and tracheobronchial tree. Cardiovascular disorders most frequently responsible for cough include those that lead to pulmonary venous hypertension, interstitial and alveolar pulmonary edema, pulmonary infarction, and compression of the tracheobronchial tree (aortic aneurysm).

Cough due to pulmonary venous hypertension secondary to left ventricular failure or mitral stenosis tends to be dry, irritating, spasmodic, and nocturnal. When cough accompanies exertional dyspnea, it suggests either chronic obstructive lung disease or heart failure, whereas in a patient with a history of allergy and/or wheezing, cough is often a concomitant of bronchial asthma. A history of a combination of cough with hoarseness without upper respiratory disease may be due to pressure of a greatly enlarged left atrium on an enlarged pulmonary artery compressing the recurrent laryngeal nerve. A history of cough associated with expectoration for months or years occurs in chronic obstructive lung disease and/or chronic bronchitis.

The character of the sputum may be helpful in the differential diagnosis. Thus, a cough producing frothy, pink-tinged sputum occurs in pulmonary edema, whereas blood-streaked sputum suggests tuberculosis, bronchiectasis, carcinoma of the lung, or pulmonary infarction.

HEMOPTYSIS

The expectoration of blood or of sputum, either streaked or grossly contaminated with blood, may be due to (1) escape of red cells into the alveoli from congested vessels in the lungs (acute pulmonary edema); (2) rupture of dilated endobronchial vessels that form collateral channels between the pulmonary and bronchial venous systems (mitral stenosis); (3) necrosis and hemorrhage into the alveoli (pulmonary infarction); (4) ulceration of the bronchial mucosa or the slough of a caseous lesion (tuberculosis); (5) minor damage to the tracheobronchial mucosa, produced by excessive coughing of any cause, which can result in mild hemoptysis; (6) vascular invasion (carcinoma of the

lung); or (6) necrosis of the mucosa with rupture of pulmonary-bronchial venous connections (bronchiectasis).

The history is often decisive in pinpointing the etiology of hemoptysis.[56] Recurrent episodes of minor bleeding are observed in patients with chronic bronchitis, bronchiectasis, tuberculosis, and mitral stenosis. Rarely, these conditions result in the expectoration of large quantities of blood (i.e., more than one-half cup). Massive hemoptysis may also be due to rupture of a pulmonary arteriovenous fistula; exsanguinating hemoptysis may occur with rupture of an aortic aneurysm into the bronchopulmonary tree.[55] [57] [58]

Hemoptysis associated with shortness of breath suggests mitral stenosis; in this condition the hemoptysis is often precipitated by sudden elevations in left atrial pressure during effort or pregnancy and is attributable to rupture of small pulmonary or bronchopulmonary anastomosing veins. Blood-tinged sputum in patients with mitral stenosis may also be due to transient pulmonary edema; in these circumstances it is usually associated with severe dyspnea. A history of hemoptysis associated with acute pleuritic chest pain suggests pulmonary embolism with infarction. Recurrent hemoptysis in a young, otherwise asymptomatic woman favors the diagnosis of bronchial adenoma. Hemoptysis associated with congenital heart disease and cyanosis suggests Eisenmenger's syndrome.

OTHER SYMPTOMS

Cardiovascular disorders can cause symptoms emanating from every organ system. Several of these are mentioned here primarily to point out how detailed the history should be in providing a comprehensive evaluation of a patient suspected of having cardiovascular disease; fuller discussions are found elsewhere in this text.

FATIGUE.

This is among the most common symptoms in patients with impaired cardiovascular function. However, it is also one of the most nonspecific of all symptoms. In patients with impaired systemic circulation as a consequence of a depressed cardiac output, fatigue may be associated with muscular weakness. In other patients with heart disease, fatigue may be caused by drugs, such as beta-adrenoceptor blocking agents. It may be the result of excessive blood pressure reduction in patients treated too vigorously for hypertension or heart failure. In patients with heart failure, fatigue may also be caused by excessive diuresis and by diuretic-induced hypokalemia. Extreme fatigue sometimes precedes or accompanies acute myocardial infarction.

OTHER SYMPTOMS.

Nocturia is a common early complaint in patients with congestive heart failure. *Anorexia,* abdominal fullness, right upper quadrant discomfort, weight loss, and cachexia are symptoms of advanced heart failure (see Chap. 17) . Anorexia, *nausea, vomiting,* and *visual changes* are important signs of digitalis intoxication (see Chap. 18) . Nausea and

vomiting occur frequently in patients with acute myocardial infarction. Hoarseness may be caused by compression of the recurrent laryngeal nerve by an aortic aneurysm, a dilated pulmonary artery, or a greatly enlarged left atrium. A history of *fever* and *chills* is common in patients with infective endocarditis (see Chap. 47) .

THE HISTORY IN SPECIFIC FORMS OF HEART DISEASE

Just as the history is of central importance in determining whether or not a specific symptom is caused by heart disease, it is equally valuable in elucidating its etiology. A few examples are given below, whereas considerably greater detail is provided in chapters that deal with each specific disease entity.

Heart Disease in Infancy and Childhood (See Chaps. 43 and 45)

The history is particularly helpful in establishing the diagnosis of congenital heart disease. In view of the familial incidence of certain congenital malformations (see Chaps. 43 and 56) , a history of congenital heart disease, cyanosis, or heart murmur in the family should be ascertained. Rubella in the first 2 months of pregnancy is associated with a number of congenital cardiac malformations (patent ductus arteriosus, atrial and ventricular septal defect, tetralogy of Fallot, and supravalvular aortic stenosis). A maternal viral illness in the last trimester of pregnancy may be responsible for neonatal myocarditis. Exertional syncope in a child with congenital heart disease suggests a lesion in which the cardiac output is fixed, such as aortic or pulmonic stenosis. Exertional angina in a child suggests severe aortic stenosis, pulmonary stenosis, primary pulmonary hypertension, or anomalous origin of the left coronary artery. A history of syncope or faintness with straining and associated with cyanosis suggests tetralogy of Fallot.

In infants or children with cardiac murmurs, it is important to ascertain by history as precisely as possible when the murmur was first detected. Murmurs due to either aortic or pulmonic stenosis are usually audible within the first 48 hours of life, whereas those produced by a ventricular septal defect are usually apparent a few days or weeks later. On the other hand, the murmur produced by an atrial septal defect often is not heard until age 2 to 3 months.

Frequent episodes of pneumonia early in infancy suggest a large left-to-right shunt, and a history of excessive diaphoresis

occurs in left ventricular failure, most commonly due to ventricular septal defect in this age group. A history of squatting is most frequently associated with tetralogy of Fallot or tricuspid atresia. Dysphagia in early infancy suggests the presence of an aortic arch anomaly such as double aortic arch or an anomalous origin of the right subclavian artery passing behind the esophagus. A history of headaches, weakness of the legs, and intermittent claudication is compatible with the diagnosis of coarctation of the aorta.

Weakness or lack of coordination in a child with heart disease suggests cardiomyopathy associated with Friedreich's ataxia or muscular dystrophy (see Chap. 71) . Recurrent bleeding from the nose, lips, or mouth, associated with dizziness and visual disturbances, and a family history of bleeding in a cyanotic child suggest hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) with pulmonary arteriovenous fistula(s). A cerebrovascular accident in a cyanotic patient may be due to cerebral thrombosis or abscess or paradoxical embolization.

MYOCARDITIS AND CARDIOMYOPATHY

Rheumatic fever (see Chap. 66) is suggested by a history of sore throat followed by rash and chorea (St. Vitus' dance). The latter is characterized by twitching or clumsiness for a few months in childhood, as well as by frequent episodes of epistaxis and growing pains (i.e., nocturnal pains in the legs). In patients suspected of having myocarditis or cardiomyopathy, a history of Raynaud's phenomenon, dysphagia, or tight skin suggests *scleroderma* (see Chap. 67) . A history of dyspnea following an influenza-like illness with myalgia suggests *acute myocarditis*. Pain in the hip or lower back that awakens the patient in the morning and is followed by morning back stiffness suggests *rheumatoid spondylitis*, which is often associated with aortic valve disease (see Chap. 67) . *Carcinoid heart disease* (see Chap. 48) is associated with a history of diarrhea, bronchospasm, and flushing of the upper chest and head. A history of diabetes, particularly if resistant to insulin and associated with bronzing of the skin, suggests *hemochromatosis* (see Chap. 69) , which may be associated with heart failure due to cardiac infiltration. *Amyloid heart disease* (see Chap. 48) is often associated with a history of postural hypotension and peripheral neuropathy. *Hypertrophic cardiomyopathy* (see Chap. 48) is often associated with a family history of this condition and sometimes with a family history of sudden death. The characteristic symptoms are angina, dyspnea, and syncope, which are often intensified paradoxically by digitalis and which occur during or immediately after exercise.

HIGH-OUTPUT HEART FAILURE

Patients with symptoms of heart failure (breathlessness and excess fluid accumulation) with warm extremities often have *high-output heart failure* (see Chap. 17) . They should be questioned about a history of anemia and of its common causes and accompaniments, such as menorrhagia, melena, peptic ulcer, hemorrhoids, sickle cell disease, and the neurological manifestations of vitamin B_{12} deficiency. Also, in such patients an attempt should be made to elicit a history of thyrotoxicosis (weight loss, polyphagia, diarrhea, diaphoresis, heat intolerance, nervousness, breathlessness, muscle weakness, and goiter [see Chap. 64]). Patients with beriberi heart disease responsible for high-output heart failure often have a history characteristic of peripheral neuritis, alcoholism, poor eating habits, fad diets, or upper gastrointestinal surgery.

COR PULMONALE.

Patients with chronic cor pulmonale (see Chap. 54) frequently present with a history of smoking, chronic cough and sputum production, dyspnea, and wheezing relieved by

bronchodilators. Alternatively, they may have a history of pulmonary emboli, phlebitis, and the sudden development of dyspnea at rest with palpitations, pleuritic chest pain, and, in the case of massive infarction, syncope.

PERICARDITIS.

In patients in whom *pericarditis* or *cardiac tamponade* is suspected (see Chap. 50) , an attempt should be made to elicit a history of chest trauma, a recent viral infection, recent cardiac surgery, neoplastic disease of the chest with or without radiation therapy, myxedema, scleroderma, tuberculosis, or contact with tuberculous patients. The sequence of development of abdominal swelling, ankle edema, and dyspnea should be determined, since in patients with chronic constrictive pericarditis, ascites often precedes edema, which in turn usually precedes exertional dyspnea. A history of joint symptoms with a face rash suggests the possibility of systemic lupus erythematosus, an important cause of pericarditis, and it should be recalled that procainamide, hydralazine, and isoniazid can produce a syndrome resembling systemic lupus.

INFECTIVE ENDOCARDITIS.

The diagnosis of this condition is suggested by a history of fever, severe night sweats, anorexia, and weight loss and embolic phenomena expressed as hematuria, back pain, petechiae, tender finger pads, and a cerebrovascular accident (see Chap. 47) .

Drug-Induced Heart Disease

Because a wide variety of cardiac abnormalities can be induced by drugs,[59] a meticulous history of drug intake is of great importance. Table 3-10 summarizes the major drugs responsible for various cardiovascular manifestations.

TABLE 3-10 -- CARDIOVASCULAR MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS

Acute chest pain (nonischemic)
Bleomycin
Angina exacerbation
Alpha blockers
Beta-blocker withdrawal
Ergotamine
Excessive thyroxine
Hydralazine
Methysergide
Minoxidil
Nifedipine

- Oxytocin
- Sumatriptan
- Vasopressin

Arrhythmias

- Adriamycin
- Antiarrhythmic drugs
- Astemizole
- Atropine
- Anticholinesterases
- Beta blockers
- Cisapride
- Daunorubicin
- Digitalis
- Emetine
- Erythromycin
- Guanethidine

Arrhythmias (*cont.*)

- Ketanserin
- Lithium
- Papaverine
- Pentamidine
- Phenothiazines, particularly thioridazine
- Probucol
- Sympathomimetics
- Terfenadine
- Theophylline
- Thyroid hormone
- Tricyclic antidepressants
- Verapamil

Atrioventricular block

- Beta blockers
- Clonidine
- Methyldopa
- Verapamil

Cardiomyopathy
- Daunorubicin
- Doxorubicin
- Emetine
- Lithium
- Phenothiazines
- Sulfonamides
- Sympathomimetics

Fluid retention/congestive heart failure/edema
- Beta blockers
- Calcium blockers
- Carbenoxolone
- Diazoxide
- Estrogens
- Indomethacin
- Mannitol
- Minoxidil
- Phenylbutazone
- Steroids
- Verapamil

Hypotension (see also arrhythmias)
- Amiodarone (perioperative)
- Calcium channel blockers (e.g., nifedipine)
- Citrated blood
- Diuretics
- Interleukin-2
- Levodopa
- Morphine
- Nitroglycerin
- Phenothiazines
- Protamine
- Quinidine

Hypertension
- Clonidine withdrawal

Corticotropin

Cyclosporine

Glucocorticoids

Monoamine oxidase inhibitors with sympathomimetics

NSAIDs (some)

Oral contraceptives

Sympathomimetics

Tricyclic antidepressants with sympathomimetics

Pericarditis

Emetine

Hydralazine

Methysergide

Procainamide

Pericardial effusion

Minoxidil

Thromboembolism

Oral contraceptives

NSAIDs = nonsteroidal antiinflammatory drugs.

From Wood A: Adverse reactions to drugs. In Fauci A, Braunwald E, et al (eds): Harrison's Principles of Internal Medicine, 14th ed. New York, McGraw-Hill, 1998.

Catecholamines, whether administered exogenously or secreted by a pheochromocytoma (see Chap. 64) , may produce myocarditis and arrhythmias. *Digitalis glycosides* can be responsible for a variety of tachyarrhythmias and bradyarrhythmias as well as gastrointestinal, visual, and central nervous system disturbances (see Chap. 18) . Paradoxically, the administration of antiarrhythmic drugs is one of the major causes of serious cardiac arrhythmias (see Chap. 23) . For example, *quinidine* may cause QT prolongation, ventricular tachycardia of the torsades de pointes variety, syncope, and sudden death, presumably due to ventricular fibrillation.

Disopyramide, *beta-adrenoceptor blockers*, and the calcium channel antagonists *diltiazem* and *verapamil* may depress ventricular performance, and in patients with ventricular dysfunction these drugs may intensify heart failure. *Alcohol* is also a potent myocardial depressant and may be responsible for the development of cardiomyopathy (see Chap. 48) , arrhythmias, and sudden death. *Tricyclic antidepressants* may cause orthostatic hypotension and arrhythmias. *Lithium,* also used in the treatment of

psychiatric disorders, can aggravate preexisting cardiac arrhythmias, particularly in patients with heart failure in whom the renal clearance of this ion is impaired. *Cocaine* can cause coronary spasm with resultant myocardial ischemia, myocardial infarction, and sudden death.[60] [61]

The *anthracycline compounds* doxorubicin (Adriamycin) and daunorubicin, which are widely used because of their broad spectrum of activity against various tumors, may cause or intensify left ventricular failure, arrhythmias, myocarditis, and pericarditis (see Chap. 69) . *Cyclophosphamide,* an antineoplastic alkylating agent, may also cause left ventricular dysfunction, whereas 5-fluorouracil and its derivatives may be responsible for angina secondary to coronary spasm. Radiation therapy to the chest may cause acute and chronic pericarditis (see Chap. 50) , pancarditis, or coronary artery disease; furthermore, it may enhance the aforementioned cardiotoxic effects of the anthracyclines.

ASSESSING CARDIOVASCULAR DISABILITY (Table 3-11)

One of the greatest values of the history is in categorizing the degree of cardiovascular disability, so that a patient's status can be followed over time, the effects of a therapeutic intervention assessed, and patients compared with one another. The Criteria Committee of the New York Heart Association has provided a widely used classification that relates functional activity to the ability to carry out "ordinary" activity.[62] The term *ordinary,* of course, is subject to widely varying interpretation, as are terms such as *undue fatigue* that are used in this classification, and this has limited its accuracy and reproducibility. More recently, the New York Heart Association changed its evaluation from functional activity to a broader one, called cardiac status, which takes account of symptoms and other data gathered from the patient.[62] Cardiac status is classified as (1) uncompromised,

TABLE 3-11 -- A COMPARISON OF THREE METHODS OF ASSESSING CARDIOVASCULAR DISABILITY

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION	SPECIFIC ACTIVITY SCALE

I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.	Patients can perform to completion any activity requiring 7 metabolic equivalents (e.g., can carry 24 lb up eight steps; carry objects that weigh 80 lb; do outdoor work [shovel snow, spade soil]; do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.	Patients can perform to completion any activity requiring 5 metabolic equivalents (e.g., have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, walk at 4 mph on level ground) but cannot and do not perform to completion activities requiring 7 metabolic equivalents.

III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions.	Patients can perform to completion any activity requiring 2 metabolic equivalents (e.g., shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping) but cannot and do not perform to completion any activities requiring 5 metabolic equivalents.
IV	Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort--anginal syndrome *may be* present at rest.	Patients cannot or do not perform to completion activities requiring 2 metabolic equivalents. *Cannot* carry out activities listed above (Specific Activity Scale, Class III).

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(2) slightly compromised, (3) moderately compromised, and (4) severely compromised.

Somewhat more detailed and specific criteria were provided by the Canadian Cardiovascular Society,[63] but this classification is limited to patients with angina pectoris. Goldman and coworkers[64] developed a specific activity scale in which classification is based on the estimated metabolic cost of various activities. This scale appears to be more reproducible and to be a better predictor of exercise tolerance than either the New York Heart Association classification or the Canadian Cardiovascular

Society criteria.

A key element of the history is to determine whether the patient's disability is stable or progressive. A useful way to accomplish this is to inquire whether a specific task that now causes symptoms (e.g., dyspnea after climbing two flights of stairs) did so 3, 6, and 12 months previously. Precise questioning on this point is important because a gradual reduction of ordinary activity as heart disease progresses may lead to an underestimation of the apparent degree of disability.[65]

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Chapter 4 - Physical Examination of the Heart and Circulation

EUGENE BRAUNWALD
JOSEPH K. PERLOFF

A common pitfall in cardiovascular medicine is the failure by the cardiologist to recognize that a patient's heart disease is part of a systemic illness. Equally important is the failure by the noncardiologist to recognize the presence of a cardiac disorder that is a component of a systemic illness whose major effect may be on other organ systems. To avoid these two pitfalls, patients known to have or suspected of having heart disease require not only a detailed examination of the cardiovascular system but also a careful general physical examination. For example, the presence of coronary artery disease should prompt a careful search for frequent noncardiac concomitants such as atherosclerosis of the carotid arteries and of the arteries of the lower extremities and aorta. Conversely, the very high incidence (approximately 50 percent) of coronary artery disease in patients with cerebrovascular disorders must be considered in dealing with patients with these conditions.

As well stated by Mangione and coworkers,[1] "There are still many reasons to promote the teaching of bedside diagnostic skills such as cardiac auscultation. Among these are cost-effectiveness, the possibility of making inexpensive serial observations, the early

detection of critical findings, the intelligent and well-guided selection of costly diagnostic technology, and the therapeutic value of the physical contact between physician and patient."

Shaver has pointed out that in this era of cost containment in the practice of medicine, and the great expense of many "high tech" diagnostic procedures, the physical examination remains a relatively inexpensive, useful "test."[2] An additional benefit is that the actual physical contact, that is, the "laying on of hands" by the physician creates a valued closer bond with the patient at a time when the patient's encounter with the medical care system is often so impersonal.

The General Physical Examination

GENERAL APPEARANCE

An assessment of the patient's general appearance is usually begun with a detailed inspection at the time when the history is being obtained.[3] [4] [5] [6] [7] The general build and appearance of the patient, the skin color, and the presence of pallor or cyanosis should be noted, as well as the presence of shortness of breath, orthopnea, periodic (Cheyne-Stokes) respiration (see Chap. 17) , and distention of the neck veins. If the patient is in pain, is he or she sitting quietly (typical of angina pectoris); moving about, trying to find a more comfortable position (characteristic of acute myocardial infarction); or most comfortable sitting upright (heart failure) or leaning forward (pericarditis)? Simple inspection also reveals whether the patient's whole body shakes with each heartbeat and whether Corrigan pulses (bounding arterial pulsations, as occur with the large stroke volume of severe aortic regurgitation, arteriovenous fistula, or complete atrioventricular [AV] block) are present in the head, neck, and upper extremities. Malnutrition, and cachexia, which occur in severe chronic heart failure (see Chap. 17) , may also be readily evident. The cold, sweaty palms and frequent sighing respirations typical of *neurocirculatory asthenia* may be detected, as well as the marked obesity, somnolence, and cyanosis reflecting the *Pickwickian syndrome* (see Chap. 53) . Obesity, which is predominant in the abdomen (diameter of waist/diameter of hips >0.85; normal=0.7) is often associated with adult-onset diabetes and is a high risk factor for coronary artery disease and should also be looked for.

The distinctive general appearance of the *Marfan syndrome* (see Chap. 56) is often apparent: long extremities with an arm span that exceeds the height; a longer lower segment (pubis to foot) than upper segment (head to pubis); and arachnodactyly (spider fingers). In *Cushing syndrome,* a cause of treatable secondary hypertension (see Chap. 64) , there is truncal obesity and rounding of the face with disproportionately thin extremities.

HEAD AND FACE

Examination of the face often aids in the recognition of many disorders that can affect the cardiovascular system. For example, *myxedema* (see Chap. 64) is characterized by a dull, expressionless face; periorbital puffiness; loss of the lateral eyebrows; a large

tongue; and dry, sparse hair. An *earlobe crease* occurs more frequently in patients with coronary artery disease than in those without this condition.[8] [9]

Bobbing of the head coincident with each heartbeat (de Musset sign) is characteristic of severe aortic regurgitation. Facial edema may be present in patients with *tricuspid valve disease* or *constrictive pericarditis.*

The *muscular dystrophies,* the cardiac manifestations of which are described in Chapter 71 , also affect facial appearance profoundly. Patients with *myotonic dystrophy* exhibit a dull, expressionless face, with ptosis due to weakness of the levator muscles.

EYES

External ophthalmoplegia and ptosis due to muscular dystrophy of the extraocular muscles occur in the *Kearns-Sayre syndrome,* which may be associated with complete heart block.

Exophthalmos and stare occur in hyperthyroidism, an important cause of high-output cardiac failure (see Chap. 17) . Severe tricuspid regurgitation can also cause pulsation of the eyeballs[10] (pulsatile exophthalmos), as well as of the earlobes.[11]

Blue sclerae may be seen in patients with osteogenesis imperfecta,[12] a disorder that may be associated with aortic dilatation, regurgitation, and dissection and with prolapse of the mitral valve (see Chap. 56) .

FUNDI.

Examination of the fundi allows classification of arteriolar disease in patients with hypertension (Fig. 4-1 *A*) and may also be helpful in the recognition of arteriosclerosis. Beading of the retinal artery may be present in patients with hypercholesterolemia (see Fig. 4-1 *B*). Hemorrhages near the discs with white spots in the center (Roth spots) occur in infective endocarditis (see Fig. 47-7). Embolic retinal occlusions may occur in patients with rheumatic heart disease, left atrial myxoma, and atherosclerosis of the aorta or arch vessels. Papilledema may be present not only in patients with malignant hypertension (see Chap. 28) but also in those with cor pulmonale with severe hypoxia (see Chap. 54) .

SKIN AND MUCOUS MEMBRANES

Central cyanosis (due to intracardiac or intrapulmonary right-to-left shunting) involves the entire body, including warm, well-perfused sites such as the conjunctivae and the mucous membranes of the oral cavity. Peripheral cyanosis (due to reduction of peripheral blood flow, such as occurs in heart failure and peripheral vascular disease) is

characteristically most prominent in cool, exposed areas that may not be well perfused, such as the extremities, particularly the nail beds and nose. Polycythemia can often be suspected from inspection of the conjunctivae, lips, and tongue, which are darkly congested in polycythemia and pale in anemia.

Bronze pigmentation of the skin and loss of axillary and pubic hair occur in *hemochromatosis* (which may result in cardiomyopathy owing to iron deposits in the heart [see Chap. 69]). Jaundice may be observed in patients after pulmonary infarction as well as in patients with congestive hepatomegaly or cardiac cirrhosis. *Lentigines,* which are small brown macular lesions on the neck and trunk that begin at about age 6 and do not increase in number with sunlight, are observed in patients with pulmonic stenosis and hypertrophic cardiomyopathy.[13]

Figure 4-1 *A,* Severe hypertensive retinopathy. The patient was a 43-year-old man with the symptoms of malignant hypertension. He subsequently died of massive cerebral hemorrhage. *B,* Beading of the retinal artery in a patient with hypercholesterolemia. The patient was a 37-year-old man with a serum cholesterol level of 400 mg/dl. *C,* Proliferative retinopathy of Takayasu-Ohnishi disease. The patient was a 27-year-old Asian woman with postural amaurosis and hemiplegia. Brachial pulses were unobtainable. *D,* Roth spots (hemorrhage with white center) in a patient with subacute bacterial endocarditis. *(From Cogan DG: Ophthalmic Manifestations of Systemic Vascular Disease. Philadelphia, WB Saunders, 1974, p 52.)*

Figure 4-2 Tendinous xanthomas of the knees in a patient with familial hypercholesterolemia. The patient was a 10-year-old girl with a serum cholesterol level of 665 mg/dl. Several other members of her family had a similar syndrome. *(From Cogan DG: Ophthalmic Manifestations of Systemic Vascular Disease. Philadelphia, WB Saunders, 1974, pp 14 and 15.)*

Several types of *xanthomas* (i.e., cholesterol-filled nodules) are found either subcutaneously or over tendons in patients with hyperlipoproteinemia (see Chap. 31) . Premature atherosclerosis frequently develops in these individuals. *Tuberoeruptive xanthomas,* present subcutaneously or on the extensor surfaces of the extremities, and *xanthoma striatum palmare,* which produce yellowish, orange, or pink discoloration of the palmar and digital creases, occur most commonly in patients with type III hyperlipoproteinemia. Patients with *xanthoma tendinosum* (Fig. 4-2) (i.e., nodular swellings of the tendons, especially of the elbows, extensor surfaces of the hands, and Achilles tendons) usually have type II hyperlipoproteinemia. *Eruptive xanthomas* are tiny yellowish nodules, 1 to 2 mm in diameter on an erythematous base, that may occur anywhere on the body and are associated with hyperchylomicronemia and are therefore often found in patients with type I and type V hyperlipoproteinemia.

Hereditary telangiectases are multiple capillary hemangiomas occurring in the skin, lips (Fig. 4-3) , nasal mucosa, and upper respiratory and gastrointestinal tracts and

resemble the spider nevi seen in patients with liver disease. When present in the lung, they are associated with pulmonary arteriovenous fistulas and cause central cyanosis.

EXTREMITIES

A variety of congenital and acquired cardiac malformations are associated with characteristic changes in the extremities. Among the congenital lesions, short stature, cubitus valgus, and medial deviation of the extended forearm are characteristic of *Turner syndrome* (see Chap. 43) . Patients with the *Holt-Oram syndrome*[14] (i.e., atrial septal defect with skeletal deformities) often have a thumb with an extra

Figure 4-3 Hemorrhagic telangiectasia on the lips of a 25-year-old woman with pulmonary arteriovenous fistulas. *(From Perloff JK: The Clinical Recognition of Congenital Heart Disease. 4th ed. Philadelphia, WB Saunders, 1994, p 719.)*

Figure 4-4 *A,* Normal finger. *B,* Advanced clubbing in a young cyanotic adult. *(From Perloff JK: The Clinical Recognition of Congenital Heart Disease. 4th ed. Philadelphia, WB Saunders, 1994, p 7.)*

phalanx, a so-called fingerized thumb, which lies in the same plane as the fingers, making it difficult to appose the thumb and fingers. In addition, they may exhibit deformities of the radius and ulna, causing difficulty in supination and pronation.

Arachnodactyly is characteristic of Marfan syndrome (see Chap. 56) . Normally, when a fist is made over a clenched thumb the latter does not extend beyond the ulnar side of the hand, but it usually does so in Marfan syndrome.

Systolic flushing of the nail beds, which can be readily detected by pressing a flashlight against the terminal digits (Quincke sign), is a sign of aortic regurgitation and of other conditions characterized by a greatly widened pulse pressure. *Differential cyanosis,* in which the hands and fingers (especially on the right side) are pink and the feet and toes are cyanotic, is indicative of patent ductus arteriosus with reversed shunt due to pulmonary hypertension (see Chap. 53) ; this finding can often be brought out by exercise. On the other hand, *reversed differential cyanosis,* in which cyanosis of the fingers exceeds that of the toes, suggests Taussig-Bing anomaly with pulmonary vascular disease and reversed flow through a patent ductus arteriosus. Alternatively, it may occur with transposition of the great arteries, pulmonary hypertension, preductal narrowing of the aorta, and reversed flow through a patent ductus arteriosus.[15]

CLUBBING OF THE FINGERS AND TOES.

Clubbing of the digits is characteristic of central cyanosis (cyanotic congenital heart disease or pulmonary disease with hypoxia) (Fig. 4-4) .[16] It may also appear within a few weeks of the development of infective endocarditis. The earliest forms of clubbing

are characterized by increased glossiness and cyanosis of the skin at the root of the nail.[17] After obliteration of the normal angle between the base of the nail and the skin, the soft tissue of the pulp becomes hypertrophied, the nail root floats freely, and its loose proximal end can be palpated. In the more severe forms of clubbing, bony changes occur (i.e., *hypertrophic osteoarthropathy*); these changes involve the terminal digits and in rare instances even the wrists, ankles, elbows, and knees. *Unilateral clubbing* of the fingers is rare but can occur when an aortic aneurysm interferes with the arterial supply to one arm.

Osler nodes are small, tender, purplish erythematous skin lesions due to infected microemboli and occurring most frequently in the pads of the fingers or toes and in the palms of the hands or soles of the feet,[18] whereas *Janeway lesions* are slightly raised, nontender hemorrhagic lesions in the palms of hands and soles of the feet; both of these lesions as well as petechiae occur in infective endocarditis (see Chap. 47) . When the latter occur under the nail beds, they are termed *splinter hemorrhages.*

EDEMA.

The presence of edema of the lower extremities is a common finding in congestive heart failure (see Chap. 3) [19] ; however, if it is present in only one leg, it is more likely due to obstructive venous or lymphatic disease than to heart failure. Firm pressure on the pretibial region for 10 to 20 seconds may be necessary for the detection of edema. In patients confined to bed, edema appears first in the sacral region. Edema may involve the face in children with heart failure of any etiology and in adults with heart failure associated with marked elevation of systemic venous pressure (e.g., constrictive pericarditis and tricuspid valve disease).

CHEST AND ABDOMEN

Examination of the thorax should begin with observations of the rate, effort, and regularity of respiration. The shape of the chest is important as well; thus, a barrel-shaped chest with low diaphragm suggests emphysema, bronchitis, and cor pulmonale.

Inspection of the chest is an integral part of the cardiac examination (see p. 54). It may reveal a bulging to the right of the upper sternum caused by an aortic aneurysm. The latter can also produce a venous collateral pattern caused by obstruction of the superior vena cava. *Kyphoscoliosis* of any etiology can cause cor pulmonale; this skeletal abnormality, as well as pectus excavatum (funnel chest)[20] [21] [22] and pectus carinatum (pigeon breast), is often present in Marfan syndrome.

Left ventricular failure and other causes of elevation of pulmonary venous pressure may cause pulmonary rales; wheezing is sometimes audible in pulmonary edema (cardiac

asthma).

Painful enlargement of the liver may be due to venous congestion; the tenderness disappears in long-standing heart failure. Hepatic systolic expansile pulsations occur in patients with severe tricuspid regurgitation, and presystolic pulsations can be felt in patients with tricuspid stenosis and sinus rhythm. Patients with constrictive pericarditis also often have pulsatile hepatomegaly, the contour of the pulsations resembling those of the jugular venous pulse in this condition.[23] When firm pressure over the abdomen causes cervical venous distention, that is, when there is *abdominojugular reflux,* right-sided heart failure[24] [25] (see later) or tricuspid valve disease is usually present. *Ascites* is also characteristic of heart failure, but it is especially characteristic of tricuspid valve disease and chronic constrictive pericarditis.

Splenomegaly may occur in the presence of severe congestive hepatomegaly, most frequently in patients with constrictive pericarditis or tricuspid valve disease. The spleen may be enlarged and painful in infective endocarditis, as well as after splenic embolization. Splenic infarction is frequently accompanied by an audible friction rub.

Both *kidneys* may be palpably enlarged in patients with hypertension secondary to polycystic disease. Auscultation of the abdomen should be carried out in all patients with hypertension; a systolic bruit secondary to renal artery stenosis may be audible near the umbilicus or in the flank.

Atherosclerotic aneurysms of the abdominal aorta are usually readily detected on palpation of the abdomen below the umbilicus (see Chap. 40) , except in markedly obese patients. In patients with *coarctation of the aorta,* no abdominal pulsations are palpable despite the presence of prominent arterial pulses in the neck and upper extremities; arterial pulses in the lower extremities are reduced or absent.

JUGULAR VENOUS PULSE

Important information concerning the dynamics of the right side of the heart can be obtained by observation of the jugular venous pulse.[6] [26] [27] [28] [29] The *internal* jugular vein is ordinarily examined; the venous pulse can usually be analyzed more readily on the right than on the left side of the neck, because the right innominate and jugular veins extend in an almost straight line cephalad to the superior vena cava, thus favoring transmission of hemodynamic changes from the right atrium, while the left innominate vein is not in a straight line and may be kinked or compressed by a variety of normal structures, by a dilated aorta, or by an aneurysm.

During the examination the patient should be lying comfortably. Although the head should rest on a pillow, it must not be at a sharp angle from the trunk. The jugular venous pulse may be examined effectively by shining a light tangentially across the neck. Most patients with heart disease are examined most effectively in the 45-degree position, but in patients in whom venous pressure is high, a greater inclination (60 or even 90 degrees) is required to obtain visible pulsations, whereas in those in whom

jugular venous pressure is low, a lesser inclination (30 degrees) is desirable.

The internal jugular vein is located deep within the neck, where it is covered by the sternocleidomastoid muscle and is therefore not usually visible as a discrete structure except in the presence of venous hypertension. However, its pulsations are transmitted to the skin of the neck, where they are usually easily visible. Sometimes difficulty may be experienced in differentiating between the carotid and jugular venous pulses in the neck, particularly when the latter exhibits prominent v waves, as occurs in patients with tricuspid regurgitation, in whom the valves in the internal jugular veins may be incompetent. However, there are several helpful clues:

1. The arterial pulse is a sharply localized rapid movement that may not be readily visible but that strikes the palpating fingers with considerable force; in contrast, the venous pulse, whereas more readily visible, often disappears when the palpating finger is placed lightly on or below the pulsating area.
2. The arterial pulse usually exhibits a single upstroke, whereas (in patients in sinus rhythm) the venous pulse has two peaks and two troughs per cardiac cycle.
3. The arterial pulsations do not change when the patient is in the upright position or during respiration, whereas venous pulsations usually disappear or diminish greatly in the upright position and during inspiration, unless the venous pressure is greatly elevated.
4. Compression of the root of the neck does not affect the arterial pulse but usually abolishes venous pulsations, except in the presence of extreme venous hypertension.

Two principal observations can usually be made from examination of the neck veins: the level of venous pressure and the type of venous wave pattern. To estimate jugular venous pressure, the height of the oscillating top of the distended proximal portion of the internal jugular vein, which reflects right atrial pressure, should be determined. The upper limit of normal is 4 cm above the sternal angle, which corresponds to a central venous pressure of approximately 9 cm H_2O, since the right atrium is approximately 5 cm below the sternal angle. When the veins in the neck collapse in a subject breathing normally in the horizontal position, it is likely that the central venous pressure is subnormal. When obstruction of veins in the lower extremities is responsible for edema, pressure in the neck veins is not elevated and the abdominal-jugular reflux is negative.

ABDOMINAL-JUGULAR REFLUX.

This can be tested by applying firm pressure to the periumbilical region for 10 to 30 seconds with the patient breathing quietly while the jugular veins are observed[24] [25] [30] ; increased respiratory excursions or straining should be avoided. In normal subjects, jugular venous pressure rises less than 3 cm H_2O and only transiently while abdominal pressure is continued, whereas in right or left ventricular failure and/or tricuspid regurgitation the jugular venous pressure remains elevated. In the absence of these conditions, a positive abdominal-jugular reflux suggests an elevated pulmonary artery wedge[26] or central venous pressure.[25]

PATTERN OF THE VENOUS PULSE.

The events of the cardiac cycle, shown in Figure 14-22 , provide an explanation for the details of the jugular venous waveform (Fig. 4-5) . The a wave in the venous pulse results from venous distention due to right atrial systole, whereas the *x* descent is due to atrial relaxation and descent of the floor of the right atrium during right ventricular systole. The c wave, which occurs simultaneously with the carotid arterial pulse, is an inconstant wave in the jugular venous pulse and/or interruption of the *x* descent after the peak of the a wave. The continuation of the *x* descent after the c wave is referred to as the *x*
descent. The v wave results from the rise in right atrial pressure when blood flows into this chamber during ventricular systole when the tricuspid valve is shut, and the *y* descent (i.e., the downslope of the v wave) is related to the decline in right atrial pressure when the tricuspid valve reopens. After the bottom of the *y*

Figure 4-5 *Top,* Normal jugular venous pulse: the jugular v wave is built up during systole, and its height reflects the rate of filling and the elasticity of the right atrium. Between the bottom of the y descent (y trough) and beginning of the a wave is the period of relatively slow filling of the "atrioventricle" or diastasis period. The wave built up during diastasis is the H wave. The H wave height also reflects the stiffness of the right atrium. S_1 and S_2 refer to the first and second heart sounds, respectively. *Center,* As the degree of tricuspid regurgitation (TR) increases, the x descent is increasingly encroached upon. With severe TR, no x descent is seen, and the jugular pulse wave is said to be "ventricularized." *Bottom,* Black broken line=normal jugular venous pulse and sinus rhythm; red continuous line=after development of atrial fibrillation. The dominant descent in atrial fibrillation is almost always the y descent; that is, it has the superficial appearance of the pulse wave of TR. *(From Constant J: Bedside Cardiology. 4th ed. Boston, Little, Brown & Co, 1994, pp 81 and 89.)*

descent (the *y* trough) and beginning of the a wave is a period of relatively slow filling of the atrium or ventricle, the diastasis period, a wave termed the H wave.

Although all or most of these events can usually be recorded, they may not be readily distinguishable on inspection. The descents or downward collapsing movements of the jugular veins are more rapid, produce larger excursions, and are therefore more prominent to the eye than are the ascents (see Fig. 4-5) . The normal dominant jugular venous descent, the *x* descent, occurs between the first (S_1) and second (S_2) heart sounds, whereas the *y* descent ends well after S_2 . With an increase in central venous pressure, the v wave becomes higher and the *y* collapse becomes more prominent. The a wave occurs just before the first sound or carotid pulse and has a sharp rise and fall. The v wave occurs just after the arterial pulse and has a slower, undulating pattern.

ALTERATIONS IN DISEASE.

Elevation of jugular venous pressure reflects an increase in right atrial pressure and occurs in heart failure, reduced compliance of the right ventricle, pericardial disease, hypervolemia, obstruction of the tricuspid orifice, and obstruction of the superior vena cava. During inspiration, the jugular venous pressure normally declines but the *amplitude* of the pulsations increases. *Kussmaul sign* is a paradoxical rise in the height of the jugular venous pressure during inspiration, which typically occurs in patients with chronic constrictive pericarditis and sometimes in patients with congestive heart failure and tricuspid stenosis.

The a wave is particularly prominent in conditions in which the resistance to right atrial contraction is increased, such as right ventricular hypertrophy, pulmonary hypertension, and tricuspid stenosis (Fig. 4-6 *A*). The a wave may also be tall in left ventricular hypertrophy when the thickened ventricular septum interferes with right ventricular filling. Tall a waves are present in patients with sinus rhythm and tricuspid stenosis or atresia, right atrial myxoma, or reduced compliance and/or marked hypertrophy of the right ventricle. Cannon (amplified) a waves are noted in patients with AV dissociation when the right atrium contracts against a closed tricuspid valve. In atrial fibrillation, the a wave and *x* descent disappear and the v wave and *y* descent (see Fig. 4-5 , *bottom*) become more prominent. In right ventricular failure and sinus rhythm, there may be increases in prominence of both the a and v waves. A steeply rising H wave (see Fig. 4-5) is observed (or recorded) in restrictive cardiomyopathy, constrictive pericarditis, and right ventricular infarction. The *x* descent may be prominent in patients with large a waves, as well as in patients with right ventricular volume overload (atrial septal defect).

Constrictive pericarditis (see Fig. 4-6 *B*) is characterized by a rapid and deep *y* descent followed by a rapid rise to a diastolic plateau (H wave) without a prominent a wave; occasionally, the *x* descent is prominent in this condition as well, causing a "W"-shaped jugular venous pulse. However, it is in *cardiac tamponade* that the *x* descent is most prominent. A prominent v wave or a c-v wave (i.e., fusion of the c and v waves in the absence or attenuation of an *x* descent) occurs in tricuspid regurgitation, sometimes causing a systolic movement of the earlobe[29] (see Fig. 4-5 , *center*) and a right-to-left head movement with each ventricular systole. Equal a and v waves are seen in atrial septal defect; the *y* descent is gradual when right atrial emptying is impeded, as in tricuspid stenosis, and rapid when it is unimpeded, as in tricuspid regurgitation. A steep *y* descent is seen in any condition in which there is myocardial dysfunction, ventricular dilatation, and an elevated central venous pressure.

SPHYGMOMANOMETRIC MEASUREMENT OF ARTERIAL PRESSURE

Systolic arterial pressure can be *estimated* without a sphygmomanometer by gradually compressing the brachial artery while palpating the radial artery; the force required to obliterate

Figure 4-6 *A,* Jugular venous pressure (JVP) in mitral stenosis with pulmonary hypertension. The JVP is dominated by a very large a wave resulting from diminished compliance of the right ventricle associated with pulmonary hypertension. The peaked a wave represents a brief period of retrograde flow from right atrium to great veins. *B,* JVP in constrictive pericarditis. In this severe and long-standing case, the x descent has become very shallow and the y descent is the principal feature, indicating that antegrade flow from the venous system to the right side of the heart is now limited to early diastole. A pericardial knock (K) is seen at approximately the nadir of the y descent. *(From Craige E, Smith P: Heart sounds. In Braunwald E [ed]: Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, pp 61 and 62.)*

the radial pulse represents the systolic blood pressure, and, with practice, one can often estimate this level within 20 mm Hg. Ordinarily, however, a sphygmomanometer is used to obtain an indirect measurement of blood pressure.[31] [32] The cuff should fit snugly around the arm, with its lower edge at least 1 inch above the antecubital space, and the diaphragm of the stethoscope should be placed close to or under the edge of the sphygmomanometer cuff. The width of the cuff selected should be at least 40 percent of the circumference of the limb to be used.

The standard size, with a 5-inch-wide cuff, is designed for adults with an arm of average size. When this cuff is applied to a large upper arm or a normal adult thigh, arterial pressure is overestimated, leading to spurious hypertension in the obese (arm circumference >35 cm)[33] [34] ; when it is applied to a small arm, the pressure is underestimated. The cuff width should be approximately 1.5 inches in infants and small children, 3 inches in young children (2 to 5 years), and 8 inches in obese adults. The rubber bag should be long enough to extend at least halfway around the limb (10 inches in adults). In patients with rigid, sclerotic arteries the systolic pressure may also be overestimated, by as much as 30 mm Hg. Mercury manometers are, in general, more accurate and reliable than the aneroid type; the latter should be calibrated at least once yearly.

BLOOD PRESSURE IN THE UPPER EXTREMITIES.

To measure arterial pressure in an upper extremity,[35] [36] [37] the patient should be seated or lying comfortably and relaxed, the arm should be slightly flexed and at heart level, and the arm muscles should be relaxed. The cuff should be inflated rapidly to approximately 30 mm Hg above the anticipated systolic pressure. These maneuvers, which diminish the volume of blood in the venous bed, decrease the tissue pressure distal to the cuff and thereby increase the flow into the occluded brachial artery. The cuff is then deflated slowly, no faster than 3 mm Hg/sec; the pressure at which the brachial pulse can be palpated is close to the systolic pressure.

The cuff should be deflated rapidly after the diastolic pressure is noted and a full minute allowed to elapse before pressure is remeasured in the same limb. Although excessive pressure on the stethoscope head does not affect systolic pressure, it does erroneously lower diastolic readings. In one study, the anxiety associated with blood pressure measurement was shown to elevate arterial pressure by an average of 27/17 mm Hg[38]

("white coat hypertension," see Chap. 28) .

BLOOD PRESSURE IN THE LOWER EXTREMITIES.

To measure pressure in the legs, the patient should lie on the abdomen, an 8-inch-wide cuff should be applied with the compression bag over the posterior aspect of the mid thigh and should be rolled diagonally around the thigh to keep the edges snug against the skin, and auscultation should be carried out in the popliteal fossa. To measure pressure in the lower leg, an arm cuff is placed over the calf and auscultation is carried out over the posterior tibial artery. Regardless of where the cuff is applied, care must be taken to avoid letting the rubber part of the balloon of the cuff extend beyond its covering and to avoid placing the cuff on so loosely that central ballooning occurs.

KOROTKOFF SOUNDS.

There are five phases of Korotkoff sounds (i.e., sounds produced by the flow of blood as the constricting blood pressure cuff is gradually released). The first appearance of clear, tapping sound (phase I) represents the systolic pressure. These sounds are replaced by soft murmurs during phase II and by louder murmurs during phase III, as the volume of blood flowing through the constricted artery increases. The sounds suddenly become muffled in phase IV, when constriction of the brachial artery diminishes as arterial diastolic pressure is approached. Korotkoff sounds disappear in phase V, which is usually within 10 mm Hg of phase IV.

Diastolic pressure measured directly through an intraarterial needle and external manometer corresponds closely to phase V. In severe aortic regurgitation, however, when the disappearance point is extremely low, sometimes 0 mm Hg, the sound of muffling (phase IV) is much closer to the intraarterial diastolic pressure than is the disappearance point (phase V). When the difference between phases IV and V of the Korotkoff sounds exceeds 10 mm Hg, both pressures should be recorded (e.g., 142/54/10 mm Hg).

Korotkoff sounds may be difficult to hear and arterial pressure difficult to measure when arterial pressure rises at a slow rate (as in severe aortic stenosis), when the arteries are markedly constricted (as in shock), and when the stroke volume is reduced (as in severe heart failure). Very soft or inaudible Korotkoff sounds can often be accentuated by dilating the blood vessels simply by opening and closing the fist repeatedly. Sometimes in states of shock, the indirect method of measuring blood pressure is unreliable and arterial pressure should be measured through an intraarterial needle.

The Auscultatory Gap.

This is a silence that sometimes separates the first appearance of the Korotkoff sounds from their second appearance at a lower pressure. The phenomenon tends to occur

when there is venous distention or reduced velocity of arterial flow into the arm. If the first muffling of sounds is considered to be the diastolic pressure, it will be overestimated. If the second appearance is taken as the systolic pressure, it will be underestimated. On the other hand, sounds transmitted through the arterial tree from prosthetic aortic valves may be responsible for falsely high readings.

BLOOD PRESSURE IN THE BASAL CONDITION.

To determine arterial pressure in the basal condition, the patient should have rested in a quiet room for 15 minutes. It is desirable to record the arterial pressure in both arms at the time of the initial examination; differences in systolic pressure between the two arms that exceed 10 mm Hg when measurements are made simultaneously or in rapid sequence[37] suggest obstructive lesions involving the aorta or the origin of the innominate and subclavian arteries or supravalvular aortic stenosis (in which pressure in the right arm exceeds that in the left). In patients with vertebral-basal artery insufficiency, a difference in pressure between the arms may signify that a subclavian "steal" is responsible for the cerebrovascular symptoms.

To be certain from physical examination that the systolic pressure is different in the two arms or in the upper and lower extremities, two examiners should measure the pressures simultaneously and then switch extremities and measure the pressures again.

ORTHOSTATIC HYPOTENSION.

To determine whether orthostatic hypotension is present, arterial pressure should be determined with the patient in both the supine and the erect positions. However, regardless of the patient's posture, the brachial artery should be at the level of the heart to avoid superimposition of the effects of gravity on the recorded pressure.

Normally, the systolic pressure in the legs is up to 20 mm Hg higher than in the arms but the diastolic pressures are usually virtually identical. The recording of a higher diastolic pressure in the legs than in the arms suggests that the thigh cuff is too small. When systolic pressure in the popliteal artery exceeds that in the brachial artery by more than 20 mm Hg (Hill sign), aortic regurgitation is usually present.[39] Blood pressure should be measured in the lower extremities in patients with hypertension to detect coarctation of the aorta or when obstructive disease of the aorta or its immediate branches is suspected.

ARTERIAL PULSE

The volume and contour of the arterial pulse are determined by a combination of factors, including the left ventricular stroke volume, the ejection velocity, the relative compliance and capacity of the arterial system, and the pressure waves that result from the antegrade flow of blood and reflections of the arterial pressure pulse returning from the peripheral circulation.[39] Bilateral palpation of the carotid, radial, brachial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses should be part of the examination of

all cardiac patients (Fig. 4-7) . Caution should be exercised in bilateral carotid palpation, especially in the elderly. The frequency, regularity, and shape of the pulse wave and the character of the arterial wall should be determined.[40]

The carotid pulse (see Fig. 4-7 A) provides the most accurate representation of the central aortic pulse.[41] The

Figure 4-7 *A,* Technique for evaluating the carotid artery pulsations. *B,* Technique for timing the femoral and radial arteries. *C,* Technique for palpation of the dorsalis pedis arteries. *D,* Technique for palpation of the posterior tibial arteries. *(From Swartz MH [ed]: Textbook of Physical Diagnosis: History and Examination. 3rd ed. Philadelphia, WB Saunders, 1998, pp 300, 329, and 330.)*

brachial artery is the vessel ordinarily most suitable for appreciating the rate of rise of the pulse and the contour, volume, and consistency of the peripheral vessels. This artery is located at the medial aspect of the elbow, and it may be helpful to flex the arm to improve palpation; palpation of the artery should be carried out with the thumb exerting pressure on the artery until its maximal movement is detected. A normal rate of rise of the arterial pulse suggests that there is no obstruction to left ventricular outflow, whereas a pulse wave of small amplitude with normal configuration suggests a reduced stroke volume.

THE NORMAL PULSE.

The pulse in the ascending aorta normally rises rapidly to a rounded dome (Fig. 4-8) ; this initial rise reflects the peak velocity of blood ejected from the left ventricle. A slight anacrotic notch or pause is frequently recorded, but only occasionally felt, on the ascending limb of the pulse. The descending limb of the central aortic pulse is less steep than is the ascending limb, and it is interrupted by the incisura, a sharp downward deflection related to closure of the aortic valve. Immediately thereafter, the pulse wave rises slightly and then declines gradually throughout diastole. As the pulse wave is transmitted to the periphery, its upstroke becomes steeper, the systolic peak becomes higher, the anacrotic shoulder disappears, and the sharp incisura is replaced by a smoother, later dicrotic notch followed by a dicrotic wave.[42] [43] [44] Normally, the height of this dicrotic wave diminishes with age, hypertension, and arteriosclerosis. In the central arterial pulse (central aorta and innominate and carotid arteries), the rapidly transmitted impact of left ventricular ejection results in a peak in early systole, referred to as the *percussion wave;* a second, smaller peak, the *tidal wave,* presumed to represent a reflected wave from the periphery, can often be recorded but is not normally palpable. However, in older subjects, particularly those with increased peripheral resistance, as well as in patients with arteriosclerosis and diabetes, the tidal wave may be somewhat higher than the percussion wave; that is, the pulse reaches a peak in late systole. In peripheral arteries, the pulse wave normally has a single sharp peak.

ABNORMAL PULSES.

When peripheral vascular resistance and arterial stiffness are increased, as in hypertension or with the increased arterial stiffness that accompanies normal aging, there is an elevation in pulse wave velocity and the pulse contour has a more rapid upstroke and greater amplitude. Reduced or unequal carotid arterial pulsations occur in patients with carotid atherosclerosis and with diseases of the aortic arch, including aortic dissection, aneurysm, and Takayasu disease (see Chap. 40) . In *supravalvular aortic stenosis,* there is a selective streaming of the jet toward the innominate artery, the carotid and brachial arterial pulses are stronger and rise more rapidly on the right than on the left side, and pressures may be higher in the right than in the left arm (see Chap. 43) . The pulses of the upper extremities may be reduced or unequal in a variety of other conditions, including arterial embolus or thrombosis, anomalous origin or aberrant path of the major vessels, and cervical rib or scalenus anticus syndrome. Asymmetry of right and left popliteal pulses is characteristic of iliofemoral obstruction. Weakness or absence of radial, posterior tibial, or dorsalis pedis pulses on one side suggests arterial insufficiency (see Fig. 4-7 *C* and *D*). In *coarctation of the aorta* the carotid and brachial pulses are bounding, rise rapidly, and have large volumes, whereas in the lower extremities, the systolic and pulse pressures are reduced, their rate of rise is slow, and there is a late peak. This delay in the femoral arterial pulses can usually be readily detected by simultaneous palpation of the femoral and brachial arterial pulses (see Fig. 4-7B) .

In patients with fixed obstruction to left ventricular outflow (valvular aortic stenosis and congenital fibrous subaortic stenosis), the carotid pulse rises slowly *(pulsus tardus)* (see Fig. 4-8 *B*); the upstroke is frequently characterized by a thrill (the *carotid shudder*); and the peak is reduced, occurs late in systole, and is sustained. There is a notch on the upstroke of the carotid pulse (anacrotic notch) that is so distinct that two separate waves can be palpated in what is termed an *anacrotic pulse. Pulsus parvus* is a pulse of small amplitude, usually because of a reduction of stroke volume. *Pulsus parvus et tardus* refers to a small pulse with a delayed systolic peak, which is characteristic of severe aortic stenosis. This type of pulse is more readily appreciated by palpating the carotid rather than a more peripheral artery. Patients with severe aortic stenosis and heart failure usually exhibit simply a reduced pulse amplitude (i.e., *pulsus parvus*), and the delay in the upstroke is not readily apparent. However, this delay is readily recorded. In elderly patients with inelastic peripheral arteries, the pulse may rise normally despite the presence of aortic stenosis.

The carotid arterial pulse may be prominent or exaggerated in any condition in which pulse pressure is increased, including anxiety, the hyperkinetic heart syndrome, anemia, fever, pregnancy, or other high cardiac output states (see Chap. 17) , as well as in bradycardia and

Figure 4-8 Schematic diagrams of the configurational changes in the carotid pulse and their differential diagnosis. Heart sounds are also illustrated. *A,* Normal. *B,* Anacrotic pulse with slow initial upstroke. The

peak is close to the second heart sound. These features suggest fixed left ventricular outflow obstruction. *C,* Pulsus bisferiens with both percussion and tidal waves occurring during systole. This type of carotid pulse contour is most frequently observed in patients with hemodynamically significant aortic regurgitation or combined aortic stenosis and regurgitation with dominant regurgitation. It is rarely observed in mitral valve prolapse or in normal individuals. *D,* Pulsus bisferiens in hypertrophic obstructive cardiomyopathy. It is rarely appreciated at the bedside by palpation. *E,* Dicrotic pulse results from an accentuated dicrotic wave and tends to occur in sepsis, severe heart failure, hypovolemic shock, and cardiac tamponade and after aortic valve replacement. S_4 =fourth heart sound; S_1 =first heart sound; A_2 =aortic component of the second heart sound; P_2 =pulmonic component of the second heart sound. *(From Chatterjee K: Bedside evaluation of the heart: The physical examination. In Chatterjee K, et al [eds]: Cardiology: An Illustrated Text/Reference. Philadelphia, JB Lippincott, 1991, pp 3.11-3.51.)*

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peripheral arteriosclerosis with reduction in arterial distensibility. In patients with *mitral regurgitation* or *ventricular septal defect,* the forward stroke volume (from the left ventricle into the aorta) is usually normal but the fraction ejected during early systole is greater than normal; hence, the arterial pulse is of normal volume (the pulse pressure is normal) but the pulse may rise abnormally rapidly.[45] Exaggerated or bounding arterial pulses may be observed in patients with an elevated stroke volume, with sympathetic hyperactivity, and in patients with a rigid, sclerotic aorta. In *aortic regurgitation,* there is a very brisk rate of rise with an increased pulse pressure.

The *Corrigan* or *water-hammer pulse* of aortic regurgitation consists of an abrupt upstroke (percussion wave) followed by rapid collapse later in systole but no dicrotic notch. Corrigan pulse reflects a low resistance in the reservoir into which the left ventricle rapidly discharges an abnormally elevated stroke volume, and it can be exaggerated by raising the patient's arm. In *acute* aortic regurgitation, the left ventricle may not be significantly dilated and premature closure of the mitral valve may occur and limit the volume of aortic reflux; therefore, the aortic diastolic pressure may *not* be very low, the arterial pulse *not* bounding, and the pulse pressure *not* widened despite a serious abnormality of valve function (see Chap. 46) .

Signs characteristic of severe chronic aortic regurgitation include "pistol shot" sounds heard over the femoral artery when the stethoscope is placed on it (*Traube sign*); a systolic murmur heard over the femoral artery when the artery is gradually compressed proximally; a diastolic murmur when the artery is compressed distally (*Duroziez sign*[39]) and Quincke sign (phasic blanching of the nail bed). Of these, Duroziez sign is the most predictive of severe aortic regurgitation. Bounding arterial pulses are also present in patients with patent ductus arteriosus or large arteriovenous fistulas; in hyperkinetic states such as thyrotoxicosis, pregnancy, fever, and anemia; in severe bradycardia; and in arteries proximal to coarctation of the aorta. In *Hill sign* of aortic regurgitation (or any condition leading to an increased stroke volume or the hyperkinetic circulatory state) the indirectly recorded systolic pressures in the lower extremities exceed that in the arms by more than 20 mm Hg. Other signs of increased pulse pressure include *Becker sign* (visible pulsations of the retinal arterioles) and *Mueller sign* (pulsating uvula).

In the presence of AV dissociation, when atrial activity is irregularly transmitted to the

ventricles, the strength of the peripheral arterial pulse depends on the time interval between atrial and ventricular contractions. In a patient with rapid heart action, the presence of such variations suggests ventricular tachycardia; with an equally rapid rate, an absence of variation of pulse strength suggests a supraventricular mechanism.

BISFERIENS PULSE.

A bisferiens pulse (see Fig. 4-8 *C*) is characterized by *two systolic peaks,* the percussion and tidal waves, separated by a distinct midsystolic dip; the peaks may be equal, or either may be larger. This type of pulse is detected most readily by palpation of the carotid and, less commonly, of the brachial arteries. It occurs in conditions in which a large stroke volume is ejected rapidly[46] and is observed most commonly in patients with pure aortic regurgitation or with a combination of aortic regurgitation and stenosis; it may disappear as heart failure supervenes.

A bisferiens pulse also occurs in patients with *hypertrophic obstructive cardiomyopathy,*[46] but the bifid nature may only be recorded, not palpated; on palpation there may merely be a rapid upstroke. In these patients the initial prominent percussion wave is associated with rapid ejection of blood into the aorta during early systole, followed by a rapid decline as obstruction becomes manifest in midsystole and by a tidal (reflected) wave. In some patients with hypertrophic cardiomyopathy with no or little obstruction to left ventricular outflow, the arterial pulse is normal or simply hyperkinetic in the basal state, but obstruction and a bisferiens pulse can be elicited by means of the Valsalva maneuver or inhalation of amyl nitrite. Occasionally, a bisferiens pulse is observed in hyperkinetic circulatory states, and very rarely it occurs in normal individuals.

DICROTIC PULSE.

Not to be confused with a bisferiens pulse, in which both peaks occur in systole, is a dicrotic pulse, in which the second peak is in diastole immediately after S_2 (see Fig. 4-8 *E*).[40] [41] [43] [44] The normally small wave that follows aortic valve closure (i.e., the dicrotic notch) is exaggerated and measures more than 50 percent of the pulse pressure on direct pressure recordings and in which the dicrotic notch is low (i.e., near the diastolic pressure). A dicrotic wave may be present in normal hypotensive subjects with reduced peripheral resistance, as occurs in fever, and it may be elicited or exaggerated by inhalation alone or the inhalation of amyl nitrite. Rarely, a dicrotic pulse is noted in healthy adolescents or young adults, but it usually occurs in conditions such as cardiac tamponade, severe heart failure, and hypovolemic shock, in which a low stroke volume is ejected into a soft elastic aorta. In these conditions the dicrotic pulse is due to a reduction of the systolic wave with preservation of the incisura. A dicrotic pulse is rarely present when systolic pressure exceeds 130 mm Hg.

PULSUS ALTERNANS (Alternating Strong and Weak Pulses).

Mechanical alternans is a sign of depression of left ventricular function (see Chap. 17) .[47] [48] Although more readily recognized on sphygmomanometry, when the systolic

pressure alternates by more than 20 mm Hg, pulsus alternans can be detected by palpation of a peripheral (femoral or brachial) pulse more frequently than by a more central pulse. Palpation should be carried out with light pressure and with the patient's breath held in mid expiration to avoid the superimposition of respiratory variation on the amplitude of the pulse. Pulsus alternans is generally accompanied by alternation in the intensity of the Korotkoff sounds and occasionally by alternation in intensity of the heart sounds. Rarely, pulsus alternans is so marked that the weak beat is not perceived at all.[49] Aortic regurgitation, systemic hypertension, and reducing venous return by administration of nitroglycerin or by tilting the patient into the upright position all exaggerate pulsus alternans and assist in its detection. Pulsus alternans, which is frequently precipitated by a premature ventricular contraction, is characterized by a regular rhythm and must be distinguished from pulsus bigeminus (see later), which is usually irregular.

PULSUS BIGEMINUS.

A bigeminal rhythm is caused by the occurrence of premature contractions, usually ventricular, after every other beat and results in alternation of the strength of the pulse, which can be confused with pulsus alternans. However, in contrast to the latter, in which the rhythm is regular, in pulsus bigeminus the weak beat always follows the shorter interval. In normal persons or in patients with fixed obstruction to left ventricular outflow, the compensatory pause after a premature beat is followed by a stronger-than-normal pulse. However, in patients with hypertrophic obstructive cardiomyopathy, the postpremature ventricular contraction beat is weaker than normal because of increased obstruction to left ventricular outflow[50] (see Chap. 48) .

PULSUS PARADOXUS.

This is an exaggerated reduction in the strength of the arterial pulse during normal inspiration due to an exaggerated inspiratory fall in systolic pressure (more than 10 mm Hg during quiet breathing) (see Chap. 50) . When marked (i.e., an inspiratory reduction of pressure greater than 20 mm Hg), the paradoxical pulse can be detected by simple palpation of the brachial arterial pulse[51] ; in severe cases there is inspiratory disappearance of the pulse. Milder degrees of a paradoxical pulse can be readily detected on sphygmomanometry: the cuff is inflated to suprasystolic levels and is deflated slowly at a rate of about 2 mm Hg per heartbeat; the peak systolic pressure during exhalation is noted. The cuff is then deflated even more slowly, and the pressure is again noted when Korotkoff sounds become audible throughout the respiratory cycle. Normally, the difference between the two pressures should not exceed 10 mm Hg during quiet respiration. (Pulsus alternans can also be detected by this maneuver by noting whether peak systolic pressure or the intensity of the Korotkoff sounds alternates when the breath is held.)

Pulsus paradoxus represents an exaggeration of the normal decline in systolic arterial pressure with inspiration. It results from the reduced left ventricular stroke volume and

the transmission of negative intrathoracic pressure to the aorta. It is a frequent, indeed characteristic, finding in patients with cardiac tamponade, occurs less frequently (in about half) in patients with chronic constrictive pericarditis, and is also observed in patients with emphysema and bronchial asthma (who have wide respiratory swings of intrapleural pressure),[52] as well as in hypovolemic shock, pulmonary embolus, pregnancy, and extreme obesity. Aortic regurgitation tends to prevent the development of pulsus paradoxus despite the presence of cardiac tamponade. *Reversed* pulsus paradoxus (an inspiratory rise in arterial pressure) may occur in hypertrophic obstructive cardiomyopathy.[53]

THE ARTERIAL PULSE IN VASCULAR DISEASE.

(See also Chap. 41.) Examination of the arterial pulses is of critical importance in the diagnosis of extracardiac obstructive arterial disease. Systematic bilateral palpation of the common carotid, brachial, radial, femoral, popliteal, dorsalis pedis, and posterior tibial vessels (see Fig. 4-7 *C* and *D*), as well as palpation of the abdominal aorta (both above and below the umbilicus), should be part of every examination in patients suspected of having ischemic heart disease. A normal aorta is often palpable above the umbilicus, but a palpable aorta below the umbilicus suggests the presence of an aneurysm of the abdominal aorta. To diminish cold-induced vasoconstriction, peripheral pulses should be palpated after the patient has been in a warm room for at least 20 minutes.[54] Absent or weak peripheral pulses usually signify obstruction. However, the dorsalis pedis and posterior tibial arteries may be absent in approximately 2 percent of normal persons because they pursue an aberrant course.

Arterial bruits should be sought at specific anatomical sites. When the lumen diameter is reduced by approximately 50 percent, a soft short systolic bruit is heard; as the obstruction becomes more severe, the bruit becomes high pitched, louder, and longer. With approximately 80 percent diameter reduction the murmur spills into early diastole, but it disappears with more severe stenosis or complete occlusion. Arterial bruits are augmented by elevation of the cardiac output (e.g., as occurs in anemia), by poor development of collaterals, and by increased arterial outflow (as occurs in regional exercise).

Auscultation over the spine in the interscapular region in patients with coarctation of the aorta may reveal a systolic or continuous murmur, and a systolic murmur may be heard over the lower abdomen in patients with aortic or iliofemoral obstructions.

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The Cardiac Examination

INSPECTION

The cardiac examination proper should commence with inspection of the chest, which can usually best be accomplished with the examiner standing at the side or foot of the bed or examining table. Respirations--their frequency, regularity, and depth--as well as the relative effort required during inspiration and exhalation, should be noted. Simultaneously, one should search for cutaneous abnormalities, such as spider nevi (seen in hepatic cirrhosis and Osler-Weber-Rendu disease). Dilation of veins on the anterior chest wall with caudal flow suggests obstruction of the superior vena cava, whereas cranial flow occurs in patients with obstruction of the inferior vena cava. Precordial prominence is most striking if cardiac enlargement developed before puberty, but it may also be present, although to a lesser extent, in patients in whom cardiomegaly developed in adult life, after the period of thoracic growth.[55] [56]

A heavy muscular thorax, contrasting to less developed lower extremities, may occur in coarctation of the aorta, in which collateral arteries may be visible in the axillae and along the lateral chest wall. The upper portion of the thorax exhibits symmetrical bulging in children with stiff lungs in whom the inspiratory effort is increased. A "shield chest" is a broad chest in which the angle between the manubrium and the body of the sternum is greater than normal and is associated with widely separated nipples; shield chest is frequently observed in Turner and Noonan syndromes (see Chap. 43) . Careful note should be made of other deformities of the thoracic cage, such as *kyphoscoliosis,* which may be responsible for cor pulmonale (see Chap. 54) ; *ankylosing spondylitis,* sometimes associated with aortic regurgitation (see Chap. 67) ; and *pectus carinatum* (pigeon chest), which may be associated with Marfan syndrome but does not directly

affect cardiovascular function.

Pectus excavatum,[20] [21] [22] a condition in which the sternum is displaced posteriorly, is commonly observed in Marfan syndrome, homocystinuria, Ehlers-Danlos syndrome, Hunter-Hurler syndrome, and a small fraction of patients with mitral valve prolapse. This thoracic deformity rarely compresses the heart or elevates the systemic and pulmonary venous pressures, and the signs of heart disease are more often apparent rather than real.[57] Displacement of the heart into the left thorax, prominence of the pulmonary artery, and a parasternal midsystolic murmur, all key features of this deformity, may falsely suggest the presence of organic heart disease. Pectus excavatum may be associated with palpitations, tachycardia, fatigue, mild dyspnea, and some impairment of cardiac function.[57] Lack of normal thoracic kyphosis (i.e., the *straight back* syndrome) is often associated with expiratory splitting of S_2 , a parasternal midsystolic murmur, and prominence of the pulmonary artery on radiography.

CARDIOVASCULAR PULSATIONS

Cardiovascular pulsations should be looked for on the entire chest but specifically in the regions of the cardiac apex, the left parasternal region, and the third left and second right intercostal spaces. Prominent pulsations in these areas suggest enlargement of the left ventricle, right ventricle, pulmonary artery, and aorta, respectively. A thrusting apex exceeding 2 cm in diameter suggests left ventricular enlargement; systolic retraction of the apex may be visible in constrictive pericarditis. Normally, cardiac pulsations are not visible lateral to the midclavicular line; when present there, they signify cardiac enlargement unless there is thoracic deformity or congenital absence of the pericardium. Shaking of the entire precordium with each heartbeat may occur in patients with severe valvular regurgitation, large left-to-right shunts, especially patent ductus arteriosus, complete AV block, hypertrophic obstructive cardiomyopathy, and various hyperkinetic states (see Chap. 17) . Aortic aneurysms may produce visible pulsations of one of the sternoclavicular joints of the right anterior thoracic wall.

PALPATION

Pulsations of the heart and great arteries that are transmitted to the chest wall are best appreciated when the examiner is positioned on the right side of a supine patient. To palpate the movements of the heart and great arteries, the examiner should use the fingertips or the area just proximal thereto. Precordial movements should be timed with the simultaneously palpated carotid pulse or auscultated heart sounds.[58] [59] The examination should be carried out with the chest completely exposed and elevated to 30 degrees, both with the patient supine and in the partial left lateral decubitus positions (Fig. 4-9) . [2] Rotating the patient into the left lateral decubitus position with the left arm elevated over the head causes the heart to move laterally and increases the palpability of both normal and pathological thrusts of the left ventricle. The subxiphoid region, which allows palpation of the right ventricle, should be examined with the tip of the index finger during held inspiration. Obese, muscular, emphysematous, and elderly persons may have weak or undetectable cardiac pulsations in the absence of cardiac abnormality, and thoracic deformities (e.g.,

Figure 4-9 *A,* Palpation of the anterior wall of the right ventricle by applying the tips of three fingers in the third, fourth, and fifth interspaces, left sternal edge (arrows), during full held exhalation. Patient is supine with the trunk elevated 30 degrees. *B,* Subxiphoid palpation of the inferior wall of the right ventricle (RV) with the relative position of the abdominal aorta (Ao) shown by the arrow. *C,* The bell of the stethoscope is applied to the cardiac apex while the patient lies in a partial left lateral decubitus position. The thumb of the examiner's free left hand is used to palpate the carotid artery for timing purposes. *D,* The soft, high-frequency early diastolic murmur of aortic regurgitation or pulmonary hypertensive regurgitation is best elicited by applying the stethoscopic diaphragm very firmly to the mid-left sternal edge. The patient leans forward with breath held in full exhalation. *E,* Palpation of the left ventricular impulse with a fingertip (arrow). The patient's trunk is 30 degrees above the horizontal. The examiner's right thumb palpates the carotid pulse for timing purposes. *F,* Palpation of the liver. The patient is supine with knees flexed to relax the abdomen. The flat of the examiner's right hand is placed on the right upper quadrant just below the expected inferior margin of the liver; the left hand is applied diametrically opposite. *(From Perloff JK: Physical Examination of the Heart and Circulation. 2nd ed. Philadelphia, WB Saunders, 1990.)*

kyphoscoliosis, pectus excavatum) can alter the pulsations transmitted to the chest wall. In the course of cardiac palpation, precordial tenderness may be detected; this finding may result from costochondritis (Tietze syndrome) and may be an important indication that chest pain is not due to myocardial ischemia.

THE LEFT VENTRICLE.

The *left ventricular impulse*, also referred to as the cardiac impulse, the *apex beat,* and the apical thrust, is normally produced by left ventricular contraction and is the lowest and most lateral point on the chest at which the cardiac impulse can be appreciated and is normally above the anatomical apex. Although the left ventricular impulse may also be the point of maximal impulse, this is not necessarily the case, because the pulsations produced by other structures (e.g., an enlarged right ventricle, a dilated pulmonary artery, or an aneurysm of the aorta) may be more powerful than the apex beat. Normally, the left ventricular impulse is medial and superior to the intersection of the left midclavicular line and the fifth intercostal space and is palpable as a single, brief outward motion. Although it may not be palpable in the supine position in as many as half of all normal subjects more than 50 years of age, the left ventricular impulse can usually be felt in the left lateral decubitus position. Displacement of the apex beat lateral to the midclavicular line or more than 10 cm lateral to the midsternal line is a sensitive but not specific indicator of left ventricular enlargement. However, when the patient is in the left lateral decubitus position a palpable apical impulse that has a diameter of more than 3 cm is an accurate sign of left ventricular enlargement.[60] Thoracic deformities--particularly scoliosis, straight back, and pectus excavatum--can result in the lateral displacement of a normal-sized heart.

APEX CARDIOGRAM.

This recording reflects the movement of the chest wall and represents the pulsation of the entire left ventricle. Its contour differs from what is perceived on palpation of the apex or what is recorded by the kinetocardiogram, a device in which the motion of specific points on the chest wall is recorded relative to a fixed point in space[61] and which therefore presents a more faithful graphic registration of the movements of the palpating finger on the chest wall.

SYSTOLIC MOTION

During isovolumetric contraction, the heart normally rotates counterclockwise (as one faces the patient), and the lower anterior portion of the left ventricle strikes the anterior chest wall, causing a brief outward motion followed by medial retraction of the adjacent chest wall during ejection. The peak outward motion of the left ventricular impulse occurs simultaneously with, or just after, aortic valve opening; then the left ventricular apex moves inward. In asthenic persons, in patients with mild left ventricular enlargement, and in subjects with a normal left ventricle but an augmented stroke volume, as occurs in anxiety and other hyperkinetic states, and in mitral or aortic regurgitation, the cardiac impulse may be overactive but with a normal contour; that is, the outward thrust during systole is exaggerated in amplitude but it is not sustained during ejection.

HYPERTROPHY AND DILATATION.

With moderate or severe left ventricular concentric hypertrophy, the outward systolic thrust persists throughout ejection, often lasting up to the second heart sound,[62] and this motion is accompanied by retraction of the left parasternal region. This rocking motion can often be appreciated by placing the index finger of one hand on the apex beat and that of the other hand in the parasternal region and by palpating the simultaneous outward motion of the former while observing retraction of the latter. The left ventricular heave or lift, which is more prominent in concentric hypertrophy than in left ventricular dilatation without volume overload, is characterized by a sustained outward movement of an area that is larger than the normal apex; that is, it is more than 2 to 3 cm in diameter. In patients with left ventricular enlargement the systolic impulse is displaced laterally and downward into the sixth or seventh interspaces. In patients with ischemic heart disease a sustained apex beat is usually associated with a reduced ejection fraction.[63]

In patients with volume overload and/or sympathetic stimulation, the left ventricular impulse is *hyperkinetic,* that is, it is brisker and larger than normal. It is hypokinetic in patients with reduced stroke volume, especially in acute myocardial infarction or dilated cardiomyopathy.

OTHER CONDITIONS.

Left ventricular aneurysm produces a larger-than-normal area of pulsation of the left ventricular apex. Alternatively, it may produce a sustained systolic bulge several centimeters superior to the left ventricular impulse, sometimes termed an *ectopic impulse*.

A double systolic outward thrust of the left ventricle is characteristic of patients with hypertrophic obstructive cardiomyopathy, who may also often exhibit a typical presystolic cardiac expansion, thus resulting in three separate outward movements of the chest wall during each cardiac cycle.[64]

Constrictive pericarditis is characterized by systolic retraction of the chest, particularly of the ribs in the left axilla (Broadbent sign). This inward movement results from interference with the descent of the base of the heart and the compensatory exaggerated motion of the free wall of the left ventricle during ventricular ejection.[64]

DIASTOLIC MOTION.

The outward motion of the apex characteristic of rapid left ventricular diastolic filling is most readily palpated with the patient in the left lateral decubitus position and in full exhalation. The outward motion is accentuated when the inflow of blood into the left ventricle is accelerated. This occurs in mitral regurgitation, when the volume of the left ventricle is increased or its function is impaired.[56] This motion is the mechanical equivalent of and occurs simultaneously with a third heart sound (S_3). Prominent early diastolic left ventricular filling in constrictive pericarditis may be palpable.

PRESYSTOLIC EXPANSION.

When the atrial contribution to ventricular filling is augmented, as occurs in patients with reduced left ventricular compliance associated with concentric left ventricular hypertrophy, myocardial ischemia, and myocardial fibrosis, a presystolic pulsation (usually accompanying a fourth heart sound [S_4]) is palpable, resulting in a double outward movement of the left ventricular impulse. This presystolic expansion is most readily discernible during exhalation, when the patient is in the left lateral decubitus position, and it can be confirmed by detecting the motion of the stethoscope placed over the left ventricular impulse or by observing the motion of an X mark over the left ventricular impulse. Presystolic expansion of the left ventricle can be enhanced by sustained handgrip and is usually associated with marked elevation of left ventricular end-diastolic (rather than early diastolic) pressure. In patients with ischemic heart disease, presystolic pulsation is usually associated with a reduction in left ventricular compliance.[63] Presystolic expansion of the right ventricle occurs in right ventricular hypertrophy and pulmonary hypertension and may be appreciated by subxiphoid palpation of the right ventricle during inspiration.

RIGHT VENTRICLE

Except in the first few months of life, neither this chamber, nor its motion, is palpable. A palpable anterior systolic movement (replacing systolic retraction) in the left parasternal region, best felt by the proximal palm or fingertips, and with the patient supine, usually represents *right ventricular enlargement* or hypertrophy. [65] In the absence of associated left ventricular enlargement, the right ventricular impulse is accompanied by reciprocal systolic retraction of the apex. In patients with pulmonary emphysema, even an enlarged right ventricle is not readily palpable at the left sternal edge but is better appreciated in the subxiphoid region. Exaggerated motion of the entire parasternal area (i.e., a hyperdynamic impulse with normal contour) usually reflects increased right ventricular contractility due to augmented stroke volume, as occurs in patients with atrial septal defect or tricuspid regurgitation. A sustained left parasternal outward thrust reflects right ventricular hypertrophy due to pressure overload, as occurs in pulmonary hypertension or pulmonic stenosis. With marked right ventricular enlargement, this chamber occupies the apex because the left ventricle is displaced posteriorly.

PULMONARY ARTERY

Pulmonary hypertension and/or increased pulmonary blood flow frequently produce a prominent systolic pulsation of the pulmonary trunk in the second intercostal space just to the left of the sternum. This pulsation is often associated with a prominent left parasternal impulse, reflecting right ventricular enlargement, or with hypertrophy and a palpable shock synchronous with the second heart sound, reflecting forceful closure of the pulmonic valve.

LEFT ATRIUM.

An enlarged left atrium or a large posterior left ventricular aneurysm can make right ventricular pulsations more prominent by displacing the right ventricle anteriorly against the left parasternal area; and in severe mitral regurgitation an expanding left atrium may be responsible for marked left parasternal movement, even in the absence of right ventricular hypertrophy. The systolic bulging of the left atrium, which is transmitted through the right ventricle, commences and terminates *after* the left ventricular thrust. Movement imparted by the systolic expansion of the left atrium can be appreciated by placing the index finger of one hand at the left ventricular apex and the index finger of the other in the left parasternal region in the third intercostal space; the movement of the latter finger begins and ends slightly later than that of the former.

AORTA.

Enlargement or aneurysm of the ascending aorta or aortic arch may cause visible or palpable systolic pulsations of the right or left sternoclavicular joint and may also cause a systolic impulse in the suprasternal notch or the first or second right intercostal space.[1]

THRILLS

The flat of the hand or the fingertips usually best appreciate thrills, which are vibratory sensations that are palpable manifestations of loud, harsh murmurs *having low- to medium-frequency components.*[66] Because the vibrations must be quite intense before they are felt, far more information can be obtained from the auscultatory than from the palpatory features of heart murmurs. High-pitched murmurs such as those produced by valvular regurgitation, even when loud, are not usually associated with thrills.

PERCUSSION

Palpation is far more helpful than is percussion in determining cardiac size. However, in the absence of an apical beat, as in patients with pericardial effusion, or in some patients with dilated cardiomyopathy, heart failure, and marked displacement of a hypokinetic apical beat, the left border of the heart can be approximately outlined by means of percussion. Also, percussion of dullness in the right lower parasternal area may, in some instances, aid in the detection of a greatly enlarged right atrium. Percussion aids materially in determining visceral situs, that is, in ascertaining the side on which the heart, stomach, and liver are located. When the heart is in the right side of the chest but the abdominal viscera are located normally, congenital heart disease is usually present. When both the heart and abdominal viscera are in the opposite side of the chest (situs inversus), congenital heart disease is uncommon.

CARDIAC AUSCULTATION

Principles and Technique

The modern binaural stethoscope is a well-crafted, airtight instrument with earpieces selected for comfort, with metal tubing joined to single flexible 12-inch-long, thick-walled rubber tubing (internal diameter of 1/8 inch), and with dual chest pieces--diaphragm for high frequencies, bell for low or lower frequencies--designed so that the examiner can readily switch from one chest piece to the other.[67] [68] [69] [70] [71] When the bell is applied with just enough pressure to form a skin seal, low frequencies are accentuated; when the bell is pressed firmly, the stretched skin becomes a diaphragm, damping low frequencies. Variable pressure with the bell provides a range of frequencies from low to medium.

Cardiac auscultation is best accomplished in a quiet room with the patient comfortable and the chest fully exposed. Palpation and percussion should precede auscultation to establish visceral and cardiac situs, so that auscultation can be carried out with confidence in the topographical anatomy of the heart. Terms such as "mitral area," "tricuspid area," "pulmonary area," and "aortic area" should be avoided because they assume situs solitus without ventricular inversion and with normally related great arteries. The topographical areas for auscultation (Fig. 4-10) , irrespective of cardiac

situs, are best designated by descriptive terms--cardiac apex, left and right sternal borders interspace by interspace, and subxiphoid. For patients in situs solitus with a left-sided thoracic heart, auscultation should begin at the cardiac apex (best identified in the left lateral decubitus) and contiguous lower left sternal edge (inflow), proceeding interspace by interspace up the left sternal border to the left base and then to the right base (outflow). In addition, the stethoscope should be applied regularly to the axillae, the back, the anterior chest on the opposite side, and above the clavicles. In patients with increased anteroposterior chest dimensions (emphysema), auscultation is often best achieved by applying the stethoscope in the epigastrium (subxiphoid).

In auscultation, benefits are derived not only from knowledge of the cardiac situs but also from identification of palpable and visible movements of the ventricles. During auscultation, the examiner is generally on the patient's right; three positions are routinely employed: left lateral decubitus (assuming left thoracic heart), supine, and sitting. Auscultation should begin by applying the stethoscope to the cardiac apex with the patient in the left lateral decubitus position (Fig. 4-11) . If tachycardia makes identification

Figure 4-10 Maximal intensity and radiation of six isolated systolic murmurs. HCM=hypertrophic cardiomyopathy; MR=mitral regurgitation; Pulm=pulmonary; VSD=ventricular septal defect. *(From Barlow JB: Perspectives on the Mitral Valve. Philadelphia, FA Davis, 1987, p 140.)*

of S_1 difficult, timing can be established, with few exceptions, by simultaneous palpation of the carotid artery with the thumb of the free left hand. Once the S_1 is identified, analysis then proceeds by systematic, methodical, sequential attention to early, mid, and late systole, S_2 , then early, mid, and late diastole (presystole), and returning to S_1 . When auscultation at the apex has been completed, the patient is turned into the supine position. Each topographical area--lower to upper left sternal edge interspace by interspace and then the right base--is interrogated using the same systematic sequence of analysis (Fig. 4-12) .

Assessment of pitch or frequency ranging from low to moderately high can be achieved by variable pressure of the stethoscopic bell, whereas for high frequencies the diaphragm should be employed. It is practical to begin by using the stethoscopic bell with varying pressure at the apex and lower left sternal edge, changing to the diaphragm when the base is reached. Low frequencies are best heard by applying the bell just lightly enough to achieve a skin seal. High-frequency events are best elicited with firm pressure of the diaphragm, often with the patient sitting, leaning forward in full held exhalation.

Figure 4-11 The bell of the stethoscope is applied to the cardiac apex while the patient lies in a left lateral decubitus position. The thumb of the examiner's free left hand palpates the carotid artery (arrow) for timing purposes.

Figure 4-12 The soft, high-frequency early diastolic murmur of aortic regurgitation or pulmonary hypertensive regurgitation is best elicited by applying the diaphragm of the stethoscope very firmly to the mid-left sternal edge (arrow) as the patient sits and leans forward with breath held in full exhalation.

The Heart Sounds

Heart sounds are relatively brief, discrete auditory vibrations that can be characterized by intensity (loudness), frequency (pitch), and quality (timbre). S_1 identifies the onset of ventricular systole, and S_2 identifies the onset of diastole. These two auscultatory events establish a framework within which other heart sounds and murmurs can be placed and timed.[1] [4]

The basic heart sounds are the S_1 , S_2 , S_3 , and S_4 (Fig. 4-13 *A*). Each of these events can be normal or abnormal. Other heart sounds are, with few exceptions, abnormal, either intrinsically so or iatrogenic (e.g., prosthetic valve sounds, pacemaker sounds). A heart sound should first be characterized by a simple descriptive term that identifies where in the cardiac cycle the sound occurs. Accordingly, heart sounds within the framework established by S_1 and S_2 are designated as "early systolic, midsystolic, late systolic," and "early diastolic, mid-diastolic, late diastolic (presystolic)" (see Fig. 4-13) . [2] The next step is to draw conclusions based on what a sound so identified represents.

For example, an *early systolic* sound might be an ejection sound (aortic or pulmonary) or an aortic prosthetic sound. Mid- and late systolic sounds are typified by the click(s) of mitral valve prolapse but occasionally are "remnants" of pericardial rubs. *Early diastolic* sounds are represented by opening snaps (usually mitral), an early S_3 (constrictive pericarditis, less commonly mitral regurgitation), the opening of a mechanical inflow prosthesis, or the abrupt seating of a pedunculated mobile atrial myxoma ("tumor plop"). *Mid-diastolic* sounds are generally S_3 or summation sounds (synchronous occurrence of S_3 and S_4). *Late diastolic* or *presystolic* sounds are almost always S_4 sounds, rarely pacemaker sounds.

First Heart Sound

S_1 consists of two components (see Fig. 4-13 *C*). The initial component is most prominent at the cardiac apex when the apex is occupied by the left ventricle.[72] The second component, if present, is normally confined to the lower left sternal edge, is less commonly heard at the apex, and is seldom heard at the base. The first major component is associated with closure of the mitral valve and coincides with abrupt arrest of leaflet motion when the cusps--especially the larger and more mobile anterior mitral cusp--reach their fully closed positions. The origin of the second component of S_1

has been debated but is generally assigned to closure of the tricuspid valve based on an analogous line of reasoning.[73] Opening of the semilunar valves with ejection of blood into the aortic root or pulmonary trunk usually produces no audible sound in the normal heart, although phonocardiograms sometimes record a low-amplitude sound following the mitral and tricuspid components and coinciding with the maximal opening excursion of the aortic cusps.[1] In complete right bundle branch block, S_1 is widely split as a result of delay of the tricuspid component.[74] In complete left bundle branch block, S_1 is single as a result of delay of the mitral component.[75]

When S_1 is split, its first component is normally louder. The softer second component is confined to the lower left sternal edge but may also be heard at the apex. Only the louder first component is heard at the base. The intensity of the S_1 , particularly its first major audible component, depends chiefly on the position of the bellies of the mitral leaflets, especially the anterior leaflet, at the time the left ventricle begins to contract and less on the rate of left ventricular contraction.[76] S_1 is therefore loudest when the onset of left ventricular systole finds the mitral leaflets maximally recessed into the left ventricular cavity, as in the presence of a rapid heart rate, a short PR interval[77] (Fig. 4-14) , short cycle lengths in atrial fibrillation, or mitral stenosis with a mobile anterior leaflet. When this mobility is lost the intensity of S_1 decreases.

Figure 4-13 *A,* The basic heart sounds consist of the first heart sound (S_1), the second heart sound (S_2), the third heart sound (S_3), and the fourth heart sound (S_4). *B,* Heart sounds within the auscultatory framework established by S_1 and S_2 . The additional heart sounds are designated descriptively as early systolic (ES), midsystolic (MS), late systolic (LS), early diastolic (ED), mid-diastolic (MD), and late diastolic (LD) or presystolic. *C,* Upper tracing illustrates a low-frequency S_4 , and the lower tracing illustrates a split S_1 , the two components of which are of the same quality.

Figure 4-14 *Top,* Phonocardiogram and electrocardiogram (lead 2) from a 12-year-old girl with congenital complete heart block. The first heart sound (S_1) varies from soft (long PR interval) to loud (short PR interval). There is a grade 2/6 vibratory midsystolic murmur (SM). A soft fourth heart sound (arrow) follows the second P wave. *Bottom,* Phonocardiogram and electrocardiogram from a 15-year-old boy with congenital complete heart block. Arrows point to independent P waves. The S_1 varies from loud to soft depending on the PR interval. The short diastolic murmurs (DM) are especially prominent when atrial contraction (P wave) coincides with and reinforces the rapid filling phase (shortly after the T wave).

Early Systolic Sounds

Aortic or pulmonary ejection sounds are the most common early systolic sounds.[78] [79] "Ejection sound" is preferred to the term ejection "click," with the latter designation best

reserved for the mid- to late systolic clicks of mitral valve prolapse (see Chap. 46) . Ejection sounds coincide with the fully opened position of the relevant semilunar valve, as in congenital aortic valve stenosis (Fig. 4-15 *A*), bicuspid aortic valve in the left side of the heart, or pulmonary valve stenosis in the right side of the heart.[75] [77] Ejection sounds are relatively high frequency events and, depending on intensity, have a pitch similar to that of S_1 . An ejection sound originating in the aortic valve (congenital aortic stenosis or bicuspid aortic valve) or in the pulmonary valve (congenital pulmonary valve stenosis) indicates that the valve is mobile because the ejection sound is caused by abrupt cephalad doming (see Fig. 4-15 *B*).[80] Less certain is the origin of an ejection sound within a dilated arterial trunk distal to a normal semilunar valve (Fig. 4-16 *A*). Origin of the sound is assigned either to opening movement of the leaflets that resonate in the arterial trunk or to the wall of the dilated great artery. Aortic ejection sounds do not vary with respiration.

Pulmonary ejection sounds often selectively and distinctively decrease in intensity during normal inspiration (Fig. 4-17) . Early systolic sounds accompany mechanical prostheses in the aortic location, especially the Starr-Edwards ball-in-cage valve, less so with a tilting disc valve such as the Bjork-Shiley. Early systolic sounds do not occur with bioprosthetic valves (tissue valves) in either the aortic or pulmonary location.

Figure 4-15 *A,* Phonocardiogram over the left ventricular impulse in a patient with mild congenital bicuspid aortic valve stenosis. The aortic ejection sound (E) is louder than the first heart sound (S_1). A_2 =aortic component of the second heart sound. *B,* Left ventriculogram (LV) in another patient with congenital aortic valve stenosis. The cephalad systolic doming of the stenotic valve (arrows) produces the ejection sound.

Figure 4-16 *A,* Tracings from a 32-year-old woman with an ostium secundum atrial septal defect, pulmonary hypertension, and a small right-to-left shunt. In the second left intercostal space (2LICS), the first heart sound is followed by a prominent pulmonary ejection sound (E). The second sound remains split. The pulmonic component (P_2) is very loud and is transmitted to the apex. CAR=carotid pulse. *B,* Phonocardiogram recorded in the left lateral decubitus position over the left ventricular impulse in a patient with pure rheumatic mitral stenosis. The first heart sound (S_1) is loud. The second heart sound (S_2) is followed by an opening snap (OS). There is a mid-diastolic murmur (MDM). The prominent presystolic murmur (PM) goes up to the subsequent loud S_1 .

Figure 4-17 Phonocardiogram from an 11-year-old girl with tetralogy of Fallot and pulmonary atresia. The upper tracing from the second right intercostal space (2RICS) shows an aortic ejection sound (E) that is prominent during exhalation (EXP) but absent during inspiration (INSP). S_1 =first heart sound.

Mid- to Late Systolic Sounds

The most common mid- to late systolic sound(s) are associated with mitral valve prolapse[4] [81] (see Chap. 46) . The term "click" is appropriate because these mid- to late systolic sounds are of relatively high frequency. Mid- to late systolic clicks of mitral valve prolapse coincide with maximal systolic excursion of a prolapsed anterior leaflet (or scallop of the posterior leaflet) into the left atrium and are ascribed to sudden tensing of the redundant leaflet(s) and elongated chordae tendineae. Physical or pharmacological interventions that *reduce* left ventricular volume, such as the Valsalva maneuver, or a change in position from squatting to standing (Fig. 4-18) causes the click(s) to occur earlier in systole.[81] [82] Conversely, physical or pharmacological interventions that *increase* left ventricular volume, such as squatting or sustained hand grip, delay the click(s). Multiple clicks are thought to arise from asynchronous tensing of different portions of redundant mitral leaflets, especially the triscalloped posterior leaflet.

The Second Heart Sound (Table 4-1)

S_2 , like S_1 , has two components. The first component of the second heart sound is designated "aortic" (A_2) and the second "pulmonic" (P_2) (Fig. 4-19) .[83] [84] Each component coincides with the incisura of its great arterial pressure pulse.

Figure 4-18 A midsystolic nonejection sound (C) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to the second heart sound (S_2). Standing decreases venous return; the heart becomes smaller; C moves closer to the first heart sound (S_1) and the mitral regurgitant murmur has an earlier onset. With prompt squatting, venous return increases; the heart becomes larger; C moves toward S_2 and the duration of the murmur shortens. *(From Shaver JA, Leonard JJ, Leon DF: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 13. Copyright 1990, American Heart Association.)*

TABLE 4-1 -- CAUSES OF SPLITTING OF THE SECOND HEART SOUND

NORMAL SPLITTING
Delayed Pulmonic Closure
Delayed electrical activation of the right ventricle
Complete right bundle branch block (proximal type)
Left ventricular paced beats
Left ventricular ectopic beats
Prolonged right ventricular mechanical systole
Acute massive pulmonary embolus
Pulmonary hypertension with right-sided heart failure

Pulmonic stenosis with intact septum (moderate to severe)
Decreased impedance of the pulmonary vascular bed (increased hangout)
Normotensive atrial septal defect
Idiopathic dilatation of the pulmonary artery
Pulmonic stenosis (mild)
Atrial septal defect, postoperative (70%)
Early Aortic Closure
Shortened left ventricular mechanical systole (LVET)
Mitral regurgitation
Ventricular septal defect
REVERSED SPLITTING
Delayed Aortic Closure
Delayed electrical activation of the left ventricle
Complete left bundle branch block (proximal type)
Right ventricular paced beats
Right ventricular ectopic beats
Prolonged left ventricular mechanical systole
Complete left bundle branch block (peripheral type)
Left ventricular outflow tract obstruction
Hypertensive cardiovascular disease
Arteriosclerotic heart disease
Chronic ischemic heart disease
Angina pectoris
Decreased impedance of the systemic vascular bed (increased hangout)
Poststenotic dilatation of the aorta secondary to aortic stenosis or insufficiency
Patent ductus arteriosus
Early Pulmonic Closure
Early electrical activation of the right ventricle
Wolff-Parkinson-White syndrome, type B
LVET=left ventricular ejection time.
Modified from Shaver JA, O'Toole JD: The second heart sound: Newer concepts. Parts 1 and 2. Mod Concepts Cardiovasc Dis 46:7 and 13, 1977.

Inspiratory splitting of S_2 is due chiefly to a delay in P_2 , less to earlier timing of A_2 .[85]

During inspiration, the pulmonary arterial incisura moves away from the descending limb of the right ventricular pressure pulse because of an inspiratory increase in capacitance of the pulmonary vascular bed, delaying P_2 .[86] Exhalation has the opposite effect. The earlier inspiratory timing of A_2 is attributed to a transient reduction in left ventricular volume coupled with unchanged impedance (capacitance) in the systemic vascular bed. Normal respiratory variations in the timing of S_2 are therefore ascribed principally to the variations in impedance characteristics (capacitance) of the pulmonary vascular bed and secondarily to an inspiratory increase in right ventricular volume as originally proposed.[69] [72] When an increase in capacitance of the pulmonary bed is lost because of a rise in pulmonary vascular resistance, inspiratory splitting of S_2 narrows and, if present at all, reflects an increase in right ventricular ejection time and/or earlier timing of A_2 .[4]

The frequency compositions of the aortic and pulmonary components of S_2 are similar, but their normal amplitudes differ appreciably, the aortic component being the louder,

Figure 4-19 *Top,* Normal physiological splitting. During expiration, the aortic (A_2) and pulmonic (P_2) components of the second heart sound are separated by less than 30 milliseconds and are appreciated as a single sound. During inspiration, the splitting interval widens, and A_2 and P_2 are clearly separated into two distinct sounds. *Bottom,* Audible expiratory splitting. In contrast to normal physiological splitting, two distinct sounds are easily heard during expiration. Wide physiological splitting is caused by a delay in P_2 . Reversed splitting is caused by a delay in A_2 , resulting in paradoxical movement; that is, with inspiration P_2 moves toward A_2 , and the splitting interval narrows. Narrow physiological splitting occurs in pulmonary hypertension, and both A_2 and P_2 are heard during expiration at a narrow splitting interval because of the increased intensity and high-frequency composition of P_2 . *(From Shaver JA, Leonard JJ, Leon DF: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 17. Copyright 1990, American Heart Association.)*

reflecting the differences in systemic (aortic) and pulmonary arterial closing pressures. Splitting of S_2 is most readily identified in the second left intercostal space, because the softer P_2 is normally confined to that site, whereas the louder A_2 is heard at the base, sternal edge, and apex.[4] [83]

ABNORMAL SPLITTING OF THE SECOND HEART SOUND.

Three general categories of abnormal splitting are recognized: (1) persistently single, (2) persistently split (fixed or nonfixed), and (3) paradoxically split (reversed). When S_2 remains single throughout the respiratory cycle, one component is absent or the two components are persistently synchronous. The most common cause of a single S_2 is inaudibility of the P_2 in older adults with increased anteroposterior chest dimensions. In

the setting of congenital heart disease, a single S_2 due to absence of the pulmonary component is a feature of pulmonary atresia, severe pulmonary valve stenosis, dysplastic pulmonary valve, or complete transposition of the great arteries (pulmonary component inaudible because of the posterior position of the pulmonary trunk). Conversely, a single S_2 due to inaudibility of the A_2 occurs when the aortic valve is immobile (severe calcific aortic stenosis) or atretic (aortic atresia). A single S_2 due to persistent synchrony of its two components is a feature of Eisenmenger syndrome with nonrestrictive ventricular septal defect, in which the aortic and pulmonary arterial incisurae are virtually identical in timing.[78]

Both components of the S_2 are sometimes inaudible at *all* precordial sites. This is likely to be so in older adults in whom fibrocalcific changes limit mobility of the aortic valve, whereas the pulmonary component is inaudible because of a large anteroposterior chest dimension (see earlier).

A single semilunar valve, as in truncus arteriosus, does not necessarily generate what is judged on auscultation to be a single S_2 . Instead, the S_2 may be perceived as "split" because of asynchronous closure of the unequal cusps of a quadricuspid valve.[78] In systemic or pulmonary hypertension, the duration of a single loud S_2 may be sufficiently prolonged and slurred (reduplicated) to encourage the mistaken impression of splitting.

Persistent Splitting of S_2 .

This term applies when the two components remain audible (or recordable) during both inspiration and exhalation (see Fig. 4-19) . Persistent splitting may be due to a delay in P_2 , as in simple complete right bundle branch block,[72] or to early timing of the A_2 , as occasionally occurs in mitral regurgitation. [87] Normal directional changes in the interval of the split (greater with inspiration, lesser with exhalation) in the presence of persistent audibility of both components defines the split as *persistent* but not *fixed.*

Fixed Splitting of the S_2 .

This term applies when the interval between the A_2 and P_2 is not only wide and persistent but also remains unchanged during the respiratory cycle.[72] Fixed splitting is an auscultatory hallmark of uncomplicated ostium secundum atrial septal defect (Fig. 4-20 (Figure Not Available) ; see Chaps. 43 and 44) . A_2 and P_2 are widely separated during exhalation and exhibit little or no change in the degree of splitting during inspiration or with the Valsalva maneuver. The *wide* splitting is caused by a delay in the P_2 because a marked increase in pulmonary vascular capacitance prolongs the interval between the descending limbs of the pulmonary arterial and right ventricular pressure pulses ("hangout"), and therefore delays the pulmonary incisura and the P_2 . The capacitance (impedance) of the pulmonary bed is appreciably increased, and the right ventricular stroke volume is not influenced by respiration, so there is little or no additional increase during inspiration and little or no inspiratory delay in the P_2 . Phasic changes in systemic venous return during respiration in atrial septal defect are

associated with reciprocal changes in the volume of the left-to-right shunt, minimizing respiratory variations in right ventricular filling. The net effect is the characteristic wide, fixed splitting of the two components of the S_2 .[78]

Paradoxical (Reversed) Splitting of S_2 .

This term refers to a reversed sequence of semilunar valve closure, the P_2 preceding the A_2 .[72] Common causes of paradoxical splitting

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Figure 4-20 (Figure Not Available) Simultaneous base and apex phonocardiograms recorded with the carotid pulse during quiet respiration in a young woman with a large atrial septal defect. Wide fixed splitting of the second heart sound (S_2) is present, and the pulmonic component (P_2) is easily recorded at the apex. A prominent systolic ejection murmur (SEM) is recorded at the base and is attributable to the large stroke volume across the RV outflow tract. The tricuspid component of S_1 is prominent at the apex. EKG=electrocardiogram. *(From Shaver JA: Innocent murmurs. Hosp Med 14:8-35, 1978. Copyright 1999, QUADRANT HEALTHCOM, INC.)*

are complete left bundle branch block[88] or a right ventricular pacemaker, both of which are associated with initial activation of the right side of the ventricular septum, and delayed activation of the left ventricle owing to transseptal (right-to-left) depolarization.[89] When the S_2 splits paradoxically, its two components separate during *exhalation* and become single (synchronous) during *inspiration* (see Fig. 4-19) . Inspiratory synchrony is achieved as the two components fuse because of a delay in the P_2 , less to earlier timing of the aortic component.

ABNORMAL LOUDNESS (INTENSITY) OF THE TWO COMPONENTS OF S_2 .

Assessment of intensity requires that both components be compared when heard simultaneously at the same site. The relative softness of the normal P_2 is responsible for its localization in the second left intercostal space, whereas the relative loudness of the normal A_2 accounts for its audibility at all precordial sites (see earlier). An increase in intensity of the A_2 occurs with systemic hypertension. The intensity of the A_2 also increases when the aorta is closer to the anterior chest wall, owing to root dilatation or transposition of the great arteries or when an anterior pulmonary trunk is small or absent, as in pulmonary atresia.[78]

A loud P_2 is a feature of pulmonary hypertension, and the loudness is enhanced by dilatation of a hypertensive pulmonary trunk. An accentuated P_2 can be transmitted to the mid or lower left sternal edge and, when very loud, throughout the precordium to the apex and right base. A loud P_2 in the second left interspace may obscure a closely preceding A_2 . In this eventuality, auscultation at other precordial sites often identifies

the transmitted but attenuated P_2 and allows detection of splitting. A moderate increase in loudness of the P_2 sometimes occurs in the absence of pulmonary hypertension when the pulmonary trunk is dilated, as in ostium secundum atrial septal defect or when there is a decrease in anteroposterior chest dimensions (loss of thoracic kyphosis) that places the pulmonary trunk closer to the chest wall.[90] [91]

Early Diastolic Sounds

The opening snap of rheumatic mitral stenosis is the best known early diastolic sound (see Fig. 4-16 *B*). The diagnostic value derived from the pitch, loudness, and timing of the opening snap in the assessment of rheumatic mitral stenosis was established by Wood in his classic monograph, *An Appreciation of Mitral Stenosis*.[92] An audible opening snap indicates that the mitral valve is mobile, at least its longer anterior leaflet.[93] The snap is generated when superior systolic bowing of the anterior mitral leaflet is rapidly reversed toward the left ventricle in early diastole in response to high left atrial pressure. The mechanism of the opening snap is therefore a corollary to the loud S_1 (see Fig. 4-16 *B*), which is generated by abrupt superior systolic displacement of a mobile anterior mitral leaflet that was recessed into the left ventricle during diastole by high left atrial pressure until the onset of left ventricular isovolumetric contraction (see earlier). The designation "snap" is appropriate because of the relatively high frequency of the sound.

The timing of the opening snap relative to the A_2 has important physiological meaning.[4] A short A_2 /opening snap interval generally reflects the high left atrial pressure of *severe* mitral stenosis. However, in older subjects with systolic hypertension, mitral stenosis of appreciable severity can occur without a short A_2 /opening snap interval because the elevated left ventricular systolic pressure takes longer to fall below the left atrial pressure. In the presence of atrial fibrillation, the A_2 /opening snap interval varies inversely with cycle length, because (all else being equal) the higher the left atrial pressure (short cycle length), the earlier the stenotic valve opens and vice versa.

Early diastolic sounds are not confined to the opening snap of rheumatic mitral stenosis but include the pericardial "knock" of chronic constrictive pericarditis.[94] [95] The term "knock" has also been applied to an early diastolic sound in pure severe mitral regurgitation with reduced left ventricular compliance. Both the "pericardial knock" and the "knock" of mitral regurgitation are rapid filling sounds that are early and loud because a high-pressure atrium rapidly decompresses across an unobstructed mitral valve into a recipient ventricle whose compliance is impaired.

Early diastolic sounds are sometimes caused by atrial myxomas[96] (see Chap. 49) . The generation of such a sound, called a tumor "plop," requires a mobile myxoma attached to the atrial septum by a long stalk. The "plop" is believed to result from abrupt diastolic seating of the tumor within the right or left AV orifice.[96]

An early diastolic sound can also be generated by the opening movement of a mechanical prosthesis in the mitral position. This opening sound is especially prominent

with a ball-in-cage prosthesis (Starr-Edwards) and less prominent with a tilting disc prosthesis (Bjork-Shiley).

Mid-Diastolic and Late Diastolic (Presystolic) Sounds

Mid-diastolic sounds are, for all practical purposes, either normal or abnormal S_3 sounds, and most, if not all, late diastolic or presystolic sounds are S_4 sounds (Fig. 4-21) . Each sound coincides with its relevant diastolic filling phase.[97] In sinus rhythm, the ventricles receive blood during two filling phases. The first phase occurs when ventricular pressure drops sufficiently to allow the AV valve to open; blood then flows from atrium into ventricle. This flow coincides with the *y* descent of the atrial pressure pulse and is designated the "rapid filling phase," accounting for about 80 percent of normal ventricular filling. The rapid filling phase is not a passive event in which the recipient ventricle merely expands in response to augmented inflow volume. Rather, ventricular relaxation is an active, complex, energy-dependent process (see Chaps. 14 and 15) .

Figure 4-21 Atrial pressure pulse showing the a wave and *x* descent and the v wave and *y* descent. The fourth heart sound (S_4) coincides with the phase of ventricular filling after atrial contraction. The third heart sound (S_3) coincides with the *y* descent (the phase of rapid ventricular filling). S_1 =first heart sound; S_2 =second heart sound.

S_3 is generated during the rapid filling phase (see Fig. 4-21) .[98] The second filling phase--diastasis--is variable in duration, usually accounting for less than 5 percent of ventricular filling. The third phase of diastolic filling is in response to atrial contraction, which accounts for about 15 percent of normal ventricular filling. S_4 is generated during the atrial filling phase (see Fig. 4-21) . Both S_3 and S_4 occur *within* the recipient ventricle as that chamber receives blood. The addition of either an S_3 or an S_4 to the cardiac cycle produces a *triple* rhythm. If both S_3 and S_4 are present, a *quadruple* rhythm is produced. When diastole is short or the PR interval is long, S_3 and S_4 occur simultaneously to form a summation sound. [4]

Children and young adults often have a normal (physiological) S_3 but do not have a normal S_4 .[99] A normal S_3 sometimes persists beyond age 40 years, especially in women.[100] After that age, however, especially in men, S_3 is likely to be abnormal.[101] An S_4 is sometimes heard in healthy older adults without clinical evidence of heart disease, particularly after exercise.[102] Such observations have led to the conclusion, still debated, that such an S_4 may be normal in the elderly.

Because an S_4 requires active atrial contribution to ventricular filling, the sound disappears when coordinated atrial contraction ceases, as in atrial fibrillation. When the atria and ventricles contract independently as in complete heart block (see Fig. 4-14) , an S_4 or summation sound occurs randomly in diastole because the relationship between the P wave and the QRS of the electrocardiogram is random. S3 and S4 are events caused by rapid ventricular filling, so obstruction of an AV valve, by impeding ventricular inflow, removes one of the prime preconditions for the generation of these filling sounds. Accordingly, the presence of an S3 or S4 implies an unobstructed (or relatively unobstructed) AV orifice on the side of the heart in which the sound originates. An S3 or S4 originating from the right ventricle often responds selectively and distinctively to respiration, becoming more prominent during inspiration.[4] The inspiratory increase in right atrial flow is converted into an inspiratory augmentation of both mid-diastolic and presystolic filling.

S_3 and S_4 , either normal or abnormal, are relatively low-frequency events that vary considerably in intensity (loudness), that originate in either the left or right ventricle, and that are best elicited when the bell of the stethoscope is applied with just enough pressure to provide a skin seal. An S_3 or S_4 originating from the left ventricle should be sought over the left ventricular impulse identified with the patient in the left lateral decubitus position. An S_3 or S_4 originating from the right ventricle should be sought over the right ventricular impulse (lower left sternal edge, occasionally subxiphoid) with the patient supine. An understanding of these simple principles sets the stage for bedside detection. The same principles can be used with advantage to distinguish an S_4 preceding a single S_1 from splitting of the two components of the S_1 (see Fig. 4-13 *C*). The two components of S_1 are similar in frequency (pitch) although not in intensity (loudness) but differ in pitch from a preceding S_4 . Selective pressure with the bell of the stethoscope enhances these distinctions.

Audibility of S_3 is improved by isotonic exercise that augments venous return and mid-diastolic AV flow. A few sit-ups usually suffice to produce the desired increase in venous return and acceleration in heart rate that increase the rate and volume of AV flow. Venous return can be increased by simple passive raising of both legs with the patient supine. The heart rate is also transiently increased by vigorous coughing. Left ventricular S_4 , especially in patients with ischemic heart disease, can be induced or augmented when resistance to left ventricular discharge is increased by sustained hand-grip (isometric exercise, see later).

In the presence of sinus tachycardia, atrial contraction may coincide with the rapid filling phase, making it impossible to determine whether a given filling sound is an S_3 , an S_4 , or a summation sound. Carotid sinus massage transiently slows the heart rate, so the diastolic sound or sounds can be assigned their proper timing in the cardiac cycle.[4]

CAUSES OF S_3 AND S_4 .

The normal S_3 is believed to be caused by sudden limitation of longitudinal expansion of the left ventricular wall during brisk early diastolic filling.[103] [104] [105] [106] [107] The majority of *abnormal* S_3 sounds are generated by altered physical properties of the recipient ventricle and/or an increase in the rate and volume of AV flow during the rapid filling phase of the ventricle.[108] An abnormal S_4 occurs when augmented atrial contraction generates presystolic ventricular distention (an increase in end-diastolic segment length) so that the recipient chamber can contract with greater force.[109] [110] [111] [112] Typical substrates are the left ventricular hypertrophy of aortic stenosis or systemic hypertension[113] or the right ventricular hypertrophy of pulmonary stenosis or pulmonary hypertension in the right side of the heart.[109] S_4 sounds are also common in ischemic heart disease and are almost universal during angina pectoris or acute myocardial infarction because the atrial "booster pump" is needed to assist the relatively stiff ischemic ventricle.[114]

A variation on the theme is the presystolic pacemaker sound. A pacemaker electrode in the apex of the right ventricle may produce a presystolic sound that is relatively high pitched and clicking and therefore different in pitch from an S_4 . The presystolic pacemaker sound is believed to be extracardiac, resulting from contraction of chest wall muscle after spread of the electrical impulse from the pacemaker site.[115] [116]

HEART MURMURS

A cardiovascular murmur is a series of auditory vibrations that are more prolonged than a sound and are characterized according to timing in the cardiac cycle, intensity (loudness), frequency (pitch), configuration (shape), quality, duration, and direction of radiation. When these features are established, the stage is set for diagnostic conclusions.[2] [117] The principal causes of heart murmurs are listed in Table 4-2 .

Intensity or loudness is graded from 1 to 6, based on the original recommendations of Samuel A. Levine in 1933.[118] A grade 1 murmur is so faint that it is heard only with special effort. A grade 2 murmur is soft but readily detected; a grade 3 murmur is prominent but not loud; a grade 4 murmur is loud (and usually accompanied by a thrill); a grade 5 murmur is very loud. A grade 6 murmur is loud enough to be heard with the stethoscope just removed from contact with the chest wall. Frequency or pitch varies from high to low. The configuration or shape of a murmur is best characterized as crescendo, decrescendo, crescendo-decrescendo (diamond-shaped), plateau (even), or variable

TABLE 4-2 -- PRINCIPAL CAUSES OF HEART MURMURS

A. Organic Systolic Murmurs

1. Midsystolic (ejection)

a. Aortic

(1) Obstructive

(a) Supravalvular--supraaortic stenosis, coarctation of the aorta

(b) Valvular--aortic stenosis and sclerosis

(c) Infravalvular--HOCM

(2) Increased flow, hyperkinetic states, aortic regurgitation, complete heart block

(3) Dilatation of ascending aorta, atheroma, aortitis, aneurysm of aorta

b. Pulmonary

(1) Obstructive

(a) Supravalvular--pulmonary arterial stenosis

(b) Valvular--pulmonic valve stenosis

(c) Infravalvular--infundibular stenosis

(2) Increased flow, hyperkinetic states, left-to-right shunt (e.g., ASD, VSD)

(3) Dilatation of pulmonary artery

2. Pansystolic (regurgitant)

a. Atrioventricular valve regurgitation (MR, TR)

b. Left-to-right shunt to ventricular level

B. Early Diastolic Murmurs

1. Aortic regurgitation

a. Valvular: rheumatic deformity; perforation postendocarditis, posttraumatic, postvalvulotomy

b. Dilatation of valve ring: aorta dissection, annuloectasia, cystic medial necrosis, hypertension

c. Widening of commissures: syphilis

d. Congenital: biscuspid valve, with VSD

2. Pulmonic regurgitation

a. Valvular: postvalvulotomy, endocarditis, rheumatic fever, carcinoid

b. Dilatation of valve ring: pulmonary hypertension; Marfan syndrome

c. Congenital: isolated or associated with tetralogy of Fallot, VSD, pulmonic stenosis

C. Mid-Diastolic Murmurs

1. Mitral stenosis

2. Carey-Coombs murmur (mid-diastolic apical murmur in acute rheumatic fever)

3. Increased flow across nonstenotic mitral valve (e.g., MR, VSD, PDA, high-output states, and complete heart block)

4. Tricuspid stenosis

5. Increased flow across nonstenotic tricuspid valve (e.g., TR, ASD, and anomalous pulmonary venous return)

6. Left and right atrial tumors

D. Continuous Murmurs

1. PDA

2. Coronary arteriovenous fistula

3. Ruptured aneurysm of sinus of Valsalva

4. Aortic septal defect

5. Cervical venous hum

6. Anomalous left coronary artery

7. Proximal coronary artery stenosis

8. Mammary souffle

9. Pulmonary artery branch stenosis

10. Bronchial collateral circulation

11. Small (restrictive) ASD with mitral stenosis

12. Intercostal arteriovenous fistula

A and C, Modified from Oram S (ed): Clinical Heart Disease. London, Heinemann, 1981. D, Modified from Fowler NO (ed): Cardiac Diagnosis and Treatment. Hagerstown, MD, Harper & Row, 1980.

HOCM=hypertrophic obstructive cardiomyopathy; ASD=atrial septal defect; VSD=ventricular septal defect; MR=mitral regurgitation; TR=tricuspid regurgitation; PDA=patent ductus arteriosus.

From O'Rourke RA: Approach to the patient with a heart murmur. In Goldman L, Braunwald E (eds): Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 155-173.

(uneven). The duration of a murmur varies from short to long, with all gradations in between. A loud murmur radiates from its site of maximal intensity, and the direction of radiation is sometimes diagnostically useful.

There are three broad categories of murmurs--systolic, diastolic, and continuous. A *systolic* murmur begins with or after S_1 and ends at or before S_2 on its side of origin. A *diastolic* murmur begins with or after S_2 and ends before the subsequent S_1 . A *continuous* murmur begins in systole and continues without interruption through the S_2 into all or part of diastole. The following classification of murmurs is based on their timing relative to S_1 and S_2 .

Systolic Murmurs

Systolic murmurs are classified according to their time of onset and termination as midsystolic, holosystolic, early systolic, or late systolic (Fig. 4-22) [119] [120] A midsystolic murmur begins after S_1 and ends perceptibly before S_2 . The termination of a systolic murmur must be related to the relevant component of S_2 . Accordingly, midsystolic murmurs originating in the *left* side of the heart end before A_2 ; midsystolic murmurs originating in the *right* side of the heart end before P_2 . A *holosystolic* murmur begins with S_1 , occupies all of systole, and ends with the S_2 on its side of origin. Holosystolic murmurs originating in the *left* side of the heart end with A_2 , and holosystolic murmurs originating in the *right* side of the heart end with P_2 .

The term "regurgitant systolic murmur," originally applied to murmurs that occupied all of systole,[72] has fallen out of use because "regurgitation" can be accompanied by holosystolic, midsystolic, early systolic, or late systolic murmurs.[2] Similarly, the term "ejection systolic murmur," originally applied to midsystolic murmurs, should be discarded, because midsystolic murmurs are not necessarily due to "ejection."[4]

Figure 4-22 Systolic murmurs as illustrated here are descriptively classified according to their time of onset and termination as midsystolic, holosystolic, early systolic, and late systolic. The termination of the murmur must be related to the component of the second heart sound on its side of origin, that is, the aortic component (A_2) for systolic murmurs originating in the left side of the heart and the pulmonic component (P_2) for systolic murmurs originating in the right side of the heart.

MIDSYSTOLIC MURMURS.

Midsystolic murmurs occur in five settings: (1) obstruction to ventricular outflow, (2) dilatation of the aortic root or pulmonary trunk, (3) accelerated systolic flow into the aorta or pulmonary trunk, (4) innocent (normal) midsystolic murmurs, and (5) some forms of mitral regurgitation. The physiological mechanism of *outflow* midsystolic murmurs reflects the pattern of phasic flow across the left or right ventricular outflow tract as originally described by Leatham (Fig. 4-23) .[72] Isovolumetric contraction generates S_1 . Ventricular pressure rises, the semilunar valve opens, flow commences, and the murmur begins. As flow proceeds, the murmur increases in crescendo; as flow decreases, the murmur decreases in decrescendo. The murmur ends before ventricular pressure drops below the pressure in the central great artery, at which time the aortic and pulmonary valves close, generating A_2 and P_2 .

Aortic valve stenosis (see Chap. 46) is associated with a midsystolic murmur, which

may have an early systolic peak and a short duration, a relatively late peak and a prolonged duration, or all gradations in between. Whether long or short, however, the murmur retains a symmetrical diamond shape beginning after S_1 (or with an aortic ejection sound), rising in crescendo to a systolic peak, and declining in decrescendo to end before A_2 . The high-velocity jet within the aortic root results in radiation of the murmur upward, to the right (second right intercostal space), and into the neck. An important variation occurs in older adults with previously normal trileaflet aortic valves rendered sclerotic or stenotic by fibrocalcific changes. The accompanying murmur in the second right intercostal space is harsh, noisy, and impure, whereas the murmur over the left ventricular impulse is pure and often musical (Fig. 4-24) . These two distinctive midsystolic murmurs--the noisy right basal and the musical apical--were described in 1925 by Gallavardin,[121] and the designation "Gallavardin dissociation" is still used. The impure right basal component of the murmur originates within the aortic root because of turbulence caused by the high-velocity jet. The pure musical component of the murmur heard over the left ventricular impulse originates from periodic high-frequency vibrations of the fibrocalcific aortic cusps. The musical apical midsystolic murmur is sometimes dramatically loud.

The high-frequency apical midsystolic murmur of aortic sclerosis or stenosis should be distinguished from the high-frequency apical murmur of mitral regurgitation, a distinction that may be difficult or impossible, especially if A_2 is

Figure 4-23 Illustration of the physiological mechanism of a midsystolic murmur generated by phasic flow into aortic root or pulmonary trunk. Ventricular (V) and great arterial (GA) pressure pulses are shown with phonocardiogram. The midsystolic murmur begins after the first heart sound (S_1), rises in crescendo to a peak as flow proceeds, then declines in decrescendo as flow diminishes, ending just before the second heart sound (S_2) as ventricular pressure falls below the pressure in the great artery.

soft or absent. However, when premature ventricular contractions are followed by pauses longer than the dominant cycle length, the apical midsystolic murmur of aortic stenosis or sclerosis increases in intensity in the beat after the premature contraction, whereas the intensity of the murmur of mitral regurgitation (whether midsystolic or holosystolic) remains relatively unchanged.[115] The same patterns hold after longer cycle lengths in atrial fibrillation.

The murmur of *pulmonary valve stenosis* (see Chaps. 43 and 44) is prototypical of a midsystolic murmur originating in the *right* side of the heart. [78] The murmur begins after S_1 or with a pulmonary ejection sound, rises in crescendo to a peak, then decreases in a slower decrescendo to end before a delayed or soft P_2 . The length and configuration of the murmur are useful signs of the severity of obstruction.[78] When the ventricular septum is intact (Fig. 4-25 , *left*), as obstruction becomes more severe, the murmur lengthens and envelops A_2 , and P_2 becomes softer. When obstruction to right ventricular outflow is accompanied by a ventricular

Figure 4-24 *A,* Illustration of "Gallavardin dissociation" of the basal and apical murmurs associated with a fibrocalcific trileaflet aortic valve in older adults. The impure, noisy midsystolic murmur at the right base originates within the aortic root because of turbulence caused by the high-velocity jet. The pure, musical midsystolic murmur at the apex results from high-frequency vibrations originating in the fibrocalcific but mobile aortic cusps and radiates selectively into the left ventricular cavity (LV). *B,* Left ventricular intracardiac phonocardiogram of an older adult with calcific aortic stenosis on a previously normal trileaflet valve. The pure, musical midsystolic murmur (SM) is recorded over the apex of the left ventricle (LV). A prominent fourth heart sound (S_4) coincides with presystolic distention of the left ventricle (lower vertical arrow). Upper vertical arrow identifies inaudible low-frequency vibrations preceding S_4. S_1 =first heart sound; S_2 =second heart sound.

Figure 4-25 *Left,* In valvular pulmonic stenosis with intact ventricular septum, right ventricular systolic ejection becomes progressively longer, with increasing obstruction to flow. As a result, the murmur becomes louder and longer, enveloping the aortic component of the second heart sound (A_2). The pulmonic component (P_2) occurs later, and splitting becomes wider but more difficult to hear because A_2 is lost in the murmur and P_2 becomes progressively fainter and lower pitched. As pulmonic diastolic pressure progressively decreases, isometric contraction shortens until the pulmonary valvular ejection sound fuses with the first heart sound (S_1). In severe pulmonic stenosis with concentric hypertrophy and decreasing right ventricular compliance, a fourth heart sound appears. *Right,* In tetralogy of Fallot with increasing obstruction at pulmonic infundibular area, an increasing amount of right ventricular blood is shunted across the silent ventricular septal defect and flow across the obstructed outflow tract decreases. Therefore, with increasing obstruction the murmur becomes shorter, earlier, and fainter. P_2 is absent in severe tetralogy of Fallot. A large aortic root receives almost all cardiac output from both ventricular chambers, and the aorta dilates and is accompanied by a root ejection sound that does not vary with respiration. *(From Shaver JA, Leonard JJ, Leon DF: Examination of the Heart, Part 4, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 45. Copyright 1990, American Heart Association.)*

septal defect (tetralogy of Fallot), the midsystolic murmur becomes shorter with increased severity of obstruction (see Fig. 4-25 , *right*).

Short, soft midsystolic murmurs originate within a dilated aortic root or dilated pulmonary trunk. Midsystolic murmurs are also generated by rapid ejection into a *normal* aortic root or pulmonary trunk, as during pregnancy, fever, thyrotoxicosis, or anemia. The pulmonary midsystolic murmur of ostium secundum atrial septal defect results from *rapid* ejection into a *dilated* pulmonary trunk (see Fig. 4-22) . *Normal* (innocent) systolic murmurs are, except for the systolic mammary souffle, all midsystolic.[78]

The normal vibratory midsystolic murmur (Still murmur) is short, buzzing, pure, and medium in frequency (Fig. 4-26) and is believed to be generated by low-frequency periodic vibrations of normal pulmonary leaflets at their attachments or periodic vibrations of a left ventricular false tendon.[122] [123] A second type of innocent midsystolic murmur occurs in children, adolescents, and young adults and represents an exaggeration of normal ejection vibrations within the pulmonary trunk. This normal

pulmonary midsystolic murmur is relatively impure and is best heard in the second left intercostal space, in contrast to the vibratory

Figure 4-26 Four vibratory midsystolic murmurs (SM) from healthy children. These murmurs, designated "Still murmur," are pure, medium frequency, relatively brief in duration, and maximal along the lower left sternal border (LSB). The last of the four murmurs was from a 5-year-old girl who was febrile. After defervescence, the murmur decreased in loudness and duration.

midsystolic murmur of Still, which is typically heard between the lower left sternal edge and apex. Normal pulmonary midsystolic murmurs are also heard in patients with diminished anteroposterior chest dimensions (e.g., loss of thoracic kyphosis).[90]

The most common form of "innocent" midsystolic murmur in older adults has been designated the "aortic sclerotic" murmur (see earlier). The cause of this functionally benign murmur is fibrous or fibrocalcific thickening of the bases of otherwise normal aortic cusps as they insert into the sinuses of Valsalva.[78] As long as the fibrous or fibrocalcific thickening is confined to the *base* of the leaflets, the free edges remain mobile. No commissural fusion and no obstruction occur. The Gallavardin dissociation phenomenon associated with such an aortic valve was described earlier.

It is not uncommon for *mitral regurgitation* to generate a midsystolic murmur.[87] [124] The clinical setting is usually ischemic heart disease associated with left ventricular regional wall motion abnormalities. The physiological mechanism responsible for the midsystolic murmur of mitral regurgitation in this setting reflects impaired integrity of the muscular component of the mitral apparatus, with early systolic competence of the valve, and midsystolic incompetence, followed by a late systolic decline in regurgitant flow. These midsystolic murmurs are unrelated to "ejection."

HOLOSYSTOLIC MURMURS.

Just as the term "midsystolic" is preferable to "ejection" systolic, the term "holosystolic" is preferable to "regurgitant" because holosystolic murmurs are not necessarily due to regurgitant flow. A holosystolic murmur begins with S_1 and occupies all of systole up to the S_2 on its side of origin (see Fig. 4-22) .[72] Such murmurs are generated by flow from a vascular bed whose pressure or resistance throughout systole is higher than the pressure or resistance in the vascular bed receiving the flow. Holosystolic murmurs occur in the left side of the heart with mitral regurgitation, in the right side of the

Figure 4-27 Illustration of great arterial (GA), ventricular (VENT), and atrial pressure pulses with phonocardiogram showing the physiological mechanism of a holosystolic murmur in some forms of mitral

regurgitation and in high-pressure tricuspid regurgitation. Ventricular pressure exceeds atrial pressure at the very onset of systole, so regurgitant flow and murmur commence with the first heart sound (S_1). The murmur persists up to or slightly beyond the second heart sound (S_2) because regurgitation persists to the end of systole (ventricular pressure still exceeds atrial pressure). V=atrial v wave.

heart with high-pressure tricuspid regurgitation, between the ventricles through a restrictive ventricular septal defect, and between the great arteries through aortopulmonary connections.

The timing of holosystolic murmurs reflects the physiological and anatomical mechanisms responsible for their genesis. Figure 4-27 illustrates the mechanism of the holosystolic murmur of mitral regurgitation or high-pressure tricuspid regurgitation. Ventricular pressure exceeds atrial pressure at the very onset of systole (isovolumetric contraction), so regurgitant flow begins with the S_1 . The murmur persists up to or slightly beyond the relevant component of the S_2 , provided that ventricular pressure at end systole exceeds atrial pressure and provided that the AV valve remains incompetent.

Direction of radiation of the intraatrial jet of mitral regurgitation determines the chest wall distribution of the murmur.[87] [125] When the direction of the intraatrial jet is forward and medial against the atrial septum near the origin of the aorta, the murmur radiates to the left sternal edge, to the base, and even into the neck (Fig. 4-28) . When the flow generating the murmur of mitral regurgitation is directed posterolaterally within the left atrial cavity, the murmur radiates to the axilla, to the angle of the left scapula, and occasionally to the vertebral column, with bone conduction from the cervical to the lumbar spine.

The *murmur of tricuspid regurgitation* is holosystolic when there is a substantial elevation of right ventricular systolic pressure, as schematically illustrated in Figure 4-27 . A distinctive and diagnostically important feature of the tricuspid murmur is its selective inspiratory increase in loudness--Carvallo sign.[126] The tricuspid murmur is occasionally audible only during inspiration. The increase in intensity occurs because the inspiratory augmentation in right ventricular volume is converted into an increase in stroke volume and in the velocity of regurgitant flow.[127] When the right ventricle fails, this capacity is lost; thus, Carvallo sign vanishes.

The murmur of an uncomplicated restrictive *ventricular septal defect* (see Chap. 43) is holosystolic because left ventricular systolic pressure and systemic resistance exceed right ventricular systolic pressure and pulmonary resistance from the onset to the end of systole. Holosystolic murmurs are perceived as such in patients with large aortopulmonary connections (aortopulmonary window, patent ductus arteriosus) when a rise in pulmonary vascular resistance abolishes the diastolic portion of the continuous murmur, leaving a murmur that is holosystolic or nearly so.[78]

EARLY SYSTOLIC MURMURS.

Murmurs confined to early systole begin with S_1 , diminish in decrescendo, and end well

before S_2 , generally at or before midsystole (see Fig. 4-22) . Certain types of mitral regurgitation, tricuspid regurgitation, or ventricular septal defects are the substrates.

Acute severe mitral regurgitation is accompanied by an early systolic murmur or a holosystolic murmur that is decrescendo, diminishing if not ending before S_2 (Fig. 4-29 *A*).[128] [129] The physiological mechanism responsible for this early systolic decrescendo murmur is acute severe regurgitation into a relatively normal-sized left atrium with limited distensibility. A steep rise in left atrial v wave approaches the left ventricular pressure at end systole; a late systolic decline in left ventricular pressure favors this tendency (see Fig. 4-29 *B*). The stage is set for regurgitant flow that is maximal in early systole and minimal in late systole.

Figure 4-28 Phonocardiograms illustrating wide radiation of the murmur of mitral regurgitation. *A,* The holosystolic murmur (SM) radiates from the apex to the second left intercostal space (2LICS) to the second right intercostal space (2RICS) and into the neck. S_1 =first heart sound; A_2 =aortic component of the second sound; P_2 =pulmonic component of the second sound; S_3 =third heart sound; MDM=mid-diastolic murmur; CAR=carotid pulse; DN=dicrotic notch. *B,* The murmur of mitral regurgitation radiates to the cervical spine, down the thoracic spine (T4-T5, T10) to the lumbar spine.

Figure 4-29 *A,* Phonocardiogram recorded from the cardiac apex of a patient with acute severe mitral regurgitation due to ruptured chordae tendineae. There is an early systolic decrescendo murmur (SM) diminishing if not ending before the aortic component (A_2) of the second heart sound. P_2 =pulmonic component of the second heart sound; S_1 =first heart sound; S_3 =third heart sound. *B,* Left ventricular (LV) and left atrial (LA) pressure pulses with schematic illustration of the phonocardiogram showing the relationship between the decrescendo configuration of the early systolic murmur and late systolic approximation of the tall left atrial v wave and left ventricular end-systolic pressure. Regurgitant flow diminishes or ceases. The murmur therefore is early systolic and decrescendo, paralleling the hemodynamic pattern of regurgitation.

The systolic murmur parallels this pattern, declining or vanishing before S_2 .

An early systolic murmur is a feature of tricuspid regurgitation with *normal* right ventricular systolic pressure.[130] An example is tricuspid regurgitation caused by infective endocarditis in drug abusers. The mechanisms responsible for the timing and configuration of the early systolic murmur of low-pressure tricuspid regurgitation are analogous to those just described for mitral regurgitation. The crest of the right atrial v wave reaches the level of normal right ventricular pressure in latter systole; the regurgitation and murmur are therefore chiefly, if not exclusively, *early* systolic. These murmurs are of medium frequency because normal right ventricular systolic pressure generates comparatively low-velocity regurgitant flow in contrast to elevated right ventricular systolic pressure that generates a high-frequency holosystolic murmur (see

earlier).

Early systolic murmurs also occur through ventricular septal defects, but under two widely divergent anatomical and physiological circumstances. A soft, pure, high-frequency, early systolic murmur localized to the mid- or lower left sternal edge is typical of a very small ventricular septal defect in which the shunt is confined to early systole.[78] A murmur of similar timing and configuration occurs through a nonrestrictive ventricular septal defect when an elevation in pulmonary vascular resistance decreases or abolishes late systolic shunting.

LATE SYSTOLIC MURMURS.

The term "late systolic" applies when a murmur begins in mid- to late systole and proceeds up to the S_2 (see Fig. 4-22) . The late systolic murmur of *mitral valve prolapse* is prototypical (see Figs. 4-18 and 4-30) .[131] [131A] One or more mid- to late systolic clicks often introduce the murmur. The responses of the late systolic murmur and clicks to postural maneuvers (see earlier discussion) are illustrated in Figure 4-18 . In response to a *diminution* in left ventricular volume, best achieved by prompt standing after squatting but also achieved by the Valsalva maneuver, the late systolic murmur becomes longer although softer.[82] In response to an *increase* in left ventricular volume associated with squatting or with sustained handgrip, the late systolic murmur becomes shorter but louder.[82] Pharmacological interventions that variably alter left ventricular volume, especially amyl nitrite (see Fig. 4-30) , produce analogous effects but are less practical at the bedside.

The late systolic murmur of mitral valve prolapse is occasionally replaced by an intermittent, striking, and sometimes disconcerting systolic whoop or honk, either spontaneously or in response to physical maneuvers. The whoop is of high frequency, musical, widely transmitted, and occasionally loud enough to be disturbing to the patient.[132] The musical whoop is thought to arise from mitral leaflets and chordae tendineae set into high-frequency periodic vibration.

SYSTOLIC ARTERIAL MURMURS.

Systolic murmurs can originate in anatomically normal arteries in the presence of normal or increased flow or in abnormal arteries because of tortuosity or luminal narrowing. Detection of systolic arterial murmurs requires auscultation at nonprecordial sites. Timing with S_1 and S_2 is imprecise because the murmurs begin at variable distances from the heart. Nevertheless, the arterial murmurs dealt with here are essentially systolic and tend to have a crescendo-decrescendo configuration that reflects the rise and fall of pulsatile arterial flow.[4]

The "supraclavicular systolic murmur," often heard in children and adolescents, is believed to originate at the aortic origins of normal major brachiocephalic arteries. The configuration of these murmurs is crescendo-decrescendo, the onset is abrupt, the duration is brief, and the intensity at times is surprisingly loud with radiation below the clavicles. Normal supraclavicular systolic murmurs decrease or vanish in response to

hyperextension of the shoulders, which is achieved by bringing the elbows back until the shoulder girdle muscles are drawn taut.

In older adults, the most common cause of a systolic arterial murmur is atherosclerotic narrowing of a carotid, subclavian, or iliofemoral artery. A variation on this theme is the "compression artifact" that can be induced in the femoral artery in the presence of free aortic regurgitation. When the femoral artery is moderately compressed by the examiner's stethoscopic bell, a systolic arterial murmur is generated. Further compression causes the systolic murmur to continue into diastole, a sign described in 1861 by Duroziez.[78] The eponym is still in use.

A systolic "mammary souffle" is sometimes heard over the breasts because of increased flow through normal arteries during late pregnancy or more especially in the postpartum period in lactating women.[78] [133] The murmur begins well after S_1 because of the interval between left ventricular ejection and arrival of flow at the artery of origin.

A systolic arterial murmur is present in the interscapular region over the site of coarctation of the aortic isthmus.[78] Transient systolic arterial murmurs originating in the pulmonary artery and its branches are occasionally heard in normal neonates because the angulation and disparity in size between the pulmonary trunk and its branches set the stage for turbulent systolic flow. These normal or innocent pulmonary arterial systolic murmurs disappear with maturation of the pulmonary bed, generally within the first few weeks or months of life.[78] [134] Similar if not identical pulmonary arterial systolic murmurs

Figure 4-30 Phonocardiograms illustrating the response of the systolic clicks (C) and late systolic murmur (SM) of mitral valve prolapse to amyl nitrite inhalation. At 20 to 30 seconds, the clicks become earlier and the systolic murmur becomes longer but softer. At 50 seconds, the murmur is holosystolic and louder. M_1 =mitral component of the first heart sound; T_1 =tricuspid component of the first heart sound; A_2 =aortic component of the second heart sound; P_2 =pulmonary component of the second sound.

are generated at sites of congenital stenosis of the pulmonary artery and its branches. Rarely, a pulmonary arterial systolic murmur is caused by luminal narrowing after a pulmonary embolus.[109]

Diastolic Murmurs

Diastolic murmurs are classified according to their time of *onset* as early diastolic, mid-diastolic, or late diastolic (presystolic) (Fig. 4-31) . An *early* diastolic murmur begins with A_2 or P_2 , depending on its side of origin. A mid-diastolic murmur begins at a clear

interval *after* S_2 . A late diastolic or presystolic murmur begins immediately before S_1 .

EARLY DIASTOLIC MURMURS.

An early diastolic murmur originating in the left side of the heart occurs in *aortic regurgitation* (see Chap. 46) . This murmur is heard best with the diaphragm of the stethoscope, with the patient leaning forward and during a held, deep, exhalation (see Fig. 4-12) . The murmur begins with the aortic component of S_2 (Fig. 4-32 *A*), that is, as soon as left ventricular pressure falls below the aortic incisura. The configuration of the murmur tends to reflect the volume and rate of regurgitant flow. In chronic aortic regurgitation of moderate severity, the aortic diastolic pressure consistently and appreciably exceeds left ventricular diastolic pressure, so the decrescendo is subtle and the murmur is well heard throughout diastole. In chronic *severe* aortic regurgitation, the decrescendo is more obvious, paralleling the dramatic decline in aortic root diastolic pressure. Selective radiation of the murmur of aortic regurgitation to the *right* sternal edge implies aortic root dilatation, as in Marfan syndrome. When an inverted cusp is set into high-frequency periodic vibration by aortic regurgitation, the accompanying murmur is musical, early diastolic, and decrescendo (see Fig. 4-32 *B*).

The diastolic murmur of *acute severe* aortic regurgitation differs importantly from the murmur of chronic severe aortic regurgitation as just described[135] (Fig. 4-33) . When regurgitant flow is both sudden *and* severe (as may occur in

Figure 4-31 Diastolic murmurs are descriptively classified according to their time of onset as early diastolic, mid-diastolic, or late diastolic (presystolic). Diastolic murmurs originate in either the left or the right side of the heart.

infective endocarditis or aortic dissection), the diastolic murmur is relatively short because the aortic diastolic pressure rapidly equilibrates with the steeply rising diastolic pressure in the unprepared, nondilated left ventricle. The pitch of the murmur is likely to be medium rather than high because the velocity of regurgitant flow is less rapid than in chronic severe aortic regurgitation. This short, medium-frequency diastolic murmur of sudden severe aortic regurgitation may be quite soft (grade 2). These auscultatory features are in contrast to the long, pure, high-frequency,

Figure 4-32 *A,* Phonocardiogram recorded from the mid-left sternal edge of a patient with chronic pure severe aortic regurgitation. An early diastolic murmur (EDM) proceeds immediately from the aortic component (A_2) of the second heart sound. The murmur has an early crescendo followed by a late long decrescendo. There is a prominent midsystolic flow murmur (SM) across an unobstructed aortic valve. *B,* Phonocardiogram in the third left intercostal space (3LICS) records a high-frequency, musical, early diastolic decrescendo murmur (EDM) caused by eversion of an aortic cusp. S_1 =first heart sound; SM=midsystolic murmur; A_2 =aortic component of the second sound.

Figure 4-33 Contrast between the auscultatory findings in chronic and acute aortic regurgitation. In chronic aortic regurgitation, a prominent systolic ejection murmur resulting from the large forward stroke volume is heard at the base and the apex and ends well before the second heart sound (S_2). The aortic diastolic regurgitant murmur begins with S_2 and continues in a decrescendo fashion, terminating before the first heart sound (S_1). At the apex, the early diastolic component of Austin Flint murmur (AF) is introduced by a prominent third heart sound (S_3). A presystolic component of the AF is also heard. In acute aortic regurgitation there is a significant decrease in the intensity of the systolic ejection murmur compared with that of chronic aortic regurgitation because of the decreased forward stroke volume. The S_1 is markedly decreased in intensity because of preclosure of the mitral valve, and at the apex the presystolic component of the AF murmur is absent. The early diastolic murmur at the base ends well before S_1 because of equilibration of the left ventricle and aortic end-diastolic pressures. Significant tachycardia is usually present. *(From Shaver JA: Diastolic murmurs. Heart Dis Stroke 2:100, 1994.)*

blowing and often loud (grade 4) early diastolic murmur of chronic severe aortic regurgitation (see Figs. 4-32 and 4-33) .

The *Graham Steell* murmur of pulmonary hypertensive pulmonary regurgitation begins with a loud P_2 because the elevated pressure exerted on the incompetent pulmonary valve begins at the moment that right ventricular pressure drops below the pulmonary arterial incisura. The high diastolic pressure generates high-velocity regurgitant flow and results in a high-frequency blowing murmur that may last throughout diastole. Because of the persistent and appreciable difference between pulmonary arterial and right ventricular diastolic pressures, the amplitude of the murmur is usually relatively uniform throughout most, if not all, of diastole.

MID-DIASTOLIC MURMURS.

A mid-diastolic murmur begins at a clear interval after S_2 (see Figs. 4-31 and 4-34) . The majority of mid-diastolic murmurs originate across mitral or tricuspid valves during the rapid filling phase of the cardiac cycle (AV valve obstruction or abnormal patterns of AV flow) or across an incompetent pulmonary valve in the absence of pulmonary hypertension.

The mid-diastolic murmur of rheumatic mitral stenosis is a prime example.[136] [137] The murmur characteristically follows the mitral opening snap (see Fig. 4-16 *B*). Because the murmur originates within the left ventricular cavity, transmission to the chest wall is maximal over the left ventricular impulse. Care must be taken to place the bell of the stethoscope lightly against the skin precisely over the left ventricular impulse with the patient turned into the left lateral decubitus position (see Fig. 4-11) . Soft mid-diastolic murmurs are reinforced when the heart rate and mitral valve flow are transiently increased by vigorous voluntary coughs or a few sit-ups. In atrial fibrillation, the *duration* of the mid-diastolic murmur is a useful sign of the degree of obstruction at the mitral

orifice. A murmur that lasts up to S_1 even after long cycle lengths indicates that the stenosis is severe enough to generate a persistent gradient even at the end of long diastoles.

The mid-diastolic murmur of *tricuspid* stenosis occurs in the presence of atrial fibrillation. The tricuspid mid-diastolic murmur differs from the *mitral* mid-diastolic murmur in two important respects: (1) the loudness of the tricuspid murmur increases with inspiration, and (2) the tricuspid murmur is confined to a relatively localized area along the left lower sternal edge. The inspiratory increase in loudness occurs because inspiration is accompanied by an augmentation in right ventricular volume, by a fall in right ventricular

Figure 4-34 Diastolic filling murmur (rumble) in mitral stenosis. In mild mitral stenosis, the diastolic gradient across the valve is limited to the two phases of rapid ventricular filling in early diastole and presystole. The rumble may occur during either period or both periods. As the stenotic process becomes severe, a large pressure gradient exists across the valve during the entire diastolic filling period, and the rumble persists throughout diastole. As the left atrial pressure becomes greater, the interval between A_2 and the opening snap shortens. In severe mitral stenosis, secondary pulmonary hypertension develops and results in a loud P_2 and the splitting interval usually narrows. ECG=electrocardiogram. *(From Shaver JA, Leonard* ***JJ, Leon DF:*** *Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright 1990, American Heart Association.)*

Figure 4-35 Phonocardiogram recorded over the left ventricular impulse of a patient with pure mitral regurgitation. When regurgitant flow is augmented in response to a pressor amine, the holosystolic crescendo murmur (SM) becomes more prominent and a mid-diastolic flow murmur (MDM) appears.

diastolic pressure, and by an increase in gradient and flow rate across the stenotic tricuspid valve.[138] The murmur is localized to the lower left sternal edge because it originates within the inflow portion of the right ventricle and is transmitted to the overlying chest wall.

Mid-diastolic murmurs across *unobstructed* AV valves occur in the presence of augmented volume and velocity of flow. Examples in the left side of the heart are the mid-diastolic flow murmur of pure mitral regurgitation (Fig. 4-35) and the mid-diastolic mitral flow murmur that accompanies a large left-to-right shunt through a ventricular septal defect (Fig. 4-36 *A*). Mid-diastolic murmurs due to augmented flow across unobstructed *tricuspid* valves are generated by severe tricuspid regurgitation or by a large left-to-right shunt through an atrial septal defect (see Fig. 4-36 *B*). These mid-diastolic murmurs indicate appreciable AV valve incompetence or large left-to-right shunts and are often preceded by an S_3 , especially in the presence of mitral or tricuspid regurgitation.

Short, mid-diastolic AV flow murmurs occur intermittently in complete heart block when atrial contraction coincides with the phase of rapid diastolic filling (see Fig. 4-14) . These murmurs are believed to result from antegrade flow across AV valves that are closing rapidly during filling of the recipient ventricle.[136] A similar mechanism is believed to be responsible for the Austin Flint murmur (see Fig. 4-33) . [139] [140] [141]

A mid-diastolic murmur is a feature of pulmonary valve regurgitation, provided that the pulmonary arterial pressure is not elevated (Fig. 4-37 *A*). The diastolic murmur typically begins at a perceptible interval after P_2 is crescendo-decrescendo, ending well before the subsequent S_1 . [78] The physiological mechanism responsible for the timing of this

Figure 4-36 *A,* Phonocardiogram recorded at the apex of a patient with a moderately restrictive ventricular septal defect and increased pulmonary arterial blood flow. The mid-diastolic murmur (DM) results from augmented flow across the mitral valve. SM=holosystolic murmur; S_1 =first heart sound; S_2 =second heart sound. *B,* Phonocardiogram at the lower left sternal edge of a patient with an ostium secundum atrial septal defect and increased pulmonary arterial blood flow. A mid-diastolic murmur (DM) resulted from augmented flow across the tricuspid valve. SM=midsystolic murmur; A_2 and P_2 =aortic and pulmonic components of a conspicuously split S_2 .

murmur is shown in Figure 4-37 *B*. The diastolic pressure exerted on the incompetent pulmonary valve is negligible at the inception of P_2 , so regurgitant flow is minimal. Regurgitation accelerates as right ventricular pressure dips below the diastolic pressure in the pulmonary trunk; at that point the murmur reaches its maximum intensity. Late diastolic equilibration of pulmonary arterial and right ventricular pressures eliminates regurgitant flow and abolishes the murmur before the next S_1 .

LATE DIASTOLIC OR PRESYSTOLIC MURMURS.

A late diastolic murmur occurs immediately before S_1 , that is, in *presystole* (see Fig. 4-31) . With few exceptions, the late diastolic timing of the murmur coincides with the phase of ventricular filling that follows atrial systole and implies the presence of sinus rhythm and coordinated atrial contraction. Late diastolic or presystolic murmurs usually originate at the mitral or tricuspid orifice because of obstruction, but occasionally because of abnormal patterns of presystolic AV flow.

The best known presystolic murmur accompanies rheumatic mitral stenosis in sinus rhythm as AV flow is augmented in response to an increase in the force of left atrial contraction (see Figs. 4-16 *B* and 4-38*A*). [92] Presystolic accentuation of a mid-diastolic murmur is occasionally heard

Figure 4-37 *A,* Phonocardiogram illustrating the mid-diastolic murmur (DM) of low-pressure pulmonary regurgitation in a heroin addict who had pulmonary valve infective endocarditis. The murmur begins well

after the second heart sound (S_2) and is of medium frequency and mid-diastolic, ending well before the subsequent first heart sound (S_1). *B,* Pressure pulses and phonocardiogram illustrate the physiological mechanism of the mid-diastolic murmur of low-pressure pulmonary regurgitation. Because the pressure exerted against the incompetent pulmonary valve is low, the murmur does not begin until well after the right ventricular (RV) and pulmonary arterial (PA) pressure pulses diverge. The murmur is maximal when the diastolic gradient (cross-hatched area) is greatest. After an early diastolic dip in the RV pressure pulse, there is equilibration of the PA and RV pressures in later diastole, so the regurgitant gradient is abolished and the murmur disappears.

Figure 4-38 *A,* Phonocardiogram from the cardiac apex of a patient with pure rheumatic mitral stenosis. A presystolic murmur (PM) rises in a crescendo that is interrupted by a loud first heart sound (S_1). S_2 =second heart sound; OS=mitral opening snap. *B,* Phonocardiogram from the lower left sternal edge of a patient with rheumatic tricuspid stenosis. The first cycle is during inspiration and is accompanied by a prominent presystolic murmur (PM) that is crescendo-decrescendo, decreasing before the S_1 . During exhalation (second cycle), the presystolic murmur all but vanishes.

in mitral stenosis with atrial fibrillation, especially during short cycle lengths[142] [143] ; but the timing is actually early systolic, and the mechanism differs from the true presystolic murmur as described earlier and as shown in Figure 4-38 *A*.

In *tricuspid* stenosis with sinus rhythm, a late diastolic or presystolic murmur typically occurs in the absence of a perceptible mid-diastolic murmur (see Fig. 4-38 *B*). This is so because the timing of tricuspid diastolic murmurs reflects the maximal acceleration of flow and gradient, which is usually negligible until powerful right atrial contraction.[138] The presystolic murmur of tricuspid stenosis is crescendo-decrescendo and relatively discrete, fading before S_1 (see Fig. 4-38 *B*). This is in contrast to the presystolic murmur of mitral stenosis, which tends to rise in a crescendo up to S_1 (see Fig. 4-38 *A*). The most valuable auscultatory sign of tricuspid stenosis in sinus rhythm is the effect of respiration on the intensity of the presystolic murmur (see Figs. 4-38 and 4-39) . Inspiration increases right atrial volume, provoking an increase in right atrial

Figure 4-39 Pressure pulses and phonocardiogram illustrating the physiological mechanism of the respiratory variation in the presystolic murmur of tricuspid stenosis. During inhalation, a fall in intrathoracic pressure and an increase in systemic venous return result in an increase in the right atrial (RA) A wave and a decline in right ventricular (RV) end-diastolic pressure, so the presystolic murmur (PSM) increases in loudness. During exhalation, the right atrial A wave declines, the RV diastolic pressure increases, the tricuspid gradient is at its minimum, and the PSM all but vanishes.

contractile force that coincides with a fall in right ventricular end-diastolic pressure. The result is an increase in the tricuspid gradient, in the velocity of tricuspid flow, and in the intensity of the tricuspid stenotic presystolic murmur (see Fig. 4-39) .[138]

Short, crescendo-decrescendo presystolic murmurs are occasionally heard in *complete heart block* when atrial contraction falls in late diastole. However, the murmur is usually mid-diastolic, as already described, occurring when atrial contraction coincides with and reinforces the rapid filling phase of the cardiac cycle (see Fig. 4-16) .

In 1862, Austin Flint described a presystolic murmur in patients with aortic regurgitation and proposed a mechanism that was astonishingly perceptive.[139] [140] [141] [144] [145] "Now in cases of considerable aortic insufficiency, the left ventricle is rapidly filled with blood flowing back from the aorta as well as from the auricle, before the auricular contraction takes place. The distention of the ventricle is such that the mitral curtains are brought into coaptation; and when the auricular contraction takes place, the mitral direct current passing between the curtains throws them into vibration and gives rise to the characteristic blubbering murmur."[139]

Continuous Murmurs

The term "continuous" appropriately applies to murmurs that begin in systole and *continue* without interruption through S_2 into all or part of diastole (Fig. 4-40) . The presence of murmurs throughout both phases of the cardiac cycle (holosystolic followed by holodiastolic) is *not* the criterion for the designation "continuous." Conversely, a murmur that fades completely before the subsequent S_1 *may be* continuous, provided that the systolic portion of the murmur proceeds without interruption through S_2 .

Continuous murmurs are generated by uninterrupted flow from a vascular bed of higher pressure or resistance into a vascular bed of lower pressure or resistance without phasic interruption between systole and diastole. Such murmurs are due chiefly to (1) aortopulmonary connections, (2) arteriovenous connections, (3) disturbances of flow patterns in arteries, and (4) disturbances of flow patterns in veins (Table 4-3) .

The best known continuous murmur is associated with the aortopulmonary connection of *patent ductus arteriosus* (Fig. 4-41) (see Chaps. 43 and 44) . The murmur characteristically peaks just before and after S_2 , which it envelops, decreases in late diastole (often appreciably), and may be soft or even absent before the subsequent first heart sound.[78] George Gibson's description in 1900 was even more precise.[146] "It persists through S_2 and dies away gradually during the long pause. The murmur is rough and thrilling. It begins softly and increases in intensity so as to reach its acme just about, or immediately after, the incidence of the second sound, and from that point gradually wanes until its termination" (see Fig. 4-41) .

Figure 4-40 Comparison of the continuous murmur and the to-fro murmur. During abnormal

communication between high-pressure and low-pressure systems, a large pressure gradient exists through the cardiac cycle, producing a continuous murmur. A classic example is patent ductus arteriosus. At times this type of murmur is confused with a to-fro murmur, which is a combination of systolic ejection murmur and a murmur of semilunar valve incompetence. A classic example of a to-fro murmur is aortic stenosis and regurgitation. A continuous murmur crescendos to around the second heart sound (S_2), whereas a to-fro murmur has two components. The midsystolic ejection component decrescendos and disappears as it approaches S_2. *(From Shaver JA, Leonard JJ, Leon DF: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright 1990, American Heart Association.*

ARTERIOVENOUS CONTINUOUS MURMURS.

These can be congenital or acquired and are represented in part by arteriovenous fistulas, coronary arterial fistulas, anomalous origin of the left coronary artery from the pulmonary trunk, and sinus of Valsalva-to-right side of heart communications.[78] The configuration, location, and intensity of arteriovenous continuous murmurs vary considerably among these different lesions. *Acquired* systemic arteriovenous fistulas are created surgically by forearm shunts for hemodialysis. *Congenital* arteriovenous continuous murmurs occur when a coronary arterial fistula enters the pulmonary trunk, right atrium, or right ventricle. At the latter site, the continuous murmur can be either softer or louder in systole, depending on the degree of compression exerted on the fistulous coronary artery by right ventricular contraction.[78] Rupture of a congenital aortic sinus aneurysm into the right side of the heart results in a continuous murmur that tends to be louder in either systole or diastole, sometimes creating a to-and-fro impression.[78]

ARTERIAL CONTINUOUS MURMURS.

These originate in either *constricted* or *nonconstricted* arteries. A common example of a continuous murmur arising in a constricted artery is carotid or femoral arterial atherosclerotic obstruction. Not surprisingly, these murmurs are characteristically louder in systole and more often than not are purely systolic.

Disturbances of flow patterns in *normal, nonconstricted* arteries sometimes produce continuous murmurs. The "mammary souffle" described earlier,[133] an innocent murmur heard during late pregnancy and the puerperium, is an arterial murmur that, when continuous, is typically louder in systole and maximal over either lactating breast. A distinct gap separates the S_1 from the onset of the mammary souffle because of the relatively long interval that elapses before blood ejected from the left ventricle arrives at the artery of origin.[78] Light pressure with the stethoscope tends to augment the murmur and bring out its continuous features, whereas firm pressure with the stethoscope or by digital compression adjacent to the site of auscultation often abolishes the murmur.

Continuous murmurs in nonconstricted arteries originate in the large systemic-to-pulmonary arterial collaterals in certain types of cyanotic congenital heart disease, typically tetralogy of Fallot with pulmonary atresia. These continuous murmurs are randomly located throughout the thorax because of the random location of the aortopulmonary collaterals.[78]

CONTINUOUS VENOUS MURMURS.

These are well represented by the innocent cervical venous hum (Fig. 4-42) . The hum is by far the most common type of normal continuous murmur, universal in healthy children, and frequently present in healthy young adults, especially during pregnancy. Thyrotoxicosis and anemia, by augmenting cervical venous flow, initiate or reinforce the venous hum. The term "hum" does not necessarily characterize the quality of these cervical venous murmurs, which may be rough and noisy and are occasionally accompanied by a high-pitched whine.[78] The hum is truly continuous, although typically louder in diastole, as is generally the case with venous continuous murmurs. The mechanism of the venous hum is unsettled. Silent laminar flow in the internal jugular vein may be disturbed by deformation of the vessel at the level of the transverse process of the atlas during head rotation designed to elicit the hum.[147]

Approach to the Patient with a Heart Murmur

Although a careful physical examination with emphasis on detailed auscultation is useful in establishing a cardiac diagnosis, or excluding serious cardiac disease, echocardiography is decisive in confirming the diagnosis and determining the severity of the condition (Fig. 4-43) . As delineated by O'Rourke,[148] the approach to the patient with a heart murmur depends on its intensity, timing, location, response to maneuvers, and the presence of other cardiac and noncardiac symptoms and signs. Patients with diastolic murmurs, or continuous murmurs that are not cervical venous

TABLE 4-3 -- DIFFERENTIAL DIAGNOSIS OF CONTINUOUS THORACIC MURMURS (IN ORDER OF FREQUENCY)

DIAGNOSIS	KEY FINDINGS
Cervical venous hum	Disappears on compression of the jugular vein
Hepatic venous hum	Often disappears with epigastric pressure
Mammary souffle	Disappears on pressing hard with stethoscope
Patent ductus arteriosus	Loudest at second left intercostal space
Coronary arteriovenous fistula	Loudest at lower sternal borders
Ruptured aneurysm of sinus of Valsalva	Loudest at upper right sternal border, sudden onset
Bronchial collaterals	Associated signs of congenital heart disease
	High-grade coarctation
	Brachial pedal arterial pressure gradient

Anomalous left coronary artery arising from pulmonary artery	Electrocardiographic changes of myocardial infarction
Truncus arteriosus	
Pulmonary artery branch stenosis	Heard outside the area of cardiac dullness
Pulmonary arteriovenous fistula	Same as above
Atrial septal defect with mitral stenosis or atresia	Altered by the Valsalva maneuver
Aortic-atrial fistulas	

Adapted from Sapira JD: The Art and Science of Bedside Diagnosis. Baltimore, Urban & Schwartzenberg, 1990.

Figure 4-41 The classic continuous murmur of patent ductus arteriosus recorded from within the main pulmonary artery (upper tracing) and simultaneously on the chest wall at the second left intercostal space (2LICS). The murmur "begins softly and increases in intensity so as to reach its acme just about, or immediately after, the incidence of the second sound, and from that point gradually wanes until its termination," as originally described by Gibson in 1900.[146]

hums, or mammary souffles of pregnancy, should ordinarily go to two-dimensional and Doppler echocardiography, and subsequent work-up, including cardiac consultation, is guided by the echocardiographic findings. In general, echocardiography is also advised for patients with systolic murmurs having the following characteristics: (1) loud murmur (i.e.,
grade 3); (2) holosystolic or late systolic murmur, especially at the left sternal edge or apex; (3) systolic murmurs that become louder or longer during the strain of the Valsalva maneuver (suggesting the diagnosis of hypertrophic obstructive cardiomyopathy or mitral valve prolapse respectively; see p. 76); (4) other systolic murmurs in patients with clinical findings suggesting infective endocarditis (see Chap. 47) , thromboembolism, or syncope; (5) a systolic murmur accompanied by an abnormal electrocardiogram.

According to this schema, a large majority of patients with heart murmurs (i.e., patients with grade 1 or grade 2 midsystolic murmurs) without any other clinical manifestations

Figure 4-42 The phonocardiogram shows the continuous murmur of a normal venous hum. The diastolic component is louder (paired arrows). Digital pressure over the right internal jugular vein (vertical arrow) abolishes the murmur. The photographs show maneuvers used to elicit or abolish the venous hum. *Left,* The bell of the stethoscope is applied to the medial aspect of the right supraclavicular fossa as the examiner's left hand grasps the patient's chin from behind and pulls it tautly to the left and upward,

stretching the neck. *Right,* The patient's head has returned to a more neutral position, and digital compression of the right internal jugular vein (arrow) abolishes the hum.

of cardiac disease ordinarily do not require extensive work-up.

Pericardial Rubs (see Chap. 50)

In sinus rhythm, the typical pericardial rub is triple phased, that is, midsystolic, mid-diastolic, and presystolic. Recognition is simplest when all three phases are present and when the characteristic superficial scratchy, leathery quality is evident. Pericardial rubs may be more readily detected when the patient is on elbows and knees (Fig. 4-44) , a physical maneuver designed to increase the contact

Figure 4-43 An approach to the evaluation of a heart murmur that also uses the results of the electrocardiogram (ECG), chest radiograph, and echocardiogram in asymptomatic patients with soft midsystolic murmurs and no other physical findings. This algorithm is useful in patients older than age 40 years in whom the prevalence of coronary artery disease and aortic stenosis increases as the cause of systolic murmurs. *(From O'Rourke RA: Approach to the patient with a heart murmur. In Goldman L, Braunwald E [eds]: Primary Cardiology. Philadelphia, WB Saunders, 1998, pp 155-173.)*

Figure 4-44 A technique for eliciting a pericardial rub. The diaphragm of the stethoscope is firmly applied to the precordium (arrow) while the patient rests on elbows and knees.

of visceral and parietal pericardium (see earlier). The term "rub" is appropriate because the auscultatory sign is generated by abnormal visceral and parietal pericardial surfaces "rubbing" against each other. In the supine position, firm pressure with the stethoscopic diaphragm during full held exhalation reinforces visceral and parietal pericardial contact and accentuates the rub. Apposition of visceral and parietal pericardium can be even better achieved by examination while the patient rests on elbows and knees.

Of the three phases of the pericardial rub, the systolic phase is the most consistent, followed by the presystolic phase. In atrial fibrillation, the presystolic component necessarily disappears. The diagnosis of a pericardial rub is least secure when only one phase remains, which is typically the midsystolic. The most common clinical setting in which pericardial rubs are heard is immediately after open heart surgery. However, auscultation often detects instead a "crunch" synchronous with the heartbeat, especially in the left lateral decubitus position. This is not a pericardial rub but is Hamman sign caused by air in the mediastinum.[149] Pericardial rubs are frequently audible in acute pericarditis. They may become softer or even disappear in the presence of a large pericardial effusion.

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Dynamic Auscultation

Dynamic auscultation refers to the technique of altering circulatory dynamics by a variety of physiological and pharmacological maneuvers and determining the effects of these maneuvers on heart sounds and murmurs.[150] [151] [152] [153] The conditions and interventions most commonly employed in dynamic auscultation include respiration, postural changes, the Valsalva maneuver, premature ventricular contractions, isometric exercise, and one of the vasoactive agents--amyl nitrite, methoxamine, or phenylephrine. The clinical applications of dynamic auscultation are summarized in Table 4-4 .

RESPIRATION

SECOND HEART SOUND.

The splitting of S_2 is most audible along the left sternal border and can usually be appreciated when A_2 and P_2 are separated by more than 0.02 second. The effects of respiration on the splitting of the second heart sound are discussed on p. 60.

DIASTOLIC SOUNDS AND EJECTION SOUNDS.

When S_3 and S_4 originate from the right ventricle, they are characteristically augmented during inspiration and diminished during exhalation, whereas they exhibit the opposite response when they originate from the left side of the heart. Like other left-sided events, the opening snap of the mitral valve may become softer during inspiration and louder during exhalation owing to respiratory alterations in venous return, whereas the opening snap of the tricuspid valve behaves in the opposite fashion. Inspiration also diminishes

the intensity of ejection sounds in pulmonary valve stenosis because the elevation of right ventricular diastolic pressure causes partial presystolic opening of the pulmonary valve and therefore less upward motion of the valve during systole. On the other hand, respiration does not affect the intensity of aortic ejection sounds, except in tetralogy of Fallot with pulmonary atresia.

MURMURS.

Respiration exerts more pronounced and consistent alterations on murmurs originating from the right than from the left side of the heart. During inspiration, the diastolic murmurs of tricuspid stenosis (see Fig. 4-39) and low pressure pulmonary regurgitation, the systolic murmurs of tricuspid regurgitation[154] (Carvallo sign), and the presystolic murmur of Ebstein anomaly may all be accentuated. The inspiratory reduction in left ventricular size in patients with mitral valve prolapse increases the redundancy of the mitral valve and therefore the degree of valvular prolapse; consequently, the midsystolic click and the systolic murmurs occur earlier during systole and may become accentuated.[155]

THE VALSALVA MANEUVER.

This maneuver consists of a relatively deep inspiration followed by forced exhalation against a closed glottis for 10 to 20 seconds. The patient should first be instructed on how to perform the maneuver. Simulation by the examiner is a simple means of doing so. The examiner then places the flat of the hand on the abdomen to provide the patient with a force against which to strain and to permit assessment of the degree and duration of the straining effort.[156] [157] [158] The normal response to the Valsalva maneuver consists of four phases. *Phase I* is associated with a transient rise in systemic arterial pressure as straining commences. *Phase II* is accompanied by a perceptible decrease in systemic venous return, systolic pressure, and pulse pressure (small pulse) and by reflex tachycardia. *Phase III* begins promptly with cessation of straining and is associated with an abrupt, transient decrease in arterial pressure. *Phase IV* is characterized by an overshoot of systemic arterial pressure and reflex bradycardia. During phase II, S_3 and S_4 are attenuated and the A_2 -P_2 interval narrows or is abolished (Fig. 4-45) . As stroke volume and systemic arterial pressure fall, the systolic murmurs of aortic and pulmonary stenosis and of mitral and tricuspid regurgitation diminish and the diastolic murmurs of aortic and pulmonary regurgitation and of tricuspid and mitral stenosis soften. As left ventricular volume is reduced, the systolic murmur of hypertrophic obstructive cardiomyopathy amplifies and the click and late systolic murmur of mitral valve prolapse begin earlier. In phase III, the sudden increase in systemic venous return is accompanied by wide splitting of the S_2 and by augmentation of murmurs and filling sounds in the right side of the heart. Murmurs and filling sounds in the left side of the heart return to control levels and may transiently increase during the overshoot of phase IV.

In patients with atrial septal defect, mitral stenosis, or heart failure, the Valsalva maneuver provokes a "square

TABLE 4-4 -- RESPONSE OF MURMURS AND HEART SOUNDS TO PHYSIOLOGICAL AND PHARMACOLOGICAL INTERVENTIONS

CLINICAL DISORDER	INTERVENTION AND RESPONSE
Systolic Murmurs	
Aortic outflow obstruction	
Valvular aortic stenosis	Louder with passive leg-raising, with sudden squatting, with Valsalva release (after five to six beats), following a pause induced by a premature beat, or after amyl nitrite; fades during Valsalva strain and with isometric handgrip
Hypertrophic obstructive cardiomyopathy	Louder with standing, during Valsalva strain, or with amyl nitrite; fades with sudden squatting, recumbency, or isometric handgrip
Pulmonic stenosis	Midsystolic murmur increases with amyl nitrite except with marked right ventricular hypertrophy; also increases during first few beats after Valsalva release
Mitral regurgitation	
Rheumatic	Murmur louder with sudden squatting, isometric handgrip, or phenylephrine; softens with amyl nitrite
Mitral valve prolapse	Midsystolic click moves toward S_1 and late systolic murmur starts earlier with standing, Valsalva strain, and amyl nitrite; click may occur earlier on inspiration; murmur starts later and click moves toward S_2 during squatting, with recumbency, and often after pause induced by a premature beat
Papillary muscle dysfunction	Late systolic murmur generally softer after a pause induced by a premature beat; response to amyl nitrite variable, depending on acute or chronic nature of this disorder
Tricuspid regurgitation	Murmur increases during inspiration, with passive leg-raising, and with amyl nitrite
Ventricular septal defect	
Small defect with pulmonary hypertension	Fades with amyl nitrite; increases with isometric handgrip or phenylephrine

Large defect with hyperkinetic pulmonary hypertension	Louder with amyl nitrite; fades with phenylephrine
Large defect with severe pulmonary vascular disease	Little change with any of above interventions
Tetralogy of Fallot	Murmur softens with amyl nitrite
Supraclavicular bruit	Altered by compression of subclavian artery; may be eliminated by extension of ipsilateral shoulder
Diastolic Murmurs	
Aortic regurgitation	Increases with sudden squatting, isometric handgrip, or phenylephrine
Blowing diastolic murmur	
Austin Flint murmur	Fades with amyl nitrite
Pulmonary regurgitation	Early or mid-diastolic rumble increases on inspiration and with amyl nitrite
Congenital	High-frequency blowing murmur not altered by above interventions
Pulmonary hypertension	
Mitral stenosis	Mid-diastolic and presystolic murmurs louder with exercise, left lateral position, coughing, isometric handgrip, or amyl nitrite; phenylephrine widens A_2 /OS interval; inspiration produces sequence of A_2 /P_2 /OS
Tricuspid stenosis	Mid-diastolic and presystolic murmurs increase during inspiration, with passive leg-raising, and with amyl nitrite
Continuous Murmurs	
Patent ductus arteriosus	Diastolic phase amplified with isometric handgrip or phenylephrine; diastolic phase fades with amyl nitrite
Cervical venous hum	Obliterated by direct compression of jugular veins or by Valsalva strain
Added Heart Sounds	
Gallop rhythm	
Ventricular gallop (S_3) and atrial gallop (S_4)	Accentuated by lying flat with passive leg-raising; decreased by standing or during Valsalva; right-sided gallop sounds usually increase during inspiration; left-sided during expiration

Summation gallop	Separates into ventricular gallop (S_3) and atrial gallop (S_4) sounds when heart rate slowed by carotid sinus massage
Ejection sounds	Ejection sound in pulmonary stenosis fades and occurs closer to the first sound during inspiration

OS=opening snap of mitral valve.

From Criscitiello MG: Physiologic and pharmacologic aids in cardiac auscultation. In Fowler NO (ed): Cardiac Diagnosis and Treatment. Hagerstown, MD, Harper & Row, 1980.

wave" response, negating the four phases and their auscultatory equivalents. The Valsalva maneuver should not be performed in patients with ischemic heart disease because of the accompanying fall in coronary blood flow.

THE MULLER MANEUVER.

This maneuver is the converse of the Valsalva maneuver but is less frequently employed because it is not as useful.[81] In this maneuver the patient forcibly *inspires* while the nose is held closed and the mouth is firmly sealed for about 10 seconds. The Muller maneuver exaggerates the inspiratory effort, widens the split S_2, and augments murmurs and filling sounds originating in the right side of the heart.

Figure 4-45 Changes in four left-sided systolic murmurs during the strain phase of the Valsalva maneuver. *(From Grewe K, Crawford MH, O'Rourke RA: Differentiation of cardiac murmurs by auscultation. Curr Probl Cardiol 13:669, 1988.)*

POSTURAL CHANGES AND EXERCISE (See Fig. 4-46.)

Sudden assumption of the lying from the standing or sitting position or sudden passive elevation of both legs results in an increase in venous return, which augments first right ventricular and, several cardiac cycles later, left ventricular stroke volume. The principal auscultatory changes include widening of the splitting of S_2 in all phases of respiration and augmentations of right-sided S_3 and S_4 and, several cardiac cycles later, left-sided S_3 and S_4. The systolic murmurs of pulmonic valve stenosis and aortic stenosis, the systolic murmurs of mitral and tricuspid regurgitation and ventricular septal defect, and most functional systolic murmurs are augmented. On the other hand, because left ventricular end-diastolic volume is increased, the systolic murmur of hypertrophic obstructive cardiomyopathy is diminished and the midsystolic click and late systolic murmur associated with mitral valve prolapse are delayed and sometimes attenuated

(see Fig. 4-18 and p. 68).

Rapid standing or sitting up from a lying position or rapid standing from a squatting posture has the opposite effect; in patients in whom there is relatively wide splitting of S_2 during exhalation--a finding that may be confused with fixed splitting--the width of the splitting is reduced, so that a normal pattern emerges during the respiratory cycle. No change in splitting occurs in patients with true fixed splitting. The decrease in venous return reduces stroke volume and innocent pulmonary flow murmurs as well as the murmurs of semilunar valve stenosis and of AV valve regurgitation. The auscultatory changes in hypertrophic cardiomyopathy and mitral valve prolapse are opposite to those on assumption of the lying posture just described.

SQUATTING.

A sudden change from standing to squatting increases venous return and systemic resistance simultaneously. Stroke volume and arterial pressure rise, and the latter may induce a transient reflex bradycardia. The auscultatory features include augmentation of S_3 and S_4 (from both ventricles) and as a consequence of an increase in stroke volume, the systolic murmurs of pulmonary and aortic stenosis and the diastolic murmurs of tricuspid and mitral stenosis become louder, with right-sided events preceding left-sided events. Squatting may make audible a previously inaudible murmur of aortic regurgitation.

The elevation of arterial pressure increases blood flow through the right ventricular outflow tract of patients with tetralogy of Fallot and increases the volume of mitral regurgitation and of the left-to-right shunt through a ventricular septal defect, thereby increasing the intensity of the systolic murmur in these conditions. Also, the diastolic murmur of aortic regurgitation is augmented consequent to an increase in aortic reflux. The combination of elevated arterial pressure and increased venous return increases left ventricular size, which reduces the obstruction to outflow and thus the intensity of the systolic murmur of hypertrophic obstructive cardiomyopathy, the midsystolic click and the late systolic murmur of mitral valve prolapse are delayed.

OTHER POSITIONAL CHANGES.

Assumption of the left lateral recumbent position accentuates the intensity of S_1 , S_3 , and S_4 originating from the left side of the heart; the opening snap and the murmurs associated with mitral stenosis and regurgitation; the midsystolic click and late systolic murmur of mitral valve prolapse; and the Austin Flint murmur associated with aortic regurgitation. *Sitting up and leaning forward* (see Fig. 4-12) make the diastolic murmurs of aortic and pulmonary regurgitation more readily audible.

Hyperextension of the shoulders is an important positional maneuver that assists in assessing supraclavicular systolic murmurs. The mechanism responsible for diminution in the intensity of normal supraclavicular systolic murmurs with hyperextension of the shoulders is apparently related to the effect of the maneuver on the site of origin of the murmurs in the proximal brachiocephalic arteries as they leave the aortic arch.

Stretching the neck to elicit a venous hum is illustrated in Figure 4-42 . *Passive elevation of the legs* with the patient supine transiently increases venous return and augments S_3 .

ISOMETRIC EXERCISE.

This can be carried out simply and reproducibly using a calibrated handgrip device or hand ball. (It is useful to carry out isometric exercise bilaterally simultaneously.) Isometric exercise should be avoided in patients with ventricular arrhythmias and myocardial ischemia, both of which can be intensified by this activity. Handgrip should be sustained for 20 to 30 seconds, but a Valsalva maneuver during the handgrip must be avoided. Isometric exercise results in transient but significant increases in systemic vascular resistance, arterial pressure, heart rate, cardiac output, left ventricular filling pressure, and heart size. As a consequence, (1) S_3 and S_4 originating from the left side of the heart become accentuated, (2) the systolic murmur of aortic stenosis is diminished as a result of reduction of the pressure gradient across the aortic valve,[158] [159] (3) the diastolic murmur of aortic regurgitation and the systolic murmurs of rheumatic mitral regurgitation and ventricular septal defect increase in intensity, (4) the diastolic murmur of mitral stenosis becomes louder consequent to the increase in cardiac output, and (5) the systolic murmur of hypertrophic obstructive cardiomyopathy diminishes and the systolic click and late systolic murmur of mitral valve prolapse are delayed because of the increased left ventricular volume.

Figure 4-46 Diagrammatic representation of the character of the systolic murmur and of the second heart sound in five conditions. The effects of posture, amyl nitrite inhalation, and phenylephrine injection on the intensity of the murmur are shown. *(Modified from Barlow JB: Perspectives on the Mitral Valve. Philadelphia, FA Davis, 1987, p 138.)*

PHARMACOLOGICAL AGENTS (See Fig. 4-46.)

Inhalation of *amyl nitrite* is carried out by placing an ampule in gauze near the supine patient's nose and then crushing the ampule. The patient is asked to take three or four deep breaths over 10 to 15 seconds, after which the amyl nitrite is removed. The drug produces marked vasodilatation, resulting in the first 30 seconds in a reduction of systemic arterial pressure and 30 to 60 seconds later in a reflex tachycardia, followed in turn by a reflex *increase* in cardiac output, velocity of blood flow, and heart rate.[4] [150] [151] [152] [153] [160] The major auscultatory changes occur in the first 30 seconds after inhalation. S_1 is augmented, and A_2 is diminished. The opening snaps of the mitral and tricuspid valves become louder, and as arterial pressure falls, the A_2 /opening snap interval shortens. An S_3 originating in either ventricle is augmented, owing to greater rapidity of ventricular filling; but because mitral regurgitation is reduced, the S_3

associated with this lesion is diminished. The systolic murmurs of aortic valve stenosis, pulmonary stenosis, hypertrophic obstructive cardiomyopathy, tricuspid regurgitation, and functional systolic murmurs are all accentuated.

In patients with tetralogy of Fallot, the reduction of arterial pressure increases the right-to-left shunt and decreases the blood flow from the right ventricle to the pulmonary artery and diminishes the midsystolic murmur. The increase in cardiac output augments the diastolic murmurs of mitral and tricuspid stenosis and of pulmonary regurgitation and the systolic murmur of tricuspid regurgitation. However, as a result of the fall in systemic arterial pressure, the systolic murmurs of mitral regurgitation and ventricular septal defect, the diastolic murmurs of aortic regurgitation, and the Austin Flint murmur as well as the continuous murmurs of patent ductus arteriosus and of systemic arteriovenous fistula are all diminished.[158] The reduction of cardiac size results in an earlier appearance of the midsystolic click and late systolic murmur of mitral valve prolapse; the intensity of the systolic murmur exhibits a variable response.

The response to amyl nitrite is useful in distinguishing (1) the systolic murmur of aortic stenosis (which is augmented) from that of mitral regurgitation (which is diminished),[160] (2) the systolic murmur of tricuspid regurgitation (augmented) from that of mitral regurgitation (diminished), (3) the systolic murmur of isolated pulmonary stenosis (augmented) from that of tetralogy of Fallot (diminished), (4) the diastolic rumbling murmur of mitral stenosis (augmented) from the Austin Flint murmur of aortic regurgitation (diminished), and (5) the early blowing diastolic murmur of pulmonary regurgitation (augmented) from that of aortic regurgitation (diminished).

Methoxamine and *phenylephrine* increase systemic arterial pressure and exert an effect opposite to that of amyl nitrite. In general, methoxamine, 3 to 5 mg intravenously, elevates arterial pressure by 20 to 40 mm Hg for 10 to 20 minutes, but phenylephrine is preferred because of its shorter duration of action; 0.3 to 0.5 mg of phenylephrine administered intravenously elevates systolic pressure by approximately 30 mm Hg for only 3 to 5 minutes. Both drugs cause reflex bradycardia and decreased contractility and cardiac output. They should not be used in the presence of congestive heart failure and systemic hypertension.

After administration, the intensity of S_1 is usually reduced, and the A_2 /mitral opening snap interval becomes prolonged. The responses of S_3 and S_4 are variable. As a

result of the increased arterial pressure, the diastolic murmur of aortic regurgitation, the systolic murmurs of mitral regurgitation (see Fig. 4-35) , ventricular septal defect, and tetralogy of Fallot, and the continuous murmurs of patent ductus arteriosus and systemic arteriovenous fistula all become louder. On the other hand, as a consequence of the increase in left ventricular size, the systolic murmur of hypertrophic obstructive cardiomyopathy becomes softer and the click and late systolic murmur of mitral valve prolapse are delayed. The reduction in cardiac output diminishes the systolic murmur of

aortic valve stenosis, functional systolic murmurs, and the diastolic murmur of mitral stenosis. The rumbling diastolic murmurs of mitral regurgitation and the Austin Flint murmur also diminish.

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Chapter 5 - Electrocardiography

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The electrocardiogram (ECG), as used today, is the product of a series of technological and physiological advances pioneered over the past two centuries.[1] Early demonstrations of the heart's electrical activity reported during the last half of the 19th century, for example, by Marchand and others, were closely followed by direct recordings of cardiac potentials by Waller in 1887. Invention of the string galvanometer by Willem Einthoven in 1901 provided a reliable and direct method for registering electrical activity of the heart. By 1910, use of the string galvanometer had emerged from the research laboratory into the clinic. Subsequent achievements built on the limited, but very solid foundation supplied by the early electrocardiographers. The result has become a widely used and invaluable clinical tool for the detection and diagnosis of a broad range of cardiac conditions, as well as a technique that has contributed to the understanding and treatment of virtually every type of heart disease. Furthermore, the ECG is essential in the management of major metabolic abnormalities such as hyperkalemia and certain other electrolyte disorders, as well as assessing drug effects and toxicities such as caused by digitalis, antiarrhythmic agents, and tricyclic antidepressants. Moreover, it has remained the most direct method for assessing

abnormalities of cardiac rhythm.

FUNDAMENTAL PRINCIPLES

Use of the ECG for any of these clinically important purposes is the final outcome of a complex series of physiological and technological processes. This sequence is depicted in Figure 5-1 . First, an extracellular cardiac electrical field is generated by ion fluxes across cell membranes and between adjacent cells. These ion currents are synchronized by cardiac activation and recovery sequences to generate a cardiac electrical field in and around the heart that varies with time during the cardiac cycle.

This electrical field passes through numerous other structures, including the lungs, blood, and skeletal muscle, before reaching the body surface. These structures--known as *transmission factors*--differ in their electrical properties and perturb the cardiac electrical field as it passes through them. The potentials reaching the skin are then detected by electrodes placed in specific locations on the extremities and torso and configured to produce *leads*. The outputs of these leads are amplified, filtered, and displayed by a variety of electronic devices to construct an ECG recording. Finally, diagnostic criteria are applied to these recordings to produce an interpretation. The criteria have statistical characteristics that determine the clinical utility of the findings. Each of these steps influences the final product--the clinical ECG--and will be considered in detail in this chapter to provide a foundation for considering the common abnormalities found in clinical practice and as a basis for further learning.

GENESIS OF THE CARDIAC ELECTRICAL FIELD

CARDIAC ELECTRICAL FIELD GENERATION DURING ACTIVATION.

Transmembrane ionic currents are ultimately responsible for the cardiac potentials that are recorded as an ECG. Current may be analyzed as though carried by positively charged or negatively charged ions. Through a purely arbitrary choice, electrophysiological currents are considered to be the movement of positive charge. A positive current moving in one direction is equivalent to a negative current of equal strength moving in the opposite direction.

The process of generating the cardiac electrical field during activation can be illustrated by considering the events in a single cardiac fiber that is activated by a stimulus applied to its left-most margin[2] (Fig. 5-2 , left, panel *A*). Transmembrane potentials (V_m) are recorded as the difference between intracellular and extracellular potentials (k_i and k_e , respectively). Figure 5-2 , left, panel *B* plots V_m along the length of the fiber at the instant during the propagation (t_0) at which activation has reached the point designated as X_0 . As each site is activated, the polarity of the transmembrane potential is converted from negative to positive. Thus, sites to the left of the point X_0 , which have already undergone excitation, have positive transmembrane potentials (that is, the inside of the cell is positive relative to the outside of the cell), whereas those to the right of X_0 (which remain in a resting state) have negative transmembrane potentials. Near

the site undergoing activation (site X_0), the potentials reverse polarity over a short distance.

Figure 5-2 , left, panel C displays the direction and magnitude of transmembrane currents (I_m) along the fiber at the instant (t_o) at which excitation has reached site X_0 . Current flow is inwardly directed in fiber regions that have undergone activation (that is, to the left of point X_0) and outwardly directed in neighboring zones still at rest (that is, to the right of X_0). Sites of outward current flow are *current sources* and those with inward current flow are *current sinks*. As depicted in this panel, current flow is most intense in each direction near the site of activation X_0 . Because the border between inwardly and outwardly directed currents is relatively sharp, we can visualize these currents as though they were limited to the sites of maximal current flow, as depicted in panel D, and separated by distance d that is usually 1.0 mm or less. As activation proceeds along the fiber, the source-sink pair moves to the right at the speed of propagation for the particular type of fiber.

Two point sources of equal strength but of opposite polarity located very near each other, such as the current source and the current sink depicted in Figure 5-2 , left, panel *D*, may be represented as a current dipole (arrow in panel *D*). Thus, activation of a fiber can be modeled as a current dipole that moves in the direction of propagation of activation. Such a dipole is fully characterized by three parameters--strength or *dipole moment*, location, and orientation. In this case, the location of the dipole is the site undergoing activation (point X_0), and its orientation is in the direction of activation (that is, from left to right along the fiber). Dipole moment is proportional to the rate of change of intracellular potential with respect to distance along the fiber, that is, action potential shape.

A current dipole produces a characteristic potential field with positive potentials projected ahead of and negative potentials projected behind the moving dipole. The actual potential recorded at any site within this field is directly proportional to the dipole moment, inversely proportional to the square of the distance from the dipole to the recording site, and directly proportional to the cosine of the angle between the axis of the dipole and a line drawn from the dipole to the recording site (Fig. 5-2 , right).

Figure 5-1 Schematic representation of the factors resulting in recording the electrocardiogram (ECG). The major paths leading to the ECG are marked by solid arrows, while factors influencing or perturbing this path are shown with dotted arrows.

This example from one cardiac fiber can be generalized to the more realistic case in which multiple adjacent fibers are activated in synchrony to produce an *activation front*. Activation of each fiber creates a dipole oriented in the direction of activation. The net

effect of all the dipoles in this wave front is a single dipole equal to the (vector) sum of the effects of all the simultaneously active component dipoles. Thus, an activation front propagating through the heart can be represented by a single dipole that projects positive potentials ahead of it and negative potentials behind it.

This relationship between activation direction, orientation of the current dipole, and polarity of potentials is a critical one in electrocardiography. It describes a fundamental relationship between the polarity of potentials sensed by an electrode and the direction of movement of an activation front--*an electrode senses positive potentials when an activation front is moving toward it and negative potentials when the activation front is moving away from it.*

The dipole model, while useful in describing cardiac fields and understanding clinical electrocardiography, has significant theoretical limitations. These limits derive primarily from the inability of a single dipole to accurately represent more than one wave front that is propagating through the heart at any one instant. As will be discussed, during much of the time of ventricular excitation, more than one wave front is present.

One important and commonly used method of estimating the potentials projected to some point away from an activation front is an application of the *solid angle theorem*.[3] A *solid angle* is a geometric measure of the size of a region when viewed from a distant site. It equals the area on the surface of a sphere of unit radius constructed around an electrode that is cut by lines drawn from the recording electrode to all points around the boundary of the region of interest. This region may be a wave front, a zone of infarction, or any other region in the heart.

The solid angle theorem states that the potential recorded by a remote electrode (Phi) is defined by Phi=(
/4pi)(V_{m2} - V_{m1})K where
 is the solid angle, V_{m2} - V_{m1} is the potential difference across the boundary under study, and K is a constant reflecting differences in intracellular conductivity. This equation indicates that the recorded potential equals the product of two factors. First, the solid angle reflects *spatial parameters*, such as the size of the boundary of the region under study and the distance from the electrode to that boundary. The potential will rise as the boundary size increases and as the distance to the electrode shrinks. A second set of parameters includes *nonspatial factors*, such as the potential difference across the surface and intracellular and extracellular conductivity. Nonspatial effects include, as one example, myocardial ischemia, which changes transmembrane action potential shapes and alters conductivity.

CARDIAC ELECTRICAL FIELD GENERATION DURING VENTRICULAR RECOVERY.

The cardiac electrical field during recovery (phases 1 through 3 of the action potential) differs in fundamental ways from that described for activation. First, intercellular potential differences and, hence, the directions of current flow during recovery are the opposite of those described for activation. As a cell undergoes recovery, its intracellular potential becomes progressively more negative. Hence, for two adjacent cells, the

intracellular potential of the cell whose recovery has progressed further is more negative than that of an adjacent, less recovered cell. Intracellular currents then flow from the less toward the more recovered cell. An equivalent dipole can then be constructed for recovery, just as for activation. Its orientation, however, points from less to more recovered cells. Thus, the recovery dipole is oriented away from the activation front, that is, in the direction opposite that of the activation dipole.

The moment or strength of the recovery dipole also differs from that of the activation dipole. As described previously, the strength of the activation dipole is proportional to the rate of change in transmembrane potential. Rates of change in potential during the recovery phases of the action potential are considerably slower than during activation, so dipole moment at any one instant during recovery is less than that during activation.

A third difference between activation and recovery is the rate of movement of the activation and recovery dipoles. Activation, because it is rapid (as fast as 1 millisecond in duration), occurs over only a small distance along the fiber. Recovery, in contrast, lasts 100 milliseconds or longer and occurs simultaneously over extensive portions of the fiber.

These features result in characteristic ECG differences between activation and recovery patterns. All other factors being equal (an assumption that is often not true, as described below), ECG waveforms generated during recovery of a linear fiber with uniform recovery properties may be expected to be of opposite polarity, lower amplitude, and longer duration than those due to activation. As will be described, these features are explicitly demonstrated in the clinical ECG.

THE ROLE OF TRANSMISSION FACTORS.

These activation and recovery forces exist within a complex three-dimensional physical environment (the *volume conductor*). The structures within the volume conductor modify the cardiac electrical field in significant ways.[4] They may be called *transmission factors* to emphasize their effects on transmission of the cardiac electrical field throughout the body and may be grouped into four broad categories--*cellular factors*, *cardiac factors*, *extracardiac factors*, and *physical factors*.

Cellular factors determine the intensity of current fluxes that result from local transmembrane potential gradients and include intracellular and extracellular resistance and the concentration of relevant ions, especially the sodium ion. Lower ion concentrations reduce the intensity of current flow by reducing the equivalent dipole moment and lowering extracellular potentials.

Cardiac factors affect the relationship of one cardiac cell to another. Two major factors are (1) *anisotropy*, that is, the property of cardiac tissue that results in greater current flow and more rapid propagation along the length of a fiber than transversely, and (2) the presence of connective tissue between cardiac fibers that disrupts effective electrical coupling between adjacent fibers. These factors alter the paths of extracellular currents and produce changes in the amplitude and configuration of recorded electrograms. Recording electrodes oriented along the long axis of a cardiac fiber

register larger potentials than do electrodes oriented perpendicular to the long axis, and waveforms recorded from fibers with little or no intervening connective tissue are narrow in width and smooth in contour, whereas those recorded from tissues with abnormal fibrosis are prolonged and heavily fractionated.[5]

Extracardiac factors encompass all the tissues and structures that lie between the activation region and the body surface, including the ventricular walls, intracardiac and intrathoracic blood volume, the pericardium, and the lungs, as well as skeletal muscle, subcutaneous fat, and skin. These tissues alter the cardiac field because of differences in the electrical resistivity of adjacent tissues, that is, the presence of *electrical inhomogeneities* within the torso. For example, intracardiac blood has much lower resistivity (162
-cm) than do the lungs (2150
-cm). When the cardiac field encounters the boundary between two tissues with differing resistivity, the field is altered.

Other transmission factors reflect basic laws of physics. First, changes in the distance between the heart and the recording electrode reduce potential magnitudes in accord with the *inverse square law*, that is, amplitude decreases in proportion to the square of the distance. A related factor is the effect of *eccentricity*. The heart is located eccentrically within the chest in that it lies closer to the anterior than to the posterior of the torso, so the right ventricle and the anteroseptal aspect of the left ventricle are located closer to the anterior of the chest than are other parts of the left ventricle and the atria. Therefore, ECG potentials will be higher anteriorly than posteriorly, and waveforms projected from the anterior of the left ventricle will be greater than those generated by posterior ventricular regions.

As a result of all of these factors, body surface potentials have an amplitude of only 1 percent of the amplitude of transmembrane potentials and are smoothed in detail so that surface potentials have only a general spatial relationship to the underlying cardiac events.

Figure 5-2 Example of potentials and currents generated by the activation of a single (e.g., ventricular) cardiac fiber. *Left, Panel A,* Intracellular (Phi_i) and extracellular (Phi_e) potentials are recorded with a voltmeter (V_m) from a fiber 20 mm in length. The fiber is stimulated at site X=0, and propagation proceeds from left to right. *B,* Plot of transmembrane potential (V_m) at the instant in time at which activation reaches point X_0 as a function of the length of the fiber. Positive potentials are recorded from activated tissue to the left of site X_0, and negative ones are registered from not yet excited areas to the right of site X_0. *C,* Membrane current (I_m) flows along the length of the fiber at time t_o. The outward current is the depolarizing current that propagates ahead of activation site X_0, while an inward one flows behind site X_0. *D,* Representation of the sites of peak inward and outward current flow as two point sources, a sink (at the site of peak inward current flow) and a source (at the site of peak outward current

flow) separated by distance d. The dipole produced by the source-sink pair is represented by the arrow.*(Modified from Barr RC: Genesis of the electrocardiogram. In MacFarlane PW, Lawrie TDV [eds]: Comprehensive Electrocardiography. New York, Pergamon, 1989.) Right, Formula for computing the electrical potential (phi) recorded by an electrode in terms of the distance from an extracellular dipole generated during activation of a linear cardiac fiber to the electrode (r=radius), the angle between the radius to the electrode and the dipole (O), the dipole moment (M) and extracellular conductivity (sigma). The direction of activation of the fiber is indicated.*

The modifying effect of these physical structures is a biophysical one dependent on the physical properties of the structures and the related laws of physics, in contrast to the biological cardiac generators, whose output is dependent on cellular structure and physiological and biochemical processes. Thus, ECG potentials on the body surface are dependent on both biological and biophysical properties.[6]

RECORDING ELECTRODES AND LEADS

Potentials generated by the cardiac electrical generator and modified by transmission factors are processed by a series of electrical and electronic devices to yield a clinical ECG (Fig. 5-3) . They are first sensed by electrodes placed on the torso that are configured to form various types of *leads*.

ELECTRODE CHARACTERISTICS.

Electrodes used to sense the cardiac electrical field are not passive devices that merely detect the field. Rather, they are intricate systems that are affected by the properties of the dermal and epidermal layers of the skin, the electrolytic paste applied to the skin, the electrode itself, and the mechanical contact between the electrode and skin. The net effect is a complex electrical circuit that includes the resistance, capacitance, and voltage produced by these different components and the interfaces between them. Each of these factors modifies the cardiac potentials that reach the electrodes themselves before they are displayed as an ECG.[7]

BIPOLAR AND UNIPOLAR LEAD CONFIGURATIONS.

ECG leads may be subdivided into two general types--*bipolar leads* and *unipolar leads*. A bipolar lead consists of two electrodes placed at two different sites. These leads register the difference in potential between these two sites. The actual potential at either electrode is not known, and only the difference between them is recorded. One electrode is designated as the positive input; the potential at the other, or negative, electrode is subtracted from the potential at the positive electrode to yield the bipolar potential.

Unipolar leads, in contrast, measure the absolute electrical potential at one site. To do so requires a *reference site*, that is, a site at which the potential is deemed to be zero. The reference site may be a location far away from the active electrode (as in an experimental

Figure 5-3 Components used in the recording and processing of an electrocardiogram. *(From Mirvis DM: Electrocardiography: A Physiologic Approach. St Louis, Mosby-Year Book, 1993.)*

preparation) or, as in clinical electrocardiography, a specially designed electrode configuration such as described below. The unipolar recording is then the potential sensed by a single electrode at one site--the *recording* or *active* or *exploring electrode*--in relation to the designated zero or reference potential.

Clinical Electrocardiographic Lead Systems

The standard clinical ECG includes recordings from 12 leads. These 12 leads include three *bipolar limb leads* (leads I, II, and III), six *unipolar precordial leads* (leads V_1 through V_6), and three modified unipolar limb leads (the *augmented limb leads* aV_r, aV_l, and aV_f). Definitions of the positive and negative inputs for each lead are listed in Table 5-1 .

BIPOLAR LIMB LEADS.

Bipolar limb leads record the potential differences between two limbs, as detailed in Table 5-1 and illustrated in Figure 5-4 , top. As bipolar leads, the output is the potential difference between the limbs serving as positive and negative inputs. Lead I represents the potential difference between the left arm (positive electrode) and the right arm (negative electrode), lead II displays the potential difference between the left foot (positive electrode) and the right arm (negative electrode), and lead III represents the potential difference between the left foot (positive electrode) and the left arm (negative electrode). The electrode on the right foot that is not included in these leads serves as a ground connection.

The electrical connections for these leads are such that the potential in lead II equals the sum of potentials sensed in leads I and III. That is,
I+III=II.
This relationship is known as *Einthoven's law*.

UNIPOLAR PRECORDIAL LEADS AND THE WILSON CENTRAL TERMINAL.

The unipolar precordial leads register the potential at each of the six designated torso sites (Fig. 5-4 , bottom left panel) in relation to a theoretical zero reference potential. To do so, an exploring electrode is placed on each precordial site and connected to the positive input of the recording system (Fig. 5-4 , bottom right panel).

The negative or reference input is composed of a *compound electrode* (that is, a

configuration of more than one electrode connected electrically) known as the *Wilson central terminal*. This terminal is formed by combining the output of the left arm, right arm, and left leg electrodes through 5000-
resistances (Fig. 5-4 , bottom right panel). The result is that each precordial lead registers the potential at a precordial site with reference to the average potential on three limbs. The potential recorded by the Wilson central terminal remains relatively constant during the cardiac cycle, so the output of a precordial lead is determined

TABLE 5-1 -- LOCATION OF ELECTRODES AND LEAD CONNECTIONS FOR THE STANDARD 12-LEAD ELECTROCARDIOGRAM AND ADDITIONAL LEADS

LEAD TYPE, LEAD	POSITIVE INPUT	NEGATIVE INPUT
BIPOLAR LIMB LEADS		
Lead I	Left arm	Right arm
Lead II	Left leg	Right arm
Lead III	Left leg	Left arm
AUGMENTED UNIPOLAR LIMB LEADS		
aV_r	Right arm	Left arm + left leg
aV_l	Left arm	Right arm + left leg
aV_f	Left leg	Left arm + left arm
PRECORDIAL LEADS*		
V_1	Right sternal margin,4th intercostal space	Wilson central terminal
V_2	Left sternal margin,4th intercostal space	Wilson central terminal
V_3	Midway between V_2 and V_4	Wilson central terminal
V_4	Left midclavicular line,5th intercostal space	Wilson central terminal
V_5	Left anterior axillary line	Wilson central terminal
V_6	Left midaxillary line	Wilson central terminal
V_7	Posterior axillary line	Wilson central terminal
V_8	Posterior scapular line	Wilson central terminal
V_9	Left border of spine	Wilson central terminal

*The right-sided precordial leads V_3 R to V_6 R are taken in mirror image positions on the right side of the chest: V_1 R ¬ V_2 ; V_2 R ¬ V_1 .

Leads V_5 to V_9 are taken in the same horizontal plane as V_4 .QT interval (corrected) DURATION (msec)

Figure 5-4 *Top,* Electrode connections for recording the three bipolar limb leads I, II, and III. R, L, and F indicate locations of electrodes on the right arm, the left arm, and the left foot, respectively. *Bottom,* Electrode locations and electrical connections for recording a unipolar precordial lead. *Left,* The positions of the exploring electrode (V) for the six precordial leads. *Right,* Connections to form the Wilson central terminal for recording a precordial (V) lead. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

predominantly by changes in the potential at the precordial site.

AUGMENTED UNIPOLAR LIMB LEADS.

The three augmented limb leads aV_r , aV_l , and aV_f are modified or *augmented unipolar leads*. The exploring electrode (Fig. 5-5) is the right arm electrode for lead aV_r , the left arm electrode for lead aV_l , and the left foot electrode for aV_f . It is the reference electrode that is modified. Instead of consisting of a full Wilson central terminal composed of the output from three limb electrodes, the reference potential is

Figure 5-5 Electrode locations and electrical connections for recording the three augmented unipolar leads aV_r , aV_l , and aV_f . Dotted lines indicate connections to generate the reference electrode potential.

Figure 5-6 Lead vectors for the three bipolar limb leads, the three augmented unipolar limb leads *(left),* and the six unipolar precordial leads *(right).*

the mean of the potentials sensed by only two of the three limb electrodes; the electrode used for the exploring electrode is excluded from the reference electrode. For lead aV_l , for example, the exploring electrode is on the left arm and the reference electrode is the

mean output of the electrodes on the right arm and the left foot. Similarly, for lead aV_f , the reference potential is the mean of the output of the two arm electrodes.

This modified reference system was designed to increase the amplitude of the output. The output of the limb leads without augmentation tended to be small, in part because the same electrode potential was included in both the exploring and reference potential input. Eliminating this duplication results in a theoretical increase in amplitude of 50 percent.

OTHER LEAD SYSTEMS.

Other lead systems may be used for specific purposes. For example, additional unipolar right precordial leads may be used to assess right ventricular lesions, and locations posterior to V_6 may be used to detect posterior infarctions[8] [8A] [8B] (see Table 5-1) . Such posterior locations include lead V_7 with the exploring electrode at the left posterior axillary line at the level of V_6 , lead V_8 with the exploring electrode on the left midscapular line, lead V_4 R with the exploring electrode on the right midclavicular line in the 4th intercostal space, and so forth. A vertical parasternal bipolar pair may facilitate detection of P waves for diagnosing arrhythmias.[9] Precordial and anterior-posterior thoracic electrode arrays of up to 150 (or more) electrodes may be used to display the spatial distribution of body surface potentials as *body surface isopotential maps*.[10] Modified lead systems are also used in ambulatory ECG recording and exercise stress testing, as described elsewhere, and for bedside cardiac monitoring.[11]

Other lead systems that have had clinical utility include those designed to record a *vectorcardiogram* (VCG). The VCG depicts the orientation and strength of a single cardiac dipole or vector at each instant during the cardiac cycle. Lead systems for recording the VCG are referred to as *orthogonal systems* because they record the three orthogonal or mutually perpendicular components of the dipole moment--the horizontal (x axis), frontal (y axis) and sagittal or anteroposterior (z axis) axes. Clinical use of the VCG has waned in recent years. However, the VCG may be useful in certain situations,[12] and as described below, vectorial principles remain essential to understanding the physiology and pathology of ECG waveform genesis.

LEAD VECTORS AND HEART VECTORS

A lead can be represented as a vector (the *lead vector).* For simple bipolar leads, such as leads I, II, and III, the lead vectors are directed from the negative electrode toward the positive one (see Fig. 5-6 , left). For unipolar leads such as the augmented limb and precordial leads, the origin of the lead vectors lies on the axis connecting the electrodes that make up the compound electrode. That is, for lead aV_l , the vector points from the midpoint of the axis connecting the right arm and left leg electrodes toward the left arm (see Fig. 5-6 , left). For the precordial leads, the lead vector points from the center of the torso to the precordial electrode site (Fig. 5-6 , right).

Instantaneous cardiac activity may also be approximated as a single dipole representing

the vector sum of the various active wave fronts (the *heart vector)*. Its location, orientation, and intensity vary from instant to instant because of the changing pattern of cardiac activation.

The amplitude and polarity of the potentials sensed in a lead equal the length of the projection of the heart vector on the lead vector multiplied by the length of the lead vector:

V_L =(H)(cos O) (L)

where L and H are the length of the lead and heart vectors, respectively, and O is the angle between the two vectors, as illustrated in Figure 5-7 .

If the projection of the heart vector on the lead vector points toward the positive pole of the lead axis, the lead will record a positive potential. If the projection is directed away from the positive pole of the lead axis, the potential will be negative.

The lead axes of the six frontal plane leads can be overlaid to produce the *hexaxial reference system*. As depicted in Figure 5-8, the six lead axes divide the frontal plane into 12 segments subtending 30 degrees.

Figure 5-7 The heart vector H and its projections on the lead axes of leads I and III. Voltages recorded in lead I will be positive whereas potentials in lead III will be negative.

Figure 5-8 The hexaxial reference system composed of the lead axes of the six frontal plane leads. The lead axes of the six frontal plane leads have been rearranged so that their centers overlay one another. These axes divide the plane into 12 segments, each subtending 30 degrees. Positive ends of each axis are labeled with the name of the lead.

The Electrical Axis

The concepts of the heart vector and the lead vector allow calculation of the *mean electrical axis* of the heart. The process for computing the axis of the mean force during activation (the *mean electrical axis*) is illustrated in Figure 5-9 and is the reverse of that used to compute potential magnitudes in the leads from the orientation and moment of the heart vector. The mean force during activation is represented by the area under the QRS waveform measured as millivolt-milliseconds. Areas above the baseline are assigned a positive polarity and those below the baseline have a negative polarity; the overall area equals the sum of the positive and the negative areas.

The area in each lead (typically two are chosen) is represented as a vector oriented

along the appropriate lead axis in the hexaxial reference system (see Fig. 5-8) , and the

Figure 5-9 Calculation of the mean electrical axis during the QRS complex from the areas under the QRS complex in leads I and III. Magnitudes of the areas of the two leads are plotted as vectors on the appropriate lead axes, and the mean QRS axis is the sum of these two vectors.*(From Mirvis DM: Electrocardiography: A Physiologic Approach. St Louis, Mosby-Year Book, 1993.)*

mean electrical axis equals the resultant or the sum of the two vectors. An axis directed toward the positive end of the lead axis of lead I, that is, oriented horizontally away from the right arm and toward the left arm, is designated as an axis of zero degrees. Axes oriented in a clockwise direction from this zero level are assigned positive values and those oriented in a counterclockwise direction are assigned negative values.

The mean electrical axis in the horizontal plane can be computed in an analogous manner by using the areas and the lead axes of the six precordial leads (see Fig. 5-6 , right). A horizontal plane axis located along the lead axis of lead V_6 is assigned a value of zero degrees, and those directed more anteriorly have positive values.

This process can be applied to compute the mean electrical axis for other phases of cardiac activity. Thus, the mean force during atrial activation will be represented by the areas under the P wave, and the mean force during ventricular recovery will represented by the areas under the ST-T wave. In addition, the instantaneous electrical axis can be computed at each instant during ventricular activation by using voltages or amplitudes at a specific point in time rather than using areas to calculate the axis.

The orientation of the mean electrical axis represents the direction of the activation front (or recovery direction) in an "average" cardiac fiber. The direction of the front, in turn, is determined by the interaction of three factors--the anatomical position of the heart in the chest, the properties of the cardiac conduction system, and the activation and recovery properties of the myocardium. Differences in the anatomical position of the heart within the chest would be expected to change the relationship between cardiac regions and the lead axes and would thus change recorded voltages. Similarly, changes in conduction patterns, even of minor degree, can significantly alter relationships between activation (or recovery) of various cardiac areas and, hence, the direction of instantaneous as well as mean electrical force. In practice, differences in anatomy contribute relatively little to shifts in axis[13] ; the major influences on the mean electrical axis are the properties of the conduction system and cardiac muscle.

ELECTROCARDIOGRAPHIC DISPLAY SYSTEMS

Another group of factors that determines ECG waveforms includes the characteristics of the electronic systems used to amplify, filter, and digitize the sensed signals. ECG amplifiers are *differential amplifiers*, that is, they amplify the difference between two inputs. For bipolar leads, the differential output is the difference between the two active leads; for unipolar leads, the difference is between the exploring electrode and the reference electrode. This differential configuration significantly reduces the electrical

noise that is sensed by both inputs and hence is canceled. The standard amplifier gain for routine electrocardiography is 1000 but may vary from 500 (*half-standard*) to 2000 (*double standard*).

Amplifiers respond differently to the range of signal frequencies included in an electrophysiological signal. The *bandwidth* of an amplifier defines the frequency range over which the amplifier accurately amplifies the input signals. Waveform components with frequencies above or below the bandwidth may be artifactually reduced or increased in amplitude. In addition, recording devices include high- and low-pass filters that intentionally reduce the amplitude of specific frequency ranges of the signal. Such reduction in amplitude may be done, for example, to reduce the effect of body motion or line voltage frequencies, that is, 60-Hz interference. For routine electrocardiography, the standards of the American Heart Association require a bandwidth of 0.05 to 100 Hz.

Amplifiers for routine electrocardiography include a capacitor stage between the input and the output terminals; that is, they are *capacitor coupled*. This configuration blocks direct-current (DC) voltage while permitting flow of alternating-current (AC) signals. Because the ECG waveform may be viewed as an AC signal (which accounts for the waveform shape) that is superimposed on a DC baseline (which determines the actual voltage levels of the recording), this coupling has significant effects on the recording process. First, unwanted DC potentials, such as those produced by the electrode interfaces, are eliminated. Second, elimination of the DC potential from the final product means that ECG potentials are not calibrated against an external reference level. ECG potentials must be measured in relation to an internal standard. Thus, amplitudes of waves are measured in millivolts or microvolts relative to another portion of the waveform. The TP segment, which begins at the end of the T wave of one cardiac cycle and ends with onset of the P wave of the next cycle, is usually the most appropriate internal ECG baseline.

An additional issue is the *digitizing* or *sampling rate* for computerized systems. Too low a sampling rate will miss brief signals such as

notches in QRS complexes or brief bipolar spikes and reduce the precision and accuracy of waveform morphologies. Too fast a sampling rate may introduce artifacts, including high-frequency noise, and requires excessive digital storage capacity.[14] In general, the sampling rate should be at least twice the frequency of the highest frequencies of interest in the signal being recorded. Standard electrocardiography is most commonly performed with a sampling rate of 500 Hz, with each sample representing a 2-millisecond period.

Cardiac potentials may be processed for display in numerous formats. The most common of these formats is the classic *scalar ECG*. Scalar recordings depict the potentials recorded from one lead as a function of time. For standard electrocardiography, amplitude is displayed on a scale of 1 mV to 10-mm vertical

displacement and time as 200 msec/cm on the horizontal scale. Other display formats are used for ambulatory electrocardiography, as described in Chapter 23 , and for bedside ECG monitoring.[11]

THE NORMAL ELECTROCARDIOGRAM

The heart is activated with each cardiac cycle in a very characteristic manner determined by the anatomy and physiology of working cardiac muscle and the specialized cardiac conduction systems. The waveforms and intervals that make up the standard ECG are displayed in the diagram in Figure 5-10 , and a normal 12-lead ECG is shown in Figure 5-11 . The *P wave* is generated by activation of the atria, the *PR segment* represents the duration of atrioventricular (AV) conduction, the *QRS complex* is produced by activation of both ventricles, and the *ST-T wave* reflects ventricular recovery. Table 5-2 includes normal values for the various intervals and waveforms of the ECG.

Atrial Activation and the P Wave

Atrial activation[15] begins with impulse generation in the atrial pacemaker complex in or near the sinoatrial (SA) node. The rate of discharge of the SA node and, hence, the heart rate is dependent on parasympathetic and sympathetic tone, as well as the intrinsic properties of the SA node, extrinsic factors such as mechanical stretch,[16] and various pharmacological effects (see Chap. 22) .

Increasing attention is being directed at the beat-to-beat changes in heart rate, termed *heart rate variability,* to gain insight into neuroautonomic control mechanisms and their perturbations with aging, disease, and drug effects.[17] [18] [19] [172A] [178A] [187A] [187B] For example, high-frequency (0.15-0.5 Hz) fluctuations mediated by the vagus nerve occur phasically, with heart

Figure 5-10 The waves and intervals of a normal electrocardiogram. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

rate increasing during inspiration and decreasing during expiration. Attenuation of this respiratory sinus arrhythmia is a consistent marker of physiological aging and also occurs with diabetes mellitus, congestive heart failure, and a wide range of other cardiac and noncardiac conditions that alter autonomic tone.[18] [19] [20] [187A] [187B] Lower-frequency (0.05-0.15 Hz) physiological oscillations in heart rate are associated

TABLE 5-2 -- NORMAL VALUES FOR DURATIONS OF ELECTROCARDIOGRAPHIC WAVES AND INTERVALS IN ADULTS

WAVE/INTERVAL	DURATION (msec)
P wave duration	<120
PR interval	<120-200*
QRS duration	<120*

QT interval (corrected)	440-460*

*See the text for further discussion.

Figure 5-11 Normal electrocardiogram recorded from a 48-year-old woman. The vertical lines on the grid on which the scalar electrocardiogram is recorded represent time, with lines spaced at 40-millisecond intervals. Horizontal lines represent voltage amplitude, with lines spaced at 100-muV intervals. Every fifth line in each direction is typically darkened. The heart rate is about 72 beats/min; the PR interval, QRS, and QT_c durations measure about 140, 84, and 400 milliseconds, respectively; and the mean QRS axis is approximately +35 degrees.

with baroreflex activation and appear to be jointly regulated by sympathetic and parasympathetic interactions. A variety of complementary signal processing techniques are being developed to analyze heart rate variability, including the very low-frequency (<0.05 Hz) components and circadian rhythms. These methods include time-domain statistics, frequency domain techniques based on spectral (Fourier) methods, and tools derived from nonlinear dynamics, including chaos (complexity) theory and statistical physics.[21] For further discussion, see Chapter 22 .

Once the impulse leaves this pacemaker site, atrial activation spreads in several directions. First, propagation is rapid along the crista terminalis and moves anteriorly toward the lower portion of the right atrium. It also spreads across the anterior and posterior surfaces of the atria toward the left atrium. The last area to be activated is over the inferolateral aspect of the left atrium, which is activated by convergence of these anterior and posterior wave fronts moving from right to left. Although right atrial activation begins before activation of the left atrium, activation occurs simultaneously in both atria during much of the overall atrial activation time. At the same time, activation spreads through the interatrial septum, beginning high on the right side and moving around the fossa ovalis to the reach the top of the interventricular septum.

The pattern of atrial activation noted above produces the normal P wave. Activation beginning high in the right atrium and proceeding simultaneously leftward toward the left atrium and inferiorly toward the AV node corresponds to a mean frontal plane P wave axis of approximately 60 degrees. Based on this orientation of the heart vector, normal atrial activation projects positive or upright P waves in leads I, II, aV_l , and aV_f . The pattern in lead III may be either upright or downward, depending on the exact orientation of the mean axis, that is, upright if the mean axis is more positive than +30 degrees and negative otherwise.

P wave patterns in the precordial leads correspond to the direction of atrial activation wave fronts in the horizontal plane. Atrial activation early in the P wave is oriented primarily anteriorly over the right atrium and later posteriorly over the left atrium. Thus, the P wave in the right precordial leads (V_1 and, occasionally, V_2) is commonly biphasic, with an initial positive deflection followed by a later negative one. In the more lateral leads, the P wave is upright and reflects right-to-left spread of the activation fronts.

P wave duration is normally under 120 milliseconds. The amplitude in the limb leads is normally under 250 muV, and the terminal negative deflection in the right precordial leads is normally under 100 muV in depth.

Atrial depolarization is followed by atrial repolarization. The potentials generated by atrial repolarization are not usually seen on the surface ECG because of their low amplitude (usually under 100 muV) and because they are superimposed on the much higher amplitude QRS complex.[22] They may be observed as a low-amplitude wave with a polarity opposite that of the P wave (the T_a *wave*) during heart block and may have special significance in influencing ECG patterns during exercise testing.[23] Deviation of the PR segment (corresponding to the atrial ST segment) is, as described below, also an important marker of acute pericarditis and, more rarely, atrial infarction.

AV Node Conduction and the PR Segment

The *PR segment* is the isoelectric region beginning with the end of the P wave and ending with onset of the QRS complex. It forms part of the *PR interval*, which extends from onset of the P wave to onset of the QRS complex. The normal PR interval measures 120 to 200 milliseconds in duration.

The PR segment is the temporal bridge between atrial activation and ventricular activation. It is during this period that activation of the AV node, the bundle of His, the bundle branches, and the intraventricular specialized conduction system occurs. As noted above, atrial repolarization also occurs during this period. Most of the conduction delay during this segment is due to slow conduction within the AV node.[24]

Upon exiting the AV node, the impulse traverses the bundle of His to enter the bundle branches and then travels through the specialized intraventricular conduction paths to finally activate ventricular myocardium. The PR segment appears isoelectric because the potentials generated by these structures are too small to produce detectable voltage on the body surface at the normal amplifier gains used in clinical electrocardiography. The standard ECG detects only activation and recovery of working myocardium, not the specialized conduction system. Signals from elements of the conduction system can be recorded from the body surface by using very high gains (over 25,000) and signal-averaging techniques[25] or from intracardiac recording electrodes placed against the base of the interventricular septum near the bundle of His, as described in Chapter 25 .

Ventricular excitation is the product of two temporally overlapping functions--*endocardial activation* and *transmural activation.*[26] Endocardial activation is guided by the anatomical distribution and physiology of the His-Purkinje system. The broadly dispersed ramifications of this treelike or fractal system[27] and the rapid conduction within it result in depolarization of most of the endocardial surfaces of both ventricles within several milliseconds and the simultaneous activation of multiple endocardial sites.

The sequence of ventricular endocardial activation is depicted in Figure 5-12. Earliest activity begins in three sites: (1) the anterior paraseptal wall of the left ventricle, (2) the posterior paraseptal wall of the left ventricle, and (3) the center of the left side of the septum. These loci generally correspond to the sites of insertion of the three branches of the left bundle branch. Wave fronts spread from these sites in anterior and superior directions to activate the anterior and lateral walls of the left ventricle. The posterobasal areas of the left ventricle are the last to be activated. Septal activation begins in the middle third of the left side and spreads across the septum from left to right and from apex to base.

Excitation of the right ventricle begins near the insertion point of the right bundle branch close to the base of the anterior papillary muscle and spreads to the free wall. The final areas to be involved are the pulmonary conus and posterobasal areas. Thus, in both ventricles, the overall endocardial excitation pattern begins on septal surfaces and

Figure 5-12 Activation sequence of the normal right and left ventricles. A portion of the left and right ventricles has been removed to visualize the endocardial surfaces of the ventricles and the interventricular septum. Isochrone lines connect sites that are activated at equal instants after the earliest evidence of ventricular activation.*(From Durrer D: Electrical aspects of human cardiac activity: A clinical-physiological approach to excitation and stimulation. Cardiovasc Res 2:1, 1968.)*

sweeps down and around the anterior free walls to the posterior and basal regions in an apex-to-base direction.

The activation fronts then move from endocardium to epicardium. Excitation of the endocardium begins at sites of Purkinje-ventricular muscle junctions and proceeds by muscle cell-to-muscle cell conduction in an oblique direction toward the epicardium.

This sequence of endocardial and transmural activation results in the characteristic waveforms of the QRS complex. QRS patterns are described by the sequence of waves constituting the complex. An initial negative deflection is called the *Q wave*, the first positive wave is the *R wave,* and the first negative wave after a positive wave is the *S*

wave. A second upright wave following an S wave is an *R wave*. Tall waves are denoted by capital letters and smaller ones by lowercase letters. A monophasic negative complex is referred to as a *QS complex*. Thus, for example, the overall QRS complex may be described as qRS if it consists of an initial small negative wave (the q wave) followed by a tall upright one (the R wave) and a deep negative one (an S wave). In an RSr complex, initial R and S waves are followed by a small positive wave (the r wave).

The complex pattern of activation described above can be simplified into two vectors representing septal and left ventricular free wall activation (Fig. 5-13) . Initial activation of the interventricular septum corresponds to a vector oriented from left to right in the frontal plane and anteriorly in the horizontal plane, as determined by the anatomical position of the septum within the chest. This arrangement produces an initial positive wave in leads with axes directed to the right (lead aV_r) or anteriorly (lead V_1). Leads with axes directed to the left (leads I, aV_l , V_5 , and V_6) will register initial negative waves (*septal q waves*). These initial forces are normally of low amplitude and are brief (less than 40 milliseconds). Absence of these septal q waves is associated with septal infarction or fibrosis and commonly correlates with other ECG evidence of myocardial infarction[28] and left ventricular mechanical dysfunction.[29]

Subsequent parts of the QRS complex reflect activation of the free walls of the left and right ventricles. Because right ventricular muscle mass is considerably smaller than that of the left ventricle, it contributes little to QRS complexes recorded in the standard ECG. Thus, the second phase of the normal QRS can be considered to represent only left ventricular activity with relatively little oversimplification.

Once free wall activation begins, leads with leftward axes (leads I, aV_l , V_5 , and V_6) show positive deflections following the initial septal q waves. Leads with axes oriented to the right (including lead aV_r) record negative potentials. As activation proceeds, the height of the R waves and the depth of the S waves progressively increase. Thus, leads I, aV_l , V_5 , and V_6 typically show qR patterns and lead aV_r registers rS waveforms.

The forms of the QRS complex frontal plane leads are variable and reflect differences in the mean QRS electrical axis. The normal mean QRS axis in adults lies between -30 degrees and +90 degrees. Mean QRS axes more positive than +90 degrees represent *right axis deviation,* and those more negative than -30 degrees represent *left axis deviation*. Mean axes lying between -90 and -180 degrees (or equivalently between +180 and +270 degrees) are referred to as *extreme axis deviations*. The designation *indeterminate axis* is applied when all six extremity leads show biphasic (QR or RS) patterns; this finding can occur as a normal variant or may be seen in a variety of pathological conditions.[30]

The wide span of the normal axis results in a range of QRS patterns, especially in the inferior leads. This characteristic can be understood by referring to the hexaxial reference system in Figure 5-8 . If the mean axis is near 90 degrees, the QRS complex in leads II, III, and aV_f will be predominantly upright with qR complexes; lead I will record

an isoelectric qRS pattern because the heart vector lies perpendicular to the lead axis. This configuration is commonly referred to as a *vertical heart* position, although it probably has little to do with the anatomical position of the heart within the chest.[13] If the mean axis is nearer 0 degrees, the patterns will be reversed; lead I (and aV_l) will register a predominantly upright qR pattern, and leads II, III, and aV_f will show rS or RS patterns, a configuration often referred to as a *horizontal heart* pattern.

PRECORDIAL LEADS.

In the precordial leads V_1 and V_2 , free wall activation generates S waves following the initial r waves. These S waves are produced by the spread of activation in the free wall to the left and posteriorly, with generation of a heart vector directed away from the axes of these leads. Thus, these leads are characterized by rS patterns.

Patterns in the midprecordial leads V_3 and V_4 are more variable. Potentials sensed in these leads reflect, as in the case of the right precordial leads, the activation front in the ventricular free wall approaching the exploring electrode, followed by it moving leftward and posterior to more remote regions of the left ventricle. This front generates an R or r wave and later an S wave to produce rS or RS complexes in these leads. As the exploring electrode moves laterally to the left, however, the R wave becomes more dominant and the S wave becomes smaller because of the greater time period during which the activation front moves toward the positive end of the electrode.

Thus, in the precordial leads, the QRS complex is usually characterized by consistent progression from an rS complex in the right precordial leads to a qR pattern in the left precordial leads. The point during this transition at which the pattern changes from an rS to an Rs configuration,

Figure 5-13 Schematic representation of ventricular depolarization as two sequential vectors representing septal *(left)* and left ventricular free wall *(right)* activation. QRS waveforms generated by each stage of activation in leads V_1 and V_6 are shown.

that is, the lead in which an isoelectric RS pattern is present, is known as the *transition zone* and normally occurs in leads V_3 or V_4 . An example of a normal precordial QRS pattern is shown in Figure 5-11 . Transition zones shifted to the right, i.e., to lead V_2 , are referred to as *early transitions,* and those shifted leftward to V_5 or V_6 are *delayed transitions*. These variations in the horizontal plane axis are sometimes described as *counterclockwise* and *clockwise rotations*, respectively, although these descriptors do not necessarily correlate with cardiac anatomical findings.

QRS DURATION.

The upper normal value for QRS duration is traditionally given as <120 milliseconds. In a survey of 1224 men with normal QRS morphology and frontal plane axis, the 98 percent upper bound of QRS duration was 116 milliseconds.[31] Women, on average, have somewhat smaller (about 5 to 8 milliseconds) QRS durations than men do.[32]

An additional feature of the QRS complex is the *intrinsicoid deflection*. An electrode overlying the ventricular free wall will record a rising R wave as transmural activation of the underlying ventricular free wall proceeds. Once the activation front reaches the epicardium, the full thickness of the wall under the electrode will be in an active state with no propagating electrical activity. At that moment, the electrode will register negative potentials from remote cardiac areas still undergoing activation. The sudden reversal of potential with a sharp downslope is the intrinsicoid deflection and marks the timing of activation of the epicardium under the electrode.

Ventricular Recovery and the ST-T Wave

The normal ST-T wave begins as a low-amplitude, slowly changing wave (the *ST segment*) that gradually leads to a larger wave, the *T wave*. Onset of the ST-T wave is the *junction* or *J point* and is normally at or near the isoelectric baseline of the ECG (see Fig. 5-10) .

The polarity of the ST-T wave is generally the same as the net polarity of the preceding QRS complex. Thus, T waves are upright in leads I, II, aV_l , aV_f , and the lateral precordial leads. They are negative in leads aV_r and variable in leads III and V_1 through V_3 .

Like activation, recovery in the ventricles occurs in a characteristic geometrical pattern. Differences in recovery timing occur both across the ventricular wall and between regions of the left ventricle. Transmural differences in recovery times are the net result of two effects--differences in action potential duration across the ventricular wall and the relatively slow spread of activation across the wall.[33] As activation moves from endocardium to epicardium, sites further away from the endocardium are activated later and later in sequence. However, action potential durations are longest near the endocardium and shortest near the epicardium, which produces a transmural gradient in recovery periods. Differences in action potential duration are greater than differences in activation times, so recovery is completed near the epicardium before it is completed near the endocardium. For example, one endocardial site may be excited 10 milliseconds earlier than the overlying epicardium (that is, transmural activation may require 10 milliseconds), and the action potential duration at the endocardium may be 22 milliseconds longer than on the epicardium. As a result, recovery will be completed 12 milliseconds earlier in the epicardium than in the endocardium.

The resulting recovery dipole will then be directed from sites of less recovery (that is, the endocardium) toward sites of greater recovery (that is, near the epicardium). The

orientation of this dipole is in the same direction as transmural activation dipoles and is contrary to the expected direction as described earlier in this chapter; this difference is due to the presence of nonuniform recovery properties across the wall. If recovery times were uniform across the wall (or if differences in recovery times were less than differences in transmural activation times), the recovery dipole would have been directed toward the endocardium, that is, in the direction opposite the activation dipole. The result is, in normal persons, *concordant* QRS and ST-T wave patterns.

Regional differences in recovery properties likewise exist. Under normal conditions, it is the transmural gradients that predominantly determine ST patterns. However, as will be described, these regional differences account for the discordant ST-T patterns observed with intraventricular conduction defects.

THE QRST ANGLE.

This concordance between orientation of the QRS complex and ST-T wave can also be expressed vectorially. An angle can be visualized between the vector representing the mean QRS force and that representing the mean ST-T force--the *QRST angle*. This angle in the frontal plane is normally less than 60 degrees and usually under 30 degrees. Abnormalities of the QRST angle reflect abnormal relationships between the properties of activation and recovery.

THE VENTRICULAR GRADIENT.

If the two vectors representing mean activation and mean recovery forces are added, a third vector known as the *ventricular gradient* is created. The concept of the ventricular gradient was developed to assess differences in the properties of ventricular activation and recovery. According to this concept, the more variability that exists in regional repolarization properties, the greater the difference from zero of the sum of the QRS and ST-T areas will be. In other words, the net QRST area, as measured by the ventricular gradient, correlates with the magnitude of regional differences in recovery properties. In addition, because changes in activation patterns produced by, for example, bundle branch block also cause corresponding changes in recovery patterns (see below), the ventricular gradient should allow a measure of regional recovery properties that is independent of the activation pattern. This measurement has possible relevance to the genesis of reentrant arrhythmias that are due, in part, to regional variations in refractory periods.

The U Wave

The T wave may be followed by an additional low-amplitude wave known as the *U wave*. It is usually under 100 muV in amplitude, normally has the same polarity as the preceding T wave, and is largest in the midprecordial leads and at slow heart rates. Its basis in cardiac electrophysiology is uncertain, but it may be caused by repolarization of the Purkinje fibers or by delayed repolarization in areas of the ventricle that undergo late mechanical relaxation.[34]

The QT Interval

A final interval of the ECG waveform is the *QT interval*, which is measured from the beginning of the QRS complex to the end of the T wave. It includes the total duration of ventricular activation and recovery and, in a general sense, corresponds to the duration of the ventricular action potential.

The normal QT interval is defined by its duration, measured in milliseconds. Like the ventricular action potential duration, the duration of the QT interval decreases as heart rate increases. Thus, the normal range for the QT interval is rate dependent. One formula for relating QT interval duration to heart rate was developed by Bazett in 1920. The result is computation of a *corrected QT interval,* or QT_c , by using the equation $QT_c = QT/(R - R)^{½}$ where the QT and RR intervals are measured in seconds. The normal QT_c is generally accepted to be less than or equal to 440 milliseconds. Some studies suggest that it may be 20 milliseconds longer, and it is slightly longer, on average, in women (see Chapter 25) . Because the end of the T wave can overlap with the beginning of a U wave, the QT interval is sometimes referred to as the *QT(U) interval*; this designation is particularly appropriate when considering the ECG effects of certain metabolic abnormalities that alter the duration of repolarization and the amplitude of the U wave (see below).

The Bazett formula, while widely used to adjust the QT interval duration for the effects of heart rate, has limited accuracy in predicting the effects of heart rate on the QT interval. Many other formulas and methods for correcting the QT interval for the effects of heart rate, including logarithmic, hyperbolic, and exponential functions, have been developed and tested, but they also have limitations.[35] [36] These limitations result from both physiological and computational problems. On one hand, the Bazett formula predicts an ever-increasing increment in the QT interval as the heart rate slows and an ever-decreasing increment as the rate rises, both of which are physiologically improbable. In addition, all these formulas do not account for the effects of autonomic tone on the QT interval independent of the effects on rate. They also do not account for the relatively slow adaptation of repolarization to changes in rate; for example, several minutes

may be required for the QT interval to reach a new steady state after an abrupt change in heart rate.

A second property of the QT interval is that its duration is lead dependent, that is, the duration of the QT interval varies from lead to lead. In normal persons, the QT interval varies between leads by up to 50 milliseconds and is longest in the midprecordial leads V_2 and V_3 . This range of intervals, referred to as *QT interval dispersion*,[37] [38] may be

related to electrical instability and the risk of ventricular arrhythmogenesis.[38A]

Normal Variants

These descriptions of the waveforms of the normal ECG represent patterns most often observed in normal adults. It is important to understand the limitations of assigning and interpreting normal ranges to ECG measurement. Values for many of the intervals and amplitudes to be described vary widely within the population as a function of age, race, gender, and body habitus and within individuals as a function of autonomic tone and activity level. Thus, what is normal in one condition may be abnormal in another. Tables of values for these and other measures for different population subgroups have been published.[39] Some variations have been described above, including, for example, variations in rate, QRS axis, and QT intervals.

Other common variations occur in patterns of the ST segment and T wave. These variations are important to recognize because they may be mistaken for significant abnormalities. First, ST-T patterns are affected by maneuvers that change autonomic tone. For example, changing body position, hyperventilating, drinking cold water, and performing the Valsalva maneuver can produce modest ST segment depression and T wave inversion in as many as one-third of subjects.[40]

T waves can be inverted in the right precordial leads (Fig. 5-14). In adults, this inversion reflects the uncommon, but not necessarily abnormal persistence of patterns commonly seen in infants and children. T waves can be inverted in all precordial leads at birth and usually become more limited to the right side of the chest as time passes; by the age of 10 years, T wave inversion is generally limited to leads V_1 and V_2 . A *persistent juvenile pattern* is more common in women than in men and among the black population than among other racial or ethnic groups.[41]

Figure 5-14 Normal tracing with a juvenile T wave inversion pattern in leads V_1 , V_2 , and V_3 , as well as early repolarization pattern manifested by ST segment elevation in leads I, II, aV_f , V_4 , V_5 , and V_6 . *(Courtesy of C. Fisch, M.D.)*

Second, the ST segment can be significantly elevated, especially in the midprecordial leads (Fig. 5-15). The elevation begins from an elevated J point, is usually concave in form, is commonly associated with notching of the downstroke of the QRS complex, and can reach 500 muV in amplitude.[42] This pattern is more common at slow than at rapid heart rates and in men than in women and is most often seen among black men.[41] [42A] Although this physiological ST segment elevation pattern is commonly referred to as *early repolarization*, clinical studies have failed to demonstrate an earlier than normal onset of ventricular recovery.[43]

THE ABNORMAL ELECTROCARDIOGRAM

Atrial Abnormalities

Various pathological and physiological events alter the normal sequence of atrial activation and produce abnormal P wave patterns in the ECG. Three general categories of P

Figure 5-15 Normal variant pattern with functional ST elevations ("early repolarization" variant). These benign ST segment elevations are usually most marked in the midprecordial leads (V_4 here). Note the absence of reciprocal ST depression (except in lead aV_r), as well as the absence of PR segment deviation, which may be helpful in the differential diagnosis of ischemia and pericarditis, respectively. Note also that lead II has a baseline recording shift. *(From Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

wave changes will be described, including those reflecting abnormal sites or patterns of activation, those caused by left atrial abnormalities, and those resulting from right atrial abnormalities.

ABNORMAL SITES OF ATRIAL ACTIVATION.

Shifts in the site of initial activation away from the SA node to other, ectopic sites can lead to major changes in the pattern of atrial activation and, hence, in the morphology of P waves.[44] These shifts can occur either as escape rhythms if the normal SA nodal pacemaker fails or as accelerated ectopic rhythms if the automaticity of an ectopic site is enhanced (see AV dissociation, Chap. 25) . The resulting ECG abnormalities most commonly include recording negative P waves in the leads in which P waves are normally upright (leads I, II, aV_f , and V_4 through V_6), with or without shortening of the PR interval.

P wave patterns may suggest the site of impulse formation based on simple vectorial principles.[44A] For example, a negative P wave in lead I predicts a left atrial rhythm. Inverted P waves in the inferior leads normally correspond to a posterior atrial site. Because of the uncertainties with this localization, these ECG patterns can as a group be referred to as *ectopic atrial rhythms*.

Left Atrial Abnormality

ECG ABNORMALITIES.

Anatomical or functional abnormalities of the left atrium alter the morphology, duration, and amplitude of the P waves in the clinical ECG. Specific abnormalities include

increases in the amplitude and duration of the P wave in the limb leads, as well as an increase in the amplitude of the terminal negative portion of the P wave in lead V_1 . These features are illustrated in Figures 5-16 and 5-17 .

DIAGNOSTIC CRITERIA.

Commonly used criteria for diagnosing left atrial abnormality are listed in Table 5-3 .

MECHANISMS FOR ECG ABNORMALITIES.

These ECG patterns may reflect increases in left atrial mass or chamber size or reflect conduction delays within the atria. Increasing mass causes increased P wave amplitudes. Because the left atrium is activated (in general) late during the P wave, the increased electrical force accounts for the prolonged P wave duration and the augmented P terminal force in the right precordial leads.

Clinical conditions associated with these patterns also correlate with delays in interatrial conduction. For example, the interval between the onset of the P wave marking the onset of right atrial activation and the onset of left atrial activation is commonly prolonged. This delay prolongs P wave duration and shortens the PR segment. It also reduces the overlap between right and left atrial activation so that the ECG patterns generated by each atrium are separated as two notches in lead II (*P mitrale*).

DIAGNOSTIC ACCURACY.

The diagnostic accuracy of these criteria is limited. Comparison of the various ECG abnormalities to echocardiographic criteria for left atrial enlargement demonstrates limited sensitivity but high specificity for the ECG criteria. For example, recent studies have demonstrated that the presence of classic P mitrale patterns has a sensitivity of only 20 percent but a specificity of 98 percent for detecting echocardiographically enlarged left atria[45] and that P wave duration has limited correlation with left atrial pressure and dimension.[46] Others have reported better correlations of these ECG abnormalities with ventricular dysfunction (e.g., with reduced ventricular compliance) than with atrial morphology.[47] Because of the correlation of these ECG features with high atrial pressure, intraatrial conduction defects, and ventricular dysfunction, as well as increased atrial size, these ECG abnormalities are preferably referred to as criteria for *left atrial abnormality* rather than left atrial enlargement.

CLINICAL SIGNIFICANCE.

ECG findings of left atrial abnormality are associated with more severe left ventricular dysfunction in patients with ischemic heart disease and with more severe valve damage in patients with mitral or

Figure 5-16 Schematic representation of atrial depolarization *(diagram)* and P wave patterns associated with normal atrial activation (left panel) and with right *(middle panel)* and left *(right panel)* atrial abnormalities. *(Modified from Park MK, Guntheroth WG: How to Read Pediatric ECGs. 3rd ed. St Louis, Mosby-Year Book, 1993.)*

Figure 5-17 Biatrial abnormality, with tall P waves in lead II (right atrial abnormality) and an abnormally large terminal negative component of the P wave in lead V_1 (left atrial abnormality). The P wave is also notched in lead V_5 .

aortic valve disease.[48] Patients with left atrial changes may have paroxysmal atrial tachyarrhythmias.

Right Atrial Abnormality

ECG ABNORMALITIES.

ECG features of *right atrial abnormality* are illustrated in Figures 5-16 and 5-17 . They include abnormally high P wave amplitudes in the limb and right precordial leads. As in the case of left atrial abnormality, the term *right atrial abnormality* is preferred over others such as right atrial enlargement.

DIAGNOSTIC CRITERIA.

Criteria commonly used to diagnose right atrial abnormality are listed in Table 5-3 .

MECHANISMS FOR ECG ABNORMALITIES.

Greater right atrial mass generates greater electrical force early during overall atrial activation, with production of taller P waves and augmentation of the initial P wave deflection in lead V_1 . In patients with chronic lung disease, the abnormal P pattern may reflect a more vertical heart position within the chest caused by pulmonary hyperinflation rather than true cardiac damage. The QRS changes commonly associated with right atrial abnormalities correspond to the underlying pathology that is producing the right atrial hemodynamic changes--right ventricular hypertrophy (RVH), which produces tall R waves in the right precordial leads, and a shift of the position of the heart within the chest by obstructive lung disease, which produces initial Q waves.

DIAGNOSTIC ACCURACY.

As in the case of ECG criteria for left atrial abnormality, the finding of right atrial abnormality has limited sensitivity but high specificity. Echocardiographic correlations

have shown, for example, that P pulmonale has very low sensitivity but very high specificity for detecting right atrial enlargement.[49] The highest sensitivities are found for cases with a P wave initial force in lead V_1 of over 0.06 mm-sec (38 percent) or with low-amplitude QRS complexes in lead V_1 (33 percent).

CLINICAL SIGNIFICANCE.

ECG findings of right atrial abnormality are found in patients with chronic obstructive pulmonary disease. Patients with this ECG pattern have more severe pulmonary dysfunction, as well as significantly reduced survival.[50] However, comparison of ECG and hemodynamic parameters has not demonstrated a close correlation of P wave patterns and right atrial hypertension.[51]

Other Atrial Abnormalities

Patients with abnormalities in both atria--that is, biatrial abnormality--may have ECG patterns reflecting each defect. Suggestive findings include large biphasic P waves in lead V_1 and tall and broad P waves in leads II, III, and aV_f (see Fig. 5-17) .

P wave and PR segment changes can also be seen in patients with atrial infarction or pericarditis. The changes caused by these conditions will be described later in this chapter.

Ventricular Hypertrophy and Enlargement

Left Ventricular Hypertrophy and Enlargement

ECG ABNORMALITIES.

Left ventricular hypertrophy (LVH) or enlargement produces changes in the QRS complex, the ST segment, and the T wave. The most characteristic finding is increased amplitude of the QRS complex. R waves in leads facing the left ventricle (that is, leads I, aV_l , V_5 , and V_6) are taller than normal, while S waves in leads overlying the right ventricle (that is, V_1 and V_2) are deeper than normal. These changes are illustrated schematically in Figure 5-18 .

ST-T wave patterns vary widely in patients with left ventricular enlargement and hypertrophy. ST segment and T wave amplitudes may be normal or increased in leads with tall R waves. In many patients, however, the ST segment is depressed and followed by an inverted T wave (Fig. 5-19) . Most often, the ST segment slopes downward from a depressed J point and the T wave is asymmetrically inverted. These repolarization changes usually occur in patients with QRS changes but can appear alone. Particularly prominent inverted T waves, or so-called *giant negative T waves*, are characteristic of hypertrophic cardiomyopathy

TABLE 5-3 -- COMMON DIAGNOSTIC CRITERIA FOR LEFT AND RIGHT ATRIAL ABNORMALITIES*

LEFT ATRIAL ABNORMALITY
Prolonged P wave duration of >120 msec in lead II
Prominent notching of the P wave, usually most obvious in lead II, with an interval between the notches of >40 msec (*p mitrale*)
Ratio between the duration of the P wave in lead II and the duration of the PR segment of >1.6
Increased duration and depth of the terminal negative portion of the P wave in lead V_1 (the *P terminal force*) so that the area subtended by it exceeds 0.04 mm-sec
Leftward shift of the mean P wave axis to between -30 and +45 degrees
RIGHT ATRIAL ABNORMALITY
Peaked P waves with amplitudes over 250 muV in lead II (*p pulmonale*)
Rightward shift of the mean P wave axis to above 75 degrees
Increased area under the initial positive portion of the P wave in lead V_1 to >0.06 mm-sec

*In addition to criteria based on P wave morphologies, right atrial abnormalities are suggested by QRS changes, including (1) Q waves (especially qR patterns) in the right precordial leads without evidence of myocardial infarction and (2) low amplitude (under 600 muV) QRS complexes in lead V_1 with a threefold or greater increase in lead V_2 .

Figure 5-18 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left (and posteriorly). In addition, repolarization abnormalities can cause ST segment depression and T wave inversion in leads with a prominent R wave (formerly referred to as a "strain" pattern). Right ventricular hypertrophy (RVH) can shift the QRS vector to the right; this effect is usually associated with an R, RS, or qR complex in lead V_1 , especially when due to severe pressure overload. T wave inversions may be present in the right precordial leads.*(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

with predominant apical thickening, especially in patients from the Pacific Rim (Yamaguchi syndrome)[52] (see also Fig. 5-48) .

Other ECG changes can also be seen in LVH, including widening and notching of the QRS complex. An increase in QRS duration beyond 110 milliseconds and a delay in the intrinsicoid deflection may reflect the longer duration of activation in a thickened ventricular wall or damage to the ventricular conduction system. Notching of the QRS

complex may also be observed.

These ECG features are most typical of LVH induced by pressure or "systolic" overload of the left ventricle. Volume overload or "diastolic overload" can produce a somewhat different ECG pattern, including tall, upright T waves and sometimes narrow (under 25 milliseconds), but deep (0.2 mV or greater) Q waves in leads facing the left side of the septum (Fig. 5-20) . The diagnostic value of these changes in predicting the underlying hemodynamics is, however, very limited.

MECHANISMS FOR ECG ABNORMALITIES.

High voltages may be produced by any of several mechanisms. They may be due directly to an increase in left ventricular mass. This increase in mass is due to an enlargement in cell size, with an increase in surface area increasing transmembrane current flow and an increase in the number of intercalated disks enhancing intercellular current flow. This effect is augmented by an increase in the size of activation fronts moving across the thickened wall; these larger wave fronts subtend larger solid angles and result in higher body surface voltage. The high voltage as well as QRS prolongation may also be due to conduction system delays.[53] The delay in intrinsicoid deflection is a result of the prolonged transmural activation time required to activate the thickened wall, as well as delayed endocardial activation, while notching may be produced by the fractionation of activation wave fronts by intramural scarring associated with wall thickening and damage.

In addition, changes in transmission factors can contribute to ECG abnormalities. Left ventricular enlargement can shift the position of the heart so that the lateral free wall lies closer than normal to the chest wall, which as described above, would increase body surface potentials in accordance with the inverse square law. Also, ventricular dilatation increases the size of the highly conductive intraventricular blood pool.[4] This enhanced blood volume results in an increase in potentials produced by transmural activation fronts, a phenomenon referred to as the *Brody effect*.

Repolarization abnormalities may reflect a primary disorder of repolarization that accompanies the cellular processes of hypertrophy.

Figure 5-19 Marked left ventricular hypertrophy (LVH) pattern with prominent precordial lead QRS voltages. ST depression and T wave inversion may be seen with severe LVH in leads with a predominant R wave (compare with Fig. 5-20) . Left atrial abnormality is also present.

Figure 5-20 Left ventricular hypertrophy with prominent positive anterior T waves from a patient with

severe aortic regurgitation. This pattern has been described with "diastolic overload" syndrome but has limited sensitivity and specificity. Serum potassium was normal.

Alternatively, they may reflect subendocardial ischemia. Patients with LVH may have coronary artery disease; hypertension--a major cause of ventricular hypertrophy--is a risk factor for coronary atherosclerosis. Ischemia may be induced in the absence of coronary artery disease by the combination of high oxygen demand caused by high wall tension and limited blood flow to the subendocardium of the thickened wall.

DIAGNOSTIC CRITERIA.

Several sets of diagnostic criteria for LVH have been developed on the basis of these ECG abnormalities. Details of widely used criteria are presented in Table 5-4 . Most commonly used methods assess the presence or absence of LVH as a binary function based on an empirically determined set of criteria. For example, the Sokolow-Lyon and the Cornell[54] voltage criteria require that voltages in specific leads exceed certain values. The Romhilt-Estes point score system assigns point values to amplitude and other criteria; definite LVH is diagnosed if 5 points are computed and probable LVH is diagnosed if 4 points are computed. The Cornell voltage-duration method[55] includes measurement of QRS duration as well as amplitudes.

Other methods seek to quantify left ventricular mass as a continuum. Diagnosis of LVH can then be based on a computed mass that exceeds an independently determined threshold. Two recently developed sets of criteria applying this approach are the Cornell regression equation[54] and the Novacode[56] system.

DIAGNOSTIC ACCURACY.

The relative diagnostic accuracy of these methods has been tested by radiographic, echocardiographic, and autopsy measurements of left ventricular size as standards.[54] [55] In general, these studies have reported low sensitivity and high specificity. Sensitivities are lowest (approximately 10 to 30 percent) for the Sokolow-Lyon and Romhilt-Estes criteria and higher for the Cornell voltage and voltage-duration criteria and for the Cornell and Novacode regression methods (35 to 50 percent). Specificities, in contrast, for all measures vary from 85 percent to 95 percent. Thus, all methods are limited as screening tests in which high sensitivities (few false-negatives) are critical but have good reliability as diagnostic tests when few false-positives are desired.

TABLE 5-4 -- COMMON DIAGNOSTIC CRITERIA FOR LEFT VENTRICULAR HYPERTROPHY

Sokolow-Lyon index
S_{V1} +(R_{V5} or R_{V6})>3.5 mV
R_{aVl} >1.1 mV
Romhilt-Estes point score system *

Any limb lead R wave or S wave 2.0 mV	3 points
S_{V1} or S_{V2} 3.0 mV	3 points
R_{V5} to R_{V6} 3.0 mV	3 points
ST-T wave abnormality (no digitalis therapy)	3 points
ST-T wave abnormality (digitalis therapy)	1 point
P terminal force in V_1 >4 mV-msec	3 points
Left axis deviation	1 point
Intrinsicoid deflection in V_5 or V_6 50 msec	1 point

Cornell voltage criteria [54]

S_{V3} +R_{aVl} 2.8 mV (for men)

S_{V3} +R_{aVl} 2.0 mV (for women)

Cornell regression equation[54]

$Risk=1/(1+e^{-exp})$

Where

$exp=4.558-0.092\ (R_{aV1}+S_{V3})-0.306\ T_{V1}-0.212\ QRS-0.278\ PTF_{V1}-0.859\ (sex)$

Where voltages are in mV, QRS is QRS duration in mV, PTF is the area in the P terminal force in lead V_1 (in mm-sec), and sex=1 for men and 2 for women; LVH is present if exp is less than -1.55

Cornell voltage-duration measurement[55]

QRS duration×Cornell Voltage>2436

QRS duration×sum of voltages in all 12 leads>17,472

Novacode criterion (for men) [56]

$LVMI\ (gm/m^2)=-36.4+0.010\ R_{V5}+0.20\ S_{V1}+0.28\ S_{III}+0.182\ T_{(neg)}\ V_6-0.148\ T_{(pos)}\ aV_r+1.049\ QRS_{duration}$

where neg and pos refer to amplitudes of the negative and positive portions of the T waves, respectively; S indicates the amplitude of the S, Q, and QS wave, whichever is larger

*Probable left ventricular hypertrophy is diagnosed if 4 points are present and definite left ventricular hypertrophy is diagnosed if 5 or more points are present.

LVH=left ventricular hypertrophy; LVMI=left ventricular mass index.R/S in V_1 >1 with R >0.5 mV

Several reasons may be suggested for the limited accuracy of these criteria. Many of the clinical studies that were used to define the criteria included a disproportionate number of white men, thus limiting applicability of the tests to other populations; LVH is more common among blacks.[57] In addition, the criteria for dichotomous tests such as the Sokolow-Lyon and Cornell voltage criteria are based on quantitative differences in normally occurring measures, i.e., QRS voltage, between normal and abnormal cohorts; these tests by their nature are limited to detecting only the extreme end of the spectrum of LVH because milder degrees overlap with normal populations.[58] Finally, these voltage measurements are subject to the influence of many noncardiac factors, such as body habitus, which blurs the distinction between normal and abnormal.[59] [59A]

CLINICAL SIGNIFICANCE.

The presence of ECG criteria for LVH identify a subset of the general population with a significantly increased risk for cardiovascular morbidity and mortality.[56] [57] [58] [59] [59A] [60] This increased risk is particularly true in women and if ST-T wave abnormalities are present; the relative risk of cardiovascular events for patients with LVH voltage criteria alone is approximately 2.8, whereas the relative risk increases to over 5.0 if ST segment depression is also present.[57] [61] [62]

In patients with cardiac disease, the ECG finding of LVH correlates with more severe disease, including higher blood pressure in hypertensives and greater ventricular dysfunction in patients with hypertension or coronary artery disease.[63] In contrast, effective treatment of hypertension reduces ECG evidence of LVH and decreases the associated risk of cardiovascular mortality.[61] Patients with repolarization abnormalities have, on average, more severe degrees of LVH and more commonly have symptoms of left ventricular dysfunction,[64] in addition to a greater risk of cardiovascular events.[61]

Right Ventricular Hypertrophy and Enlargement

ECG ABNORMALITIES.

The ECG changes invoked by RVH or right ventricular enlargement are different from those produced by left ventricular enlargement because the right ventricle is considerably smaller than the left ventricle and produces electrical forces that are largely canceled by those generated by the larger left ventricle. Thus, for RVH to be manifested on the ECG, it must be severe enough to overcome the canceling effects of the larger left ventricular forces. In addition, increasing dominance of the right ventricle changes the ECG in fundamental ways, whereas an enlarged left ventricle produces

predominantly quantitative changes in underlying normal waveforms.

ECG changes associated with moderate to severe concentric hypertrophy of the right ventricle[65] include abnormally tall R waves in anteriorly and rightward directed leads (leads aV_r , V_1 , and V_2) and deep S waves and abnormally small r waves in leftward directed leads (I, aV_l , and lateral precordial leads) (see Figs. 5-18 and 5-21) . These changes result in a reversal of normal R wave progression in the precordial leads, a shift in the frontal plane QRS axis to the right, and sometimes the presence of S waves in leads I, II, and III (*so-called S_1 S_2 S_3 pattern*).

Several other ECG patterns of RVH also exist. Less severe hypertrophy, especially when limited to the outflow tract of the right ventricle that is activated late during the QRS complex, produces less marked changes. ECG abnormalities may be limited to an rSr
pattern in V_1 and persistence of s (or S) waves in the left precordial leads. This pattern is typical of right ventricular volume overload as produced by an atrial septal defect.

Chronic obstructive pulmonary disease can induce ECG changes by producing RVH, changes in the position of the heart within the chest, and hyperinflation of the lungs (Fig. 5-22). QRS changes caused by the insulating and positional changes produced by hyperinflation of the lungs include reduced amplitude of the QRS complex, right axis deviation in the frontal plane, and delayed transition in the precordial leads (probably reflecting a vertical and caudal shift in heart position because of hyperinflation and a flattened diaphragm). Evidence of true RVH includes (1) marked right axis deviation (more positive than 110 degrees), (2) deep S waves in the lateral precordial leads,

Figure 5-21 Right ventricular hypertrophy pattern most consistent with severe pressure overload. Note the combination of findings, including (1) a tall R wave in V_1 (as part of the qR complex), (2) right axis deviation, (3) T wave inversion in V_1 through V_3 , (4) delayed precordial transition zone (rS in V_6), and (5) right atrial abnormality. An S_1 Q_3 pattern is also present and can occur with acute or chronic right ventricular overload syndrome.

Figure 5-22 Pulmonary emphysema simulating anterior infarction in a 58-year-old man with no clinical evidence of coronary disease. Note the relative normalization of R wave progression with placement of the chest leads an interspace below their usual position ($5V_1$, $5V_2$, and so forth). *(From Chou TC: Pseudo-infarction (noninfarction Q waves). In Fisch C [ed]: Complex Electrocardiography. Vol 1. Philadelphia, FA Davis, 1973.)*

and (3) *an S_1 Q_3 T_3 pattern*, with an S wave in lead I (as an RS or rS complex), an

abnormal Q wave in lead III, and an inverted T wave in the inferior leads.

Finally, acute right ventricular pressure overload such as produced by pulmonary embolism may produce a characteristic ECG pattern (Fig. 5-23) , including (1) a QR or qR pattern in the right ventricular leads; (2) an S_1 Q_3 T_3 pattern with an S wave in lead I and new or increased Q waves in

Figure 5-23 Acute cor pulmonale secondary to pulmonary embolism simulating inferior and anterior infarction. This tracing exemplifies the classic pseudoinfarct patterns sometimes seen: an S_1 Q_3 T_3 , a QR in V_1 with poor R wave progression in the right precordial leads ("clockwise rotation"), and right precordial to midprecordial T wave inversion (V_1 to V_4). Sinus tachycardia is also present. The S_1 Q_3 pattern is usually associated with a QR or QS complex, but not an rS, in aV_r . Furthermore, acute cor pulmonale per se does not cause prominent Q waves in II (only in III and aV_f). *(From Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

TABLE 5-5 -- COMMON DIAGNOSTIC CRITERIA FOR RIGHT VENTRICULAR HYPERTROPHY

CRITERION	SENSITIVITY(%)	SPECIFICITY(%)
R in V_1 0.7 mV	<10	--
QR in V_1	<10	--
R/S in V_1 >1 with R >0.5 mV	25	89
R/S in V_5 or V_6 <1	<10	--
S in V_5 or V_6 0.7 mV	17	93
R in V_5 or V_6 0.4 mV with S in V_1 0.2 mV	<10	--
Right axis deviation (+90 degrees)	14	99
S_1 Q_3 pattern	11	93
S_1 S_2 S_3 pattern	<10	--
P pulmonale	11	97

From Murphy ML, Thenabadu PN, de Soyza N, et al: Reevaluation of electrocardiographic criteria for left, right and combined cardiac ventricular hypertrophy. Am J Cardiol 53:1140-1147, 1984.

lead III and sometimes aV_f , with T wave inversions in those leads; (3) ST segment deviation and T wave inversions in leads V_1 to V_3 ; and (4) incomplete or complete right bundle branch block (RBBB). Sinus tachycardia is usually present. Arrhythmias such as atrial fibrillation can also occur. However, even with major pulmonary artery obstruction, the ECG is notoriously deceptive and may show little more than minor or nonspecific waveform changes, or it may even be normal.[66] The classic S_1 Q_3 T_3 pattern occurs in only about 10 percent of cases of acute pulmonary embolism. Furthermore, the specificity of this finding is limited since it can occur acutely with other causes of pulmonary hypertension.

DIAGNOSTIC CRITERIA.

These ECG abnormalities form the basis for the diagnostic criteria for RVH. The most commonly relied on criteria for the ECG diagnosis of RVH are listed in Table 5-5 .

MECHANISMS FOR ECG ABNORMALITIES.

These ECG patterns result from three effects of RVH. First, current fluxes between hypertrophied cells are stronger than normal and produce higher than normal voltage on the body surface. Second, activation fronts moving through the enlarged right ventricle are larger than normal and produce higher surface potentials as predicted by the solid angle theorem.[67] Third, the activation time of the right ventricle is prolonged.[67] This last effect is particularly important in producing ECG changes; right ventricular activation now ends after the completion of left ventricular activation, so its effects are no longer canceled by the more powerful forces of the left ventricle and may merge in the ECG. Because the right ventricle is located anterior as well as to the right of the left ventricle, the effects produce increased potentials in leads directed anteriorly and to the right, especially late during the QRS complex. As noted above, changes in cardiac position in patients with obstructive lung disease can produce ECG changes without intrinsic cardiac electrophysiological derangements.

DIAGNOSTIC ACCURACY.

The sensitivity and specificity of the individual ECG criteria are also shown in Table 5-5 . As in the case of ECG criteria for other abnormalities, the sensitivities of individual criteria are low and specificities are high. If any one feature is present, the sensitivity rises to over 50 percent with a specificity of over 90 percent; requiring any two features to make a diagnosis markedly reduces the sensitivity and raises the specificity to very high levels. These low sensitivities may reflect the marked degree of hypertrophy required to produce ECG abnormalities.

CLINICAL SIGNIFICANCE.

ECG evidence of RVH has limited value in assessing the severity of pulmonary hypertension or lung disease. QRS changes do not generally appear until ventilatory function is significantly depressed, with the earliest change commonly being a rightward shift in the mean QRS axis, and correlation with either ventilatory function or hemodynamics is poor. The presence of either right atrial abnormality, an $S_1\ S_2\ S_3$ pattern, or both is associated with reduced survival, especially if an increased arterial-alveolar oxygen gradient is also present.[52] ECG findings of acute right ventricular overload in patients with pulmonary embolism correspond to obstruction of over 50 percent of the pulmonary arterial bed and significant pulmonary hypertension.

Biventricular Enlargement

Enlargement or hypertrophy of both ventricles produces complex ECG patterns.[67A] In contrast to biatrial enlargement, the result is not the simple sum of the two sets of abnormalities. The effects of enlargement of one chamber may cancel the effects of enlargement of the other; for example, anterior forces produced by RVH may be canceled by enhanced posterior forces generated by LVH. In addition, the greater left ventricular forces generated in LVH increase the degree of RVH needed to overcome the dominance of the left ventricle.

Because of these factors, specific ECG criteria for either RVH or LVH are seldom observed with biventricular enlargement. Rather, ECG patterns are usually modification of the features of LVH and include (1) tall R waves in both the right and left precordial leads, (2) vertical heart position or right axis deviation in the presence of criteria for LVH, (3) deep S waves in the left precordial leads in the presence of ECG criteria for LVH, or (4) a shift in the precordial transition zone to the left in the presence of LVH. The presence of prominent left atrial abnormality or atrial fibrillation with evidence of right ventricular or biventricular enlargement (especially LVH with a vertical or rightward QRS axis) should suggest chronic rheumatic valvular disease (Fig. 5-24) (see Chap. 46) .

Intraventricular Conduction Delays and Preexcitation

The ECG patterns described in this section reflect abnormalities in the conduction system (see Chaps. 22 , 23 , and 25 .)

Fascicular Blocks

Under normal conditions, activation of the left ventricle begins simultaneously at the insertion sites of the fascicles. Delayed conduction in a fascicle--*fascicular block*--results in activation of these sites sequentially rather than simultaneously and produces an abnormal sequence of early left ventricular activation. This altered sequence produces characteristic ECG patterns. Even modest delays in conduction through the affected structure may be enough to alter ventricular activation patterns sufficiently to produce

characteristic ECG patterns; complete block of conduction is not required.

LEFT ANTERIOR FASCICULAR BLOCK.

Damage to the left anterior fascicle is a very common occurrence because of the delicate nature of the structure. The ECG features of left anterior fascicular block (LAFB) are listed in Table 5-6 and illustrated in Figure 5-25. The most characteristic finding is marked left axis deviation. However, LAFB is not synonymous with left axis deviation. Axis shifts to between -30 and -45 degrees commonly reflect other conditions, e.g., LVH, without conduction system damage and are best referred to as *left axis deviation* rather than LAFB.

Left axis shift is a result of delayed activation of the anterosuperior left ventricular wall. Delayed activation causes unbalanced inferior and posterior forces early during ventricular activation and unopposed anterosuperior forces later during the QRS complex. The abnormal pattern results in initial r waves followed by deep S waves in the inferior

Figure 5-24 This electrocardiogram from a 45-year-old woman with severe mitral stenosis shows multiple abnormalities. The rhythm is sinus tachycardia. Right axis deviation and a tall R wave in lead V_1 are consistent with right ventricular hypertrophy. The very prominent biphasic P wave in lead V_1 indicates left atrial abnormality/enlargement. The tall P waves in lead II suggest concomitant right abnormality. Nonspecific ST-T changes and incomplete right bundle branch block are also present. The combination of right ventricular hypertrophy and marked left or biatrial abnormality is highly suggestive of mitral stenosis. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

TABLE 5-6 -- COMMON DIAGNOSTIC CRITERIA FOR UNIFASCICULAR BLOCKS

LEFT ANTERIOR FASCICULAR BLOCK
Frontal plane mean QRS axis of -45 to -90 degrees with rS patterns in leads II, III, and aV_f and a qR pattern in lead aV_l
QRS duration less than 120 msec
LEFT POSTERIOR FASCICULAR BLOCK
Frontal plane mean QRS axis of 120 degrees
RS pattern in leads I and aV_l with qR patterns in inferior leads
QRS duration of less than 120 msec

Exclusion of other factors causing right axis deviation (e.g., right ventricular overload patterns, lateral infarction)

leads (left axis deviation with rS patterns) and a qR pattern in left-looking leads (leads aV_l and usually V_5 and V_6). Initial q waves in these leads reflect the normal left-to-right activation of the septum. The overall QRS duration is not prolonged; fascicular block only alters the sequence of left ventricular activation but does not by itself prolong the overall duration of ventricular excitation or the QRS complex. LAFB usually does not produce prominent changes in the precordial leads. V_1 and V_3 are usually unchanged; V_4 through V_6 commonly show deep S waves related to superiorly directed late QRS forces.[68]

LAFB is common in persons without overt cardiac disease, as well as a wide range of diseases, and has minimal or no independent prognostic significance. Commonly associated

Figure 5-25 Diagrammatic representation of fascicular blocks in left ventricles. Interruption of the left anterior fascicle (LAF) *(left)* results in an initial inferior (1) followed by a dominant superior (2) direction of activation; interruption of the left posterior fascicle (LPF) *(right)* results in an initial superior (1) followed by a dominant inferior (2) direction of activation. AVN=atrioventricular node; HB=His bundle; LB=left bundle; RB=right bundle. *(Courtesy of C. Fisch, M.D.)*

cardiac and systemic conditions include myocardial infarction, especially occlusion of the left anterior descending coronary artery,[69] LVH, hypertrophic and dilated cardiomyopathy, and degenerative diseases. The development of LAFB with rS complexes in II, III, and aV_f can mask the Q waves of a prior inferior myocardial infarction.

LEFT POSTERIOR FASCICULAR BLOCK.

Conduction delay in the left posterior fascicle is considerably less common than delay in the anterior fascicle because of its thicker structure and more protected location near the left ventricular inflow tract. The conduction delay results in sequential activation of the anterosuperior left ventricular free wall, followed by activation of the inferoposterior aspect of the left ventricle, that is, the reverse of the pattern observed with LAFB.

ECG features of left posterior fascicular block (LPFB), listed in Table 5-6 and illustrated in Figure 5-25 , reflect this altered activation pattern. Right axis deviation with rS patterns in leads I and aV_l , as well as qR complexes in the inferior leads, is the result of early unopposed activation forces from the anterosuperior aspect of the left ventricle (producing the initial q and r waves) and late unopposed forces from the inferoposterior

free wall (generating the late S and R waves). As in the case of LAFB, the overall activation time of the ventricles is not prolonged and the QRS duration remains normal.

LPFB, like LAFB, can occur in almost any cardiac disease but is unusual in otherwise healthy persons. Other conditions that enhance electrical forces from the right ventricle, such as right ventricular enlargement and extensive lateral infarction, can produce similar ECG patterns and must be excluded before a diagnosis of LPFB is made.

Figure 5-26 Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6 . Note the secondary T wave inversions (*arrows*) in leads with an rSR
complex with RBBB and in leads with a wide R wave with LBBB. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

TABLE 5-7 -- COMMON DIAGNOSTIC CRITERIA FOR BUNDLE BRANCH BLOCKS

COMPLETE LEFT BUNDLE BRANCH BLOCK
QRS duration 120 msec
Broad, notched R waves in lateral precordial leads (V_5 and V_6) and usually leads I and aV_l
Small or absent initial r waves in right precordial leads (V_1 and V_2) followed by deep S waves
Absent septal q waves in left-sided leads
Prolonged intrinsicoid deflection (>60 msec) in V_5 and V_6 *
COMPLETE RIGHT BUNDLE BRANCH BLOCK
QRS duration 120 msec
Broad, notched R waves (rsr , rsR , or rSR patterns) in right precordial leads (V_1 and V_2)
Wide and deep S waves in left precordial leads (V_5 and V_6)

*Criterion required by some authors.

Left bundle branch block (LBBB) results from conduction delay or block in any of several sites in the intraventricular conduction system, including the main left bundle branch, in each of the two fascicles, or less commonly, within the fibers of the bundle of His that become the main left bundle branch. The result is extensive reorganization of the activation pattern of the left ventricle.

ECG ABNORMALITIES.

LBBB produces a prolonged QRS duration, abnormal QRS complexes, and ST-T wave abnormalities (Fig. 5-26). Commonly accepted diagnostic criteria for LBBB are listed in Table 5-7 . Basic requirements include a prolonged QRS duration to 120 milliseconds or beyond; broad, sometimes notched R waves in leads I and aV_L and the left precordial leads; narrow r waves followed by deep S waves in the right precordial leads; and absent septal q waves. R waves are typically tall and S waves are deep. The mean QRS axis with LBBB is highly variable; it can be normal or deviated to the left. Left axis deviation is associated with more severe conduction system disease that includes the fascicles as well as the main left bundle.[70] In addition to these features, some electrocardiographers require a delayed intrinsicoid deflection (60 milliseconds) to diagnose LBBB.

ST-T wave changes are also prominent with LBBB. In most cases, the ST wave and the T wave are *discordant* with the QRS complex; that is, the ST segment is depressed and the T wave is inverted in leads with positive QRS waves (leads I, aV_L , V_5 , and V_6), while the ST segment is elevated and the T wave is upright in leads with negative QRS complexes (leads V_1 and V_2).

An incomplete form of LBBB may result from lesser degrees of conduction delay in the left bundle branch system. Left ventricular activation begins, as in complete LBBB, on the right side of the septum, but much of left ventricular activation occurs through the normal specialized conduction system. ECG features include (1) loss of septal q waves (reflecting reversal of the normal pattern of septal activation), (2) slurring and notching of the upstroke of R waves (because of the presence of competing activation fronts), and (3) modest prolongation of the QRS complex (between 100 and 120 milliseconds).

MECHANISMS FOR ECG ABNORMALITIES.

The ECG abnormalities of LBBB result from an almost completely reorganized pattern of left ventricular activation. Initial septal activation occurs on the right (rather than on the left) septal surface, and right ventricular excitation occurs earlier than normal. This sequence of septal activation results in the absence of normal septal q waves in the ECG.

The excitation wave then spreads slowly, by conduction from muscle cell to muscle cell, to the left side of the septum; the earliest left ventricular activation begins as late as 30 to 50 milliseconds into the QRS complex. Endocardial activation of the left ventricle may then require an additional 40 to over 180 milliseconds, depending largely on the

functional status of the distal left bundle and Purkinje systems.[71] Thus, the overall QRS complex is prolonged and can be very wide in patients with, for example, ventricular scarring from prior myocardial infarction. Once left ventricular activation begins, it proceeds in a relatively simple and direct manner around the free wall and, finally, to the base of the heart. Direct progression of activation

across the left ventricle projects continuous positive forces to left-sided leads and continuous negative ones to right-sided leads. Spread predominantly through working muscle fibers rather than the specialized conduction system results in notching and slurring as a consequence of discontinuous anisotropy, as described above.

The discordant ST-T wave pattern is a result of the transventricular recovery gradients referred to above. With LBBB, the right ventricle is activated and recovers earlier than the left, so recovery vectors or dipoles are directed toward the right and away from the left. Hence, positive ST-T waves will be registered over the right ventricle and negatives ones over the left ventricle. These transventricular gradients play only a minor role in normal conduction because the simultaneous activation of multiple regions cancels the forces that they produce; with bundle branch block, activation is sequential, so cancellation is reduced. Because the ST-T wave changes with LBBB are generated by abnormalities in conduction, they are called *secondary T wave abnormalities*; as will be discussed below, ST-T wave changes produced by direct abnormalities of the recovery process are referred to as *primary T wave abnormalities.*

CLINICAL SIGNIFICANCE.

LBBB usually appears in patients with underlying heart disease. It is associated with significantly reduced long-term survival, with 10-year survival rates as low as 50 percent, probably reflecting the severity of the underlying cardiac disease. Among patients with coronary artery disease, the presence of LBBB correlates with more extensive disease, more severe left ventricular dysfunction, and reduced survival rates.[72] Patients with associated left axis deviation have more severe clinical manifestations.[73] The paradoxical combination of complete LBBB with right axis deviation has been reported as a marker of severe myocardial disease, especially dilated cardiomyopathy.[74]

In addition to the hemodynamic abnormalities produced by these underlying conditions, the abnormal ventricular activation pattern of LBBB itself induces hemodynamic perturbations,[75] including abnormal systolic function with dysfunctional contraction patterns, reduced ejection fraction and lower stroke volumes, and abnormal diastolic function; reversed splitting of the second heart sound and functional mitral regurgitation are common. In addition, functional abnormalities in phasic coronary blood flow and reduced coronary flow reserve caused by delayed diastolic relaxation[76] often result in septal or anteroseptal defects on exercise perfusion scintigraphy in the absence of coronary artery disease.[77] Pharmacological stress testing with dobutamine or

adenosine may be more specific than exercise scintigraphy in diagnosing left anterior descending coronary stenosis in the presence of LBBB.[78]

A major impact of LBBB lies in obscuring or simulating other ECG patterns. The diagnosis of LVH is complicated by the increased QRS amplitude and axis shifts intrinsic to LBBB; in addition, the very high prevalence of anatomical LVH in combination with LBBB makes defining criteria with high specificity difficult. The diagnosis of infarction may be obscured; as will be described, the emergence of abnormal Q waves with infarction is dependent on a normal initial sequence of ventricular activation, which is absent with LBBB. In addition, ECG patterns of LBBB, including low R wave amplitude in the midprecordial leads and ST-T wave changes, can simulate anterior infarct patterns.

Right Bundle Branch Block

RBBB is a result of conduction delay in any portion of the right-sided intraventricular conduction system. The delay can occur in the main right bundle branch itself, in the bundle of His, or in the distal right ventricular conduction system. The latter is the common cause of RBBB after right ventriculotomy performed, for example, to correct the tetralogy of Fallot. The relative fragility of the right bundle branch, as suggested by the development of RBBB after minor trauma produced by right ventricular catheterization, corresponds to the high prevalence of RBBB in the general population.

ECG ABNORMALITIES.

Major features of RBBB are illustrated in Figure 5-26, and commonly used diagnostic criteria are listed in Table 5-7 . As with LBBB, the QRS complex duration exceeds 120 milliseconds. The right precordial leads show prominent and notched R waves with rsr, rsR
, or rSR
patterns, while leads I, aV_L , and the left precordial leads demonstrate wide S waves that are longer in duration than the preceding R wave. Septal q waves are preserved because the initial ventricular activation remains unchanged. The ST-T waves are, as in LBBB, discordant with the QRS complex, so T waves should be inverted in the right precordial leads (and other leads with a terminal R
wave) and upright in the left precordial leads and in leads I and aV_L .

The mean QRS axis is not altered by RBBB. Axis shifts can occur, however, as a result of the simultaneous occurrence of fascicular block along with RBBB. This concurrence of RBBB with either LAFB (producing left axis deviation) or LPFB (producing right axis deviation) is termed *bifascicular block*, as described below. The electrophysiological consequences of these abnormalities are discussed in Chapters 22 , 23 , and 25 .

Features indicative of *incomplete right bundle branch block* (IRBBB), produced by lesser delays in conduction in the right bundle branch system, are commonly seen. This finding is most frequently characterized by an rSr

pattern in lead V_1 with a QRS duration between 100 and 120 milliseconds.

MECHANISMS FOR ECG ABNORMALITIES.

With delay or block in the proximal right bundle branch system, activation of the right side of the septum is initiated after slow transeptal spread of activation from the left septal surface. The right ventricular free wall is then excited slowly, with variable participation of the specialized conduction system. The result is slowed and delayed activation of the right ventricle with much or all of the right ventricle undergoing activation after activation of the left ventricle has been completed. Consequently, the electrical forces generated by the right ventricle are not, as in normal conduction, canceled by the more powerful forces from the left ventricle and emerge in the ECG late in the QRS complex. In addition, because left ventricular activation remains relatively intact, the early portions of the QRS complex are normal. Delayed activation of the right ventricle causes prolongation of the QRS duration, while the late and unopposed emergence of right ventricular forces produces increased anterior and rightward voltage in the ECG. Discordant ST-T wave patterns are generated by same mechanisms as for LBBB; with RBBB, recovery forces are directed toward the earlier-activated left ventricle and away from the right. While these ECG changes of IRBBB are commonly attributed to conduction defects, they can reflect RVH without intrinsic dysfunction of the conduction system.

CLINICAL SIGNIFICANCE.

RBBB is a common finding in the general population, and many persons with it have no clinical evidence of structural heart disease. In this group without overt heart disease, the ECG finding has no prognostic significance. However, the new onset of RBBB does predict a higher rate of coronary artery disease, congestive heart failure, and cardiovascular mortality. When cardiac disease is present, the coexistence of RBBB suggests advanced disease with, for example, more extensive multivessel disease and reduced long-term survival in patients with ischemic heart disease.[79] An apparently specific entity known as the *Brugada syndrome* has been described in which RBBB with persistent ST segment elevation in the right precordial leads is associated with susceptibility to ventricular tachyarrhythmias and sudden cardiac death[80] [81] (see Chapter 25) .

RBBB interferes with other ECG diagnoses, although to a lesser extent than LBBB does. The diagnosis of RVH is more difficult to make with RBBB because of the accentuated potentials in lead V_1 . RVH is suggested, although with limited accuracy, by the presence of an R wave in lead V_1 that exceeds 1.5 mV and a rightward shift of the mean QRS axis. The usual criteria for LVH can be applied but have lower sensitivities than with normal conduction. The combination of left atrial abnormality or left axis deviation with RBBB also suggests underlying LVH.[82]

Figure 5-27 Sinus rhythm at 95 beats/min with 2:1 atrioventricular block. Conducted ventricular beats show a pattern consistent with bifascicular block with delay or block in the right bundle and left anterior fascicle. The patient underwent pacemaker implantation.

Multifascicular Blocks

The term *multifascicular block* refers to conduction delay in more than one of the structural components of the specialized conduction system, that is, the left bundle branch, the left anterior and posterior fascicles, and the right bundle branch. Conduction delay in any two fascicles is called *bifascicular block,* and delay in all three fascicles is called *trifascicular block*.

Bifascicular block can have several forms, including RBBB with LAFB, which is characterized by the ECG pattern of RBBB plus left axis deviation beyond -45 degrees (Fig. 5-27) , or RBBB with LPFB, with an ECG pattern of RBBB and a mean QRS axis deviation to the right of +120 degrees (Fig. 5-28) . LBBB is often considered to reflect unifascicular block, although as discussed above, it can result from delay in both the anterior and posterior fascicles.

Figure 5-28 Sinus rhythm with a 2:1 atrioventricular block. QRS morphology in the conducted leads is consistent with bifascicular block with delay or block in the right bundle and left posterior fascicle. Subsequently, complete heart block was also noted. The patient underwent pacemaker implantation.

Figure 5-29 Multifascicular block manifested by alternating bundle branch blocks and PR intervals. *Top panel,* V_1 right bundle branch block (RBBB) with a PR interval of 280 milliseconds. *Middle panel*, V_1 left bundle branch block (LBBB) with a PR interval of 180 milliseconds. *Lower panel*, RBBB alternating with LBBB, along with alternation of the PR interval. The electrocardiographic records shown in leads I, II, and III (L1 to L3) exhibit left anterior fascicular block. An alternating bundle branch block of this type is consistent with trifascicular conduction delay. *(From Fisch C: Electrocardiography of Arrhythmias. Philadelphia, Lea & Febiger, 1990, p 433.)*

This paradox represents one of the inadequacies of current ECG terminology and the simplification inherent in the trifascicular schema of the conduction system.[83]

Trifascicular block involves conduction delay in the right bundle branch plus delay in either the main left bundle branch or both the left anterior and the left posterior fascicles.

The resulting ECG pattern is dependent on (1) the relative degree of delay in the affected structures and (2) the shortest conduction time from the atria to the ventricles through any one fascicle. Ventricular activation begins at the site of insertion of the branch with the fastest conduction time and spreads from there to the remainder of the ventricles. For example, if delay in the right bundle branch is less than the delay in the left main bundle branch, activation will begin in the right ventricle and the QRS pattern will resemble that of LBBB. If the delay were greater in the right bundle branch than in the left bundle branch, the ECG pattern would be that of RBBB. The fascicle with the greatest delay can vary with, for example, the heart rate and lead to changing or alternating conduction patterns, as illustrated in Figure 5-29 .

What distinguishes ECG patterns of trifascicular block from those of bifascicular block is an increased overall AV conduction interval that results specifically from prolongation of the His-ventricular time. In bifascicular block, conduction time through the unaffected fascicle (and hence, overall AV conduction time) is normal. In trifascicular block, however, the delay in conduction through even the least affected fascicle is abnormal and results in relative prolongation of the overall AV conduction interval. (Note that only delay, not block of conduction is required. If block were present in all fascicles, conduction would fail and complete heart block would result. This situation is perhaps best illustrated by cases of alternating bundle branch block [see Fig. 5-29]; if the block were total in one bundle branch, development of block in the other would produce complete AV block rather than a change in bundle branch block patterns.) Thus, a diagnosis of trifascicular block requires an ECG pattern of bifascicular block *plus* evidence of prolonged AV conduction.

Detecting AV conduction delay is best accomplished by intracardiac recordings as a prolongation of the H-V interval. On the surface ECG, AV conduction delay may be manifested as a prolonged PR interval. However, the PR interval includes conduction time in the AV node, as well as in the intraventricular conduction system. Prolonged intraventricular conduction may be insufficient to extend the PR interval beyond normal limits, while a prolonged PR interval can reflect concomitant delay in the AV node rather than in all three intraventricular fascicles. Thus, the finding of a prolonged PR interval in the presence of an ECG pattern of bifascicular block is not diagnostic of trifascicular block, while the presence of a normal PR interval does not exclude this finding (see Chap. 25) .

The major clinical implication of a multifascicular block is its relation to advanced conduction system disease. It may be a marker for advanced myocardial disease and may identify patients at risk for heart block (see Figs. 5-27 and 5-28), as discussed further in Chapter 25 .

Rate-Dependent Conduction Block (Aberration)

Intraventricular conduction delays can result from the effects of changes in the heart rate, as well as from fixed pathological lesions in the conduction system.[84] *Rate-dependent block* or *aberration* can occur at either high or low heart rates. In *acceleration (tachycardia)-dependent block* or *phase 3 block*, conduction delay occurs when the heart rate exceeds a critical value. At the cellular level, this aberration is the

result of encroachment of the impulse on the relative refractory period (usually in phase 3 of the action potential) of the preceding impulse, which results in slower conduction. This form of block is relatively common and can have the ECG pattern of RBBB or LBBB (Figs. 5-30 and 5-31) .

Figure 5-30 Atrial tachycardia with a Wenckebach (type I) atrioventricular (AV) block, ventricular aberration resulting from the Ashman phenomenon, and probably concealed transseptal conduction. The long pause of the atrial tachycardia is followed by five QRS complexes with right bundle branch block (RBBB) morphology. The RBBB of the first QRS reflects the Asman phenomenon. The aberration is perpetuated by concealed transseptal activation from the left bundle (LB) into the right bundle (RB) with block of anterograde conduction of the subsequent sinus impulse in the RB. Foreshortening of the R-R cycle, a manifestation of the Wenckebach structure, disturbs the relationship between transseptal and anterograde sinus conduction, and RB conduction is normalized. In the ladder diagram below the tracing, the solid lines represent the His bundle, the dashes represent the RB, the dots represent the LB, and the solid horizontal bars denote the refractory period. P waves and the AV node are not identified in the diagram. *(Courtesy of C. Fisch, M.D.)*

In *deceleration (bradycardia)-dependent block* or *phase 4 block*, conduction delay occurs when the heart rate falls below a critical level. Although the mechanism is not clearly established, it may reflect abnormal phase 4 depolarization of cells so that activation occurs at lower resting potentials. Deceleration-dependent block is less common than acceleration-dependent block and is usually seen only in patients with significant conduction system disease (Fig. 5-32) .

Other mechanisms of ventricular aberration include concealed conduction (anterograde or retrograde) in the bundle branches (Figs. 5-30 and 5-31), premature excitation, depressed myocardial conduction as a result of drug effects or hyperkalemia (see Fig. 5-51 , top), and the effect of changing cycle length on refractoriness (the *Ashman phenomenon*). The duration of the refractory period is a function of the immediately preceding cycle length: the longer the preceding cycle, the longer the subsequent refractory period. Therefore, abrupt prolongation of the immediately preceding cycle can result in aberration as part of a long cycle-short cycle sequence. These so-called Ashman beats usually have a RBBB morphology (see Fig. 5-30) .

WOLFF-PARKINSON-WHITE PREEXCITATION.

This abnormality is discussed in Chapter 25 .

Figure 5-31 Acceleration-dependent QRS aberration with the paradox of persistence at a longer cycle and normalization at a shorter cycle than what initiated the aberration. The duration of the basic cycle (C) is 760 milliseconds. Left bundle branch block (LBBB) appears at a cycle length of 700 milliseconds (dot) and is perpetuated at cycle lengths of 800 (

) and 840 (
) milliseconds; conduction normalizes after a cycle length of 600 milliseconds. Perpetuation of LBBB at a cycle length of 800 and 840 (
) milliseconds is probably due to transseptal concealment, similar to that described in Figure 5-30. Unexpected normalization of the QRS (S) following the atrial premature contraction is probably due to equalization of conduction in the two bundles; however, supernormal conduction in the left bundle cannot be excluded. *(From Fisch C, Zipes DP, McHenry PL: Rate dependent aberrancy. Circulation 48:714, 1973.)*

Myocardial Ischemia and Infarction (See Chap. 35)

The ECG remains a key test in the diagnosis of acute and chronic coronary syndromes.[85] [86] [87] The findings vary considerably, depending importantly on four major factors: (1) the *duration* of the ischemic process (acute vs. evolving/chronic), (2) its *extent* (transmural vs. subendocardial), (3) its *topography* (anterior vs. inferior-posterior and right ventricular), and (4) the presence of *other underlying abnormalities* (e.g., LBBB, Wolff-Parkinson-White [WPW], or pacemaker patterns) that can mask or alter the classic patterns.

Repolarization (ST-T Wave) Abnormalities

The earliest and most consistent ECG finding during acute ischemia is deviation of the ST segment as a result of a *current-of-injury mechanism*. Under normal conditions, the ST segment is usually nearly isoelectric (i.e., flat along the baseline) because healthy myocardial cells attain approximately the same potential during early repolarization, which corresponds to the plateau phase of the ventricular action potential. Ischemia has complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia can reduce the resting membrane potential, shorten the duration of the action potential in the ischemic area, and also decrease the rate of rise and amplitude of phase 0 (Fig. 5-33) . These changes cause a voltage

Figure 5-32 Deceleration-dependent aberration. The basic rhythm is sinus with a Wenckebach (type I) atrioventricular (AV) block. With 1:1 AV conduction, the QRS complexes are normal in duration; with a 2:1 AV block or after the longer pause of a Wenckebach sequence, left bundle branch block (LBBB) appears. Slow diastolic depolarization (phase 4) of the transmembrane action potential during the prolonged cycle is implicated as the cause of the LBBB. *(Courtesy of C. Fisch, M.D.)*

Figure 5-33 Acute ischemia may alter ventricular action potentials by inducing lower resting membrane potential, decreased amplitude and velocity of phase 0, and an abbreviated action potential duration (pathological early repolarization). These electrophysiological effects create a voltage gradient between ischemic and normal cells during different phases of the cardiac electrical cycle. The resulting currents of

injury are reflected on the surface electrocardiogram by deviation of the ST segment (see Fig. 5-34) .

gradient between normal and ischemic zones that leads to current flow between these regions. These currents of injury are represented on the surface ECG by deviation of the ST segment.

Both *diastolic* and *systolic injury currents* have been invoked to explain ischemic ST elevations (Fig. 5-34). According to the diastolic-current-of-injury hypothesis, ischemic ST elevation is attributable to negative (downward) displacement of the electrical "diastolic" baseline (TQ segment of the ECG). At least partly because of transmembrane leakage of intracellular potassium ions, ischemic cells may remain relatively depolarized during phase 4 of the ventricular action potential (i.e., lower membrane resting potential) (see Fig. 5-33).[88] Depolarized muscle carries a negative extracellular charge relative to repolarized muscle. Therefore, during electrical diastole, current (diastolic current of injury) will flow between the partly or completely depolarized ischemic myocardium and the normally repolarized uninjured myocardium. The *injury current vector* will be directed away from the more negative ischemic zone toward the electropositive normal myocardium. As a result, leads overlying the ischemic zone will record a negative deflection during electrical diastole and produce depression of the TQ segment.

TQ segment depression, in turn, appears as ST segment elevation because the ECG recorders in clinical practice use AC-coupled amplifiers that automatically "compensate" for any negative shift in the TQ segment. As a result of this electronic compensation, the ST segment will be proportionately elevated. Therefore, according to the diastolic-current-of-injury theory, ST segment elevation represents an *apparent shift.* The true shift, observable only with DC-coupled ECG amplifiers, is the negative displacement of the TQ baseline.

Current evidence suggests that ischemic ST elevations (and hyperacute T waves) are also related to systolic injury currents. Three factors may make acutely ischemic myocardial cells relatively positive in comparison to normal cells with respect to their extracellular charge during electrical systole (QT interval): (1) pathological early repolarization (shortened action potential duration), (2) decreased action potential upstroke velocity, and (3) decreased action potential amplitude (see Fig. 5-33) . The presence of one or more of these effects will establish a voltage gradient between normal and ischemic zones during the QT interval such that the current-of-injury vector will be directed toward the ischemic region. This systolic-current-of-injury mechanism will result in primary ST elevation, sometimes with tall positive (hyperacute) T waves.[89]

When acute ischemia is *transmural* (whether caused by diastolic and/or systolic injury currents), the overall ST vector is usually shifted in the direction of the outer (epicardial) layers, and ST elevation and sometimes tall positive (hyperacute) T waves are produced over the ischemic zone (Fig. 5-35) . Reciprocal ST depressions can appear in leads reflecting the contralateral surface of the heart. (Occasionally, the reciprocal changes can be more apparent than the primary ST elevations.)[90] [91] [92] When ischemia is confined primarily to the *subendocardium*, the overall ST vector typically shifts toward the inner ventricular layer and the ventricular cavity such that the overlying (e.g.,

anterior precordial) leads show ST segment depression with ST elevation in lead aV_r (see Fig. 5-35). This subendocardial ischemic pattern is the typical finding during spontaneous episodes of angina pectoris or during symptomatic or asymptomatic ("silent") ischemia induced by exercise or pharmacological stress tests (see Chaps. 34 and 35) .

Multiple factors can affect the *amplitude* of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. Conversely, prompt resolution of ST elevation following thrombolytic therapy[93] [94] [94A] or primary angioplasty[95] is a specific marker of successful reperfusion. However, these relationships are not universal since severe ischemia or even infarction

Figure 5-34 Pathophysiology of ischemic ST elevation. Two basic mechanisms have been advanced to explain the elevation seen with acute myocardial injury. *A, Diastolic current of injury*. In this case (first QRS-T complex), the ST vector will be directed away from the relatively negative, partly depolarized, ischemic region during electrical diastole (TQ interval), and the result will be primary TQ depression. Conventional alternating-current electrocardiograms compensate for the baseline shift, and an apparent ST elevation (second QRS-T complex) results. *B, Systolic current of injury*. In this case, the ischemic zone will be relatively positive during electrical systole because the cells are repolarized early and the amplitude and upstroke velocity of their action potentials may be decreased. This injury current vector will be oriented toward the electropositive zone, and the result will be primary ST elevation. (After Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)

Figure 5-35 Current-of-injury patterns with acute ischemia. With predominant subendocardial ischemia *(A)*, the resultant ST vector is directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore record ST depression. With ischemia involving the outer ventricular layer *(B)* (transmural or epicardial injury), the ST vector is directed outward. Overlying leads record ST elevation. Reciprocal ST depression can appear in contralateral leads.

can occur with slight or even absent ST-T changes. Furthermore, a relative increase in T wave amplitude (hyperacute T waves) can accompany or precede the ST elevations as part of the injury current pattern attributable to ischemia with or without infarction[89] (Fig. 5-36) .

QRS Changes

With actual infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities (Fig. 5-37) . Necrosis of sufficient myocardial tissue can lead to decreased R wave amplitude or Q waves in the anterior, lateral, or inferior leads as a result of loss of electromotive forces in the infarcted area.[85] Local conduction delays caused by acute ischemia can also contribute to Q wave pathogenesis in selected

cases. Abnormal Q waves were once considered markers of transmural myocardial infarction, while subendocardial (nontransmural) infarcts were thought to not produce Q waves. However, careful experimental and clinical ECG-pathological correlative studies have indicated that transmural infarcts can occur without Q waves and that subendocardial infarcts can sometimes be associated with Q waves.[96] [97] Accordingly, infarcts are better classified electrocardiographically as "Q wave" or "non-Q-wave" based on the ECG. The findings may be somewhat different with posterior or lateral infarction (Fig. 5-38) . Loss of depolarization forces in these regions can reciprocally *increase* R wave amplitude in lead V_1 and sometimes V_2 , rarely without causing diagnostic Q waves in any of the conventional leads.[98] The differential diagnosis of prominent right precordial R waves is given in Table 5-8 .

Evolution of ECG Changes

When ischemic ST elevation and hyperacute T wave changes occur as the earliest sign of acute infarction, they are typically followed within a period ranging from hours to days by evolving T wave inversion and sometimes Q waves in the same lead distribution (see Fig. 5-37) . T wave

Figure 5-36 Hyperacute phase of extensive anterior-lateral myocardial infarction. Marked ST elevation melding with prominent T waves is present across the precordium, as well as in leads I and aV_l . ST depression, consistent with a reciprocal change, is seen in leads III and aV_f . Q waves are present in leads V_3 through V_6 . Marked ST elevations with tall T waves caused by severe ischemia are sometimes referred to as a monophasic current-of-injury pattern. A paradoxical increase in R wave amplitude (V_2 and V_3) may accompany this pattern. This tracing also shows left axis deviation with small or absent inferior R waves, which raises the possibility of a prior inferior infarct.

Figure 5-37 Sequence of depolarization and repolarization changes with *(A)* acute anterior-lateral and *(B)* acute inferior wall Q wave infarctions. With anterior-lateral infarcts, ST elevation in leads I, aV_l , and the precordial leads may be accompanied by reciprocal ST depression in leads II, III, and aV_f . Conversely, acute inferior (or posterior) infarcts may be associated with reciprocal ST depression in leads V_1 to V_3 . (After Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)

inversion from evolving or chronic ischemia correlates with increased ventricular action potential duration, and these ischemic changes are often associated with QT prolongation. The T wave inversion can resolve after days or weeks or persist indefinitely. The extent of the infarct may be an important determinant of T wave evolution.[98A] In one series, T waves that were persistently negative for more than 1 year in leads with Q waves were associated with a transmural infarction with fibrosis of the

entire wall; in contrast, T waves that were positive in leads with Q waves correlated with nontransmural infarction with viable myocardium within the wall.[99]

In the days to weeks or longer following infarction, the QRS changes can persist or begin to resolve. Complete normalization of the ECG following Q wave infarction is uncommon but can occur, particularly with smaller infarcts and when the left ventricular ejection fraction and regional wall motion improve. The latter is usually associated with spontaneous recanalization or good collateral circulation[100] and is a good prognostic sign. [101] In contrast, persistent Q waves and ST elevation several weeks or more after an infarct correlate strongly with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm. The presence of

Figure 5-38 Evolving inferoposterolateral infarction. Note the prominent Q waves in II, III and aV_f , along with ST elevation and T wave inversion in these leads, as well as V_3 through V_6 . ST depression in I, aV_r , V_1 , and V_2 is consistent with a reciprocal change. Relatively tall R waves are also present in V_1 and V_2 .

TABLE 5-8 -- DIFFERENTIAL DIAGNOSIS OF TALL R WAVES IN V_1 /V_2

Physiological/positional factors
Misplacement of chest leads
Normal variants
Displacement of heart toward right side of chest (dextroversion): congenital or acquired
Myocardial injury
Posterior (and/or lateral) myocardial infarction (see Fig. 5-38)
Duchenne muscular dystrophy (see Chap. 71)
Ventricular enlargement
Right ventricular hypertrophy (usually with right axis deviation)
Hypertrophic cardiomyopathy
Altered ventricular depolarization
Right ventricular conduction abnormalities
Wolff-Parkinson-White patterns (caused by posterior or lateral wall preexcitation)
Modified from Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.

an rSR
or similar complex in the midleft chest leads or lead I is another reported marker of ventricular aneurysm (*el-Sherif sign*).

OTHER ISCHEMIC ST-T PATTERNS.

Reversible transmural ischemia caused, for example, by coronary vasospasm may cause transient ST segment elevation (Fig. 5-39). This pattern is the ECG marker of Prinzmetal variant angina (see Chap. 36) . Depending on the severity and duration of such noninfarction ischemia, the ST elevation can either resolve completely within minutes or be followed by T wave inversion that can persist for hours or even days. Some patients with ischemic chest pain have deep *coronary* T wave inversion in multiple precordial leads (e.g., V_1 through V_4), with or without cardiac enzyme elevations. This finding is typically caused by severe ischemia associated with a high-grade stenosis in the proximal left anterior descending coronary artery system (*LAD-T wave* pattern).[102] The T wave inversion may actually be preceded by a transient ST elevation that resolves by the time that the patient arrives at the hospital. These T wave inversions, in the setting of unstable angina, can correlate with segmental hypokinesis of the anterior wall and suggest a "myocardial stunning" syndrome.[103] The natural history of this syndrome is unfavorable, with a high incidence of recurrent angina and myocardial infarction. On the other hand, patients whose baseline ECG already shows abnormal T wave inversion can experience paradoxical T wave normalization (pseudonormalization) during episodes of acute transmural ischemia[85] [89] (Fig. 5-40) . (Postinfarction regional pericarditis can also cause T wave normalization.[104]) The four major classes of acute ECG-coronary artery syndromes in which myocardial ischemia leads to different ECG findings are summarized in Figure 5-41 .

ISCHEMIC U WAVE CHANGES.

Alterations in U wave amplitude or polarity have been reported with acute ischemia or infarction. For example, exercise-induced transient inversion of precordial U waves has been correlated with severe stenosis of the left anterior descending coronary artery.[105] Rarely, U wave inversion may be the earliest ECG sign of acute coronary syndromes.[106]

QT INTERVAL DISPERSION.

Increasing interest has been shown in the effects of acute myocardial ischemia and infarction on the disparity among QT intervals in various ECG leads, referred to as QT dispersion.[38] [107] [108] [109] The greater the difference between maximum and minimum QT intervals, i.e., increased QT dispersion, the greater the variability in myocardial repolarization. An increased index has been proposed as a marker of arrhythmia risk after myocardial infarction[110] and as a marker of acute ischemia with atrial pacing.[111] The practical utility of QT dispersion measurements, in coronary syndromes[111A] [111B] and certain other cardiac pathologies, [38] is a focus of current investigation (see Chap. 25) .

Localization of Ischemia or Infarction

The ECG leads are more helpful in localizing regions of transmural than subendocardial ischemia. As examples, ST elevation and/or hyperacute T waves are seen in (1) one or more of the precordial leads (V_1 through V_6) and in leads I and aV_l with acute transmural anterior or anterolateral wall ischemia; (2) leads V_1 to V_3 with anteroseptal ischemia; (3) leads V_4 to V_6 with apical or lateral ischemia; (4) leads II, III, and aV_f with inferior wall ischemia; and (5) right-sided precordial leads with right ventricular ischemia. Posterior wall infarction, which induces ST elevation in leads placed over the back of the heart, e.g., leads V_7 to V_9 ,[8] [112] [113]

Figure 5-39 *A,* Prinzmetal angina with ST segment and T wave alternans. *B,* ST segment and T wave alternans associated with nonsustained ventricular tachycardia. *(Courtesy of C. Fisch, M.D.)*

Figure 5-40 Pseudo (paradoxical) T wave normalization. *A,* The baseline electrocardiogram of a patient with coronary artery disease shows ischemic T wave inversion. *B,* T wave "normalization" during an episode of ischemic chest pain. *C,* Following resolution of the chest pain, the T waves have reverted to their baseline appearance. *(From Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

can be induced by lesions in the right coronary artery or left circumflex artery. These lesions can produce both inferior and posterior-lateral injury, which may be indirectly recognized by reciprocal ST depression in leads V_1 to V_3 .[114] Similar ST changes can also be the primary ECG manifestation of anterior subendocardial ischemia. Posterior inferior wall infarction with reciprocal changes can be differentiated from primary anterior wall ischemia by the presence of ST segment elevations in posterior leads.

The ECG can also provide more specific information about the location of the occlusion within the coronary system. In patients with an inferior wall myocardial infarction, the presence of ST segment elevation in lead III exceeding that in lead II, particularly when combined with ST elevation in V_1 , may be a useful predictor of an occlusion in the proximal to midportion of the right coronary artery[115] (Fig. 5-42) . Right-sided ST elevation is indicative of acute right ventricular injury[116] [117] [117A] and usually correlates with occlusion of the proximal right coronary artery.[117] Of note is the finding that acute right ventricular infarction can project an injury current pattern in leads V_1 through V_3 or even V_4 and simulate anterior infarction. [118] In other cases, simultaneous ST elevation in V_1 (V_2 R) and ST depression in V_2 (V_1 R) can occur[119] (see Fig. 5-42) . These and other criteria proposed for localization of the site of coronary occlusion based on the

initial ECG[120] [121] [122] [123] [124] [125] [125A] require additional validation in test populations. In some cases, ischemia can affect more than one region of the myocardium (e.g., inferolateral) (see Fig. 5-38) .[125B] Not uncommonly, the ECG will show the characteristic findings of involvement in each region. Sometimes, however, partial normalization can result from cancellation of opposing vectorial forces. Inferior lead ST segment elevation accompanying acute anterior wall infarction suggests occlusion of a left anterior descending artery that extends onto the inferior wall of the left ventricle ("wrap around" vessel). [126]

Figure 5-41 Variability of electrocardiogram (ECG) patterns with acute myocardial ischemia. The ECG may also be normal or nonspecifically abnormal. Furthermore, these categorizations are not mutually exclusive. For example, a non-Q-wave infarct can evolve into a Q wave infarct, ST elevation can be followed by a non-Q-wave infarct, or ST depression and T wave inversion can be followed by a Q wave infarct. *(Modified from Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

Figure 5-42 Acute right ventricular infarction with acute inferior wall infarction. Note the ST elevation in the right precordial leads, as well as in leads II, III, and aV_f , with reciprocal change in I and aV_l . ST elevation in lead III greater than in lead II[115] and right precordial ST elevation are consistent with proximal to middle occlusion of the right coronary artery. The combination of ST elevation in conventional lead V_1 (V_2 R here) and ST depression in lead V_2 (lead V_1 R here) has also been reported with acute right ventricular ischemia/infarction.[119]

ECG Diagnosis of Bundle Branch Blocks and Myocardial Infarction

The diagnosis of myocardial infarction is often more difficult in cases in which the baseline ECG shows a bundle branch block pattern, or a bundle branch block develops as a complication of the infarct.[85] The diagnosis of Q wave infarction is not usually impeded by the presence of RBBB, which affects primarily the terminal phase of ventricular depolarization. The net effect is that the criteria for the diagnosis of a Q wave infarct in a patient with RBBB are the same as in patients with normal conduction (Fig. 5-43) . The diagnosis of infarction in the presence of LBBB is considerably more complicated and confusing since LBBB alters both the early and the late phases of ventricular depolarization and produces secondary ST-T changes. These changes may both mask and mimic the findings of myocardial infarction. As a result, considerable attention has been directed to the problem of diagnosing acute and chronic myocardial infarction in patients with LBBB[85] [127] [128] [129] (Fig. 5-44) .

Infarction of the left ventricular free (or lateral) wall ordinarily results in abnormal Q waves in the midprecordial to lateral precordial leads (and selected limb leads). However, the initial septal depolarization forces with LBBB are directed from right to left.

These leftward forces produce an initial R wave in the midprecordial to lateral precordial leads, usually masking the loss of electrical potential (Q waves) caused by the infarction. Therefore, acute or chronic left ventricular free wall infarction by itself will not usually produce diagnostic Q waves in the presence of LBBB. Acute or chronic infarction involving both the free wall and the septum (or the septum itself) may produce abnormal

Figure 5-43 Right bundle branch block with acute anterior infarction. Loss of anterior depolarization forces results in QR-type complexes in the right precordial to midprecordial leads, with ST elevations and evolving T wave inversions (V_1 through V_6).

Figure 5-44 Complete left bundle branch block with acute inferior myocardial infarction. Note the prominent ST segment elevation in leads II, III, and aV_f , with reciprocal ST segment depression in I and aV_l superimposed on secondary ST-T changes. The underlying rhythm is atrial fibrillation.

Q waves (usually as part of the QRS complex or QrS types of complexes) in leads V_4 to V_6 . These initial Q waves probably reflect posterior and superior forces from the spared basal portion of the septum (Fig. 5-45). Thus, a wide Q wave (0.04 second) in one or more of these leads is a more reliable sign of underlying infarction. The sequence of repolarization is also altered in LBBB, with the ST segment and T wave vectors being directed opposite the QRS complex. These changes can mask or simulate the ST segment changes of actual ischemia.

The following points summarize the ECG signs of myocardial infarction in LBBB: (1) ST segment elevation with tall positive T waves are frequently seen in the right precordial leads with uncomplicated LBBB. Secondary T wave inversions are characteristically seen in the lateral precordial leads. However, the appearance of ST elevations in the lateral leads or ST depressions or deep T wave inversions in leads V_1 to V_3 strongly suggests underlying ischemia. More marked ST elevations (
0.5 mV) in leads with QS or rS waves may also be due to acute ischemia.[127] (2) The presence of QR complexes in leads I, V_5 , or V_6 or in II, III, and aV_f with LBBB strongly suggests underlying infarction, and (3) chronic infarction is also suggested by notching of the ascending part of a wide S wave in the midprecordial leads (*Cabrera sign*) or the ascending limb of a wide R wave in V_5 or V_6 (*Chapman sign*).[127] Similar principles may apply to the diagnosis of acute and chronic infarction in the presence of right ventricular pacing.[130] Comparison between

Figure 5-45 *A,* With uncomplicated left bundle branch block, early septal forces are directed to the left. Therefore, no Q waves will be seen in V_5 and V_6 (*right panel*). *B,* With left bundle branch block complicated by anteroseptal infarction, early septal forces may be directed posteriorly and rightward (*left panel*). Therefore, prominent Q waves may appear in V_5 and V_6 as a paradoxical marker of septal infarction (*right panel*). *(Adapted from Dunn MI, Lipman BS: Lipman-Massie Clinical Electrocardiography. 8th ed. Chicago, Year Book, 1989.) C,* Anterior wall infarction (involving septum) with left bundle branch block. Note the presence of QR complexes in leads I, aV_l , V_5 , and V_6 .

an ECG exhibiting the LBBB prior to the infarction and the present ECG is often helpful to show these changes.

Atrial Infarction

A number of ECG clues to the diagnosis of atrial infarction have been suggested, including localized deviations of the PR segment (e.g., PR elevation in V_5 or V_6), changes in P wave morphology, and atrial arrhythmias.[131] However, the sensitivity and specificity of these signs are limited. Diffuse PR segment changes (PR elevation in aV_r with depression in the inferolateral leads) with acute infarction usually indicate concomitant pericarditis (see below).

ECG Differential Diagnosis of Ischemia and Infarction

The ECG has important limitations in both sensitivity and specificity in the diagnosis of coronary syndromes. An initially normal ECG does not exclude ischemia or even acute infarction. However, a normal ECG throughout the course of an alleged acute infarct is distinctly uncommon. As a result, prolonged chest pain without diagnostic ECG changes should always prompt a careful search for noncoronary causes of chest pain (see Chap. 35) . Pathological Q waves may be absent even in patients with depressed left ventricular function caused by severe coronary disease and a previous infarct.[132] As noted, the diagnosis of acute or chronic infarction can be completely masked by ventricular conduction disturbances, especially those resulting from LBBB, as well as ventricular pacing and WPW preexcitation. On the other hand, diagnostic confusion can arise because Q waves, ST elevation, ST depression, tall positive T waves, and deep T wave inversion can be seen in a wide variety of noncoronary settings.[85]

Noninfarction Q Waves

Q waves simulating coronary artery disease can be related to one (or a combination) of the following four factors (Table 5-9) : (1) physiological or positional variants, (2) altered ventricular conduction, (3) ventricular enlargement, and (4) myocardial damage or replacement. Depending on the electrical axis, prominent Q waves (as part of QS- or QR-type complexes) can also appear in the limb leads (aV_l with a

TABLE 5-9 -- DIFFERENTIAL DIAGNOSIS OF NONINFARCTION Q WAVES (WITH SELECTED EXAMPLES)

Physiological or positional factors
Normal-variant "septal" Q waves
Normal-variant Q waves in V_1 -V_2 , III, and aV_f
Left pneumothorax or dextrocardia: Loss of lateral R wave progression
Myocardial injury or infiltration
Acute processes: Myocardial ischemia without infarction, myocarditis, hyperkalemia (rare cause of transient Q waves)
Chronic myocardial processes: Idiopathic cardiomyopathies, myocarditis, amyloid, tumor, sarcoid
Ventricular hypertrophy/enlargement
Left ventricular (poor R wave progression*)
Right ventricular (reversed R wave progression or poor R wave progression, particularly with chronic obstructive lung disease)
Hypertrophic cardiomyopathy (can simulate anterior, inferior, posterior, or lateral infarcts) (see Fig. 5-46)
Conduction abnormalities
Left bundle branch block (poor R wave progression*)
Wolff-Parkinson-White patterns
Modified from Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.

*Small or absent R waves in the right precordial to midprecordial leads.

Progressive decrease in R wave amplitude from V_1 to the midlateral precordial leads.

vertical axis and III and aV_f with a horizontal axis). A QS complex can appear in lead V_1 as a normal variant and rarely in leads V_1 and V_2 . Prominent Q waves can be associated with a variety of other positional factors that alter the orientation of the heart vis-a-vis a given lead axis. Poor R wave progression, sometimes with actual QS waves, can be due solely to improper placement of chest electrodes above their usual position. In dextrocardia, provided that no underlying structural abnormalities are present, normal R wave progression can be restored by recording leads V_2 to V_6 on the right side of the chest. A rightward mediastinal shift in left pneumothorax can contribute to the apparent loss of left precordial R waves. Other positional factors associated with poor R wave progression include pectus excavatum, congenitally corrected transposition of the great vessels, and congenital absence of the left pericardium.

An intrinsic change in the sequence of ventricular depolarization can lead to

pathological, noninfarct Q waves. The two most important conduction disturbances associated with pseudoinfarct Q waves are LBBB and the WPW preexcitation patterns. With LBBB, QS complexes can appear in the right precordial to midprecordial leads and occasionally in one or more of leads II, III, and aV_f .. Depending on the location of the bypass tract, WPW preexcitation can mimic anteroseptal, lateral, or inferior-posterior infarction. LAFB is often cited as a cause of anteroseptal infarct patterns. However, LAFB has only minor effects on the QRS complex in horizontal plane leads. Probably the most common findings are relatively prominent S waves in leads V_5 and V_6 . Poor R wave progression is not a routine feature of LAFB, although some authors have reported minuscule q waves in leads V_1 to V_3 in this setting. These small q waves can become more apparent if the leads are recorded one interspace above their usual position and disappear in leads one interspace below their usual position.[68] However, as a general clinical rule, prominent Q waves (as part of QS or QR complexes) in the right precordial to midprecordial leads should *not* be attributed to LAFB alone.

In contrast, poor R wave progression is commonly observed with LVH and with acute or chronic right ventricular overload. Q waves in such settings can reflect a variety of mechanisms, including a change in the balance of early ventricular depolarization forces and altered cardiac geometry and position. A marked loss of R wave voltage, sometimes with frank Q waves from V_1 to the lateral chest leads, may be seen with chronic obstructive pulmonary disease (see Fig. 5-22). The presence of low limb voltage and P pulmonale can serve as additional diagnostic clues. This loss of R wave progression may, in part, reflect right ventricular dilation. Furthermore, downward displacement of the heart in an emphysematous chest may play a major role in the genesis of poor R wave progression in this syndrome. Partial or complete normalization of R wave progression may be achieved in such cases simply by recording the chest leads an interspace lower than usual (see Fig. 5-22) .

A variety of pseudoinfarct patterns can occur with acute cor pulmonale caused by pulmonary embolism. Acute right ventricular overload in this setting can cause poor R wave progression and sometimes right precordial to midprecordial T wave inversion (right ventricular "strain") mimicking anterior infarction. The classic S_1 Q_3 T_3 pattern can occur but is neither sensitive nor specific. A prominent Q wave (usually as part of a QR complex) can also occur in lead aV_f along with this pattern (see Fig. 5-23) . However, acute right overload by itself does not cause a pathological Q wave in lead II. Right heart overload, acute or chronic, may also be associated with a QR complex in lead V_1 and simulate anteroseptal infarction.

Pseudoinfarct patterns are an important finding in patients with hypertrophic cardiomyopathy, and the ECG can simulate anterior, inferior, posterior, or lateral infarction.[85] [133] The pathogenesis of depolarization abnormalities in this cardiomyopathy is not certain. Prominent inferolateral Q waves (II, III, aV_f , and V_4 to V_6) and tall right precordial R waves are probably related to increased depolarization forces generated by the markedly hypertrophied septum (Fig. 5-46) . Abnormal septal depolarization may also contribute to the bizarre QRS complexes.

Loss of electromotive force associated with myocardial necrosis contributes to R wave

loss and Q wave formation in myocardial infarction. This mechanism of Q wave pathogenesis, however, is not specific for coronary artery disease with infarction. Any process, acute or chronic, that causes sufficient loss of regional electromotive potential can result in Q waves. For example, replacement of myocardial tissue by electrically inert material such as amyloid or tumor may cause noninfarction Q waves. A variety of dilated cardiomyopathies associated with extensive myocardial fibrosis may be characterized by pseudoinfarct patterns. Ventricular hypertrophy can also contribute to Q wave pathogenesis in this setting. Finally, Q waves caused by myocardial injury, whether ischemic or nonischemic in origin, can appear transiently and do not necessarily signify irreversible heart muscle damage.[85] Severe ischemia can cause regional loss of electromotive potential without actual cell death ("electrical stunning" phe

Figure 5-46 Hypertrophic cardiomyopathy simulating inferolateral infarction. This 11-year-old girl had a family history of hypertrophic cardiomyopathy. Note the W-shaped QS waves and the qrS complexes in the inferior and lateral precordial leads.*(From Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

nomenon). Transient conduction disturbances can also cause alterations in ventricular activation and result in noninfarctional Q waves. In some cases, transient Q waves may represent unmasking of a prior Q wave infarct. New, but transient Q waves have been described with severe hypotension from a variety of causes, as well as with tachyarrhythmias, myocarditis, Prinzmetal's angina, protracted hypoglycemia, phosphorus poisoning, and hyperkalemia.[85]

ST-T Changes Simulating Ischemia

The differential diagnosis of ST segment elevation includes acute pericarditis (Fig. 5-47), acute myocarditis, normal-variant "early repolarization" (see Fig. 5-15), and a number of other conditions[85] [134] [134A] [135] [135A] listed in Table 5-10 . Acute pericarditis, in contrast to acute myocardial infarction, typically induces diffuse ST segment elevation, usually in most of the chest leads and also in leads I, aV_l , II, and aV_f . Reciprocal ST depression is seen in lead aV_r . An important clue to acute pericarditis, in addition to the diffuse nature of the ST elevation, is the frequent presence of PR segment elevation in aV_r , with reciprocal PR segment depression in other leads, caused by a concomitant atrial current of injury[136] (see Fig. 5-47). Abnormal Q waves do not occur with acute pericarditis, and the ST elevation may be followed by T wave inversion after a variable period (see Chap. 50) . Myocarditis (see Chap. 48) can, in some patients, exactly simulate the ECG pattern of acute myocardial infarction, including ST elevation and Q waves. In one series,[137] these pseudoinfarct findings were associated with a rapidly progressive course and increased mortality.

A variety of factors such as digitalis, ventricular hypertrophy, hypokalemia, and hyperventilation can cause ST segment depression mimicking subendocardial ischemia. Similarly, tall positive T waves do not invariably represent hyperacute ischemic changes but can reflect normal variants, hyperkalemia, cerebrovascular injury, and left ventricular volume loads resulting from mitral or aortic regurgitation, among other causes.[85] ST elevation and tall positive T waves are also common findings in leads V_1 and V_2 with LBBB or LVH patterns. In addition, tall T waves may be seen occasionally in the left chest leads with LVH, especially with volume (diastolic) overload syndrome (see Fig. 5-20) .

T WAVE INVERSION.

When caused by physiological variants, T wave inversion is sometimes mistaken for ischemia. T waves in the right precordial leads can be slightly inverted, particularly in leads V_1 and V_2 . Some adults show persistence of the *juvenile T wave pattern* (see Fig. 5-14), with more prominent T wave inversion in right precordial to midprecordial leads showing an rS or RS morphology. The other normal variant that may be associated with prominent T wave inversion is the early repolarization pattern (see Fig. 5-15). Some subjects with this variant have prominent, biphasic T wave inversion in association with the ST elevation. This pattern, which may simulate the

TABLE 5-10 -- DIFFERENTIAL DIAGNOSIS OF ST SEGMENT ELEVATION

Myocardial ischemia/infarction
Noninfarction, transmural ischemia (Prinzmetal angina pattern) (see Fig. 5-39)
Acute myocardial infarction (see Fig. 5-36)
Post-myocardial infarction (ventricular aneurysm pattern)Acute pericarditis (see Fig. 5-47) Normal variant ("early repolarization" pattern) (see Fig. 5-15) LVH/LBBB (V_1 -V_2 or V_3 only)Other (rarer)
Myocardial injury
Myocarditis (may look like myocardial infarction or pericarditis)
Tumor invading the left ventricle
Trauma to the ventricles
Hypothermia (J wave/Osborn wave) (see Fig. 5-52)
After DC-cardioversion
Intracranial hemorrhage
Hyperkalemia*
Brugada's pattern (RBBB and ST elevations in right precordial leads)*
Type 1C antiarrhythmic drugs*
Hypercalcemia*

LBBB=left bundle branch block; LVH=left ventricular hypertrophy; RBBB=right bundle branch block.

Modified from Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.

*Usually localized to V_1 to V_2 .

Figure 5-47 *Top,* Acute pericarditis is often characterized by two apparent injury currents: one atrial, the other ventricular. The atrial injury current vector (ST_a) is usually directed upward and to the right and produces PR segment elevation in aV_r with reciprocal PR depression in II, V_5 , and V_6 . The ventricular injury current (ST_V) is directed downward and to the left, associated with ST elevation in II, V_5 , and V_6 with reciprocal ST depression in aV_r . This characteristic PR-ST segment discordance is illustrated in the *Bottom*, Note the diffuse distribution of ST segment elevation in acute pericarditis (e.g., I, II, and V_2 through V_6 , with reciprocal changes in aV_r and perhaps minimally in V_1). Note the PR segment elevation in aV_r *(From Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991.)*

initial stages of an evolving infarct, is most prevalent in young adult black males and among athletes. These functional ST-T changes are probably due to regional disparities in repolarization and can be normalized by exercise.[85]

Primary and Secondary T Wave Inversions.

A variety of pathological factors can alter repolarization and cause prominent T wave inversion (see Fig. 5-48). As noted above, T wave alterations are usefully classified as primary or secondary. Primary T wave changes are caused by alterations in the duration or morphology of ventricular action potentials in the absence of changes in the activation sequence. Examples include ischemia, drug effects, and metabolic factors. Prominent primary T wave inversion (or in some cases, tall positive T waves) is also a well-described feature of the ECG in cerebrovascular accidents (CVAs), particularly with subarachnoid hemorrhage. The "CVA T wave pattern" is characteristically diffuse, with a widely splayed appearance usually associated with marked QT prolongation (Fig. 5-48). Some studies have implicated structural damage (myocytolysis) in the hearts of patients with such T wave changes, probably induced by excessive sympathetic stimulation mediated via the hypothalamus.[138] A role for concomitant vagal activation in the pathogenesis of such T wave changes, which are usually associated with

Figure 5-48 Deep T wave inversion can be due to a variety of causes (see Table 5-11) . Note the marked QT prolongation in conjunction with the cerebrovascular accident (CVA) T wave pattern caused here by subarachnoid hemorrhage. Apical hypertrophic cardiomyopathy (HCM) is another cause of deep T wave inversion that can be mistaken for coronary disease.*(From Goldberger AL: Deep T wave inversions. ACC Curr J Rev Nov/Dec:28-29, 1996.)*

bradycardia, has also been postulated. Similar T wave changes have been reported after truncal vagotomy, radical neck dissection, and bilateral carotid endarterectomy.[109] In addition, the massive diffuse T wave inversion seen in some patients following Stokes-Adams syncope may be related to a similar neurogenic mechanism. Patients with subarachnoid hemorrhage may also show transient ST elevation, as well as arrhythmias, including torsades de pointes. Ventricular dysfunction may even occur.[139] [140]

In contrast to these primary T wave abnormalities, secondary T wave changes are caused by altered ventricular activation, without changes in action potential characteristics. Examples include bundle branch block, WPW preexcitation, and ventricular ectopic or paced beats. In addition, altered ventricular activation (associated with QRS interval prolongation) can induce persistent T wave changes that appear after normal ventricular depolarization has resumed. The term "cardiac memory T wave changes" has been used in this context to describe repolarization changes subsequent to depolarization changes caused by ventricular pacing, intermittent LBBB, intermittent WPW preexcitation, and other alterations of ventricular activation.[141] [142] Finally, the designation idiopathic *global T wave inversion* has been applied[143] in cases in which no identifiable cause for often marked, diffuse repolarization abnormalities can be defined. An unexplained female preponderance has been reported.[144] Major causes of prominent T wave inversion are summarized in Table 5-11 , with selected examples in Figure 5-48 .

Drug Effects

Numerous drugs can affect the ECG, often in association with nonspecific ST-T alterations. More marked changes, as well as AV and intraventricular conduction disturbances, may occur with selected agents. The proarrhythmic effects of "antiarrhythmic" medications are described in Chapter 23 .

Digitalis effect refers to the relatively distinctive "scooped" appearance of the ST-T complex and shortening of the QT interval, which correlates with abbreviation of the ventricular action potential duration (Fig. 5-49). Digitalis-related ST-T changes may be accentuated by an increased heart rate during exercise and result in false-positive stress test results (see Chap. 6) . Digitalis effect may occur with therapeutic or toxic doses of the drug. The term *digitalis toxicity* refers specifically to systemic effects (nausea and anorexia among other effects) or conduction disturbances and arrhythmias

caused by drug excess or increased sensitivity (see Chap. 23) .

TABLE 5-11 -- DIFFERENTIAL DIAGNOSIS OF PROMINENT T WAVE INVERSION

Normal variants
Juvenile T wave pattern (see Fig. 5-14)
Early repolarization
Myocardial ischemia/infarction (see Fig. 5-48)
Cerebrovascular accident (especially intracranial bleeds) and related neurogenic patterns (e.g., radical neck dissection, Stokes-Adams syndrome) (see Fig. 5-48)
Left or right ventricular overload
Classic "strain" patterns
Apical hypertrophic cardiomyopathy (Yamaguchi syndrome) (see Fig. 5-48)
Post-tachycardia T wave pattern
Idiopathic global T wave inversion
Secondary T wave alterations: bundle branch blocks, Wolff-Parkinson-White patterns
Intermittent left bundle branch block, preexcitation, or ventricular pacing ("memory T waves")
Modified from Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.

Figure 5-49 *Top,* Digitalis effect. Digitalis glycosides characteristically produce shortening of the QT interval with a "scooped" or downsloping ST-T complex. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.) Bottom, Digitalis effect in combination with digitalis toxicity. The underlying rhythm is atrial fibrillation. A "group beating" pattern of QRS complexes with shortening of the R-R intervals is consistent with nonparoxysmal junctional tachycardia with exit (atrioventricular Wenckebach) block. ST segment depression and "scooping" (V_6) are consistent with digitalis effect, although ischemia or left ventricular hypertrophy cannot be excluded. Findings are strongly suggestive of digitalis excess; the serum digoxin level was greater than 3 ng/ml. Digitalis effect does not necessarily imply digitalis toxicity, however.*

ECG effects and toxicities of other cardioactive agents may be anticipated, in part, from ion channel effects (see Chap. 22) . Inactivation of sodium channels by class 1 agents (e.g., quinidine, procainamide, disopyramide, flecainide) can cause QRS prolongation. Class 1A and class 3 agents (e.g., sotalol, amiodarone) can induce an acquired long QT(U) syndrome (see Chap. 23) . Psychotropic drugs (e.g., tricyclic antidepressants and phenothiazines), which have class 1A-like properties, can also lead to QRS and QT(U) prolongation.[144A] Toxicity may produce asystole or torsades de pointes. Right

axis shift of the terminal 40-millisecond frontal plane QRS axis was reported to be a helpful marker of tricyclic antidepressant overdose.[145]

Electrolyte and Metabolic Abnormalities

In addition to the structural and functional cardiac conditions already discussed, numerous systemic metabolic aberrations affect the ECG,[86] including electrolyte abnormalities and acid-base disorders, as well as systemic hypothermia.

CALCIUM.

Hypercalcemia and hypocalcemia predominantly alter the action potential duration. An increased extracellular calcium concentration shortens the ventricular action potential duration by shortening phase 2 of the action potential. In contrast, hypocalcemia prolongs phase 2 of the action potential. These cellular changes correlate with abbreviation and prolongation of the QT interval (ST segment portion) with hypercalcemia and hypocalcemia, respectively (Fig. 5-50) . Severe hypercalcemia (e.g., serum Ca^{2+}
15 mg/dl) can also be associated with decreased T wave amplitude, sometimes with T wave notching or inversion.[146] Hypercalcemia sometimes produces a high takeoff of the ST segment in leads V_1 and V_2 and can thus simulate acute ischemia (see Table 5-10) .

POTASSIUM.

Hyperkalemia is associated with a distinctive sequence of ECG changes (Fig. 5-51 *A*). The earliest effect is usually narrowing and peaking (*tenting*) of the T wave. The QT interval is shortened at this stage associated with decreased action potential duration. Progressive extracellular hyperkalemia reduces atrial and ventricular resting membrane potentials, thereby inactivating sodium channels, which decreases Vmax and conduction velocity. The QRS begins to widen and P wave amplitude decreases. PR interval prolongation can occur, followed sometimes by second- or third-degree AV block. Complete loss of P waves may be associated with a junctional escape rhythm or *sinoventricular rhythm*. In the latter instance, sinus rhythm persists with conduction between the SA and AV nodes and occurs without producing an overt P wave. Moderate to severe

Figure 5-50 Prolongation of the QT interval (ST segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval. *(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

hyperkalemia occasionally induces ST elevations in the right precordial leads (V_1 and V_2

) and simulates an ischemic current-of-injury pattern. However, even severe hyperkalemia can be associated with atypical or nondiagnostic ECG findings.[147] [148] Very marked hyperkalemia leads to eventual asystole, sometimes preceded by a slow undulatory (sine-wave) ventricular flutter-like pattern. The ECG triad of (1) peaked T waves (from hyperkalemia), (2) QT prolongation (from hypocalcemia), and (3) LVH (from hypertension) is strongly suggestive of chronic renal failure.[149]

Figure 5-51 Electrocardiographic changes in hyperkalemia *(A)* and hypokalemia *(B)*. *A,* On day 1, at a K^+ level of 8.6 mEq/liter, the P wave is no longer recognizable and the QRS complex is diffusely prolonged. Initial and terminal QRS delay is characteristic of K^+ -induced intraventricular conduction slowing and is best illustrated in leads V_2 and V_6 . On day 2, at a K^+ level of 5.8 mEq/liter, the P wave is recognizable with a PR interval of 0.24 seconds, the duration of the QRS complex is approximately 0.10 seconds, and the T waves are characteristically "tented." *B,* On day 1, at a K^+ level of 1.5 mEq/liter, the T and U waves are merged. The U wave is prominent and the QU interval prolonged. On day 4, at a K^+ level of 3.7 mEq/liter, the tracing is normal. *(Courtesy of C. Fisch, M.D.)*

The electrophysiological changes associated with hypokalemia, in contrast, include hyperpolarization of myocardial cell membranes and increased action potential duration. The major ECG manifestations are ST depression with flattened T waves and increased U wave prominence (Fig. 5-51 *B*). The U waves can exceed the amplitude of T waves. Hypokalemia is an important cause of acquired long QT(U) syndrome that predisposes to torsades de pointes (see Chap. 25) . Hypokalemia also predisposes to tachyarrhythmias from digitalis (see Chap. 23) .

MAGNESIUM.

Specific ECG effects of mild to moderate isolated abnormalities in magnesium ion concentration are not well characterized. Severe hypermagnesemia can cause AV and intraventricular conduction disturbances that may culminate in complete heart block and cardiac arrest (Mg^{2+} >15 mEq/L).[150] Hypomagnesemia is usually associated with hypocalcemia or hypokalemia. Hypomagnesemia can potentiate certain digitalis toxic arrhythmias (see Chap. 23) . The role of magnesium deficiency in the pathogenesis and treatment of the acquired long QT(U) syndrome with torsades de pointes is discussed in Chapters 23 and 25 .

OTHER FACTORS.

Isolated hypernatremia or hyponatremia does not produce consistent effects on the ECG. Acidemia and alkalemia are often associated with hyperkalemia and hypokalemia, respectively. *Systemic hypothermia* may be associated with the appearance of a distinctive convex elevation at the junction (J point) of the ST segment and QRS complex (*J wave* or *Osborn wave*) (Fig. 5-52) . The cellular mechanism of this type of pathological *J wave* appears to be related to an epicardial-endocardial voltage gradient associated with the localized appearance of a prominent epicardial action potential notch.[151]

Low QRS voltage is said to be present when the total amplitude of the QRS complexes in each of the six extremity leads is 0.5 mV or less or 1.0 mV or less in leads V_1 through V_6 . Low QRS voltage can relate to a variety of mechanisms (Table 5-12) , including increased insulation of the heart by air (chronic obstructive pulmonary disease) or adipose tissue (obesity); replacement of myocardium, for example, by fibrous tissue (ischemic or nonischemic cardiomyopathy), amyloid, or tumor; or short-circuiting effects (pericardial or pleural effusions). The combination of relatively low limb voltage (QRS voltage
0.8 mV in each of

Figure 5-52 Systemic hypothermia. The arrows (V_3 through V_6) point to the characteristic convex J waves, termed Osborn waves. Prominent sinus bradycardia is also present.*(From Goldberger AL: Clinical Electrocardiography: A Simplified Approach. 6th ed. St Louis, CV Mosby, 1999.)*

the limb leads), relatively prominent QRS voltage in the chest leads (SV_1 or SV_2 +RV_5 or RV_6
3.5 mV), and poor R wave progression (R wave less than the S wave in V_1 through V_4) has been reported as a relatively specific, but not sensitive sign of dilated-type cardiomyopathies (*ECG-congestive heart failure triad*).[152]

Multiple factors in addition to ischemia (e.g., postural changes, meals, drugs, hypertrophy, electrolyte and metabolic disorders, central nervous system lesions, infections, pulmonary diseases) can affect the ECG.[85] Ventricular repolarization is particularly sensitive to these effects, which can lead to a variety of *nonspecific ST-T changes*. The term is usually applied to slight ST depression or T wave inversion or to T wave flattening without evident cause. Care must be taken to not overinterpret such changes, especially in subjects with a low prior probability of heart disease. At the same time, subtle repolarization abnormalities can be markers of coronary or hypertensive heart disease or other types of structural heart disease and probably account for the association of relatively minor but persistent nonspecific ST-T changes with increased cardiovascular mortality in middle-aged men.[153]

TABLE 5-12 -- CAUSES OF LOW-VOLTAGE QRS COMPLEXES

Adrenal insufficiency
AnasarcaArtifactual or spurious, e.g., unrecognized standardization of the electrocardiogram at half the usual gain (i.e., 5 mm/mV)

Cardiac infiltration or replacement (e.g., amyloidosis, tumor)
Cardiac transplantation, especially with acute or chronic rejection
Cardiomyopathies, idiopathic or secondary*
Chronic obstructive pulmonary disease
Constrictive pericarditis
Hypothyroidism (usually with sinus bradycardia)
Left pneumothorax (mid-left chest leads)
Myocardial infarction, extensive
Myocarditis, acute or chronic
Normal variant
Obesity
Pericardial tamponade (usually with sinus tachycardia)
Pleural effusions

*Dilated cardiomyopathies may be associated with a combination of relatively low limb lead voltage and prominent precordial voltage.[152]

Alternans Patterns

The term *alternans* applies to conditions characterized by the sudden appearance of a periodic beat-to-beat change in some aspect of cardiac electrical or mechanical behavior. These abrupt changes (AAAA
ABAB pattern) are reminiscent of a generic class of subharmonic (period-doubling) bifurcation patterns, well described in perturbed *nonlinear control systems*. [21] [154] [155] Many different examples of electrical alternans have been described clinically[156] [157] [158] [159] [160] [160A] (Table 5-13) ; a number of others have been reported in the laboratory.[161] Most familiar is total electrical alternans with sinus tachycardia, a specific but not highly sensitive marker of pericardial effusion with tamponade physiology[162] (Fig. 5-53) (see Chap. 50) . This finding is associated with an abrupt transition from a 1:1 to a 2:1 pattern in the "to-fro" swinging motion of the heart in the effusion.[163] Other alternans patterns are due to primary electrical rather than mechanical causes. ST-T alternans has long been recognized as a marker of electrical instability in acute ischemia, where it may precede ventricular tachyarrhythmia[164] (see Fig. 5-39) . Considerable interest has recently been shown in the detection of microvolt T wave (or ST-T) alternans as a noninvasive marker of the risk of ventricular tachyarrhythmia in patients with chronic heart disease[165] [166] [167] [168] [169] (see Chap. 23) . Similarly, TU wave alternans (Fig. 5-54) may be a marker of imminent risk of a ventricular tachyarrhythmia such as torsades de pointes in hereditary or acquired long QT syndromes.[170] [171]

CLINICAL ISSUES IN ELECTROCARDIOGRAPHIC INTERPRETATION

These principles and diagnostic ECG guidelines are, finally, subject to appropriate use in the clinical setting. Their effectiveness as a diagnostic tool depends on factors such as the indications for the procedure, the clinical context in which the ECG is used, and proper technique and skills of the ECG reader.

INDICATIONS FOR AN ECG.

Little attention has been paid to the indications for an ECG, probably because of its seeming simplicity and low cost. However, the cumulative expense of low-cost tests performed at high volume is significant, and the risk to the patient of false diagnoses of

TABLE 5-13 -- EXAMPLES OF ALTERNANS PATTERNS IN ECG DIAGNOSIS

PATTERN	COMMENT
P wave alternans	Rarely reported; e.g., in pulmonary embolism [159]
"Total" electrical alternans (P-QRS-T) with sinus tachycardia	Swinging-heart mechanism in pericardial effusion/tamponade* (see Fig. 5-53)
PR interval alternans	Dual AV nodal pathway physiology; alternating bundle branch block (see Fig. 5-29)
ST segment alternans	Can precede ischemic ventricular tachyarrhythmias (see Fig. 5-39)
T wave (or ST-T) alternans	Can precede nonischemic ventricular tachyarrhythmias
TU wave alternans	Can precede torsades de pointes in long QT(U) syndromes, congenital or acquired (see Fig. 5-54)
QRS alternans in supraventricular or ventricular tachycardia	Most common with AV reentrant tachycardia (concealed bypass tract)
R-R (heart rate) alternans	With sinus rhythm, e.g., in congestive heart failure[157] With non-sinus rhythm tachyarrhythmias, e.g., PSVT
Bidirectional tachycardias	Usually ventricular in origin; may be caused by digitalis excess

Intermittent bundle branch/fascicular blocks or Wolff-Parkinson-White patterns	Rarely occur on beat-to-beat basis (see Fig. 5-29)

AV=atrioventricular; PSVT=paroxysmal supraventricular tachycardia.

*Also case report of QRS-T alternans with sinus tachycardia in acute pulmonary embolism.[160]

cardiac disease can be damaging. Specific indications for the use of ECGs have been proposed and evaluated.[172] [172A] [173] [174] In patients with known cardiac disease, ECGs are warranted as part of a baseline examination; after therapy known to produce ECG changes that correlate with therapeutic responses, progression of disease, or adverse effects; and for intermittent follow-up with changes in signs or symptoms or relevant laboratory findings or after significant intervals (usually 1 year or longer), even in the absence of clinical changes. In patients suspected of having cardiac disease or at high risk for cardiac disease, an ECG is appropriate as part of an initial evaluation in the presence of signs or symptoms suggesting cardiac disease; in patients with important risk factors such as cigarette abuse, diabetes mellitus, peripheral vascular disease, or a family history of cardiac disease (including long QT interval syndromes and ventricular preexcitation); during therapy with cardioactive medications; and during follow-up if clinical events develop or at prolonged intervals (usually 1 year or more) if clinically stable. Preoperative tracings are appropriate for patients with known or suspected cardiac disease, although this application too may be questioned, especially if the cardiac condition is hemodynamically insignificant or the procedure is simple.[174]

It has been common practice to include an ECG as part of routine health examinations, before any surgical procedure, and on any admission to a hospital in patients without current evidence of cardiac disease and without major risk factors. These ECGs are assumed to be of value in detecting any unknown abnormalities, serving as a baseline against which to compare later tracings, and assessing future risk of cardiovascular events. There is little evidence to support these practices. The overall sensitivity of the ECG for identifying specific patients who will have future events and the number of therapeutic or diagnostic changes provoked by routine ECG findings are too low to warrant universal screening.[57] [172] In these cases, use of the ECG should be based on clinical judgment rather than rigid protocol

Figure 5-53 Total electrical alternans (P-QRS-T) caused by pericardial effusion with tamponade. This finding, particularly in concert with sinus tachycardia and relatively low voltage, is a highly specific, although not sensitive marker of cardiac tamponade.

Figure 5-54 The QT(U) interval is prolonged and measures approximately 600 milliseconds with TU wave alternans. The tracing was recorded in a patient with chronic renal disease shortly following dialysis. This type of repolarization alternans may be a precursor to torsades de pointes. *(Courtesy of C. Fisch, M.D.)*

requirements. Flexible guidelines for ordering ECGs on general hospital admission and preoperatively have been proposed on the basis of age, gender, medical history, and physical examination.[172] [172A]

KNOWLEDGE OF THE CLINICAL CONTEXT AND PRIOR ECG FINDINGS.

Although most ECGs are read without a priori knowledge of the clinical condition of the patient, the accuracy and the value of the interpretation are enhanced by having clinical information about the patient. Such knowledge may include, for example, information about drug therapy, which may be a cause of observed ECG abnormalities, or prior myocardial infarction, which may produce ECG changes mimicking acute ischemia.[175] [176]

Similarly, the availability of prior ECGs can improve the clinical value of the ECG. For example, knowledge of prior ECG patterns can improve diagnostic accuracy and triage decisions for patients with current ECG and clinical evidence of ischemia or infarction, as well as improve the proper interpretation of, for example, bundle branch block in the setting of acute infarction.[177] [178] [178A]

TECHNICAL ERRORS AND ARTIFACTS.

Technical errors can lead to significant diagnostic mistakes that can result in false diagnoses that place patients at risk for unneeded and potentially dangerous diagnostic tests and treatments and unnecessarily use limited health care resources.[179] Misplacement of one or more ECG electrodes is a common cause for errors in ECG interpretation. Some misplacements produce ECG patterns that can aid in identification of the error.[180] [181] [182] Reversal of the two arm electrodes, for example, results in an inverted waveform in lead I but not in lead V_6 , two leads that would normally be expected to have similar polarities. Others are not as obvious. For example, placing the right precordial electrodes too high on the chest can yield patterns that mimic those produced by anterior myocardial infarction (poor R wave progression) or intraventricular conduction delay (rSr patterns). Electrical or mechanical artifacts such as produced by poor electrode contacts or tremors can simulate life-threatening arrhythmias[179] (Fig. 5-55) , and excessive body motion can cause excessive baseline wander that may simulate an ST segment shift of myocardial ischemia or injury.

READING ERRORS.

Errors in interpreting ECGs are common.[182] Studies assessing the accuracy of routine interpretations have demonstrated significant numbers of errors that can lead to clinical mismanagement, including failure to appropriately detect and triage patients with acute

myocardial ischemia and other life-threatening situations.[183] Organizations such as the American College of Cardiology have proposed minimal training and experience standards for electrocardiographers to help reduce these potentially serious errors.[184]

A final issue concerns overreliance on computerized interpretations. Computer systems have facilitated storage and retrieval of large numbers of ECGs and, as diagnostic algorithms have become more accurate, have provided important adjuncts to the clinical interpretation of ECGs. However, the current systems are not sufficiently accurate,[185] [186] especially in the presence of rhythm disturbances or complex abnormalities, to be relied on in critical clinical environments without expert review. New analysis techniques based upon artificial intelligence concepts may lead to future improvements,[187] [187A] and new hardware technology may result in expanded deployment of systems for prompt expert interpretation.[187B]

Figure 5-55 Artifacts simulating serious arrhythmias. *A,* Motion artifact mimicking ventricular tachyarrhythmia. Partly obscured normal QRS complexes (arrows) can be seen with a heart rate of about 100 beats/min. *B,* Parkinsonian tremor causing baseline oscillations mimicking atrial fibrillation. The regularity of QRS complexes may provide a clue to this artifact.

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GUIDELINES
ELECTROCARDIOGRAPHY

Thomas H. Lee

Electrocardiograms (ECGs) are among the most commonly performed tests in medicine and are "the procedure of first choice" in the evaluation of patients with chest pain, syncope, or dizziness. Guidelines published in 1992 by a task force of the American College of Cardiology and American Heart Association (ACC/AHA) described conditions for which it is generally agreed that ECGs are useful (Class I); conditions for which opinion differs with respect to their usefulness (Class II); and conditions for which it is generally agreed that ECGs are of little or no usefulness (Class III).[1] These guidelines addressed categories of patients defined by whether they had known, suspected, or no evidence of cardiovascular disease. For each patient category, the guidelines evaluated use of the ECG as a baseline test, for evaluation of response to therapy, for follow-up, and before surgery (Table 5-G-1). Further discussion of some of the ongoing controversies and disagreements regarding use of the ECG in clinical settings is given in the chapter.

Patients with Known Cardiovascular Disease or Dysfunction

The ECG is so critical to the evaluation of all patients with a cardiovascular condition that this test was considered appropriate (Class I) for all patients during the initial evaluation and to evaluate the short- and long-term responses to therapies known to produce ECG changes. The guidelines offer no specific recommendations about the frequency of follow-up ECGs but noted that for several acute cardiovascular problems,

serial ECGs are warranted until the patient has returned to a stable condition. Even in the absence of new symptoms or signs, ECGs were considered appropriate for the follow-up of patients with several conditions, including syncope or near syncope, chest pain, and unexplained fatigue (see Table 5-G-1). The ECG was not considered appropriate for patients with mild chronic cardiovascular conditions that were not considered likely to progress (e.g., mild mitral valve prolapse). ECGs at *each* visit were considered inappropriate for patients with stable heart disease who were seen frequently (e.g., within 4 months) and had no evidence of clinical change.

Before cardiac or noncardiac surgery, the ACC/AHA guidelines considered ECGs appropriate for all patients with known cardiovascular disease or dysfunction, except those with insignificant or mild conditions such as mild systemic arterial hypertension.

Patients with Suspected or at High Risk for Cardiovascular Disease

The ECG was considered an appropriate baseline test for all patients with suspected cardiovascular conditions and those at high risk for the development of such conditions. It was also considered an appropriate test after the administration of any drug known to influence cardiac

TABLE 5-5-G-1 -- ACC/AHA GUIDELINES FOR ELECTROCARDIOGRAPHY (1992)

Setting	Class I (appropriate)	Class II (equivocal)	Class III (inappropriate)
Patients with Known Cardiovascular Disease or Dysfunction			
Baseline or initial evaluation	All patients	None	None

Response to therapy	Patients in whom prescribed therapy is known to produce ECG changes that correlate with therapeutic responses or progression of disease Patients in whom prescribed therapy may produce adverse effects that may be predicted from or detected by ECG changes	None	Patients receiving pharmacological or nonpharmacological therapy not known to produce ECG changes or to affect conditions that may be associated with such changes
Follow-up	Patients with a change in symptoms, signs, or relevant laboratory findings	None	Adult patients whose cardiovascular condition is benign and unlikely to progress (e.g., patients with mild mitral prolapse, mild hypertension, or premature contractions in the absence of organic heart disease
	Patients with an implanted pacemaker or antitachycardia device Patients with syndromes such as the following conditions, even in the absence of new symptoms of signs, after an interval of time appropriate for the condition or disease: Syncope and near syncope Unexplained change in the usual pattern of angina pectoris Chest pain New or worsening dyspnea Extreme and unexplained fatigue, weakness, and prostration Palpitations New signs of congestive heart failure A new organic murmur		Adult patients with chronic stable heart disease seen at frequent intervals (i.e., 4 mo) and who have no new or unexplained findings

	unexplained fatigue, weakness, and prostration Palpitations New signs of congestive heart failure A new organic murmur or pericardial friction rub New findings suggesting pulmonary hypertension Acceleration or poorly controlled systemic arterial hypertension Evidence of a recent cerebrovascular accident Unexplained fever in patients with known valvular disease New onset of cardiac arrhythmis or inappropriate heart rate Chronic known congenital or acquired cardiovascular disease		
Before surgery	All patients with known cardiovascular disease or dysfunction, except as noted under Class II	Patients with hemodynamically insignificant heart disease, mild systemic arterial hypertension, or infrequent premature complexes in the absence of organic heart disease	None

Patients Suspected of Having or Who Are at Increased Risk for Cardiovascular Disease or Dysfunction

Baseline or initial evaluation	All patients suspected of having or at increased risk for cardiovascular disease Patients who may have used cocaine, amphetamines, or other illicit drugs known to have cardiac effects Patients who may have received an overdose of a drug known to have cardiac effects	None	None

Response to therapy	To assess therapy with cardioactive drugs in patients with suspected cardiac disease To assess response to the administration of any agent known to result in cardiac abnormalities or ECG abnormalities (e.g., antineoplastic drugs, lithium, antidepressant agents)	To assess the response to administration of any agent known to alter serum electrolyte concentrations	To assess the response to administration of agents known not to influence cardiac structure or function
Follow-up	The presence of any change in clinical status or laboratory findings suggesting interval development of cardiac disease or dysfunction Periodic follow-up (e.g., every 1--5 yr) of patients known to be at increased risk for heart disease Follow-up of patients after resolution of chest pain	None	Follow-up ECGs more often than once yearly are not indicated in patients who remain clinically stable, who are not at increased risk for the development of cardiac disease, and who have not been demonstrated to have cardiac disease with previous studies
Before surgery	As part of the preoperative evaluation of any patient with suspected or at increased risk for cardiac disease or dysfunction	None	None

Patients with No Apparent or Suspected Heart Disease or Dysfunction

Baseline or initial evaluation	Persons aged 40 or more yr undergoing physical examination Before administration of pharmacological agents known to have a high incidence of cardiovascular effects (e.g., antineoplastic agents) Before exercise stress testing People of any age who are in special occupations that require very high cardiovascular performance (e.g., fire fighters, police officers) or whose cardiovascular performance is linked to public safety (e.g., pilots, air traffic controllers, critical process operators, bus or truck drivers, and railroad engineers)	To evaluate competitive athletes	Routine screening or baseline ECGs in asymptomatic persons younger than 40 yr with no risk factors
Response to therapy	To evaluate patients in whom prescribed therapy (e.g., doxorubicin) is known to produce cardiovascular effects	None	To assess treatment that is known to not produce any cardiovascular effects
Follow-up	To evaluate asymptomatic persons > 40 yr of age	None	To evaluate asymptomatic adults who have had no interval change in symptoms, signs, or risk factors and who have had a normal ECG with the recent past
Before surgery	Patients >40 yr of age Patients being evaluated as a donor for heart transplantation or as a recipient of a noncardiopulmonary transplant	Patients 30--40 yr of age	Patients younger than 30 yr with no risk factors for coronary artery disease

Class I: Conditions for which or patients for whom it is generally agreed that electrocardiography is useful (appropriate).
Class II: Conditions for which or patients for whom electrocardiography is frequently used but opinion differs with respect to its usefulness (equivocal).
Class III: Conditions for which or patients for whom it is generally agreed that electrocardiography is of little or no usefulness (inappropriate).

From Schlant RC, Adolph RJ, DiMarco JP, et al: Guidelines for electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Electrocardiography). J Am Coll Cardiol 19:473-481, 1992. Reprinted with permission from the American College of Cardiology. See also Chapter 5 text for further discussion and alternative recommendations.

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structure or function. Follow-up ECGs more often than once per year were not recommended for patients who remained clinically stable, as long as they had not been previously demonstrated to have cardiac disease. However, for patients known to be at increased risk for the development of heart disease, ECGs every 1 to 5 years were considered appropriate (Class I). ECGs were considered appropriate before cardiac or noncardiac surgery for all patients in this population.

Patients Without Known or Suspected Heart Disease

For patients without evidence suggesting cardiovascular disease, ECGs were considered appropriate during the baseline evaluation in the ACC/AHA guidelines for those aged 40 years or older. The ACC/AHA guidelines also recommended ECGs for patients for whom drugs with a high incidence of cardiovascular effects (e.g., chemotherapy) or exercise testing was planned and for people of any age in occupations with high cardiovascular demands or whose cardiovascular status might affect the well-being of many other people (e.g., airline pilot). These guidelines are similar to those of the U.S. Preventive Services Task Force,[2] which suggested ECG screening for those with occupations in which their cardiovascular health might jeopardize the lives of others.

Guidelines vary on the performance of baseline ECGs. An American Heart Association panel recommended in 1987 that ECGs be obtained at ages 20, 40, and 60 years in persons with normal blood pressure,[3] while a task force assembled by the Canadian government has discouraged the use of any screening ECGs.[4]

Before cardiac or noncardiac surgery, the ACC/AHA guidelines recommend ECGs for all people aged 40 years or older,[1] and ECGs are considered equivocal in appropriateness (Class II) for surgical patients aged 30 to 40 years. Guidelines issued by the American College of Physicians[5] recommend ECGs preoperatively and upon hospital admission for men aged 40 years or older and women aged 50 years or older, as well as all patients having elective intrathoracic, intraperitoneal, or aortic surgery; elective major neurosurgery; or emergency operations under general or regional

anesthesia.

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Chapter 6 - Exercise Stress Testing

BERNARD R. CHAITMAN

Exercise is a common physiological stress used to elicit cardiovascular abnormalities not present at rest and to determine adequacy of cardiac function.[1] [2] [3] [4] [5] [6] [7] [8] [9] Exercise electrocardiography (ECG) is one of the most frequent noninvasive modalities used to assess patients with suspected or proven cardiovascular disease. The test is mainly used to estimate prognosis and to determine functional capacity, the likelihood and extent of coronary artery disease (CAD), and the effects of therapy.[5] [6] Hemodynamic and ECG measurements combined with ancillary techniques such as metabolic gas analysis, radionuclide imaging, and echocardiography enhance the information content of exercise testing in selected patients.[9] [10] [11]

EXERCISE PHYSIOLOGY (See also Chap. 39)

Anticipation of dynamic exercise results in an acceleration of ventricular rate due to vagal withdrawal, increase in alveolar ventilation, and increased venous return primarily as a result of sympathetic venoconstriction.[12] In normal persons, the net effect is to increase resting cardiac output before the start of exercise. The magnitude of hemodynamic response during exercise depends on the severity and amount of muscle mass involved. In the early phases of exercise in the upright position, cardiac output is

increased by an augmentation in stroke volume mediated through the use of the Frank-Starling mechanism and heart rate; the increase in cardiac output in the latter phases of exercise is primarily due to a sympathetic-mediated increase in ventricular rate. At fixed submaximal workloads below anaerobic threshold, steady-state conditions are usually reached after the second minute of exercise, following which heart rate, cardiac output, blood pressure, and pulmonary ventilation are maintained at reasonably constant levels.[7] During strenuous exertion, sympathetic discharge is maximal and parasympathetic stimulation is withdrawn, resulting in vasoconstriction of most circulatory body systems, except for that in exercising muscle and in the cerebral and coronary circulations. Venous and arterial norepinephrine release from sympathetic postganglionic nerve endings, as well as plasma renin levels, is increased; the catecholamine release enhances ventricular contractility. As exercise progresses, skeletal muscle blood flow is increased, oxygen extraction increases by as much as threefold, total calculated peripheral resistance decreases, and systolic blood pressure, mean arterial pressure, and pulse pressure usually increase. Diastolic blood pressure does not change significantly. The pulmonary vascular bed can accommodate as much as a sixfold increase in cardiac output with only modest increases in pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure; in normal individuals, this is not a limiting determinant of peak exercise capacity.

Cardiac output increases by four- to sixfold above basal levels during strenuous exertion in the upright position, depending on genetic endowment and level of training.[12] The maximum heart rate and cardiac output are decreased in older individuals, partly because of decreased beta-adrenergic responsivity.[13] [14] [15] Maximum heart rate can be estimated from the formula 220 - age (years) with a standard deviation of 10 to 12 beats/min. The age-predicted maximum heart rate is a useful measurement for safety reasons. However, the wide standard deviation in the various regression equations used and the impact of drug therapy limit the usefulness of this parameter in estimating the exact age-predicted maximum for an individual patient.

In the postexercise phase, hemodynamics return to baseline within minutes of termination. Vagal reactivation is an important cardiac deceleration mechanism after exercise and is accelerated in well-trained athletes but blunted in patients with chronic heart failure.[16] Intense physical work or significant cardiorespiratory impairment may interfere with achievement of a steady state, and an oxygen deficit occurs during exercise. The total oxygen uptake in excess of the resting oxygen uptake during the recovery period is the oxygen debt.

PATIENT'S POSITION.

At rest, the cardiac output and stroke volume are higher in the supine than in the upright position. With exercise in normal supine persons, the elevation of cardiac output results almost entirely from an increase in heart rate with little augmentation of stroke volume. In the upright posture, the increase in cardiac output in normal individuals results from a combination of elevations in stroke volume and heart rate. A change from supine to upright posture causes a decrease in venous return, left ventricular end-diastolic volume and pressure, stroke volume, and cardiac index. Renin and norepinephrine levels are increased. End-systolic volume and ejection fraction are not significantly changed. In

normal individuals, end-systolic volume decreases and ejection fraction increases to a similar extent from rest to exercise in the supine and upright positions. The magnitude and direction of change in end-diastolic volume from rest to maximum exercise in both positions are small and may vary according to the patient population studied. The net effect on exercise performance is an approximate 10 percent increase in exercise time, cardiac index, heart rate, and rate pressure product at peak exercise in the upright as compared with the supine position.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing involves measurements of respiratory oxygen uptake (O_2), carbon dioxide production (CO_2), and ventilatory parameters during a symptom-limited exercise test. During testing, the patient usually wears

a nose clip and breathes through a nonrebreathing valve that separates expired air from room air. Important measurements of expired gas are P_{O_2} , P_{CO_2} , and airflow. Ventilatory measurements include respiratory rate, tidal volume, and minute ventilation ($_E$) P_{O_2} and P_{CO_2} are sampled breath by breath or by use of a mixing chamber. The O_2 and CO_2 can be computed on line from ventilatory volumes and differences between inspired and expired gases.[9] Under steady-state conditions, O_2 and CO_2 measured at the mouth are equivalent to total-body oxygen consumption and carbon dioxide production. The relationship between work output, oxygen consumption, heart rate, and cardiac output during exercise is linear (Fig. 6-1) . O_2 max is the product of maximal arterial-venous oxygen difference and cardiac output and represents the largest amount of oxygen a person can use while performing dynamic exercise involving a large part of total muscle mass. The O_2 max decreases with age, is usually less in women than in men, and can vary between individuals as a result of genetic factors.[14] [15] O_2 max is diminished by degree of cardiovascular impairment and by physical inactivity. In untrained persons, the arterial-mixed venous oxygen difference at peak exercise is relatively constant (14 to 17 vol percent), and O_2 max is an approximation of maximum cardiac output. Measured O_2 max can be compared with predicted values from empirically derived formulas based on age, sex, weight, and height.[9] [17] Most clinical studies that use exercise as a stress to assess cardiac reserve report peak O_2 that is the highest O_2 attained during graded exercise testing rather than O_2 max. Peak exercise capacity is decreased when the ratio of measured to predicted

O_2 max is less than 85 to 90 percent. Oximetry, performed noninvasively, can be used to monitor arterial oxygen saturation, and the value normally does not decrease by more than 5 percent during exercise. Estimates of oxygen saturation during strenuous exercise using pulse oximetry may be unreliable in some patients.[18]

ANAEROBIC THRESHOLD.

Anaerobic threshold is a theoretical point during dynamic exercise when muscle tissue switches over to anaerobic metabolism as an additional energy source. All tissues do not shift simultaneously, and there is a brief interval during which exercise muscle tissue shifts from predominantly aerobic to anaerobic metabolism.[9] [12] [17] [19] Lactic acid begins to accumulate when a healthy untrained subject reaches about 50 to 60 percent of the maximal capacity for aerobic metabolism. The increase in lactic acid becomes greater as exercise becomes more intense, resulting in metabolic acidosis. As lactate is formed, it is buffered in the serum by the bicarbonate system, resulting in increased carbon dioxide excretion, which causes reflex hyperventilation. The gas exchange anaerobic threshold is the point at which
Eincreases disproportionately relative to
O_2 and work; it occurs at 40 to 60 percent of
O_2 max in normal, untrained individuals.[9] Below the anaerobic threshold, carbon dioxide production is proportional to oxygen consumption. Above the anaerobic threshold, carbon dioxide is produced in excess of oxygen

Figure 6-1 Cardiopulmonary exercise test in a healthy 53-year-old man using the Bruce protocol. The progressive linear increase in work output, heart rate, and oxygen consumption (O_2) is noted, with steady-state conditions reached after 2 minutes in each of the first two stages *(top panel).* Open arrows indicate the beginning of each new 3-minute stage. The subject completed 7 minutes and 10 seconds of exercise, and peak O_2 was 3.08 liters/min. The anaerobic threshold (AT_{ge}), determined by the V-slope method, is the point at which the slope of the relative rate of increase in CO_2 relative to O_2 changes; it occurred at a O_2 of 1.5 liters/min, or 49 percent of peak O_2 , within predicted values for a normal sedentary population *(bottom panel).* The AT_{ge} determined by the point at which the O_2 and CO_2 slopes intersect (1.8 liters/min) *(top panel)* is slightly greater than the AT_{ge} determined by the V-slope method *(bottom panel).* The V-slope method usually provides a more reproducible estimate of AT_{ge} . $PETO_2$ = end-tidal pressure of oxygen; RER = respiratory exchange ratio; VE/O_2 = ratio ventilation to oxygen uptake.

consumption. There are several methods to determine anaerobic threshold, which

include (1) the V-slope method, the point at which the rate of increase in CO_2 relative to O_2 increases (see Fig. 6-1) ; (2) the point at which the O_2 and CO_2 slopes intersect; and (3) the point at which the ratio of V_E/O_2 and end-tidal oxygen tension begins to increase systematically without an immediate increase in the V_E/O_2 (see Fig. 6-1) . The anaerobic threshold is a useful parameter because work below this level encompasses most activities of daily living. Anaerobic threshold is often reduced in patients with significant cardiovascular disease. An increase in anaerobic threshold with training can enhance an individual's capacity to perform sustained submaximal activities, with consequent improvement in quality of life and daily living. Changes in anaerobic threshold and peak O_2 with repeat testing can be used to assess disease progression, response to medical therapy, and improvement in cardiovascular fitness with training.

VENTILATORY PARAMETERS.

In addition to peak O_2 , minute ventilation and its relation to CO_2 and oxygen consumption are useful indices of cardiac and pulmonary function. The respiratory exchange ratio represents the amount of carbon dioxide produced divided by the amount of oxygen consumed. The respiratory exchange ratio ranges from 0.7 to 0.85 at rest and is partly dependent on the predominant fuel used for cellular metabolism (e.g., respiratory exchange rate for predominant carbohydrate use is 1.0, whereas respiratory exchange ratio for predominant fatty use is 0.7). At high exercise levels, carbon dioxide production exceeds O_2 , and a respiratory exchange ratio greater than 1.0 often indicates that the subject has performed at maximal effort.

METABOLIC EQUIVALENT.

The current use of the term metabolic equivalent (MET) refers to a unit of sitting, resting oxygen uptake; 1 MET is equivalent to 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ of body weight. Measured O_2 in ml/min/kg divided by 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ determines number of METs associated with activity. Work activities can be calculated in multiples of METs; this measurement is useful to determine exercise prescriptions, assess disability, and standardize the reporting of submaximal and peak exercise workloads when different protocols are used. An exercise workload of 3 to 5 METs is consistent with activities such as raking leaves, light carpentry, golf, and walking at 3 to 4 mph. Workloads of 5 to 7 METs are consistent with exterior carpentry, singles tennis, and light backpacking. Workloads in excess of 9 METs are compatible with heavy labor, handball, squash, and running at 6 to 7 mph. Estimating O_2 from work rate or treadmill time in individual patients may lead to misinterpretation of data if exercise equipment is not correctly calibrated, when the patient holds onto the front handrails, if the patient fails to achieve steady state, is obese, or has peripheral

vascular disease, pulmonary vascular disease, or cardiac impairment.
O_2 does not increase linearly in some patients with cardiovascular or pulmonary disease as work rate is increased, and
O_2 may thus be overestimated.[9] The measurements obtained with cardiopulmonary exercise testing are useful in understanding an individual patient's response to exercise and can be useful in the diagnostic evaluation of a patient with dyspnea.[9] [19] [20]

EXERCISE PROTOCOLS

The main types of exercise are isotonic or dynamic exercise, isometric or static exercise, and resistive (combined isometric and isotonic) exercise. Dynamic protocols most frequently are used to assess cardiovascular reserve, and those suitable for clinical testing should include a low-intensity warm-up phase. In general, 6 to 12 minutes of continuous progressive exercise during which the myocardial oxygen demand is elevated to the patient's maximal level is optimal for diagnostic and prognostic purposes.[1] [2] [3] The protocol should include a suitable recovery or cool-down period. If the protocol is too strenuous for an individual patient, early test termination results and will not allow an opportunity to observe clinically important responses. If the exercise protocol is too easy for an individual patient, the prolonged procedure tests endurance and not aerobic capacity. Thus, exercise protocols should be individualized to accommodate a patient's limitations. Protocols may be set up at a fixed duration of exercise for a certain intensity to meet minimal qualifications for certain industrial tasks or sports programs.

STATIC EXERCISE.

This form of isometric exercise generates force with little muscle shortening and produces a greater blood pressure response than with dynamic exercise. Cardiac output does not increase as much as with dynamic exercise because increased resistance in active muscle groups limits blood flow. In a common form of static exercise, the patient's maximal force on a hand dynamometer is recorded. The patient then sustains 25 to 33 percent of maximal force for 3 to 5 minutes while ECG and blood pressures are recorded. The increase in myocardial
O_2 is often insufficient to initiate an ischemic response.

ARM ERGOMETRY.

Arm crank ergometry protocols involve arm cranking at incremental workloads of 10 to 20 W for 2- or 3-minute stages. The heart rate and blood pressure responses to a given workload of arm exercise usually are greater than those for leg exercise. A bicycle ergometer with the axle placed at the level of the shoulders is used, and the subject sits or stands and cycles the peddles so that the arms are alternately fully extended. The most common frequency is 50 rpm. In normal individuals, maximal
O_2 and
Efor arm cycling approximates 50 to 70 percent of leg cycling. Peak heart rate is approximately 70 percent of that during leg testing. Arm ergometry exercise protocols are useful for risk stratification of patients with suspected or documented CAD before

noncardiac surgery when leg exercise is not possible or insufficient to test cardiac reserve.

BICYCLE ERGOMETRY.

Bicycle protocols involve incremental workloads calibrated in watts or kilopond/meters/minute (kpm). One watt is equivalent to approximately 6 kpm. Because exercise on a cycle ergometer is not weight bearing, kpm or watts can be converted to oxygen uptake in milliliters per minute. In mechanically braked bicycles, work is determined by force and distance and requires a constant pedaling rate of 60 to 80 rpm, according to the patient's preference. Electronically braked bicycles provide a constant workload despite changes in pedaling rate and are less dependent on a patient's cooperation. They are more costly than a mechanically braked bicycle but are preferred for diagnostic and prognostic assessment. Most protocols start with a power output of 10 or 25 W (150 kpm/min), usually followed by increases of 25 W every 2 or 3 minutes until endpoints are reached. Younger subjects may start at 50 W, with 50-W increments every 2 minutes. A ramp protocol differs from the staged protocols in that the patient starts at 3 minutes of unloaded pedaling at a cycle speed of 60 rpm. Work rate is increased by a uniform amount each minute, ranging from 5- to 30-W increments, depending on a patient's expected performance.[9] Exercise is terminated if the patient is unable to maintain a cycling frequency above 40 rpm. In the cardiac catheterization laboratory, hemodynamic measurements may be made during supine bicycle ergometry at rest and at one or two submaximal workloads.

The bicycle ergometer is associated with a lower maximal O_2 and anaerobic threshold than the treadmill; maximal heart rate, maximal E, and maximal lactate values are often similar. The bicycle ergometer has the advantage of requiring less space than a treadmill; it is quieter and permits sensitive precordial measurements without much motion artifact. However, in North America, treadmill protocols are more widely used in the assessment of patients with coronary disease.

TREADMILL PROTOCOL.

The treadmill protocol should be consistent with the patient's physical capacity and the purpose of the test. In healthy individuals, the standard

Bruce's protocol is popular, and a large diagnostic and prognostic data base has been published.[1] [2] [3] [4] Bruce's multistage maximal treadmill protocol has 3-minute periods to allow achievement of a steady state before workload is increased (Figs. 6-1 and 6-2) . In older individuals or those whose exercise capacity is limited by cardiac disease, Bruce's protocol can be modified by two 3-minute warm-up stages at 1.7 mph and 0 percent grade and 1.7 mph and 5 percent grade. A limitation of Bruce's protocol is the relatively large increase in

O_2 between stages and the additional energy cost of running as compared with walking at stages in excess of Bruce's stage III. The Naughton and Weber protocols use 1- to 2-minute stages with 1-MET increments between stages; these protocols may be more suitable for patients with limited exercise tolerance such as patients with congestive heart failure. The Asymptomatic Cardiac Ischemia Pilot trial (ACIP) and modified ACIP (mACIP) protocols use 2-minute stages with 1.5-MET increments between stages after two 1-minute warm-up stages with 1-MET increments. The ACIP protocols were developed to test patients with established CAD and result in a linear increase in heart rate and
O_2 , distributing the time to occurrence of ST segment depression over a wider range of heart rate and exercise time than protocols with more abrupt increments in workload between stages.[21] [22] The mACIP protocol produces a similar aerobic demand as the standard ACIP protocol for each minute of exercise and is well suited for short or elderly individuals who cannot keep up with a walking speed of 3 mph (see Fig. 6-2) .

Ramp protocols start the patient at relatively slow treadmill speed, which is gradually increased until the patient has a good stride. The ramp angle of incline is progressively increased at fixed intervals (e.g., 10 to 60 seconds), starting at zero grade with the increase in grade calculated on the basis of the patient's estimated functional capacity such that the protocol will be complete at between 6 and 12 minutes.[2] [3] [4] In this type of protocol, the rate of work increase is continuous and steady-state conditions are not reached. A limitation of ramp protocols is the requirement to estimate functional capacity from an activity scale; underestimation or overestimation of functional capacity occasionally results in an endurance test or premature cessation. One formula for estimating
O_2 from treadmill speed and grade is

$$O_2 \text{ (ml } O_2 \cdot kg^{-1} \cdot min^{-1}) = (\text{mph} \times 2.68) + (1.8 \times 26.82 \times \text{mph} \times \text{grade} \div 100) + 3.5$$ [23]

The peak
O_2 is usually the same regardless of treadmill protocol used; the difference is the rate of time at which the peak
O_2 is achieved.

It is important to encourage patients not to grasp the handrails of the treadmill during exercise. Functional capacity can be overestimated by as much as 20 percent in tests in which handrail support is permitted, and
O_2 is decreased. Because the degree of handrail support is difficult to quantify from one test to another, more consistent results can be obtained during serial testing when handrail support is not permitted.

The *6-minute walk test* can be used for patients who have marked left ventricular dysfunction or peripheral arterial occlusive disease and who cannot perform bicycle or treadmill exercise.[24] [25] Patients are instructed to walk down a 100-foot corridor at their own pace, attempting to cover as much ground as possible in 6 minutes. At the end of the 6-minute interval, the total distance walked is determined and the symptoms experienced by the patient are recorded. The 6-minute walk test as a clinical measure of

ambulatory function requires highly skilled personnel following a rigid protocol to elicit reproducible and reliable results. The coefficient of variation for distance walked during two 6-minute walk tests was 10 percent in one series of patients with peripheral arterial occlusive disease.[25]

Figure 6-2 Estimated oxygen cost of bicycle ergometer and selected treadmill protocols. The standard Bruce protocol starts at 1.7 mph and 10 percent grade (5 METs), with a larger increment between stages than protocols such as the Naughton, ACIP, and Weber protocols, which start at less than 2 METs at 2 mph and increase by 1- to 1.5-MET increments between stages. The Bruce protocol can be modified by two 3-minute warm-up stages at 1.7 mph and 0 percent grade and 1.7 mph and 5 percent grade.*(Adapted from Fletcher GF, Balady G, Froelicher VF, et al: Exercise standards. A statement for healthcare professionals from the American Heart Association. Circulation 91:580, 1995. Copyright 1995 American Heart Association.)*

TECHNIQUES.

Patients should be instructed not to eat, drink caffeinated beverages, or smoke for 3 hours before testing and to wear comfortable shoes and loose-fitting clothes. Unusual physical exertion should be avoided before testing. A brief history and physical examination should be performed, and patients should be advised about the risks and benefits of the procedure. A written informed consent form is usually required.[7] [8] The indication for the test should be known. In many laboratories, the presence or absence of atherosclerotic risk factors is noted and cardioactive medication recorded. A 12-lead ECG should be obtained with the electrodes at the distal extremities. The timing of cardioactive medication ingestion before testing depends on the test indication.

After the standard 12-lead ECG is recorded, a torso ECG should be obtained in the supine position and in the sitting or standing position. Postural changes can elicit labile ST-T wave abnormalities. Hyperventilation is not recommended before exercise. If a false-positive test result is suspected, hyperventilation should be performed after the test, and the hyperventilation tracing compared with the maximal ST segment abnormalities observed. The ECG and blood pressure should be recorded in both positions, and patients should be instructed on how to perform the test.

Adequate skin preparation is essential for high-quality recordings, and the superficial layer of skin needs to be removed to augment signal-to-noise ratio. The areas of electrode application are rubbed with an alcohol-saturated pad to remove oil and rubbed with free sandpaper or a rough material to reduce skin resistance to 5000 ohms or less. Silver chloride electrodes with a fluid column to avoid direct metal-to-skin contact produce high-quality tracings; these electrodes have the lowest offset voltage.

Cables connecting the electrodes and recorders should be light, flexible, and properly shielded. In a small minority of patients, a fishnet jersey may be required over the

electrodes and cables to reduce motion artifact. The electrode-skin interface can be verified by tapping on the electrode and examining the monitor or by measuring skin impedance. Excessive noise indicates that the electrode needs to be replaced; replacement before the test rather than during exercise can save time. The ECG signal can be digitized systematically at the patient's end of the cable by some systems, reducing power line artifact. Cables, adapters, and junction box have a finite life span and require periodic replacement to obtain the highest quality tracings. Exercise equipment should be calibrated regularly. Room temperature should be between 64 and 72°F (18 and 22°C) and humidity less than 60 percent.

Treadmill walking should be demonstrated to the patient. The heart rate, blood pressure, and ECG should be recorded at the end of each stage of exercise, immediately before and immediately after stopping exercise, at the onset of an ischemic response, and for each minute for at least 5 to 10 minutes in the recovery phase. A minimum of three leads should be displayed continuously on the monitor during the test. There is some controversy about optimal patient position in the recovery phase. In the sitting position, less space is required for a stretcher, and patients are more comfortable immediately after exertion. The supine position increases end-diastolic volume and has the potential to augment ST segment changes.[26]

ELECTROCARDIOGRAPHIC MEASUREMENTS

LEAD SYSTEMS.

The Mason-Likar modification of the standard 12-lead ECG requires that the extremity electrodes be moved to the torso to reduce motion artifact. The arm electrodes should be located in the most lateral aspects of the infraclavicular fossae, and the leg electrodes in a stable position above the anterior iliac crest and below the rib cage. The Mason-Likar modification results in a right-axis shift and increased voltage in the inferior leads and may produce a loss of inferior Q waves and the development of new Q waves in lead aV_L . Thus, the body torso limb lead positions cannot be used to interpret a diagnostic rest 12-lead ECG. The more cephalad the leg electrodes are placed, the greater is the degree of change and the greater is the augmentation of R wave amplitude, potentiating exercise-induced ST segment changes.

Bipolar lead groups place the negative or reference electrode over the manubrium (CM_5), right scapula (CB_5), RV_5 (CC_5), or on the forehead (CH_5), and the active electrode at V_5 or proximate location to optimize R wave amplitude. In bipolar lead ML, which reflects inferior wall changes, the negative reference is at the manubrium and the active electrode in the left leg position. Bipolar lead groups may provide additional diagnostic information, and in some medical centers, lead CM_5 is substituted for lead aV_r in the Mason-Likar modified lead system (Fig. 6-3) . Bipolar leads are frequently used when only a limited ECG set is required (e.g., in cardiac rehabilitation programs). In one series of patients, the use of right precordial leads (V3-5 R) increased the sensitivity to detect exercise-induced ST segment shifts.[27] The use of more elaborate lead set systems is usually reserved for research purposes.

In normal persons, the PR, QRS, and QT intervals shorten as heart rate increases. P amplitude increases, and the PR

Figure 6-3 J point depression of 2 to 3 mm in leads V_4 to V_6 with rapid upsloping ST segments depressed approximately 1 mm 80 msec after the J point. The ST segment slope in leads V_4 and V_5 is 3.0 mV/sec. This response should not be considered abnormal.

segment becomes progressively more downsloping in the inferior leads. J point, or junctional, depression is a normal finding during exercise (see Fig. 6-3) . In patients with myocardial ischemia, however, the ST segment usually becomes more horizontal (flattens) as the severity of the ischemic response worsens. With progressive exercise, the depth of ST segment depression may increase, involving more ECG leads, and the patient may develop angina. In the immediate postrecovery phase, the ST segment displacement may persist, with downsloping ST segments and T wave inversion, gradually returning to baseline after 5 to 10 minutes (Figs. 6-4 and 6-5) . Ischemic ST segment displacement may be seen only during exercise, emphasizing the importance of adequate skin preparation and electrode placement to capture high-quality recordings during maximum exertion (see Fig. 6-6) . In about 10 percent of patients, the ischemic response may appear only in the recovery phase. The prevalence of recovery-onset ischemic ST segment changes is higher in asymptomatic populations compared with those with symptomatic CAD.[28] Patients should not leave the exercise laboratory area until the postexercise ECG has returned to baseline. Figure 6-7 illustrates eight different ECG patterns seen during exercise testing.[29]

MEASUREMENT OF ST SEGMENT DISPLACEMENT.

For purposes of interpretation, the PQ junction is usually chosen as the isoelectric point. The TP segment represents a true isoelectric point but is an impractical choice for most routine clinical measurements. The development of 0.10 mV (1 mm) or greater of J point depression measured

Figure 6-4 Bruce protocol. In lead V_4 , the exercise ECG result is abnormal early in the test, reaching 0.3 mV (3 mm) of horizontal ST segment depression at the end of exercise. The ischemic changes persist for at least 1 minute and 30 seconds into the recovery phase. The right panel provides a continuous plot of the J point, ST slope, and ST segment displacement at 80 msec after the J point (ST level) during exercise and in the recovery phase. Exercise ends at the vertical line at 4.5 min. The computer trends permit a more precise identification of initial onset and offset of ischemic ST segment depression. This

type of ECG pattern, with early onset of ischemic ST segment depression, reaching more than 3 mm of horizontal ST segment displacement and persisting several minutes into the recovery phase, is consistent with a severe ischemic response.

Figure 6-5 Bruce protocol. In this type of ischemic pattern, the J point at peak exertion is depressed 2.5 mm, the ST segment slope is 1.5 mV/sec, and the ST segment level at 80 msec after the J point is depressed 1.6 mm. This "slow upsloping" ST segment at peak exercise indicates an ischemic pattern in patients with a high coronary disease prevalence pretest. A typical ischemic pattern is seen at 3 minutes of the recovery phase when the ST segment is horizontal and 5 minutes after exertion when the ST segment is downsloping. Exercise is discontinued at the vertical line in the right panel at 7.5 minutes.

from the PQ junction, with a relatively flat ST segment slope (<1 mV/sec), depressed greater than or equal to 0.10 mV 80 msec after the J point (ST 80) in three consecutive beats with a stable baseline is considered to be an abnormal response (Fig. 6-8) . When the ST 80 measurement is difficult to determine at rapid heart rates (e.g., >130 beats/min), the ST 60 measurement should be used. The ST segment at rest may occasionally be depressed. When this occurs, the J point and ST 60 or ST 80 measurements should be depressed an additional 0.10 mV or greater to be considered abnormal.

When the degree of resting ST segment depression is 0.1 mV or greater, the exercise ECG becomes less specific, and myocardial imaging modalities should be considered.[5] [11] In patients with early repolarization and resting ST segment elevation, return to the PQ junction is normal. Therefore, the magnitude of exercise-induced ST segment depression in a patient with early repolarization should be determined from the PQ junction and not from the elevated position of the J point before exercise. Exercise-induced ST segment depression does *not* localize the site of myocardial ischemia, *nor* does it provide a clue about which coronary artery is involved. For example, it is not unusual for patients with isolated right CAD to exhibit exercise-induced ST segment depression only in leads V_4 to V_6 , nor is it unusual for patients with disease of the left anterior descending coronary artery to exhibit exercise-induced ST segment displacements in leads II, III, and aV_f . Exercise-induced ST segment elevation is relatively specific for the territory of myocardial ischemia and the coronary artery involved.

UPSLOPING ST SEGMENTS.

Junctional or J point depression is a normal finding during maximal exercise, and a

Figure 6-6 Bruce protocol. The exercise ECG result is not yet abnormal at 8:50 minutes but becomes abnormal at 9:30 minutes (horizontal arrow *right*) of a 12-minute exercise test and resolves in the

immediate recovery phase. This ECG pattern in which the ST segment becomes abnormal only at high exercise workloads and returns to baseline in the immediate recovery phase may indicate a false-positive result in an asymptomatic individual without atherosclerotic risk factors. Exercise myocardial imaging would provide more diagnostic and prognostic information if this were an older person with several atherosclerotic risk factors.

rapid upsloping ST segment (>1 mV/sec) depressed less than 0.15 mV (1.5 mm) after the J point should be considered to be normal. Occasionally, however, the ST segment is depressed 0.15 mV (1.5 mm) or greater at 80 msec after the J point. This type of slow upsloping ST segment may be the only ECG finding in patients with well-defined obstructive CAD and may depend on the lead set used (see Fig. 6-5) . In patient subsets with a high CAD prevalence, a slow upsloping ST segment depressed 0.15 mV or greater at 80 msec after the J point should be considered to be abnormal. The importance of this finding in asymptomatic individuals or those with a low CAD prevalence is less certain. Increasing the degree of ST segment depression at 80 msec after the J point to 0.20 mV (2.0 mm) or greater in patients with a slow upsloping ST segment increases specificity but decreases sensitivity.[29]

ST SEGMENT ELEVATION.

Exercise-induced ST segment elevation may occur in an infarct territory where Q waves are present or in a noninfarct territory. The development of 0.10 mV (1 mm) or greater of J point elevation, persistently elevated greater than 0.10 mV at 60 msec after the J point in three consecutive beats with a stable baseline, is considered an abnormal response (see Fig. 6-7) . This finding occurs in approximately 30 percent of patients with anterior myocardial infarctions and 15 percent of those with inferior ones tested early (within 2 weeks) after the index event and decreases in frequency by 6 weeks. As a group, postinfarct patients with exercise-induced ST segment elevation have a lower ejection fraction than those without, a greater severity of resting wall motion abnormalities, and a worse prognosis. Exercise-induced ST segment elevation in leads with abnormal Q waves is *not* a marker of more extensive CAD and rarely indicates myocardial ischemia. Exercise-induced ST-segment elevation may occasionally occur in a patient who has regenerated embryonic R waves after an acute myocardial infarction; the clinical significance of this finding is similar to that observed when Q waves are present.

When ST segment elevation develops during exercise in a non-Q wave lead in a patient without a previous myocardial infarction, the finding should be considered as likely evidence of transmural myocardial ischemia caused by coronary vasospasm or a high-grade coronary narrowing (Fig. 6-9) . This finding is relatively uncommon, occurring in approximately 1 percent of patients with obstructive CAD. The ECG site of ST segment elevation is relatively specific for the coronary artery involved, and myocardial perfusion scintigraphy usually reveals a defect in the territory involved.

T WAVE CHANGES.

The morphology of the T wave is influenced by body position, respiration, hyperventilation, drug therapy, and myocardial ischemia/necrosis. In patient populations

with a low CAD prevalence, pseudonormalization of T waves (inverted at rest and becoming upright with exercise) is a nondiagnostic finding (Fig. 6-10) . In rare instances, this finding may be a marker for myocardial ischemia in a patient with documented CAD, although it would need to be substantiated by an ancillary technique, such as the concomitant finding of a reversible myocardial perfusion defect.[30]

OTHER ELECTROCARDIOGRAPHIC MARKERS.

Changes in R wave amplitude during exercise are relatively nonspecific and are related to the level of exercise performed. When the R wave amplitude meets voltage criteria for left ventricular hypertrophy, the ST segment response *cannot* be used reliably to diagnose CAD, even in the absence of a left ventricular strain pattern. Loss of R wave amplitude, commonly seen after myocardial infarction, reduces the sensitivity of the ST segment response in that lead to diagnose obstructive CAD. Adjustment of the extent of ST segment depression by R wave height in individual leads has not been consistently shown to improve the diagnostic value of the exercise ECG for CAD. U wave inversion may occasionally be seen in the precordial leads at heart rates of 120 beats/min. Although this finding is relatively specific for CAD, it is relatively insensitive.[31]

COMPUTER-ASSISTED ANALYSIS

The use of computers has facilitated the routine analysis and measurements required from exercise ECG and can be performed on line as well as off line.[32] When the raw ECG data are high quality, the computer can filter and average or select median complexes from which the degree of J point displacement, ST segment slope, and ST displacement 60 to 80 msec after the J point (ST 60 to 80) can be measured. The selection of ST 60 or ST 80 depends on the heart rate response. At ventricular rates greater than 130 beats/min, the ST 80 measurement may fall on the upslope of the T wave, and the ST 60 measurement should be used instead. In some computerized systems, the PQ junction or isoelectric interval is detected by scanning before the R wave for the 10-msec interval with the least slope. J point, ST slope, and ST levels are determined (see Figs. 6-4 , 6-5 , and 6-6) ; the ST integral can be calculated from the area below the isoelectric line from the J point to ST 60 or ST 80.[29] Computerized treatment of ECG complexes permits reduction of motion and myographic artifacts. However, the averaged or median beats may occasionally be erroneous because of ECG signal distortion caused by noise, baseline wander, or changes in conduction, and identification of the PQ junction and ST segment onset may be imperfect. Therefore, it is crucial to ensure that the computer-determined averages or median complexes reflect the raw ECG data, and physicians should program the computer to print out raw data during exercise and inspect the raw data to be certain that the QRS template is accurately reproduced before accepting the automatic measurements.

ST/HEART RATE SLOPE MEASUREMENTS.

Heart rate adjustment of ST segment depression appears to improve the sensitivity of the exercise test, particularly the prediction of multivessel CAD.[33] The ST/heart rate slope depends on the type of exercise performed, number and location of monitoring electrodes, method of measuring ST segment depression, and clinical characteristics of

the study population. Calculation of maximal ST/heart rate slope in mV/beats/min is performed by linear regression analysis relating the measured amount of ST segment depression in individual leads to the heart rate at the end of each stage of exercise, starting at the end of exercise. An ST/heart

Figure 6-7 Illustration of eight typical exercise ECG patterns at rest and at peak exertion. The computer-processed incrementally averaged beat corresponds with the raw data taken at the same time point during exercise and is illustrated in the last column. The patterns represent worsening ECG responses during exercise. In the column of computer-averaged beats, ST 80 displacement (top number) indicates the magnitude of ST segment displacement 80 msec after the J point relative to the PQ junction or E point. ST segment slope measurement (bottom number) indicates the ST segment slope at a fixed time point after the J point to the ST 80 measurement. At least three noncomputer average complexes with a stable baseline should meet criteria for abnormality before the exercise ECG result can be considered abnormal (see Fig. 6-9) . The normal and rapid upsloping ST segment responses are normal responses to exercise. J point depression with rapid upsloping ST segments is a common response in an older, apparently healthy population. Minor ST depression can occur occasionally at submaximal workloads in patients with coronary disease; in this illustration, the ST segment is depressed 0.09 mV (0.9 mm) 80 msec after the J point. The slow upsloping ST segment pattern often demonstrates an ischemic response in patients with known coronary disease or those with a high pretest clinical risk of coronary disease. Criteria for slow upsloping ST segment depression include J point and ST 80 depression of 0.15 mV or more and ST segment slope of more than 1.0 mV/sec. Classic criteria for myocardial ischemia include horizontal ST segment depression observed when both the J point and ST 80 depression are 0.1 mV or more and ST segment slope is within the range of 1.0 mV/sec. Downsloping ST segment depression occurs when the J point and ST 80 depression are 0.1 mV and ST segment slope is -1.0 mV/sec. ST segment elevation in a non-Q wave noninfarct lead occurs when the J point and ST 60 are 1.0 mV or greater and represents a severe ischemic response. ST segment elevation in an infarct territory (Q wave lead) indicates a severe wall motion abnormality and in most cases is not considered an ischemic response.*(From Chaitman BR: Exercise electrocardiographic stress testing. In Beller GA [ed]: Chronic Ischemic Heart Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 5. Chronic Ischemic Heart Disease. Philadelphia, Current Medicine, 1995, pp 2.1-2.30.)*

rate slope of 2.4 mV/beats/min is considered abnormal, and values that exceed 6 mV/beats/min are suggestive evidence of three-vessel CAD. The use of this measurement requires modification of the exercise protocol such that increments in heart rate are gradual, as in the Cornell protocol, as opposed to more abrupt increases in heart rate between stages, as in the Bruce's or Ellestad's protocols, which limit the ability to calculate statistically valid ST segment heart rate slopes. The measurement is not accurate in the early postinfarction phase. A modification of the ST segment/heart rate slope method is the ST segment/heart rate index calculation, which represents the average change of ST segment depression with heart rate throughout the course of the exercise test. The ST/heart rate index measurements are less than the ST/heart rate slope measurements, and a ST/heart rate index of 1.6 is defined as abnormal. A slight increase in the prognostic content of ST segment/heart rate slope measurements as compared with standard criteria was demonstrated in the Multiple Risk Factor Interventional Trial.[34] [35]

PATHOPHYSIOLOGY OF THE MYOCARDIAL ISCHEMIC RESPONSE.

Myocardial oxygen consumption (M_2) is determined by heart rate, systolic blood pressure, left ventricular end-diastolic volume, wall thickness, and contractility (see Chap. 34) .[2] [7] [12] The rate-pressure or double product (heart rate × systolic blood pressure) increases progressively with increasing work and can be used to estimate the myocardial perfusion requirement in normal persons and in many patients with coronary artery disease. The heart is an aerobic organ with little capacity to generate energy through anaerobic metabolism. Oxygen extraction in the coronary circulation is nearly maximal at rest. The only significant mechanism available to the heart to increase oxygen consumption is to increase perfusion, and there is a direct linear relationship between M_2 and coronary blood flow in normal individuals. The principal mechanism for increasing coronary blood flow during exercise is to decrease resistance at the coronary arteriolar level.[36] In

Figure 6-8 Magnified ischemic exercise-induced ECG pattern. Three consecutive complexes with a relatively stable baseline are selected. The PQ junction (1) and J point (2) are determined; the ST 80 (3) is determined at 80 msec after the J point. In this example, average J point displacement is 0.2 mV (2 mm) and ST 80 is 0.24 mV (24 mm). The average slope measurement from the J point to ST 80 is -1.1 mV/sec.

patients with progressive atherosclerotic narrowing of the epicardial vessels, an ischemic threshold occurs, and exercise beyond this threshold can produce abnormalities in diastolic and systolic ventricular function, ECG changes, and chest pain. The subendocardium is more susceptible to myocardial ischemia than the subepicardium because of increased wall tension, causing a relative increase in myocardial oxygen demand in the subendocardium.

Dynamic changes in coronary artery tone at the site of an atherosclerotic plaque may result in diminished coronary flow during static or dynamic exercise; i.e., perfusion pressure distal to the stenotic plaque actually falls as during exercise, resulting in reduced subendocardial blood flow.[37] Thus, regional left ventricular myocardial ischemia may result not only from an increase in myocardial oxygen demand during exercise but also from a limitation of coronary flow as a result of coronary vasoconstriction and inability of vessels to dilate near the site of an atherosclerotic plaque.

In normal persons, the action potential duration of the endocardial region is longer than

that of the epicardial region, and ventricular repolarization is from epicardium to endocardium. The action potential duration is shortened in the presence of myocardial ischemia, and electrical gradients are created, resulting in ST segment depression or elevation, depending on the surface ECG leads.[38] Increased myocardial oxygen demand associated with a failure to increase or an actual decrease in regional coronary blood flow usually causes ST segment depression; ST segment elevation may occasionally occur in patients with more severe coronary flow reduction.

NONELECTROCARDIOGRAPHIC OBSERVATIONS

The ECG is only one part of the exercise response, and abnormal hemodynamics or functional capacity is just as important if not more so than ST segment displacement.

BLOOD PRESSURE.

The normal exercise response is to increase systolic blood pressure progressively with increasing workloads to a peak response ranging from 160 to 200 mm Hg, with the higher range of the scale in older patients with less compliant vascular systems.[2] [7] As a group, African American patients--here and elsewhere--tend to have a higher systolic blood pressure response than do whites.[39] At high exercise workloads, it is sometimes difficult to obtain a precise determination of systolic blood pressure by auscultation.[40] In normal persons, the diastolic

Figure 6-9 A 48-year-old man with several atherosclerotic risk factors and a normal rest ECG result developed marked ST segment elevation (4 mm [arrows]) in leads V_2 and V_3 with lesser degrees of ST segment elevation in leads V_1 and V_4 and J point depression with upsloping ST segments in lead II, associated with angina. This type of ECG pattern is usually associated with a full-thickness, reversible myocardial perfusion defect in the corresponding left ventricular myocardial segments and high-grade intraluminal narrowing at coronary angiography. Rarely, coronary vasospasm produces this result in the absence of significant intraluminal atherosclerotic narrowing.*(From Chaitman BR: Exercise electrocardiographic stress testing. In Beller GA [ed]: Chronic Ischemic Heart Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 5. Chronic Ischemic Heart Disease. Philadelphia, Current Medicine, 1995, pp 2.1-2.30.)*

Figure 6-10 Pseudonormalization of T waves in a 49-year-old man referred for exercise testing. The patient had previously been seen for typical angina. The rest electrocardiogram in this patient with coronary artery disease shows inferior and anterolateral T wave inversion, an adverse long-term prognosticator. The patient exercised to 8 METs, reaching a peak heart rate of 142 beats/min and a peak systolic blood pressure of 248 mm Hg. At that point, the test was stopped because of hypertension. During exercise, pseudonormalization of T waves occurs, and it returns to baseline (inverted T wave) in the postexercise phase. The patient denied chest discomfort, and no arrhythmia or ST segment displacement was noted. Transient conversion of a negative T wave at rest to a positive T wave during

exercise is a nonspecific finding in patients without prior myocardial infarction and does not enhance the diagnostic or prognostic content of the test; however, the ability to exercise to 8 METs without ischemic changes in the ST segment places this patient into a subset of lower risk. *(From Chaitman BR: Exercise electrocardiographic stress testing. In Beller GA [ed]: Chronic Ischemic Heart Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 5. Chronic Ischemic Heart Disease. Philadelphia, Current Medicine, 1995, pp 2.1-2.30.*

blood pressure does not usually change significantly. Failure to increase systolic blood pressure beyond 120 mm Hg, or a sustained decrease greater than 10 mm Hg repeatable within 15 seconds, or a fall in systolic blood pressure below standing rest values is abnormal and reflects either inadequate elevation of cardiac output because of left ventricular systolic pump dysfunction or an excessive reduction in systemic vascular resistance.[41] An abnormal systolic blood pressure response in patients with a high prevalence of CAD is associated with more extensive CAD and more extensive myocardial perfusion defects; exertional hypotension ranges from 3 to 9 percent and is higher in patients with three-vessel or left main CAD. Conditions other than myocardial ischemia that have been associated with the failure to increase or an actual decrease in systolic blood pressure during progressive exercise are cardiomyopathy, cardiac arrhythmias, vasovagal reactions, left ventricular outflow tract obstruction, ingestion of antihypertensive drugs, hypovolemia, and prolonged vigorous exercise.[42]

It is important to distinguish between a decline in blood pressure in the postexercise phase and a decrease or failure to increase systolic blood pressure *during* progressive exercise. The incidence of postexertional hypotension in asymptomatic subjects was 1.9 percent in 781 asymptomatic volunteers in the Baltimore Longitudinal Study on Aging, with a 3.1 percent incidence noted in subjects younger than 55 years and 0.3 percent incidence in patients older than 55 years.[43] In this series, most hypotensive episodes were symptomatic, and only two patients had hypotension associated with bradycardia and vagal symptoms. Although ST segment abnormalities suggestive of ischemia occurred in one-third of the patients with hypotension, none of the patients had a cardiac event during 4 years of follow-up. Rarely, in young patients, vasovagal syncope can occur in the immediate postexercise phase, progressing through sinus bradycardia to several seconds of asystole and hypotension before reverting to sinus rhythm.

MAXIMAL WORK CAPACITY.

This variable is one of the most important prognostic measurements obtained from an exercise test.[44] [45] [46] [47] [48] Maximal work capacity in normal individuals is influenced by familiarization with the exercise test equipment, level of training, and environmental conditions at the time of testing. In patients with known or suspected CAD, a limited exercise capacity is associated with an increased risk of cardiac events, and in general, the more severe the limitation, the worse the CAD extent and prognosis. In estimating functional capacity, the amount of work performed (or exercise stage achieved) should be the parameter measured and not the number of minutes of exercise. Estimates of peak functional capacity for age and gender have been well established for most of the exercise protocols in common use, subject to the limitations described in the section on cardiopulmonary testing. Comparison of an individual's performance against normal standards provides an estimate of the degree of exercise impairment. There is a rough correlation between observed peak functional capacity during exercise treadmill testing

and estimates derived from clinical data and specific activity questionnaires.[49]

Serial comparison of functional capacity in individual patients to assess significant interval change requires a careful examination of the exercise protocol used during both tests, of drug therapy and time of ingestion, of systemic blood pressure, and of other conditions that might influence test performance. All these variables need to be considered before attributing changes in functional capacity to progression of CAD or worsening of left ventricular function. Major reductions in exercise capacity usually indicate significant worsening of cardiovascular status; modest changes may not.

SUBMAXIMAL EXERCISE.

The interpretation of exercise test results for diagnostic and prognostic purposes requires

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consideration of maximal work capacity. When a patient is unable to complete moderate levels of exercise or reach at least 85 to 90 percent of age-predicted maximum, the level of exercise performed may be inadequate to test cardiac reserve. Thus, ischemic ECG, scintigraphic, or ventriculographic abnormalities may not be evoked and the test may be nondiagnostic. Nondiagnostic test results are more common in patients with peripheral vascular disease, orthopedic limitation, or neurological impairment and in patients with poor motivation. Pharmacologic stress imaging studies should be considered in this setting.[5] [6] [11]

HEART RATE RESPONSE.

The sinus rate increases progressively with exercise, mediated in part through sympathetic and parasympathetic innervation of the sinoatrial node and circulating catecholamines. In some patients who may be anxious about the exercise test, there may be an initial overreaction of heart rate and systolic blood pressure at the beginning of exercise, with stabilization after approximately 30 to 60 seconds. An inappropriate increase in heart rate at low exercise workloads may occur in patients who are in atrial fibrillation, physically deconditioned, hypovolemic, or anemic or who have marginal left ventricular function; this increase may persist for several minutes in the recovery phase. The term *chronotropic incompetence* refers to a heart rate increment per stage of exercise that is less than normal or a peak heart rate below predicted at maximal workloads.[50] [51] This finding may indicate sinus node disease, may be present with drug therapy such as beta blockers or in patients with compensated congestive heart failure, or may indicate a myocardial ischemic response. In a series of 2953 low-risk subjects who were referred for treadmill exercise myocardial perfusion imaging and who were not taking beta-adrenergic blocking drugs, failure to achieve 85 percent of age-predicted maximal heart rate, or a low chronotropic index (<80% of heart rate reserve at peak exercise) was associated with an approximate two-fold increased risk of death during 2

years of follow-up)[50] (Fig 6-11) .

RATE-PRESSURE PRODUCT.

The heart rate-systolic blood pressure product, an indirect measure of myocardial oxygen demand, increases progressively with exercise, and the peak rate pressure product can be used to characterize cardiovascular performance. Most normal individuals develop

Figure 6-11 Estimated 2.5-year survival rate of 762 subjects with a low chronotropic index was significantly less than in 2191 subjects with a normal chronotropic index ($p < 0.001$). In this report, the chronotropic index is considered as the fraction of heart rate reserve used at peak exercise and is measured from resting heart rate, peak heart rate, and age.*(From Lauer MS: Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 281:524, 1999.)*

a peak rate pressure product of 20 to 35 mm Hg×beats/min×10^{-3} . In many patients with significant ischemic heart disease, rate-pressure products exceeding 25 mm Hg×beats/min×10^{-3} are unusual. However, the cutpoint of 25 mm Hg×beats/min×10^{-3} is not a useful diagnostic parameter; significant overlap exists between patients with disease and those without disease. Furthermore, cardioactive drug therapy significantly influences this mea-surement.

CHEST DISCOMFORT.

Characterization of chest discomfort during exercise can be a useful diagnostic finding, particularly when the symptom complex is compatible with typical angina pectoris. In some patients, the exercise level during the test may exceed that which the patient exhibits in day-to-day activities. Exercise-induced chest discomfort usually occurs after the onset of ischemic ST segment abnormalities and may be associated with diastolic hypertension.[52] However, in some patients, chest discomfort may be the only signal that obstructive CAD is present. In patients with chronic stable angina, exercise-induced chest discomfort occurs less frequently than ischemic ST segment depression. The severity of myocardial ischemia in a patient with exercise-induced angina and a normal ECG can often be assessed using a myocardial imaging technique.[5] [6] [11] The new development of an S_3 , holosystolic apical murmur, or basilar rates in the early recovery phase of exercise enhances the diagnostic accuracy of the test.

Exercise Test Indications

The most frequent indications for exercise testing are to aid in establishing the diagnosis of CAD, in determining functional capacity, and in estimating prognosis. The indications continue to evolve, with some that are uniformly accepted and others that are more controversial. The American Heart Association (AHA) and American College of Cardiology (ACC) Exercise Task Force determined several categories of test indications drawn from a large body of published literature on exercise testing[5] (see Guidelines

Section, p. 155). Exercise testing should not be used to screen very low-risk, asymptomatic individuals because the test has limited diagnostic and prognostic value in this situation, and the resultant undesirable consequences of a false-positive exercise test result may result in unnecessary follow-up, additional procedures, anxiety, and exercise restrictions.[5] [6] Most asymptomatic subjects who are enrolled in an exercise screening program for CAD and who die suddenly of cardiac causes have had a previous normal exercise test result. In patients with established CAD, low-risk patients with an estimated annual mortality less than 1 percent per year do not require repeat testing for several years after their initial evaluation. Higher-risk patients (estimated annual mortality >3%) might require more frequent follow-up testing on an annual basis in the absence of a change of symptoms.[53]

DIAGNOSTIC USE OF EXERCISE TESTING

Appreciation of the noninvasive test literature to diagnose CAD requires an understanding of standard terminology such as sensitivity, specificity, and test accuracy[1] [2] [3] [4] [5] [6] (Tables 6-1 and 6-G-2) . The sensitivity of the exercise ECG in patients with CAD is approximately 68 percent, and specificity is 77 percent.[2] In patients with single-vessel disease, the sensitivity ranges from 25 to 71 percent, with exercise-induced ST displacement most frequent in patients with left anterior descending CAD, followed by those with right CAD and those with isolated left circumflex CAD. In patients with multivessel CAD, sensitivity is approximately 81 percent and specificity is 66 percent.[2] The sensitivity and specificity for left main or three-vessel CAD are approximately

TABLE 6-1 -- TERMS USEFUL IN EVALUATION OF TEST RESULTS

True positive (TP)=abnormal test results in individual with disease
False positive (FP)=abnormal test results in individual without disease
True negative (TN)=normal test result in individual without disease
False negative (FN)=normal test result in individual with disease
Sensitivity: percentage of patients with CAD who have an abnormal result=TP/(TP+FN)
Specificity: percentage of patients without CAD who have a normal result=TN/(TN+FP)
Predictive value: percentage of patients with abnormal result who have CAD=TN/(TN+FN)
Test accuracy: percentage of true test results=(TP+TN)/total number tests performed
Likelihood ratio: odds of a test result being true: of an abnormal test: sensitivity/(1-specificity); of a normal test: specificity/(1-sensitivity)

CAD=coronary artery disease.

86 percent and 53 percent. The exercise ECG tends to be less sensitive in patients with extensive anterior wall myocardial infarction and when a limited exercise ECG lead set is used. Approximately 75 to 80 percent of the diagnostic information on exercise-induced ST segment depression in patients with a normal rest ECG is contained in leads V_4 to V_6 . Exercise ECG is less specific when patients in whom false-positive results are more common are included--i.e., those with valvular heart disease, left ventricular hypertrophy, marked resting ST segment depression, or digitalis therapy.[5] Table 6-2 lists the more common causes of noncoronary exercise-induced ST segment depression.

The traditional reference standard against which the exercise ECG has been measured is a qualitative assessment of the coronary angiogram using 50 to 70 percent obstruction of the luminal diameter as the angiographic cutpoint. Limitations are inherent in angiographic classification of patients into one-, two-, and three-vessel CAD, and the length of the coronary artery narrowing and the impact of serial lesions are not accounted for in correlative studies comparing diagnostic exercise testing with coronary angiographic findings. Other approaches, including intracoronary Doppler flow studies and quantitative coronary angiography, have been proposed to assess coronary vascular reserve; these may be more accurate than qualitative assessment of the angiogram.[54] [55] [56] [57] [58] In patients with ischemic-appearing ST segment depression during exercise and normal findings on coronary angiography (syndrome X), coronary endothelial dysfunction as measured by coronary vasomotor responsiveness to acetylcholine does not account for the ischemic ST segment response.[59]

TABLE 6-2 -- NONCORONARY CAUSES OF ST SEGMENT DEPRESSION

Severe aortic stenosis	Glucose load
Severe hypertension	Left ventricular hypertrophy
Cardiomyopathy	Hyperventilation
Anemia	Mitral valve prolapse
Hypokalemia	Intraventricular conduction disturbance
Severe hypoxia	Preexcitation syndrome
Digitalis use	Severe volume overload (aortic, mitral regurgitation)
Sudden excessive exercise	Supraventricular tachyarrhythmias

Selective referral of patients with a positive test result for further study both decreases the rate of detection of true negative test results and increases the rate of detection of false-positive results, thus increasing sensitivity and decreasing specificity.[1] [2] [3] [4] Froelicher and colleagues, in a study of 814 consecutive patients who presented with

angina pectoris and agreed to undergo both exercise testing and coronary angiography, reported an exercise ECG sensitivity and specificity of 45 percent and 85 percent, respectively for obstructive CAD using visual analysis in this population with reduced work-up bias.[60] Computerized ST segment measurements were similar to visual ST segment measurements in this study. A false-positive result is more common when only the inferior lead group (leads 2, 3, aV_f) is abnormal at high exercise workloads.

BAYESIAN THEORY.

The depth of exercise-induced ST-segment depression and the extent of the myocardial ischemic response can be thought of as continuous variables. Cutpoints such as 1 mm of horizontal or downsloping ST segment depression as compared with baseline cannot completely discriminate patients with disease from those without disease, and the requirement of more severe degrees of ST segment depression to improve specificity will decrease sensitivity. Sensitivity and specificity are inversely related, and false-negative and false-positive results are to be expected when ECG or angiographic cutpoints are selected to optimize the diagnostic accuracy of the test.[1] [2] [3] [4] [5] [6] [61]

The use of Bayesian theory incorporates the pretest risk of disease and the sensitivity and specificity of the test (likelihood ratio) to calculate the posttest probability of coronary disease. The results of a patient's clinical information and exercise test results are used to make a final estimate of the probability of CAD. Atypical or probable angina in a 50-year-old man or a 60-year-old woman is associated with approximately 50 percent probability for CAD before exercise testing is performed. The diagnostic power of the exercise test is maximal when the pretest probability of CAD is intermediate (30 to 70 percent).

MULTIVARIATE ANALYSIS.

Multivariate analysis of noninvasive exercise tests to estimate posttest risk also can provide important diagnostic information. Multivariate analysis offers the potential advantage that it does not require that the tests be independent of each other or that sensitivity and specificity remain constant over a wide range of disease prevalence rates. However, the multivariate technique depends critically on how patients are selected to establish the reference data base. Both Bayesian and multivariate approaches are commonly used to provide diagnostic and prognostic estimates of patients with CAD.

SEVERITY OF ELECTROCARDIOGRAPHIC ISCHEMIC RESPONSE.

The exercise ECG result is more likely to be abnormal in patients with more severe coronary arterial obstruction, with more extensive CAD, and after more strenuous levels of exercise. Early onset of angina, ischemic ST segment depression, and fall in blood pressure at low exercise workloads are the most important exercise parameters associated with an adverse prognosis and multivessel CAD.[62] Additional adverse markers include profound ST segment displacement, ischemic changes in five or more ECG leads, and persistence of the changes late in the recovery phase of exercise

(Table 6-3) .

EXERCISE TESTING IN DETERMINING PROGNOSIS

Exercise testing provides not only diagnostic information but also more importantly prognostic data. The value of exercise testing to estimate prognosis must be considered in light of what is already known about a patient's risk status. Left ventricular dysfunction, CAD extent, electrical instability,

TABLE 6-3 -- EXERCISE PARAMETERS ASSOCIATED WITH AN ADVERSE PROGNOSIS AND MULTIVESSEL CORONARY ARTERY DISEASE

Duration of symptom-limiting exercise <6 METs
Failure to increase systolic blood pressure 120 mm Hg, or a sustained decrease 10 mm Hg, or below rest levels, during progressive exercise
ST segment depression 2 mm, downsloping ST segment, starting at <6 METs, involving 5 leads, persisting 5 min into recovery
Exercise-induced ST segment elevation (aV_r excluded)
Angina pectoris at low exercise workloads
Reproducible sustained (>30 sec) or symptomatic ventricular tachycardiaAcute systemic illness (pulmonary embolism, aortic dissection)

and noncoronary comorbid conditions must be taken into consideration when estimating long-term outcome.

ASYMPTOMATIC POPULATION.

The prevalence of an abnormal exercise ECG result in middle-aged asymptomatic men ranges from 5 to 12 percent.[63] [64] [65] [66] The risk of developing a cardiac event such as angina, myocardial infarction, or death in men is nine times greater when the test result is abnormal as when it is normal; however, over 5 years of follow-up, only one in four such men will suffer a cardiac event, and this will most commonly be the development of angina. The risk is slightly greater when the test result is strongly positive. In the LRC Prevention Trial, a strongly positive test result was defined as one in which the ST response was 0.2 mV (2 mm) or greater or occurred during the first 6 minutes of exercise or at heart rate at or below 163 - 0.66 × age. Of 3806 middle-aged asymptomatic men who had a total cholesterol level of 265 mg/dl at entry, 3 percent had a strongly positive test result; the event rate was 2 percent per year over an average of

4 years of follow-up.[63] A positive test result was *not* significantly associated with nonfatal myocardial infarction; this indicates the difficulty in identifying patients destined to develop abrupt changes in plaque morphology.

In the Seattle Heart Watch, Bruce noted that an abnormal ST response to exercise in asymptomatic men did *not* increase the likelihood of developing cardiac events within 6 years in the absence of conventional risk factors. However, the likelihood of developing a cardiac event was increased when the patient had any conventional atherosclerotic risk factor and two or more abnormal responses to exercise, with an abnormal exercise response defined as chest discomfort during the test, exercise duration less than 6 minutes or two stages, failure to achieve 90 percent of age-predicted maximum heart rate, or 0.1 mV (1 mm) or greater of horizontal or downsloping ST depression with exercise in early recovery. Only 1.1 percent of the asymptomatic healthy men in this study were in a high-risk category.[65] In the Baltimore Longitudinal Study on Aging, the 9-year risk of developing a cardiac event (angina pectoris, myocardial infarction, or coronary death) was 3.4 percent in 611 subjects without ischemic ST segment changes, 14.6 percent in 151 subjects with ischemic ST segment changes that started during exercise, and 19 percent in 63 subjects with ischemic ST segment changes that started only in recovery; age, cholesterol level, and presence of ST segment depression were independent predictors of cardiac events, approximately half of which were onset of angina pectoris[28] (Fig. 6-12) . In asymptomatic middle-aged or older men with several atherosclerotic risk factors, a markedly abnormal exercise response is associated with a significantly increased risk of subsequent cardiac events, particularly when there is additional supporting evidence for underlying CAD (e.g., coronary calcification, abnormal results of thallium scan, and the like).[66] [67] Serial change of a negative exercise ECG result to a positive one in an asymptomatic person carries the same prognostic importance as an initially abnormal test result.[68] However, when an asymptomatic individual with an initially abnormal test result has significant worsening of the ECG abnormalities at lower exercise workloads, this finding may indicate significant CAD progression and warrants a more aggressive diagnostic work-up.

The prevalence of an abnormal exercise ECG result in middle-aged asymptomatic women ranges from 20 to 30 percent.[1] [2] In general, the prognostic value of an ST segment shift in women is less than in men. Although the use of multivariate scores to predict CAD in women has improved diagnostic accuracy, false-positive results continue to be a problem in many patients, and supplemental imaging techniques are often necessary to enhance the diagnostic performance of the test.[5] [6] [11]

SYMPTOMATIC PATIENTS.

Exercise testing should be routinely performed (unless this is not feasible or unless there are contraindications) before coronary angiography in patients with chronic ischemic heart disease. Patients who have excellent exercise tolerance (e.g., >10 METs) usually have an excellent prognosis regardless of the anatomical extent of CAD. The test provides an estimate of the functional significance of angiographically documented coronary artery stenoses. The impact of exercise testing in patients with proven or suspected CAD was studied by Weiner and colleagues in 4083 medically treated patients in the CASS study.[69] A high-risk patient subset was identified (12

percent of the population), with an annual mortality of 5 percent a year when exercise workload was less than Bruce's stage I (<4 METs) and the exercise ECG exhibited 0.1 mV (1 mm) or greater ST segment depression. A low-risk patient subset (34 percent of the population) who were able to exercise into Bruce's stage III or greater and who had a normal exercise ECG result had an annual mortality less than 1 percent per year over 4 years of follow-up. Similar ECG and workload parameters were useful in risk

Figure 6-12 Event-free survival (absence of cardiac death, myocardial infarction, or angina) in 825 healthy volunteers (ages 22 to 89 years) without clinical evidence of coronary heart disease enrolled in the Baltimore Longitudinal Study of Aging. The cardiac event rate in patients whose ischemic ST segment response occurred only during the recovery phase was similar to that in subjects who developed the ischemic ST segment response during exercise; the cardiac event rate was significantly greater than in subjects with normal results on an exercise electrocardiogram.*(From Rywik TM, Zink RC, Gittings NS, et al: Independent prognostic significance of ischemic ST segment response limited to recovery from treadmill exercise in asymptomatic subjects. Circulation 97:2117-2122, 1998.)*

stratifying patients with three-vessel CAD likely to benefit from coronary bypass grafting.

Mark and colleagues developed a treadmill score based on 2842 consecutive patients in the Duke data bank with chest pain; these patients underwent treadmill testing using Bruce's protocol and cardiac catheterization.[70] Patients with left bundle branch block (LBBB) or those with exercise-induced ST elevation in a Q wave lead were excluded. The treadmill score is calculated as follows:

Angina index was assigned a value of zero if angina was absent, one if typical angina occurred during exercise, and two if angina was the reason the patient stopped exercising. Exercise-induced ST deviation was defined as the largest net ST displacement in any lead. The 13 percent of patients with a treadmill score of -11 or less had a 5-year survival of 72 percent, compared with 97 percent in the 34 percent of patients at low risk with a treadmill score +5 or greater. The score added independent prognostic information to that provided by clinical data, coronary anatomy, and left ventricular ejection fraction. The stratified annual mortality rates predicted from the treadmill score were less in 613 outpatients referred for exercise testing from the same institution[71] (Fig. 6-13) . Exercise scoring systems can be used to identify prognostic, intermediate-high-risk patients in whom coronary angiography would be indicated to define coronary anatomy.[70] [71] [72] [73] However, the decision to perform coronary revascularization should take into consideration the fact that in patients with less extensive CAD (e.g., one to two vessels narrowed and well-preserved left ventricular function), a similar degree of exercise-induced myocardial ischemia does not carry the same significant increased risk of cardiac events as in patients with more extensive

disease (e.g., three vessels narrowed or those with impaired left ventricular function).[48] [74] [75]

SILENT MYOCARDIAL ISCHEMIA (see Chap. 37) .

In patients with documented coronary artery disease, the presence of exercise-induced ischemic ST segment depression confers increased risk of subsequent cardiac events regardless of whether angina occurs during the test.[76] [77] [78] [79] [80] The magnitude of the prognostic gradient in patients with an abnormal exercise ECG result with or without angina varies considerably in the published literature, most likely a feature

Figure 6-13 Nomogram of prognostic relations using the Duke treadmill score, which incorporates duration of exercise (in minutes) - (5 × maximal ST segment deviation during or after exercise) (in mm) - (4 × treadmill angina index). Treadmill angina index is 0 for no angina, 1 for nonlimiting angina, and 2 for exercise-limiting angina. The nomogram can be used to assess the prognosis of ambulatory outpatients referred for exercise testing. In this example, the observed amount of exercise-induced ST segment deviation (minus resting changes) is marked on the line for ST segment deviation during exercise (1). The degree of angina during exercise is plotted (2), and the points are connected. The point of intersect on the ischemic reading line is noted (3). The number of METs (or minutes of exercise if the Bruce protocol is used) is marked on the exercise duration line (4). The marks on the ischemia reading line and duration of exercise line are connected, and the intersect on the prognosis line determines 5-year survival rate and average annual mortality for patients with these selected specific variables. In this example, the 5-year prognosis is estimated at 78 percent in this patient with exercise-induced 2-mm ST depression, nonlimiting exercise angina, and peak exercise workload of 5 METs.*(Adapted from Mark DE, Shaw L, Harrell FE Jr, et al: Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 325:849, 1991. Copyright Massachusetts Medical Society.)*

of patient selection. In the CASS data bank, 7-year survival in patients with silent or symptomatic exercise-induced myocardial ischemia was similar in patients stratified by coronary anatomy and left ventricular function, with the worst survival in patients with the most extensive CAD. In the ACIP trial, coronary revascularization was a more effective treatment strategy to reduce exercise-induced myocardial ischemia than was medical therapy.[79]

UNSTABLE ANGINA (see Chap. 36) .

The incidence of exercise-induced angina or ischemic ST segment abnormalities in patients who have unstable angina and who undergo a predischarge low-level protocol ranges from 30 to 40 percent. The finding of ischemic ST segment changes or limiting chest pain is associated with a significantly increased risk of subsequent cardiac events in men and postmenopausal women.[81] [82] [83] The absence of these findings identifies a low-risk patient subset. Exercise testing should be considered in the outpatient evaluation of low-risk patients with unstable angina and should be performed in hospitalized low-to-intermediate-risk ambulatory patients who are free of angina or heart

failure symptoms for at least 48 hours.[82] Prognostic risk assessment should incorporate clinical and serum markers to optimize mortality and morbidity estimates[83] (Fig. 6-14) .

MYOCARDIAL INFARCTION.

Exercise testing after myocardial infarction is useful to determine (1) risk stratification and assessment of prognosis, (2) functional capacity for activity prescription after hospital discharge, and (3) assessment of adequacy of medical therapy and need to use supplemental diagnostic or treatment options.[1] [2] [3] [4] [5] [6] [7] The incidence of fatal or nonfatal cardiac events associated with exercise testing after myocardial infarction is low. The risk of events is approximately twofold greater for symptom-limited protocols compared with submaximal tests, although the overall fatal event rate is extremely low with both types of exercise protocols. A low-level exercise test (achievement of 5 to 6 METs or 70 to 80 percent of age-predicted maximum) is frequently performed before hospital discharge to

Figure 6-14 Rate of cardiac death or myocardial infarction after 5 months in relation to exercise test (ET) response and maximum troponin T (TnT) level in patients hospitalized for unstable angina. High-risk response: ST segment depression in
3 leads and maximal workload <90/70 W (men/women); intermediate risk response: ST segment depression in
3 leads and maximal workload <90/70 W (men/women); and low risk response: no ST segment depression in
3 leads or maximal workload >90/70 W (men/women). *(From Lindahl B: Noninvasive risk stratification in unstable coronary artery disease: Exercise test and biochemical markers. Am J Cardiol 80:40E, 1997.)*

Figure 6-15 One-year mortality of patients assigned to the conservative strategy enrolled in the Thrombolysis in Myocardial Infarction (TIMI) II trial. All patients were treated with thrombolytic therapy within 4 hours of symptom onset. Patients unable to perform the exercise test were compared with individuals able to complete 200 kpm (stage 2) or 200 to 400 kpm (stage 2) on a supine bicycle ergometry study performed within 2 weeks of the index event. Although the absolute mortality rates are less than patient series studied in the prethrombolytic era, a similar gradient of worsening prognosis is noted in patients unable to perform the low-level exercise test within 2 weeks of the index event, patients able to perform the test but unable to complete the protocol, and patients able to complete the low-level exercise test.*(From Chaitman BR: Impact of treatment strategy on predischarge exercise test in the Thrombolysis in Myocardial Infarction [TIMI] II trial. Am J Cardiol 71:131, 1993.)*

establish the hemodynamic response and functional capacity.[84] [85] [86] [87] [88] [89] [90] The ability to complete 5 to 6 METs of exercise or 70 to 80 percent of age-predicted maximum in the absence of abnormal ECG or blood pressure abnormalities is associated with a 1-year mortality of 1 to 2 percent and may help guide the timing of early hospital discharge[91] (Fig. 6-15) . Parameters associated with increased risk include inability to perform the low-level predischarge exercise test, poor exercise capacity, inability to increase or a decrease in exercise systolic blood pressure, and angina or exercise-induced ST segment depression at low workloads.[1] [2] [3] [4] [5] [6] [48] Many postinfarct patients referred for exercise testing have been prescribed beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors.

Although beta-adrenergic blocking drugs may attenuate the ischemic response, they do not interfere with poor functional capacity as a marker of adverse prognosis and should be continued in patients referred for testing.[7] The relative prognostic value of a 6-week postdischarge exercise test is minimal once clinical variables and the results of the low-level predischarge test are adjusted for. For this reason, the timing of the exercise test after the infarct event favors predischarge exercise testing to allow implementation of a definitive treatment plan in patients in whom coronary anatomy is known as well as risk stratification of patients in whom coronary anatomy has not yet been determined.[48] [86] There is a trend toward early predischarge exercise testing (within 3 to 5 days) in uncomplicated cases after acute myocardial infarction. A 6-week test is useful in clearing patients to return to work in occupations involving physical labor and to provide a better estimate of cardiovascular reserve at peak exercise performance.

The goals and basic principles of the predischarge evaluation have not been changed by the advent of reperfusion or direct percutaneous transluminal coronary angioplasty

(PTCA) therapy for acute infarction. After receiving intravenous thrombolytic therapy or direct coronary angioplasty, patients with uncomplicated myocardial infarct tend to exhibit exercise-induced angina and ST segment depression less frequently than do consecutive postinfarct patients before these treatment strategies were widely applied. The occurrence of reciprocal ST segment depression associated with exercise-induced ST segment elevation in patients who undergo testing approximately 6 to 8 weeks after Q wave infarction with single-vessel disease may indicate residual tissue viability in the infarct-related area.[92] In patients with negative T waves after infarction, stress-induced normalization of the T waves may also indicate higher coronary flow reserve than in patients unable to normalize their T waves.[30]

RISK STRATIFICATION IN THE EMERGENCY DEPARTMENT.

Patients who present to the emergency department are a heterogeneous population with a large range of pretest risk for CAD. Clinical algorithms can identify lower-risk persons who can safely be further risk stratified using exercise testing. The cost-effectiveness of this approach has been demonstrated in both low- and intermediate-risk patients. The accuracy of exercise testing in the emergency department setting follows Bayesian principles, with the greatest diagnostic and prognostic estimates in intermediate-risk clinical patient subsets. Exercise testing in the emergency department should not be performed when (1) new or evolving ECG abnormalities are noted on the rest tracing, (2) the levels of cardiac enzymes are abnormal, (3) the patient cannot adequately perform exercise, (4) the patient reports worsening or persistent chest pain symptoms, or (6) clinical risk profiling indicates imminent coronary angiography is likely. Several series of clinically low-risk subjects reported 6-month cardiac event rates less than 1 percent with a normal exercise test result.[93] [94] [95]

PREOPERATIVE RISK STRATIFICATION BEFORE NONCARDIAC SURGERY (see Chap. 61) .

Exercise ECG before elective noncardiac surgery provides an objective measurement of functional capacity and the potential to identify likelihood of perioperative myocardial ischemia in patients with a low ischemic threshold. In patients with intermittent claudication and no prior history of cardiac disease, approximately 20 to 25 percent will have an abnormal exercise ECG result. In patients with a prior history of myocardial infarction or abnormal rest ECG, 35 to 50 percent will have an abnormal exercise ECG result. The risk of perioperative cardiac events and adverse long-term outcome is significantly increased in patients with an abnormal exercise ECG results at low workloads, and coronary angiography with revascularization when feasible should be considered before the noncardiac operative intervention.[96] [97] [98]

CONGESTIVE HEART FAILURE.

Cardiac and peripheral compensatory mechanisms are activated in patients with chronic congestive heart failure to partly or fully restore impaired left ventricular performance. Abnormal baroreflex function and increased norepinephrine spillover, sympathetic discharge, downregulation of beta-adrenergic receptors, and depletion of myocardial sympathetic stores characterize the disease process resulting in the hemodynamic response to exercise.[99] [100] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110] [111] [112] [113] [114] [115] [116] [117] [118] There is a wide range of exercise capacity in patients who have a markedly reduced ejection fraction, with some patients having near-normal peak exercise capacity. The magnitude of exercise capacity impairment is a function of abnormalities in skeletal muscle metabolism, which may be the predominant cause of functional limitation in a significant proportion of patients with heart failure. Fatigue may be related to altered skeletal muscle metabolism secondary to chronic physical deconditioning as well as impaired perfusion.[101] [109] Symptoms in patients with congestive heart failure are related to an excessive increase in blood lactate during low exercise levels, reduction in quantity of oxygen consumed at peak exertion, and disproportionate increase in ventilation at submaximal and peak workloads. The increased ventilatory requirement assessed by the hyperventilatory response to exercise and increase in pulmonary dead space leads to rapid, shallow breathing during exercise. Dyspnea and fatigue are the usual reasons for exercise termination.

Peak o_2 measurements in patients with compensated congestive heart failure are useful in risk stratifying patients with congestive heart failure to determine the subsequent incidence of cardiac events[102] [104] [108] [118] (Fig. 6-16) . The ability to achieve a peak o_2 of greater than 20 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and anaerobic threshold greater than 14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ is associated with a relatively good long-term prognosis and maximal cardiac output greater than 8 liters/min/m^2 . Patients who are unable to achieve a peak o_2 of 10 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and anaerobic threshold of 8 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ have a poor prognosis, and their maximal exercise cardiac output is usually less than 4 liters/min/m^2 . Failure of o_2 to decrease within 30 seconds after peak exertion is associated with more severe

reductions in left ventricular ejection fraction and moderate to severe impairment of pulmonary gas exchange. Inability to increase oxygen pulse (milliliters of oxygen per beat) is related to lack or minimal increase of stroke volume. A blunted heart rate response is not uncommon in patients with congestive heart failure caused by postsynaptic desensitization of beta-adrenergic receptors.

Exercise protocols that limit exercise duration to 5 to 7 minutes are associated with the most reproducible peak o_2 measurements in patients with heart failure. The interpretation of cardiopulmonary exercise test results in patients with heart failure can occasionally be difficult, because some patients hyperventilate during exercise, producing falsely low peak oxygen consumption, and it can be difficult to distinguish patients who are deconditioned from those who have impaired exercise performance and low peak o_2 due to cardiac pathology. Randomized controlled trials of long-term moderate exercise training in chronic heart failure report a 15 to 20 percent improvement in peak o_2 and prolonged onset of anaerobic metabolism.[109] Thus, clinical decisions such as listing a patient for cardiac transplantation based on peak o_2 measurements need to take into consideration interval training effects.[107] [109] [110] The 6-minute walk test also can be used to evaluate functional capacity and to estimate prognosis in patients unable to exercise on a bicycle ergometer or treadmill.[24]

CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES

The genesis of cardiac arrhythmias includes reentry, triggered activity, and enhanced automaticity (see Chap. 22) . Increased catecholamines during exercise accelerate impulse conduction velocity, shorten the myocardial refractory period, increase the amplitude of afterpotentials, and increase the slope of phase 4 spontaneous depolarization of the action potential. Other potentiators of cardiac rhythm disturbance include metabolic acidosis and exercise-induced myocardial ischemia. Ventricular premature complexes occur frequently during exercise testing and increase with age. Repetitive forms occur in 0 to 5 percent of asymptomatic subjects without suspected cardiac disease and are not associated with an increased risk of cardiac death. Exercise-induced ventricular ectopic activity is not a useful diagnostic marker of ischemic heart disease in the absence of ischemic ST segment depression. Suppression of ventricular ectopic activity during exercise is a nonspecific finding and may occur in patients with CAD as well as in normal subjects. The prognostic importance of ventricular arrhythmias in patients with chronic ischemic heart disease

Figure 6-16 Cardiopulmonary exercise test in a 51-year-old man with cardiomyopathy in New York Heart Association Class III. A modified Bruce protocol was used. The patient reached a peak o_2 of 14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (4 METs), 44 percent of predicted for age, gender, and weight *(top panel).* Anaerobic threshold (AT_{ge}) occurred at a

O_2 of 977 ml/min *(bottom panel).* The blunted cardiopulmonary response is typical for a patient with severe cardiomyopathy and marked impairment of cardiac reserve. This patient was listed for cardiac transplantation.

after adjustment for baseline, clinical, and left ventricular function characteristics is small. Approximately 20 percent of patients with known heart disease and 50 to 75 percent of sudden cardiac death survivors have repetitive ventricular beats induced by exercise. In patients with a recent myocardial infarction, the presence of exercise-induced repetitive forms is associated with an increased risk of subsequent cardiac events.

Exercise-induced ventricular arrhythmias tend to be more frequent in the recovery phase of exercise because peripheral plasma norepinephrine levels continue to increase for several minutes after cessation of exercise and vagal tone is high in the immediate recovery phase. Beta-adrenergic blocking times may suppress exercise-induced ventricular arrhythmias.

EVALUATION OF VENTRICULAR ARRHYTHMIAS.

Exercise testing is useful in the assessment of patients with ventricular arrhythmias and has an important adjunctive role along with ambulatory monitoring and electrophysiological studies. Exercise testing provokes repetitive ventricular premature beats in most patients with a history of sustained ventricular tachyarrhythmia, and in approximately 10 to 15 percent of such patients, spontaneously occurring arrhythmias are observed only during exercise testing (Fig. 6-17) . The test is useful in evaluating the effects of antiarrhythmic drugs, detecting supraventricular arrhythmias, treating patients with chronic atrial fibrillation to test for ventricular rate control, and exposing possible drug toxicity in patients placed on antiarrhythmic drugs. Paradoxical prolongation of the QT_C interval greater than 10 msec with exercise identifies patients likely to develop a proarrhythmic effect on type 1A antiarrhythmic drugs.[119] Exercise-induced widening of the QRS complex in patients using type 1C drugs may favor reentry induction of ventricular tachycardia. Amiodarone therapy increases the QRS duration during exercise by approximately 6 percent in patients with a QRS duration less than 110 msec, compared with 15 percent in patients with a QRS duration greater than 110 msec.[120]

SUPRAVENTRICULAR ARRHYTHMIAS.

Supraventricular premature beats induced by exercise are observed in 4 to 10 percent of normal persons and up to 40 percent of patients with underlying heart disease. Sustained supraventricular tachyarrhythmias occur in only 1 to 2 percent of patients, although the frequency may approach as much as 10 to 15 percent in patients referred for management of episodic supraventricular arrhythmias. The presence of supraventricular arrhythmias is not diagnostic for ischemic heart disease.[121]

ATRIAL FIBRILLATION.

Patients with chronic atrial fibrillation tend to have a rapid ventricular response in the initial stages of exercise, and 60 to 70 percent of the total change in heart rate usually occurs within the first few minutes of exercise (Fig. 6-18) . The effect of digitalis preparations and beta-adrenergic and selected calcium antagonists such as diltiazem on attenuating this rapid increase in heart rate for individual patients can be measured using exercise testing. Pharmacological control of the ventricular rate does not necessarily result in a significant increase in

Figure 6-17 A 67-year-old man with ischemic cardiomyopathy referred for exercise testing had a left bundle branch block and first-degree atrioventricular (AV) block on the resting ECG. There was no worsening of the AV conduction disturbance immediately before ventricular tachycardia (VT) onset (arrow). At 4:55 minutes into the test, a 27-beat run of VT was noted, reproducing the patient's symptoms of dizziness and chest pounding. The exercise test proved useful in directing subsequent patient management to treatment of the ventricular arrhythmia.

exercise capacity, which in many patients is related to the underlying cardiac disease process and not adequacy of control of the ventricular rate.

SICK SINUS SYNDROME.

In general, patients with sick sinus syndrome have a lower heart rate at submaximal and maximal workloads compared with control subjects. However, as many as 40 to 50 percent of patients will have a normal exercise heart rate response.

ATRIOVENTRICULAR BLOCK.

Exercise testing may help determine the need for atrioventricular (AV) sequential pacing in selected patients. In patients with congenital AV block, exercise-induced heart rates are low and some patients develop symptomatic rapid junctional rhythms that can be suppressed with DDD devices. In patients with acquired conduction disease, exercise can occasionally elicit advanced AV block.

LEFT BUNDLE BRANCH BLOCK.

Exercise-induced ST segment depression is found in most patients with LBBB and cannot be used as a diagnostic or prognostic indicator regardless of the degree of ST segment abnormality. In patients who are referred to a tertiary center and in whom exercise testing is carried out, the new development of exercise-induced transient left hemiblock is 0.3 percent and LBBB is 0.4 percent, with a slightly greater incidence in older patients.[122] The relative risk of death or other major cardiac events in patients with exercise-induced LBBB is increased approximately threefold compared with patients

without this abnormality. In one series, permanent LBBB was reported in approximately half the patients who developed transient LBBB during exercise and who were monitored for an average of 6.6 years. High-grade AV block did not develop in any of the patients in this 15-patient series.[123] The development of ischemic ST segment depression before the LBBB pattern appears or in the recovery phase after the LBBB has resolved does not attenuate the diagnostic yield of the ST segment shift. The ventricular rate at which the LBBB appears and disappears can be significantly different (Fig. 6-19) .

RIGHT BUNDLE BRANCH BLOCK.

The resting ECG in right bundle branch block (RBBB) is frequently associated with T wave and ST segment changes in the early anterior precordial leads (V_1 to V_3). Exercise-induced ST depression in leads V_1 to V_4 is a common finding in patients with RBBB and is nondiagnostic (Fig. 6-20) . The new development of exercise-induced ST segment depression in leads V_5 and V_6 or leads 2 and aV_f , reduced exercise capacity, and inability to adequately increase systolic blood pressure are useful in detecting patients who have CAD and a high clinical pretest risk of disease.[5] The presence of RBBB decreases the sensitivity of the test.[124] The new development of exercise-induced RBBB is relatively uncommon, occurring in approximately 0.1 percent of tests.

Figure 6-18 A 75-year-old woman with chronic atrial fibrillation and a 6-month history of atypical chest pain underwent mitral valve repair 1 year before testing, at which time nonobstructive coronary disease was noted. The patient exercised for 6 minutes, achieving a peak heart rate of 176 beats/min and peak blood pressure of 170/90 mm Hg. The resting ECG shows atrial fibrillation with a controlled ventricular response and minor ST segment depression. At peak exertion, marked ST segment depression is seen in the anterior leads, consistent with either digitalis effect or myocardial ischemia. In this type of patient, initial exercise testing with myocardial perfusion tracers or echocardiography would provide more useful diagnostic information than exercise testing alone.

Figure 6-19 A 58-year-old hypertensive diabetic man with prior history of cigarette smoking was referred for evaluation of dyspnea and early fatigability during exercise. At 6:48 minutes into the test, the patient developed a rate-related left bundle branch block (LBBB) at a heart rate of 133 beats/min, which persisted during exercise and resolved at 1:36 minutes into the postexercise phase. The abnormal 2.5- to 3-mm downsloping ST segment depression in lead 2 during the LBBB is nondiagnostic for coronary artery disease because of the conduction disturbance. The test was stopped because of dyspnea at a peak heart rate of 138 beats/min (85 percent of predicted) and estimated workload of 6 METs. Peak blood pressure at end exercise was 174/94 mm Hg. Time to onset and offset of LBBB occurred at different ventricular rates related to fatigue in the left bundle, a common finding.

PREEXCITATION SYNDROME.

The presence of Wolff-Parkinson-White (WPW) syndrome invalidates the use of ST segment analysis as a diagnostic method for detecting CAD in preexcited as well as normally conducted beats; false-positive ischemic changes are frequently registered (Fig. 6-21) . In patients with persistent preexcitation, exercise may normalize the QRS complex, with disappearance of the delta wave in 20 to 50 percent of cases, depending on the series studied.[125] Abrupt disappearance of the delta wave is presumptive evidence of a longer anterograde effective refractory period of the accessory pathway. Progressive disappearance of the delta wave is less reassuring and occurs when the improvement in AV node conduction is greater than in the accessory pathway; this finding does not preclude a possible significant or even critical shortening of the anterograde effective refractory period in the accessory pathway under the influence of sympathetic stimulation. Exercise-induced disappearance of the delta wave is more frequent with left sided than right sided accessory pathway positions. Although tachyarrhythmias appearing during an exercise test in patients with WPW syndrome are rare, when they do occur, they provide an opportunity to evaluate AV conduction velocity. The presence of WPW syndrome does not cause a limitation of physical work capacity.

CARDIAC PACEMAKERS AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR DEVICES.

The exercise protocol used to assess chronotropic responsiveness in patients before and after cardiac pacemaker insertion should adjust for the fact that many such patients are older individuals and may not tolerate high exercise workloads or abrupt and relatively large increments in work between stages of exercise. An optimal physiological cardiac pacemaker should normalize the heart rate response to exercise in proportion to oxygen uptake and should increase heart rate 2 to 4 beats/min for an increase in $_{O_2}$ of 1 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, with a slightly steeper slope for patients with severe left ventricular function impairment.[126] [127]

When testing patients with an implantable cardioverter-defibrillator (ICD) device, the program detection interval of

Figure 6-20 Exercise-induced ST segment depression is noted in leads V_2 to V_3 (arrows) in this patient with a resting right bundle branch block pattern. Exercise-induced horizontal or downsloping ST segment responses in the early anterior precordial leads (V_1 through V_4) are common in patients with right bundle branch block and are secondary to the conduction disturbance. The presence of this finding in leads V_1 through V_4 is not diagnostic of obstructive coronary disease; however, if ischemic changes are seen in leads II, aV_F , or in leads V_5 or V_6 , the specificity for coronary disease is improved.

Figure 6-21 A 61-year-old man with atypical angina and a hiatal hernia was referred for diagnostic exercise testing. The test was stopped because of dyspnea. The standing rest ECG shows an intermittent Wolff-Parkinson-White pattern (arrows). In the nonpreexcited beats, ST segment depression does not occur either at peak exercise or in the postexercise phase. However, in the preexcited beats (arrows), an additional 1.3 mm of downsloping ST segment depression is noted as compared with baseline during and after exertion.

the device should be known. If the ICD device is implanted for ventricular fibrillation or fast ventricular tachycardia, the rate will normally exceed that attainable during sinus tachycardia and the test can be terminated as the heart rate approaches 10 beats/min below the detection interval of the device. In patients with slower programmed detection rates, the ICD may be reprogrammed to a faster rate to avoid accidental discharge during exercise testing or may be temporarily deactivated by a magnet. Exercise testing may be used to test the efficacy of tachycardic detection algorithms that apply criteria such as suddenness of onset and R-R variability.

SPECIFIC CLINICAL APPLICATIONS

INFLUENCE OF DRUGS AND OTHER FACTORS.

Patients with CAD demonstrate individual variability in time to onset of exercise-induced angina, time to onset of exercise-induced ischemic ST segment depression of 0.1 mV or greater, and cardiovascular efficiency during exercise testing.[2] [5] [22] The average individual variability in time to onset of exercise-induced myocardial ischemia or peak anaerobic capacity approximates as much as 20 percent in placebo-controlled trials of antianginal drugs. Variability can be reduced by patients' familiarization with the exercise protocol and equipment, controlling for antianginal drug therapy at the time of testing, and stable test performance conditions. When two or three exercise tests are conducted within weeks of each other, the greatest increase in exercise time usually occurs between test one and test two.[128] In one series of 24 subjects with stable angina less than class II, exercise time was increased by approximately 1 minute, and time to onset of angina or ischemic ST segment depression by 3 minutes when two exercise tests were performed 15 minutes apart.[129] The mechanisms of the attenuation response with reexercise may be the results of ischemic preconditioning, familiarization with the exercise protocol, and improved musculoskeletal efficiency but do not appear to be dependent on exercise protocol intensity or downregulation of myocardial contractility induced by the initial ischemic stimulus. In cold-sensitive individuals, exercise testing in a cooler environment results in onset of ischemic ST segment depression earlier than under normal temperature-controlled conditions.[130] Conditions that increase carbon monoxide levels, such as chronic cigarette smoking, lower the ischemic response threshold.

Digitalis glycosides can produce exertional ST segment depression even if the effect is

not evident on the resting ECG and can accentuate ischemic exercise-induced ST segment changes, particularly in older individuals. Absence of ST segment deviation during an exercise test in a patient receiving a cardiac glycoside is considered a valid negative response. Hypokalemia in patients on long-term diuretic therapy may be associated with exercise-induced ST segment depression. Antiischemic drug therapy with nitrates, beta-blocking drugs, or calcium channel blocking drugs prolongs the time to onset of ischemic ST segment depression, increases exercise tolerance, and, in a small minority of patients (10 to 15 percent), may normalize the exercise ECG response in patients with documented CAD.[1] [2] [22] The time and dose of drug ingestion may affect exercise performance. In some laboratories, cardioactive drug therapy is withheld for three to five half-lives and digitalis for 1 to 2 weeks before diagnostic testing. However, this is impractical in many cases. Heparin therapy may increase total exercise duration and ability to achieve a higher rate pressure product before the onset of angina and at peak exertion.[131]

WOMEN.

The sensitivity and specificity of exercise-induced ST segment depression for obstructive CAD are less in women than in men. The decreased diagnostic accuracy results in part from a lower prevalence and extent of CAD in young and middle-aged women. Women tend to have a greater release of catecholamines during exercise, which could potentiate coronary vasoconstriction and augment the incidence of abnormal exercise ECGs results, and false-positive results have been reported to be more common during menses or preovulation. In a series of 976 symptomatic women referred for exercise testing and coronary angiography, a low- moderate- and high-risk Duke treadmill score were associated with CAD of 75 percent or greater luminal narrowing in 19.1, 34.9, and 89.2 percent of subjects, respectively. The frequency of three-vessel disease 75 percent or greater or left main CAD was 3.5, 12.4, and 46 percent respectively.[131] In a retrospective population-based cohort study of 1452 men and 741 women, exercise-induced angina, ischemic ECG changes, and workload were strongly associated with all-cause mortality and cardiac events in both sexes. The relationship between workload and outcome was linear, with an increment of 1 MET in workload associated with a 20 to 25 percent reduction in risk of death and cardiac events.[132] Alexander and colleagues compared the Duke treadmill score in 976 women and 2249 men; the 2-year mortality for women was 1, 2.2, and 3.6 percent for low-moderate- and high-risk scores, compared with 1.7, 5.8, and 16.6 percent in men. In this report, women had a similar frequency of angina on the treadmill as men, but exertional angina in women was less often correlated with CAD presence.[133] Thus, in women with established

CAD, exercise testing provides useful prognostic information for risk stratification and identification of low and higher-risk patient subsets.[131] [133] [134] [135]

HYPERTENSION.

Exercise testing has been used in an attempt to identify patients who have an abnormal blood pressure response and are destined subsequently to develop hypertension. In asymptomatic normotensive individuals, an exaggerated exercise systolic and diastolic blood pressure response during exercise or exaggerated peak systolic blood pressure response to 214 mm Hg or greater or an elevated systolic or diastolic blood pressure at the third minute of recovery is associated with significant increased long-term risk of hypertension[136] [137] (Fig. 6-22) . Severe systemic hypertension may interfere with subendocardial perfusion and cause exercise-induced ST segment depression in the absence of atherosclerosis, even when the rest ECG does not show significant ST or T wave changes.[138] Beta and calcium channel blocking drugs decrease submaximal and peak systolic blood pressure in many hypertensive patients. Exercise tolerance is decreased in patients with poor blood pressure control.[139]

ELDERLY PATIENTS.

Maximal aerobic capacity (O_2 max) declines 8 to 10 percent per decade in sedentary men and women, with approximately 50 percent reduction in exercise capacity between the ages of 30 and 80 years.[15] The exercise protocol in elderly patients should be selected according to estimated aerobic capacity. In patients with limited exercise tolerance, the test should be started at the slowest speed with a 0 percent grade and adjusted according to the patient's ability. Older patients may need to grasp the handrails for support. The frequency of abnormal exercise ECG patterns is greater in older than younger individuals, and the risk of cardiac events is significantly increased because of a concomitant increase in prevalence of more extensive CAD.[140] [141] The greater test sensitivity of the exercise ECG in elderly individuals is accompanied by a slight reduction in specificity. Cardiac arrhythmias, chronotropic incompetence, and hypertensive responses are more common in older individuals.

DIABETES MELLITUS.

Coronary atherosclerosis and peripheral vascular disease are significantly increased in adult diabetic as compared with nondiabetic patients; the likelihood of atherosclerosis correlates closely with duration of diabetes. In patients with autonomic dysfunction and sensory neuropathy, anginal threshold may be increased, and abnormal exercise-induced heart rate and blood pressure responses are common.[142] Once CAD disease is established, the incidence of exercise-induced ECG changes is similar to that of nondiabetic persons.[143] The probability of an adverse cardiac outcome in a diabetic as compared with a nondiabetic individual for a similar abnormal exercise test result is likely to be increased because of the increased risk of dyslipidemia, impaired fibrinolysis, and hypertension associated with the diabetic process. Further research is required to determine optimal noninvasive test procedures to diagnose early endothelial dysfunction in diabetic patients and the presence and extent of obstructive CAD.

The hemodynamics of exercise provide an excellent opportunity to measure gradients across stenotic valves, to assess ventricular function in patients with primary valvular regurgitation or mixed lesions, and to assess pulmonary and systemic vascular resistance[144] [145] [146] (see Chap. 46) . The use of echocardiographic Doppler techniques (see Chap. 7) is particularly valuable in evaluating patients whose symptoms are out of proportion to the degree of valvular disease observed and in assessing the results of valvulotomy or valve replacement.[146A] [146B] Clinical and exercise noninvasive assessment of patients with valvular heart disease can provide useful information on the timing of operative intervention and help achieve a more precise estimate of a patient's degree of incapacitation than can assessment of symptoms alone.[145] Studies of adults with moderate to severe aortic stenosis (e.g., valve area 0.5 to 1.5 cm^2 and mean gradients of 18 to 64 mm Hg) show that exercise testing can be safely performed when appropriate exercise protocols and precautions are used. In patients with mitral stenosis, excessive heart rate response to relatively low levels of exercise, reduction of cardiac output with exercise (exercise-induced hypotension), and chest pain (ischemia secondary to low output or pulmonary hypertension) are indicators that favor earlier valve repair. In patients with mitral valve prolapse without regurgitation at rest, exercise-induced mitral regurgitation has been associated with the subsequent development of progressive mitral regurgitation, heart failure symptoms, or syncope.

Peak
o_2 and anaerobic threshold are reduced in symptomatic patients with hypertrophic cardiomyopathy compared

Figure 6-22 Probability of developing systemic hypertension within 8 years after exercise testing as a function of exercise-induced systolic and diastolic blood pressure responses in men and women. *Left panel:* Exercise systolic blood pressure. *Right panel:* Exercise diastolic blood pressure. Crude probabilities of developing hypertension are displayed for mean systolic or diastolic blood pressure value for each of exercise response during the second stage of treadmill testing.*(From Singh JP, Larson MG, Manolio TA, et al: Blood pressure response during treadmill testing is a risk factor for new onset hypertension. The Framingham Heart Study. Circulation 99:1831-1836, 1999.)*

with sedentary subjects (see Chap. 48) . In a 50-patient series of hypertrophic cardiomyopathy, 59 percent of symptomatic subjects were unable to achieve a peak o_2 60 percent of predicted; only two patients achieved a peak
o_2 greater than 80 percent of predicted.[147] [148] In 20 symptomatic patients with hypertrophic cardiomyopathy, 9 who had an abnormal exercise blood pressure response before transcoronary alcoholic septal ablation normalized their blood pressure response after treatment; exercise time was only mildly increased.[149]

CORONARY REVASCULARIZATION

Coronary Bypass Grafting (see Chap. 37) .

The degree of improvement in exercise-induced myocardial ischemia and aerobic capacity after coronary bypass grafting depends in part on the degree of revascularization achieved and left ventricular function.[150] [151] Exercise-induced ischemic ST segment depression may persist when incomplete revascularization is achieved, albeit at higher exercise workloads, and in approximately 5 percent of patients in whom complete revascularization has been achieved.[152] [153] [154] It usually takes at least 6 weeks of convalescence before maximum exercise can be performed. The natural history of saphenous vein grafts and internal mammary artery conduits is different, and serial conversion from an initially normal to abnormal exercise ECG result over time depends in part on the type of conduit used and CAD progression in nongrafted vessels. The diagnostic and prognostic utility of exercise testing late after coronary revascularization (e.g., 5 to 10 years) is much greater than early (<1 year) testing, because a late abnormal exercise response is more likely to indicate graft occlusion, stenosis, or progression of CAD. In selected patients with severe left ventricular dysfunction and symptomatic heart failure, coronary bypass surgery is associated with a significant increase in exercise capacity when a large amount of viable myocardium (e.g., >25% of left ventricular mass) can be determined using positron emission tomography.[155]

Percutaneous Coronary Intervention (see Chap. 38) .

After PTCA, restenosis occurs in approximately 20 to 40 percent of patients, usually within the first 6 months, and is more common in patients with proximal left anterior descending CAD, in patients with long coronary artery narrowings, in diabetic patients, in patients with multivessel or multilesion dilation, and those in whom post-PTCA luminal obstruction exceeds 50 percent. The restenosis rate is less in patients who have a coronary stent placed. In the early post-PTCA phase (<1 month), an abnormal exercise ECG result may be secondary to a suboptimal PTCA result, impaired coronary vascular reserve in a successfully dilated vessel, or incomplete revascularization.[156] [157] The optimal time to perform an exercise test after PTCA depends in part on the success of the procedure and the degree of revascularization obtained. Exercise testing early after PTCA (within days) can often be used to help determine the need for a staged procedure and to provide a reference baseline for subsequent follow-up. In an otherwise asymptomatic patient, a 6-month postprocedure test allows sufficient time to document restenosis should it occur and allows the dilated vessel an opportunity to heal. Serial conversion of an initially normal exercise test result after PTCA to an abnormal result in the initial 6 months after the procedure, particularly when it occurs at a lower exercise workload, is usually associated with restenosis. The use of exercise myocardial imaging in selected patients enhances the diagnostic content of the test and can help localize the territory of myocardial ischemia and guide indications for repeat coronary angiography in patients who have undergone multivessel/multilesion PTCA.[11] In a small uncontrolled series of patients who had end-stage CAD and who underwent transmyocardial laser revascularization, exercise capacity was significantly increased by

26 W.[158]

CARDIAC TRANSPLANTATION (see Chap. 20) .

Cardiopulmonary exercise testing is useful in selecting patients with end-stage heart failure for cardiac transplantation. A peak O_2 of less than 12 to 14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ or 40 to 50 percent of predicted O_2 is associated with 2-year survival rates ranging from 30 to 50 percent (Fig. 6-23) .[159] The use of percent of predicted O_2 , which adjusts an individual patient's peak O_2 for age, gender, and weight rather than weight alone, has been shown to further enhance prognostic estimates in patients who have a low peak exercise O_2 [102] [104] In patients awaiting heart transplantation, with initial poor exercise capacity, ability to increase peak oxygen uptake with increased peak oxygen pulse identifies a relatively lower-risk group in whom cardiac transplantation may be able to be deferred if the patient's clinical status is stable. Exercise performance in transplant recipients is influenced by the fact that the donor heart is surgically denervated without efferent parasympathetic or sympathetic innervation and by the occurrence of rejection and scar formation, systemic and pulmonary vascular resistance, level of training, and development of coronary atherosclerosis in the graft.[160] [161] [162] [163] Maximal oxygen uptake and work capacity are reduced after cardiac transplantation compared with age-matched controls but usually are markedly improved compared with preoperative findings. Abnormalities of the ventricular rate response include a resting tachycardia due to parasympathetic denervation, a slow heart rate response during mild to moderate exercise, a more rapid response during more strenuous exercise, and a more prolonged

Figure 6-23 The 3-year survival of patients with congestive heart failure referred for cardiac transplant evaluation with a peak O_2 14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ stratified according to percent predicted peak O_2 > 50 percent or 50 percent. The 91 ± 5 percent 3-year survival rate of the 44 patients with a percent predicted O_2 > 50 percent was similar to the survival rates of patients with a peak O_2 14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and significantly greater than the 61 ± 5 percent of the 110 patients with a peak O_2 50 percent. The data indicate that a low peak O_2 and percent predicted O_2 identify high-risk patients with congestive heart failure whose survival may be improved by cardiac transplantation. *(From Osada N, Chaitman BR, Miller LW, et al: Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. J Am Coll Cardiol 31:577, 1998.)*

time for the ventricular rate to return to baseline during recovery. The transplanted heart relies heavily on the Frank-Starling mechanism to increase cardiac output during mild to moderate exercise. Systemic vascular resistance may be increased because of cyclosporine therapy. The exercise ECG is relatively insensitive in detecting coronary artery vasculopathy after cardiac transplantation.[160] [162] However, the new development of an abnormal exercise ECG result several years after cardiac transplantation may indicate focal intraluminal narrowing.

SAFETY AND RISKS OF EXERCISE TESTING

Exercise testing has an excellent safety record. The risk is determined by the clinical characteristics of the patient referred for the procedure. In nonselected patient populations, the mortality is less than 0.01 percent and morbidity less than 0.05 percent.[164] The risk is greater when the test is performed soon after an acute ischemic event. In a survey of 151,941 tests conducted within 4 weeks of an acute myocardial infarction, mortality was 0.03 percent, and 0.09 percent of patients either had a nonfatal reinfarction or were resuscitated from cardiac arrest.[165] The relative risk of a major complication is about twice as great when a symptom-limited protocol is used as compared with a low-level protocol. Nevertheless, in the early postinfarction phase, the risk of a fatal complication during symptom-limited testing is only 0.03 percent. The risk is less for low-risk patients who are seen in the emergency department and who undergo exercise testing for risk stratification.[93] Exercise testing can be safely performed in patients with compensated congestive heart failure, with no major complications reported in 1286 tests in which a bicycle ergometer was used.[166] The risk of exercise testing in patients referred for life-threatening ventricular arrhythmias was examined by Young and colleagues[167] in a series of 263 patients who underwent 1377 tests; 2.2 percent developed sustained ventricular tachyarrhythmias that required cardioversion, cardiopulmonary resuscitation, or antiarrhythmic drugs to restore sinus rhythm. The ventricular arrhythmias were more frequent in tests performed on antiarrhythmic drug therapy as compared with the baseline drug-free state. In contrast to the high risk in the aforementioned patient subsets, the risk of complications in asymptomatic subjects is extremely low, with no fatalities reported in several series.[1] [2] [3] [4] [5] [6]

The risk of incurring a major complication during exercise testing can be reduced by performing a careful history and physical examination before the test and observing patients closely during exercise with monitoring of the ECG, arterial pressure, and symptoms. The standard 12-lead ECG should be verified before the test for any acute or recent change. The contraindications to exercise testing are well defined (Table 6-4) . Patients with critical obstruction to left ventricular outflow are at increased risk of cardiac events during exercise. In selected patients, low-level exercise can be useful in determining the severity of the left ventricular outflow tract gradient. The cool-down period should be prolonged to at least 2 minutes in patients with

TABLE 6-4 -- CONTRAINDICATIONS TO EXERCISE TESTING

Acute myocardial infarction (<2 d)
Unstable angina with recent rest pain
Untreated life-threatening cardiac arrhythmias
Advanced atrioventricular block
Acute myocarditis or pericarditis
Critical aortic stenosis
Severe hypertrophic obstructive cardiomyopathy
Uncontrolled hypertension
Acute systemic illness (pulmonary embolism, aortic dissection)

TABLE 6-5 -- INDICATIONS FOR TERMINATING EXERCISE TESTING

ABSOLUTE INDICATIONS
Drop in systolic blood pressure of >10 mm Hg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia
Moderate to severe angina (grade ¾)
Increasing nervous system symptoms (e.g., ataxia, dizziness, or near-syncope)
Signs of poor perfusion (cyanosis or pallor)
Technical difficulties in monitoring ECG or systolic blood pressure
Subject's desire to stop
Sustained ventricular tachycardia
ST elevation (1.0 mm) in noninfarct leads without diagnostic Q waves (other than V_1 or aV_r)
RELATIVE INDICATIONS
Drop in systolic blood pressure of 10 mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia
ST or QRS changes such as excessive ST depression (>3 mm of horizontal or downsloping ST segment depression) or marked axis shift
Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
Fatigue, shortness of breath, wheezing, leg cramps, or claudication
Development of bundle branch block of intraventricular conduction delay that cannot be distinguished from ventricular tachyardia
Increasing chest pain
Hypertensive response

ECG=electrocardiogram; PVCs=premature ventricular contractions. *Modified from Fletcher GF: Exercise standards: A standard for healthcare professionals from the American Heart Association Writing Group. Circulation 91:580, 1995.*

stenotic valves to avoid sudden pressure-volume shifts that occur in the immediate postexercise phase.

Uncontrolled systemic hypertension is a contraindication to exercise testing. Patients should continue antihypertensive drug therapy on the day of testing. Patients who present with systemic arterial pressure readings of 220/120mm Hg or greater should rest for 15 to 20 minutes, and their blood pressure should be remeasured. If blood pressure remains at these levels, the test should be postponed until the hypertension is better controlled.

A resuscitator cart and defibrillator should be available in the room where the test procedure is carried out, as should appropriate cardioactive medication available to treat cardiac arrhythmias, AV block, hypotension, and persistent chest pain. An intravenous line should be started in high-risk patients such as those being tested for adequacy of control of life-threatening ventricular arrhythmias. The equipment and supplies in the cart should be checked on a regular basis. A previously specified routine for cardiac emergencies needs to be determined; this includes patient transfer and admission to a coronary care unit if necessary.

Clinical judgment is required to determine which patients can be safely tested in an office as opposed to a hospital-based setting. High-risk patients, such as those with evident left ventricular dysfunction, severe angina pectoris, a history of cardiac syncope, and significant ambient ventricular ectopy on the pretest examination, should be tested in the hospital. Low-risk patients, such as asymptomatic individuals and those with a low pretest risk of disease, may be tested by specially trained nurses or physician assistants who have received advanced cardiac life support certification, with a physician in close proximity.

TERMINATION OF EXERCISE.

The use of standard test indications to terminate an exercise test reduces risk (Table 6-5) .

TABLE 6-6 -- EXERCISE TEST REPORT INFORMATION

Demographic data: name, patient identifier, date of birth/age, gender, weight, height, test date
Indication(s) for test

Patient descriptors: atherosclerotic risk profile, drug usage, resting ECG findings
Exercise test results
Protocol used
Reason(s) for stopping exercise
Hemodynamic data: rest and peak heart rate, rest and peak blood pressure, percent maximum achieved heart rate, maximum rate of perceived exertion (Borg's scale), peak workload, peak METs, total exercise duration in minutes
Evidence for myocardial ischemia: time to onset and offset of ischemic ST segment deviation or angina, maximum depth of ST segment deviation, number of abnormal exercise ECG leads, abnormal systemic blood pressure responses
General comments
ECG=electrocardiogram.

Termination of exercise should be determined in part by the patient's recent activity level. The rate of perceived patient exertion can be estimated by the Borg's scale. The scale is linear, with values of 9, very light; 11, fairly light; 13, somewhat hard; 15, hard; 17, very hard; and 19, very, very hard. Borg's readings of 14 to 16 approximate anaerobic threshold, and readings of 18 or greater approximate a patient's maximum exercise capacity. It is helpful to grade exercise-induced chest discomfort on a 1 to 4 scale, with 1 indicating the initial onset of chest discomfort and 4 the most severe chest pain the patient has ever experienced. The exercise technician should note the onset of grade 1 chest discomfort on the work sheet, and the test should be stopped when the patient reports grade 3 chest pain. In the absence of symptoms, it is prudent to stop exercise when a patient demonstrates 0.3 mV (3 mm) or greater of ischemic ST segment depression or 0.1 mV (1 mm) or greater of ST segment elevation in a noninfarct lead without an abnormal Q wave. Significant worsening of ambient ventricular ectopy during exercise or the unsuspected appearance of ventricular tachycardia is an indication to terminate exercise. A progressive, reproducible decrease in systolic blood pressure of 10 mm Hg or more may indicate transient left ventricular dysfunction or an inappropriate decrease in systemic vascular resistance and is an indication to terminate exercise. The test should be stopped if the arterial blood pressure is 250 to 270/120 to 130 mm Hg or greater. Ataxia may indicate cerebral hypoxia.

The exercise test report should contain basic demographic data, the indication for testing, a brief description of the patient's profile, and exercise test results (Table 6-6) .

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GUIDELINES
USE OF EXERCISE TOLERANCE TESTING

Thomas H. Lee

Guidelines for the use of exercise testing were published by an American College of Cardiology/American Heart Association (ACC/AHA) task force in1997.[1] These guidelines consider the usefulness of exercise testing for (1) diagnosis (2) risk stratification in patients with chronic coronary artery disease or after acute myocardial infarction, and (3) several specific populations. This document updated prior guidelines from the ACC/AHA from 1986[2] and drew on other guidelines and position statements on topics related to exercise testing from the ACC/AHA and drew on other guidelines and position statements on topics related to exercise testing from the ACC/AHA and other organizations.

PERFORMANCE OF THE TEST.

The ACC/AHA guidelines agreed with prior recommendations that exercise testing should be supervised by an appropriately trained physician.[3] The test itself can be performed by properly trained nonphysician personnel, but these personnel should be working under the supervision of a physician who should be in the immediate vicinity and available for emergencies. The guidelines note that exercise tests do not always require the involvement of a cardiologist.

Absolute and relative contraindications to exercise testing were adapted from a prior statement from the AHA[4] (Table 6-G-1) . The guidelines note that for some patients with relative contraindications, the benefits of exercise testing outweigh the risks; in

such patients, testing may be appropriate. Absolute and relative indications for terminating exercise are summarized in Table 6-5 , p. 151.

DIAGNOSIS OF OBSTRUCTIVE CORONARY ARTERY DISEASE.

Exercise testing is considered clearly appropriate for the purpose of diagnosis of coronary artery disease in most adults with an intermediate probability of coronary artery disease (Table 6-G-2) . The focus on the use of this test in patients with an intermediate probability of coronary disease recognizes that testing is unlikely to change the diagnosis for patients with either a low or a high probability of coronary disease based on age and other clinical data. The guidelines provided a framework for qualitative assessment of the probability of coronary disease on the basis of such information (Table 6-G-3) .

The ACC/AHA guidelines specifically note that exercise testing is appropriate in patients with a complete right bundle branch block or less than 1 mm of resting ST depression. They also conclude that cessation of therapy with digoxin or beta blockers is not necessary before exercise testing, even though the effects of these agents can sometimes complicate interpretation of test results.

RISK STRATIFICATION IN PATIENTS WITH PROBABLE CORONARY DISEASE.

Even if the evidence for coronary disease is so clear for a patient that an exercise test cannot influence the diagnosis, testing may improve management through risk stratification. Exercise testing is especially likely to be valuable as part of the initial evaluation of patients with suspected or known coronary disease (see Table 6-G-2) since the results may help identify high-risk subsets of patients who are likely to have their survival improved with coronary artery bypass graft surgery or coronary angioplasty. Exercise testing is also appropriate in patients who have had a significant change in clinical status because the test may clarify whether the new symptoms are due to coronary artery

TABLE 6-6-G-1 -- CONTRAINDICATIONS TO EXERCISE TESTING (ACC/AHA GUIDELINES)

Absolute	Relative*

Acute myocardial infarction (within 2d) Unstable angina not previously stabilized by medical therapy Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise Symptomatic severe aortic stenosis Uncontrolled symptomatic heart failure Acute pulmonary embolus or pulmonary infarction Acute myocarditis or pericarditis Acute aortic dissection	Left main coronary stenosis Moderate stenotic valvular heart disease Electrolyte abnormalities Severe arterial hypertension Tachyarrhythmias or bradyarrhythmias Hypertrophic cardiomyopathy and other forms of outflow tract obstruction Mental or physical impairment leading to an inability to exercise adequately High-degree atrioventricular block

From Gibbons RJ, Balady GJ, Beasley FW, et al: ACC/AHA guidelines for exercise testing: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 30:260-315, 1997; modified from Fletcher GF, Balady G, Froelicher VF, et al: Exercise standards: A statement for healthcare professionals from the American Heart Association Writing Group. Special Report. Circulation 91: 580-615, 1995.

*Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

The appropriate timing of testing depends on the level of risk of unstable angina.

In the absence of definitive evidence, the committee suggests systolic blood pressure greater than 200 mm Hg and/or diastolic blood pressure greater than 110 mm Hg.

TABLE 6-6-G-2 -- APPROPRIATENESS OF EXERCISE TESTING FOR SPECIFIC PATIENT SUBSE
AND INDICATIONS

Indication	**Class I: Appropriate**	**Class IIa: Probably Appropriate**	**Class IIb: Probably Not Appropriate**	**Class III: Inappropriate**

Exercise testing in diagnosis of obstructive CAD	Adult patients (including those with complete right bundle branch block or less than 1 mm of resting ST depression) with an intermediate pretest probability of CAD (see Table 6-G-3) based on gender, age, and symptoms (specific exceptions are noted in Classes II and III)	Patients with vasospastic angina	Patients with a high pretest probability of CAD by age, symptoms, and gender	Patients with the following baseline EC abnormalities: Preexcitation (Wolff-Parkinson-Wh syndrome Electronically pac ventricular rhythm Greater than 1 m of resting ST depression Complete left bundle branch block
			Patients with a low pretest probability of CAD by age, symptoms, and gender	Patients with a documented myocar infarction or prior coronary angiograph demonstrating significant disease ha an established diagnosis of CAD; however, ischemia a risk can be determine by testing
			Patients with less than 1 mm of baseline ST depression and taking digoxin	
			Patients with ECG criteria for left ventricular hypertrophy and less than 1 mm of baseline ST depression	
Risk assessment and prognosis in patients with symptoms or a prior history of CAD	Patients undergoing initial evaluation with suspected or known CAD. Specific exceptions are noted below in Class IIb	None	Patients with the following ECG abnormalities: Preexcitation (Wolff-Parkinson-White) syndrome Electronically paced ventricular rhythm Greater than 1 mm of resting ST depression Complete left bundle branch block	Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization
	Patients with suspected or known CAD previously evaluated with significant change in clinical status		Patients with a stable clinical course who undergo periodic monitoring to guide treatment	

After myocardial infarction	Before discharge for prognostic assessment, activity prescription, and evaluation of medical therapy (submaximal at about 4 to 7 d) Early after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the predischarge exercise test was not done (symptom limited/about 14-21 d) Late after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (symptom limited/about 3-6 wk)	After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization	Before discharge in patients who have undergone cardiac catheterization to identify ischemia in the distribution of a coronary lesion of borderline severity Patients with the following ECG abnormalities: Complete left bundle branch block Preexcitation syndrome Left ventricular hypertrophy Digoxin therapy Greater than 1 mm of resting ST segment depression Electronically paced ventricular rhythm Periodic monitoring in patients who continue to participate in exercise training or cardiac rehabilitation	Severe comorbidity likely to limit life expectancy and/or candidacy for revascularization

Exercise testing using ventilatory gas analysis	Evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation	Evaluation of exercise capacity when indicated for medical reasons in patients whom subjective assessment of maximal exercise in unreliable	Evaluation of the patient's response to specific therapeutic interventions in which improvement in exercise tolerance is an important goal or endpoint	Routine use to evalu exercise capacity
	Assistance in the differentiation of cardiac vs. pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain		Determination of the intensity of exercise training as part of comprehensive cardiac rehabilitation	
Exercise testing in asymptomatic persons without known CAD	None	None	Evaluation of persons with multiple risk factors (see the text) Evaluation of asymptomatic men older than 40 yr and women older than 50 yr Who plan to start vigorous exercise (especially if sedentary) *or* Who are involved in occupations in which impairment might have an impact on public safety *or* Who are at high risk for CAD because of other diseases (e.g., chronic renal failure)	Routine screening of asymptomatic men o women

Valvular heart disease	None	None	Evaluation of exercise capacity of patients with valvular heart disease	Diagnosis of CAD is patients with valvular heart disease
Exercise testing before and after revascularization	Demonstration of ischemia before revascularization	After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization	Detection of restenosis in selected, high-risk asymptomatic patients within the first months after angioplasty	Localization of ischer for determining the s of intervention
	Evaluation of patients with recurrent symptoms suggesting ischemia after revascularization		Periodic monitoring of selected, high-risk asymptomatic patients for restenosis, graft occlusion, or disease progression	Routine, periodic monitoring of asymptomatic patien after percutaneous transluminal coronary angioplasty or corona artery bypass graft surgery without spec indications
Investigation of heart rhythm disorders	Identification of appropriate settings in patients with rate-adaptive pacemakers	Evaluation of patients with known or suspected exercise-induced arrhythmias	Investigation of isolated ventricular ectopic beats in middle-aged patients without other evidence of CAD	Investigation of isolat ectopic beats in your patients
		Evaluation of medical, surgical, or ablative therapy in patients with exercise-induced arrhythmias (including atrial fibrillation)		

CAD = coronary artery disease; ECG = electrocardiogram.

disease. Exercise testing for patients with unstable angina is recommended as soon as the patient has stabilized clinically. In contrast, the ACC/AHA guidelines do not offer strong support for routine exercise testing of patients with a stable clinical course (see Table 6-G-3) .

The ACC/AHA guidelines explicitly state that the exercise test should be the standard initial mode of stress testing for risk stratification of patients with a normal electrocardiogram who are not taking digoxin. The guidelines assert that "There is no compelling evidence in patients who are classified as low risk based on clinical and exercise testing information that an imaging modality adds significant new prognostic information to a standard exercise test." In intermediate-risk patients, the text

acknowledges that myocardial perfusion imaging appears to add value for risk stratification.

AFTER MYOCARDIAL INFARCTION.

The ACC/AHA guidelines are strongly supportive of one to two exercise tests for risk stratification after acute myocardial infarction (see Table 6-G-3) . Submaximal tests are appropriate prior to discharge from the hospital. If predischarge testing is not performed, symptom-limited tests about 14 to 21 days after the myocardial infarction are appropriate. If predischarge testing was performed, a full symptom-limited test 3 to 6 weeks after infarction is appropriate.

These guidelines indicated that cardiac rehabilitation should be "considered standard care that should be integrated into the treatment plan of patients with" coronary artery disease, and they supported exercise testing for this purpose. However, the guidelines indicated that the appropriateness of some uses of exercise testing as part of cardiac rehabilitation was not established. Use of exercise testing after patients have undergone coronary revascularization was considered uncertain, but supported by most evidence (Class IIa). However, periodic monitoring with exercise testing in patients who are participating in cardiac rehabilitation programs was considered to have less support from research data.

USE OF VENTILATORY GAS ANALYSIS.

The ACC/AHA guidelines were explicitly supportive of the use of ventilatory gas analysis for certain specific indications in patients with cardiovascular and pulmonary disease. The most clearly appropriate indications were when cardiac transplantation was being considered or when differentiation between cardiac and pulmonary limitations in functional status was uncertain because of other clinical data. Some evidence exists to support the appropriateness of such testing when patients' subjective assessment of maximal exercise is unreliable (Class IIa). Routine use of ventilatory gas analysis to assess exercise capacity was considered inappropriate.

EXERCISE TESTING IN WOMEN.

The guidelines recommend that strategies for exercise testing in women be the same as those used in men. The text acknowledged problems with false-positive results but indicated that the data were insufficient to support routine stress imaging as the initial test for coronary disease in women.

ASYMPTOMATIC PATIENTS WITHOUT KNOWN CORONARY ARTERY DISEASE.

The ACC/AHA guidelines were generally not supportive of the use of exercise testing to

screen for coronary artery disease in asymptomatic patients. The guideline authors acknowledged that this assessment was discordant with widespread practice patterns but concluded that existing data indicate that such screening leads to a high rate of false-positive results. This lack of support for screening asymptomatic patients with exercise testing is consistent with guidelines from the U.S. Preventive Services Task Force[5] and the American College of Physicians.[6]

The ACC/AHA guidelines identified some indications of uncertain appropriateness for which the weight of evidence was not strong. One such "Class IIb" indication was evaluation of patients with multiple risk factors, which was defined as hypercholesterolemia (>240 mg/dl), hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), smoking, diabetes, and a family history of heart attack or sudden cardiac death in a first-degree relative younger than 60 years. An alternative approach is to select patients with a Framingham risk score consistent with at least a moderate risk of serious cardiac events within 5 years.

Exercise testing was also considered to be of marginal (Class IIb) appropriateness for men older than 40 years or women older than 50 who (1) were starting a vigorous exercise program, (2) might endanger the safety of others if they had a sudden cardiac event, or (3) had a high risk for coronary disease because of other diseases. A minority of the ACC/AHA committee favored a Class III recommendation for exercise testing in patients with multiple risk factors or people starting

TABLE 6-6-G-3 -- PROBABILITY OF CORONARY ARTERY DISEASE BY AGE, GENDER, AND SYMPTOMS (FROM ACC/AHA GUIDELINES)

Age* (yr)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30-39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40-49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50-59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60-69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

*No data exist for patients younger than 30 or older than 69 years, but it can be assumed that prevalence of coronary artery disease increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range. High indicates 90 percent; intermediate, 10 to 90 percent; low, less than 10 percent; and very low, less than 5 percent.

exercise programs. Support for these positions is provided by guidelines from the American College of Sports Medicine, which recommends exercise electrocardiography for men older than 40 years, women older than 50, and other asymptomatic persons with multiple cardiac risk factors prior to beginning a vigorous exercise program.[7]

VALVULAR HEART DISEASE.

The ACC/AHA guidelines supported only limited use of exercise testing as part of the routine care of patients with valvular heart disease. The primary value of exercise testing in such patients is to assess atypical symptoms, exercise capacity, and the extent of disability (Class IIb). However, use of the exercise test to screen for coronary artery disease was considered inappropriate.

The guidelines noted that exercise testing may sometimes be useful and appropriate in patients with aortic stenosis. Although severe symptomatic aortic stenosis is considered a contraindication to exercise testing, this evaluation can be safely performed under close observation by an experienced physician.

BEFORE AND AFTER REVASCULARIZATION.

The ACC/AHA guidelines were supportive of the use of exercise testing to demonstrate ischemia before revascularization or to evaluate the significance of recurrent symptoms afterward. However, routine periodic testing of asymptomatic patients was considered inappropriate (Class III). The appropriateness of testing was considered equivocal in patients who were undergoing cardiac rehabilitation after revascularization or in asymptomatic patients who were considered to be at high risk for restenosis, graft occlusion, or disease progression.

INVESTIGATION OF HEART RHYTHM DISORDERS.

Exercise testing was considered to have narrow appropriate indications for use in the evaluation of rhythm disorders, including the assessment of settings for rate-adaptive pacemakers. Patients with known or suspected exercise-induced arrhythmias were considered reasonably appropriate (Class IIa) candidates for exercise testing. Exercise testing was also considered reasonably appropriate for assessment of therapy in patients who had been shown to have exercise-induced arrhythmias. Use of exercise testing for assessment of isolated ectopic beats was discouraged.

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Chapter 7 - Echocardiography

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Echocardiography is a group of interrelated applications of ultrasound including two-dimensional anatomical imaging, M-mode echocardiography, Doppler techniques, and contrast echocardiography. Echocardiography uses sound in the frequency range of 1 to 10 MHz. Typically when imaging adult patients, frequencies range from 2 to 5 MHz. For pediatric and some specialized adult applications higher frequencies of 7.5 and 10 MHz may also be used.

PRINCIPLES OF CARDIAC ULTRASONOGRAPHY

IMAGE GENERATION

The underlying premise of cardiac ultrasonography is that the speed of sound through tissue is equal to that in water (1450 m/sec). Ultrasound scanners emit a series of ultrasound bursts at a given frequency. The number of bursts or pulses per second is the "pulse repetition frequency." The ultrasound energy is then reflected from cardiac and other structures and returned to the transducer. By determining the time required for round trip transit, the distance of a reflective object from the transducer can be

calculated. The returning strength of the ultrasound signal is directly proportional to the reflective intensity of the object and likewise is integrated into the displayed image. The resolution with which structures can be defined is dependent on the transducer frequency, with higher resolution provided by high-frequency transducers but at the cost of reduced depth of penetration. The nature of the image that is acquired and displayed is determined by the number of ultrasound interrogation lines and the manner in which they are processed.

M-mode echocardiography was the earliest form of cardiac ultrasonography used clinically. M-mode echocardiography relies on interrogation along a single line of ultrasound either emitted from an independent transducer or along a cursor within a two-dimensional image. The M-mode echocardiogram only provides information with respect to the distance of each object from the transducer and provides no information in the lateral dimension (Fig. 7-1) . M-mode echocardiography was once the mainstay of echocardiography, but in modern laboratories it is relegated to a secondary role. It may still have some incremental value for highly precise measurements, and its temporal resolution far exceeds that of two-dimensional scanning.

A two-dimensional echocardiogram is created when a fan-shaped array, consisting of multiple interrogation lines, is emitted typically over a 90-degree sector from the transducer and analyzed. There are two methods by which the fan-shaped sector of ultrasound beams can be created. Most widely used is a phased-array system in which a linear array of ultrasound crystals is electronically steered through an imaging arc. The second method relies on high-speed mechanical rotation of one or usually more ultrasound crystals to mechanically steer the ultrasound beam through the predefined arc.

Doppler ultrasonography relies on analysis of a shift in the frequency of the ultrasound beam due to interaction with moving targets. The Doppler shift data can be displayed as a velocity profile or a color flow image. In the following sections we first discuss the methods by which anatomical images are recorded and then discuss Doppler methodology. The actual clinical echocardiographic examination consists of simultaneous and integrated two-dimensional and Doppler evaluation, supplemented by other specific and goal-oriented imaging modalities.

Figure 7-1 Normal M-mode echocardiogram in which the M-mode beam is swept from the aortic valve through the mitral valve and to the level of the papillary muscles. Note the normal boxlike opening of the aortic valve and the biphasic, "M"-shaped opening pattern of the mitral valve. There is posterior motion of the ventricular septum synchronous with anterior motion of the posterior wall. AV = aortic valve; DAo = descending aorta; LA = left atrium; LV = left ventricle; MV = mitral valve; RV = right ventricle.

Figure 7-2 Schematic of the transducer orientation used for acquiring parasternal views. The scanning plane of the ultrasound beam is superimposed on a schematic of the heart. Plane 1 represents a parasternal long-axis view in which the right ventricular outflow tract, proximal portion of the aorta and aortic valve, anterior ventricular septum, cavity of the left ventricle containing the mitral valve, and inferoposterior wall of the left ventricle can be visualized. Scanning plane 1 results in an ultrasound image as noted in Figure 7-1 . Scanning plane 2 is obtained by rotating the transducer 90 degrees and can be used to obtain a family of short-axis views of the heart. *(From Feigenbaum H: Echocardiography, 4th ed. Malvern, PA, Lea & Febiger, 1986.)*

THE ANATOMICAL ECHOCARDIOGRAPHIC EXAMINATION (SeeChap. 3.)

The mainstay of the echocardiographic examination is transthoracic two-dimensional echocardiography (TTE). The fan-shaped scan plane is directed into the chest to provide tomographic imaging planes (Figs. 7-2 , 7-3 , 7-4 , 7-5 , 7-6 , and 7-7). Each returning ultrasound signal is then registered and converted to a two-dimensional image of the interrogated plane. This process is repeated 20 to 120 times per second, resulting in a frame rate of 20 to 120 Hz. The sequence of imaged frames results in a real-time moving image of the heart. The frame rate for two-dimensional imaging is dependent on line density and scanning depth. Smaller areas can be imaged at substantially higher (100-120 Hz) frame rates than can be larger sectors, which typically are imaged at 30 Hz.

For the transthoracic examination, patients are typically placed in a left lateral position and scanned from several different left intercostal spaces. The standard transthoracic views (Table 7-1) are recorded from parasternal and apical transducer positions. Subcostal and suprasternal transducer positions can also be used. From any transducer position, the Doppler modalities, including pulsed, continuous-wave, and color flow imaging, can be recorded. Other imaging windows, such as the right sternal border, can be used for specific examinations.

Traditionally, two-dimensional echocardiograms and Doppler echocardiograms have been recorded on videotape for subsequent analysis and activities. In modern ultrasound equipment the image is acquired in a digital format and stored as such (Fig. 7-8) . Digital images can be displayed side by side or as a quad screen containing multiple views for visualization simultaneously. Digital images are free from degradation seen when the source image is transferred to analog videotape and can be transmitted to remote sites for review.[1] [2]

Figure 7-3 Parasternal long-axis view of the left ventricle in diastole *(top)* and systole *(bottom)*. Chambers and cardiac structures are as noted. This view corresponds to plane 1 of Figure 7-1 . AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricular outflow tract; MV = mitral valve.

Figure 7-4 Schematic showing the relationship of the parasternal long- and short-axis views of the heart. The central figure is a schematized parasternal long-axis view. Images 1 through 4 can be obtained by rotating the probe 90 degrees from the long axis and then angling the probe through the positions noted as 1 through 4 on the central schematic. Echocardiograms recorded from these different planes are

presented in Figure 7-5 . *(From Feigenbaum H: Echocardiography. 4th ed. Malvern, PA, Lea & Febiger, 1986.)*

Figure 7-5 Short-axis two-dimensional echocardiograms recorded in planes depicted in Figure 7-4 . The two left panels are recorded at the level of the papillary muscles in diastole *(top)* and systole *(bottom)*. Note the symmetrical thickening of the myocardium and inward motion of the endocardium representing normal ventricular function in systole. The top right panel is recorded at the level of the aortic valve, and the bottom right panel is recorded at the level of the mitral valve in diastole. Abbreviations are as per other figures; TV = tricuspid valve; RA = right atrium; PA = pulmonary artery; IVC = inferior vena cava.

Figure 7-6 Schematic of the ultrasound scanning planes for apical four- and two-chamber views. With the scanning plane directed as in plane 1, all four chambers are intersected. Scanning plane 1 results in an image as presented in the left panel of Figure 7-7 . By rotating the probe approximately 90 degrees, scanning plane 2 intersects only the left ventricle and left atrium, as is noted in the right panel of Figure 7-7 . *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

Examination and Appearance of the Normal Heart

PARASTERNAL LONG-AXIS VIEW.

In this view (see Fig. 7-3) , both the inferoposterior wall and interventricular septum are visualized, each of which is mildly concave toward the other. The normal ascending aorta is visualized, including its annulus, sinus of Valsalva, and proximal portion of the ascending aorta. The anterior and posterior leaflets of the mitral valve can be visualized in the parasternal long-axis position, with the anterior leaflet appearing more elongated. Typically, the posterolateral papillary muscle is also visualized from this transducer position. Anterior to the aorta, a portion of the right ventricular outflow tract is visualized. By medially angulating the transducer the right ventricular inflow tract can be visualized in which the inferior vena cava, right atrium, tricuspid valve, and right ventricle are visualized (Fig. 7-9) . From the parasternal transducer position a short-axis view of the heart can be obtained by rotating the transducer 90 degrees (see Figs. 7-4 and 7-5) . At the base of the heart, the circular aorta and the aortic valve with three equally sized leaflets are visualized, as well as the right ventricular outflow tract, which is seen as an inverted "U" overlying the aorta. By angling the transducer toward the apex, a short-axis view of the mitral valve can be visualized from which the actual orifice can be seen and quantified. With further angulation, the circular cavity of the left ventricle is visualized, including both of the papillary muscles. The normal short-axis geometry of the left ventricle is circular, whether it is visualized at the level of the mitral valve, papillary muscle, or apex. In the

Figure 7-7 Apical four- and two-chamber views of the left ventricle corresponding to the schematic presented in Figure 7-6 . Note the normal "bullet shape" geometry of the left ventricle and the more triangular right ventricle. Note also the more apical insertion of the tricuspid valve compared with the mitral valve. Abbreviations are as per other figures.

short-axis projections at the level of the mitral valve and below, the right ventricle appears as a more trabeculated crescent-shaped structure.

FOUR-CHAMBER VIEW.

From this view, the left ventricle has a normal bullet-shaped geometry. The anterior and posterior mitral valve leaflets can be visualized. The left atrium and pulmonary veins are visualized in high-quality studies as well (see Fig. 7-7) . In the four-chamber view, the right ventricle appears as a triangular structure. The

TABLE 7-1 -- TWO-DIMENSIONAL ECHOCARDIOGRAPHIC EXAMINATION

PARASTERNAL APPROACH
Long-axis plane
Root of aorta-aortic valve, left atrium, left ventricular outflow tract
Body of left ventricle-mitral valve
Left ventricular apex
Right ventricular inflow tract-tricuspid valve
Short-axis plane
Root of the aorta-aortic valve, pulmonary valve, tricuspid valve, right ventricular outflow tract, left atrium, pulmonary artery, coronary arteries
Left ventricle-mitral valve
Left ventricle-papillary muscles
Left ventricle-apex
APICAL APPROACH
Four-chamber plane
Four chamber
Four chamber with aorta
Long-axis plane
Two chamber-left ventricle, left atrium
Two chamber with aorta

SUBCOSTAL APPROACH
Four-chamber plane--all four chambers and both septa
Short-axis plane
Left ventricle
Right ventricle
Inferior vena cava
SUPRASTERNAL APPROACH
Four-chamber plane
Arch of aorta-descending aorta
Long-axis plane
Arch of aorta-pulmonary artery, left atrium

tricuspid valve inserts into the annulus of the right ventricle at a position slightly more apical than the mitral valve. This results in a small portion of the ventricular septum (the atrioventricular septum) falling between the septal leaflets of the tricuspid and mitral valves. By rotating the transducer 90 degrees from the four-chamber view, a two-chamber view of the left ventricle and atrium can be obtained (see Fig. 7-7) .

SUBCOSTAL AND SUPRASTERNAL VIEWS.

In addition to parasternal and apical transducer positions, subcostal and suprasternal positions also provide imaging windows in adult patients. The subcostal transducer position can be very effective in patients with chronic lung disease in whom parasternal and apical views are obscured by intervening lung tissue. Typically, patients are imaged in the supine position with the knees bent and the transducer placed in the subxiphoid position. Imaging during held inspiration often is effective at bringing the heart into optimal position. Views similar to a four-chamber view as well as a series of short-axis views can be obtained from this transducer position. The subcostal views also provide excellent visualization of the atrial septum and the connection between the inferior vena cava (IVC) and right atrium (Fig. 7-10) .

SUPRASTERNAL VIEWS.

These views are obtained by placing the transducer in the suprasternal notch. This transducer position may be somewhat uncomfortable for many patients. It provides a view of the arch of the aorta and includes the great vessels in the majority of patients and portions of the main pulmonary artery (Fig. 7-11) .

Anatomical Variants

Several well-recognized anatomical and developmental variants can be seen with echocardiography. It is important to recognize these as normal variants to avoid

confusion with pathological processes.[3] [4]

MUSCLE TRABECULATIONS.

The right ventricle is more heavily trabeculated than the left, and, similarly, the right atrium is more trabeculated than the left atrium. High-resolution scanning virtually always detects multiple muscle trabeculations in the right ventricle, the most prominent of which is the moderator band, which is a muscular structure traversing from the lateral wall to the septum of the right ventricle near the apex (Fig. 7-12) . On occasion, secondary

Figure 7-8 Demonstration of quad screen format for displaying of digitized echocardiograms. This format allows simultaneous display in real time (here depicted as still images) of four different images of the heart for immediate evaluation and comparison.

muscle bundles are likewise noted. In any situation in which right ventricular hypertrophy occurs the trabeculations become more prominent. It is important to recognize this phenomenon to avoid confusing a heavily trabeculated right ventricle with tumor, vegetation, thrombus, or other mass.

The left ventricle is typically less trabeculated than the right, and other than the papillary muscles it is infrequent to note muscle trabeculations in the left ventricle. Occasionally, a trabeculated left ventricular apex is encountered, the degree of which rarely approaches that seen in the right ventricle. Not infrequently, pseudochordae are seen in the left ventricular apex. Anatomically, these are structures similar to mitral valve chordae but take an aberrant course,

Figure 7-9 Two-dimensional echocardiogram of the right ventricular inflow tract, recorded from the parasternal transducer position. Abbreviations are as per other figures.

typically across the apex of the left ventricle. They are less often seen in the left ventricular outflow tract. They are more easily visualized in patients with cardiomyopathy and dilated hearts than in normal hearts, where they may lie against the endocardium and therefore not be visible.

RIGHT AND LEFT ATRIAL STRUCTURES.

Several developmental remnants can be noted in the right atrium. These include the eustachian valve (Fig. 7-13) and Chiari network. In the embryo, a continuous membrane courses from the IVC to the coronary sinus to direct oxygenated blood from the IVC

directly across the foramen ovale. During cardiac development this membrane reabsorbs. In the majority of patients a small remnant known as the eustachian valve can be seen at the margin of the right atrial-IVC junction. A second remnant is occasionally seen attached to the coronary sinus. This is known as a Chiari network and consists of a fine filamentous membrane, with multiple perforations attached to the coronary sinus. On rare occasions, the complete eustachian valve is seen as a linear echo coursing from the IVC to the coronary sinus. In this instance it has multiple perforations and rarely, if ever, is truly obstructive. Either the eustachian valve or a Chiari network can result in redirection of blood flow within the atrium and unusual patterns of blood flow noted with contrast echocardiography.

The right atrial appendage is typically visualized only with transesophageal echocardiography (TEE). It is a more trabeculated structure than the left atrial appendage, and, on occasion, trabeculae in the right atrial appendage have been confused for thrombi. Recognizing the full range of appearance of the right atrial appendage is essential to avoid this error.

The left atrium has a smoother wall than the right atrium. The left atrial appendage is occasionally visualized from TTE, either in the apical two-chamber view or in a parasternal short-axis view. It is optimally visualized with TEE, where it has the appearance of a "dog's ear" (Fig. 7-14) . A substantial percentage of individuals have a multilobed

Figure 7-10 Two-dimensional echocardiograms recorded from the subcostal transducer position. The upper panel is a subcostal four-chamber view in which all four cardiac chambers are visualized as well as the plane of the mitral and tricuspid valves. The interatrial septum is visualized in its entire length in this view. The lower panel is recorded in a short-axis view at the level of the aortic valve from the subcostal position. The right atrium, tricuspid valve, right ventricle, and pulmonary artery are visualized as well as the circular aorta. The interatrial septum and inferior vena cava are both visualized in this view as well. Abbreviations are as per other figures; IVC = inferior vena cava; IAS = interatrial septum.

left atrial appendage, which can result in a confusing appearance because the septation between the two lobes may be confused for thrombus.[4]

ATRIAL SEPTUM.

The normal interatrial septum is visualized both in its primum and more superior portions, connected by thin tissue of the foramen ovale. There is substantial variation in the thickness and prominence of the more muscular primum and superior portions of the atrial septum. A commonly encountered anomaly of the atrial septum is lipomatous atrial hypertrophy in which there is benign infiltration by lipomatous tissue of the primum and superior atrial septum (Fig. 7-15) . The valve of the foramen ovale is spared, resulting in a "dumbbell" configuration of the atrial septum. The amount of infiltration is highly

variable and can range from less than 1.0 cm to 5 cm or more. The tissue is homogeneous and somewhat brighter than the normal atrial septum. It should not be confused with intracardiac tumor or thrombus.

Figure 7-11 Two-dimensional echocardiogram recorded from a suprasternal transducer position. The arch of the aorta as well as a portion of the ascending and descending aorta can be visualized. Note also the great vessels arising from the arch (arrows). DA = descending aorta; LCA = left carotid artery; LSA = left subclavian artery.

Quantification of Ventricular Performance

Echocardiography provides an excellent method for quantification of ventricular function. Linear measurements such as wall thickness, internal chamber dimension, and the derived parameters such as fractional shortening traditionally have been obtained from M-mode echocardiography. Normal values for adults and children are well established (Table 7-2) .[5] [6] [7] [53A] [55A] [55B] [65A] Global ventricular function and cardiac volumes can be measured with a variety of algorithms using two-dimensional echocardiography.[7A] The most commonly

Figure 7-12 Apical four-chamber view of the heart revealing a prominent moderator band. The moderator band (arrow) appears as a muscle density structure traversing the apex of the right ventricle (arrow). This is a normal anatomical structure that should not be confused with a pathological process.

Figure 7-13 Transthoracic parasternal echocardiograms recorded in a patient with a prominent eustachian valve (EV). This is a normal anatomical variant that should not be confused for a mass, vegetation, or other pathological structure. The top panel is a right ventricular inflow tract view recorded from the left sternal border. Both the right atrium and right ventricle can be seen, and the tricuspid valve is closed. Note the linear echo arising from the junction of the right atrium and inferior vena cava coursing into the body of the right atrium. In real time this linear echo has highly mobile motion, mimicking valvular motion. The bottom panel is recorded in a parasternal short-axis view at the base of the heart. The same linear echo is noted in the bottom of the right atrium (arrow).

employed method for quantitation of ventricular volume is Simpson's rule (Fig. 7-16) . Once the chamber volumes have been determined, ejection fraction can be calculated. Calculation of ejection fraction represents only a small aspect of quantification of ventricular performance. Determination of left ventricular volume requires manual tracings of the endocardial border in diastole and systole. Instrumentation exists that can automatically determine the endocardial border and calculate volumes and ejection fraction (Fig. 7-17)[8] Application of this technology requires high-quality images with a favorable signal-to-noise ratio. These automatically determined ventricular volumes can

be combined with arterial pressure measurements to create pressure-volume loops for more sophisticated evaluation of ventricular performance.[9] [10]

Figure 7-14 Transesophageal echocardiogram recorded at a 30-degree angle demonstrating the appearance of normal left atrial appendage. The body of the left atrium is at the apex of the scan and the normal "ear-shaped" left atrial appendage can be seen communicating with the body of the left atrium (arrow).

Figure 7-17 Apical four-chamber image in which an algorithm for automatic border detection has been used to determine instantaneous left ventricular volume. The white line outlining the endocardial border has been automatically drawn by the ultrasound machine. A graphic output of instantaneous ventricular volume and calculated ejection fraction is presented below the echocardiographic image.

Left ventricular mass can be measured by several different methods. One of the earliest was the "cube" method, which used M-mode septal, posterior wall, and left ventricular internal dimensions and assumed normal ventricular geometry.[7] [11] [11A] More recently, several two-dimensional

Figure 7-15 Transesophageal echocardiogram recorded in a patient with lipomatous atrial septum. From the transthoracic view, marked homogeneous thickening of the atrial septum is noted. In the transesophageal echocardiogram this can be appreciated as disproportionate infiltration and thickening of the basal and primum portions of the atrial septum with relative sparing of the area of the foramen ovale.

TABLE 7-2 -- NORMAL VALUES OF M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS IN ADULTS

	RANGE (cm)	MEAN (cm)	NO. OF SUBJECTS
Age (years)	13 to 54	26	134
Body surface area (M^2)	1.45 to 2.22	1.8	130
RVD--flat	0.7 to 2.3	1.5	84
RVD--left lateral	0.9 to 2.6	1.7	83
LVID--flat	3.7 to 5.6	4.7	82
LVID--left lateral	3.5 to 5.7	4.7	81
Posterior LV wall thickness	0.6 to 1.1	0.9	137

Posterior LV wall amplitude	0.9 to 1.4	1.2	48
IVS wall thickness	0.6 to 1.1	0.9	137
Mid IVS amplitude	0.3 to 0.8	0.5	10
Apical IVS amplitude	0.5 to 1.2	0.7	38
Left atrial dimension	1.9 to 4.0	2.9	133
Aortic root dimension	2.0 to 3.7	2.7	121
Aortic cusps' separation	1.5 to 2.6	2.9	93
Percentage of fractional shortening-	34% to 44%	36%	20%
Mean rate of circumferential shortening (Vcf) or mean normalized shortening velocity	1.02 to 1.94 circ/sec	1.3 circ/sec	38

RVD = right ventricular dimension; LVID = left ventricular internal dimension; d = end diastole; s = end systole; LV = left ventricle; IVS = interventricular septum.

methods have been shown to provide enhanced accuracy, especially in abnormally shaped ventricles.[12]

Normal wall motion consists of simultaneous myocardial thickening and inward motion of the endocardium toward the center of the chamber.[13] The most common cause of a regional wall motion abnormality is myocardial ischemia or infarction. The extent of a wall motion abnormality can be measured in several different ways. Echocardiography is a tomographic technique that visualizes all of the cardiac walls. Traditionally for quantitative purposes the left ventricle is divided into 16 segments.[14] Each segment can be attributed to one of the three major epicardial coronary arteries (Fig. 7-18) . There is substantial overlap in the posterior segments and inferior and lateral apical segments. For each of these 16 segments a wall motion score can be assigned (Fig. 7-19) . This is a unitless hierarchical number in which 1 represents normal motion; 2, hypokinesis; 3, akinesis;

Figure 7-16 Apical four-chamber view from which left ventricular volume has been calculated using Simpson's rule. The endocardium has been traced and automatically subdivided into a series of discs. The volume of each of the discs is then calculated as disc area (pir^2) multiplied by the height of each disc. The volume of each separate disc is then summed to provide the volume of the ventricle (116 ml).

and 4, dyskinesis. Each wall is then assigned a score, and the average score for the 16 segments is then calculated. This number is directly proportional to the extent and severity of wall motion abnormalities. There are several variations on a wall motion score, including addition of scores for aneurysm, mild hypokinesis, and hyperkinesis.

The wall motion score can be calculated for all 16 segments of the left ventricle or separately for anterior and posterior segments, representing the left anterior descending and right plus circumflex coronary artery territories, respectively. An M-mode interrogation line can be used to quantify endocardial excursion and myocardial thickening in any targeted segment (Fig. 7-20) .

There are several more complex methods for quantification of left ventricular function. Most rely on tracing the endocardial border in diastole and systole in either a short-axis or apical view. Radians are then constructed from the center of mass, and either changes in radian length or changes in area subtended by an arc are then quantified. [15]

ABNORMALITIES OF SEPTAL MOTION.

The interventricular septum is a shared wall between the right and left ventricles, and thus its motion can be affected by processes in either ventricle. Myocardial ischemia and infarction cause a fairly characteristic absence of systolic thickening and dyskinesis of the septum. There are multiple nonischemic causes for septal wall motion abnormalities as well.

Conduction Disturbances.

Both left bundle branch block and Wolff-Parkinson-White syndrome,[16] with a septal pathway, can result in abnormalities of septal motion. Left bundle branch block characteristically causes an early systolic downward motion followed by relaxation of the ventricular septum and a secondary downward contraction. This is best appreciated with M-mode echocardiography. This phenomenon is most common in the proximal anterior septum and is less prominent in the distal septum. A similar pattern is seen in patients with ventricular pacing; however, the maximum location of abnormal motion is highly variable, depending on the location of the pacemaker lead.

Wolff-Parkinson-White syndrome results in ventricular preexcitation in a localized area of the left or right ventricle. The preexcited area contracts slightly earlier than the remainder of the heart and can be seen in the ventricular septal posterior or lateral walls. The abnormality associated with Wolff-Parkinson-White syndrome is less dramatic than that seen with left bundle branch block. Although newer

Figure 7-18 Schematic representation of a 16-segment division of the left ventricle and the associated coronary artery distributions.

two-dimensional scanning instruments have temporal resolution sufficient to detect an abnormality of wall motion due to a conduction disturbance, the high temporal resolution of M-mode echocardiography may be necessary for precise identification of the wall

motion abnormalities.

CONSTRICTIVE PERICARDITIS (see Chap. 50) .

Constrictive pericarditis interferes with the normal sequence of right and left ventricular filling and results in subtle septal wall motion abnormalities.[17] This typically causes early downward motion of the septum, followed by paradoxical motion. Multiple patterns of septal motion abnormalities have been noted in constrictive pericarditis. As with electrical conduction disturbances, these may be best identified with M-mode echocardiography.

VENTRICULAR OVERLOAD.

Either a volume or pressure overload of the right ventricle results in a ventricular septal motion abnormality.[18] In each instance the right ventricle is dilated. In a pure volume overload there is diastolic flattening of the ventricular septum so that the left ventricular geometry in diastole assumes a "D" shape rather than circular geometry. Because this is a low pressure phenomenon the left ventricle becomes circular in early systole before onset of ventricular ejection (Fig. 7-21) . A right ventricular pressure overload results in flattening of the septum not only in diastole but also in systole. The degree of flattening is directly proportional to the elevation in right ventricular systolic pressure. Frank reversal of septal curvature is seen in individuals with systemic level right-sided heart pressures.

A final septal motion abnormality that is commonly encountered is the "postoperative septum." This abnormality is characterized by paradoxical anterior motion of the septum in systole, with preserved myocardial thickening. Often posterior wall excursion appears exaggerated.[19] This phenomenon may be seen in any form of cardiac surgery in which the pericardium has been opened. It often resolves 3 to 5 years after surgery.

Doppler Principles and Equations

The Doppler principle states that the frequency of ultrasound reflected from a stationary object is identical to the transmitted frequency. If an object is moving toward the transducer, the reflected frequency will be higher than the transmitted frequency; and conversely if an object is moving away from the transducer, the reflected frequency will be lower. The difference between the transmitted and received frequencies is the Doppler shift (Fig. 7-22) . The magnitude of the Doppler shift is determined by the velocity and direction of the moving object and can be calculated by the Doppler equation. The Doppler equation relates the angle of interrogation, the Doppler shift, or change in frequency between the transmitted and reflected frequency, and a constant that is equal to the speed of sound in water, to the velocity and direction of the moving object (Fig. 7-23) . A major contributor to this equation is the angle theta, with which the interrogating beam intercepts flow. For

Figure 7-19 Typical wall motion score presentation. For each of the 16 segments a score of 1 to 4 has been assigned, representing normal or abnormal wall motion. The scores are then summed and averaged to calculate an overall wall motion score that is directly proportionate to the size and severity of the wall motion abnormality.

maximum accuracy, interrogation should be directly in the line of flow, that is, theta = 0 degrees. Because the cosine of 0 degrees = 1.0, solving the Doppler equation is a fairly straightforward process. With increasing angle theta the cosine becomes progressively less than 1.0 and when incorporated into the equation results in a systematic and increasingly severe underestimation of the true velocity. For practical purposes an angle of interrogation less than 20 degrees is essential to ensure clinically accurate information. Most modern instrumentation contains algorithms for correcting theta when it is not equal to 0 degrees. Unfortunately, the true direction of the laminar flow is often not known, and attempts at correction are likely to result in creation of additional error. For the purposes of cardiac imaging, Doppler echocardiography is most commonly employed for determining the direction and velocity of red blood cells moving

Figure 7-20 M-mode echocardiogram recorded in a patient with severe left ventricular systolic dysfunction. Note the dilated left ventricle and a decreased excursion of the septum and posterior wall compared with the normal example seen in Figure 7-1 . There is additional evidence of left ventricular systolic dysfunction in that the mitral valve E point septal separation is increased (double-headed arrow). Evidence of elevated end-diastolic pressure is noted in the "B bump" (arrowhead), which delays final closure of the mitral valve.

Figure 7-21 Short-axis two-dimensional echocardiogram depicting a right ventricular volume overload pattern. Compare the normal geometry of the left ventricle in a short-axis view (see Fig. 7-5) to that noted here. In the right ventricular volume overload pattern there is dilation of the right ventricle and flattening of the ventricular septum (downward pointing arrows) so that in diastole the ventricle takes on a "D"-shaped configuration rather than circular geometry. With systole there is restitution of normal circular geometry (upward arrows).

within the cardiovascular system. By convention, motion toward the transducer is recorded as a signal above the zero velocity line and motion away from the transducer as a signal below this line (Fig. 7-24) .

CALCULATION OF PRESSURE GRADIENTS.

Once the velocity of the target has been determined, this information can be used to determine pressure gradients across a restrictive orifice using the Bernoulli equation.[20] The Bernoulli equation contains multiple elements, including convective acceleration and viscous friction (Fig. 7-25) . Of note, convective acceleration and viscous friction are relatively weak contributors in most biological systems and can

Figure 7-22 Demonstration of the Doppler effect. In each instance the transmitted ultrasound beam is denoted emanating from the upper transducer and the returning beam off of the reflecting object (dark circle) coming to the lower transducer. The upper panel depicts a stationary target in which the transmit frequency (f_t) is equal to the returning frequency (f_r) and there is no Doppler shift. The middle panel depicts an object moving toward the transducer in which the returning frequency (f_r) is greater than the transmit frequency (f_t). In the lower schematic the object is moving away from the transducer and the returning frequency (f_r) is less than the transmit frequency (f_t). The Doppler shift (f_d) equals the difference between these two frequencies. *(From Feigenbaum H: Echocardiography. 4th ed. Malvern, PA, Lea & Febiger, 1986.)*

be effectively ignored. The Bernoulli equation in its simplest form states that DeltaP (the pressure gradient across a restrictive orifice) = $4V^2$, where V = the peak instantaneous velocity of flow through the restrictive orifice. In reality, the equation incorporates not only the peak instantaneous velocity at the restrictive orifice but also the velocity noted

Figure 7-23 Demonstration of the Doppler equation for determining the velocity of a moving object. The Doppler shift (f_d) is calculated as the difference between the returning (f_r) and transmit (f_t) frequencies. The Doppler equation relates the Doppler shift (f_d) to the transmit frequency, the angle of interrogation (theta), the velocity of the moving object (V), and the speed of sound (C). The equation can be rearranged to solve for velocity as is noted in the third equation above. *(From Feigenbaum H: Echocardiography. 4th ed. Malvern, PA, Lea & Febiger, 1986.)*

Figure 7-24 Combination of aortic stenosis and aortic insufficiency demonstrating the directional nature of spectral Doppler. The continuous-wave Doppler is recorded from the apex of the left ventricle along a line oriented through the aortic valve. Aortic stenosis is present with a peak velocity of 4 m/sec (400 cm/sec) that is directed away from the transducer and hence recorded below the zero crossing line. Aortic insufficiency is also present and is noted as a diastolic signal recorded above the zero crossing line. AI = aortic insufficiency; AS = aortic stenosis.

in the acceleration zone, V2. For most clinically relevant conditions such as severe

aortic stenosis, V1 is substantially greater than V2 and hence V2 can effectively be ignored. There are several instances in which the V2 velocity must be included. These include the obvious case of a serial obstruction, as well as other situations in which V2 is relatively large compared with V1, such as in milder degrees of aortic stenosis and aortic stenosis combined with aortic insufficiency.

THE BASIC DOPPLER EXAMINATION: NORMAL FLOW PATTERNS.

All four cardiac valves can be interrogated using either pulsed or continuous-wave Doppler and substantial physiological data derived from the recorded signals.[20] Figure 7-26 is a representation of normal Doppler flow patterns across the aortic and mitral valves. Highly sensitive Doppler instrumentation frequently picks up mild amounts of physiological regurgitation, which is more common for the tricuspid and pulmonic than the aortic and

Figure 7-25 The Bernoulli equation can be used to calculate a pressure gradient across any restrictive orifice. The components of the Bernoulli equation are convective acceleration, flow acceleration, and viscous friction. The full equation can be modified to $P1 - P2 = V_2^2 - V_1^2 \times 4$ and further simplified in the absence of a significant V_1 velocity to $\Delta P = 4V^2$. P2 = pressure diastole to an obstruction; V_2 = Doppler velocity diastole to an obstruction; V_1 = velocity proximal to an obstruction; P1 = pressure proximal to an obstruction. *(From Feigenbaum H: Echocardiography. 4th ed. Malvern, PA, Lea & Febiger, 1986.)*

Figure 7-26 Pulsed Doppler spectral recordings of normal mitral and aortic valve flows. The top panel is recorded from the left ventricular apex and shows normal mitral valve inflow with a relatively higher E than A velocity. The bottom panel is also recorded from the left ventricular apex and shows flow moving away from the transducer in the left ventricular outflow tract with a peak velocity of approximately 1 m/sec.

mitral valves. In the normal heart under physiological circumstances, the maximum velocity typically encountered is approximately 1.6 m/sec. Pulmonary vein and hepatic vein flows can also be recorded in the majority of patients (Fig. 7-27) .

PULSED VERSUS CONTINUOUS-WAVE DOPPLER.

Doppler ultrasonography is used in two basic methods. The first is pulsed Doppler, which can be considered a "steerable stethoscope" in which a sample volume of variable size can be superimposed on the two-dimensional echocardiographic image. Range gating is used to ensure that only Doppler shifts from one discrete site are interpreted for velocity calculations. Thus, pulsed Doppler allows determination of direction and flow velocity at a precise point within the cardiac system. It is limited,

however, in its maximum velocity by the Nyquist limit. The Nyquist limit is defined as the pulse repetition frequency divided by 2. For typical imaging systems the maximum recordable velocity with a pulsed rate system is 1.5 to 2 m/sec. Many stenotic and regurgitant velocities exceed this limit, at which point the spectral display is paradoxically recorded as a velocity in the opposite direction of the moving target. This phenomenon is known as "aliasing" (Fig. 7-28) . [21]

Continuous-wave Doppler imaging continuously interrogates the returning ultrasound beam for Doppler shifts. The line of interrogation is identifiable; however, the precise location of the maximum velocity must be deduced by integrating the interrogation line direction with known cardiac anatomy. Whereas continuous-wave Doppler imaging provides less precise localization of gradients, it is not limited by velocity limits and hence can record velocities exceeding those anticipated in a biological system.

MULTIGATE DOPPLER.

In an effort to increase the maximum velocity detectable with pulsed Doppler, a technique of multigating can be employed in which multiple pulsed gates are simultaneously employed, thus increasing the effective Nyquist limit.[22] Multigate Doppler allows detection of velocities as high as 3.5 to 5 m/sec with the ability to identify one of the gates as the site of origin. In large part, multigate Doppler has been fully supplanted by steerable continuous-wave Doppler methodology.

COLOR FLOW DOPPLER.

Color flow Doppler imaging represents a variation on multigate pulsed Doppler imaging and thus is subject to its velocity limitations. In color flow Doppler, instead of only a single site being interrogated for a Doppler shift, a variable-sized matrix of sampling points can be created and used to simultaneously interrogate velocity

Figure 7-27 Normal pulmonary (upper panel) and hepatic (lower panel) vein flows. Nearly continuous, multiphasic flow is seen in the normal pulmonary and hepatic veins. Note that there is higher velocity of pulmonary vein inflow during ventricular systole then during diastole.

Figure 7-28 Pulsed *(top)* and continuous-wave *(bottom)* Doppler recording of mitral regurgitation. The lower panel recorded with continuous-wave Doppler is free of the aliasing phenomenon, and the true peak velocity of the mitral regurgitation jet (5.5 m/sec) is fully displayed. The top panel was recorded in pulsed Doppler, which results in "aliasing." Once the velocity has exceeded the Nyquist limit (in this case 1.6 m/sec) the signal is paradoxically displayed above the zero crossing line.

over a large area of the heart. Because this represents multiple pulsed sample volumes, each of which must be independently interrogated, frame rates are relatively low in Doppler flow imaging. Color flow imaging is the display solution for managing the data that are derived from thousands of sample sites simultaneously. The typical color flow display algorithm involves displaying velocities toward the transducer in varying shades of red and those heading away from the transducer in varying shades of blue with either the intensity or hue paralleling the actual velocity.[23] [24] If multiple velocity shifts are present at an interrogation point, this is defined as "variance" and may be colored in a yellow or green confetti-like image. Normal color flow Doppler findings include the ability to track mitral and tricuspid inflow patterns and left and right ventricular outflow. Normal mitral inflow appears as a red encoded signal moving from the mitral orifice along the lateral wall to the left ventricular apex, where it reverses course and appears as a blue encoded signal along the septum. The flow profile accelerates with atrial systole. With systole the organized flow in the left ventricular outflow tract appears as a series of color shifts as the accelerating flow exceeds the relatively low Nyquist limit of color Doppler imaging. Pathological flow will be detected either as turbulence due to a restricted orifice, as pathological flow through an abnormal communication (e.g., an atrial septal defect), or as a regurgitant flow signal in a downstream chamber. The above represents traditional color flow imaging algorithms. In reality, multiple different color schemes and variance maps can be employed. It should be emphasized that the visualized jet area is heavily dependent on Doppler gain settings. At higher heart rates, the relatively low frame rate of color flow imaging also compromises accuracy. Substantial experience and attention to technical detail is essential to provide accurate clinical information from color flow Doppler imaging.

DOPPLER CALCULATION OF RIGHT VENTRICULAR SYSTOLIC PRESSURE.

Obviously, application of the Bernoulli equation allows calculation of gradients across stenotic valves, but likewise it can be used to calculate a gradient between any high-pressure and low-pressure chamber. A commonly used application of the Bernoulli equation is the determination of the right ventricular systolic pressure.[25] Tricuspid regurgitation is very common in many disease states. By determining the peak velocity of a tricuspid regurgitation jet one can then calculate the right ventricular to right atrial pressure gradient (Fig. 7-29) . A key component of this is estimation of right atrial pressure. Approaches to this determination include assigning an empirical constant, assigning a floating constant of 5, 10, or 15 mm Hg (depending on the size of the right atrium, severity of regurgitation, and appearance of the inferior vena cava), or assigning a floating constant of 10 percent of the peak gradient. Each of these methodologies appears to result in satisfactory estimation of intercardiac pressure.

CALCULATION OF FLOW.

Because the Doppler spectral profile provides a highly accurate measure of the velocity of the moving blood, this value when combined with a measured or calculated area can provide data regarding actual volumetric flow (Fig. 7-30) . Multiplying the cross-sectional area of the flow times the velocity time integral yields the actual volume of flow during that pulse interval. If the left ventricular outflow tract is interrogated, this value then represents the stroke volume of the left ventricle.[26] [27] This, in turn, can be used to

calculate cardiac output. The greatest source of error in this calculation is often determination of the cross-sectional area of the left ventricular outflow tract, which may not assume circular geometry. Additionally, because of the formula for determining area from diameter ($A = pir^2$), any error in measuring the diameter of the flow channel is squared. Thus, determination of stroke volume and cardiac output may have greater clinical value in following serial trends than in precise

Figure 7-29 Measurement of right ventricular systolic pressure using the tricuspid regurgitation jet. The gradient between the right ventricle and right atrium ($P_1 - P_2$) can be calculated from the velocity of the tricuspid regurgitation jet using the modified Bernoulli equation ($DeltaP = 4V^2$). Actual right ventricular systolic pressure is then calculated as the sum of the pressure gradient between the two chambers and an assumed right atrial pressure (P_{ra}). Right atrial pressure can be estimated from examination of the jugular veins, by evaluation of the inferior vena cava for collapse during inspiration, or by using an empirical or floating constant (see text for further details). *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

Figure 7-30 Principle of Doppler determination of volumetric flow. Flow through the tubular object can be calculated as area (A) times mean velocity (V). This phasic flow times the heart rate (HR) equals cardiac output (CO) in a biological system. The velocity is determined from the pulsed Doppler signal. The instantaneous stroke volume can be determined on a beat-by-beat basis; in addition, stroke volume multiplied times heart rate yields cardiac output. The cross section or area can be either directly measured or calculated from the diameter of the circular structure. *(From Feigenbaum H: Echocardiography. 4th ed. Philadelphia, Lea & Febiger, 1986.)*

determination of volumetric flow. For clinical purposes, however, this remains a valuable technique. Similar calculations of flow volume can be performed for the pulmonic and mitral valves as well.[28]

An expansion of volume flow calculation involves the "continuity equation" (Fig. 7-31) . The underlying principle of the continuity equation is that the volume of flow entering a channel must equal the volume of flow exiting that channel.[29] If the cross-sectional area is equal at the entrance and exit points, then flow velocity will likewise be equal at those two points. If, however, the cross-sectional area decreases at the downstream site, then, of necessity, velocity must increase to maintain the same volumetric flow. The continuity equation can be applied for determination of aortic valve area in aortic stenosis and less often for mitral valve area or other conditions.

The relatively low Nyquist limit of color Doppler flow imaging can be used to determine volumetric flow as well. Flow converging on a relatively restrictive area will accelerate as it nears the downstream exit. Because of the relatively low Nyquist limit of color flow Doppler imaging, this results in a series of aliasing lines where the color flow signal will alternately change from blue to red. By purposely utilizing relatively low Nyquist limits

and expanded views, the echocardiographer can determine the distance from the actual flow exit point to one of the aliasing lines. Because the velocity at which flow aliases is known, the velocity of flow at that point is likewise known. If one assumes that flow converges at equal velocities symmetrically toward an orifice, then by applying the geometric formula for a hemisphere one can determine the surface area of flow in motion at any of the aliasing points that represents identifiable velocities (Fig. 7-32). From this, one can then calculate the actual volume of flow from this proximal isovelocity surface area as velocity times surface area.[30] [31] In general terms, for any given Nyquist limit the larger the proximal isovelocity surface area, the greater the amount of flow involved. Therefore, quantitation of proximal isovelocity surface area allows an additional clue as to the volume of regurgitant flow. Proximal isovelocity surface area calculations can be performed for any flow that accelerates toward a relatively restrictive orifice, including mitral regurgitation, aortic insufficiency, and shunt lesions. The major limitation of the use of proximal isovelocity surface area is the assumption that flow moves in a hemispherical manner. This assumption is true only for flow converging on a relatively flat surface. If flow is channeled through a funnel, corrections must be made for a surface area less than a full hemisphere.

Figure 7-32 Demonstration of the proximal isovelocity surface area method for determining flow. The figure on the right is a color flow image of the acceleration of flow toward a regurgitant orifice in a patient with mitral regurgitation. Note the sequential shift in color from blue to red and back to blue. The boundary between blue and red represents an aliasing line at which velocity has exceeded the Nyquist limits, which are displayed on the color bar. The schematic on the left outlines the calculations necessary to determine flow. For any given aliasing line a hemisphere of flow is assumed. The surface area of a hemisphere is calculated as $2\ pir^2$. Flow is equal to the product of the surface area times the velocity, which is determined from the Nyquist limit.

Close inspection of a regurgitant jet between either ventricle and its corresponding atrium can also provide clues to ventricular performance. It should be recognized that in early systole ventricular pressure exceeds atrial pressure by a wide margin and thus ejection of blood into the downstream atrium is at low resistance, resulting in a high dP/dt that corresponds to the forcefulness of ventricular contraction.[32] [33] If myocardial failure occurs, the ability of the ventricle to eject forcefully is compromised and dP/dt decreases. This is also noted in spectral Doppler echocardiography of continuous-wave ejection parameters by a decrease in the ejection velocity slope (Fig. 7-33). Actual dP/dt can be calculated by determining the time in milliseconds between a regurgitant velocity of 1 and 3 m/sec. This corresponds to a pressure difference of 32 mm Hg. If the time over which this pressure difference is obtained is measured, a noninvasive dP/dt can be calculated.

Figure 7-31 Principle of using Doppler calculations for the continuity equation to determine the area of the stenotic orifice. The continuity equation stipulates that the volume of flow entering a tubular chamber must equal that exiting it. Because flow equals volume times area at each end of the flow stream, the calculation for flow at each end can be solved for the unknown restricted orifice area (A_2). A_1 = area proximal to the stenosis; A_2 = area of stenosis; V_1 = velocity proximal to the stenosis; V_2 = velocity

through the stenosis.

Figure 7-33 Use of the mitral regurgitation spectral display to determine positive and negative dP/dt of left ventricular contraction. The spectral mitral regurgitation jet is displayed at high sweep speed to maximize temporal resolution. The time in milliseconds required for velocity to increase from 1 to 3 m/sec is then measured. This time is then divided into 32 mm Hg (the pressure difference between 1 and 3 m/sec) to determine dP/dt noninvasively.

The continuous-wave spectral profile can also provide clues as to the nature of obstruction in many disease states. It should be emphasized that the spectral profile provides high temporal resolution for determining the timing of pressure gradients. Thus, the contour of the spectral profile provides clues as to whether an obstruction is fixed or develops over time, in which case the peak gradient will occur late rather than early.[34] The latter is classic for dynamic obstruction in hypertrophic cardiomyopathy. Close examination of a regurgitant profile can also reveal evidence that atrial pressure has acutely elevated toward the end of ejection when velocities taper off rapidly in the latter half of systole.

Much attention has been paid to mitral valve inflow patterns as they relate to diastolic function of the left ventricle.[35] [36] [37] [37A] This assessment must be done in patients who are in sinus rhythm, during which there are discrete E and A wave velocities of the mitral valve inflow. In normal individuals, early velocities exceed later velocities and the E to A ratio is typically greater than 1.2. With impaired relaxation of the left ventricle this ratio declines and the rate of decay of the E wave velocity likewise decreases. Figure 7-34 schematizes several mitral valve Doppler inflow patterns. There are a number of other influences on the E to A ratio, including age and heart rate. With a pathological increase in left ventricular stiffness accompanied by excess volume, there is an augmentation of the normal E to A ratio. This increased E to A ratio is classic for a restrictive cardiomyopathy and constrictive pericarditis but is also typically seen in patients with end-stage heart disease of virtually any type who have markedly elevated diastolic pressures. It is imperative to incorporate the anatomical and other Doppler information into an assessment of mitral valve inflow patterns in an effort to provide clinically relevant information. Evaluation of mitral valve closure patterns with M-mode echocardiography can provide additional information on intracardiac hemodynamics.[38]

Doppler can be used to evaluate the inflow patterns of the hepatic and pulmonary veins as well.[39] [40] Both hepatic and pulmonary vein inflow are biphasic with predominant flow in ventricular systole (see Fig. 7-27) . Examination of the flow patterns can provide valuable clues in a variety of disease states, including mitral regurgitation, restrictive and constrictive processes, and other diseases that elevate left ventricular diastolic pressure.

Figure 7-34 Schematic depiction of mitral valve and pulmonary vein inflow patterns. *A,* A normal mitral valve inflow pattern with both early (E) and atrial contraction related (A) flow velocities. Note that the E velocity exceeds the A velocity in the normal situation. The isovolumetric relaxation time (IVRT) is as noted. The deceleration time (DT) is defined as the milliseconds from peak E-wave velocity to zero velocity. *B,* The same, normal mitral valve inflow pattern on which normal pulmonary vein flow velocities have been superimposed. Note that systolic pulmonary vein flow (PVs) exceeds the velocity of diastolic pulmonary vein flow (PVd) and that there is a normal amount of retrograde pulmonary vein flow (PVa) related to atrial contraction. *C,* The mitral valve inflow and pulmonary vein flow pattern in a noncompliant stiff ventricle with poor relaxation. There is a characteristic decrease in the E to A ratio of the mitral valve inflow pattern associated with a decrease in the diastolic component of pulmonary vein flow. *D,* The example of "restrictive physiology" with decreased left ventricular compliance and high left atrial pressures. Note the exaggerated E to A ratio and the short deceleration time of mitral valve E-wave flow. The diastolic component of pulmonary vein flow is accentuated and the systolic component decreased, and the pulmonary vein retrograde flow during atrial contraction is also accentuated. *E,* The situation of "pseudo-normalization" in which the mitral valve inflow pattern falls between that seen in *C* and *D* and thus mimics the normal mitral valve inflow seen in *A.* Pulmonary vein flow, however, remains abnormal, with a relative predominance of diastolic pulmonary vein flow compared with the systolic flow. There is also accentuation of pulmonary vein retrograde flow during atrial systole.

SPECIFIC IMAGING FORMATS AND TECHNIQUES

TRANSESOPHAGEAL ECHOCARDIOGRAPHY.

For this technique the ultrasound transducer has been miniaturized and mounted on the tip of a flexible gastroscope-like instrument. The mechanics of the instrument allow both flexion and lateral motion of the tip to optimize views. Early TEE probes provided only a single plane of interrogation, with subsequent probes providing two perpendicularly oriented planes that could be viewed in alternate fashion. Modern TEE probes contain an array of ultrasound crystals at the tip of the probe that allow rotation of the ultrasound scanning plane through 360 degrees.

There are specific indications and contraindications to TEE as well as well-recognized inherent risks. TEE is indicated in patients in whom TTE is either unlikely to provide diagnostic information or has been nondiagnostic. Specific examples in which TEE is of proven incremental yield include detection of aortic dissection, evaluation of the mechanism of mitral regurgitation, and evaluation of patients for source of cardiac emboli. TEE is relatively contraindicated in individuals with significant esophageal pathology.

TEE is typically performed under intravenous conscious sedation after local anesthesia of the oropharynx. The exact choice of intravenous agents is institutionally dependent but frequently consists of a combination of narcotics and a benzodiazepine agent. Complications associated with TEE include those associated with the agents used for conscious sedation as well as complications related to the mechanical aspects of probe insertion. The latter can involve trauma to any aspect of the teeth, gums, oropharynx, or esophagus. Esophageal complications are most likely to arise in individuals with

preexisting esophageal disorders; and trauma to the oropharynx, teeth, and gums is more likely in patients who are uncooperative.

There are a family of fairly standardized views that are obtained during the TEE examination.[41] Most echocardiographers begin by examining the heart from behind the left atrium because this view provides a fairly rapid means for

Figure 7-39 Routine gray scale and color B-mode scans demonstrating the enhanced visual sensitivity for faint signals. The upper panels are two views of a left atrial appendage recorded in a patient with atrial fibrillation; the left panel is recorded in routine gray scale. There are very vague ;qosmokelike;qc echoes swirling within the body of the left atrial appendage consistent with stagnant blood. The right-hand panel was recorded in the same patient at the same gain and dynamic range settings but using color encoded imaging. Note the greater ease with which the low intensity echoes are visually depicted. The two bottom panels represent spectral Doppler of aortic insufficiency recorded in gray scale *(bottom left)* and in B-color *(bottom right),* again demonstrating the greater ease of visual detection with the color encoded signal.

orienting the operator. Figures 7-35 and 7-36 outline views in the horizontal and longitudinal planes that correspond to 0- and 90-degree scanning planes using a multidirectional rotating transducer. Figures 7-37 and 7-38 are transesophageal echocardiograms recorded from several of the transducer positions schematized in Figures 7-35 and 7-36 .

COLOR B-MODE SCANNING.

In an effort to enhance visual detection of anatomical boundaries and spectral Doppler signals, the fundamental gray scale image can be colorized.[42] This has shown promise for detection and tracking of endocardial boundaries and for visualization of faint spectral Doppler signals (Fig. 7-39).

HARMONIC IMAGING.

A recent adaptation of cardiac ultrasonography relies on the generation of harmonic frequencies during transmission of the ultrasound beam.[43] [44] [45] [45A] [45B] Traditionally, transducers have had narrow bandwidth ultrasound elements that transmit and receive at narrowly defined frequencies. Modern transducers have a wide bandwidth that allows transmission and receipt of ultrasound over a broad range of frequencies. The traditional view of harmonics is that an object once insonated with ultrasound may resonate and hence reflect back ultrasound not only at the fundamental, transmitted frequency but also at harmonics of that frequency. In the traditional view of harmonics an object can be imaged at 2 MHz but reflect ultrasound back at 2 MHz and at 4- and 8-MHz harmonics. Recently, it has been recognized that the transmission of ultrasound through tissue actually creates harmonic frequencies during propagation. Because the transmitted frequency is not a narrow discrete frequency but rather a broad range of frequencies, the full range of reflected frequencies and the resultant harmonics are likewise substantially broader than originally conceived. This is the premise for what has

been termed *tissue harmonic imaging.* Harmonic frequencies increase in strength with depth of penetration but represent

Figure 7-35 Schematic demonstrating the transesophageal echocardiographic images that can be obtained in a horizontal plane. Figures 2A and 2B are obtained from the transgastric location, 3A and 3B from the midesophageal position, and 1A and 1B from the upper esophageal position. (Images can be displayed with the apex of the sector either up [A figures] or the apex down [B figures].) Echocardiographic images corresponding to figures 1A, 2A, and 3A are presented in Figure 7-37 . RPA = right pulmonary artery; SVC = superior vena cava; LPA = left pulmonary artery; IVC = inferior vena cava; S = stomach; FO = fossa ovalis; other abbreviations are as per previous figures. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

Figure 7-36 Transesophageal echocardiographic views obtained in the longitudinal transducer position. The A series of figures are recorded with the apex down and the B series with the apex up. 3A and 3B are recorded in the gastric position, 2A and 2B from the midesophagus, and 1A and 1B from the upper esophagus. LUPV = left upper pulmonary vein; LAA = left atrial appendage; other abbreviations are as per previous figures. *(From Feigenbaum H: Echocardiography, 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

only a small portion of the total reflected ultrasound energy. The advantage of the reflected harmonic frequencies is that they are free of near-field reverberation and shadowing effect. This results in an increased signal-to-noise ratio of the harmonic signal (Fig. 7-40) . This type of imaging shows tremendous promise for improved visualization of the myocardium but at the cost of a minor reduction in resolution. Additionally, tissue signature is brighter than usual and there is loss of detail for evaluation of fine valvular structures.

COLOR M-MODE.

Color M-mode echocardiography combines routine M-mode scanning with superimposed color Doppler information. As with M-mode echocardiography, the *x* axis represents time and the *y* axis represents distance from the transducer. The M-mode component is identical to that previously discussed for routine M-mode echocardiography. Along the single line of interrogation, Doppler information is then color encoded and superimposed on the M-mode display (Fig. 7-41). This technique provides high temporal resolution for timing cardiac events and can have particular value in determining the timing of a regurgitant valvular lesion and in determining the rate of inflow into the left ventricle.[45C] [45D] It is limited in that it provides information regarding velocity of flow in only one dimension.

CONTRAST ECHOCARDIOGRAPHY.

Ultrasound reflects off all structures but increasingly off structures with different acoustic properties.[46] Thus, a tissue fluid interface is a more potent reflector of ultrasound than the interior of a solid structure. An even more potent reflector of ultrasound is a gas/fluid interface, such as can be created by microcavitations or bubbles. Contrast echocardiography is a complex field currently in evolution. The simplest contrast agent is agitated saline, created by forcefully injecting saline mixed with a small quantity of air between two syringes. This creates a solution of microbubbles that are 30 to 200 mum in diameter. The resultant microbubbles are intrinsically unstable and subject to coalescence, and their effect is relatively transient. Their large size precludes passage through the pulmonary bed. Agitated saline contrast is the standard technique for detection of intracardiac shunts.[47] Because

Figure 7-41 Color M-mode echocardiography. With this methodology color flow imaging is superimposed on an M-mode echocardiogram. This provides excellent temporal resolution for timing intracardiac events. The left panel was recorded in a normal, disease-free individual from the apex of the left ventricle. Notice that both early and late (E and A) mitral inflow can be detected. The systolic interval (white arrowheads) is devoid of flow. The right panel was recorded in a patient with mitral valve prolapse and late systolic mitral regurgitation. Note the prominent early flow velocity through the mitral valve and a late systolic regurgitant flow (white arrowheads).

saline microbubbles are too large to pass through the pulmonary capillary bed,[48] their appearance in the left side of the heart is indirect evidence of a pathological intracardiac shunt.[49]

Attempts at creating a more stable population of microbubbles have been undertaken for a number of years and have included stabilizing agitated saline with indocyanine green dye and creation of manufactured microbubbles. The available manufactured microbubbles have been based on albumin[50] or other protein spheres, and more recently the air has been substituted with a perfluorocarbon.[51] [52] Perfluorocarbon agents have low diffusibility and intense echo-reflective properties. These agents provide full and complete opacification of the left ventricular cavity after intravenous injection (Fig. 7-42) .[45A] [45B] [51] [52] [53] [53A] These agents can also be used to enhance spectral Doppler signals of both right- and left-sided valves.[54] [55] A role in detection of left ventricular and atrial appendage thrombus has recently been suggested.[55A] [55B] They have also shown tremendous promise for evaluation of myocardial perfusion. Myocardial perfusion echocardiography should be considered a developmental tool of immense promise rather than a routine clinical tool at this time.

Specialized imaging techniques are necessary to optimize contrast detection. Compared with fundamental imaging, harmonic imaging is substantially more sensitive for detection of contrast medium in the ventricular cavity and myocardium. It has recently been recognized that contrast microbubbles are destroyed by interaction with the ultrasound beam, especially at high-energy levels.[56] Intermittently triggering the imaging beam avoids this destruction and results in more effective detection of ultrasound contrast.[57] [58] Use of a low mechanical index also results in less bubble

destruction.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY.

There are two basic approaches to three-dimensional echocardiography. The first is to compile a series of sequential two-dimensional scans using either an external frame of reference or internal transducer locator to then create a three-dimensional matrix of the cardiac image.[59] [60] [61] This can then be surface rendered to create an actual three-dimensional image of the cardiac structures (Fig. 7-43) , or the three-dimensional data set can be "resliced" to provide a secondary two-dimensional image along any imaging plane. The second approach to three-dimensional imaging has

Figure 7-37 Transesophageal echocardiograms recorded in a horizontal plane. The upper and lower panels were recorded in a true 0-degree plane at a high level behind the left atrium and at a midesophageal level, respectively. In the left atrial view a typical four-chamber view of the heart is obtained in which all four cardiac chambers as well as the mitral and tricuspid valves are clearly visualized. The lower panel was recorded at 0 degrees with the probe inserted deeper in the esophagus. A typical short-axis view of the left ventricle is obtained in which a circular left ventricle and crescent-shaped right ventricle are seen. This view is analogous to a parasternal short-axis view; however, the orientation is inverted such that the inferior wall is at the top of the image and the anterior wall at the bottom. The bottom panel was recorded at 35 degrees and with pull back of the transducer slightly from the position needed for the upper panel. This provides a short-axis view at the base of the heart at which the circular aorta with an open aortic valve is clearly visualized.

been real-time three-dimensional imaging in which a transducer creates an actual three-dimensional volume of interrogation.[62] [63] [64] This three-dimensional data set can then be rendered into a three-dimensional image, or secondarily two-dimensional imaging planes can be derived. Three-dimensional imaging has advantages with respect to quantitative precision in unusually shaped ventricles and in accurate anatomical description of complex anatomy such as complex congenital heart disease.[60] [61] [65] [65A] It is still limited by relatively low frame rates and/or the time required for processing the three-dimensional image.

INTRAVASCULAR ULTRASONOGRAPHY.

Intracardiac ultrasonography is a discipline largely employed by the invasive

Figure 7-38 Transesophageal echocardiographic images recorded in view orthogonal to the horizontal images seen in Figure 7-37 . The top panel is recorded at the same level in the esophagus as the top panel in Figure 7-37 at a 95-degree angle. In this view the left atrium and left ventricle as well as left atrial appendage (LAA) are clearly visualized. Distinct scallops of the closed mitral valve are also well seen. The middle panel is likewise recorded at the same level in the esophagus with rotation of the probe

clockwise. In this view the left atrium and right atrium as well as inferior vena cava (IVC) and superior vena cava (SVC) are clearly visualized. The bottom panel was recorded at 135 degrees. This view provides excellent visualization of the left ventricular outflow tract and proximal aorta.

Figure 7-40 Parasternal long-axis view recorded in both fundamental *(top)* and second harmonic imaging *(bottom).* The orientation of this image is identical to that in Figure 7-3 . Note the marked increase in echogenicity of the septum and posterior wall, as well as increased echo density of the aortic and mitral valves. In this example, tissue harmonic imaging has provided an obvious distinction between the blood pool and myocardium, compared with fundamental imaging. Abbreviations are as per previous figures.

cardiologist in the catheterization laboratory. This ultrasound technique relies on ultraminiaturization of ultrasound transducers that are then incorporated into the tip of intracardiac catheters. The catheters can be as small as 5 French for intracoronary work or as large as 10 or 12 French, which can be used inside cardiac chambers.[66] [67] Typically, either a phased array of crystals is placed circumferentially around the catheter tip or a single crystal, often reflected by a mirror, is mechanically rotated at the tip of a catheter. In either instance, high frequencies of 10 to 40 MHz are used. The smaller catheters can be placed, through a guiding catheter, into epicardial coronary arteries. They provide a high-resolution view of intracardiac anatomy (Fig. 7-44) and have provided previously unavailable visualization of morphology within the coronary artery and characterization of the intracoronary tissue.[68] [69] [70] Calcification and atherosclerosis can be identified and the eccentric or concentric nature of plaque likewise determined. Intracoronary ultrasonography has been instrumental in determining the success of interventions such as stent deployment in coronary artery disease.[71] [71A] [71B] Figure 7-45 (Figure Not Available) depicts intracoronary ultrasound studies demonstrating increasing degrees of severity of atherosclerosis. A closely related technology is the use of miniaturized Doppler wires for monitoring intracoronary flow velocity.[72] [73] Intravascular ultrasonography has also been used in the evaluation of patients with known or suspected aortic dissection, in which case it provides a high-resolution intraluminal view of dissection pathology and yields incremental information with respect to the origin of branch vessels. It has been instrumental in refining the techniques of emergent fenestration in stenting for acute type III dissections.

TISSUE CHARACTERIZATION.

Tissue characterization refers to the detailed evaluation of the entire reflected ultrasound signal in an effort to extract information regarding actual tissue character. Typically, this has relied on evaluation of data in the radiofrequency signal component before processing into a diagnostic, visual image. One of the more promising applications has been in evaluating the cyclic variation in returning ultrasound signal intensity (cyclic variation in backscatter) as a marker of myocardial ischemia.[74]

DOPPLER TISSUE INTERROGATION.

With specific alteration in Doppler filters, the myocardium can be targeted for Doppler interrogation. The resulting Doppler signals can be color encoded and incorporated into the two-dimensional image, thus displaying directional information. Additionally, quantitative data regarding velocity of motion in diastole and systole can be extracted.[75] [76] [76A] [76B] [76C]

Advantages and Limitations of Echocardiography

As with any diagnostic technique, echocardiography has distinct advantages and disadvantages. Cardiac ultrasonography itself carries no risk to the patient, operator, bystanders, pregnant women, or fetus. Specialized examinations such as contrast echocardiography, TEE, and stress echocardiography carry the minimal risk associated with the procedural modifications necessary for their undertaking. Modern ultrasound instruments are capable of visualizing all four cardiac chambers, all four cardiac valves, and the great vessels. They provide high-resolution tomographic views in unlimited planes, which facilitates the ability to diagnose virtually all forms of anatomical cardiovascular disease. The addition of Doppler interrogation allows determination of physiological parameters as they relate to blood flow and myocardial velocities.

Echocardiography does have specific limitations. Because ultrasound does not transmit well through calcified structures or bone, an appropriate acoustic window is necessary for optimal visualization. In neonates and infants, ultrasound can pass through noncalcified cartridge and the windows available exceed those in adults. In the adult population a noncalcified window must be obtained that typically is in the intercostal spaces or from the subxiphoid positions. In patients with narrow intercostal spaces, imaging can be problematic. A greater limitation is the degree to which the air-filled structures reflect ultrasound. Intervening lung tissue in patients with obstructive lung disease can result in suboptimal or even inadequate imaging. Another area of concern for echocardiography is its potential for overuse. Because it is low cost and carries no risk, the tendency for its overuse or inappropriate use is substantial.

The American College of Cardiology, American Heart Association, and American Society of Echocardiography have outlined recommendations for appropriate training in echocardiography[77] and likewise recommendations on its appropriate clinical use.[78]

Figure 7-42 Demonstration of left ventricular contrast medium enhancement after intravenous injection of a perfluorocarbon-based agent. The panels on the left are recorded before administration of contrast agent, and those on the right after opacification of the left ventricular cavity. Note the enhanced ability to

identify the left ventricular cavity and distinguish it from the endocardial border after opacification.

ACQUIRED VALVULAR HEART DISEASE (see Chap. 46)

Mitral Valve Disease

Virtually all types of mitral valve disease can be characterized anatomically using echocardiography. Doppler techniques provide accurate physiological information that complements the anatomical assessment. Figure 7-46 outlines the motion pattern of the normal mitral valve and the valve in multiple disease states, each of which are discussed.

Mitral Stenosis

Mitral stenosis was the first valvular lesion to be comprehensively evaluated with echocardiography. Two-dimensional echocardiography and Doppler ultrasonography remain the mainstay of diagnosis and characterization of this lesion. In the vast majority of adult patients, mitral stenosis is the result of rheumatic heart disease, with rarer cases of congenital mitral stenosis being encountered in adult patients. Rarely, heavy calcification of the mitral annulus results in functional restriction of the left ventricular inflow and can result in a left atrial to left ventricular gradient mimicking valvular mitral stenosis.

Figure 7-43 Surface-rendered three-dimensional echocardiogram showing a normal aortic valve. The panel on the left shows the valve in the open position, and a roughly triangular orifice is seen. The image has been captured at mid opening. At the right the valve is seen in the closed position and the right, left, and noncoronary cusps are clearly visualized.

Figure 7-44 Intracardiac ultrasound image recorded from within the cavity of the right atrium. Note the fairly thick tissue at the primum and more superior aspect of the atrial septum and the very thin valve of the foramen ovale.

The hallmark of mitral stenosis on two-dimensional echocardiography is thickening and restriction of motion of both mitral valve leaflets, with the predominant pathological process being at the tips of the leaflets and proximal chordae (Fig. 7-47) . In more advanced cases, the body of the leaflet itself may become involved; and in even more advanced cases substantial calcification occurs within the leaflet itself and on the subvalvular apparatus, including the chordae and papillary muscle tips (Fig. 7-48) . The earliest effect of rheumatic disease on the mitral valve is the result of inflammation and thickening of leaflet tips that restricts the motion of the tips while allowing free motion of

the body of the leaflets. This results in a characteristic "doming" diastolic motion of the mitral valve. The motion

Figure 7-45 (Figure Not Available) Intracoronary ultrasonic images demonstrating the different severity of coronary atherosclerosis. *A,* Small rim of thickened endothelium (arrow). *B,* Larger amount of eccentric endothelial thickening (arrows). *C,* Massive atherosclerotic plaque that is wider (arrows) than the residual lumen. *D,* Calcification in the plaque (CA) produces shadowing (S). *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

Figure 7-46 Schematic outlining both normal and abnormal mitral valve closure patterns. See text for details.

Figure 7-47 Parasternal long-axis view of a patient with mitral stenosis and a pliable noncalcified mitral valve leaflet. Note the "doming" motion of the mitral valve leaflets (arrowheads). Valves with these morphologic features are excellent candidates for percutaneous balloon valvotomy.

of the anterior leaflet has also been described as a "hockey stick" configuration. Restriction of the tips effectively results in a funnel-like mitral valve apparatus with the restrictive orifice being at the tips of the leaflets. This appearance is easily recognized from TTE in both the parasternal long-axis and apical four-chamber views. With careful attention to detail, the actual restrictive orifice of the mitral valve can be visualized and planimetered from a parasternal short-axis view (Fig. 7-49) . This planimetered area correlates well with the area determined in the catheterization laboratory. M-mode echocardiography was the initial diagnostic tool for evaluation of mitral stenosis. By using this technique, the thickened leaflets could be identified as well as the restricted motion. The restricted motion pattern resulted in a flattening of the E-F slope of the mitral valve (Fig. 7-50) . The E-F slope can be quantified and tracked as a measure of stenosis severity but provides no truly quantitative value by today's standards.

ASSESSMENT OF SEVERITY.

In addition to determining the anatomical extent and severity of the stenotic lesion, assessment of physiological significance is made using Doppler echocardiography.[79] [79A] Color flow imaging is instrumental in determining the degree of concurrent mitral regurgitation. Both continuous-wave and pulsed Doppler echocardiography can be obtained at rest and with exercise and provide accurate quantification of the transvalvular gradient (Fig. 7-51) . [80] Determination of the transvalvular gradient should be performed in patients both at rest and with modest degrees of exercise. A population of symptomatic patients exists who have relatively unimpressive gradients at rest that increase dramatically with mild exercise.

A second Doppler method for determining the severity of mitral stenosis involves calculating the pressure half time ($P_{½}$ t), which is the time in milliseconds required for the peak pressure gradient to decline to one half of its original value. The pressure half time can be related to an anatomical valve area by the formula: mitral valve area =P ½ t ÷ 220 milliseconds. This relationship is probably valid only for isolated mitral stenosis and is not accurate for quantitation of the mitral valve orifice if concurrent mitral regurgitation[81] or significant aortic insufficiency is present.[82] The relationship also has diminished accuracy in instances in which left ventricular diastolic compliance is markedly abnormal, such as in patients with severe hypertension or aortic stenosis[83] and immediately after mitral balloon valvotomy.[84]

Other more detailed methods for determining the mitral valve area involve determination of quantitative mitral valve flow. This can be performed using the continuity equation in a manner analogous to that for aortic stenosis.[85] Either flow and dimensions at the level of the mitral valve annulus or forward going flow in the left ventricular outflow tract can be used in this equation. Obviously this approach has limitations in patients with concurrent regurgitation or multivalve disease.

Figure 7-48 Parasternal long-axis view in diastole *(top)* and systole *(bottom)* in a patient with rheumatic heart disease and mitral stenosis. In the top panel note the diffuse thickening of the mitral valve. The reduced orifice can be seen in this end-diastolic frame (arrow). The bottom panel was recorded in systole and provides a view of the chordal apparatus, which can be seen to be diffusely thickened and fibrotic. Valves with this appearance are less ideal candidates for percutaneous intervention than the valve presented in Figure 7-47 .

Figure 7-49 Parasternal short-axis view at the level of the mitral valve orifice recorded in a patient with mitral stenosis. The frame was recorded in end diastole, and the actual orifice of the stenotic mitral valve can be visualized and in this instance has been planimetered. The measured mitral valve area is approximately 1.1 cm^2 .

In addition to determining the presence and severity of mitral stenosis, it is important to evaluate the heart for secondary effects. Secondary effects of mitral stenosis include left atrial dilation with subsequent stasis and thrombus formation and secondary pulmonary hypertension. Evaluation of the left atrium for blood stasis and thrombus requires TEE (Fig. 7-52) . The aortic, tricuspid, and pulmonic valves can likewise be directly interrogated for evidence of rheumatic involvement. The most common significant sequelae of mitral stenosis is development of secondary pulmonary hypertension with subsequent right-sided heart dysfunction and tricuspid regurgitation. As with other diseases in which the right side of the heart is evaluated, the tricuspid regurgitation jet can be interrogated for determination of right ventricular systolic and, presumably,

pulmonary artery systolic pressures.

It is important to fully evaluate the anatomical features of mitral stenosis in patients in whom a mitral balloon valvotomy is contemplated. Four features of mitral valve anatomy have been identified that correlate with success of this procedure. These include valve pliability, thickening, calcification, and subvalvular involvement. Each of these can be quantified on a score of 0 to 4 and a total score tabulated. Scores above 14 represent valves unlikely to be successfully treated with a percutaneous approach.[86] [87] There is a disproportionate impact of calcification and subvalvular involvement on the likelihood of successful valvotomy.

Mitral Regurgitation

Two-dimensional echocardiography and Doppler techniques can be used to detect the presence of mitral regurgitation, to determine its severity, and also to determine the etiology of regurgitation and look for secondary effects. Mitral

Figure 7-50 M-mode echocardiogram recorded in a patient with typical mitral stenosis. Compare this mitral valve opening pattern to the mitral valve motion in Figure 7-1 . With mitral stenosis there is thickening at the leaflets and flattening of the E-F slope.

Figure 7-51 Transmitral Doppler recordings obtained in a patient with mitral stenosis at rest *(top)* and with exercise *(bottom).* Heart rate has increased from 85 to 110 beats/min, resulting in an increase in the mean pressure gradient from 6.3 to 13.6 mm Hg. Abbreviations are as per previous figures.

Figure 7-52 Transesophageal echocardiogram recorded in a patient with severe mitral stenosis. Note the marked thickening of the mitral valve (arrows), including involvement of the chordal apparatus. The left ventricle and right ventricle are small, and the left atrium is massively dilated. Note the homogeneous echoes filling the right and left atria. In real-time scanning these are appreciated as a swirling, "smokelike" echo signal consistent with stagnant blood. Abbreviations are as per previous figures.

regurgitation can be due to a wide variety of cardiac conditions, some of which are presented in schematic form in Figure 7-46 . Typically, mitral regurgitation will first be documented using Doppler color flow imaging. In the presence of significant mitral regurgitation, volume overload of left ventricle and left atrium occurs, resulting in chamber dilation, the degree of which is dependent on both the severity and duration of mitral regurgitation.[88] The etiology of mitral regurgitation is determined by assessing the anatomy of the left ventricle and the mitral valve apparatus. Many forms of mitral regurgitation are due to intrinsic disease of the mitral valve, examples of which would be

mitral regurgitation concurrent with mitral stenosis, myxomatous degeneration with mitral valve prolapse, chordal rupture, endocarditis, and infarct-related papillary muscle rupture. Functional forms of mitral regurgitation also occur in which the mitral valve may be anatomically normal but fails to coapt because of dilation of the left ventricle.[88] This can occur due to either cardiomyopathy or coronary artery disease. In the vast majority of instances the anatomical and functional abnormality responsible for mitral regurgitation can be documented with TTE. On occasion, TEE is necessary to refine the anatomical assessment and may be particularly helpful in identifying rupture of a papillary muscle head and flail leaflets and in detecting smaller vegetations or perforations.[89] [90]

ASSESSMENT OF SEVERITY.

Doppler color flow imaging is used to determine the severity of mitral regurgitation. The severity of mitral regurgitation is directly proportional to the size of the regurgitant jet within the left atrium.[91] [92] [93] Multiple studies have confirmed the relationship between the size of the regurgitant jet and the severity of regurgitation determined with angiography or other techniques. Typically, the size of the jet is indexed to the size of the left atrium. Figure 7-53 demonstrates examples of mitral regurgitation. Jets that are peripheral or impinging on a wall, rather than central, cause predictable problems with assessment of severity.[94] [95] Owing to the Coanda effect, a regurgitant jet impinging on a wall results in a smaller color flow area than an equivalent central regurgitant volume. The underlying

Figure 7-53 Four panels depicting varying degrees of mitral regurgitation; the two top panels are apical four-chamber transthoracic views showing, on the left, mild mitral regurgitation and, on the right, moderate to severe mitral regurgitation. On the left note the relatively narrow jet directed from the tips of the mitral valve toward the posterior left atrial wall. On the right note the larger jet, filling approximately 40 percent of the left atrial cavity. The two bottom panels are transesophageal echocardiograms. On the left note the mitral regurgitation occurring in two discrete jets and, on the right, the highly eccentric jet, which courses along the extreme lateral wall of the left atrium. Abbreviations are as per previous figures.

mechanism of this phenomenon is that a regurgitant volume "recruits" the adjacent blood flow into motion. As color Doppler flow detects cells in motion, irrespective of their origin, the visualized regurgitant jet is the sum of the regurgitant volume and the recruited blood cells. A centrally located jet recruits in all of its dimensions, whereas a jet adjacent to a wall recruits only on the free surface, hence being relatively smaller than an equal volume of central regurgitation. A jet impinging on a wall underestimates the regurgitant volume by approximately 40 percent. In cases of moderate and severe mitral regurgitation, flow in the pulmonary veins may reverse direction in systole.[96] A variation on this finding is attenuation of normal forward flow in the pulmonary vein during ventricular systole. More recently, three-dimensional reconstruction of mitral regurgitation jets has been shown to be feasible.[97] [98] The incremental value of this method has not yet been shown.

Several characteristics of a regurgitant jet can give clues as to the etiology. In the

presence of chamber dilation due to cardiomyopathy, leaflet coaptation is abnormal and the leaflets are convex into the left ventricular cavity rather than concave (Fig. 7-54). In extreme examples of this phenomenon the actual regurgitant orifice, owing to failure of coaptation, can be directly visualized. These jets are typically central in location. By using either color Doppler M-mode or careful interrogation of the spectral display, the timing of the mitral regurgitation jet can also be determined. Lesions such as mitral prolapse may result in regurgitation confined to mid and late systole.

Anatomical disruption of any portion of the mitral valve will result in regurgitation. This can range from a few ruptured chordae with isolated prolapse of a single scallop to disruption of entire papillary muscle head with flail of an entire leaflet. TEE is often incrementally helpful in determining the precise degree of anatomical disruption of the valve (Fig. 7-55) . Irrespective of the etiology of a flail leaflet the resultant jet is often highly eccentric and its flow is directed opposite of the leaflet bearing the pathology; that is, a flail posterior mitral valve leaflet results in an anteriorly directed jet. An eccentric jet should lead to a higher index of suspicion of a flail leaflet. Three-dimensional echocardiography has shown promise for detailed assessment of mitral valve pathology in mitral regurgitation (Fig. 7-56) .

Quantitation of mitral regurgitation is heavily dependent on the color Doppler flow area. Other techniques for quantifying mitral regurgitation rely on determining the width of the jet at its origin and on evaluation of the proximal isovelocity area. In general terms, for any given Nyquist limit, the larger the size of proximal isovelocity surface area the greater the degree of regurgitation.[99] Calculation of flow volume from proximal isovelocity surface area has already been discussed and can be applied to determine regurgitant volume.

Mitral Valve Prolapse

The detection and characterization of mitral valve prolapse remains a common use of echocardiography. Early studies suggested a prevalence of prolapse of up to 21 percent in otherwise healthy young females. It should be emphasized

Figure 7-54 Apical four-chamber view in a patient with a dilated cardiomyopathy and severe mitral regurgitation due to a dilated annulus and abnormal mitral valve coaptation. The solid horizontal white line represents the plane of the mitral annulus. Note that the mitral valve closes well within the cavity of the left ventricle. The actual origin of the mitral regurgitation jet can be seen as it accelerates toward the regurgitant orifice (arrow) and is likewise displaced into the cavity of the left ventricle.

Figure 7-55 Transesophageal echocardiogram recorded in a patient with a flail posterior mitral valve leaflet. The echocardiogram is recorded in a longitudinal view in which the left atrium, left ventricle, and

pulmonary artery are visualized. Because flail leaflets occur in atypical locations, it is often necessary to scan in unusual planes to identify the leaflet. In this projection a substantial portion of the posterior leaflet (arrow) can be seen to protrude into the left atrium, with the tip of the leaflet no longer attached to the chordal apparatus.

that many individuals identified as having mitral prolapse in these earlier studies are recognized today to simply have normal bowing of the mitral valve. The normal mitral valve closure pattern is for the tips of the leaflets to point toward the left ventricular apex and for there to be gentle bowing of the leaflet with a concavity toward the apex of the left ventricle. Based largely on these dimensional reconstruction techniques, the mitral valve annulus is known not to be a planar structure but rather to have complex three-dimensional geometry.[100] Depending on the tomographic plane of interrogation, a portion of one or both leaflets may bow behind the imaginary annular line. In the presence of otherwise anatomically normal thin leaflets, this represents a variation of normal and does not represent pathological mitral valve prolapse.

The most extreme forms of mitral valve prolapse involve myxomatous degeneration of the valves with visible leaflet thickening (defined as greater than 3 to 5 mm in thickness) and either marked symmetrical bowing of the valve behind the majority of the annular plane or highly asymmetrical buckling of one or both leaflets into the plane of the left atrium (Figs. 7-57 and 7-58) . This will be associated with variable degrees of mitral regurgitation, which may be either wholly systolic or confined to mid to late systole. Because of the eccentric buckling of the myxomatous valve, the mitral regurgitation jet can be eccentric rather than central. The key aspects to the diagnosis of mitral valve prolapse rely not on the mere detection of a valve that buckles into the plane of the left atrium but on characterization of the valve morphology.[101] [102] As mentioned earlier, normal thin leaflets that bow gently into the left atrial plane probably represent no more than a variation of normal closure patterns. Patients with thickened redundant valves and myxomatous changes of the leaflet have a true form of structural heart disease. It is these individuals who are most at risk for endocarditis, spontaneous rupture of chordae, and progressive mitral regurgitation. It also appears that there is a higher than usual incidence of ventricular arrhythmias and neurological events in this subset of patients.

Aortic Valve Disease

Aortic Stenosis

Evaluation of patients with known or suspected aortic valve disease requires integration of anatomical information from two-dimensional echocardiography and physiological information from Doppler studies. Aortic stenosis is most commonly due to one of three pathological processes. These include a bicuspid aortic valve, rheumatic heart disease, and degenerative aortic stenosis. On rare occasions, aortic stenosis can be the result of endocarditis or radiation heart

Figure 7-56 Three-dimensional echocardiogram recorded in a patient with a partial flail mitral anterior leaflet. For both panels the orientation is a view of the mitral valve from within the left atrium. The left panel was recorded in diastole, and the unrestricted orifice can be seen. The right panel was recorded in

mid systole. Note the two scallops of the anterior leaflet that protrude into the left atrium (arrows).

Figure 7-57 Parasternal long-axis view in diastole *(top)* and systole *(bottom)* in a patient with mitral valve prolapse and myxomatous changes. In the upper panel note the open mitral valve and the diffuse thickening of the posterior mitral valve leaflet (arrow). The lower panel was recorded in systole. Note that both leaflets prolapse behind the plane of the mitral valve annulus. The prolapse of the posterior leaflet is somewhat more prominent (arrow).

disease. Bicuspid aortic valve typically presents as a hemodynamically significant lesion in the fourth or fifth decade of life and calcific degenerative aortic stenosis in the seventh decade and beyond. Rheumatic aortic valve disease

Figure 7-58 M-mode echocardiogram of the mitral valve recorded in the same patient noted in Figure 7-55 . Note that the posterior leaflet is diffusely thickened and in systole prolapses posteriorly from the normal closure line (arrow).

will virtually always be seen in patients who have concurrent rheumatic mitral valve disease.

The bicuspid aortic valve is the single most common congenital cardiac defect and occurs in approximately 2 percent of the population. There is a broad range of anatomical and physiological abnormalities associated with this condition. The bicuspid aortic valve is commonly thought of as a two-leaflet valve with roughly equal leaflet proportions. There is a range of abnormality in the "bicuspid valve" that includes nearly unicuspid valves and distribution of leaflet tissue other than 50/50 percent. Bicuspid aortic valves are commonly described as having either an anterior-posterior or a lateral orientation of the leaflets. In reality, virtually any direction of the major coaptation can be seen. TTE is a reliable method for detecting the bicuspid aortic valve. With the use of this technique, the hallmark of the bicuspid valve will be eccentric closure of the leaflets within the aorta. In approximately 80 percent of cases, two rather than three leaflets can be directly visualized (Fig. 7-59) . With closer scrutiny by way of TEE, what at first appears to be a true bicuspid valve often is found to represent a three-leaflet valve with unequal leaflet sizes and fusion of one of the three commissures, resulting in a functional bicuspid valve (Fig. 7-60) . It is important to examine the

Figure 7-59 Transthoracic echocardiogram in a patient with bicuspid aortic valve. In the upper panel, note that the leaflets of the aortic valve do not open all the way to the margins of the aorta but are "tethered" in lumen of the proximal aorta. The two bottom panels are recorded in the short-axis view at the base of the heart. The lower left panel was recorded in diastole and reveals the closed bicuspid valve with a single commissure oriented from 10 o'clock to 4 o'clock (arrows). The lower right panel is recorded

in systole, and the oval opening of the bicuspid valve can be appreciated within the circular aorta. Abbreviations are as per previous figures.

Figure 7-60 Transesophageal echocardiogram recorded in a patient with an anatomical three-leaflet valve with a fused commissure resulting in a functional bicuspid aortic valve. In the top panel note the three cusps (N = noncoronary, L = left coronary, R = right coronary). The upper frame was recorded in diastole, and the closure lines would suggest presence of three leaflets. The lower panel is recorded in systole; and instead of opening fully to the margins of the aorta with a circular orifice, the valve opens with an oval, fishmouth-shaped orifice. Note the commissure between the right and left cusps is fused, resulting in a functionally bicuspid valve. Abbreviations are as per previous figures.

opening pattern of the aortic valve to determine that it is functionally bicuspid. There is a strong association between coarctation of the aorta and bicuspid valve. When either of these conditions is clinically suspected, the other should also be evaluated.

Degenerative calcific valves appear as three-leaflet structures with marked thickening of the leaflets. Thickening and calcification may be more prominent at the base of the leaflets than at the tips. There is a broad range of immobility and stenosis, depending on the duration and severity of disease (Fig. 7-61) . Rheumatic aortic stenosis typically results in leaflet thickening along the commissural edges. It will be seen almost exclusively in the presence of rheumatic mitral stenosis.

Once aortic stenosis is anatomically defined, secondary effects can also be evaluated. These include poststenotic dilation of the aorta and left ventricular hypertrophy. Assessment of left ventricular systolic function should also be undertaken.

ASSESSMENT OF SEVERITY.

Doppler echocardiography is essential for assessment of the physiological significance of aortic stenosis (see Figs. 7-24 and 7-61) .[103] [103A] [103B] In clinically significant aortic stenosis the gradient is likely to exceed 50 mm Hg. This corresponds to a Doppler velocity of approximately 3.5 m/sec, which is out of the range for accurate quantitation using pulsed-wave Doppler. For this reason, continuous-wave Doppler is essential for quantitation. From continuous-wave Doppler both instantaneous peak and mean gradients can be determined using the Bernoulli equation. Either online or offline outlining of the spectral display and automatic calculation of these values can be performed. In some instances determination of the gradient at rest and with exercise may be beneficial. The gradients determined from Doppler echocardiography correlate very well with simultaneously determined invasive measurements.[103B] This correlation is maximal during simultaneous measurement and when micromanometer tip catheters are used (Fig. 7-62) . The commonly measured "peak to peak" gradient determined in the catheterization laboratory has no basis in physiological reality and will not correspond to either a peak instantaneous or mean gradient determined by either

micromanometer catheters or Doppler interrogation. In most instances, cardiac output and hence stroke volume are augmented in the catheterization laboratory compared with rest. For this reason Doppler-determined

Figure 7-61 Echocardiogram recorded in a patient with severe aortic stenosis. The top panel is a parasternal long-axis view recorded in systole. Left ventricular function is diminished. The aortic valve is markedly thickened and partially calcified. Its motion is markedly reduced and in systole it appears that the valve occludes the orifice (arrow). The lower panel is a continuous-wave Doppler recorded from the apex of the left ventricle along a line aimed through the stenotic aortic valve. Note the aortic stenosis signal below the zero crossing line. The peak velocity is 430 cm/sec, which corresponds to a maximum gradient of 77 mm Hg and a mean gradient of 49.4 mm Hg. Abbreviations are as per previous figures.

Figure 7-62 Graphic comparison of Doppler- and catheterization-determined gradients in patients with aortic stenosis. On the left are simultaneously recorded gradients and on the right are nonsimultaneous gradients. Note the stronger correlation between Doppler and catheterization when gradients are obtained in a simultaneous manner. *(From Currie PJ, Hagler DJ, Seward JB, et al: Instantaneous pressure gradient: A simultaneous Doppler and dual catheter correlative study. J Am Coll Cardiol 7:800-806, 1986.)*

gradients in the echocardiography laboratory may be lower than a catheterization-determined gradient.[103B]

On occasion, the Doppler gradient underestimates the gradient measured. This is common with nonsimultaneous recordings as noted earlier but also occurs when the angle of interrogation (theta) exceeds approximately 20 degrees. Off-angle interrogation is the single most common cause for underestimation of an aortic stenosis gradient. In instances in which there is a serial obstruction consisting of both valvular and subvalvular obstruction, both the V1 and V2 components of the Doppler equation must be incorporated.

The actual valve orifice is usually not visualized to a reliable degree from TTE. TEE can be used to obtain a direct measurement of the aortic valve orifice in many patients with aortic stenosis. In severe aortic stenosis, the orifice may be highly irregular and not all portions of it may lie in the same plane. With scrupulous attention to detail it is possible in many instances to directly planimeter the area (Fig. 7-63) .[104]

An additional method for determining the aortic valve area relies on the continuity equation.[105] [106] Typically, in aortic stenosis the left ventricular outflow tract area can be derived from the annulus diameter, assuming circular geometry. Pulsed Doppler is then used to determine the velocity of flow at that site. The product of the two is volumetric flow in the outflow tract. At the stenotic orifice continuous-wave Doppler is used to determine the average velocity. The algebraic equation can then be solved for the aortic

valve area. A modification of this technique uses mitral valve flow instead of left ventricular outflow. Because the velocity of flow increases at the restrictive orifice, several investigators have suggested using the V1/V2 ratio

Figure 7-63 Transesophageal echocardiogram recorded in a patient with severe aortic stenosis. In the left panel note the three aortic valve cusps (N = noncoronary, L = left coronary, R = right coronary). The leaflets are diffusely thickened and have restricted opening motion. The right-hand panel is the same systolic frame in which the stenotic area of the aortic valve has been planimetered. Note that the area of the aortic valve is calculated as 0.67 cm^2 , consistent with severe aortic stenosis.

Figure 7-64 Composite of echocardiograms recorded in patients with aortic regurgitation. The two top panels were recorded in the same patient and show, on the left, an apical long-axis view and, on the right, a parasternal short-axis view. In the apical long-axis view note the fairly extensive confetti-like aortic regurgitation jet arising from the proximal aorta and traversing to the left ventricular apex. Note also that the aortic regurgitation jet velocities merge with the mitral inflow velocities, rendering quantitation problematic. The top right hand panel is recorded in the same patient and shows a central aortic regurgitation jet. The bottom left panel is a transesophageal echocardiogram recorded in a longitudinal view. Note the highly eccentric aortic regurgitation jet that appears to fill the entire width of the left ventricular outflow tract. This apparent filling of the left ventricular outflow tract is due to the posterior to anterior jet direction (white arrow) rather than to a substantial true width of the jet. The lower right panel is a color M-mode echocardiogram recorded in a patient with aortic insufficiency in which the normal systolic flow can be appreciated as well as a continuous diastolic flow in the lumen of the aorta that represents aortic insufficiency. The two downward pointing arrows denote the duration of systole, and the two upward pointing arrows indicate the duration of diastole.

as a marker of significant aortic stenosis.[105] Other methods for determining the severity of aortic stenosis involve calculation of aortic valve resistance [107] and using echo-Doppler data in variations of the Gorlin formula.

From a practical standpoint it is often not necessary to determine an aortic valve area. In a patient with thickened restricted leaflets and a mean gradient exceeding 50 mm Hg, the presence of severe aortic stenosis is clinically assured. Likewise, in patients with normal ventricular function and with low gradients the likelihood of significant aortic stenosis becomes negligible. Patients with reduced left ventricular function, typically with ejection fractions of 25 to 35 percent, and a modest transvalvular gradient of 25 to 30 mm Hg are problematic. This situation may either represent mild aortic valve disease and unrelated left ventricular dysfunction or, conversely, critical aortic stenosis with secondary left ventricular dysfunction. In the latter situation, patients will benefit from aortic valve replacement, whereas for the former medical management is indicated. Dobutamine infusion, while monitoring left ventricular function and transvalvular

gradients, can be a useful means for separating these two entities.[108] [109] If left ventricular function augments with a dobutamine infusion and the gradient increases to clinically pertinent levels, the diagnosis is most likely severe aortic stenosis with secondary left ventricular dysfunction, and these patients will benefit from valve replacement. Conversely, if ventricular function improves without a change in the gradient it is less likely that the aortic stenosis is the limiting factor.

Aortic Regurgitation

Detection and quantitation of aortic regurgitation relies predominantly on Doppler techniques.[110] [111] Using color flow imaging the regurgitant jet can be visualized in the left ventricular outflow tract from several different planes (Fig. 7-64). In the majority of instances, there will be an underlying anatomical abnormality of the aortic valve such as endocarditis, disease of the aortic root, rheumatic valve disease, or a bicuspid valve.

Several features of the regurgitant jet have been investigated as markers of the severity of aortic regurgitation. Unlike mitral regurgitation, in which the overall jet size correlates

Figure 7-66 Continuous-wave spectral recordings of patients with mild *(top)* and severe *(bottom)* aortic insufficiency. Note the relatively flat slope pressure decay in the mild instance and a steeper slope of pressure decay, denoting near equalization of aortic and left ventricular diastolic pressures, seen in severe aortic insufficiency.

Figure 7-65 Parasternal long-axis two-dimensional echocardiograms in a patient with minimal *(top)* and moderate *(bottom)* aortic regurgitation. In the top panel note the thin color jet of aortic regurgitation that fills less than 10 percent of the left ventricular outflow tract, compared with the wider aortic insufficiency profile, filling over one third of the left ventricular outflow tract in the lower panel. Abbreviations are as per previous figures.

with regurgitation severity, neither the overall size nor depth of penetration of the aortic regurgitation jet correlate strongly with the severity of aortic regurgitation. This is in large part due to the difficulty in separating the regurgitant flow stream from mitral valve inflow. A greater degree of success has been obtained by measuring either the width or cross-sectional area of the regurgitant jet in the outflow tract and indexing this to the width or cross-sectional area of the outflow tract (Fig. 7-65). These measurements are dependent on imaging the jet in its minor axis, and an eccentric jet, crossing across the outflow tract, will result in a disproportionately sized jet compared with its true dimension. TEE often provides more accurate visualization of the true direction and size

of the regurgitant jet.

By using continuous-wave Doppler from the apex one can record the actual flow velocity profile of the regurgitant jet (Fig. 7-66) . The velocity of the regurgitant jet is directly related to pressure gradient between the aorta and left ventricle.[112] If this gradient remains high throughout diastole, the slope of velocity and pressure decay is relatively flat. This implies a relatively mild degree of aortic regurgitation in which there has been little equilibration of aortic and left ventricular diastolic pressures. Conversely, with severe aortic regurgitation there is a greater degree of equilibration of left ventricular and aortic diastolic pressures and the terminal aortic regurgitation velocities are relatively low, resulting in a fairly steep slope of velocity decay over the diastolic pressure curve. The pressure half time of the regurgitant jet, defined as the time in milliseconds required for the initial transvalvular diastolic gradient to decline to one half of its peak value, can be calculated and is inversely related to the severity of aortic regurgitation. A pressure half time less than 400 milliseconds correlates with severe aortic regurgitation. In high-quality studies the continuity equation can be used to calculate the aortic regurgitant volume.[113] Quantitation of aortic regurgitation has also been performed using the proximal isovelocity surface area method.[114]

There are several secondary Doppler and anatomical features that should also be noted in aortic regurgitation. The proximal aorta often has progressive dilation with long-standing aortic regurgitation.[115] Left ventricular dilation is a natural consequence of long-standing hemodynamically significant aortic regurgitation.[116] [117] Left ventricular size can be normal in the acute phase. With moderate and severe aortic regurgitation, diastolic flow reversal in the descending thoracic aorta can frequently be detected from the suprasternal notch. Two-dimensional echocardiography often reveals an indentation of the anterior mitral valve leaflet during diastole. This is due to the impinging regurgitant jet that distorts the symmetrical opening pattern of the mitral leaflet. This is typically seen only in cases of moderate and severe aortic insufficiency. With M-mode echocardiography fine high-velocity flutter of the anterior mitral leaflet and occasionally the septum can be appreciated (Fig. 7-67) .

TIMING OF SURGERY.

Echocardiography plays a significant role in the timing of surgery for aortic regurgitation.[116] [117] This decision is based largely on left ventricular size and performance rather than on the Doppler assessment of severity. Traditional echocardiographic findings that represent indications for surgery have included dilation of the left ventricle beyond 70 mm in diastole or beyond 55 mm in systole with a fractional shortening less than 25 percent. Additionally, progressive dilation of the left ventricle of 1.0 cm or more over a 12-month duration typically represents an indication for valve replacement.

Figure 7-67 M-mode echocardiogram recorded in a patient with aortic insufficiency. Note the fine fluttering of the mitral valve leaflet secondary to impingement by the aortic insufficiency jet. PW =

posterior wall.

Finally, left ventricular performance can be monitored with exercise, and a flat or falling ejection fraction likewise represents an indication for surgical intervention.

Tricuspid Valve Disease

TRICUSPID REGURGITATION.

Probably due to the complex closure pattern of the tricuspid valve, minimal and mild degrees of tricuspid regurgitation are commonly seen in normal individuals. The most common form of tricuspid valve disease is annular dilation due to right-sided heart overload, resulting in abnormal leaflet coaptation and tricuspid regurgitation. This is typically secondary to pulmonary hypertension, which most commonly is due to left-sided heart pathology. Tricuspid regurgitation due to annular dilation can be the result of virtually any form of heart disease, resulting in elevation of right ventricular pressure or volume. In these instances, the tricuspid valve typically appears anatomically normal but is found to be regurgitant. Quantitation of tricuspid regurgitation is done in a manner similar to that for mitral regurgitation and in clinical practice is a qualitative assessment (Fig. 7-68).[118] Minimal and mild degrees of tricuspid regurgitation are nearly ubiquitous in adult populations, even in the absence of identifiable structural heart disease.[118] Moderate and severe tricuspid regurgitation and tricuspid regurgitation associated with elevated right ventricular systolic pressure are typically associated with cardiac pathology. Primary tricuspid valve disease can result in tricuspid regurgitation as well. Involvement by rheumatic heart disease,[119] endocarditis, trauma with rupture of a papillary muscle,[120] Ebstein anomaly, radiation heart disease, carcinoid heart disease,[121] [122] and prolapse all have characteristic anatomical features that result in regurgitation. TEE can be useful in determining the feasibility of tricuspid valve repair. Carcinoid heart disease is a rare abnormality but has classic echocardiographic features (Fig. 7-69) .[121] [122] In this syndrome, the leaflets appear stiffened and immobile. The annulus is secondarily dilated and the leaflets may fail to coapt. This lesion is typically associated with severe tricuspid regurgitation without elevation in right ventricular systolic pressure.

Figure 7-68 Two-dimensional echocardiograms with color flow imaging of patients with tricuspid regurgitation. *Top,* Echocardiogram is recorded in a patient with a mild degree of tricuspid insufficiency. *Bottom,* Echocardiogram of a patient with severe tricuspid regurgitation.

Irrespective of the cause of tricuspid regurgitation, one can capitalize on this lesion to accurately calculate right ventricular systolic pressure, as noted in the section on Doppler calculations. In the absence of obstruction to right ventricular outflow, this pressure equals pulmonary artery systolic pressure (see Fig. 7-29) . Calculation of right ventricular systolic pressure can be measured both at rest and with exercise and is a

valuable means of noninvasively determining pulmonary artery systolic pressures.

TRICUSPID STENOSIS.

Isolated tricuspid stenosis is a very rare clinical entity. Tricuspid stenosis can be seen in individuals with rheumatic heart disease, in which case concurrent mitral stenosis will invariably be present.[119] The carcinoid syndrome can result in tricuspid stenosis as well. Calculation of transvalvular gradients across the tricuspid valve is done in a manner identical to that for the mitral valve. In the majority of cases, tricuspid valve stenosis is associated with regurgitation.

Pulmonic Valve Disease (See Chaps. 43 and 44.)

Primary disease of the pulmonic valve is uncommon in adult patients. Occasional patients with pulmonic stenosis (Fig. 7-70) , either in isolation or in combination with other congenital lesions, may be encountered in the adult cardiology practice. Congenital pulmonic stenosis results in thickening of the leaflets and restricted motion on two-dimensional echocardiography. Because the orientation of the pulmonary outflow tract is anterior to posterior, Doppler interrogation is quite easily performed within an angle of integration (theta) close to 0 degrees. The degree of stenosis and regurgitation across the pulmonic valve is determined

Figure 7-69 Right ventricular inflow tract view recorded in a patient with carcinoid disease and tricuspid regurgitation. The right atrium and right ventricle are both visualized in this systolic frame. The tricuspid valve leaflets are abnormally dense and immobile. In this systolic frame the leaflets fail to coapt with the leaflet tip separated by approximately 2 cm. In real time the leaflets are nearly immobile.

Figure 7-70 Two-dimensional *(A)* and continuous-wave Doppler *(B)* recorded in a patient with valvular pulmonic stenosis. The two-dimensional study shows a thickened pulmonic valve with restricted motion (arrowheads). The continuous-wave Doppler shows a peak velocity of 4.4 m/sec, which is consistent with a systolic gradient of approximately 78 mm Hg. Abbreviations are as per previous figures. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

in a manner analogous to that for the aortic valve. In the presence of pulmonic regurgitation, the pressure gradient between the pulmonary artery and right ventricle in diastole can be calculated, and from this an estimate of pulmonary artery diastolic pressure can be obtained.[123] This is done by calculating the end-diastolic pulmonary artery to right ventricular gradient and adding an assumed right ventricular diastolic pressure.

Several characteristic patterns of pulmonary valve motion should be recognized on M-mode echocardiography. The first is that of pulmonic stenosis in which there is an augmented a wave but otherwise normal motion. In the presence of infundibular stenosis, coarse fluttering of the pulmonic valve is seen. In the presence of significant

pulmonary hypertension there is midsystolic notching of the pulmonic valve and loss of the pulmonary valve a wave (Fig. 7-71) . These findings are qualitative and may be seen only in the more advanced or severe forms of pathology. In modern practice, determination of pulmonary artery hemodynamics relies heavily on Doppler interrogation.

Evaluation of the right ventricular outflow tract or pulmonary artery Doppler flow profile can provide valuable clues in patients with known or suspected pulmonary hypertension.[124] Normally, after the onset of ejection, pulmonary artery flow reaches its maximum velocity within 140 milliseconds of the onset of ejection. In pulmonary hypertension this acceleration time is progressively shortened (Fig. 7-72) . There is a linear and inverse correlation between the ejection time, defined as the time from onset of ejection to reaching peak velocity and pulmonary artery systolic and mean pressures. In general, a pulmonary artery acceleration time less than 70 milliseconds implies presence of a pulmonary artery systolic pressure exceeding 70 mm Hg. Other findings in pulmonary hypertension include notching of the pulmonary artery flow profile on spectral Doppler.

Miscellaneous Valvular Heart Diseases

Several miscellaneous forms of valvular heart disease deserve comment. Recently, attention has been drawn to the association between the use of anorectic drugs, particularly the combination of phentermine and fenfluramine (PhenFen), and development of valvular heart disease.[125] [126] [127] [128] [128A] [128B] [128C] [128D] The exact incidence of drug-related valvular heart disease is unknown. Most studies have suggested that the predominant

Figure 7-71 M-mode echocardiograms of the pulmonic valve recorded in a normal individual *(top)* and in an individual with pulmonic stenosis *(bottom)*. In the top tracing, note that the a wave is approximately 5 mm in depth. In contrast, in the patient with pulmonic stenosis, there is an exaggerated depth of the a wave (arrow) due to right ventricular pressure exceeding pulmonary artery diastolic pressure after atrial contraction.

lesions are similar to that seen in carcinoid or ergot heart disease. The leaflets of the mitral valve and chordae appear thickened and immobile, and mitral regurgitation is present. More commonly, aortic insufficiency has been noted in association with the use of these drugs, and it often appears out of proportion to the anatomical abnormalities noted on the aortic valve.

Radiation therapy can result in valvular dysfunction, most often thickening and insufficiency. The severity of the valvular insufficiency is dependent on the degree of anatomical damage to the valve, and the precise valves involved are dependent entirely on the radiation portal and dose. Typically, more anterior structures are involved and

there may be concurrent myocardial dysfunction due to radiation myocarditis.

Evaluation of Prosthetic Heart Valves (See also Chap. 46.)

Two-dimensional echocardiography can be used to determine the appropriate prosthesis size to implant in the aortic position.[129] [130] [131] The evaluation of prosthetic heart valves can be a complex and time-consuming process. Prosthetic heart valves can be divided into three basic groups: mechanical prostheses, such as single or dual disc valves or ball and cage valves; stented bioprostheses, which use either porcine aortic valves or bovine pericardium for valve leaflets; and a newer generation of stentless porcine valves that at this time are approved for use only in the aortic position. Each valve has unique echocardiographic characteristics, and different valves can be evaluated to varying degrees using TTE and TEE. Doppler echocardiography is obviously crucial for determining the presence of regurgitation and the flow characteristics of a valve.[132] [133] It is often not possible to fully evaluate a prosthetic valve with TTE, and TEE is often necessary. This is particularly true for visualization of mitral prostheses. Even with TEE, complete anatomical visualization of an aortic mechanical prosthesis can be problematic. For all but the new stentless aortic prosthesis the sewing ring is characteristically visualized as an echo-dense circular structure within the appropriate annulus.

The ball and cage valve is typically visualized as an echo-dense sewing ring with three wire struts forming the cage and a ball moving within the cage. Depending on the composition of the ball, the ball itself may appear either as a spherical structure or as a single echo-dense line in motion. Single-disc mechanical prostheses are visualized as a sewing ring in which the disc can be seen to move. Typically from the transthoracic route all one sees is a single bright echo-dense line with phasic motion during the cardiac cycle above and into the plane of the sewing ring. The discs of a two-disc valve cast a smaller echo signature, and actual disc motion can be difficult to discern from TTE. Using TEE both leaflets of a two-disc valve are easily visualized in the mitral position and have a characteristic butterfly wing motion (Fig. 7-73) .[134] Identifying motion of both leaflets in the aortic position is more problematic. The stented porcine valves are visualized as a sewing ring, impinging on the actual orifice of the valve annulus in which three separate leaflets can be seen. These leaflets have the characteristics of a normal aortic valve. With fibrosis and degeneration or endocarditis the leaflets may become thickened and brighter than usual (Fig. 7-74) .[135] The newer stentless prosthesis and aortic homograft valves can be difficult to distinguish from a native aortic valve. Depending on the implantation technique, there may be few clues as to the presence of a stentless prosthesis other than subtle echodensities at the line of attachment in the annulus or, if implanted within the native aorta, a double-density aortic wall can be seen.[136] [137]

Figure 7-72 Pulsed-wave Doppler in the right ventricular outflow tract demonstrating varying degrees of

pulmonary artery systolic pressure. *A,* Record of a normal individual. Note the normal acceleration time, defined as the time in milliseconds from onset of ejection to reaching peak velocity. In this instance the acceleration time is approximately 200 milliseconds. *B,* Record in a patient with modest pulmonary hypertension. Note the shortened acceleration. *C,* Record in a patient with severe pulmonary hypertension. Note the remarkably short acceleration time as well as the systolic notching in the flow pattern.

Complete evaluation of prosthetic valves requires detailed *Doppler assessment.* Color flow imaging is used to determine the presence and severity of regurgitation.[138] The combination of the sewing ring and/or the mechanical valve itself results in substantial reverberation and shadowing and dramatically reduces the ability to interrogate structures posterior to the mechanical prosthesis or sewing ring with Doppler. There is frequently a minimal amount of physiological regurgitation in mechanical prostheses that represents a combination of the closing velocity of the disc or ball and small physiological leaks at the closure lines. It is not uncommon to see minimal degrees of regurgitation in association with a stented or nonstented bioprosthesis. Valvular regurgitation in prosthetic valves can be quite eccentric, and one must use caution in applying rules for determining

Figure 7-75 Transesophageal echocardiogram recorded in a patient with a St. Jude mitral valve replacement and a paravalvular leak, resulting in moderate mitral regurgitation. *Left,* Recorded in systole. Note the two discs of the St. Jude prosthesis in their closed position (upward-pointing arrows). Immediately outside the boundary of the sewing ring is a distinct color jet (horizontal arrow) representing an eccentric mitral regurgitation jet arising from outside the border of the sewing ring. *Right,* The same image with color suppressed. Again note the closed leaflets of the St. Jude valve. With the color suppressed a distinct gap between the sewing ring and tissue (downward pointing arrow) can be seen, representing partial valve dehiscence.

severity of regurgitation. This is particularly true for paravalvular regurgitation (Fig. 7-75).

Spectral Doppler is used to determine pressure gradients across prosthetic valves. Stentless bioprostheses behave in a manner nearly identical to native aortic valves and typically have a peak gradient of less than 10 to 15 mm Hg.[136] [137] [139] Because of narrowing of the outflow tract by a sewing ring, a stented prosthesis has a higher transvalvular gradient.[139] The magnitude of this gradient is dependent on both flow and the size of the valve. Because of the wide range of anticipated gradients, it is crucial to establish a baseline for prosthetic valves at a time when they are known to be functioning normally. This avoids the problem of subsequent detection of a peak gradient that can be as high as 50 mm Hg. This may be due to the combination of a high flow state and a narrowed orifice due to the sewing ring and may not represent valve deterioration. Doppler evaluation for the gradient across a mechanical prosthesis is complicated by several factors, including phenomena of localized gradients and pressure recovery.[140] [141] As flow accelerates through the noncircular orifice of a mechanical prosthesis, there are areas of rapid flow acceleration that occur over very short distances. This acceleration results in instantaneous peak velocities of 3 to 4 m/sec, corresponding to gradients of 36 to 64 mm Hg. These pathological pressure

gradients occur over a very limited distance (1-2 mm) within the sewing ring and do not reflect the true left-ventricular-to-proximal-aorta pressure difference measured in the hemodynamic laboratory. As with a stented bioprosthesis, it is crucial to obtain an early baseline pressure gradient across a mechanical prosthesis at a time when it is known to function normally for subsequent comparison. This is best done by obtaining a full echocardiographic and Doppler examination at the time of the first follow-up visit after implantation.

Dysfunction of prosthetic valves occurs due to valvular dehiscence, in which case a paravalvular leak can be seen (see Fig. 7-75), or there may be endocarditis (see Fig. 7-74) , thrombosis, or pannus interfering with motion of a mechanical valve. Typically, either stenosis or regurgitation can occur. If the mechanical valve becomes obstructed by pannus, vegetation, or thrombus, the transvalvular gradient typically will increase, although in some instances it may remain stable or even decline.[140] Regurgitation is usually seen in conjunction with restriction of the leaflet unless the leaflet has been restricted in a fully closed position. In suspected dysfunction of a prosthesis, TEE adds incremental value and is essential for complete evaluation.

Assessment of Mitral Valve Repair

Transesophageal echocardiography has been instrumental in determining the success of mitral valve repair.[142] [143] The preoperative echocardiogram is highly reliable as a means for determining which patients are candidates for mitral valve repair, and intraoperative monitoring is an integral part of the surgical routine in determining success of repair. In general, patients with elongated redundant valves, those with pathology of the posterior leaflet, and those with smaller vegetations or perforations are excellent candidates for mitral valve repair. A rheumatic etiology and patients with fibrotic leaflets are less likely to have good long-term results.

The intraoperative transesophageal echocardiogram is used to determine transvalvular gradients to exclude iatrogenic mitral stenosis and determine the degree, if any, of residual mitral regurgitation. Other adverse sequelae of mitral

Figure 7-73 Transesophageal echocardiogram of a patient with a normally functioning St. Jude mitral valve prosthesis. The scans are recorded at 0 degrees from behind the left atrium. The left panel is recorded in systole. Note the two closed leaflets of the prosthetic valve (arrows). The right-hand panel is recorded in diastole. Note the two leaflets now have a parallel position, pointing into the cavity of the left ventricle (arrows). Note the substantial shadowing from the sewing ring and discs, which reduces the ability to visualize the left ventricular cavity. Abbreviations are as per previous figures.

valve repair include development of dynamic left ventricular outflow tract obstruction, which likewise can be assessed with TEE before removing the patient from the operating room. Figures 7-55 and 7-76 are examples from a patient before and after

successful mitral valve repair.

Infective Endocarditis (See Chap. 47.)

Infective endocarditis represents an invasive infection, usually by a bacterial organism of the endothelial lining of the heart, most commonly on one of the four cardiac valves. Left-sided valves are more commonly involved than right-sided valves. The echocardiographic hallmark of bacterial endocarditis is formation of a vegetation on a valvular surface. Pathologically, a vegetation consists of a combination of thrombus, necrotic valvular debris, inflammatory material, and bacteria. Over time, a vegetation may become sterilized, at which point only the residua of the inflammatory response with variable degrees of the thrombotic component persist. On echocardiography a vegetation has the appearance of an oscillating mass attached to a valve leaflet (Fig. 7-77) . Classically, these are seen on the downstream, low-pressure side of a valve. Therefore, one typically anticipates a vegetation on the left atrial side of the mitral valve and on the left ventricular outflow tract side of the aortic valve. In reality, larger vegetations can exist on both sides of a valve and atypical locations are not uncommon. In screening for vegetations, small unrelated masses or surface irregularities are not infrequently encountered, and thus the specificity for defining a vegetation is not 100 percent. Several large-scale studies have demonstrated that echocardiography may play an incremental role in rapidly establishing the diagnosis of endocarditis,[144] [145] [146] and at least one algorithm for defining endocarditis has used echocardiography as an intrinsic component of the diagnosis.[147] Noninfectious vegetation, such as those seen in association with connective tissue disease, are also detected with echocardiographic imaging.[148] [149]

In addition to detection of a vegetation in patients with suspected endocarditis, echocardiography can be used to determine the functional significance and degree of anatomical impairment due to endocarditis and to evaluate complications of endocarditis. Typically, endocarditis results in valvular regurgitation and only rarely in significant valvular stenosis. Because of the variable location of vegetations and the highly variable degree to which the valvular surface may be interrupted, regurgitant lesions in endocarditis are more likely to be eccentric than in more classic forms of valvular heart disease.

Several studies have attempted to use echocardiographic features of vegetations as a marker for the likelihood of requiring surgery or progressing to heart failure. In general, larger and more mobile vegetations are more likely to be associated with embolic events than are smaller sessile vegetations. Vegetations due to *Staphylococcus aureus* are more likely to result in abscess formation and less likely to be sterilized with antibiotics.

COMPLICATIONS OF ENDOCARDITIS.

These include progressive valvular regurgitation leading to congestive heart failure, abscess formation, failure to sterilize, and embolic phenomena. Intracardiac abscesses are most commonly encountered in the relatively avascular areas of the heart. For aortic valve endocarditis this includes the aorta/mitral valve junction and for mitral and tricuspid valve disease the annular structures. Less commonly, intramyocardial abscess

or abscess within a papillary muscle is encountered.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY.

The relative diagnostic value of TTE and TEE has been evaluated in several studies.[150] [151] Because of the higher-quality, higher-resolution

Figure 7-74 Apical four-chamber *(top)* and parasternal short-axis views (lower panel) recorded in a patient with stented porcine bioprostheses in the mitral *(top)* and aortic *(bottom)* positions. In the upper panel, the horizontally oriented arrows denote the struts of the stented porcine valve that protrude in the cavity of the left ventricle. Within the struts note the echo-dense mass that represents vegetation. In the lower panel the three struts of the porcine bioprosthesis can be visualized at 2, 6, and 10 o'clock positions. Within the sewing ring of the bioprosthesis are noted several echo densities that represent vegetations. Abbreviations are as per previous figures.

imaging afforded by TEE, virtually all studies have demonstrated an increased sensitivity for detection of vegetations with TEE (Fig. 7-78) . Often the clinical diagnosis of endocarditis has included detection of vegetations, and, thus, many of these studies tend to overstate the sensitivity of TEE. Most studies have also suggested that when a high-quality, entirely normal transthoracic echocardiogram has been obtained in which there is no evidence of valvular mass or thickening and no evidence of pathological regurgitation, that the yield in proceeding to TEE is relatively low. Because TEE provides a high-resolution view of the heart, it also detects many limited areas of valvular thickening that are not related to an infectious process. Thus, its specificity for excluding the diagnosis of endocarditis may be less than optimal.

There are several proven advantages to TEE in patients with endocarditis. Perhaps the most well established is the detection of abscesses, particularly in the aortic root (Fig. 7-79) .[152] [153] Data suggest that detection rates from the

Figure 7-76 Two-dimensional echocardiogram recorded in a patient after mitral valve repair and annuloplasty ring. The ring is seen as an echo-dense structure in the annulus (arrows). PV = pulmonary vein; DA = descending aorta.

transthoracic approach are under 30 percent, whereas sensitivity for detecting an abscess in the aortic root with TEE exceeds 95 percent. Additionally, TEE provides more accurate characterization of the size and mobility of vegetations

Figure 7-77 Parasternal long-axis view of patient with aortic valve vegetation. Note the relatively

echo-dense, irregular mass prolapsing into the left ventricular outflow tract in this diastolic frame (arrow). Abbreviations are as per previous figures.

Figure 7-78 Transthoracic *(top)* and transesophageal echocardiogram *(bottom)* recorded in a patient with a mitral valve vegetation. In the transthoracic parasternal long-axis view, a highly mobile filamentous echo can be seen prolapsing into the left atrium during systole. This is consistent with a highly mobile vegetation. A systolic frame from the transesophageal echocardiogram is presented in the bottom panel. Again the highly filamentous mobile echo is noted (horizontal arrow). In addition there is a more sessile 8 mm diameter mass attached to the mitral valve (downward pointing arrow). Abbreviations are as per previous figures.

and detection of multiple vegetations in endocarditis. Finally, TEE is more accurate for determining the etiology of valvular regurgitation than is TTE. TEE can identify valvular perforations, ruptured chordae, and flail leaflets with a higher degree of reliability than can TTE.[154]

Calcification of the Mitral Annulus

Fibrosis and calcification of the mitral annulus are common findings with increasing age and can be seen in younger patients with renal disease and other metabolic abnormalities that result in abnormal calcium metabolism (Fig. 7-80) . The degree of calcification can range from limited, focal deposits in the annulus to deposits resulting in a masslike effect.[155] [156] [157] In advanced degrees the basal aspects of the posterior mitral valve leaflet may be involved. In rare situations, annular calcification can result in functional restriction of the mitral valve orifice and a left atrial-left ventricular pressure gradient. Only in advanced and rare cases does the degree of obstruction result in pressure gradients likely to cause symptoms or result in secondary pulmonary hypertension. More commonly, mitral annular calcification is associated with varying degrees of mitral regurgitation. Heavy annular calcification may result in a lower likelihood

Figure 7-79 Transesophageal echocardiogram recorded in a patient with an aortic root abscess, obtained in a longitudinal orientation. Note the thickened aortic valve with superimposed vegetation (arrowhead) and the echo-free space (arrow) between the wall of the aorta and the right ventricular outflow tract, which represents a periaortic abscess. Abbreviations are as per previous figures.

of successful valve replacement and a situation in which paravalvular regurgitation is not uncommon after mitral valve replacement.[146] Statistically, it also has been associated with embolic events.[147]

CONGENITAL HEART DISEASE (See Chaps. 43 and 44.)

Modern two-dimensional echocardiographic techniques provide a comprehensive means for evaluating virtually all

Figure 7-80 Two-dimensional echocardiogram recorded in a patient with renal insufficiency and calcification of the mitral annulus. Mitral annular calcium appears as an echo-dense mass in the mitral annulus.

forms of congenital heart disease found in both adults and children.[158] [159] [160] Additionally, echocardiography can be used to evaluate repaired and palliated congenital heart disease. In the modern era it is unusual for cardiac catheterization or other techniques to be necessary for defining the anatomical anomaly in congenital heart disease.[152] Cardiac magnetic resonance imaging (MRI) may provide incremental information regarding pulmonary artery anatomy and complex venous and great artery connections. Doppler echocardiography often provides the majority of physiological information necessary for the clinical decision-making.

It has become increasingly uncommon to make the diagnosis of congenital heart disease de novo in adult populations. Because of the increased access to well-trained pediatricians, family practitioners, and pediatric cardiologists, the majority of "significant" congenital heart lesions are detected in childhood and adolescence. Thus, the number and nature of lesions "escaping" detection until adulthood has changed over the past several decades. The single most common congenital lesion to be detected in adulthood, other than the bicuspid aortic valve, is the atrial septal defect. There are infrequent cases of ventricular septal defects and other anomalies that escape detection to adulthood. This chapter deals only with the more common entities likely to be encountered in adult populations and evaluation of the more common repaired and palliated lesions.

Intracardiac Shunts

ATRIAL SEPTAL DEFECT.

The most common shunt lesion to be detected de novo in adulthood is the atrial septal defect. Because atrial septal defects result in a relatively innocent murmur, they are often overlooked in childhood and may escape detection until adolescence or adulthood. Atrial septal defects result in a left-to-right shunt at a level of the atrial septum and, consequently, a volume overload of the right ventricle in diastole.[18] [161] The volume overload pattern of the right ventricle is manifest as dilation of the right ventricle and usually the right atrium. Additionally, the septum is "flattened" and the left

ventricle, rather than assuming circular geometry, has a "D"-shaped geometry (see Fig. 7-21) . This septal flattening is present predominantly in diastole, and during systole the septum assumes its normal circular geometry. This right ventricular volume overload pattern that is typically seen in atrial septal defects is also seen in any other lesion resulting in right ventricular diastolic volume overload, including significant pulmonary insufficiency, tricuspid regurgitation, and anomalous pulmonary venous return. On M-mode echocardiography the right ventricular volume overload pattern is characterized as paradoxical septal motion. It is now recognized that this "paradoxical" septal motion actually represents restitution of normal circular geometry with the onset of ventricular systole.

Detection of a right ventricular volume overload pattern may be the first clue to the presence of an atrial septal defect, after which further interrogation of the atrial septum should be undertaken to identify the location of the defect. The three most common locations of an atrial septal defect are secundum, primum, and sinus venosus, representing approximately 70 percent, 15 percent, and 15 percent of atrial septal defects, respectively. Rarer forms of atrial septal defect, including the unroofed coronary sinus, are also encountered. Whereas the secundum atrial septal defect is an isolated entity, there are strong associations between sinus venosus atrial septal defect and malalignment of the pulmonary veins, resulting in functional anomalous pulmonary venous return and abnormalities of the mitral valve seen with the primum atrial septal defect. A primum atrial septal defect is best considered a variant of endocardial cushion defect in which a small perimembranous ventricular septal defect and anomalies of the mitral valve may also

Figure 7-81 Transesophageal echocardiograms in two patients with atrial septal defects. In each case there is a distinct loss of tissue in the atrial septum, allowing direct communication between the left atrium and right atrium. The top panel is the same patient presented in the two left panels in Figure 7-82 , and the bottom panel is recorded in the same patient presented in the bottom right panel in Figure 7-82 .

be encountered. The classic mitral valve abnormality to be seen is a cleft mitral valve with varying degrees of mitral regurgitation.

On occasion, a right ventricular volume overload pattern is encountered but no anatomical defect can be visualized. In these instances, contrast echocardiography using agitated saline can be a valuable means of detecting the right-to-left component of interatrial shunting.[42] [162] Of the three common types of atrial septal defect, the sinus venosus defect is most likely to escape direct visualization on a transthoracic echocardiogram. TEE is nearly 100 percent specific and sensitive in detection of all types of atrial septal defects, including sinus venosus defects (Fig. 7-81) .[163] With TEE, the atrial septal defect is visualized as a loss of tissue. The size of the defect can be accurately measured, and color flow imaging can be used to identify abnormal transatrial flow patterns (Figs. 7-81 and 7-82). [164] Often the diagnosis can be established with a degree of accuracy and confidence that catheterization is not necessary before surgical repair.

Once identified, further characterization of the atrial septal defect can be undertaken

using two-dimensional echocardiography and Doppler techniques. Three-dimensional

Figure 7-82 Four illustrations of patients with atrial septal defects. *Top left,* Recorded from a subcostal transducer position in a patient with a small atrial septal defect (also illustrated in the lower left panel). From the subcostal transducer position the entire length of the atrial septum can be visualized. There is a defect approximately 7 mm in diameter in the secundum portion of the atrial septum with a color flow signal coursing from the left atrium into the right atrium (arrow) consistent with secundum septal defect. The lower left panel is the transesophageal echocardiogram from the same patient presented on the top left. The size of the defect can be more accurately appreciated, and again there is a distinct color flow image coursing from the left atrium into the right atrium. The upper right panel is a longitudinal view of the atrial septum showing a large patent foramen. Note the margins of the atrial septal tissue (arrows). The atrial septal tissue does not oppose, in this case leaving a 1-cm defect, through which flow shunts from the left atrium to the right atrium. SVC=superior vena cava. The lower right panel is recorded in a patient with a large secundum defect. Note the color flow image denoting a substantial flow from left atrium to right atrium. The defect is approximately 2 cm in diameter.

echocardiography can provide valuable clues as to the complex shape of an atrial septal defect.[165] [166] TEE can be an invaluable technique for determining the integrity of the tissues surrounding the atrial septal defect and plays a valuable role in determining the feasibility of a percutaneous closure using a button or umbrella device.[167] [168] Defects less than 2 cm in diameter and with relatively firm tissue at the margins are more likely to be successfully closed, compared with large defects and those with fairly thin tissue at the margin or multiple perforations.

Shunt Size.

Numerous attempts have been made to quantify the ratio of pulmonary and systemic flow in intracardiac shunt lesions, including atrial septal defect.[169] The majority of these attempts have been by calculating the instantaneous stroke volume of the pulmonary outflow tract and left ventricular outflow tract (see section on Doppler calculations). This calculation has been fairly reproducible and has correlated with hemodynamic assessment in the animal laboratory and in children. Because of the margin of error for measuring the dimension of the outflow tract, it has seen less use in adult patients. In general, the threshold for recommending closure of an atrial septal defect has diminished to a Qp/Qs (pulmonary/systemic flow ratio) of 1.5 or less. Detection of a right ventricular volume overload pattern in general denotes a shunt of at least this level, and thus the majority of detected atrial septal defects fall into the range that warrant closure.

REPAIRED ATRIAL SEPTAL DEFECT.

Depending on the magnitude of the initial shunt and the age at which an atrial septal defect is repaired, the two-dimensional echocardiogram may revert to normal with respect to chamber sizes or show evidence of residual right-sided heart dilation. In

instances in which the defect was large and repaired only late, residual right ventricular dysfunction, varying degrees of pulmonary hypertension, and right ventricular hypertrophy may persist throughout adulthood. Depending on the nature of the repair technique, the atrial septum can appear anatomically normal or can reveal areas of echo density consistent with the type of patch material used. In general, the right ventricular volume overload pattern with paradoxical septal motion resolves but can be replaced by a postoperative septal motion pattern.

OTHER ABNORMALITIES OF THE ATRIAL SEPTUM.

In addition to atrial septal defect anomalies such as aneurysm of the atrial septum,[170] [171] lipomatous atrial hypertrophy and patent foramen ovale[172] can be detected. The aneurysmal atrial septum is not infrequently associated with small perforations and minor degrees of either right-to-left or left-to-right atrial shunting (Fig. 7-83) . Contrast echocardiography can detect minor degrees of right-to-left shunting in both of these situations.[49] [173]

ANOMALOUS PULMONARY VENOUS RETURN.

A final congenital lesion that results in a right ventricular volume overload pattern is anomalous pulmonary venous return. A variation on anomalous return is seen in patients with primum atrial septal defects who have functional anomalous return due to malalignment of the right superior pulmonary vein such that its flow is directed into the superior vena cava and right atrium. True anomalous pulmonary venous return often results in creation of a venous chamber posterior to the left atrium, which then drains to the right atrium.[174] [175]

VENTRICULAR SEPTAL DEFECT.

Whereas the ventricular septal defect represents the most common congenital intracardiac shunt encountered in infants and children, it is a small percentage of those detected de novo in adults. A substantial number of small ventricular septal defects close spontaneously during childhood and thus are not present in adults, whereas the larger defects result in symptoms and are detected in childhood. Furthermore, the smaller persistent defects are associated with prominent pathological murmurs and unlikely to be confused for a flow murmur;

Figure 7-83 Apical four-chamber view recorded in a patient with an atrial septal aneurysm. Note the marked bulging of the atrial septum into the cavity of the left atrium (arrow). The right-hand panel is recorded after injection of saline contrast medium. Note the contrast medium has filled the right ventricular cavity, and there are numerous individual microbubbles seen in the cavity of both the left atrium and left ventricle, consistent with a right-to-left shunt through fenestrations in the atrial septal aneurysm. Abbreviations are as per previous figures.

Figure 7-84 Schematic depicting the location of different ventricular septal defects compared with the different echocardiographic views. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern PA, Lea & Febiger, 1994.)*

and, therefore, individuals come to medical attention promptly. On occasion, patients with small ventricular septal defects escape detection to adulthood, when the defects are found on the basis of a pathological murmur. Ventricular septal defects occur in several different locations, which are denoted echocardiographically in Figure 7-84 . The most common location is a small perimembranous septal defect; however, other locations, including supracristal, are not uncommonly encountered. Muscular defects can occur anywhere within the muscular septum, and small apical defects are frequently multiple.

A ventricular septal defect can be visualized as a dropout of myocardial tissue with communication between the left and right ventricles.[176] The resolution of TTE, using 3- and 5-MHz transducers, is such that most defects below a 3-mm size may not be directly visualized (Fig. 7-85). It is uncommon to directly visualize small muscular defects that may take an angulated or serpiginous course through the ventricular septum. Color Doppler imaging over areas of the septum is a reliable means for detecting the abnormal transseptal flow.[177] [178] It is often necessary to scan in unusual and atypical planes to identify flow through the septum, especially when searching for a muscular defect. For the isolated small perimembranous defect, continuous-wave Doppler can be used to determine the velocity of flow from the left ventricle to the right ventricle and hence the transventricular pressure gradient.[179] This can then be subtracted from arm blood pressure to estimate right ventricular systolic pressure. With the use of this methodology the small restrictive ventricular septal defect can be characterized as a defect resulting in little or no chamber dilation, of small anatomical extent on two-dimensional scanning, and associated with a high transventricular gradient.

Shunt Size.

The magnitude of shunting through a ventricular septal defect can be calculated using several Doppler techniques.[180] [181] Larger ventricular septal defects may be associated with substantial left-to-right shunts and development

Figure 7-85 Parasternal two-dimensional echocardiographic views in a patient with a moderate-sized perimembranous ventricular septal defect. The upper panel is recorded in a parasternal long-axis view and shows the proximal anterior septum. The lower panel is recorded in a short-axis view at the base of the heart. Note in each instance the distinct color jet arising on the left ventricular side of the ventricular septum and coursing in the right ventricular outflow tract. This is consistent with exclusive left-to-right

ventricular septal defect flow.

of secondary pulmonary hypertension. In this instance, the right ventricle will be dilated and hypertrophied. By using the tricuspid regurgitation signal, right ventricular systolic pressure can be calculated. In the presence of a ventricular septal defect it is important to look for associated anomalies of the right ventricular outflow tract and pulmonary valve. Pulmonic stenosis and right ventricular outflow tract obstruction are both protective of the pulmonary circuit and will lead to the scenario of elevated right ventricular systolic pressure with normal pulmonary artery pressures. This has obvious clinical implications with respect to surgical intervention.

CLOSED AND REPAIRED VENTRICULAR SEPTAL DEFECT.

As noted earlier, many small ventricular septal defects close spontaneously in infancy and childhood. This occurs by way of two basic mechanisms. The first is adherence of a portion of the tricuspid leaflet to the ventricular septal defect. In this case, one may visualize a very thin membrane closing the actual ventricular septal defect.[182] The second mechanism appears to be growth of additional tissue from the margins of the ventricular septal defect. In this instance, there may be irregular tissue closing the ventricular septal defect, the extent of which can be highly variable. In many instances, a thin-walled aneurysm may be noted in the area of the previous ventricular septal defect. The aneurysm typically bows into the right ventricular outflow tract. A small residual left-to-right shunt may be encountered that often is of little hemodynamic significance but that may result in a murmur and pose a risk for endocarditis.

TETRALOGY OF FALLOT.

Tetralogy of Fallot represents a complex of lesions including a ventricular septal defect with overriding aorta and obstruction to right ventricular outflow tract at either the infundibular or valvular level (Fig. 7-86) . The fourth component is a right-sided aortic arch. Before correction the lesion is characterized by a ventricular septal defect in which the edge of the ventricular septum is directed not at the anterior wall of the aorta but more at the aortic lumen. Varying degrees of right ventricular outflow tract obstruction including true valvular stenosis and infundibular muscular stenosis can be seen. Tetralogy of Fallot represents the most common cyanotic congenital

Figure 7-86 Two-dimensional echocardiogram recorded in a patient with an unrepaired tetralogy of Fallot. Note the fairly large perimembranous ventricular septal defect and the overriding aorta. Because of the overriding aorta both right and left ventricular outflow is directed toward the aorta equally. Abbreviations are as per previous figures. *(From Feigenbaum H: Echocardiography. 4th ed. Malvern PA,*

Lea & Febiger, 1986.)

lesion to be encountered that is likely to result in survival to adulthood and, furthermore, the most common complex lesion to be encountered in the adult population after repair.

Preoperatively, tetralogy of Fallot represents a broad spectrum of ventricular septal defect size and outflow tract obstruction. Postoperatively, varying degrees of residual abnormalities may be encountered, ranging from a nearly normal-appearing heart to one in which there are substantial degrees of right ventricular dysfunction and residual right ventricular outflow tract obstruction.[183] [184] Two-dimensional echocardiography and Doppler techniques can be a definitive means for following these individuals with respect to recovery of right ventricular function and development of complications such as recurrent right ventricular outflow tract obstruction and residual ventricular septal defect.[185]

PULMONIC STENOSIS.

Isolated pulmonic stenosis is a relatively common congenital lesion. As with the bicuspid aortic valve, its hemodynamic severity ranges from negligible to severe and life threatening early in infancy. Because of the orientation of the proximal pulmonary artery and pulmonic valve, it is easily interrogated with Doppler. Underestimation of pulmonic valve gradients due to off-angle interrogation is uncommon. Anatomically, the stenotic pulmonary valve appears somewhat thickened and has "doming" motion (see Fig. 7-70) . On M-mode echocardiography there may be an accentuation of the pulmonic valve a wave. In adult patients it is not uncommon for valvular pulmonic stenosis to be associated with secondary infundibular hypertrophy with concurrent right ventricular outflow tract obstruction. Thus, it is important to evaluate both the subvalvular and valvular aspects of the pulmonary valve in adult patients. Less frequently, peripheral pulmonic stenosis will be encountered. Identification and characterization of the peripheral pulmonary arteries in adult populations can be quite problematic and is an area in which MRI can play an incremental and valuable role.

Abnormalities of the Left Ventricular Outflow Tract

The most common abnormality of left ventricular outflow is the bicuspid aortic valve, which has been discussed previously. Additionally, both tunnel and discrete subaortic stenosis are occasionally encountered in adult patients. Tunnel aortic stenosis is visualized as a diffuse narrowing of the left ventricular outflow tract and more often is identified in children. Discrete, membranous subvalvular stenosis occasionally escapes detection until adulthood and is characterized by the presence of a thin membrane or ridge that encircles the left ventricular outflow tract (Fig. 7-87) .[186] Components of the membrane may be attached to the ventricular septum and to the anterior mitral valve leaflet. The membrane itself can be difficult to visualize from transthoracic transducer positions and may require TEE for complete visualization. The obstructing membrane results in turbulence in the left ventricular outflow tract, which can be detected with color Doppler flow imaging and eventually results in secondary pathology of the aortic valve with subsequent aortic insufficiency. M-mode echocardiography often reveals characteristic course systolic fluttering of the aortic valve leaflets. This finding can help

distinguish valvular from subvalvular obstruction. This should be contrasted to hypertrophic cardiomyopathy, in which anatomical abnormalities of the aortic valve and aortic insufficiency are uncommon.

The etiology of subvalvular membranes is uncertain, and the lesion may progress from inconsequential and undetectable to significantly obstructive in adult patients. Additionally, if detected in childhood and surgically resected, there is a definite likelihood of recurrence of the lesion in adulthood. On occasion, discrete subvalvular membranes have been seen in association with spontaneously closed ventricular septal defects.

Congenital Abnormalities of the Mitral Valve

Congenital abnormalities of the mitral valve, likely to be encountered in adult populations, include the previously mentioned cleft mitral valve, seen in association with a primum atrial septal defect as well as congenital mitral stenosis. The latter can occur either in the presence of a single papillary muscle, in which all chordae attach to a central point rendering an otherwise unremarkable valve functionally stenotic, or in a valve that is intrinsically stenotic

Figure 7-87 Transesophageal echocardiogram in a longitudinal plane of the left ventricular outflow tract demonstrating a small, discrete subaortic membrane (downward pointing arrow). The aortic leaflets are mildly thickened (horizontal arrows). This small membrane was not visualized from the transthoracic echocardiogram. Abbreviations are as per previous figures.

Figure 7-88 Transthoracic echocardiogram recorded in a patient with cor triatum in the parasternal long-axis view *(top)* and apical views *(bottom)*. A linear echo courses posteriorly from the area of the aorta. From the apical views the membrane can be seen to divide the left atrium into two chambers. PV = pulmonary vein; M = membrane; other abbreviations as per previous figures. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

but with two papillary muscle attachments. Functionally, these patients will present in a manner nearly identical to that for rheumatic mitral stenosis. Awareness of the anatomical features of congenital mitral stenosis is necessary to separate it from rheumatic causes. In many instances the congenital lesion will be characterized by an obstructive but eccentrically directed mitral valve orifice without the characteristic chordal and leaflet thickening. Transvalvular gradients can be measured across the congenitally stenotic mitral valve but may require unusual transducer angulations and lines of interrogation.

Cor triatriatum represents membrane within the body of the left atrium that likewise may be obstructive. TTE may suffice for identification of the membrane (Fig. 7-88) , but in

many instances TEE, which affords a more accurate view of the left atrium, is necessary.[187] [188] A final congenital abnormality of the mitral valve is the submitral ring or web. This represents a membrane attached near the mitral annulus within the left atrium that is obstructive to flow.

Anomalies of the Tricuspid Valve

The most common congenital tricuspid valve anomaly to escape detection to adulthood is Ebstein anomaly. In this situation the lateral leaflet is elongated and tethered to the lateral wall of the right ventricle and the septal leaflet is relatively small and apically displaced.[189] This results in conversion of a portion of the right ventricle to an "atrialized" right ventricle (Figs. 7-89 and 7-90) . Tricuspid regurgitation is invariably present and results in dilation of the right side of the heart in general but predominantly of the right atrium and atrialized right ventricle. Atrial septal defect is a common association with Ebstein anomaly and

Figure 7-89 Schematic of the anatomical and echocardiographic abnormalities seen in Ebstein anomaly including apical displacement of the septal leaflet and elongation and tethering of the lateral leaflet. Both the functional (FRV) and atrialized right ventricle (AtRV) are noted. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

Figure 7-90 Two-dimensional echocardiogram recorded in a patient with Ebstein anomaly. Note the small, apically displayed septal leaflet and the elongated lateral leaflet that is tethered to the myocardium of the right ventricular lateral wall. *(From Feigenbaum H: Echocardiography. 5th ed. Malvern, PA, Lea & Febiger, 1994.)*

should be considered in all instances. Tricuspid regurgitation is present invariably and may provide one of the major clues to the presence of Ebstein anomaly. Because the closure of the tricuspid valve is displaced toward the apex of the right ventricle the apical location of the convergence zone of the tricuspid regurgitation jet may be one of the clues to the presence of this anomaly.

Once identified, it is important to characterize several features of Ebstein anomaly that have direct relevance to the feasibility of surgical repair. Surgical repair can be undertaken in individuals with a relatively large functional right ventricle, compared with the atrialized portion, and in whom there is not extensive tethering of the lateral leaflet. This assessment can be made in a majority of patients using TTE.

Tricuspid Atresia

Tricuspid atresia is usually detected in infancy but after palliation may allow survival to adulthood. In tricuspid atresia there is no functional tricuspid valve tissue, although the tricuspid annulus may be closed by a thin membrane with small perforations.[190] Because of the atretic tricuspid valve, right ventricular hypoplasia coexists. Obviously a complete form of tricuspid atresia is incompatible with life unless a concurrent atrial or ventricular septal defect is present.

Persistent Ductus Arteriosus

Persistent ductus arteriosus represents persistence of the normal communication between the descending thoracic aorta and the left pulmonary artery. The size of the communication varies from 1 or 2 mm to a centimeter or more. The magnitude of left-to-right shunting is dependent on the size of the defect. Initially, persistent ductus results in a continuous left-to-right shunt at the great artery level that subsequently results in a left-sided heart volume overload early in childhood and adolescence. Because of the increased pulmonary flow, pulmonary hypertension may develop, in which case only the systolic component of the shunt persists. Echocardiographic detection of persistent ductus arteriosus is dependent on detection of left-sided heart enlargement and/or abnormal pulmonary artery flow.[191] With the use of suprasternal notch views it is occasionally possible to directly visualize the ductus (Fig. 7-91). More commonly, Doppler interrogation of the proximal pulmonary artery is the initial clue to the presence of a persistent ductus. By using either color Doppler flow imaging or pulsed Doppler one can detect continuous turbulent flow in the proximal pulmonary artery.[191] Further careful interrogation will frequently identify the origin of the abnormal flow from the descending aorta into the left main pulmonary artery.

Figure 7-91 Parasternal short-axis view at the level of the great vessels recorded in a patient with persistent ductus arteriosus. Note the dilated pulmonary artery and the abnormal color flow signal (large arrow) that originates from the area of descending thoracic aorta and flows into the pulmonary artery distal to the pulmonary valve. In this diastolic frame note the small pulmonic insufficiency jet (small white arrow). Abbreviations are as per previous figures.

Coarctation of the Aorta

Narrowing or coarctation of the aorta occurs after the takeoff of the left subclavian artery. It results in reduction of systolic pressure distally and may present in adulthood as a secondary cause of systemic hypertension. The anatomical extent of coarctation may be visualized from the suprasternal notch, and continuous-flow Doppler can be used to determine the coarctation gradient.[192] There is a strong association between coarctation and bicuspid aortic valve; and whenever coarctation is discovered, efforts should be made to define the aortic valve anatomy.

Transposition of the Great Arteries

Transposition refers to the situation in which there is ventricular-arterial discordance.

This is defined as a connection of the left ventricle to the pulmonary artery and the right ventricle to the aorta. There are two forms of transposition that may be encountered. D-transposition is an isolated malposition of the great vessels due to failure of the conotruncos to appropriately coil. In this situation the pulmonary artery is attached to the left ventricle, which receives blood from the left atrium. The aorta is attached to the right ventricle, which receives blood from the right atrium. This results in two parallel circulations and is obviously not compatible with life in the absence of an intracardiac shunt such as a persistent ductus or large ventricular or atrial septal defect. This lesion is invariably detected in infancy and is not encountered in adult patients in other than corrected forms. Surgical correction of transposition includes creation of an atrial septal defect early and subsequent surgical creation of a baffle that directs right atrial blood into the left ventricle and left atrial blood flow into the right ventricle. An anatomical switch of the great arteries has become the preferred surgical procedure.

L-transposition occurs when there is both inversion of the ventricles and transposition of the great arteries (Fig. 7-92) .[193] In this situation, blood flows from the anatomical right atrium through an anatomical mitral valve into the anatomical left ventricle and then into the pulmonary artery. Blood returning to the left atrium flows through an anatomical tricuspid valve into an anatomical right ventricle and then to the aorta. This results in "corrected" transposition in which physiological blood flow is maintained. L-transposition is compatible with survival to the fifth or sixth decade and often is first detected in adults. In either type of transposition the great arteries no longer have the circular and crescent orientation but rather arise from the

Figure 7-92 Transesophageal echocardiogram in an adult patient with L-transposition of the great vessels. In the top panel the connection of the anatomical right atrium to the anatomical left ventricle and the communication of the anatomical left atrium, through an anatomical tricuspid valve, into an anatomical right ventricle can be appreciated. Note the normal-appearing left atrial appendage (LAA). Note also the marked hypertrophy of the right ventricular trabeculations, which nearly obliterate the apex of the anatomical right ventricle (arrows). There is apical displacement of the atrioventricular valve contained within the anatomical right ventricle, compared with the atrioventricular (mitral) valve connecting the right atrium to the left ventricle. The lower panel depicts the parallel orientation of the pulmonary artery (PA) and aorta. The more anteriorly placed aorta is in communication with the anatomical right ventricle. Abbreviations are as per previous figures.

heart in a parallel fashion. In adult patients it can be difficult to directly visualize the parallel nature of the great vessels. Clues to the presence of congenitally "corrected" transposition include presence of a trabeculated ventricle with a more apically placed valve in a left and posterior position. L-transposition is compatible with survival into the fourth and fifth decade. After this period of time, substantial hypertrophy of the anatomical right ventricle occurs and right ventricular dysfunction is not uncommon. Regurgitation of the anatomical tricuspid valve in the systemic circuit is also quite common in adult patients.

Complex Congenital Heart Disease

The echocardiographic and clinical evaluation of complex congenital heart disease is best undertaken by individuals with specific interest and training in the area and is beyond the scope of this chapter. Three-dimensional echocardiography has been a valuable adjunct in evaluating the complex anatomy seen in complex lesions (Fig. 7-93) .[194]

DISEASES OF THE PERICARDIUM (See Chap. 50.)

PERICARDIAL EFFUSION.

Detection of pericardial effusion was one of the earliest utilizations of echocardiography, and modern ultrasound techniques remain the predominant diagnostic tool for detection, quantitation, and determination of the physiological significance of pericardial effusion.[195] [196] A pericardial effusion is viewed as an echo-free space surrounding the heart, most commonly seen posteriorly (Fig. 7-94) . Most clinical laboratories document the presence of pericardial effusion and quantify it as minimal, small, moderate, and large. A minimal effusion represents the 5 to 15 ml of normal pericardial fluid seen in disease-free individuals. This is most frequently noted as an echo-free space, confined to the posterior atrioventricular groove. A small pericardial effusion is defined as less than 5 mm in maximum dimension, which is visualized throughout the cardiac cycle. Moderate pericardial effusions typically are 10 to 15 mm in dimension and tend to be more circumferential. Large effusions are defined as those larger than 15 mm. Because patients are scanned in a supine or left lateral position the fluid tends to pool and to be mostly visible in the posterior aspects of the imaging planes. Numerous attempts have been made to quantify the amount of pericardial fluid but have not seen uniform acceptance.[197] The majority of laboratories use the semi-quantitative scheme noted earlier. Three-dimensional echocardiography has shown some promise for enhanced localization and quantitation of pericardial effusion.[198] The most commonly employed technique for quantifying the volume of effusion is to image the effusion in orthogonal planes and determine the intrapericardial volume using Simpson's rule. The entire cardiac silhouette can then likewise be traced and the total cardiac volume determined. The difference between the pericardial and cardiac volumes represents the volume of pericardial fluid. Although theoretically accurate, there are practical limitations to tracing both the cardiac and pericardial volumes that render this technique less than optimal and of little true clinical utility.

Other aspects of a pericardial effusion also can be noted with echocardiography. The presence of soft tissue density masses, thickening of the visceral pericardium, and presence of fibrinous strands can all be identified. All of these features are more common in patients with marked inflammatory or malignant causes for pericardial effusion. Additionally, the nature of the fluid can be further characterized as clear or "cloudy." The hallmark of the benign, idiopathic effusion is a clear echo-free space, whereas malignancy, bacterial infection, and hemorrhagic effusions are more likely to

have solid components or stranding.

Cardiac Tamponade.

Several echocardiographic findings are reliable indicators of elevated intrapericardial pressure, which in turn correlate with hemodynamic compromise or clinical tamponade. One of the earliest described was collapse of the right ventricular outflow tract during early diastole. This is best visualized in the parasternal views but can also be appreciated in the four-chamber view. The precise timing and duration of right ventricular collapse can best be determined with M-mode echocardiography. Cardiac tamponade occurs when pericardial effusion of sufficient magnitude has accumulated to result in equilibration of intrapericardial and passively determined intracardiac pressures. Immediately after mechanical systole the ventricle begins to relax, with a greater degree of active relaxation attributed to the left ventricle compared with the right. This results in disproportionate or favored filling of the left ventricle with a transient elevation in intrapericardial pressure. This results in early diastolic collapse of the highly compliant right ventricular outflow tract (Fig. 7-95) . Detection of transient outflow tract collapse is a reliable

Figure 7-93 Three-dimensional echocardiogram of a patient with a ventricular septal defect, transposition, and double outlet right ventricle. Note the small right ventricular cavity and the parallel orientation of the two great vessels.

Figure 7-94 Transthoracic parasternal long-axis echocardiograms recorded in a patient with a small *(top)* pericardial effusion. In the top panel note the echo-free space confined to the area posterior to the heart (arrow). The bottom panel reveals a similar pattern but with a larger echo-free space. Abbreviations are as per previous figures.

marker that intrapericardial pressure is elevated and hemodynamic compromise is present. It is correlated with the presence of overt tamponade but also has been seen in patients who subsequently developed tamponade. The atrial corollary of this phenomenon is exaggerated atrial emptying. Because of elevated intrapericardial pressures, filling of the right ventricle is impeded in early diastole (a manifestation of which is early diastolic right ventricular collapse) and occurs to an exaggerated degree with atrial systole. This results in a delayed and exaggerated contraction of the right atrium with actual invagination of the atrial wall in late diastole (Fig. 7-96) . This echocardiographic sign of hemodynamic compromise is more sensitive than right ventricular diastolic collapse but less specific, because it occurs earlier in the course of intrapericardial pressure elevation. Right ventricular collapse may be absent even in the presence of elevated pericardial pressures in patients with right ventricular hypertrophy or significant pulmonary hypertension. In the presence of loculated effusion or in

complex situations, either right- or left-sided chambers may be differentially compressed.[199] [200]

Doppler echocardiography can provide valuable clues as to the hemodynamic significance of pericardial effusions as well.[201] In hemodynamically significant effusions there is an exaggerated interplay between right and left ventricular filling, occurring with phases of the respiratory cycle. Clinically, this is manifest as an exaggerated pulsus paradoxus. Echocardiographically exaggerated respiratory variation can be documented by examining the left ventricular and right ventricular outflow tract flows in systole and noting exaggerated phasic variation in velocities and time velocity ventricles. Similarly, in a hemodynamically significant effusion, ventricular filling is impeded. The normal respiratory variation of the tricuspid valve is 25 percent, with a greater velocity in inspiration than expiration; and the normal mitral valve shows the opposite pattern with a variation of approximately 15 percent. In hemodynamically significant effusions there is a greater than usual variation in this respiratory pattern (Fig. 7-97) .

CONSTRICTIVE PERICARDITIS.

Although chronic constrictive pericarditis remains an elusive diagnosis, echocardiography and Doppler evaluation can provide valuable clues as to its presence.[202] [203] [204] [204A] The classic form of constrictive pericarditis is calcific constrictive pericarditis after tuberculosis infection. In contemporary times, constriction

Figure 7-95 Parasternal short-axis echocardiogram recorded in a patient with a pericardial effusion and evidence of hemodynamic compromise. *A,* Recorded in diastole. Note the normal shape and geometry of the right ventricular wall (RVW). *B,* Recorded in systole. Note that the tricuspid and pulmonic valves are both closed and that the right ventricular outflow tract has normal geometry. *C,* Recorded in early diastole. Note the tricuspid valve is now open and that the distal portion of the right ventricular outflow tract is compressed inward. Abbreviations are as per previous figures. *(From Armstrong WF, Schilt BF, Helper DJ, et al: Diastolic collapse of the right ventricle with cardiac tamponade: An echocardiographic study. Circulation 65:1491-1496, 1982. Copyright 1982, American Heart Association.)*

is more likely to be related to nontuberculous infections or hemorrhagic effusions or be secondary to trauma, cardiac surgery, or irradiation. The clinical presentation and echocardiographic appearance often vary from that classically described with calcific constriction. Numerous attempts have been made to quantify pericardial thickness using echocardiography. Routine transthoracic imaging has not been an accurate means for detecting pericardial thickening. TEE has shown more promise but has not seen clinical acceptance. Intracardiac ultrasonography does provide a high-resolution view of the pericardium but is an invasive

Figure 7-96 Apical four-chamber view recorded in a patient with a moderate pericardial effusion and evidence of hemodynamic compromise. The frame is recorded in early ventricular systole, immediately after atrial contraction. Note that the right atrial wall is indented inward and its curvature is frankly reversed (arrow), implying elevated intrapericardial pressure above right atrial pressure. Abbreviations are as per previous figures.

Figure 7-97 Pulsed-wave spectral Doppler recorded through the left ventricular outflow tract *(top)* and right ventricular outflow tract *(bottom)* in a patient with hemodynamic compromise due to pericardial effusion. Note the respirometry line on the bottom of each tracing. There is exaggerated respiratory velocity of flow in both the left ventricular and right ventricular outflow tracts. Note the reciprocal nature of the flow variation, with flow increasing during expiration and decreasing in early inspiration for the left ventricular outflow tract and the opposite pattern seen in the right ventricular outflow tract.

Figure 7-98 Pulsed Doppler recording through the mitral valve *(top)* and tricuspid *(bottom)* in a patient with constrictive pericarditis. Note the respirometer tracing for each. There is exaggerated respiratory variation in inflow velocities in both the mitral and tricuspid valves. Note also that the deceleration time is shorter with inspiration (150 msec) than with expiration in the mitral tracing. Reciprocal changes are noted in the tricuspid valve flow patterns. *(From Oh JK, Hatle LK, Seward JB, et al: Diagnostic role of Doppler echocardiography in constrictive pericarditis. J Am Coll Cardiol 23:154-162, 1994.)*

procedure and has been validated in only a small number of patients. Determination of pericardial thickening is probably more accurately done with computed tomography (CT) or MRI.

In the absence of direct ultrasound documentation of thickened pericardium there are indirect signs of pericardial constriction that should be evaluated in suspected cases. These include abnormalities of ventricular septal motion. The abnormalities of septal motion that occur are an exaggerated respiratory variation in septal position with marked bowing of the ventricular septum toward the left ventricle during inspiration. Additionally when viewed from the parasternal long-axis position an abnormality of septal motion is often detected. This frequently is seen as a downward motion of the ventricular septum in early systole, followed by a brief anterior motion, which can be confused with a conduction disturbance and is best detected with M-mode scanning.

The Doppler hallmarks of cardiac constriction include exaggerated respiratory variation of mitral and tricuspid inflows with a pathologically elevated E to A ratio (Fig. 7-98) . Additionally, deceleration time is abnormally short and may vary to a disproportionate degree during the respiratory cycle. Examination of the IVC frequently reveals dilation. The normal multiphasic hepatic vein flow is replaced by monophasic flow, occurring predominantly in systole.

The diagnosis of constrictive pericarditis in large part remains one of exclusion. From an

echocardiographic standpoint this diagnosis should be suspected in individuals with symptoms consistent with that diagnosis (i.e., edema, fatigue, and apparent low output state), normal left ventricular systolic function, and no valvular heart disease. Detection of abnormal septal motion, exaggerated respiratory variation, and an elevated E to A ratio provide the majority of the confirmatory evidence of this diagnosis.

MISCELLANEOUS CONDITIONS OF THE PERICARDIUM.

Congenital absence of the pericardium occurs in both partial and complete forms. In the complete form there is a marked abnormality of septal motion with exaggerated intracardiac motion within the thorax. In the partial form, varying degrees of septal motion abnormality can be detected depending on the degree to which the pericardium is anatomically deficient. Pericardial cysts are detected as echo-free spaces adjacent to the heart. The diagnosis should probably be confirmed by CT or MRI as well.

CARDIOMYOPATHIES (See Chap. 48.)

Cardiomyopathies can be divided into three basic types: dilated cardiomyopathy of any etiology, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.

DILATED CARDIOMYOPATHY.

Irrespective of the cause of a dilated cardiomyopathy, left ventricular dilation with global systolic dysfunction is noted (Fig. 7-99) .[205] Depending on the duration of the disease, left atrial dilation likewise occurs; and if significant mitral regurgitation is present, secondary pulmonary hypertension with right-sided heart dilation is common. The range of systolic dysfunction in dilated cardiomyopathy is quite broad, and ejection fraction ranges from less than 10 percent to only mildly diminished. Although dilated cardiomyopathy is a global process, because of regional wall stress and loading conditions regional heterogeneity of function is seen.[206] Typically, the proximal portions of the inferoposterior and posterolateral walls have relatively preserved systolic function whereas the more distal walls, the ventricular septum, and apex appear more severely compromised. This pattern of wall motion may initially be confused with ischemic heart disease. The absence of frank scar or aneurysm and the absence of any truly normally functioning segments should lead the observer to appropriately make a diagnosis of nonischemic cardiomyopathy. The echocardiographic appearance of nonischemic cardiomyopathy is not dependent on its etiology, and patients with alcoholic, doxorubicin (Adriamycin)-induced, idiopathic, and postviral causes will all have a similar echocardiographic appearance.

As a consequence of left ventricular dilation, the bullet-shaped geometry of the left ventricle is often distorted and the left ventricle becomes more spherical.[207] This has the effect of drawing the papillary muscles away from the mitral valve annulus and results in annular functional mitral regurgitation due to abnormal coaptation of the mitral valve (see Fig. 7-54). Mitral regurgitation severity may range from mild to severe; and, as a consequence, left atrial dilation to some degree is invariably present. Because of the diffuse nature of the initial insult, the right ventricle can be primarily affected with

dilation and hypokinesis and also secondarily affected due to subsequent pulmonary hypertension. Other complications of dilated cardiomyopathy that should be evaluated include presence of left ventricular thrombus and, in certain circumstances, development of left atrial thrombi. Detection of the latter requires TEE. The magnitude of secondary and pulmonary hypertension can be reliably determined from Doppler tracings of the tricuspid valve. Evaluation of diastolic properties of the left ventricle may provide valuable prognostic information.[208] [209]

HYPERTROPHIC CARDIOMYOPATHY.

Hypertrophic cardiomyopathy comprises a heterogeneous disease in which there is inappropriate and pathological hypertrophy of the

Figure 7-99 Transthoracic two-dimensional echocardiogram recorded in a patient with a dilated cardiomyopathy. The left panel is an apical four-chamber view showing dilation of all four cardiac chambers. Note that the mitral valve protrudes into the left ventricular cavity during systole consistent with papillary muscle dysfunction (arrows). There is also incomplete closure of the tricuspid valve due to annular dilation. The two right panels were recorded in a short-axis view in diastole *(top)* and systole *(bottom)*. Note again the dilated right ventricle in the severe systole dysfunction with global hypokinesis of both chambers when diastolic and systolic frames are compared.

left ventricle and, less commonly, the right ventricle.[210] The classic form of hypertrophic cardiomyopathy has commonly been termed "idiopathic hypertrophic subaortic stenosis" [IHSS]. In this entity there is characteristic disproportionate hypertrophy of the ventricular septum with dynamic left ventricular outflow tract obstruction (Fig. 7-100) . Because hypertrophic cardiomyopathy is a heterogeneous disease the preferred terminology is hypertrophic cardiomyopathy, secondarily described as focal, concentric, apical, and with or without obstruction. Dynamic obstruction classically occurs in the left ventricular outflow tract. From an echocardiographic perspective it is associated with systolic anterior motion of the mitral valve. This results in development of a systolic gradient that develops in the left ventricular outflow tract over the course of systole (Fig. 7-101) .[211] [212] [213] Thus, the maximum gradient is in late systole as opposed to early or mid systole, which is characteristic of a fixed valvular or discrete obstruction. Systolic anterior motion of the mitral valve can be detected either with two-dimensional echocardiography, typically from the parasternal long-axis view, and also with M-mode echocardiography (Fig. 7-102) . Although Doppler echocardiography remains the definitive examination for detection and quantification of outflow tract obstruction, secondary evidence of outflow tract obstruction can be obtained from the M-mode echocardiogram. Systolic anterior motion of the mitral valve that actually remains in contact with the septum for 40 percent of the systolic cycle is more likely to be associated with significant hemodynamic obstruction. Additionally, the outflow tract obstruction results in a characteristic systolic notching pattern on the aortic valve that is best visualized with M-mode echocardiography.

Mitral regurgitation is common in patients with obstructive hypertrophic cardiomyopathy, and the continuous wave of Doppler spectral profile of the mitral regurgitation may occasionally be confused with outflow tract obstruction. It should be kept in mind that the mitral regurgitation velocity will peak relatively early whereas the outflow tract obstruction has a characteristic late-peaking "dagger-like" appearance.

Other variants of hypertrophic cardiomyopathy include mid-cavity obstruction, in which case the maximum gradient is typically at the papillary muscle level. Other distributions of hypertrophy include nearly concentric left ventricular hypertrophy that may have no associated outflow tract obstruction. In this instance, patients can be highly symptomatic because of a relatively small left ventricular cavity with markedly elevated diastolic pressures.[214] Additionally, the small cavity, even with supernormal systolic functions, results in a low stroke volume and cardiac output. A final variant of hypertrophic cardiomyopathy is the apical variant, which is more common in Asian populations.[215] Deep T wave inversions across the precordium are seen in this variant. By definition it is not obstructive.

Two-dimensional echocardiography and Doppler imaging can be used to follow the status of outflow tract gradients at rest or exercise and after either drug, surgical, or, more recently, transcutaneous ablative therapy.[216] A reduction in both the outflow tract gradient and the severity of mitral regurgitation can be documented after successful therapy. On occasion, patients present with what appears to be a "burned-out" hypertrophic cardiomyopathy. In this instance, unexplained pathological hypertrophy is present with a relatively normal-sized left ventricle that is diffusely hypokinetic. Frequently, systolic function has deteriorated to the point that there is no longer an outflow tract gradient. Any of the forms of hypertrophic cardiomyopathy can result in long-standing elevation of diastolic pressure and secondary pulmonary hypertension.

RESTRICTIVE AND INFILTRATIVE CARDIOMYOPATHY.

Restrictive cardiomyopathies are a family of diseases in which systolic function is relatively preserved until very

Figure 7-100 Parasternal long-axis views recorded in a patient with a hypertrophic cardiomyopathy. The top panel is diastole and the bottom panel is systole. (Note this image has been recorded in tissue harmonic imaging and therefore myocardial signatures and brightness are increased. No assumptions regarding tissue characterization should be made from a tissue harmonic image.) In the top panel note the marked thickening of the ventricular septum (white arrows), which measures approximately 3 cm in thickness. The posterior wall was only mildly hypertrophied. The bottom panel was recorded in systole, and systolic anterior motion of the mitral valve (arrow) is clearly seen.

late stages but ventricular myocardium is pathologically stiff, leading to chronic elevation

of diastolic pressure. Symptoms result because of the elevated diastolic pressures. By definition, obstruction is not present, nor is there a primary cause for abnormal myocardial relaxation. The most common form of restrictive cardiomyopathy is the idiopathic restrictive cardiomyopathy in which both atria are dilated, wall thickness tends to be at the upper normal or mildly hypertrophied, systolic function is within normal limits or only mildly depressed, and there is Doppler evidence of abnormal ventricular relaxation. Typically, this is manifest as an elevated E to A ratio without exaggerated respiratory variation.

Other causes of restrictive physiology include infiltrative cardiomyopathies, the most common of which is cardiac amyloidosis. Other rarer etiologies include the glycogen storage diseases[217] and association with other systemic diseases.[218] Cardiac amyloidosis may present as either a primary or a secondary entity and is often associated with amyloid deposits in other organs. Amyloid deposition in the myocardium results in hypertrophy in the absence of hypertension and abnormal myocardial texture, which is noted as a bright "speckling" appearance (Fig. 7-103) .[219] Caution is advised when using second harmonic imaging because this type of instrumentation leads to the appearance of an abnormal myocardial signature as well. There is often evidence of diastolic dysfunction.[220] In the early phases a reduced E to A ratio with a flat deceleration slope is seen. Later, an elevated E to A ratio occurs, associated with a short deceleration time. This pattern has been associated with a worse prognosis. In advanced amyloid, virtually all cardiac structures, including valve leaflets, are involved. In late phases, systolic dysfunction is seen.

DISTINCTION OF RESTRICTIVE AND CONSTRICTIVE PHYSIOLOGY.

The distinction between constrictive pericarditis and a restrictive cardiomyopathy is often clinically problematic. Echocardiography can play several valuable roles in this clinical situation. The first is in the exclusion of primary valvular disease, left ventricular dysfunction, and pulmonary hypertension, which may have resulted in the clinical presentation. Typically, patients in whom this dilemma arises have preserved right and left ventricular

Figure 7-101 Continuous-wave Doppler recorded from the apex of the left ventricle with the interrogation being directed through the left ventricular outflow tract in a patient with an obstructive hypertrophic cardiomyopathy. Note the late peaking systolic gradient with a peak velocity of approximately 3.8 m/sec (corresponding to a peak pressure gradient of 58 mm Hg. Additionally (small arrow), there is evidence of presystolic forward flow in the left ventricular outflow tract, following atrial systole. This is consistent with a hypertrophied and noncompliant ventricle in which atrial contraction results in presystolic flow in the outflow tract.

Figure 7-102 M-mode echocardiogram recorded in the same patient depicted in Figure 7-100 . Note the markedly thickened ventricular septum. The mitral valve as seen directly below the ventricular septum and the E and A waves in diastole are noted. Note in systole there is anterior motion of the mitral valve (black/white arrow).

systolic function with signs and symptoms of biventricular heart failure. Other than detection of cardiac amyloid or patients in whom there are classic findings of constriction, the separation of these two entities relies heavily on Doppler echocardiography. In both cases the E to A ratio is elevated, but in constriction there is a greater than usual respiratory variation in inflow velocities.[221] [222] Deceleration time is short in both but varies to a greater degree in restrictive than in constrictive processes. Examination of pulmonary and hepatic vein flow can be helpful as well. In both instances vein flow is monophasic, but in restriction there is a greater degree of flow reversal in late diastole coincident with inspiration.[223] Newer techniques such as Doppler tissue imaging to interrogate the velocity of myocardial relaxation can also play a role.[224] Most patients with restrictive disease have delayed relaxation and delayed motion of the annulus compared with patients with constrictive pericarditis. The diagnosis of constrictive pericarditis and its separation from restrictive diseases remains problematic even in experienced hands, and many atypical cases of each process exist. Both processes can also coexist, and this combination is not uncommon after radiation therapy, in which there may be a constrictive component in the pericardium but a restrictive component to the right ventricle due to radiation injury.

ISCHEMIC HEART DISEASE (See Chaps. 35 , 36 , and 37 .)

BASIC PRINCIPLES.

Myocardial ischemia and infarction result in regional disturbances of ventricular contraction. After acute reduction in coronary flow, both diastolic[225] and systolic dysfunction occur. Normal systolic contraction consists of both myocardial thickening and inward motion of the endocardium (see Figs. 7-3 and 7-5) . Immediately after the onset of ischemia, myocardial thickening ceases and, depending on the size of the anatomical area and the severity of ischemia, the wall can become frankly dyskinetic (Figs. 7-104 and 7-105) . If blood flow is not restored, myocardial necrosis results and the wall motion abnormality becomes fixed. Over a period of approximately 6 weeks, actual tissue loss occurs and there is replacement by fibrous tissue and a scar forms.

MYOCARDIAL INFARCTION.

As noted earlier, myocardial necrosis, once established, results in a permanent wall motion abnormality. The degree of transmural involvement required before wall motion becomes abnormal is approximately 20 percent.[226] The implication of this is that non-Q-wave myocardial infarction will result in hypokinesis or akinesis of the wall even though the majority of the myocardial mass may still be perfused and viable. A tethering effect of nontransmural infarction or ischemia results in dysfunction of the entire wall thickness. Because the balance of the myocardium is intrinsically normal, it is capable of overriding this effect during either pharmacological stimulation or stress, therefore resulting in substantial cardiovascular reserve in segments that may be akinetic at rest.

The regional wall motion score is directly related to the size of the myocardial infarction; however, because of the tethering phenomenon, wall motion abnormalities overestimate the true anatomical extent.

Tethering occurs in several different forms. The most common occurs in substantial size myocardial infarction where the infarcted area may be frankly dyskinetic. During systole the dyskinetic segment drags the normal myocardium outward. Thus, this normal myocardium, which intrinsically has the capacity to contract, is tethered to the abnormal myocardium and is functionally abnormal. The opposite phenomenon can occur in relatively small infarctions where, during cardiovascular stress, the normal healthy adjacent myocardium contracts more vigorously and drags the abnormal segment with it, thus masking the

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Figure 7-103 Two-dimensional echocardiogram recorded in a patient with cardiac amyloid. In both the parasternal long-axis view *(top)* and short-axis view *(bottom)* note the homogeneous echo intensity of the myocardium. Both the mitral and aortic valves are also thickened. In real time the myocardium takes on a speckled appearance.

wall motion abnormality. A final form of tethering is "vertical" tethering in which ischemic or infarcted subendocardial layers exert a disproportion of effect on overall myocardial contractility. Because only 20 percent of the myocardium needs to be involved in the ischemic or infarction process for the entire wall to become dysfunctional, nontransmural (non-Q-wave myocardial infarction) results in a wall motion abnormality that is indistinguishable from that of transmural infarction.

Depending on the location and size of the necrotic area, ventricular remodeling will also occur. Remodeling takes several forms and ranges from formation of a frank aneurysm (Fig. 7-106) to progressive left ventricular dilation. Echocardiographically, an aneurysm is defined as a noncontracting area of myocardium with abnormal geometry in both diastole and systole.

In clinical echocardiography a regional wall motion abnormality, conforming to a known coronary distribution, is the hallmark of acute ischemia or myocardial infarction. Detection of a wall motion abnormality with echocardiography can be a valuable adjunct in the diagnosis of ischemia in patients who are presenting with chest pain. After successful reperfusion, wall motion abnormalities typically will resolve. The time course over which the resolve occurs is variable and may range from 12 hours to 2 weeks. Typically, wall motion abnormalities recover within 72 hours if blood flow has been restored in a timely fashion.[227]

At the time of presentation with acute myocardial infarction there are several echocardiographic findings that relate to patient prognosis. As with all imaging techniques, the greater the degree of left ventricular dysfunction, the greater the

likelihood of complications such as development of heart failure and death.[228] [229] The size of the myocardial infarction can be approximated with echocardiography by calculating a wall motion score or by calculation of an ejection fraction. Both of these values can be tracked over time to determine the status of recovery. Evaluation of the mitral valve inflow with Doppler echocardiography provides valuable prognostic information as well.[230] [231] Because myocardial ischemia causes immediate diastolic abnormalities, mitral valve inflow patterns become abnormal

Figure 7-104 Transthoracic echocardiogram recorded in a patient with an acute anterior septal myocardial infarction in a parasternal long-axis view. Note the dyskinesis of the anterior septum (upward arrows) when diastolic *(top)* and systolic *(bottom)* frames are compared. Downward arrow indicates normal septum movement.

Figure 7-105 Two-dimensional echocardiogram recorded in a patient with an inferior myocardial infarction complicated by right ventricular infarction. The two left panels are parasternal short-axis views recorded at the level of the papillary muscles. The top left panel is recorded in diastole. Note the full-thickness myocardium and the circular geometry of the left ventricle. In systole *(bottom panel)* the inferior wall (arrows) becomes frankly dyskinetic and fails to show normal systolic thickening whereas the remaining walls thickened appropriately and moved inward. The right panel is an apical four-chamber view demonstrating a dilated right ventricle that is globally hypokinetic in real time. This is consistent with right ventricular involvement.

early in the course of myocardial infarction. One may anticipate an abnormal (typically reduced) E to A ratio in myocardial ischemia. With more substantial areas of ischemia and greater degrees of diastolic dysfunction, an increased E to A ratio, suggesting restrictive physiology, may be seen. The latter is of more ominous prognostic significance.

COMPLICATIONS OF MYOCARDIAL INFARCTION.

Table 7-3 outlines the complications of myocardial infarction

Figure 7-106 Apical two-chamber view of a patient with an inferior myocardial infarction. The proximal third of the inferior wall is thin, with distorted geometry consistent with a basilar aneurysm. The right panel was recorded in systole, and this area can be seen to bulge further compared with the remaining ventricular walls, which contract normally. Abbreviations are as per previous figures.

Figure 7-107 Apical four-chamber views recorded in two different patients with anterior infarct and left ventricular thrombus. The top panel denotes a large laminar thrombus filling a substantial portion of the apex and adherent to the ventricular septum (arrows). The bottom panel denotes a smaller, more spherical thrombus in the apex of the patient with a more limited apical myocardial infarction (arrows). Abbreviations are as per previous figures.

that can be reliably detected using two-dimensional echocardiography. Virtually all mechanical complications are accurately identified.

Left ventricular thrombi may form in the first 24 hours after myocardial infarction and are most commonly seen in anterior infarctions with large areas of apical dyskinesis.[232] [233] They are far less common in inferior wall myocardial infarction. Thrombi can present either as laminar, pedunculated, or mobile masses (Fig. 7-107) . There is a substantially greater likelihood of subsequent embolization in mobile and pedunculated thrombi than in sessile and laminar thrombi.

Infarct expansion is defined as progressive dilation of the infarct zone without recurrent myocardial necrosis.[234] [235] This can occur either acutely, after myocardial infarction, in which case it can be confused with reinfarction, or more chronically over the first 3 to 6 months. When infarct expansion occurs acutely it is seen in the substrate of necrotic and highly friable myocardium. Acute infarct expansion presents as an aneurysm appearing in the first 72 hours, is the anatomical precursor of free wall rupture and ventricular septal defect, and carries a grave prognosis. Chronic infarct expansion occurs over several months, and the likelihood of mechanical complications is low. It does result in tethering of normal walls and progressive chamber dilation with reduction in overall systolic performance. It has been linked to development of both arrhythmias and progressive congestive heart failure.

Pericardial effusion occurs in approximately 40 percent of patients with transmural myocardial infarction. It is often asymptomatic and detected only with echocardiographic scanning. A pericardial effusion occurring in the presence of acute infarct expansion is far more worrisome and may be one of the earlier signs of partial myocardial rupture.

MYOCARDIAL RUPTURE.

The myocardium can rupture in one of three locations. In each case, infarct expansion usually precedes rupture. Free wall rupture complicates approximately 3 percent of acute myocardial infarction and is usually not a survivable event. Clinically, these patients present with recurrent pain and rapidly develop pericardial effusion and tamponade, and death results. In rare instances, echocardiography has been used to document the presence of free wall rupture and allow emergency corrective surgery.[236] A pseudoaneurysm forms when a partial rupture spontaneously seals off, resulting in an extra cardiac chamber the walls of which consist of pericardium and thrombus. It

typically connects to the left ventricle with a narrow mouth, distinguishing it from a true aneurysm, which communicates with the left ventricular cavity by way of a wide opening.[237] [238]

Rupture of either a papillary muscle or the ventricular septum results in signs and symptoms of heart failure and a prominent holosystolic murmur, owing to acute mitral regurgitation or ventricular septal defect ((Figs. 7-108). Two-dimensional echocardiography is a highly accurate technique for separating the two entities.[239] [240] Because of the critically ill nature of these individuals, many of them are intubated and TEE may be necessary to establish a diagnosis. Once the diagnosis is established, the degree of mechanical disruption can be determined. Additionally, echocardiography can be used to assess left and right

TABLE 7-3 -- COMPLICATIONS OF MYOCARDIAL INFARCTION DETECTED BY ECHOCARDIOGRAPHY

EARLY
Pericardial effusion
Infarct expansion
Thrombus formation
Myocardial rupture
Free wall
Ventricular septal defect
Papillary muscle
Functional mitral regurgitation
Right ventricular infarction
LATE
Infarct expansion
Left ventricular aneurysm
Left ventricular thrombus
Pericardial effusion
Functional mitral regurgitation

Figure 7-108 Apical four-chamber view recorded in a patient with acute anteroapical myocardial infarction and an infarct-related septal defect. Note the color flow, traversing the apical portion of the

septum and due to the ventricular septal defect. Abbreviations are as per previous figures.

ventricular function. Both of these are critical components of risk assessment when planning surgical intervention. Ventricular septal defect with concurrent right ventricular dysfunction carries a substantially greater mortality and morbidity.

RIGHT VENTRICULAR INFARCTION.

Some degree of right ventricular dysfunction accompanies a large proportion of patients with inferior infarction due to occlusion of the proximal right coronary artery. Both systolic and diastolic dysfunction occur, and variable degrees of tricuspid regurgitation are common. Depending on which right ventricular branches are involved, the right ventricular wall motion or abnormality can be either apical or more laterally located. Frequently, all that is noted is right ventricular dilation with fairly uniform hypokinesis of the right ventricle.[241] In many instances, right ventricular ischemia is a transient phenomenon and recovery is anticipated. An additional complication of right ventricular infarction is the opening of a patent foramen ovale with subsequent right-to-left shunting. Shunts of significant size can result in arterial oxygen desaturation. The presence of a right-to-left shunt can be reliably documented with saline contrast echocardiography.

In patients with severe multivessel disease, an ischemic cardiomyopathy can develop. This term refers to diffuse global left ventricular systolic dysfunction as a consequence of severe, multivessel coronary artery disease. In many instances there have been multiple unrecognized acute myocardial infarctions. This type of cardiomyopathy presents as a nearly globally hypokinetic ventricle, often with patchy areas of wall thinning but without distinct aneurysm. Secondary mitral regurgitation is common and is due to papillary muscle dysfunction and dilation of the mitral valve annulus.

MYOCARDIAL STUNNING AND HIBERNATION.

There are two phenomena that result in potentially reversible myocardial dysfunction.[242] [243] [244] The first of these is myocardial stunning, which occurs after a severe acute ischemic insult. In this scenario, flow is restored and there is no myocardial necrosis. The exact physiological causes of myocardial stunning are not fully understood, but the syndrome results in spontaneous recovery of myocardial function after restitution of blood flow. Typically, myocardial function recovers in 1 to 7 days. Echocardiography can be used to track recovery of function in this syndrome, and dobutamine stress echocardiography is an excellent means of predicting viability.

Myocardial hibernation is a similar phenomenon seen in a chronic situation.[245] [246] In this situation there is no identifiable recent acute event but diffuse myocardial dysfunction is seen in the presence of normal or near-normal resting blood flow. In many instances what has been termed "myocardial hibernation" may actually represent repetitive stunning. In this scenario, functional recovery of the myocardium occurs after successful revascularization. As in stunning, dobutamine stress echocardiography is an

excellent means for detecting hibernating myocardium.

STRESS ECHOCARDIOGRAPHY.

Stress echocardiography is a family of examinations in which two-dimensional echocardiographic monitoring is undertaken before, during, and after cardiovascular stress. It has been shown to be a cost-effective means for evaluating patients presenting with chest pain. The form of cardiovascular stress can include exercise with treadmill[247] [248] [249] [250] [251] [252] [252A] or bicycle ergometry.[253] [254] [255] [256] By evaluating wall motion at rest and then comparing myocardial performance at stress, one obtains indicators of inducible ischemia that can be assigned to specific coronary territory (Figs. 7-18 and 7-109) . Although treadmill exercise is often more familiar to patients, it is limited by the need to image only at rest and after exercise. It is not possible to successfully image an upright walking individual. Bicycle exercise provides the opportunity to image at each sequential stage of stress, and therefore peak exercise images are available.

For patients incapable of physical exercise, pharmacological stress, most commonly employing a dobutamine infusion, can be used.[251] [257] [258] [259] [260] [261] [262] [262A] [262B] [262C] These protocols typically rely on an incremental infusion protocol of 10, 20, 30, and 40 mug/kg/min, augmented by atropine to obtain an adequate heart rate when necessary. Images can be obtained at each stage of dobutamine infusion. Patients with significant obstructive coronary disease develop regional wall motion abnormalities identical to those seen during physical stress. The safety record of dobutamine has been excellent,[262D] and its accuracy appears equivalent to that of exercise echocardiography. An alternative to dobutamine is dipyridamole infusion, which relies on provocation of ischemia by differential vasodilation in normal and descended arteries.[263] [264]

All of the different exercise echocardiography modalities have been validated against coronary arteriography as a standard and appear to have accuracy equivalent to the competing radionuclide procedures (Table 7-4) . In general, the sensitivity of thallium scintigraphy tends to be slightly higher than that of exercise echocardiography, whereas the specificity of exercise echocardiography typically has been higher than that of thallium. As with all other forms of cardiovascular stress, exercise echocardiography has distinct advantages and disadvantages. Even in experienced laboratories there may be a 5 percent failure rate due to suboptimal imaging and patients in whom adequate levels of cardiovascular stress have not been obtained will not have positive studies, even in the presence of coronary disease. The clinical utility and value of stress echocardiography has been specifically evaluated in female populations. In female populations it appears to be an effective clinical tool for diagnosis and prognosis, however with a slightly lower overall accuracy than seen in male patients.[265] [266]

In addition to the diagnosis of coronary disease, stress echocardiography has been used extensively for determining patient prognosis in general populations[267] [268] [269] [270] [270A] and after myocardial infarction[271] [272] [273] as well as in tracking results of percutaneous interventions.[274] It plays a major role in determining myocardial viability in suspected stunning or hibernation.[275] [276] [276A] [276B] [276C] [276D] [276E] [276F] Dobutamine stress echocardiography has seen substantial success in determining preoperative risk

assessment in patients undergoing noncardiac surgery. Its accuracy for predicting cardiac events of myocardial infarction and death before major vascular surgery exceeds that of competing thallium scintigraphic techniques.[277]

MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY.

This technique relies on use of newly developed contrast agents.[278] [279] [280] [280A] These agents, once injected into the circulation, perfuse the myocardium in a manner parallel to red blood cells. This technique should be considered investigational and still in evolution at this point, but it has shown tremendous promise for detection of coronary stenosis. Multiple technologies are under development for detection of contrast medium within the myocardium, no one of which has been uniformly accepted. Technologies to detect contrast in the myocardium have included routine gray scale imaging, power Doppler imaging,[280B] second harmonic imaging, and pulse inversion imaging, and numerous others are being developed. It may also be necessary to compare perfused and nonperfused frames by using the ultrasound instrument itself to destroy contrast in the myocardium, thereby allowing creation of baseline frames immediately adjacent to perfused frames ((Figs. 7-110). Demonstration of myocardial perfusion with contrast echocardiography has

Figure 7-109 Exercise echocardiogram recorded in a patient with a disease of the right coronary artery. The two left panels were recorded at rest and the two right panels immediately after treadmill exercise; the top panels show diastole and the bottom panels show systole. In each panel the arrows note the location of the inferior wall endocardium at end diastole. At rest there is appropriate thickening and inward motion of the inferior wall that can be seen to move inward through the body of the arrows. Immediately after exercise the proximal inferior wall (lower two arrows) becomes frankly dyskinetic and the mid and diastole portion of the inferior wall is akinetic. Note that there is no incursion of the endocardium into the previously placed arrows.

also been suggested as a means of detecting myocardial viability.

DIRECT VISUALIZATION OF CORONARY ARTERIES.

Using high-frequency transducers, it is possible to directly visualize the proximal portions of the left main and right coronary arteries (Fig. 7-111) .[281] [282] [283] [284] This can be done to identify their takeoff and to exclude anomalous origin of a coronary artery. With scrupulous attention to detail one can visually characterize the wall of the left main and proximal left interior descending coronary artery and detect areas of atherosclerotic involvement and calcification. Detection of calcification within the proximal left anterior descending

TABLE 7-4 -- ACCURACY OF STRESS ECHOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE

	STRESS	NO. OF PATIENTS	SENSITIVITY		SPECIFICITY	
			%	No.	%	No.
Armstrong, et al.[247]	TME	123	88		86	
Crouse, et al.[248]	TME	228	97	170/175	64	34/35
Marwick, et al.[249]	TME	150	84	96/114	86	31/36
Roger, et al.[250]	TME	150	83	50/60	62	56/90
Beleslin, et al.[251]	TME	136	88	105/119	82	14/17
Quinones, et al.[252]	TME	112	74	64/86	88	22/26
Ryan, et al.[253]	Bike	309	91	193/211	77	76/98
Cohen, et al.[254]	Bike	52	78	29/37	87	13/15
Hecht, et al.[255]	Bike	180	93	127/137	86	37/43
Luotolahti, et al.[256]	Bike	118	93	101/108	70	7/10
Marwick, et al.[259]	DSE	217	72	102/142	83	62/75
Ling, et al.[260]	DSE	183	93	151/162	62	13/21
Marcovitz and Armstrong[261]	DSE	141	96	105/109	66	21/32
Beleslin, et al.[251]	DSE	136	82	98/119	77	13/17
Takeuchi, et al.[262]	DSE	120	85	63/74	93	43/46

DSE = dobutamine stress echocardiography; TME = treadmill exercise.

Figure 7-110 Transthoracic two-dimensional echocardiogram recorded after intravenous injection of a perfluorocarbon-based contrast agent. A fill-destruction technique has been used in which the ventricular myocardium can be seen to be opacified by the contrast agent in the left panel. After sequential ultrasound pulses contrast medium is destroyed; the nonenhanced frame appears on the right. There is homogeneous opacification of the entire ventricular myocardium in this normal example.

coronary artery appears to be a potentially reliable marker that significant obstructive coronary artery disease is present. Proximal coronary artery aneurysms can also be detected in children with Kawasaki disease.[285] Either from the transesophageal or transthoracic approach it is also possible to place a Doppler sample volume in the coronary artery lumen and to quantify phasic flow in the coronary artery.[286] [287] It is also possible to use Doppler echocardiography to determine the velocity of flow in the coronary sinus. This can be done both under basal conditions and after vasodilation.

DISEASES OF THE AORTA (See Chap. 40.)

Transthoracic echocardiography visualizes the proximal 3 to 5 cm of the ascending aorta and portions of the descending thoracic aorta behind the left atrium from parasternal positions. In the majority of patients a substantial portion of the aortic arch can be visualized from the suprasternal transducer position. The sensitivity for detecting aortic disease is relatively poor from the transthoracic approach. If disease of the aorta is suspected, TEE is necessary. TEE provides a high-resolution view of the ascending aorta and descending thoracic aorta as far as the gastroesophageal junction but does not visualize the abdominal aorta. Additionally, there is a very limited area of the aortic arch that may be suboptimally viewed. In many centers, TEE has become the preferred and standard examination for evaluation of patients with suspected aortic disease.

AORTIC DISSECTION.

Acute aortic dissection is a life-threatening disease requiring emergent surgical intervention. TTE can be used for early screening and is valuable for detecting the presence of aortic dilation, secondary aortic insufficiency, and left ventricular function. Its accuracy for actual detection of the aortic dissection flap and determining its extent is not adequate as a stand-alone technique. TEE has proven to be a highly accurate and reliable technique for diagnosing and excluding aortic dissection, determining its extent, identification of communication points, and assessment of the severity of aortic insufficiency, and obviously determining complications such as rupture and adventitial hematoma. The accuracy for detection of acute aortic dissection is equivalent to that of CT and MRI (Table 7-5) .[288] [289] [290] [291] [292] [293] [294] [295] [296] [297] [298]

Aortic dissection is classified by several schemes, all of which are designed to distinguish dissection of ascending aorta from that confined to the descending thoracic aorta. A dissection flap appears as a linear echo within the lumen of the aorta (Fig. 7-112) . In patients with connective tissue disease and relatively nonatherosclerotic aortas, the intimal flap is frequently highly mobile. It may take a spiral course as it courses through the descending thoracic aorta. More chronic dissections appear as a linear echo dividing the aorta into two or more lumens. In this instance the intimal flap may appear more rigid and less mobile than in the acute setting. In acute dissection of the ascending aorta,

Figure 7-111 Transthoracic echocardiogram of the left coronary artery. The left main (LM), left anterior descending (LAD), and a proximal portion of the circumflex (CX) coronary artery are clearly visualized.

dilation of the ascending aorta is seen in virtually all instances. Other echocardiographic findings of acute aortic dissection include presence of pleural effusion and of adventitial hematoma, which appears as a homogeneous echo-dense mass outside the wall of the aorta tracking along its course.

Specific cardiac features to be noted in aortic dissection include the presence or absence of pericardial effusion and of aortic insufficiency. Aortic insufficiency can be due either to annular dilation with abnormal coaptation, direct extension of the dissection into the annulus, disrupting the support for the aortic valve, or, less commonly, prolapse of a portion of the intimal flap through the aorta, resulting in a conduit for insufficiency.[298A]

AORTIC ANEURYSM.

Aneurysm of the ascending aorta, arch, and descending thoracic aorta can be diagnosed and characterized with TEE.[298] Characteristics of the aneurysm as fusiform or discrete and the extent of atherosclerotic involvement and secondary thrombus formation can all be determined. Because thoracic aneurysm without dissection is a chronic process requiring serial evaluation, most centers rely more heavily on CT or MRI for elective follow-up of chronic thoracic aortic aneurysms.

ATHEROSCLEROTIC DISEASE.

The transesophageal echocardiogram is an excellent tool for determining the extent and nature of atherosclerotic involvement of the thoracic aorta (Fig. 7-113) . Atherosclerotic disease can be characterized as focal or diffuse and further characterized as mild, moderate, and severe. Complex and mobile components likewise can be noted and have relevance for embolic phenomena.[299] [300] [300A] [300B] [300C]

The phenomenon of intramural hematoma has recently received much attention.[301] [302] Intramural hematoma occurs in the setting of underlying atherosclerotic disease and results in spontaneous rupture and lysis in the medial layers

TABLE 7-5 -- ACCURACY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR DETECTION OF AORTIC DISSECTION

AUTHOR	YEAR	NO. OF PATIENTS	WITH DISSECTION	SENSITIVITY	SPECIFICITY
Erbel, et al.[289]	1989	164	82	81/82 (99%)	80/82 (98%)
Hashimoto, et al.[294]	1989	22	22	22/22 (100%)	N/A
Ballal, et al.[292]	1991	61	34	33/34 (97%)	27/27 (100%)
Nienaber, et al.[293]	1993	110	44	43/44 (98%)	20/26 (77%)

Figure 7-112 Transesophageal echocardiogram recorded in a patient with an acute type A dissection of the aorta. The top panel is a longitudinal view of the ascending aorta. Note the dilation of the proximal aorta and the thin linear echo present in both in the lumen of the aorta, a portion of which prolapses through the aortic valve into the left ventricular outflow tract (arrows). The white arrowheads denote the actual margins of the aortic annulus. The bottom panel is recorded in a view orthogonal to the upper panel and reveals the external diameter of the aorta (black arrowheads) as well as the open three leaflet aortic valve (small white arrows). Within the actual orifice of the aortic valve is a portion of the dissection tear (large white arrow). Abbreviations are as per previous figures.

of the aorta. The syndrome of acute intramural hemorrhage is virtually identical to acute dissection from the standpoint of clinical presentation. Intramural hemorrhage may be a focal process resulting in local breakdown in the medial layers with ulcer formation or can result in creation of a dissection plane through the media. In this instance, rather than seeing a thin intimal flap due to classic dissection a heavily diseased atherosclerotic aorta is seen with a dissection plane through the diseased medial tissue.

MARFAN SYNDROME AND DISEASE OF THE PROXIMAL AORTA.

Marfan syndrome is a heritable disorder of connective tissue that results in abnormalities in the proximal aorta. The underlying pathology is cystic medial necrosis, which results in characteristic dilation of the proximal aorta, most prominent in the sinuses of Valsalva. There is secondary effacement of the sinotubular junction and dilation of the ascending aorta. Because the predominant area of dilation is in the proximal aorta, TTE often suffices for screening in these patients (Fig. 7-114) . Complications of the aortic process in Marfan syndrome include progressive dilation with secondary aortic insufficiency and development of aortic dissection. Echocardiography has seen tremendous success in the serial evaluation of these individuals and in the timing of elective surgery.[303] [304]

SINUS OF VALSALVA ANEURYSM.

In addition to the characteristic symmetrical dilation seen in Marfan syndrome, aneurysms can arise in the sinus of Valsalva. These range from relatively small and discrete to large "windsock" aneurysms that protrude into the right ventricular outflow tract.[305] [306] On occasion, rupture occurs, leading to a continuous shunt from the aorta into the downstream chamber. The most common site for a sinus of Valsalva aneurysm to rupture is into the right atrium or the right ventricular outflow tract. In this instance, remnants of the aneurysm can be seen prolapsing into the right ventricular outflow tract and high velocity turbulent flow is noted in the downstream chamber. Because of the rupture, coarse fluttering of the right coronary cusp of the aortic valve may be noted.

CARDIAC MASSES (See Chap. 49.)

CARDIAC TUMORS.

Echocardiography is the primary screening tool for patients with known or suspected intracardiac tumors.[307] [308] Cardiac tumors can be divided into those that are primary to

the heart and those that are secondary or metastatic. They can be further divided into benign and malignant types.

ATRIAL MYXOMA.

The most common benign primary tumor of the heart is the atrial myxoma. Approximately 75 percent of atrial myxomas are isolated, pedunculated tumors in the left atrium attached to the area of the foramen ovale by a stalk (Fig. 7-115) . Less common locations include the right atrium, either ventricle, or pulmonary vein or vena cava. The classic left atrial myxoma is a smooth, relatively homogeneously echo-dense mass with substantial mobility.[309] It moves into the orifice of the mitral valve in diastole and prolapses back into the left atrium in systole. Depending on its size, it may result in functional obstruction of the mitral valve, thereby mimicking mitral stenosis. Concurrent mitral regurgitation is not uncommon. In the presence of a typical appearance of a myxoma, the diagnosis is virtually certain from an echocardiographic standpoint and no further evaluation may be necessary. Because of the tendency to cause obstruction of the mitral valve, secondary pulmonary hypertension can occur. Additionally, emboli from the surface of the myxoma are not uncommon.

OTHER PRIMARY CARDIAC TUMORS.

Cardiac lipomas are benign primary cardiac tumors with a broad range of appearance. They are most common in the body of the left ventricle and occasionally may be present as pedunculated masses.[310] Although unlikely to embolize, they can be associated with superimposed thrombus, which can embolize. Echocardiography is useful for identification of the mass but is unable to precisely identify it as lipomatous tissue. MRI has substantially succeeded in tissue characterization of these masses.

PAPILLOMA.

Benign papillomas occasionally occur on valvular structures. These appear as homogeneous, usually spherical masses, typically less than 1 cm in diameter. They may appear on the mitral valve chordae and occasionally

Figure 7-113 Transesophageal echocardiograms recorded in three different patients, visualizing the descending thoracic aorta. The upper left panel is recorded in a normal, disease-free aorta. Notice the circular geometry and the lack of any thickening or irregularity in the wall of the aorta. The top right panel was recorded in a patient with a large descending thoracic aortic aneurysm measuring approximately 6 cm in its greatest dimension. Note the substantial atherosclerosis present as well as the vague, smokelike echoes in the lumen of the aorta representing stagnant blood. There is also a lucency posterior to the wall representing spontaneous intramural hemorrhage. The lower two panels were recorded in a patient with moderately severe atherosclerotic disease of the thoracic aorta. The panel on the left was recorded in the transverse view of the aorta. Note the irregular contour of the lumen, which is due to

atherosclerotic involvement of the wall. The panel on the right was recorded at the same level of the aorta but in a longitudinal projection. The upper pointing arrows denote the outer wall of the aorta. Note the irregularity in the aortic lumen and the protruding atheroma (arrows).

Figure 7-114 Transthoracic echocardiogram in a patient with Marfan syndrome. Note the marked dilation of the sinuses of proximal aorta (arrow).

on the aortic valve. As with other cardiac tumors, they have been associated with emboli. The main differential diagnosis is between benign papilloma and vegetation.

CARDIAC MALIGNANCIES.

The majority of cardiac malignancies represent metastatic disease, most commonly from breast, esophagus, or lung. Diffuse malignancy, such as lymphoma, can also involve the heart either primarily or secondarily. Metastatic disease of the heart is virtually always associated with pericardial involvement as well. The appearance of metastatic disease in the heart is typically of mobile echo-dense masses attached to the endothelium (Fig. 7-116) , although isolated intramural masses and diffuse myocardial invasion have also been noted.[311] [312]

There are several primary malignant tumors of the heart, including angiosarcoma and rhabdomyoma. Rhabdomyoma is more common in children. Cardiac malignancies are relatively rare occurrences and can appear in virtually any chamber. There is a greater prevalence of sarcoma and rhabdomyoma in the right atrium (Fig. 7-117) and right ventricle and involving the veins or great vessels than the actual body of the heart in adults.

INTRACARDIAC THROMBUS.

Thrombi can occur in any chamber of the heart but are most common in the left ventricular apex (see Fig. 7-107) after myocardial infarction

Figure 7-115 Transthoracic *(top)* and transesophageal *(bottom)* echocardiogram recorded in a patient with an atrial myxoma. Note the vague echo-dense mass and the transthoracic echocardiogram that is more clearly defined in the transesophageal echo. Additionally, a thin stalk connecting the mass to the atrial septum is seen in the transesophageal echocardiogram.

or in the setting of cardiomyopathy and in the left atrium in the setting of mitral stenosis or atrial fibrillation. Ventricular thrombi have been discussed previously.

Atrial thrombi appear as echo-dense masses within the body of the left atrium but more commonly in the left atrial appendage. The left atrial appendage has a fine muscular ridgelike network that can be confused with small thrombi. Because thrombi occur in the presence of stasis, frequently spontaneous contrast with "smokelike" echoes is seen in the left atrium and left atrial appendage as well.

SPECIFIC CLINICAL UTILIZATION OF ECHOCARDIOGRAPHY

The previous discussion represents an outline of the diagnostic capabilities of echocardiography. There are several specific clinical situations in which echocardiography can be used and which should be understood by the clinician. Table 7-6 outlines the role of different echocardiographic modalities in clinical problem solving.

EVALUATION OF DYSPNEA AND CONGESTIVE HEART FAILURE.

Two-dimensional echocardiography is recommended as an initial part of the evaluation in patients with known or suspected congestive heart failure.[312A] Evaluation of ventricular function can be undertaken, and determination of both primary and secondary valvular abnormalities can likewise be accurately assessed. Doppler echocardiography can play a valuable role with respect to determining diastolic function and establishing the diagnosis of diastolic heart failure. Heart failure with normal systolic function but abnormal diastolic relaxation comprises 30 to 40 percent of patients presenting with congestive heart failure. Because the therapy of this is distinctly different from that of systolic dysfunction, establishing the appropriate etiology and diagnosis is essential. This can be effectively done with the combination of two-dimensional echocardiography and Doppler echocardiography.

CARDIAC SOURCE OF EMBOLUS.

It has become increasingly recognized that many neurological events and large artery occlusions are the result of embolization from the heart or other major vascular structures. Identifying which patients are most likely to have a cardiac source of embolus has been problematic, but, in general, any patient with abrupt occlusion of a major vessel or younger individual with a neurological event (typically younger than 45 years of age) should be suspected of having a potential cardiac etiology. Additionally, older individuals with neurological events but who do not have identifiable vascular disease require screening for a cardiac etiology. Several large-scale surveillance studies have demonstrated prevalence and range of abnormalities associated with neurological and embolic events.[313] [314] [315] One of the more common abnormalities to identify in this situation is a patent foramen ovale with or without a right-to-left shunt identified by contrast echocardiography (see Fig. 7-83) . TEE is often required for

Figure 7-116 Transesophageal echocardiogram recorded in a long-axis view of the left atrium and left ventricle in a patient with an intracardiac tumor. Note the approximate 1 cm diameter spherical mass

attached to the posterior wall of the left ventricle by a thin stalk (arrow).

Figure 7-117 Apical four-chamber view *(top)* and transesophageal echocardiogram *(bottom)* in a patient with a large right atrial mass. In the top panel the mass can be seen arising from the area of the inferior vena cava and essentially filling the right atrium. A similar appearance is seen in the transesophageal echocardiogram *(bottom)* where the mass appears adjacent to the atrial septum. Abbreviations are as per previous figures.

complete evaluation because TTE is not sufficient to exclude left atrial thrombus or evaluate the thoracic aorta for atherosclerotic degree. A potential cardiac source of embolus will be identified in many patients with neurological and other events, but the identification of such a lesion does not necessarily prove cause and effect. The degree to which atherosclerotic disease of the aorta and patent foramen ovale are causative rather than coexistent with other etiologies often remains unproven. In a substantial number of patients, highly mobile strands and areas of fibrosis may be noted on either the aortic or mitral valve. The clinical implication of these anomalies is unknown.

ATRIAL FIBRILLATION.

Echocardiography plays a crucial role in the evaluation of patients with atrial fibrillation.[316] [317] [318] [319] [320] [320A] [320B] Patients with atrial fibrillation should be characterized as having underlying heart disease or having a structurally normal heart, in which case a diagnosis of lone atrial fibrillation can be made. Determination of the underlying cardiac anatomy is essential for decision-making regarding likelihood of conversion to and maintenance of sinus rhythm and for determining the embolic potential and hence the need for long-term anticoagulation. In general, patients with normal cardiac anatomy are unlikely to sustain an embolic event and highly likely to revert to sinus rhythm and have sinus rhythm maintained. Conversely, patients with cardiomyopathy and severe mitral stenosis are less likely to be maintained in sinus rhythm and have a higher likelihood of embolic events. Thus, these individuals are candidates for long-term anticoagulation. TEE has also been proposed as a management tool in determining the timing for elective cardioversion. Immediately after electrical cardioversion there is an increased likelihood of embolization. Embolization in this setting arises either from

Figure 7-118 Transesophageal echocardiogram recorded in a patient with a recent neurological event. In the top panel there is vague echo mass, which in real time has a swirling smokelike appearance (downward pointing arrow). At a slightly different transducer position, the actual apex of the left atrial appendage can be seen to contain a filling defect consistent with thrombus, noted between the two vertically oriented arrows. Abbreviations are as per previous figures.

TABLE 7-6 -- CLINICAL UTILITY OF ECHOCARDIOGRAPHY

	2D	DOPPLER	CFD	CONTINUOUS WAVE	TEE	STRESS
Pericardial disease	1	2	3	4	4	N/A
Valvular heart disease						
Murmur	1	1	1	3	4	N/A
Mitral stenosis	1	1	1	--	3	3
Mitral regurgitation	1	1	1	--	3	N/A
Aortic stenosis/regurgitation	1	1	1	--	3	3
Prosthetic heart valve dysfunction	1	1	1	--	2	N/A
Coronary artery disease						
Chest pain syndrome	1	3	3	4	4	1
Rule out coronary artery disease	1	3	3	4	4	1
Diagnose acute myocardial infarction	1	3	3	4	4	N/A
Complications of infarction						
Aneurysm	1	3	3	4	4	N/A
Thrombus	1	3	3	4	4	N/A
Ventricular septal defect/papillary muscle rupture	1	1	1	3	2	N/A
Assess left ventricular function	1	1	2	4	4	3
Congenital heart disease	1	1	1	3	3	3
Atrial septal defect	1	1	1	2	2	4
Cardiomyopathy						
Dilated	1	1	1	4	4	3
Hypertrophic	1	1	1	4	4	3
Endocarditis	1	1	1	4	2	N/A
Pulmonary hypertension						
Known	1	1	1	2	3	3

Occult	1	1	1	2	3	2
Congestive heart failure	1	1	1	4	4	3
Stroke/source of embolus	1	2	2	1	2	N/A
Aortic dissection	2	2	1	4	1	N/A
Dyspnea evaluation	1	1	1	1	4	1

1 = Indicated and essential; 2 = often required--may add, informative; 3 = necessary in select instances for specific question; 4 = rarely necessary;

2D = two-dimensional; CFD = color flow Doppler; TEE = transesophageal echocardiography; N/A = not available.

From Armstrong WF: Echocardiography. In Kelly's Textbook of Medicine. 4th ed. Philadelphia, Lippincott-Raven, 2000.

a preexisting thrombus or from atrial stunning with subsequent thrombus formation (Fig. 7-118) . A strategy of TEE to exclude left atrial thrombus, followed immediately by cardioversion, has been proposed as an efficient means of restoring sinus rhythm without requiring long-term pre-cardioversion anticoagulation. After cardioversion, atrial stunning occurs and the likelihood of new thrombus formation is actually transiently enhanced. For this reason, anticoagulation is clinically indicated in virtually all patients immediately after cardioversion.

PULMONARY EMBOLUS (See also Chap. 52) .

Patients with pulmonary embolus often present with atypical symptoms. In this instance, TEE and TTE can provide valuable clinical information.[321] [322] In a patient presenting with a combination of chest pain and dyspnea, with or without evidence of venous stasis, detection of right-sided heart dilation and dysfunction and/or elevation of pulmonary artery pressures can be valuable clues to the nature of the underlying process. Direct visualization of large pulmonary emboli is occasionally possible from either TTE but more usually TEE.[323] Additionally, by using either technique, embolus in transit can be detected as a highly mobile serpiginous mass, typically entrapped in the tricuspid valve apparatus and less commonly spanning a patent foramen ovale. Detection of typical serpiginous mass in the right atrium identifies a patient at substantial risk for further embolization and is a clinical situation requiring emergent therapy (Fig. 7-119) .

PULMONARY HYPERTENSION (See also Chap. 53) .

Pulmonary hypertension represents an elusive diagnosis. Clinically, pulmonary hypertension can occur either as a primary phenomenon or secondary to a variety of either cardiac or pulmonary processes. The majority of patients with established pulmonary hypertension have identifiable abnormalities on echocardiography, including variable degrees of right ventricular enlargement and hypertrophy ((Figs. 7-120). [324] [325] As noted earlier, pulmonary artery pressures can be estimated from the velocity of the tricuspid regurgitation jet (see Fig. 7-29) . In patients with only mild elevation of

pulmonary pressure, exercise echocardiography to track pulmonary artery pressures with stress can also be performed and provides valuable information regarding the presence of occult, exercise-induced pulmonary hypertension. Doppler echocardiography can also be used to follow pulmonary artery pressures with therapy.

FETAL ECHOCARDIOGRAPHY.

Because cardiac ultrasonography carries no risk to the pregnant women or fetus and is fully noninvasive it can be used to make the antepartum diagnosis of congenital heart disease.[326] This should be undertaken only by pediatric echocardiographers with appropriate experience in the technique. Many major intracardiac abnormalities can be detected at the end of the first trimester, and the majority of physiologically significant abnormalities can be detected in utero in the second trimester. This technique has seen substantial use in identifying fetuses with congenital heart defects who may warrant urgent transfer to a neonatal intensive care unit or an emergent intervention for life-threatening cardiac problems immediately after birth.

EVALUATION AND MONITORING OF INVASIVE AND INTERVENTIONAL PROCEDURES.

Two-dimensional echocardiography, often using TEE, has seen substantial success as a means of monitoring invasive procedures. This includes direct online monitoring of pericardiocentesis[327] and assistance in localization and placement of catheters for electro

Figure 7-120 Transthoracic echocardiogram recorded in a parasternal long- and short-axis view in a patient with severe pulmonary hypertension. Note the dilation and hypertrophy of the right ventricle and the abnormal geometry of the left ventricle in which the ventricular septum is concave toward the right ventricle.

Figure 7-119 Transesophageal echocardiogram recorded in a patient with pulmonary embolus, found to have "thromboembolism in transit." The top panel is recorded at 0 degrees. The dilated right atrium and right ventricle are obvious. Three highly mobile components of a long serpiginous thrombus can be seen in the right atrium (arrows). The bottom panel is recorded at 106 degrees and visualizes the right atrium. The serpiginous nature of the thrombus can be appreciated, and it is noted to coil on itself in the cavity of the right atrium. Abbreviations are as per previous figures.

physiological ablation as well as online monitoring of endomyocardial biopsy specimens.[328] [329] [330] Additionally, TEE is an instrumental component of transcatheter closure of atrial septal defects in the catheterization laboratory[330A] and often used in other procedures where a transatrial approach is necessary for therapy, such as mitral balloon valvotomy.[331] [332] [333]

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GUIDELINES
USE OF ECHOCARDIOGRAPHY

Thomas H. Lee

Guidelines for the use of echocardiography were published by an ACC/AHA task force in 1997.[1] These guidelines focus on transthoracic and transesophageal echocardiography (TTE and TEE, respectively), with Doppler analysis; they do not address newer technologies such as three-dimensional echocardiography, intravascular ultrasound, or contrast medium-enhanced echocardiography. In the absence of randomized trials that explictly test the impact of diagnostic tests on outcomes, these guidelines are based on expert consensus and observational studies. Additional recommendations for use of echocardiography for specific issues related to valvular heart disease were developed by a later ACC/AHA task force focusing on valvular heart disease.[2] These recommendations are summarized in the Guidelines following Chapter 46 . Recommendations for the use of echocardiography in patients with suspected endocarditis are also described in the Guidelines following Chapter 47 .

The guidelines provide recommendations regarding the appropriateness of use of echocardiography in various clinical settings, using the standard three-class system of ACC/AHA guidelines. The guidelines specify situations in which echocardiography is considered unlikely to contribute information that improves the management of patients. They also address recommendations about the frequency with which Doppler echocardiography should be repeated for some clinical issues. In general, the guidelines discourage routine use of echocardiography for patients whose initial echocardiograms show minimal or mild abnormalities, unless there is a change in clinical signs or symptoms.

MURMURS AND VALVULAR HEART DISEASE

Echocardiography is a critical tool for the assessment of patients with cardiac murmurs in the setting of cardiorespiratory symptoms and in patients with possible structural heart disease (Table 7-G-1) . However, the guidelines emphasize that echocardiography is not a substitute for a careful cardiovascular examination, and they specify that this test is not appropriate in patients with murmurs that an experienced observer identifies as functional or innocent. Characteristics of such murmurs as identified in the guidelines are a systolic murmur of short duration, grade 1 or 2 intensity at the left sternal border, a systolic ejection pattern, a normal S_2 , no other abnormal sounds or murmurs, no evidence of ventricular hypertrophy or dilatation, no thrills, and the absence of an increase in intensity with the Valsalva maneuver.

For patients with known or suspected valvular stenosis, echocardiography is an appropriate test for assessing severity of valvular stenosis and ventricular dysfunction. This test is appropriate for evaluation of changes in symptoms or signs, and also in asymptomatic patients with severe valvular stenosis or with left ventricular dysfunction or hypertrophy (see Table 7-G-1) . In contrast, the guidelines discourage routine use of echocardiography for serial re-evaluations of patients with mild aortic or mitral stenosis whose functional status and clinical examination are unchanged.

Doppler echocardiography is also the test of choice to evaluate valvular regurgitation and assess the need for surgical intervention.

TABLE 7-7-G-1 -- ACC/AHA GUIDELINES FOR USE OF ECHOCARDIOGRAPHY

Indication	Class I	Class IIa	Class IIb	Class III
Evaluation of heart murmurs	1. A murmur in a patient with cardiorespiratory symptoms 2. A murmur in an asymptomatic patient if the clinical features indicate at least a moderate probability that the murmur is reflective of structural heart disease	1. A murmur in an asymptomatic patient in whom there is a low probability of heart disease but in whom the diagnosis of heart disease cannot be reasonably excluded by the standard cardiovascular clinical evaluation		1. In an adult, an asymptomatic heart murmur that has been identified by an experienced observer as functional or innocent

Valvular stenosis	1. Diagnosis; assessment of hemodynamic severity 2. Assessment of LV and RV size, function, and/or hemodynamics 3. Reevaluation of patients with known valvular stenosis with changing symptoms or signs 4. Assessment of changes in hemodynamic severity and ventricular compensation in patients with known valvular stenosis during pregnancy 5. Reevaluation of asymptomatic patients with severe stenosis	1. Assessment of the hemodynamic significance of mild to moderate valvular stenosis by stress Doppler echocardiography 2. Reevaluation of patients with mild to moderate aortic stenosis with LV dysfunction or hypertrophy even without clinical symptoms	1. Reevaluation of patients with mild to moderate aortic valvular stenosis with stable signs and symptoms	1. Routine reevaluation of asymptomatic adult patients with mild aortic stenosis having stable physical signs and normal LV size and function 2. Routine reevaluation of asymptomatic patients with mild to moderate mitral stenosis and stable physical signs

Native valvular regurgitation	1. Diagnosis; assessment of hemodynamic severity 2. Initial assessment and reevaluation (when indicated) of LV and RV size, function, and/or hemodynamics 3. Reevaluation of patients with mild to moderate valvular changing symptoms 4. Reevaluation of asymptomatic patients with severe regurgitation 5. Assessment of changes in hemodynamic severity and ventricular compensation in patients with known valvular regurgitation during pregnancy 6. Reevaluation of patients with mild to moderate regurgitation with ventricular dilation without clinical symptoms 7. Assessment of the effects of medical therapy on the severity of regurgitation and ventricular compensation and function		1. Reevaluation of patients with mild to moderate mitral regurgitation without chamber dilation and without clinical symptoms 2. Reevaluation of patients with moderate aortic regurgitation without chamber dilation and without clinical symptoms	1. Routine reevaluation in asymptomatic patients with mild valvular regurgitation having stable physical signs and normal LV size and function

Mitral valve prolapse (MVP)	1. Diagnosis; assessment of hemodynamic severity, leaflet morphology, and/or ventricular compensation in patients with physical signs MVP	1. To exclude MVP in patients who have been diagnosed but without clinical evidence to support the diagnosis 2. To exclude MVP in patients with first-degree relatives with known myxomatous valve disease 3. Risk stratification in patients with physical signs of MVP or known MVP		1. Exclusion of MVP in patients with ill-defined symptoms in the absence of a constellation of clinical symptoms or physical findings suggestive of MVP or a positive family history 2. Routine repetition of echocardiography in patients with MVP with no or mild regurgitation and no changes in clinical signs or symptoms
Interventions for valvular heart disease and prosthetic valves	1. Assessment of the timing of valvular intervention based on ventricular compensation, function, and/or severity of primary and secondary lesions 2. Selection of alternative therapies for mitral valve disease (such as balloon valvuloplasty, operative valve repair, valve replacement)[*] 3. Use of echocardiography (especially transesophageal) in performing interventional techniques (e.g., balloon valvotomy) for valvular disease 4.	1. Routine reevaluation study after baseline studies of patients with valve replacements with mild to moderate ventricular dysfunction without changing clinical signs or symptoms	1. Routine reevaluation at the time of increased failure rate of a bioprosthesis without clinical evidence of prosthetic dysfunction	1. Routine reevaluation of patients with valve replacements without suspicion of valvular dysfunction and unchanged clinical signs and symptoms 2. Patients whose clinical status precludes therapeutic interventions

	transesophageal) in performing interventional techniques (e.g., balloon valvotomy) for valvular disease 4. Postinterventional baseline studies for valve function (early) and ventricular remodeling (late) 5. Reevaluation of patients with valve replacement with changing clinical signs and symptoms; suspected prosthetic dysfunction (stenosis, regurgitation) or thrombosis*			
Patients with chest pain	1. Diagnosis of underlying cardiac disease in patients with chest pain and clinical evidence of valvular, pericardial, or primary myocardial disease 2. Evaluation of chest pain in patients with suspected acute myocardial ischemia, when baseline ECG is nondiagnostic and when study can be obtained during pain or soon after its abatement 3. Evaluation of chest pain in patients with suspected aortic dissection 4. Chest pain in patients with severe hemodynamic instability			1. Evaluation of chest pain for which a noncardiac etiology is apparent 2. Diagnosis of chest in a patient with ECG changes diagnostic of myocardial ischemia/infarction

	dissection 4. Chest pain in patients with severe hemodynamic instability			
Diagnosis of acute myocardial ischemic syndromes	1. Diagnosis of suspected acute ischemia or infarction not evident by standard means 2. Measurement of baseline LV function 3. Patients with inferior myocardial infarction and bedside evidence suggesting possible RV infarction 4. Assessment of mechanical complications and mural thrombus (TEE is indicated when TTE studies are not diagnostic.)	1. Identification of location/severity of disease in patients with ongoing ischemia		1. Diagnosis of acute myocardial infarction already evident by standard means
Risk assessment, prognosis, and assessment of therapy in acute myocardial ischemic syndromes	1. Assessment of infarct size and/or extent of jeopardized myocardium 2. In-hospital assessment of ventricular function when the results are used to guide therapy 3. In-hospital or early postdischarge assessment of the presence/extent of inducible ischemia whenever baseline abnormalities are expected to compromise ECG interpretation	1. In-hospital or early postdischarge assessment of the presence/extent of inducible ischemia in the absence of baseline abnormalities expected to compromise ECG interpretation 2. Assessment of myocardial viability when required to define potential efficacy of revascularization 3. Reevaluation of ventricular function during recovery when results are used to guide therapy	1. Assessment of long term prognosis (2 years after acute myocardial infarction)	1. Routine reevaluation in the absence of any change in clinical status

		3. Reevaluation of ventricular function during recovery when results are used to guide therapy 4. Assessment of ventricular function after revascularization		
Diagnosis and prognosis of chronic ischemic heart disease	1. Diagnosis of myocardial ischemia in symptomatic individuals 2. Assessment of global ventricular function at rest 3. Assessment of myocardial viability (hibernating myocardium) for planning revascularization 4. Assessment of functional significance of coronary lesions (if not already known) in planning percutaneous transluminal coronary angioplasty	None	1. Diagnosis of myocardial ischemia in selected patients with an intermediate or high pretest likelihood of coronary artery disease 2. Assessment of an asymptomatic patient with positive results from a screening treadmill test 3. Assessment of a global ventricular function with exercise	1. Screening of asymptomatic persons with a low likelihood of coronary artery disease 2. Routine periodic reassessment of stable patients for whom no change in therapy is contemplated 3. Routine substitution for treadmill exercise testing in patients for whom ECG analysis is expected to suffice
Assessment of interventions in chronic ischemic heart disease	1. Assessment of LV function when needed to guide institution and modification of drug therapy in patients with known or suspected LV dysfunction 2. Assessment for restenosis after revascularization in patients with atypical recurrent symptoms	1. Assessment of restenosis after revascularization in patients with typical recurrent symptoms		1. Routine assessment of asymptomatic patients after revascularization

Patients with dyspnea, edema, or cardiomyopathy	1. Assessment of LV size and function in patients with suspected cardiomyopathy or clinical diagnosis of heart failure* 2. Edema with clinical signs of elevated central venous pressure when a potential cardiac etiology is suspected or when central venous pressure cannot be estimated with confidence and clinical suspicion of heart disease is high* 3. Dyspnea with clinical signs of heart disease 4. Patients with unexplained hypotension, especially in the intensive care unit* 5. Patients exposed to cardiotoxic agents, to determine the advisability of additional or increased dosages 6. Reevaluation of LV function in patients with established cardiomyopathy when there has been a documented change in clinical status to guide medical therapy	None	1. Reevaluation of patients with established cardiomyopathy when there is no change in clinical status 2. Reevaluation of patients with edema when a potential cardiac cause has already been demonstrated	1. Evaluation of LV ejection fraction in patients with recent (contrast or radionuclide) angiographic determination of ejection fraction 2. Routine reevaluation in clinically stable patients in whom no change is contemplated 3. In patients with edema, normal venous pressure, and no evidence of heart disease

Pericardial disease	1. Patients with suspected pericardial disease, including effusion, constriction, or effusive-constrictive process 2. Patients with suspected bleeding in the pericardial space (e.g., trauma, perforation) 3. Follow-up study to evaluate recurrence of effusion or to diagnose early constriction. Repeat studies may be goal directed to answer a specific clinical question. 4. Pericardial friction rub developing in acute myocardial infarction accompanied by symptoms such as persistent pain, hypotension, and nausea	1. Follow-up studies to detect early signs of tamponade in the presence of large or rapidly accumulating effusions. A goal-directed study may be appropriate. 2. Echocardiographic guidance and monitoring of pericardiocentesis	1. Postsurgical pericardial disease, including postpericardiotomy syndrome, with potential for hemodynamic impairment 2. In the presence of a strong clinical suspicion and nondiagnostic TTE, TEE assessment of pericardial thickness to support a diagnosis of constrictive pericarditis	1. Routine follow-up of small pericardial effusion in clinically stable patients 2. Follow-up studies in patients with cancer or other terminal illness for whom management would not be influenced by echocardiographic findings 3. Assessment of pericardial thickness in patients without clinical evidence of constrictive pericarditis 4. Pericardial friction rub in early uncomplicated myocardial infarction or early postoperative period after cardiac surgery

Patients with cardiac masses and tumors	1. Evaluation of patients with clinical syndromes and events suggesting an underlying cardiac mass 2. Evaluation of patients with underlying cardiac disease known to predispose to mass formation for whom a therapeutic decision regarding surgery or anticoagulation will depend on the results of echocardiography 3. Follow-up or surveillance studies after surgical removal of masses known to have a high likelihood of recurrence (i.e., myxoma) 4. Patients with known primary malignancies when echocardiographic surveillance for cardiac involvement is part of the disease staging process		1. Screening persons with disease states likely to result in mass formation but for whom no clinical evidence for the mass exists	1. Patients for whom the results of echocardiography will have no impact on diagnosis or clinical decision making

Suspected thoracic aortic disease	TEE: 1. Aortic dissection 2. Aortic aneurysm 3. Aortic rupture 4. Degenerative or traumatic aortic disease with clinical atheroembolism 5. Follow-up of aortic dissection especially after surgical repair when complication or progression is suspected TTE: 1. Aortic aneurysm (especially for aortic root aneurysm) 2. Aortic root dilation in Marfan or other connective tissue syndromes 3. Follow-up of aortic dissection, especially after surgical repair without suspicion of complication or progression 4. First-degree relative of a patient with Marfan syndrome or other connective tissue disorder			

Pulmonary disease	1. Suspected pulmonary hypertension 2. Pulmonary emboli and suspected clots in the right atrium or ventricle or main pulmonary artery branches [*] 3. For distinguishing cardiac vs. noncardiac etiology of dyspnea in patients in whom all clinical and laboratory clues are ambiguous[*] 4. Follow-up of pulmonary artery pressures in patients with pulmonary hypertension to evaluate response to treatment 5. Lung disease with clinical suspicion of cardiac involvement (suspected cor pulmonale)	1. Measurement of exercise pulmonary artery pressure 2. Patients being considered for lung transplantation or other surgical procedure for advanced lung disease [*]		1. Lung disease without any clinical suspicion of cardiac involvement 2. Reevaluation studies of RV function in patients with chronic obstructive lung disease without a change in clinical status

Hypertension	1. When assessment of resting LV function, hypertrophy, or concentric remodeling is important in clinical decision making 2. Detection and assessment of functional significance of concomitant coronary artery disease (stress echocardiography) 3. Follow-up assessment of LV size and function in patients with LV dysfunction when there has been a documented change in clinical status or to guide medical therapy	1. Identification of LV diastolic filling abnormalities 2. Assessment of LV hypertrophy in a patient with borderline hypertension without LV hypertrophy on ECG to guide decision making regarding initiation of therapy. A limited goal-directed echocardiogram may be indicated for this purpose	1. Risk stratification for prognosis by determination of LV performance	1. Reevaluation to guide antihypertensive therapy based on LV mass regression 2. Reevaluation in asymptomatic patients to assess LV function

Patients with neurological events or other vascular occlusive events	1. Patients of any age with abrupt occlusion of a major peripheral or visceral artery 2. Younger patients (typically < 45 years) with cerebrovascular events 3. Older patients (typically > 45 years) with neurological events without evidence of cerebrovascular disease or other obvious cause 4. Patients for whom a clinical therapeutic decision (e.g., anticoagulation) will depend on the results of echocardiography	1. Patients with suspicion of embolic disease and with cerebrovascular disease of questionable significance	1. Patients with a neurological event and intrinsic cerebrovascular disease of a nature sufficient to cause the clinical event	1. Patients for whom the results of echocardiography will not impact a decision to institute anticoagulant therapy or otherwise alter the approach to diagnosis or treatment
Patients with arrhythmias and palpitations	1. Arrhythmias with clinical suspicion of structural heart disease 2. Arrhythmia in a patient with a family history of a genetically transmitted cardiac lesion associated with arrhythmia such as tuberous sclerosis, rhabdomyoma, or hypertrophic cardiomyopathy 3. Evaluation of patients as a component of the work-up before electrophysiological ablative procedures	1. Arrhythmia requiring treatment 2. TEE guidance of transseptal catheterization and catheter placement during ablative procedures	1. Arrhythmias commonly associated with, but without clinical evidence of, heart disease 2. Evaluation of patients who have undergone radiofrequency ablation in the absence of complications. (In centers with established ablation programs, a postprocedural echocardiogram may not be necessary.)	1. Palpitation without corresponding arrhythmia or other cardiac signs or symptoms 2. Isolated premature ventricular contractions for which there is no clinical suspicion of heart disease

Before cardioversion	1. Evaluation of patient for whom a decision concerning cardioversion will be impacted by knowledge of prognostic factors (e.g., LV function, coexistent mitral valve disease) TEE only: 1. Patients requiring urgent (not emergent) cardioversion for whom extended precardioversion anticoagulation is not desirable* 2. Patients who have had prior cardioembolic events thought to be related to intraatrial thrombus* 3. Patients for whom anticoagulation is contraindicated and for whom a decision about cardioversion will be influenced by TEE results* 4. Patients for whom intraatrial thrombus has been demonstrated in previous TEE*	1. Patients with atrial fibrillation of <48 hours' duration and other heart disease (TEE only)	1. Patients with atrial fibrillation of <48 hours' duration and no other heart disease (TEE only) 2. Patients with mitral valve disease or hypertrophic cardiomyopathy who have been on long-term anticoagulation at therapeutic levels before cardioversion (TEE only) 3. Patients undergoing cardioversion from atrial flutter	1. Patients requiring emergent cardioversion 2. Patients who have been on long-term anticoagulation at therapeutic levels and who do not have mitral valve disease or hypertrophic cardiomyopathy before cardioversion 3. Precardioversion evaluation of patients who have undergone previous TEE and with no clinical suspicion of a significant interval change

Patient with syncope	1. Syncope in a patient with clinically suspected heart disease 2. Periexertional syncope	1. Syncope in a patient in a high-risk occupation (e.g., pilot)	1. Syncope of occult etiology with no findings of heart disease on history or physical examination	1. Recurrent syncope in a patient in whom previous echocardiographic or other testing demonstrated a cause of syncope 2. Syncope in a patient for whom there is no clinical suspicion of heart disease 3. Classic neurogenic syncope
Screen for the presence of cardiovascular disease	1. Patients with a family history of genetically transmitted cardiovascular disease 2. Potential donors for cardiac transplantation 3. Patients with phenotypic features of Marfan syndrome or related connective tissue diseases 4. Baseline and reevaluations of patients undergoing chemotherapy with cardiotoxic agents		1. Patients with systemic disease that may affect the heart	1. The general population 2. Competitive athletes without clinical evidence of heart disease
Critically ill	1. The hemodynamically unstable patient 2. Suspected aortic dissection (TEE)			1. The hemodynamically stable patient not expected to have cardiac disease 2. Reevaluation follow-up studies on hemodynamically stable patients

Critically injured	1. Serious blunt or penetrating chest trauma (suspected pericardial effusion or tamponade) 2. Mechanically ventilated multiple-trauma or chest trauma patient 3. Suspected preexisting valvular or myocardial disease in the trauma patient 4. The hemodynamically unstable multiple-injury patient without obvious chest trauma but with a mechanism of injury suggesting potential cardiac or aortic injury (deceleration or crush) 5. Widening of the mediastinum, post injury suspected aortic injury (TEE) 6. Potential catheter, guidewire, pacer electrode, or pericardiocentesis needle injury with or without signs of tamponade	1. Evaluation of hemodynamics in multiple-trauma or chest trauma patients with pulmonary artery catheter monitoring and data disparate with clinical situation 2. Follow-up study on victims of serious blunt or penetrating trauma		1. Suspected myocardial contusion in the hemodynamically stable patient with a normal ECG

Adult patient with congenital heart disease	1. Patients with clinically suspected congenital heart disease, as evidenced by signs and symptoms such as murmur, cyanosis, or unexplained arterial desaturation, and an abnormal ECG or radiograph suggesting congenital heart disease 2. Patients with known congenital heart disease on follow-up when there is a change in clinical findings 3. Patients with known congenital heart disease for whom there is uncertainty as to the original diagnosis or when the precise nature of the structural abnormalities or hemodynamics is unclear 4. Periodic echocardiograms in patients with known congenital heart lesions and for whom ventricular function and atrioventricular valve regurgitation must be followed (e.g., patients with a functionally single ventricle after Fontan procedure, transposition of the great vessels after Mustard procedure,		1. A follow-up Doppler echocardiographic study, annually or once every 2 years, in patients with known hemodynamically significant congenital heart disease without evident change in clinical condition	1. Multiple repeat Doppler echocardiography in patients with repaired patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of the aorta, or bicuspid aortic valve without change in clinical condition 2. Repeat Doppler echocardiography in patients with known hemodynamically insignificant congenital heart lesions (e.g., small atrial septal defect, small ventricular septal defect) without a change in clinical condition

a functionally single ventricle after Fontan procedure, transposition of the great vessels after Mustard procedure, L-transposition and ventricular inversion and palliative shunts) 5. Patients with known congenital heart disease for whom following pulmonary artery pressure is important (e.g., patients with moderate or ventricular septal defects, atrial septal defects, single ventricle ,or any of the above with an additional risk factor for pulmonary hypertension). 6. Periodic echocardiography in patients with surgically repaired (or palliated) congenital heart disease with the following: change in clinical condition or clinical suspicion of residual defects, LV or RV function that must be followed, or when there is a possibility of hemodynamic progression or a history of pulmonary hypertension 7. To direct interventional catheter valvotomy, radiofrequency ablation valvotomy interventions in the presence of complex cardiac			

	catheter valvotomy, radiofrequency ablation valvotomy interventions in the presence of complex cardiac anatomy		

LV = left ventricular; RV = right ventricular; ECG = electrocardiographic/electrocardiogram; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.
From Cheitlin MD, Alpert JS, Armstrong WF, et al: ACC/AHA guidelines for the clinical application of echocardiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Circulation 95:1686-1744, 1997. Copyright 1997, American Heart Association.

*TEE may provide incremental value in addition to information obtained by TTE. The role of TEE in first-line examination awaits further study

Exercise or pharmacological stress echocardiogram.

Dobutamine stress echocardiogram.

Because left ventricular dysfunction is such a critical issue in the natural history of such patients, this test is appropriate in asymptomatic patients with severe regurgitation, as well as those with changes in symptoms or signs. The ACC/AHA task force considered routine use of echocardiography inappropriate for patients with mild valvular regurgitation, stable physical signs, and normal left ventricular size and function and was uncertain about its appropriateness in asymptomatic patients with moderate valvular regurgitation without chamber dilation.

The guidelines emphasize that the physical examination is the optimal method of diagnosing mitral valve prolapse, in part because of the substantial possibility of false-positive results with echocardiography. Specifically discouraged is use of echocardiography to exclude mitral valve prolapse in patients with ill-defined symptoms but no other clinical evidence for this condition and also routine repetition of echocardiography in patients with mitral valve prolapse with no or mild regurgitation and no changes in clinical signs or symptoms.

Echocardiography is strongly supported in virtually all patients with known or suspected infective endocarditis. ACC/AHA guidelines on use of this procedure in patients in this setting are described in the Guidelines in Chapter 47 (see Table 47-G-6).

The ACC/AHA task force was supportive of use of echocardiography before and after operative interventions for valvular disease, but it was uncertain about the ideal interval for repeat evaluation in patients without changing clinical signs or symptoms or evidence of prosthetic valve dysfunction. The guidelines discouraged routine echocardiography in patients whose overall clinical status precludes therapeutic interventions. For patients with suspected infective endocarditis involving prosthetic valves, the guidelines acknowledge the potential incremental value of TEE compared

with TTE.

ACUTE CHEST PAIN

Many cardiac conditions that cause chest pain are associated with structural abnormalities that can be detected with echocardiography, and evidence for a useful role for echocardiography in the management of these patients has grown. The ACC/AHA guidelines supported use of echocardiography to help diagnose or exclude acute myocardial ischemia when the baseline electrocardiogram is nondiagnostic and when the study can be obtained promptly. Echocardiography was also endorsed as a test for suspected aortic dissection and in patients with severe hemodynamic instability. This test was not, however, considered appropriate for routine use for diagnostic purposes in patients with a high likelihood of myocardial ischemia or infarction.

ISCHEMIC HEART DISEASE

TTE and TEE are useful tools for detection of regional wall motion abnormalities, assessing left ventricular dysfunction, and evaluating structural complications of acute myocardial infarction (e.g., acute mitral regurgitation, free wall rupture, ventricular septal defect, or intracardiac thrombus formation). The ACC/AHA task force considered early echocardiography most useful in patients with a high clinical suspicion of acute myocardial infarction but a nondiagnostic electrocardiogram. Similarly, stress echocardiography was supported when the clinical history and electrocardiogram are not reliable sources on which to base a diagnosis.

The ACC/AHA task force was less certain but generally supportive of the use of echocardiography for assessment of the location and severity of disease in patients with ongoing ischemia, or for assessment of myocardial viability when patients were candidates for coronary revascularization (Class IIa). Routine use of echocardiography in the absence of change in clinical status or when the test was unlikely to change diagnosis or management was discouraged (Class III).

For patients with chronic ischemic heart disease, echocardiography is supported as a valuable test for assessing global left ventricular function. Echocardiography was also endorsed by the ACC/AHA guidelines as an adjunct to exercise or pharmacological stress studies for diagnosis of coronary disease and assessment of its severity. However, the ACC/AHA guidelines were not supportive of use of echocardiography to screen asymptomatic patients with a low likelihood of coronary disease, or for routine periodic assessments in patients for whom no change in therapy was contemplated. The guidelines explicitly state that echocardiography should not be routinely substituted "for treadmill exercise testing in patients for whom ECG analysis is expected to suffice" (see Table 7-G-1) .

CARDIOMYOPATHY AND ASSESSMENT OF LEFT

VENTRICULAR FUNCTION

Echocardiography is the ideal first test for assessment of global and regional left ventricular function, and thus it is a preferred initial diagnostic test for patients with symptoms such as edema and dyspnea or with unexplained hypotension. TEE is recommended when TTE studies are not diagnostic. Echocardiography was also considered useful by the ACC/AHA task force for assessment of left ventricular hypertrophy, restrictive cardiomyopathy, and heart failure due to diastolic dysfunction. The guidelines discourage use of echocardiography for routine evaluation of clinically stable patients in whom no change in management is contemplated and in patients with edema but normal venous pressures and no evidence of heart disease.

PERICARDIAL DISEASE

Echocardiography remains the procedure of choice for detection of pericardial effusion, and it is considered an appropriate test for diagnosis of other pericardial disease. Use of echocardiography is discouraged when the results are unlikely to change management. The guidelines also note that pericardiac friction rubs are common in early acute myocardial infarction and the early postoperative period after cardiac surgery, so that echocardiography is not routinely necessary. Echocardiographic assessment of pericardial thickness to assess the diagnosis of constrictive pericarditis is not supported by these guidelines, which note that more accurate assessments can be made by computed tomography or magnetic resonance imaging.

CARDIAC MASSES AND TUMORS

Echocardiography is also the first-line test for detection of cardiac masses and tumors. Examples of such patients are those with one or more embolic peripheral or neurological events or those with hemodynamic or auscultatory findings suggesting intermittent obstruction to intracardiac flow. Other candidates include those with malignancies with a high incidence of cardiovascular involvement, such as hypernephroma, metastatic melanoma, or malignancies of intrathoracic organs. The appropriateness of echocardiography for screening asymptomatic patients for intracardiac masses is uncertain.

DISEASES OF THE GREAT VESSELS

TTE provides good visualization of the aortic root and the proximal pulmonary vasculature, and it is sometimes able to detect abnormalities such as an intimal flap in patients with aortic dissection. However, TEE is a far more sensitive tool for evaluation of most conditions affecting the great vessels. Therefore, TEE is the test of choice for diagnosis of aortic dissection or rupture (see Table 7-G-1) . Because TTE is a less invasive and expensive procedure than TEE, it is recommended for follow-up of patients after repair of aortic dissection who do not have suspicion of complications or progression and of first-degree relatives of patients with Marfan syndrome or other

connective tissue disorders.

PULMONARY DISEASE

Primary pulmonary disease often compromises the quality of TTE, but echocardiography can be an appropriate test for evaluation of the right ventricle and right-sided heart pressures that may be abnormal in conditions including pulmonary hypertension and pulmonary emboli. The ACC/AHA guidelines considered echocardiography an appropriate strategy for distinguishing cardiac versus noncardiac dyspnea when other clinical data were not sufficient for diagnosis. In contrast, echocardiography was not considered appropriate for patients with lung disease without any suspicion of cardiac involvement or for reevaluation of right ventricular function in patients with chronic obstructive lung disease without any change in clinical status.

SYSTEMIC HYPERTENSION

The ACC/AHA guidelines support use of echocardiography in patients with hypertension when the assessment of left ventricular function or hypertrophy is likely to influence management. An example of appropriate use of echocardiography would be for a patient with mild hypertension for whom the presence of left ventricular hypertrophy might lead to initiation of drug therapy. The guidelines explicitly state that

not every patient with hypertension should have a left ventricular function assessment and discourage serial echocardiograms to assess changes in left ventricular mass as patients are treated.

NEUROLOGICAL DISEASE AND OTHER CARDIOEMBOLIC DISEASE

The ACC/AHA guidelines considered echocardiography an appropriate test for patients with embolic events affecting any major peripheral or visceral artery. Echocardiography was considered clearly appropriate for any patient with a cerebrovascular event in the absence of evidence of cerebrovascular disease or other obvious causes. The appropriateness of echocardiography in patients with a neurological event and intrinsic cerebrovascular disease was less clear (Class IIb). Echocardiography was considered inappropriate (Class III) when the results would not influence management, such as in a patient for whom anticoagulation was absolutely contraindicated.

ARRHYTHMIAS AND PALPITATIONS

The ACC/AHA guidelines recognized that echocardiography can be an appropriate test in patients with arrhythmias and other signs or symptoms suggestive of structural heart disease. However, the guidelines discourage use of echocardiography in most patients with palpitations or isolated ventricular premature complexes if they do not have other evidence for structural or arrhythmic cardiac disease. The guidelines supported use of echocardiography as an adjunct to some advanced electrophysiological procedures.

For patients undergoing cardioversion of atrial fibrillation, the guidelines support use of TEE in several settings. For example, TEE was considered appropriate for detection of intraatrial thrombus in patients requiring urgent cardioversion when extended precardioversion anticoagulation is not desirable and in patients who have had prior cardioembolic events or other evidence of intraatrial thrombus. The ACC/AHA task force was uncertain but generally supportive of TEE for patients with atrial fibrillation of less than 48 hours' duration in the presence of other heart disease (Class IIa). The guidelines were less supportive (Class IIb) of TEE when patients had acute onset of atrial fibrillation in the absence of other heart disease. Because echocardiography findings were unlikely to change management, the ACC/AHA guidelines discourage use of this test in patients undergoing emergent cardioversion and in patients on long-term anticoagulation without mitral valve disease or hypertrophic cardiomyopathy.

The ACC/AHA guidelines discouraged routine use of echocardiography for evaluation of classic neurogenic syncope or for patients in whom there was no suspicion of cardiac disease. This test was considered appropriate for patients who had clinical evidence of cardiac disease or periexertional syncope, and the guidelines were somewhat supportive of use of echocardiography in patients with syncope who were in high risk professions, such as airline pilots (Class IIa).

SCREENING

Echocardiography was considered an appropriate strategy for screening for cardiac disease when it was likely to change management or outcomes. Examples of indications in which echocardiography was considered appropriate for screening included families with a history of genetically transmitted cardiovascular disease, potential donors for heart transplantation, and serial evaluation of patients receiving potentially cardiotoxic chemotherapy.

CRITICALLY ILL PATIENTS

Echocardiography is often useful for establishing the diagnosis in hemodynamically unstable, critically ill patients. The ACC/AHA expert panel considered TEE to be superior to transthoracic echocardiography for:

- Hemodynamically unstable patients on a ventilator

Patients who were unable to be positioned for adequate TTE after major trauma or surgery.

Suspected aortic dissection or aortic injury.

ADULT PATIENTS WITH CONGENITAL HEART DISEASE

Echocardiography is useful for diagnosis of congenital heart disease in adults, as well as serial follow-up of ventricular function, intracardiac and other shunts, and other manifestations of disease. The guidelines discourage overuse of serial echocardiography in patients without changes in clinical conditions, especially if they have lesions known to be hemodynamically insignificant, such as small atrial or ventricular septal defects.

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Chapter 8 - Radiology of the Heart and Great Vessels

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HISTORICAL PERSPECTIVE

Cardiac imaging is almost as old as radiology itself. Within 1 year of Roentgen's discovery, Francis H. Williams of Boston reported, "I found that the outline of the heart as seen...through the fluoroscope corresponds to the outline drawn on the skin with percussion as a guide." Williams was a true pioneer. He concluded that radiography was the best method for determining heart size based on a comparison of radiographic findings, digital percussion, and autopsy specimens in 546 patients.[1] [2]

During the decades that followed, dramatic developments occurred in cardiac imaging technology. These innovations were highlighted by kymography in the 1920s, angiocardiography in the early 1930s, and image intensification in 1952.[3] Since that time, a number of new modalities, including radioisotope scanning, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI), have revolutionized cardiac imaging. These new technologies permitted anatomically detailed examination of the heart and great vessels not possible with plain film techniques. In spite of these advances, the plain chest radiograph continues to provide unique and valuable information about the structure and function of the heart and thoracic vessels.

The chest radiograph, used to screen patients upon entering the hospital or as part of a routine evaluation of cardiopulmonary and other disorders, presents an opportunity to identify subtle or overlooked cardiac pathology such as significant vascular calcification, chamber enlargement, and evidence of pulmonary arterial or venous hypertension. Adult-onset congenital heart disease, which may be overlooked clinically, can be identified by plain film chest radiography.[4]

In recent years, the bedside portable chest roentgenogram has gained special importance in the evaluation and monitoring of patients with cardiac disease in the intensive care unit (ICU), including postoperative cardiac patients and others with implanted cardiovascular devices.[5] [6] [7] [8] [9] [10] This chapter discusses the role of plain film chest radiology with an emphasis on cardiovascular anatomy and alterations of that anatomy in a variety of pathological disorders. Correlation with cross-sectional imaging is used to clarify important anatomical questions.

NORMAL CARDIAC ANATOMY

Plain Chest Radiography

The normal chest radiograph provides excellent contrast between the air-filled lung and the adjacent soft tissue and osseous structures. As a result, the pulmonary arteries and veins and the interlobar fissures are visualized in great detail. For this reason, the posteroanterior (PA) erect chest film remains the study of first choice for the evaluation of pulmonary parenchymal and vascular disease. On the other hand, the heart and other mediastinal structures appear as a featureless, opaque silhouette. Blood, myocardium, pericardium, coronary arteries and great vessels, valves, and mediastinal fat cannot be identified because they have similar radiographic attenuation characteristics, so there is little or no contrast available to differentiate these structures. However, the cardiac borders are clearly outlined, and deviation from the normal cardiac configuration does suggest disease. To take full advantage of the chest radiograph to study the cardiovascular system, it is necessary to interrogate the following structures: (1) the heart and its individual chambers; (2) the pulmonary veins and arteries, which reflect the physiological pressure and volume state of the cardiovascular system; (3) the mediastinum to evaluate the size and location of the aorta and major systemic veins; and (4) extracardiac abnormalities that may be associated with cardiac disease.[9] It is important to appreciate that an abnormal cardiac border may also be due to a nonvascular abnormality such as a pericardial cyst or tumor, a thymoma or lymphoma, and/or other solid or cystic masses that may alter the cardiac border.

Frontal View (Fig. 8-1)

In a well-positioned PA or frontal chest radiograph, the normal cardiac and other vascular structures are predictably outlined against the lung as a series of indentations and bulges along the right and left mediastinal borders.

THE LEFT MEDIASTINAL BORDER.

The left subclavian artery is the border-forming structure along the upper left portion of the mediastinum above the aortic arch. Although the left innominate vein is actually lateral to the left subclavian artery, it is adjacent to the anterior chest wall, and thus no contrast is available in the frontal view to identify the left innominate vein as a separate structure. The left subclavian artery, which extends from the clavicle to the aortic arch, usually forms a concave border with the lung. The left subclavian artery border will bulge laterally when blood flow through the vessel is increased, as in postductal coarctation of the aorta, or when the left subclavian artery is tortuous because of atherosclerosis or hypertension. A vertical or a smooth convex left supraaortic border is found in patients with persistent left superior vena cava (Fig. 8-2) .

THE AORTIC ARCH.

The normal aortic arch or "knob" forms a sharply marginated convex border immediately below the left subclavian artery. It is usually small in young patients, with a diameter of 2.0 ± 1.0 cm, and represents the left posterolateral portion of the aortic arch. The trachea is displaced slightly to the right at the level of the aortic

Figure 8-1 Frontal projection of the heart and great vessels. *A*, Left and right heart borders in the frontal projection. *B*, A line drawing in the frontal projection demonstrates the relationship of the cardiac valves, rings, and sulci to the mediastinal borders. *C*, Electron beam contrast-enhanced CT demonstrates cardiac anatomy relationships in cross section. A=ascending aorta; AZ=azygos vein; B=right and left bronchi; DA=descending aorta; LA=left atrial appendage; LV=left ventricle; PA=main pulmonary artery; RA=right atrium; RV=right ventricle; S=superior vena cava.

arch. When a right aortic arch is present, the trachea is displaced slightly to the left, a clear indication of that anomaly. A small bump or "nipple" measuring about 2 to 3 mm in diameter that represents the left superior intercostal vein can be seen along the aortic arch in 4 to 10 percent of individuals.[11] When enlarged, the left superior intercostal vein has the same significance as a dilated azygos vein; i.e., enlargement is due to increased central venous pressure or increased blood flow caused by diversion of blood flow from other major venous structures, as may occur in superior vena cava syndrome, inferior vena cava obstruction, or deep mediastinal venous obstruction[11] (Fig. 8-3) . The vertical interface between the left lung and the normal descending aorta is clearly demonstrated in a well-penetrated PA chest radiograph. A left pleural effusion, atelectasis, pneumonia, or other causes of increased lung opacity adjacent to the descending aorta may obliterate this border. Focal obliteration of the descending aortic interface may also occur normally as a result of adjacent pulmonary arteries, veins, or mediastinal fat.[12]

The aortic arch is especially prominent on the frontal view in older individuals with pronounced aortic regurgitation, systemic hypertension, or atherosclerosis (Fig. 8-4) . It is wider and higher than the normal aortic arch and may even reach the level of the clavicle. The ascending aorta protrudes further to the right side than in normal patients, and the descending aorta assumes a tortuous or serpentine configuration. The brachiocephalic vessels also dilate and become tortuous. At times, a dilated right brachiocephalic artery may mimic the appearance of a substernal thyroid or other superior mediastinal mass and require CT or MRI for diagnosis. One in 1500 adult patients has a right-sided aortic arch that is usually associated with an aberrant left subclavian artery. When no aortic knob is visible on the left side and the trachea is displaced to the left, the presence of an aortic knob or arch on the right side of the mediastinum should suggest the diagnosis of right aortic arch[4] [13] (Fig. 8-5) .

The left mediastinal border immediately below the aortic arch is characterized by a variably sized indentation of the lung into the mediastinum. This indentation is termed the *aorticopulmonary window* (see Fig. 8-1) . It is bordered superiorly by the inferior margin of the aortic arch and inferiorly by the upper margin of the left pulmonary artery. This small space contains several important anatomical structures, including the left recurrent laryngeal nerve, the ligamentum or ductus arteriosus, and the ductus node. Enlargement of the ductus node or a ductus diverticulum may cause a convex bulge in the normally concave mediastinal reflection of the aorticopulmonary window. Encroachment on the recurrent laryngeal nerve within the aorticopulmonary window by a neoplasm, a ductus diverticulum, or an enlarged lymph node or by extrinsic pressure on the left recurrent laryngeal nerve from aortic dilation or a large left atrium can cause paralysis of the left vocal cord.

MAIN PULMONARY ARTERY (Fig. 8-6) .

The origin of the left main pulmonary artery is located immediately below the aorticopulmonary window and is border-forming with the left lung. It is identified as a small to moderate-sized, smoothly marginated arc at the level where the left pulmonary artery branches. Another indication of the location of the main pulmonary artery is the position of the left main stem bronchus. The left pulmonary artery arches over the left main stem bronchus, unlike the right pulmonary artery, which is located between the right upper lobe and right middle lobe bronchus. When enlarged, the normally slightly convex main pulmonary artery will form a prominent outward bulge. Enlargement of the main pulmonary artery is caused by increased flow, as in patients with anemia or a left-to-right shunt, by turbulent blood flow, as in pulmonary valvular stenosis, or by increased pressure related to Eisenmenger physiology or other causes of pulmonary hypertension. Finally, a large main pulmonary artery may be found in disorders of vascular wall collagen such as Marfan syndrome or "idiopathic pulmonary artery dilatation." On the other hand, the main pulmonary artery border may be flat or not seen at all in patients with transposition of the great vessels, truncus arteriosus, tetralogy of Fallot, or pulmonary atresia.[4]

THE LEFT ATRIAL BORDER (Fig. 8-7) .

The left atrial appendage or auricle lies immediately below the left main stem bronchus in the frontal projection. This structure normally forms a smooth and slightly concave segment of the left heart border. When the left atrial border is straightened or bulges laterally, atrial enlargement should be suspected. Nonvascular pathology may simulate enlargement of the left atrial appendage. For example, a pericardial fibroma or cyst, lymphoma, thymoma or other mediastinal or pleural neoplasms may appear to be a convexity of the left atrial border. Congenital absence of the pericardium also causes bulging of the left atrial appendage. An important sign of

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left atrial enlargement in the frontal projection is elevation of the main stem bronchus so that the carinal angle is greater than the normal value of up to 75 degrees.

THE LEFT VENTRICULAR BORDER (see Fig. 8-1) .

The left ventricular border blends seamlessly with the left atrial border without a specific landmark to differentiate between the two chambers. The left ventricular border is mildly convex as it extends to the diaphragm. It may be rounded and the apex elevated if the left ventricle is hypertrophic as a result of aortic stenosis or cardiomyopathy (Fig. 8-8 *A*). When the left ventricle is enlarged because of dilatation, as may occur with aortic regurgitation or aneurysm, the apex is displaced downward and laterally. Much of the downward (Fig. 8-8 *B*) displacement of the apex may be obscured by the overlying left diaphragmatic dome or by extracardiac fat.

Figure 8-2 Persistent left superior vena cava (LSVC). *A*, Posteroanterior chest film in a man with a normally functioning intravenous cardiac pacemaker. The arrowhead indicates the pacemaker lead in the persistent LSVC. *B*, Left subclavian venogram illustrating the course of the LSVC: subclavian vein (single vertical arrow), the LSVC (two arrows), and the coronary sinus (three arrows).

When the left ventricle dilates because of volume overload as in mitral regurgitation, the dimensions of the chamber increase markedly and the heart assumes a globular appearance. The left ventricular border extends to the left and may reach the lateral rib convexities (see Fig. 8-7 *C*). As the left ventricle enlarges, the left atrial border is obscured. In such circumstances, the left anterior oblique (LAO) projection is helpful to separate the two chambers so that their relative sizes can be discerned. The ability to separate the left heart chambers assumes importance when the differential diagnosis lies between ischemic cardiomyopathy (in which case the left ventricle is larger than the left atrium) and mitral regurgitation (in which case the left atrium may be larger than the

left ventricle).

THE RIGHT MEDIASTINAL BORDER (Fig. 8-9) .

The right atrial border forms a gentle convex interface with the adjacent

Figure 8-3 Left superior intercostal vein (LSIV). A small nipple or bulge is visible on the aortic knob. The LSIV normally measures 2 to 3 mm in diameter. Enlargement may be due to deep venous obstruction. *A*, Magnified posteroanterior projection in a young woman. LSIV is a beaklike bulge that extends to the left at the aortic knob (arrow). *B*, Contrast-enhanced CT shows the relationship of the left superior intercostal vein (V) to the aortic arch (A).

Figure 8-4 *A*, Aortic enlargement in a 63-year-old man with longstanding systemic hypertension and aortic regurgitation. Marked dilation and uncoiling of the arc and descending aorta can be noted. *B* and *C*, Aortic dissection in an 81-year-old woman along with marked dilation, calcification (arrows), and elongation of the arch and descending aorta. *D*, CT shows a descending aortic flap between the contrast-filled true lumen (Ao) and the thrombus-filled false lumen (FL). *E*, Sagittal reconstruction vividly demonstrates the multiple false and true lumina of the descending aorta (desc A). RPA=right pulmonary artery.

right middle lobe. In the frontal projection, the superior vena cava border above the right atrium is usually straight, and in a good inspiratory film it can be clearly separated from the right atrial convexity. The outline of the normal left atrium may be visible deep to the right atrial border as an additional convex shadow. The confluence of the right pulmonary veins is directed toward the midpoint of the left atrial border. The left atrium is clearly visualized within the right atrial shadow because of intrusion of lung between the posterior portion of the left atrium and the more anterior part of the right atrium (see Fig. 8-7 *D*). If the left atrium is markedly enlarged, the left atrial border may actually be lateral to the right atrium. The borders of the right and left atria can be differentiated because the inferior border of the right atrium blends with the inferior vena cava while the left atrial shadow crosses the midline toward the left side of the heart (see Fig. 8-7 *A*). The upper right atrial convexity blends superiorly with the superior vena cava, which forms a straight border with the adjacent lung as it continues toward the neck. The right atrial border is considered enlarged when it bulges more than 5.5 cm to the right of the midline.[14]

RIGHT VENTRICLE (Fig. 8-10) .

Unlike the right atrium, the right ventricle is not border-forming in the frontal projection and cannot be directly visualized. However, as the right ventricle dilates, the left ventricle is displaced posteriorly and to the left and the right atrium is displaced to the

right, which causes widening of the cardiac shadow. In cardiac anomalies such as tetralogy of Fallot, the enlarged right ventricle displaces the left ventricle laterally and superiorly and thereby creates a high, round left ventricular border.[4]

THE ASCENDING AORTIC BORDER (see Fig. 8-8) .

The ascending aorta is superimposed on the superior vena cava and forms a convex border above the right atrium (see Fig. 8-1 *A*). The aortic valve and annulus and the coronary arteries are not visible on plain films unless they are calcified since they lie deep to the edge of the mediastinum and their x-ray attenuation characteristics are similar to those of the rest of the heart.

AZYGOS VEIN (see Fig. 8-1) .

The azygos vein is an elliptical structure at the right tracheobronchial angle. It ascends in the right paravertebral sulcus and arches forward over the right main stem bronchus to enter the back of the superior vena cava. The azygos vein and its left-sided equivalent, the hemiazygos vein, receive intercostal veins and act as an important collateral pathway when the deep mediastinal veins are obstructed.[11] [15] Normally measuring 0.7 to 1.0 cm across in the erect and 1.0 to 1.3 cm in the supine anteroposterior (AP) position, the azygos vein is a good

Figure 8-5 Right aortic arch. *A*, Right aortic arch (RAo) in a patient with truncus arteriosus I. *B*, Frontal view of the chest in an adult female. The barium column is displaced to the left by the right aortic arch. The bulge on the left is due to the patulous origin of the aberrant left subclavian artery (the diverticulum of Kommerall) (arrow). *C*, Aortography shows the right aortic arch and aberrant left subclavian artery, with a proximal bulge representing the diverticulum of Kommerall (arrowhead).

indicator of changing cardiovascular dynamics. It is enlarged in superior vena cava and inferior vena cava obstruction, in the absence of the intrahepatic portion of the inferior vena cava, in portal vein obstruction, and in both left- and right-sided cardiac failure. A change in diameter of the azygos vein will parallel changes in pulmonary venous pressure, which makes it a useful guide to the development of congestive heart failure on plain film radiographs. An azygos fissure can be found in 3 percent of the population. When a fissure is present, the azygos vein is displaced laterally and superiorly and will dilate under the same conditions as a normally positioned azygos vein.[16]

Lateral View (see Fig. 8-10)

Proper positioning of the patient in the lateral projection is critical for accurate identification of cardiac structures. The need for accurate positioning is exemplified by the right atrium. The normal right atrium is not border-forming in this projection, but if the

patient is rotated backward, the right atrium will form part of the lower posterior cardiac border and simulate enlargement. The right ventricle is border-forming in the subxiphoid region and usually extends superiorly to a point about one-third the distance between the diaphragm and the suprasternal notch. As the right ventricle dilates, it encroaches further on the retrosternal space.[17] The relationship between the size of the right ventricle and the extent of retrosternal encroachment is affected by the patient's body habitus and lung volume. For example, in a patient with emphysema, right ventricular enlargement may coexist with an expanded retrosternal space. In a patient with a small AP diameter and/or pectus excavatum deformity, the retrosternal space may be obliterated despite the absence of right ventricular enlargement (Fig. 8-11 *A* and *B*). CT and MRI, as well as echocardiography, unlike the lateral chest film, portray relationships of the right ventricle to nearby structures with great accuracy and permit a clear analysis of right ventricular volume and function[17] [18] [19] [20] [21] (Fig. 8-11 *C*).

The anterior margin of the main pulmonary artery and the ascending aorta lie above the right ventricle; however, because of abundant mediastinal fat, neither structure is visualized clearly in the lateral view in a normal patient. In patients with severe emphysema, however, the increased lung volume permits the main pulmonary artery

Figure 8-6 The pulmonary artery contour. *A*, Normal pulmonary segment (arrow) in a 36-year-old woman with sickle cell anemia and moderate cardiomegaly. *B*, The pulmonary arteries are grossly enlarged in this patient with primary pulmonary hypertension (arrowheads). *C*, A posteroanterior radiograph shows engorged pulmonary arteries (white arrows) from a patient with AIDS and pulmonary arterial hypertension. *D*, Axial CT in the same patient shows a large main pulmonary artery (PA). Ao=ascending aorta, DA=descending aorta. *E*, The pulmonary artery contour is small in this 16-year-old with tetralogy of Fallot and pulmonary infundibular stenosis (arrowhead).

and the ascending aorta to be well outlined. The arch of the aorta is usually clearly outlined in normal patients, except where the superior vena cava crosses the aorta and where the brachiocephalic arteries enter the aorta. The inferior margin of the posterior aortic arch is often visible because of intrusion of lung into the aorticopulmonary window. The semilunar lucency of the aorticopulmonary window also outlines the superior margin of the left pulmonary artery. The descending aorta is not usually discernible in a normal individual because it lies adjacent to the spine and the posterior mediastinal fat. However, in patients with hyperaeration or those with a tortuous or calcified aorta, the descending aorta is better seen.

LEFT ATRIUM.

The normal *left atrium* forms a shallow convex bulge at the upper aspect of the posterior border of the heart on the lateral view. It may be easily identified because the posterior border of the left atrium lies immediately anterior to the pulmonary venous confluence

(see Fig. 8-10) .

LEFT VENTRICLE.

The normal *left ventricle* forms a long convexity at the posteroinferior heart border just above the diaphragm. Enlargement of the left ventricle is suggested by use of the Hoffman-Rigler sign, a measurement determined by drawing a 2.0-cm vertical line upward along the inferior vena cava from the point where the posterior wall of the left ventricle and inferior vena cava cross in the lateral projection. At this point, a second line is drawn parallel to the vertebral bodies. The distance between the left ventricular border and the vertical line should not exceed 1.8 cm. If it does, left ventricular enlargement is suggested. Although this sign is helpful, it is far from accurate because poor positioning of the patient for a lateral chest film or backward displacement of the left ventricle because of right ventricular enlargement may adversely influence this measurement.[22]

ESOPHAGUS.

The *esophagus* lies immediately behind the left atrium and, when filled with contrast medium, can be used to locate the posterior border of the left atrial chamber. Normally, the left atrium does not displace the esophagus, but when the left atrium is enlarged, posterior displacement of the esophagus from the area of the left main stem bronchus to the level of the left ventricle will occur. The normal left ventricle does not usually displace the esophagus, but rather it overlaps or lies posterior and lateral to it. When both the left atrium and left ventricle are enlarged, the barium-filled esophagus may be pushed backward in one long curve (Fig. 8-12) . Sometimes, the left atrium enlarges without displacing the barium-filled esophagus because the esophagus may slide off the back of the left atrium to the left or right. When the aorta is tortuous and dilated or when scoliosis is present, the esophagus parallels the spinal curvature and cannot be used to evaluate left atrial size.

The Right Anterior Oblique Projection (Fig. 8-13)

Chest radiography in the right anterior oblique (RAO) projection is performed with the patient in a 45-degree oblique

Figure 8-7 Prominent left atrial contour. *A*, The left atrial appendage bulges laterally in this patient with multivalvular rheumatic heart disease (arrow). The double convex contour of enlarged right (curved arrow) and left (straight arrow) atria is visualized along the right atrial border (arrow). *B*, A 40-year-old woman with mitral stenosis, left atrial enlargement, and a double right-sided heart border (white arrow=right atrium; black arrow=left atrial border). The left main stem bronchus is elevated (black arrow). *C*, Giant left atrium. A wide convex bulge is seen in the area of the left atrial appendage (white arrow).

The left atrium is grossly enlarged and is border-forming on the right side overlying the smaller right atrium. The inferior border of the left atrium (black arrow) extends back toward the midline. If this were the right atrial border instead, it would have blended imperceptibly with the right hemidiaphram and inferior vena cava. *D*, Enhanced CT demonstrates the anatomical relationship between the anterior of the right atrium (RA) and the posterior of the left atrium (LA). The indentation of lung and fat between the atria (arrow) permits separation of the right-sided borders of both atria as seen in the posteroanterior chest radiograph.

relationship to the film cassette (right shoulder toward the cassette). In this view, the ventricles are elongated; the long axes of the ventricles are in view and the atrioventricular groove is in profile. This position permits optimal visualization of a calcified mitral or tricuspid valve. The RAO view is used by angiographers to determine the presence of left atrial enlargement, a common feature in mitral stenosis or regurgitation. The aortic arch is foreshortened in the RAO projection, so the arch and proximal descending aorta are often superimposed and obscured. The anterior border of the heart in the RAO projection consists of the sinus portion of the right ventricle inferiorly and the right ventricular outflow tract and the main pulmonary artery superiorly.[17] The right-sided or posterior heart border is made up of the right atrium superiorly and the left atrium inferiorly.

The Left Anterior Oblique Projection (Fig. 8-14)

The LAO projection is performed with the patient in a 60-degree oblique relationship to the cassette. This view is useful for diagnosing the presence of left ventricular enlargement. Since the ventricular septum is in profile in this projection, septal defects and abnormalities of right and left ventricular function can be identified with angiography. In this projection, the aortic and pulmonary valves are in profile, so aortic valve calcifications can be clearly visualized and aortic or pulmonary stenosis and regurgitation can be assessed. The aortic arch is also in profile in the LAO projection, so that abnormalities of the arch, including dissection, contained rupture, aortitis, aneurysm, and coarctation, can be detected with aortography or by cross-sectional imaging.[23] [24] [25] [26] The anterior (right) heart border consists of the right atrium above and right ventricle below. Along the left posterior heart border, the left atrium is border-forming superiorly and the left ventricle is border-forming inferiorly. The LAO projection is superior to other projections for detecting right ventricular enlargement, which is usually characterized by an increase in the convexity of the anterior border of the cardiac silhouette. An enlarged right atrium may cause bulging of the right upper anterior border of the cardiac shadow and produce a typical shelflike configuration.

Cardiac Fluoroscopy

In the past, cardiac fluoroscopy was performed routinely to study cardiac motion and identify cardiac and other mediastinal calcifications. Today, it is seldom performed routinely but instead used to answer specific clinical questions.[27] Because fluoroscopy potentially poses a significant radiation risk to the patient, it should be used selectively, with careful beam collimation. Exposure time should be kept to a minimum, preferably for no more than 5 minutes. Perhaps the most important applications of fluoroscopy today are to identify pacemaker lead fractures; detect coronary artery, valvular, and neoplastic or pericardial calcifications; and evaluate prosthetic valve function in selected

patients with older implanted valves.[28] [29] [30]

Cardiac fluoroscopy is usually performed with the patient in the upright position at 68 to 75 kVp to enhance contrast and reduce quantum mottle. The patient's position is determined by the structure to be studied. For example, if the presence or absence of aortic valve calcification is to be determined, positioning in the LAO projection is optimal. If mitral calcification is suspected, the RAO projection is most suitable. Coronary calcifications are best studied in the LAO and RAO projections. In the 60-degree LAO projection, the right coronary, left circumflex, and left main

Figure 8-8 Aortic valve disease. *A*, The left ventricular border is round and prominent as a result of left ventricular hypertrophy. The proximal ascending aorta is prominent because of poststenotic dilation (arrow) in this patient with aortic stenosis. *B*, Aortic regurgitation in a patient with Marfan syndrome. A prominent left ventricular border can be seen. The left ventricular chamber is dilated from regurgitant flow, and the ascending aorta (white arrows) is convex and enlarged (black arrows). *C*, Aortography in the left anterior oblique projection shows marked enlargement of the ascending aorta (Ao) with severe regurgitant flow in a patient with annuloaortic ectasia and Marfan syndrome. LV=left ventricle. *D*, Axial CT shows marked dilation of the ascending aorta (Ao) in a patient with Marfan syndrome.

coronary arteries are seen to advantage. In the lateral and RAO projections, left anterior descending artery calcifications are easily discernible.[30]

Although large deposits of calcium may be seen on the chest film, small calcifications are often obscured because of motion. On the other hand, motion is an advantage with fluoroscopy, and even small coronary artery calcifications are seen clearly as densely parallel tracks moving perpendicular to their long axes in a to-and-fro motion. The right main and circumflex coronary arteries move more vigorously than the anterior and posterior descending arteries do. Subepicardial fat represents an important landmark for the identification of vascular and valvular anatomy and is best seen with fluoroscopy. Fat surrounding the coronary arteries and within the atrioventricular groove is well visualized, so the location of the mitral and tricuspid valves, the coronary sinus, and the circumflex and right coronary arteries can be determined.

Fluoroscopy with videotape recording is useful to analyze the integrity of the radiopaque components of prosthetic valves. The results of fluoroscopic analysis of mechanical components of prosthetic valves compare favorably with echocardiography but do not yield useful information about the degree of valvular regurgitation as does Doppler echocardiography or MRI.[31]

MEASURING CARDIAC SIZE (Fig. 8-15)

Direct measurement of heart size by plain film radiographs has become practically obsolete inasmuch as more accurate analyses of cardiac chamber dimensions and

volume are available with other methods. However, since an enlarged heart is abnormal, estimation of the cardiothoracic ratio remains a valuable yardstick to gain an impression of cardiac size and, in particular, serial changes in heart size coinciding with cardiac events. This assessment may be done subjectively by estimating whether a heart is normal in size, enlarged, or grossly enlarged on the basis of an average cardiothoracic ratio of 0.50.[32] [33] [34] Using more objective criteria, the cardiothoracic ratio may be expressed as the ratio between the maximum transverse diameter of the heart divided by the maximum width of the thorax. To obtain these measurements, a vertical line is drawn on the radiograph through the midpoint of the spine from the sternum to the diaphragm. The maximum transverse diameter of the heart is obtained by adding the widest distance of the right heart border from the midline and the left heart border to the midline. This value is then divided by the maximum transverse diameter of the thorax.[34] The normal range of the transverse diameter of the heart is 10 cm in a

Figure 8-9 *A*, Normal chest film with the right atrial (RA) contour indicated by white arrowheads. *B*, The RA border is enlarged and convex (white arrow), as is the entire cardiac silhouette. The pulmonary vasculature is normal in this mildly cyanotic male. A diagnosis of Ebstein anomaly was established by echocardiography. *(Courtesy of Dr. Ahmed Farag.)*

small, thin individual to 16.5 cm in a tall, heavy person. A measurement 10 percent beyond these values represents the upper limits of normal. A normal heart may appear large in the frontal projection because of a small AP diameter of the thorax caused by a pectus excavatum deformity or straight back. A large heart may appear smaller than it really is because of a downwardly displaced cardiac apex, for example, in patients with aortic regurgitation or in an elderly patient with a large AP diameter caused by severe dorsal kyphosis. The heart will be truly small in patients with Addison disease or anorexia nervosa as a result of the absence of brown fat. Because of cardiac magnification on AP films (including portable radiographs), visual correction must be made to avoid overdiagnosis of heart enlargement. A reduction in the calculation of heart size by 10 to 12.5 percent, depending on the anode-to-tube distance, will correct this discrepancy. For the most part, calculated cardiothoracic ratios are of historical or research interest. In practice, these calculations are seldom performed because they are time consuming and more accurate estimations of cardiac volume and size may be obtained with other imaging techniques.

THE PULMONARY VASCULATURE

The pulmonary vasculature is the most difficult portion of thoracic radiological anatomy to analyze because of its complexity and overlapping patterns of interstitial, arterial, and venous structures. However, the information elicited from accurate analysis of the pulmonary circulation is certainly as valuable as analysis of cardiac shape in arriving at a correct cardiac diagnosis.[9]

Because the pulmonary blood vessels are clearly visualized on the chest film, normal as well as increased, decreased, redistributed, or asymmetrical flow can be identified and correlated with other indicators of disease.

Normal Radiographic Anatomy (Fig. 8-16)

The main pulmonary artery bifurcates within the mediastinum. The left pulmonary artery then courses to the left and backward, and its borders are visible just above the middle of the left hilum. In the lateral projection, the left pulmonary artery passes over the left main stem bronchus and parallels the aortic arch. The right pulmonary artery follows a horizontal course within the mediastinum and forms a round or elliptical opacity anterior to the right main stem bronchus on the lateral view. The right pulmonary artery divides within the mediastinum proximal to the right hilum. The intrapulmonary branches parallel the bronchi, divide in an orderly manner, and gradually taper toward the periphery of the lung. The arteries and bronchi subtending the same pulmonary segment are of approximately the same diameter at any particular level, with a ratio of about 1.2:1.0. This relationship assumes importance when objective criteria are needed to support the impression of increased or redistributed blood flow.[35]

In the erect position, blood flow is greater to the lower lobes than to the upper lobes, partly because of the effects of gravity. Another factor affecting the normal distribution of pulmonary blood flow is the differential intraalveolar pressure between the upper lung zones (higher intraalveolar pressure) and the lower lung zones (lower intraalveolar pressure). In supine and prone chest films, blood flow appears equal in both the upper and lower lung zones, but actually, blood flow is greatest in the dependent position or posterior third of each lung in the supine position, and is best appreciated with axial CT images.

In normal individuals, the pulmonary arteries and veins in the outer third of the lung are too small to be seen clearly on chest x-rays. The central pulmonary veins can usually be distinguished from pulmonary arteries because they follow different pathways. Pulmonary veins course centrally in the interlobular septa and converge in the posterior aspect of the left atrium 2 to 3 cm below the hila. The pulmonary arteries radiate from the hila several centimeters above the pulmonary venous confluence. The veins of the upper lobes are usually lateral to or superimposed on their companion pulmonary arteries, and for the most part,

Figure 8-10 *A*, Lateral chest radiograph. *B*, Superimposed anatomical drawing of the cardiac chambers and great vessels. *C*, Computer-generated diagram of the lateral projection of the heart showing the position of the cardiac chambers, valve rings, and sulci.

the veins are larger than arteries and branch less frequently. In practice, because venous drainage and arterial supply to the upper lobes are so variable, it is often difficult to distinguish vein from artery. In a normal, erect individual, the vessels in the upper lung zone are smaller than vessels at the base of the lungs because important gravitational differences between the apex and lung base cause increased distribution of blood to the base of the lung.

Abnormal Pulmonary Blood Flow

INCREASED PULMONARY FLOW (Fig. 8-17) .

In normal individuals, the size of the pulmonary arteries is proportional to the volume of pulmonary blood flow, so if right-sided cardiac output is increased, the vessels will enlarge as long as the reserve of the pulmonary vascular bed (eight times normal flow) is not exceeded. When the reserve volume is overwhelmed or the reserve volume is reduced because of obliterative vascular disease, the size of the vessels will be related to both blood flow and blood pressure or to pressure alone. The pulmonary veins also enlarge as pulmonary arterial blood flow rises. Enlarged pulmonary branches are found in a variety of conditions, including left-to-right shunt, admixture lesions such as transposition of the great arteries, and conditions that produce an increase in cardiac output, such as chronic anemia, hyperthyroidism, arteriovenous fistula, and pregnancy.[36] As pulmonary artery flow increases, radiographs demonstrate enlarged pulmonary arteries, clearly seen to the edge of the lung. In a small left-to-right shunt, the increase may appear to be confined to the lower lobes, but in larger shunts, recruitment of the upper

Figure 8-11 *A*, A hyperinflated lung from emphysema reduces the extent of right ventricular encroachment on the retrosternal space. *B*, Severe pectus excavatum in a patient with a prolapsed mitral valve (arrow). The deformity exaggerates the extent of the retrosternal encroachment. *C*, Axial T1-weighted MRI shows the relationship of the anterior border of the right ventricle (RSV) to the anterior chest wall. RA=right atrium.

lobe vessels is seen as well, and differential flow between the upper and lower lobe vessels is lost. In left-to-right shunts smaller than 1.8:1, pulmonary vascular abnormalities may not be detected at all.

The size of the pulmonary vessels has been measured by determining the average transverse diameter of the right descending pulmonary artery immediately above the origin of the right middle lobe branch. The normal transverse diameter of this vessel is 10 to 15 mm in males and 9 to 14 mm in females. A variation of ±1.0 mm beyond these limits is considered abnormal.[37]

PULMONARY ARTERIAL HYPERTENSION (see Fig. 8-17) .

When the pulmonary vascular reserve is fully recruited by increased blood flow or reduced by endothelial cell injury and vasoconstriction, pulmonary arterial pressure rises.[38] The vascular engorgement that characterizes increased pressure is accompanied by vasospasm, peripheral vasoconstriction, and vessel wall thickening. Eventually, peripheral blood flow is decreased, and the outer third of the lungs becomes more lucent radiographically. The central elastic pulmonary arteries enlarge, including the main pulmonary artery, the right and left pulmonary arteries, and second-order branching vessels. Calcification of the main pulmonary artery and the proximal branch vessels may develop in longstanding and severe pulmonary arterial hypertension. Pericardial effusion and abnormal mosaic-like pulmo

Figure 8-12 Left atrial border in the lateral view. Discrete posterior displacement of the barium column because of left atrial enlargement can be seen in a patient with mitral stenosis.

nary parenchymal patterns have been described on CT.[38] [39] [40] Pulmonary arterial hypertension may be primary, particularly in women in the childbearing age group. It may also be secondary to a wide variety of cardiac and systemic disorders, including chronic recurrent pulmonary thromboembolic disease, chronic hypoxia, HIV-1 infection, collagen-vascular disease, drugs, sleep apnea syndrome, Eienmenger physiology, or pulmonary venous hypertension.[40] [41] [42] [43] [44]

PULMONARY VENOUS HYPERTENSION (Fig. 8-18) .

Left ventricular failure, mitral stenosis, venoocclusive disease, and other causes of vascular obstruction distal to the pulmonary arterial bed produce an increase in pulmonary venous pressure above the normal range of 8 to 12 mm Hg. When pressure rises to the level of 12 to 18 mm Hg, pulmonary blood flow is redirected into the upper lobes in the erect position and anteriorly in the supine position, so the normal difference in size between the smaller upper lobe and larger lower lobe vessels is reversed.[35] [45] With further elevation of pulmonary venous pressure above 18 mm Hg, pulmonary interstitial edema occurs. With pressures above 25 mm Hg, alveolar flooding or edema is present.

Radiographically, cephalization or redistribution of pulmonary venous and arterial flow to the upper lobes is the earliest sign of pulmonary venous hypertension. A clue to the recognition of redistributed flow is the diameter of blood vessels at the first anterior interspace. Normally, vessels at that level do not measure more than 3 mm in diameter. If they are larger, increased or redirected flow should be considered. In practice, the chest radiograph is particularly useful in distinguishing significant elevations from mild

elevations, but more precise grading of pulmonary venous pressure levels is usually futile.[45] Although the exact mechanism of vascular redistribution remains unresolved, one explanation has been proposed by several authors.[45] [46] With an increase in pulmonary venous pressure, fluid leaks from the pulmonary veins into the interlobular spaces, first in the lower lobes because of gravitational effects. Fluid accumulation in the interlobular spaces decreases pulmonary compliance and increases interstitial pressure. These two phenomena restrict flow to the lower lobes. Arterial spasm may also be a factor. Since these processes first develop in the lower lobes, redirection of blood flow to the upper lobes follows.

DECREASED PULMONARY BLOOD FLOW.

When blood flow is reduced, usually because of pulmonary outflow tract obstruction or an intracardiac right-to-left shunt, the pulmonary arteries and veins are reduced in size. The central vessels narrow and the peripheral vessels are not visible. Reduced pulmonary blood flow may be generalized, as in the tetralogy of Fallot, or may be regional as a result of pulmonary embolism, emphysema, tumor invasion, or vasculitis. When pulmonary perfusion is reduced, as in pulmonary atresia or chronic pulmonary thromboembolism, the bronchial and other collateral arterial vessels may be increased. Radiographically, bronchial vessels are tortuous, small, and nontapered, and because they emanate from the aorta, they do not radiate from the hilum. Otherwise normal but small pulmonary arteries and veins also contribute to pulmonary vascularity in lungs with significant bronchial circulation because pulmonary arteries and bronchial arteries interconnect and blood preferentially flows from the higher pressure systemic bronchial arteries to the lower pressure pulmonary arteries.[47]

ASYMMETRICAL PULMONARY BLOOD FLOW.

Asymmetrical pulmonary blood flow is caused by vessels in one lung being smaller than those in the other lung. A unilateral decrease or absence of pulmonary blood flow may occur in patients with pulmonary artery branch stenosis or atresia, hemitruncus, and tetralogy of Fallot with unilateral pulmonary artery branch narrowing. In addition, asymmetrical, increased flow may be found after creation of a Blalock-Taussig, Waterston, or Potts shunt. Sometimes, the differences in blood flow in congenital heart disease are caused by orientation of the pulmonary outflow tract. For example, in pulmonary valvular stenosis, the flow of blood through the stenotic valve may be directed toward the left pulmonary artery. In patent ductus arteriosus (PDA), preferential flow is often toward the left side because the ductus is oriented toward the origin of the left pulmonary artery in most patients.

Pulmonary Alveolar and Interstitial Edema (see Fig. 8-18)

In normal individuals, fluid continuously passes from the pulmonary veins into adjacent interlobular lymphatics, which return the fluid to the central mediastinal veins. If the lymphatic reserve is overcome by increased transudate as a result of elevated pulmonary venous pressure, the interlobular septa are thickened and become visible radiographically. Redistribution of blood flow to the upper lung zone, or "cephalization," will occur after reduction in compliance or vasoconstriction in the lower lobes roughly

paralleling the increase in pulmonary venous pressure.[48] [49] [50] With a mean transmural arterial pressure of 18 to 25 mm Hg, interlobular septal lines, or Kerley B lines, are visible as thin horizontal lines present at both lung bases perpendicular to the lateral pleural surface on the frontal chest film.[51] Prominent interstitial linear opacities throughout the lung reflect additional thickened septal lines. Clear definition of the segmental and subsegmental vessels is lost, and subpleural effusions occur. If the origin of the pulmonary interstitial edema is related to the cardiovascular system, the heart may be normal or enlarged, depending on the chronicity of cardiac decompensation. Prominent interstitial lines may also occur in a wide variety of noncardiac diseases, including sarcoidosis, lymphatic spread of tumor, interstitial pneumonia, and asbestosis. When pulmonary interstitial edema is present without alveolar edema, the lungs may be clear to auscultation--a clue that the extravascular fluid is confined to the interstitium. With further increases in pulmonary venous pressure above 25 mm Hg, leakage of fluid into the pulmonary air spaces leads to alveolar edema. Small nodular areas of increased opacity representing fluid in scattered acini or primary lobules are visible,

Figure 8-13 Right anterior oblique (45-degree) projection. *A*, Chest radiograph. *(From Van Houten FX, Adams DF, Abrams HL: Radiology of valvular heart disease. In Sonnenblick E, Lesch M [eds]: Valvular Heart Disease. New York, Grune & Stratton, 1974.) B*, A computer-generated cardiac model demonstrates the valve rings, arterioventricular groove, and intercameral sulci.

followed by coalescence into larger confluent areas of opacity.[50]

Radiographically, pulmonary alveolar edema typically involves the inner two-thirds of the lung and produces a "butterfly" or "bat wing" appearance (see Fig. 8-18 *E*). An explanation for this pattern is that the outer third of the lung, aptly termed "the pulmonary cortex," has better aeration, better pumping effect during the respiratory cycle, better compliance, and more efficient lymphatic drainage than does the inner two-thirds of the lung. For these reasons, fluid concentrates preferentially in the central portion of the lung.[49] Distinguishing pulmonary edema caused by congestive heart failure from that caused by increased "capillary permeability" or "overhydration" is usually difficult. Recent studies have attempted to separate cardiovascular pulmonary edema from other forms of pulmonary edema by definable characteristics such as change in heart size, width of the pulmonary vascular pedicle, blood flow distribution, interstitial thickening, and regional distribution of pulmonary edema. In these studies, cardiovascular pulmonary edema is characteristically associated with a large heart, vascular redistribution, diffuse distribution of pulmonary edema fluid, a widened vascular pedicle, increased pulmonary blood volume, septal lines, and pleural effusions. Balanced blood flow distribution and perihilar pulmonary edema characterize overhydration pulmonary edema. In pulmonary edema caused by capillary permeability, there is no cardiac enlargement and little to no pleural effusion, the vascular pedicle is normal or reduced in size, no septal lines are found, and the pulmonary edema has a

peripheral

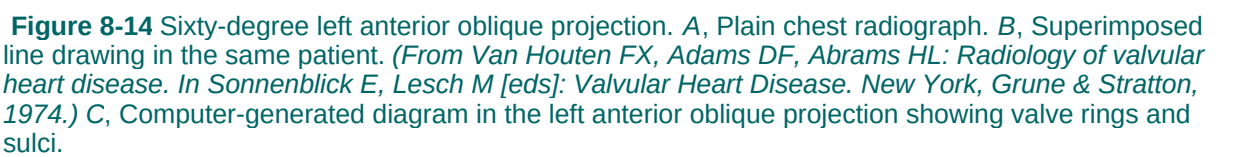

Figure 8-14 Sixty-degree left anterior oblique projection. *A*, Plain chest radiograph. *B*, Superimposed line drawing in the same patient. *(From Van Houten FX, Adams DF, Abrams HL: Radiology of valvular heart disease. In Sonnenblick E, Lesch M [eds]: Valvular Heart Disease. New York, Grune & Stratton, 1974.) C*, Computer-generated diagram in the left anterior oblique projection showing valve rings and sulci.

rather than central pattern.[52] Asymmetrical pulmonary edema is usually caused by underlying morphological changes in the lung parenchyma. Perhaps the most common etiology is emphysema in heavy cigarette smokers or in end-stage sarcoidosis or tuberculosis. Other causes of asymmetrical pulmonary edema include thromboembolism and therapeutic irradiation. Although the plain chest film is the basis for the radiographic diagnosis of the phases of cardiogenic pulmonary edema, the superior resolution of CT has led to a more precise description of the findings of both interstitial and alveolar edema. High-resolution CT will often yield additional insight into both the causes and the distribution of edema and the presence of other concurrent abnormalities. (See also Chap. 10.) [53] [54]

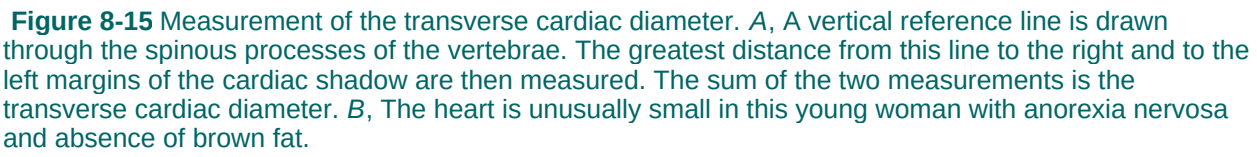

Figure 8-15 Measurement of the transverse cardiac diameter. *A*, A vertical reference line is drawn through the spinous processes of the vertebrae. The greatest distance from this line to the right and to the left margins of the cardiac shadow are then measured. The sum of the two measurements is the transverse cardiac diameter. *B*, The heart is unusually small in this young woman with anorexia nervosa and absence of brown fat.

CARDIAC CALCIFICATION

MYOCARDIAL CALCIFICATION (Fig. 8-19) .

Dystrophic calcification of the heart is usually caused by a large myocardial infarction and is reported to occur in 8 percent of infarcts more than 6 years old.[55] It has also been described in chronic renal disease and following cardiac trauma, particularly involving the anterior wall of the right ventricle.[56] Deposition of calcium in myocardial tissue is related to the production of carbon dioxide in slowly metabolizing tissue. Consequently, the development of relative alkalinity and reduced solubility of calcium leads to soft tissue deposition.[55] Myocardial calcification occurs most frequently in true left ventricular aneurysms localized to the apical and anterolateral aspects of the left ventricular wall. The calcium deposits in left ventricular aneurysms are usually

curvilinear and located within the periphery of the infarct or aneurysm and may occasionally be homogeneous when an entire infarcted area calcifies (Fig. 8-19 *A*). A false left ventricular aneurysm occurs when the chamber ruptures into the pericardium, where the blood is then contained by adhesions. False aneurysms usually occur along the posterolateral wall of the left ventricle.[9]

Calcification may also occur within the left atrium and left atrial appendage, usually in patients with rheumatic carditis, and is associated with mitral stenosis or regurgitation. Left atrial calcification is most often found in the endocardial or subendocardial layers of the heart muscle and is seen less often within an organized thrombus adherent to the chamber wall (Fig. 8-19 *B*). Left atrial calcification is usually thin walled and curvilinear and forms a shell around the circumference of the chamber or is confined to the left atrial appendage.[57] Although myocardial calcification can often be diagnosed on plain radiographs, MRI, CT, ultrasonography, and scintigraphy will augment the information derived from the plain film examination by demonstrating the extent of the aneurysm, estimate overall left ventricular function, and identify the presence of intercavitary thrombus.[57] [58] [59] [60] [61]

VALVULAR CALCIFICATION (see Figs. 8-19 C and D and 8-20).

Radiographically visible calcium within a cardiac valve suggests the presence of hemodynamically significant stenosis. In the mitral valve, calcification appears clumplike or linear, usually measuring about 2 to 4 cm in diameter, and is most often caused by rheumatic valvulitis. Isolated aortic valve calcification in patients younger than 40 years generally signifies marked aortic stenosis related to a bicuspid valve. In patients older than 65 years, aortic valve calcification can be due to "senile" sclerosis and degeneration of normal valve leaflets, or the calcification may be a manifestation of hemodynamically significant aortic stenosis.[62] [63]

The radiographic appearance of the calcification may help determine the origin of the valvular deformity. For example, a thick, irregular semilunar ring pattern with a central bar or knob is typical of a stenotic bicuspid valve and is found in 65 percent of patients with congenital aortic stenosis. The distinctive pattern of calcification of a bicuspid valve results from calcification of the valve raphe or dividing ridge and the line of insertion of the shallow conjoint leaflet and the convex unfused leaflet (see Fig. 8-19 *D*). The abundance of calcification in this entity is thought to be due to constant wear and tear from the abnormal injury-producing motion of the bicuspid valve leaflets. Occasionally, three-leaflet aortic valves will mimic bicuspid valves because of fusion of two of the three leaflets. In these patients, three sinuses of Valsalva are present.

Calcification of the pulmonary valve occurs occasionally in pulmonary valvular stenosis with gradients in excess of 80 mm Hg or in longstanding severe pulmonary hypertension. Calcification of the tricuspid valve is unusual and is caused most frequently by rheumatic disease.

ANNULAR CALCIFICATION (see Fig. 8-20).

Found in the valve rings or fibroskeleton of the heart, annular calcification is a degenerative process that occurs with aging. It is

Figure 8-16 Normal pulmonary blood flow. *A*, Detail of the normal chest radiograph shown in Figure 8-9 *A*. The lower lobe vessels (LLV) are two to three times larger in diameter than the upper lobe vessels (ULV) because of a combination of gravity and alveolar pressure differences. In a normal erect patient, the paired bronchus and vessel are approximately the same size. The arterial/bronchial ratio is helpful in analyzing alterations in pulmonary vasculature. *(Courtesy of Dr. Ahmed Farag.) B*, High-resolution CT shows the relationship of the bronchial and arterial branches lying within the secondary pulmonary lobule. The pulmonary veins follow a different course from the edge of the secondary lobule into the left atrium. *C*, Magnified view showing the relationship of the pulmonary arterial and venous branches entering the mediastinum to better advantage.

found most often in individuals older than 40 years and especially in women. Mitral annular calcification is seen radiographically as a wavy O-, J-, or C-shaped opacity. When calcification is limited to the posteromedial portion of the annulus near the base of the posterior leaflet, it usually has no effect on blood flow through the valve orifice, but when the calcification is more extensive, it may involve the valve leaflets themselves and cause limitation of motion leading to regurgitation. Aortic annular calcification may also extend into the ascending aorta and down into the interventricular septum. Atrial fibrillation, conduction abnormalities, endocarditis, and mitral valve incompetence are associated findings. Tricuspid annular calcification is rare and usually occurs in patients with longstanding pulmonary valvular stenosis, atrial septal defect (ASD), and/or right ventricular hypertension.

Several measurements have been suggested as a means of identifying the location of valvular calcification on plain films. A line drawn on the lateral chest film from the junction of the anterior chest wall and the diaphragm through the hilum to the lung apex will separate anterosuperior aortic calcification from posteroinferior mitral calcification. Another approach is to divide the heart on the lateral view into six sections; this technique will permit identification of the aortic valve in the upper row middle section and mitral calcification in the lower row posterior section.

CORONARY ARTERY CALCIFICATION (Fig. 8-21 ; see also Figs. 10-40 , 10-41 , and 10-42).

Calcium hydroxyapatite is deposited early in the formation of atherosclerotic plaque in coronary arteries. It is thought that calcification of a coronary artery is a regulated process similar to bone formation rather than passive precipitation of calcium crystals in damaged tissue.[64] [65] The presence of visible calcification can be used to monitor evolution of the atherosclerotic process. Coronary artery calcification can be detected by a number of imaging modalities, including plain radiography,

Figure 8-17 Increased pulmonary blood flow. *A*, This 41-year-old woman has an atrial septal defect, ostium primum type, with a pulmonary-to-systemic flow ratio of 5:1. Pulmonary hypertension is suggested because of disparity between the central and peripheral arterial branches. The right atrial border, the main pulmonary artery, and the upper and lower lobe vessels are enlarged and their branches are visible in the outer third of both lungs. *B*, Disparity between the large central and smaller peripheral vessels in a patient with ventricular septal defect and pulmonary arterial hypertension (Eisenmenger physiology). Arrows indicate peripheral pulmonary arteries. C=central pulmonary arteries. *C*, Lateral projection in the same patient as in *B*. Large pulmonary arteries are clearly seen on the lateral view. L=left pulmonary artery; R=right pulmonary artery. *D*, Severe longstanding pulmonary hypertension in a 64-year-old patient with an atrial septal defect and Eisenmenger physiology. The pulmonary arteries are calcified and aneurysmal. *E*, Severe longstanding pulmonary hypertension in a 30-year-old patient with an ostium secundum atrial septal defect. The pulmonary arteries are coiled and enlarged. *F*, A severe pectus excavatum deformity is often found in patients with congenital heart disease. S=posteriorly displaced sternum.

fluoroscopy, ultrafast CT, and ultrasonography.[65] [66] Of these modalities, ultrafast CT has been studied most intensively.[67]

The chest film is readily available and relatively inexpensive but has low sensitivity for the detection of coronary calcification when compared with fluoroscopy and CT.[67] Coronary artery calcifications are most often seen on the lateral chest x-ray, where a calcified left anterior descending artery is seen as a double line of calcification along the anterior border of the heart. In the PA projection, the main left coronary artery and its proximal branches may be visible just below the left main stem branches at the level of the left atrial appendage. Visualization of the coronary arteries by plain chest radiography is severely limited by superimposed structures, low contrast resolution, and motion when compared with other modalities.

While motion artifact degrades the image in a plain chest x-ray, motion is an advantage with fluoroscopy, and moving coronary artery calcifications are vividly seen and identifiable. A number of studies have compared the efficacy of fluoroscopy with coronary arteriography and exercise testing in the identification of significant coronary artery disease.[68] [69] As a result of these studies, a direct relationship between fluoroscopically identified coronary calcification and the frequency and severity of stenotic lesions was established. In one study of 360 patients undergoing coronary arteriography who also underwent cardiac fluoroscopy, 97 percent of those with calcified coronary arteries on fluoroscopy had significant (>75 percent occlusion) coronary artery stenosis of at least one major vessel on arteriography. Of those with significant coronary disease on arteriography, 56 percent had calcification at fluoroscopy.[69] Another study was performed in asymptomatic patients with type II hyperlipidemia who were younger than 55 years. Of those with both positive exercise tests and coronary calcification on fluoroscopy, 92 percent had angiographically determined coronary artery disease. Fluoroscopy had an 82 percent accuracy in the detection of significant coronary artery disease.[70] In yet a third study, 108 asymptomatic men underwent cardiac fluoroscopy and exercise testing; 81 percent of those with a positive exercise test had coronary

calcifications, and 35 percent of these had a positive exercise test. Only 4 percent of men without calcified coronary arteries had a positive exercise test. Finally, in this same series, 92 percent had at least one stenosed coronary artery diagnosed by angiography.[71] The same authors showed that approximately 90 percent of patients with fluoroscopically detectable coronary calcifications had significant coronary disease.[71]

Since exercise tests alone yield 10 to 20 percent positive results in asymptomatic middle-aged males without coronary artery disease, fluoroscopy was suggested as an effective additional screening test for the identification of patients with critical coronary artery disease.

Figure 8-18 *A*, Pulmonary blood flow redistribution. Enlargement of the upper lobe vessels is seen in a patient with ischemic cardiomyopathy and elevated pulmonary venous pressure. *B*, Pulmonary interstitial edema. The vessels are indistinct and enlarged, and peribronchial cuffing is present. *C*, Pulmonary alveolar edema in a patient with congestive cardiomyopathy. The central perihilar distribution of edema, termed "bat wing" edema, is typical of pulmonary alveolar edema caused by cardiovascular or fluid overload (uremic). *D*, Preferential right upper lobe distribution of pulmonary edema in a 65-year-old man with mitral regurgitation. *E*, Right pleural effusion and residual right upper and bilateral lower lobe edema in a patient with acute mitral regurgitation.

Fluoroscopy was most valuable for assessing atypical chest pain or for screening asymptomatic patients.

Although fluoroscopy can detect moderate to large calcifications, its ability to identify small calcifications is poor. For example, in a 1990 study, Agatston and colleagues found that only 52 percent of calcified deposits identified by CT were detected by fluoroscopy.[72] Other disadvantages of fluoroscopy are dependence on the skills of the fluoroscopist, the inability to objectively quantify the extent of calcification, and difficulty in diagnosis because of overlapping structures.[67]

Conventional CT.

Conventional CT is clearly superior to both plain film radiography and fluoroscopy for the detection of coronary calcification. In fact, approximately 50 percent more patients will be found to have calcified coronary arteries and critical coronary artery disease with CT than with fluoroscopy.[67] Recent studies with CT have emphasized its value as a screening procedure, but it also has important limitations that reduce its sensitivity,[60] [73] including slow scanning times, breathing misregistration, and volume averaging. Since CT is performed routinely for other disease indications, it is important to make note of coronary calcifications and their distribution on CT to alert the clinician to their presence and significance.

Spiral or Helical CT.

This technique is now commonly available in most radiology departments. The advantage of helical CT for the detection of coronary artery calcification is based on scan times as fast as 0.6 second with breath-holding technique. Calcific deposits are less blurred than on conventional CT, but small calcifications may still not be seen. Double-helical CT appears to be superior to single-helical CT for the identification of coronary artery calcifications because of thinner section capability and superior resolution.[74] [75] [76]

Electron Beam CT.

Electron beam or ultrafast CT (EBCT) uses an electron beam to traverse stationary tungsten targets to generate radiographic images. Three-millimeter, 100-millisecond axial slices triggered by the electrocardiogram at 80 percent of the RR interval to minimize cardiac motion are acquired during one or more breath-holds.[67] Because cardiac and respiratory motion are virtually eliminated, coronary arteries are readily identified and coronary artery wall calcification is detected. Small amounts of calcium can be detected with greater sensitivity than with either conventional or helical CT, in part because of the small pixel size (0.25 to 0.5 mm^2) possible with this technology. [65] [77] [78] [79] [80]

By using a calcium-scoring method based on an arbitrary Hounsfield number (CT values) of +130 H for calcium multiplied by the actual area of calcification, a total score is calculated. With this method, a number of investigators have demonstrated sensitivities of 85 to 100 percent for significant coronary artery stenosis.[76] [77] [78] [79] [80] [81] A recently published multicenter EBCT calcium-scoring study reviewed data from both coronary arteriography and EBCT studies. A high calcium score was very predictive in separating patients with and without cardiac events (Fig. 10-41) . Of a number of demographic variables and coronary arteriographic

Figure 8-19 Myocardial calcification. *A*, Left ventricular calcification. The thick mural calcification within the left ventricle is due to an aneurysm (arrows). *B*, A thin curvilinear calcification (arrow) is present in the superior and anterior wall of the left atrium in this patient with multivalvular rheumatic heart disease and atrial fibrillation. Prosthetic valves are seen in the aortic, tricuspid, and mitral areas. *C*, Aortic valve calcification. A fluoroscopic spot film shows that the aortic valve is densely calcified (the curved arrow indicates a calcified raphe in this patient with a biscuspid valve). *D*, Ultrafast CT demonstrates calcification of the aortic valve leaflets in a different patient with a congenital biscupid aortic valve (arrowheads). *(Courtesy of Stephanie Flicker, M.D.)*

findings, only the calcium score generated by EBCT appeared to significantly predict cardiac events.[82] However, the accumulated evidence leaves several questions

unanswered concerning the efficacy of EBCT screening in asymptomatic patients and whether the calcium screening method addresses the problem of unstable or noncalcified atherosclerotic plaque.[67]

CALCIFICATION OF THE GREAT VESSELS (Fig. 8-22) .

Aortic calcification, particularly in the region of the arch, is almost ubiquitous in individuals older than 50 years. It is usually noted on chest radiographs as a thin curvilinear opacity near the lateral border of the arch. When the calcification is located deep to the aortic border, dissection may be present. Other causes of aortic calcification are syphilis (usually involving the ascending aorta), sinus of Valsalva aneurysm, calcified ductus arteriosus, and Takayasu arteritis[83] [84] The origin of the main pulmonary artery occasionally calcifies following right ventricular outflow tract surgery for total correction of tetralogy of Fallot. Calcification of the main pulmonary artery also occurs in severe longstanding pulmonary hypertension.[85]

TUMOR CALCIFICATION.

The most common primary tumor of the heart is myxoma, a polypoid gelatinous mass occurring most frequently in the left atrium. About 10 percent of myxomas calcify sufficiently to be seen radiographically.[86] [87] Calcification in cardiac tumors varies from a speckled pattern to a round clump of calcium mimicking mitral annular or valve calcification. Calcification may be visible on plain film or may be seen only with fluoroscopy or CT. With fluoroscopy or CT, a calcified atrial tumor may be seen to prolapse through the atrioventricular valve during diastole and cause obstructive symptoms. Echocardiography and cine-MRI will demonstrate prolapse of a noncalcified myxoma.[86] [88]

PERICARDIAL CALCIFICATION (Fig. 8-23; see also Chap. 50)

Pericardial calcification occurs most often in association with previous acute inflammation or blunt trauma.[89] The most common causes of pericardial inflammation, effusion, and later calcification are viral illness, especially Coxsackie or influenza A and B viral infection; granulomatous disease, including tuberculosis and histoplasmosis; hemopericardium following trauma; and autoimmune disease, including systemic lupus erythematosus and rheumatic heart disease.

Occasionally, pericardial tumors (among them, intrapericardial teratomas and cysts) calcify. Calcification is present in up to 50 percent of patients with constrictive pericarditis.[89] The presence of calcification helps distinguish pericardial constriction from restrictive cardiomyopathy that is not associated with pericardial calcification. On the other hand, extensive calcification may be present without the signs and symptoms of pericardial constriction. Pericardial and myocardial calcifications are frequently confused with each other. However, pericardial calcification can be distinguished from myocardial calcification by differences in distribution. Pericardial calcification is most abundant along the right atrial and ventricular borders and in the area of the atrioventricular groove. The pericardium adjacent to the left ventricle is usually free of

calcification, probably because of its vigorous

Figure 8-20 *A*, Calcified aortic and mitral annulus in an elderly woman. The air in a large hiatal hernia permits excellent visualization of the mitral annulus (arrowheads) in the posteroanterior (PA) projection. *B*, In the lateral projection, calcification is present in both the aortic (white arrow) and mitral (black arrows) annuli. *C*, Aortic annular calcification (arrows) in an elderly patient without signs or symptoms of aortic stenosis. *D*, Mitral valve calcification in the PA projection. *E*, Mitral valve calcification in the lateral projection. Valve calcification (black arrows) lies below the line drawn from the left main bronchus to the anterior costophrenic sulcus, which localizes it to the mitral valve. The aortic valve in this projection lies more anteriorly and above the line (white arrows).

pulsations, and calcification rarely occurs along the left atrial border because of the absence of pericardium behind the left atrium. On the other hand, myocardial calcification is usually localized to the left ventricle and is rare in the right atrium or ventricle. Pericardial calcification is often obscured on a frontal chest film because of underexposure of the mediastinal structures. Overpenetrated films or fluoroscopic examination is helpful in localizing mediastinal calcification, including pericardial calcification, and CT may demonstrate calcium not visible on plain chest films.[89]

ACQUIRED HEART DISEASE

Diagnosis and assessment of the severity of acquired heart disease are assisted by a combination of imaging studies, including plain chest radiography. The chest film is particularly useful for assessing overall cardiac size and pulmonary vascularity. The plain chest radiograph also offers important clues to the enlargement of individual cardiac chambers through analysis of cardiac borders. Today, echocardiography, MRI, and other cross-sectional imaging techniques have largely replaced the plain film except for its role as a useful first examination in the work-up of a cardiac patient.[90] [91]

Valvular Heart Disease (Figs. 8-24 and 8-25; see also Chap. 46)

Aortic Stenosis

Isolated aortic stenosis is most frequently related to a congenital bicuspid aortic valve. Additional causes of left ventricular outflow tract narrowing resulting in left ventricular enlargement without valvular calcification are hypertrophic cardiomyopathy and supravalvular and subvalvular aortic stenoses.

The typical radiographic findings of mild to moderate aortic valvular stenosis include a normal-sized heart with rounding of the left ventricular border or an elongated cardiac silhouette with downward displacement of the cardiac apex because of concentric left ventricular hypertrophy[90] (see Fig. 8-8 *A*). A characteristic discrete bulge located on the right side of the ascending aorta just above the sinus of Valsalva is due to poststenotic

dilatation and is best visualized in the LAO or PA projection. In pure aortic stenosis, the aortic arch and descending aorta remain normal in size and aortic valve calcification is frequent. Calcification increases with the severity of stenosis and the age of the

Figure 8-21 Coronary artery calcification. *A*, Lateral projection demonstrating the "tram track" pattern of coronary artery calcification involving the left anterior descending (arrowheads) and circumflex coronary (arrow) arteries. *B*, A coned-down magnification view in another patient shows a "tramtrack" calcification of the left anterior descending (LAD, arrow) artery. A calcified bicuspid valve inferior in position to the LAD artery is also present. *C*, Calcification of the LAD and the circumflex (Cx) arteries is clearly visualized on axial CT images.

patient, so by the age of 40 years, more than 90 percent of patients with aortic stenosis have visible aortic calcification. Aortic valvular calcification has also been associated with a peak systolic gradient at the aortic valve of greater than 30 mm Hg in 97 percent of patients.[9]

With severe aortic stenosis, the left atrium and ventricle will decompensate and enlarge.[92] The degree of enlargement of both chambers is correlated with the severity of aortic stenosis and with mitral regurgitation caused by left ventricular dilatation or by associated intrinsic mitral valve disease.

CONGENITAL AORTIC STENOSIS.

This type of stenosis may take two forms. The more common is a bicuspid valve with congenital commissural fusion and a central or eccentric orifice. The second form is a bicuspid valve or a tricuspid valve that is initially nonobstructive but undergoes commissural fusion with time. Turbulent blood flow traumatizes the valve and causes irregular nodular scarring of both leaflets, which subsequently undergo gradual fusion and calcification.[4] [91] With time, these valves may also become insufficient because of either incomplete closure of the deformed valve leaflets or infective endocarditis.[4]

DEGENERATIVE AND RHEUMATIC AORTIC VALVULAR STENOSIS.

These types of stenosis may be found in normally tricuspid aortic valves. On the chest film, linear or coarse calcifications may be found in the area of the aortic valve leaflets or annulus. In patients with rheumatic aortic stenosis, mitral calcifications are also frequently present.[93]

SUBAORTIC STENOSIS.

Both the obstructive and nonobstructive forms of hypertrophic cardiomyopathy (see Chap. 48) and membranous subaortic stenosis are characterized radiographically by left

ventricular hypertrophy.[8] Although the plain film findings are suggestive, a specific diagnosis of hypertrophic cardiomyopathy can be best established with MRI, echocardiography, and/or radionuclide studies.[60] [94] [95] Since the aortic leaflets are not involved, blood flow is normal during ventricular systole, and as a result, the ascending aorta does not dilate and the aortic valve does not calcify. Left atrial enlargement, when present, is usually associated with mitral regurgitation.

Aortic Regurgitation (see Figs. 8-8 *B* and *C* and 8-24)

Aortic regurgitation may result from a stenotic bicuspid valve with incomplete closure caused by endocarditis or degeneration. Rheumatic valvulitis and infective endocarditis are other important primary causes. A secondary cause of aortic regurgitation is dilatation of the aortic annulus in diseases preferentially affecting the ascending aorta, such as

Figure 8-22 Aortic calcification. *A*, Posteroanterior projection. *B*, Lateral projection. An abundant thin line of calcification extends from the aortic root to the distal descending thoracic aorta in a young woman. Biopsy revealed Takayasu aortitis.

ankylosing spondylitis, annuloaortic ectasia, Marfan syndrome, Reiter syndrome and psoriatic arthritis.[96] [97] [98] Aortic regurgitation caused by rheumatic heart disease is commonly associated with mitral involvement alone or may involve all four cardiac valves. Aortic regurgitation may also be due to direct trauma or may accompany dissection of the ascending aorta.

In mild aortic regurgitation, the aorta is radiographically normal or mildly enlarged and the left ventricle remains normal in size. With moderate or severe regurgitation, increased dilatation of the left ventricle is seen, and the cardiothoracic ratio usually exceeds 0.55. The aorta is diffusely and often massively dilated, unlike aortic stenosis, where only the ascending aorta is involved (see Fig. 8-8 *C* and *D*). If the sinus portion of the ascending aorta is the only portion selectively dilated, Marfan syndrome (annuloaortic ectasia) is the most likely diagnosis. If the ascending aorta is also calcified, syphilis or, occasionally, Takayasu aortitis (see Chap. 40) is the likely diagnostic possibility. If the valve itself is calcified, aortic regurgitation secondary to a congenital bicuspid aortic valve or rheumatic disease should be considered. If the mitral valve is also regurgitant, the left atrium may be markedly enlarged visually and obscure the enlarged left ventricle. When aortic regurgitation occurs acutely as a result of infective endocarditis, trauma, or dissection, the left ventricle remains normal in size, but because end-diastolic pressure is dramatically increased, pulmonary venous pressure rises and pulmonary interstitial and/or alveolar edema may be observed. Pulmonary arterial hypertension has been described in longstanding aortic regurgitation.[99] In chronic compensated aortic regurgitation, progressive volume overload occurs with left ventricular dilatation and an increase in overall cardiac size but with normal-appearing

lungs.[97]

As is true of aortic stenosis, aortic regurgitation is best diagnosed by Doppler echocardiography or cine-MRI.[96] [100] In selected cases, especially those with calcified aortic valves, analysis of the plain chest radiograph will often establish the diagnosis or reveal specific findings that support the diagnosis of this abnormality.

Mitral Stenosis (see Fig. 8-25)

Rheumatic carditis is the most common cause of mitral stenosis. Isolated mitral valve involvement is most common, followed by a combination of mitral and aortic valve diseases. Left atrial myxoma and, rarely, congenital mitral stenosis, parachute mitral valve myxoma, and metastatic tumor are also causes of mitral valve obstruction. The early roentgenographic signs of mitral stenosis are often subtle and include mild left atrial enlargement with a discrete convex border in the area of the left atrial appendage on the PA projection. In most patients with mitral stenosis, the left ventricle or the pulmonary artery borders are normal in appearance.

With more severe mitral stenosis, the left atrium usually increases further in size; however, in any given patient, poor correlation is seen between the severity of mitral stenosis and the size of the left atrial chamber. The left atrial appendage can be disproportionately enlarged, but the shape of the appendage appears to bear no relationship to the presence or absence of thrombosis.[101] The left main stem bronchus may be displaced upward by the enlarged left atrium. The right atrium is displaced to the right, and pulmonary blood flow is redistributed to the upper lobes. The main pulmonary artery is enlarged, the left ventricle and aorta are usually normal or small, and the mitral valve is often calcified. In addition, calcification of the left atrial wall is most commonly found in the posterior wall and appendage and is often associated with atrial fibrillation. Patients have evidence of pulmonary interstitial edema, characterized by "hilar haze" or central vascular indistinctness, Kerley B lines or interlobular effusions at the lung bases, and subpleural stripes as pulmonary venous pressure rises to the range of 25 mm Hg.

Hemosiderosis resulting from recurrent small hemorrhages related to chronically elevated capillary pressure is often associated with chronic mitral stenosis. The radiographic appearance of hemosiderosis is that of interstitial or miliary lung disease, most prominent in the mid and lower lung zones. With chronic pulmonary interstitial edema, small punctate pulmonary opacities may be found that represent

Figure 8-23 Pericardial calcification. *A*, Posteroanterior projection. *B*, Lateral projection. Both show extensive calcification of the pericardium in the atrioventricular groove in a patient with a history of rheumatic heart disease. *C*, Axial CT at the level of the atrioventricular groove demonstrates extensive

pericardial calcification (arrowheads). LA=left atrium, RA=right atrium.

small islands of bone within the alveoli and are visible as dense nodules on the chest radiograph.

Mitral Regurgitation (see Fig. 8-18 *D*)

Acute mitral regurgitation may be related to ruptured chordae tendineae, rupture of the papillary muscles, ischemic dysfunction, or infective endocarditis. While the heart may not be enlarged in acute mitral regurgitation, severe pulmonary edema is frequently present as a result of left-sided cardiac failure (see Fig. 8-18 *E*). Although pulmonary edema secondary to mitral regurgitation is usually symmetrical, selective right upper lobe pulmonary edema has been described in as many as 9 percent of patients with acute or chronic mitral regurgitation. It is probably due to selective retrograde flow from the mitral valve to the right upper lobe pulmonary veins.[102] [103]

Chronic mitral regurgitation may be secondary to rheumatic heart disease, mitral prolapse from myxomatous degeneration, infective endocarditis, ischemic cardiomyopathy, hypertrophic cardiomyopathy, extensive mitral annulus calcification, collagen disease, Marfan syndrome, and other causes.[92] In chronic mitral regurgitation, the left atrium as well as the left ventricular border appears enlarged radiographically and may be massive in size because of volume overload and increased pressure. When the left atrium is enlarged, it may extend toward the right side and will be observed as a double shadow along the right atrial border. In the LAO projection, the large atrium causes upward displacement of the left main stem bronchus. Coexistent pulmonary arterial hypertension or tricuspid regurgitation may cause dilatation of the right atrium and ventricle and enlargement of the pulmonary arteries.[96] MRI and echocardiography can demonstrate the abnormality of the valve apparatus and evaluate the amount of regurgitant flow.[100] [104] [105]

Ischemic Heart Disease

Many imaging modalities contribute to the diagnosis of ischemic heart disease, including coronary arteriography, radionuclide scintigraphy, echocardiography, CT, and MRI.[104] [105] [106] [107] In ischemic cardiomyopathy, the chest roentgenogram may be entirely normal, even in patients with advanced disease; however, left ventricular enlargement and/or

Figure 8-24 Aortic regurgitation with massive diffuse aortic dilation in a male with severe valvular regurgitation related to annuloaortic ectasia. *A*, Posteroanterior projection. *B*, Lateral projection.

Figure 8-25 Mitral stenosis. *A*, The left atrial border is prominently convex. The aorta is small in this 19-year-old patient with mitral stenosis (arrow). *B*, A subtle convex bulge can be noted at the level of the left atrial appendage (open arrow). A double atrial shadow is present on the right atrial border (black arrow), and the heart is not enlarged in this 54-year-old woman with mitral stenosis. *C*, Mitral stenosis with chronic interstitial pulmonary edema and small punctate opacities representing small islands of ossification within the alveoli. *D*, Mitral stenosis, right anterior oblique view. This posterior displacement of the barium column is related to the enlarged left atrium.

aneurysm is often present. After infarction of 25 percent or more of the left ventricular muscle mass, pulmonary edema may occur, even in patients with a normal-sized heart.[107] When congestive heart failure persists in spite of treatment, complications of myocardial infarction such as aneurysm, pseudoaneurysm, ventricular wall or papillary muscle rupture, and interventricular septal defect must be excluded.[9]

Complications of Myocardial Infarction (see Chap. 35)

An interventricular septal defect occurs in 0.5 to 1.0 percent of patients with recent septal infarction and is characterized by cardiomegaly, pulmonary edema, and poor myocardial contractility. On the plain film radiograph, the typical shunt pattern may not be appreciated because of pulmonary edema but can emerge months later if the patient survives. Such defects usually involve the muscular septum and occur within 7 to 12 days after myocardial infarction.

The radiographic picture of post-myocardial infarction syndrome (Dressler syndrome) is that of a heart enlarged because of pericardial effusion. Unilateral or, less often, bilateral pleural effusions are common, and lower lobe consolidation, particularly on the left side, occurs in less than 20 percent of patients. It generally occurs 2 to 6 weeks after myocardial infarction and is analogous to the postpericardiotomy syndrome.[97] [108]

Aneurysm of the left ventricle is an abnormal bulge or outpouching of the myocardial wall that develops in 12 to 15 percent of patients after myocardial infarction. It occurs most commonly at the cardiac apex or along the anterior free wall of the left ventricle. The chest film shows a localized bulge along the ventricular wall near the apex, with or without a thin rim of calcification. CT, MRI, and echocardiography will all demonstrate, with precision, areas of altered contractility often augmented by pharmaceutical challenge and contrast enhancement.[109] The differential diagnosis of left ventricular aneurysm includes other deformities of the left heart border caused by pericardial cysts, mediastinal or pleural tumor, thymoma, and other mediastinal masses.

Cardiac rupture usually occurs in patients who have had an acute transmural infarction.[110] Most die immediately, but in a minority of patients the rupture is contained or enclosed by the surrounding extracardiac soft tissue and a pseudoaneurysm is formed. Radiographically, a paracardiac mass is present, with sharply marginated edges free of calcification. The mass is usually posterior on the lateral projection, unlike

the more anterior position of a true aneurysm. A firm diagnosis is made by echocardiography, MRI, or contrast-enhanced CT. Coronary arteriography will show complete absence of vessels in the wall of the pseudoaneurysm, unlike a true aneurysm, which may have a rim of mural vessels.[108]

Papillary muscle rupture follows myocardial infarction in approximately 1 percent of patients. Plain film radiographic findings vary from a normal chest to gross cardiomegaly with left atrial and ventricular enlargement and pulmonary edema. Left ventriculography, MRI, or Doppler echocardiography will demonstrate the flail mitral valve leaflets and estimate the degree of mitral regurgitation.[102]

The Cardiomyopathies (see Chap. 48)

The term cardiomyopathy describes a spectrum of myocardial disorders of varying etiology and pathophysiology. They are classified as dilated or congestive, infiltrative, restrictive, hypertrophic, and ischemic.[9] [96]

In *congestive, dilated, and ischemic cardiomyopathy*, the left ventricular ejection fraction is reduced, often severely. Chest radiographs will exhibit a wide spectrum of findings from a normal heart to diffuse nonspecific enlargement that may resemble a large pericardial effusion. Echocardiography demonstrates decreased ventricular contraction and enlargement of the left atrium and ventricle. With time, the right atrium and ventricle also enlarge. Doppler echocardiography or MRI may reveal mitral or tricuspid regurgitation caused by dilatation of the valve annulus.[96] Left-sided and, later, biventricular failure occurs in most patients, an important predictive indicator of shortened survival time.

The radiographic appearance of *hypertrophic cardiomyopathy* is variable. Chest roentgenograms may demonstrate a normal heart or enlargement of the left ventricle, which can be focal or diffuse. If mitral regurgitation is present, the left atrium is also enlarged. Unlike aortic stenosis, no dilatation of the ascending aorta is present unless the patient has coincidental systemic hypertension or atherosclerotic uncoiling of the aorta. The diagnosis of hypertrophic cardiomyopathy is usually established by echocardiography or MRI, and cardiac catheterization with angiography is reserved for cases in which noninvasive techniques are technically inadequate, coronary disease is suspected, or surgery is contemplated. During systole, angiography demonstrates a narrow slitlike left ventricular chamber, marked wall thickening, and hyperdynamic contractions. CT and MRI are less invasive alternatives to angiography.[111]

Restrictive cardiomyopathy is characterized by marked myocardial rigidity with poor left ventricular diastolic relaxation. There are no consistent radiographic features of restrictive cardiomyopathy. The heart is normal in size or may be moderately or, more rarely, markedly enlarged. The left atrium may also be enlarged when mitral regurgitation is present. Pulmonary congestion occurs in most patients, and calcification of the right or left ventricular wall may develop.

POSTOPERATIVE AND CRITICAL CARE RADIOLOGY (Fig. 8-26)

With the continued growth of coronary artery bypass graft surgery and other cardiac surgical procedures during the last three decades, the postoperative supine portable chest roentgenogram has become one of the most frequently ordered examinations. In a typical tertiary care medical center, over 50 percent of inpatient chest roentgenograms are performed at the bedside, usually in the ICU. About one-third of these studies are of postsurgical cardiac patients. To interpret the postoperative chest film properly, special attention must be given to optimization of technique.

TECHNIQUES.

Appropriate film-screen combinations, as well as careful patient positioning, are needed to overcome the effects of low-capacity portable equipment producing low-kilovoltage technique and high amounts of scatter radiation and motion artifacts.[112] The use of laser beam-aligned antiscatter grids and featureless grids that require less precise alignment with the x-ray source are approaches to obtain higher quality portable chest films than are possible with nongrid systems.[113] Although conventional analog portable chest x-rays continue to be the "norm," digital images provide a variety of advantages and are becoming a popular replacement for film-screen chest radiographs as a radiation detector, image display modality, and archival medium.[114] At present, computed radiology with storage phosphor plates as the radiation detector and laser scanning of conventional film-screen radiographs are the most frequently

Figure 8-26 The early postoperative portable chest radiograph. *A*, Multiple catheters and tubes are present and must be identified and their position determined. A=intraaortic balloon catheter; E=endotracheal tube; N=nasogastric tube; S=Swan-Ganz catheter. *B*, The Swan-Ganz catheter is in the right pulmonary artery (arrowhead). The endotracheal tube lies 2 cm above the carina (arrow). It should be repositioned proximally to prevent selective bronchial placement. *C*, This 60-year-old man had a massive myocardial infarction. The intraaortic balloon catheter (IABP) is located above the top of the arch near the orifice of the left subclavian artery.

used methods for producing digital chest images.[115] One major advantage of storage phosphor plates is their sensitivity over a wide range of exposures as opposed to the much narrower exposure range of conventional x-ray film. This difference results in consistent image quality over a wider range of exposures than is possible with conventional film-screen systems.[116] This advantage is particularly important in bedside x-rays, where overexposure and underexposure are ubiquitous. Consistency of technique from film to film in the same patient helps increase diagnostic accuracy and reduces the need for repeat films.[117]

POSTOPERATIVE FILMS.

When preoperative and postoperative chest films are compared, the differences in vascularity, cardiac size, and degree of inspiration between preoperative erect PA and postoperative supine AP films must be taken into account. For example, an 11 percent increase in cardiac diameter, a 9 percent increase in the cardiothoracic ratio, and a 15 percent increase in mediastinal width have been described when an inspiratory PA film is compared with an inspiratory AP chest film. For this reason, many surgeons and radiologists recommend that a preoperative supine AP film be taken to guarantee the availability of a comparable film. Following cardiac surgery, a daily morning film exposed in the ICU is a typical scenario. A number of studies suggest that daily films in subsets of postoperative patients are justified, including patients with an endotracheal (ET) tube and those with a Swan-Ganz catheter or following placement of a pacing device or intraaortic balloon catheter[118] [119] [120] [121] (see Fig. 8-26) .

Most cardiac surgery is performed through an extrapleural median sternotomy with the use of cardiopulmonary bypass. Except for specific problems related to the patient's preexisting cardiac disorder or the specific surgical procedure, changes in the postoperative chest film are common to all cardiac surgical procedures. In the postoperative chest x-ray, a myriad of tubes, wires, catheters, and other devices are present in or overlie the postoperative chest,[119] [122] [123] including an ET tube, which should be positioned in the midtrachea 5 ± 2 cm above the carina to allow excursion with flexion and extension of the neck. If the ET tube is too close to the carina, flexion of the head or neck may force the distal end of the tube into the right or, less often, the left main stem bronchus and cause varying degrees of atelectasis of the opposite lung and barotrauma if assisted ventilation is used.[119] If the tube is too high, the patient may run the risk of aspiration, and dead space is increased.[123] [124] However, despite the opportunity that the bedside chest radiograph gives one to assess tube position, 12 to 15 percent of patients have significant malposition of the ET tube after cardiac surgery[118] [119] (see Fig. 8-26 *B*). A spherical endotracheal cuff seen in the postoperative x-ray indicates overinflation of the cuff, which may lead to tracheal injury.[122]

The central venous pressure monitor is ideally placed between the most proximal valve of the subclavian vein and the right atrium within the superior vena cava. When the distal tip is found in the right atrium, pressure measurements will remain accurate, but the risk of perforation of the thin-walled cardiac chamber is increased. In addition to malposition, compression or "pinch-off" of the catheter by the clavicle and first rib may produce narrowing or chinking of the catheter. Pinch-off is seen in 1 percent of catheter placements.[125] When pinch-off occurs, the catheter should be removed and replaced with a more rigid catheter, one that is oval rather than round in cross section.

Peripherally inserted central catheters (PICC lines) are frequently introduced after cardiac surgery. They are small-caliber tubes placed under sterile conditions. A major

advantage of PICC lines is that they may be left in place for long periods. A Swan-Ganz catheter is usually placed in either major pulmonary artery (ideally with the tip lying within a proximal pulmonary artery 2 to 3 cm distal to the bifurcation) to monitor pulmonary artery or pulmonary capillary wedge pressure and to obtain mixed venous blood samples (see Fig. 8-26 *A* and *B*). From that position, the tip can float distally to a wedged position, whereupon the balloon is inflated. If the catheter is too peripheral in position, the inflated balloon near the tip of the catheter may damage the pulmonary artery wall and produce a perforation leading to hemorrhage or pseudoaneurysm.

Anterior mediastinal drainage catheters are located in the parasternal area, and posterior mediastinal drainage catheters usually lie on the left side behind the heart. When circulatory assistance is needed, a sausage-shaped intraaortic counterpulsation balloon (IACB) may be positioned just below the level of the left subclavian artery within the proximal descending aorta. Placement of the IACB is critical to avoid occluding the subclavian or renal arteries (see Fig. 8-26 *A* and *C*). Pacemaker leads, prosthetic valves, and implantable cardioverter-defibrillators[126] require careful observation for lead or component malposition, pouch infection, or fracture.[127] A nasogastric tube is also usually present. It may be inadvertently placed in a bronchus and pass into the lung or even the pleura. If malposition of a nasogastric tube is unrecognized, aspiration of fluid may occur and cause a chemical pulmonary edema or pneumonia.

Early recognition of the normal and abnormal positions of the large number of catheters, wires, and tubes found on the postoperative chest radiograph requires rapid interpretation by a physician thoroughly familiar with both the appearance of the postoperative chest radiograph and the possible complications that may frequently occur.

The Early Postoperative Chest Radiograph (see Fig. 8-26) .

The first postoperative chest film usually demonstrates varying degrees of left and, to a lesser extent, right lower lobe atelectasis, mediastinal widening, pulmonary edema, and pleural effusion.[128] Unilateral or bilateral lower lobe atelectasis, usually accompanied by small pleural effusions, is the source of the lower lung zone opacities found in almost all cardiac surgery patients. Lower lobe opacities representing atelectases and pleural effusion usually appear within 8 hours after surgery and clear within 5 to 7 days. Pneumonia can occur as an early postoperative complication, but it is certainly unusual. The mechanisms for preferential left lower lobe atelectasis include paralysis of the phrenic nerve caused by cardioplegic solutions or crushed ice administered for myocardial preservation or retained secretions. Decreased diaphragmatic motion may persist for many weeks after surgery but eventually resolves in most patients. Other causes of postoperative left lower lobe atelectasis include dependent pooling of secretions, preferential suctioning of the right main stem bronchi, and compression from the cardiac insulation pad used during surgery.

Pleural Effusion.

Pleural effusion is manifested radiographically by blunting of the costophrenic angle, loss of sharpness of the diaphragmatic contour, and increased opacity behind the

diaphragmatic dome. It may be difficult to identify in a postoperative supine film but is more easily identified on an erect bedside radiograph. A lateral bedside film may also help identify pleural effusion if necessary.[129] Postoperative pleural effusions are probably related to pericardial fluid that leaks into the pleural space through the surgically created pericardial window or to irritation of the pleura during surgery. Postpericardiotomy syndrome and congestive heart failure are sources of pleural effusion in some patients. Increasingly larger or persistent pleural effusions may be due to hemomediastinum, which occurs when blood escapes into the pleural space through a pleural tear. Large pleural effusions are more common after left internal mammary bypass surgery because the pleural space is entered during that procedure.

Patchy or occasionally diffuse *consolidation* in both lungs after cardiac surgery is usually caused by pulmonary edema. *Pulmonary edema* from increased capillary permeability or adult respiratory distress syndrome is common after cardiac surgery and is caused by release of vasoactive substances during cardiopulmonary bypass that affect capillary permeability. Pulmonary edema usually occurs within 2 days of surgery and is reversible with supportive therapy, including diuretics.[123] Postperfusion pulmonary edema occurs after cardiopulmonary bypass because of a marked increase in fluid in the extravascular space. The mechanism for postperfusion pulmonary edema is thought to be related to the contact of circulating blood with foreign surfaces during bypass.[123] Congestive heart failure following cardiac bypass surgery occurs in patients with poor cardiac output. Typically, vascular redistribution to the upper lobes, Kerley B lines, small bilateral pleural effusions, and the patchy opacities resulting from pulmonary edema are present.

Other early findings of cardiac surgery identified with the AP portable chest radiograph include sternal dehiscence, pneumothorax, pneumomediastinum, mediastinal hematoma, pneumopericardium, subcutaneous emphysema, and the findings of pulmonary embolism.[130] Rib fractures occur in 2 to 4 percent of patients and are usually identified by plain films. Their importance lies in the possible misdiagnosis of chest pain of another cause, such as angina or aortic dissection.

Pneumothorax is often difficult to identify in a supine patient. Unlike pneumothorax in the PA erect film, where the crisp opaque line of the visceral pleura located medial to the rib cage is diagnostic, in the supine position a pneumothorax appears as a poorly defined lucency overlying the lower lung zones.[123] Decubitus views are helpful in clearly defining the presence of a pleural air collection. Pneumomediastinum may occur when the mediastinum is entered during surgery. In most cases, the mediastinal air resolves spontaneously within several days. A radiolucency overlying the center of the sternum following median sternotomy is due to a small gap in the sternum and soft tissues at the surgical site; this finding occurs in approximately one-third of patients. No correlation between this thin radiolucency and sternal dehiscence has been proved.

MEDIASTINAL HEMORRHAGE.

Widening of the mediastinum because of hematoma is common after cardiac surgery but is seldom serious enough to require reoperation. In the typical postoperative patient, the mediastinum is widened by up to 35 percent in comparison with the preoperative PA chest film. Katzberg and associates found that if the mediastinum is widened more than

70 percent in comparison with the baseline radiograph, surgery is usually required to remove the hematoma.[131] However, considerable bleeding may be present without visible mediastinal widening, especially if the patient is receiving positive end-expiratory pressure support, which may compress the mediastinum. Moreover, some patients may have a wide mediastinum but are hemodynamically stable, have no significant bloody drainage, and do not require reoperation.

Both CT and echocardiography are helpful in establishing the diagnosis of intrapericardial hematoma. With echocardiography, the hematoma has an echo-free center and a refractile margin. CT, with and without contrast enhancement, is also useful to differentiate hematoma from other masses. On nonenhanced CT, the hematoma is denser than other soft tissues.

Enlargement of the cardiac silhouette during the early postoperative period may be due to cardiac failure with or without myocardial infarction or to a mediastinal or pericardial fluid collection. In some patients, pericardial tamponade occurs from bleeding of small arteries in the area of the sternal incision. Equalization of diastolic pressures and elevation of the pulmonary capillary wedge pressure without pulmonary redistribution or edema, together with diffuse enlargement of the cardiac silhouette, suggest pericardial tamponade. Although the chest roentgenogram may be suggestive of tamponade, both CT and echocardiography will clearly reveal the presence of pericardial fluid or thickening and tapered narrowing of both ventricles. CT is the imaging procedure of choice to detect an extrapericardial mediastinal fluid collection.

Late Complications of Cardiac Surgery

POSTPERICARDIOTOMY SYNDROME.

This common late complication of cardiac surgery is characterized by pleuritis, pericarditis, and fever. It is believed to be the result of an immune response to necrotic epicardial tissue. It generally occurs several weeks after surgery and is self-limited. Occasionally, cardiac tamponade or constrictive pericarditis occurs as a complication of the postpericardiotomy syndrome. Unilateral or bilateral pleural effusions may obscure portions of the cardiac silhouette, and small basilar pulmonary opacities are found radiographically. Echocardiography or CT will identify pleural or pericardial fluid collections. Other late postoperative complications of cardiac surgery include sternal osteomyelitis, especially after internal mammary artery surgery, dehiscence at the surgical site, mediastinitis, pneudoaneurysm of the ascending aorta, cardiac rupture, and dissection.[123] [132] [133]

PSEUDOANEURYSM OF THE THORACIC AORTA.

This rare but serious complication of cardiac surgery is associated with sternal osteomyelitis and mediastinitis following median sternotomy.[133] It may occur at the site

of an aortic cannulation or vent, the aortic clamp line, or the saphenous graft-aortic anastomosis.[133] Cardiac pseudoaneurysms can also occur at sites where full-thickness cardiac incisions were made. Although plain film radiographs will demonstrate a mass anterior to the heart or in the ascending aortic region, enhanced CT or MRI is diagnostic and should be performed before reoperation.[133]

AORTIC DISSECTION.

Although aortic dissection rarely occurs in patients who have undergone cardiac surgery, it should be considered in the differential diagnosis of mediastinal widening or a postoperative mediastinal mass. Although a dissection may appear immediately after surgery, it is more likely to occur weeks to months later. Transesophageal echocardiography in unstable patients, MRI, and contrast-enhanced CT are helpful to distinguish between dissection and hematoma, abscess, tumor, or prominent mediastinal fat.[134] [135]

Prosthetic Valve Surgery (see also Chap. 46)

The chest roentgenogram is helpful in monitoring patients for the potential complications of cardiac valve implantation. Identification of the site of a prosthetic valve is not as simple as identification of a calcified native cardiac valve because only an AP film may be available during the early postoperative period and prosthetic valves vary in position and often overlap each other. If the patient fails to improve clinically after valve replacement or if pulmonary edema occurs after a brief period of improvement, malfunction of the prosthetic valve may be the cause. Major malfunctions result from sewing ring dehiscence, tissue encroachment into the ring orifice, and infective endocarditis. The plain chest film may show enlargement of the adjacent cardiac chambers and/or pulmonary edema. Late calcification of the tissue components of a bioprothesis may be seen and is usually caused by tissue degeneration. Fracture and separation of radiopaque components and their distal migration have been described and may be identified by fluoroscopy or on radiographs of the chest and abdomen.[47] [55] However, these complications do not appear to be associated with currently implanted valves.[136]

Fluoroscopy will document prosthetic valve motion, the integrity of the mechanical components, and the presence of calcification. Reduced or absent excursion of the valve occluder suggests thrombus, tissue intrusion, or vegetation. Doppler echocardiography will document regurgitant blood flow proximal to the valve. Contrast-enhanced cine-EBCT and cine-MRI can identify and quantify valvular regurgitation.

Cardiac Transplantation (see also Chap. 20)

Most transplant candidates have a history of end-stage cardiac failure caused by ischemic cardiomyopathy. The heart is invariably enlarged, and vascular redistribution or edema is generally present. In orthotopic cardiac transplantation, the recipient heart is removed and the donor heart, with intact aorta and pulmonary arteries, is attached to

a cuff of native left atrium containing the pulmonary veins. After transplant surgery, typical radiographic changes associated with median sternotomy are found, including a widened mediastinum, pleural effusion, left lower lobe consolidation, and atelectasis. Within 2 months of transplantation, the heart becomes smaller and reaches stability 6 months after surgery. Persistent cardiomegaly is most likely caused by pericardial effusion, which may result from cyclosporine therapy or placement of a small donor heart in a large pericardial sac.[137] After transplantation, the radiograph demonstrates a double density in the vicinity of the right atrial border because of the overlapping donor and recipient atria. MRI or CT can clearly depict postoperative transplantation anatomy, as well as the presence of pericardial effusion and lymphadenopathy.[138]

If graft rejection occurs, the heart enlarges, but pulmonary edema does not usually develop. Rejection is diagnosed by demonstration of lymphocytic infiltration and myocytic necrosis on endomyocardial biopsy.[139] MRI can demonstrate alterations in signal intensity caused by moderate and severe rejection.[140]

CONGENITAL HEART DISEASE IN THE ADULT (see also Chap. 44)

The plain film findings of adult congenital heart disease can be classified in a number of ways, such as classification based on the frequency of the disorder or a combination of the hallmarks of disease, such as the state of the pulmonary vasculature, related skeletal abnormalities, the position of the aortic arch and cardiac apex, cardiac size, and abdominal situs. Combining the radiographic findings with a history of the presence or absence of cyanosis, the time of onset of the cardiac murmur, and the clinical state of the patient should narrow the diagnostic choices.[36] [41] [142] Several of the more common congenital cardiovascular disorders found with some frequency in adults are discussed below.

Coarctation of the Aorta (Fig. 8-27)

Coarctation of the aorta is a common anomaly that accounts for 8 percent of congenital heart defects in children and about 6 percent of adult congenital heart disease. Of those who escape diagnosis in early childhood, 25 percent are dead by the age of 20 and almost 50 percent by the age of 30. The clinical findings are highly variable and range from left ventricular failure in infancy to systemic hypertension in otherwise asymptomatic adult patients, depending on the site and severity of the coarctation and the presence of associated abnormalities.[143] [144] The most common associated anomaly is a bicuspid aortic valve, which occurs in as many as 85 percent of patients with coarctation of the

Figure 8-27 Coarctation of the aorta. *A*, Displacement of the barium column to the right above and below the coarctation. *B*, Thoracic aortography. The luminal narrowing at the isthmus and enlargement of the

left subclavian artery (LSCA) are characteristic of coarctation. It may be described as a "3" sign or "E" sign because of the precoarctation bulge of the LSCA, the coarctation itself, and postcoarctation aortic dilatation. Dilatation of the ascending aorta is due to a regurgitant bicuspid aortic valve. *C*, Sagittal T1-weighted MRI in the same patient shows the same findings as the aortogram but without contrast media, radiation, or catheterization.

aorta.[142] Other associated anomalies include ventricular septal defect, stenosis or atresia of the left subclavian artery, PDA, Turner syndrome PDA, and mitral valve prolapse.[145] [146]

The diagnosis of coarctation of the aorta can be established from the PA chest film alone in up to 92 percent of patients.[142] Widening of the left subclavian artery border is the most common finding, but the most useful radiographic sign is an abnormal contour of the aortic arch, which may appear as a double bulge above and below the usual site of the aortic knob. This pattern has been described as a "figure 3" sign. The upper arc of the "3" is the dilated arch proximal to the coarctation and/or a dilated left subclavian artery. The lower arc or bulge represents poststenotic dilatation of the aorta immediately below the coarctation. The indentation between the two bulges is the coarctation itself. When the esophagus is filled with barium, a reverse "3" or "E" sign is often seen and represents a mirror image of the areas of prestenotic and poststenotic dilatation. The "3" sign is variable in that the upper arc may be small and the lower arc large or vice versa. Superior mediastinal widening or sternal scalloping caused by large internal mammary collateral arteries is visible in some patients. A prominent left ventricular border often occurs with coarctation, particularly when a bicuspid aortic valve is associated with aortic stenosis.

Bilateral symmetrical rib notching, readily appreciated on the chest film, is diagnostic of aortic coarctation. It is due to obstructed blood flow at the narrowed aortic segment with collateral blood flow through the intercostal arteries. Rib notching is unusual in infancy, but becomes more frequent with increased age and is present in 75 percent of adults with coarctation. Rib notching occurs along the inferior margin of the third to the eighth ribs and is caused by pulsation of dilated intercostal arteries. The major pathways of collateral flow include (1) subclavian artery to the internal mammary artery to the intercostal arteries, (2) subclavian artery to the costovertebral trunk to the intercostal arteries, and (3) transverse cervical and suprascapular arteries to the intercostal arteries.

Cardiac catheterization and angiography are diagnostic and demonstrate both the site of the coarctation and associated anomalies, including aortic stenosis. However, MRI and echocardiography have largely replaced these procedures. Echocardiography, for example, clearly demonstrates the presence or absence of bicuspid aortic and mitral valve deformities. MRI will not only vividly portray the anatomy of the coarctation but will also demonstrate the bicuspid valve and the state of left ventricular function, as well as restenosis following angioplasty or surgical repair.[142] [147] [148] [149]

Left-to-Right Intracardiac Shunts

OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT (Fig. 8-28) .

ASD, the most common left-to-right shunt diagnosed in adult life, accounts for over 40 percent of adult congenital heart defects.[150] [151] Although the chest radiograph may be normal in a patient with a small shunt, typically, the main pulmonary artery, the peripheral pulmonary branches, the right atrium, and the right ventricular borders are enlarged. Differentiation from other left-to-right shunts is often possible. Less pulmonary artery dilatation is usually seen in PDA than in ASD, and both PDA and ventricular septal defect are associated with enlarged left-sided cardiac chambers (Fig. 8-29) . In adults older than 50 years, the radiographic findings of ASD are often atypical and may include left atrial enlargement, vascular cephalization, and pulmonary edema.[142] Echocardiography demonstrating right ventricular chamber dilatation and paradoxical anterior systolic motion of the interventricular septum is diagnostic of ASD. The size and the location of the ASD can often be visualized, as well as associated abnormalities such as mitral valve prolapse. Both CT and MRI can also demonstrate the defect of the atrial septum. However, a pitfall of MRI is the normally thin atrial septum at the fossa ovalis, which may not be visualized by MRI and thus simulate an ASD. For the diagnosis of ostium secundum ASD by MRI, at least two consecutive

Figure 8-28 Atrial septal defect. A 45-year-old woman with an ostium secundum defect has an enlarged pulmonary artery with prominence of the right atrial border. Enlargement of the right ventricle displaces the left heart border upward and to the left.

Figure 8-29 Patent ductus arteriosus in a patient with a cardiac pacemaker. An inverted "Y" calcification representing the ductus is present above an enlarged pulmonary artery (arrow).

anatomical sections showing the defect are necessary to establish the diagnosis with confidence.[152]

Pulmonary Valvular Stenosis (Fig. 8-30)

Valvular stenosis in adults is usually an isolated anomaly. Most patients are asymptomatic even with severe obstruction. Mild to moderate enlargement of the main pulmonary artery is present because of poststenotic dilatation resulting from the jet effect of blood flow through the narrowed pulmonary valve orifice. Since the jet is directed toward the left, the left pulmonary artery is often preferentially enlarged. Calcification of the pulmonary valve is rare in this condition. The differential diagnosis of pulmonary valvular stenosis includes primary and secondary pulmonary hypertension

and idiopathic pulmonary artery dilatation.[141] [142]

Congenital Corrected Transposition of the Great Arteries (Fig. 8-31)

In this condition, ventricular inversion and transposition of the pulmonary artery and aorta result from formation of a left (*levo* or *l*) rather than a right (*dextro* or *d*) bulboventricular loop. Systemic venous flow is transmitted to the lungs by way of a right-sided anatomical left ventricle and the transposed pulmonary artery. Pulmonary venous flow traverses the left atrium and a left-sided anatomical right ventricle en route to the aorta. Radiographically, the ascending aorta is positioned to the left and forms a long continuous shadow along the left cardiac border from the ventricular apex to the aortic arch. The main pulmonary artery lies behind and to the right of the aorta and is not border-forming with the lung in the PA view. A left-to-right shunt may or may not be present, and left atrioventricular valve regurgitation and conduction abnormalities leading to heart block are fairly common. The heart is normal to enlarged, depending on the degree of atrioventricular valve regurgitation. Cross-sectional imaging supports the plain film diagnosis by showing an anterior left-sided aorta and a pulmonary artery lying behind and medial to the aorta.

Cyanotic Congenital Heart Disease in the Adult (see also Chap. 44)

TETRALOGY OF FALLOT.

This abnormality is the most common cyanotic congenital cardiac lesion in adults, as well as in children. Most adults with tetralogy of Fallot demonstrate mild to moderate pulmonary hypovascularity. Those with mild infundibular pulmonary stenosis have normal pulmonary blood flow. Small tortuous bronchial arteries are found in both lungs when severe pulmonary outflow tract stenosis or atresia is present. A right aortic arch is found in 25 percent of patients[153] (see Fig. 8-5) . The combination of a right aortic arch and cyanosis should always suggest the diagnosis of tetralogy of Fallot. Echocardiography often demonstrates a high and large ventricular septal defect, overriding of the ventricular septum by the aorta, and right ventricular hypertrophy. Both EBCT and MRI also demonstrate the septal defect and the large ascending aorta, as well a right aortic arch.[147] Plain films show a boot-shaped heart in some adult patients, but this finding is less common than in children because those who survive into adulthood are less likely to have severe right ventricular outflow tract stenosis (see Fig. 8-6 *E*).

EBSTEIN ANOMALY

(see Fig. 8-9 *B*). In Ebstein anomaly, the tricuspid valve is malformed and partially fused to the walls of the right ventricle. This combination results in downward displacement of the tricuspid orifice, and regurgitation ensues. A right-to-left shunt is present at the atrial level and causes cyanosis. The right heart chambers are enlarged, often markedly, as a manifestation of the tricuspid regurgitation. The typical radiographic findings are

Figure 8-30 Asymmetrical pulmonary blood flow in a 51-year-old man with pulmonary valvular stenosis. The left pulmonary artery is larger than the right because the jet of blood is directed to the left pulmonary artery (arrow).

Figure 8-31 Corrected transposition of the great vessels (ventricular inversion). *A*, Posteroanterior chest film. The unique appearance of the left-sided ascending aorta is diagnostic (arrow). *B*, Aortography also shows the left-sided aorta originating from a morphological right ventricle.

those of a large rounded or triangular heart with a narrow vascular pedicle.[147] The pulmonary vasculature is reduced, depending on the degree of right-to-left shunting. The greater the shunt, the more diminished the vascularity. Echocardiography shows the abnormal placement of the tricuspid valve with downward displacement of the septal and posterior leaflets. Tricuspid regurgitation can be evaluated by two-dimensional and Doppler echocardiography. MRI and CT also demonstrate the downward displacement of the valve and enlargement of the right atrium.[147]

THE PERICARDIUM (see also Chap. 50)

The incidence of pericardial disease in patients with cardiac disease parallels the frequency of cardiac surgery, multisystem inflammatory disease, thoracic irradiation, and the use of an array of therapeutic agents that affect the pericardium. The presence of pericardial disease is also increasingly being recognized because cross-sectional modalities such as echocardiography and CT portray pericardial disease with great accuracy.[154] [155] [156]

THE NORMAL PERICARDIUM.

The normal pericardium is frequently identified on lateral plain film projections of the chest as a thin linear opacity separating the anterior subxiphoid mediastinal fat from subepicardial fat. The pericardium may also be visualized in the frontal projection paralleling the left heart border. The extent of normal and abnormal pericardium is best appreciated with CT and MRI in most patients because of superior contrast resolution. With both CT and MRI, the anterior, lateral, and posterior portions of the pericardium are clearly separated from mediastinal fat, and subtle discontinuous areas of pericardial thickening and loculated effusions may be clearly seen. One disadvantage of MRI and CT is that while the pericardial recesses are clearly defined, they may on occasion mimic aortic dissection or mediastinal lymphadenopathy.

PERICARDIAL EFFUSION (Fig. 8-32) .

Pericardial effusion may be a transudate or exudate, may be hemorrhagic, gaseous, or

chylous, and may be caused by a wide variety of disorders. When fluid accumulates in the pericardial space, the cardiac silhouette assumes a flasklike, triangular, or globular silhouette. The normal indentations and prominences along both the left and right heart borders are effaced, so the shape of the cardiac silhouette becomes smooth and featureless. Since the pericardium extends up to the pulmonary bifurcation, when a large pericardial effusion is present, the hilar structures are draped and obscured by the distended pericardial cavity. This radiographic appearance should help distinguish a large pericardial effusion from massive cardiomegaly, which will not obscure the hilar vessels.

In the lateral chest radiograph in a patient with pericardial effusion, the retrosternal space is typically narrowed or obliterated by the expanding cardiac silhouette. Normally, the low-density subepicardial fat merges imperceptibly with the mediastinal fat since the two fat planes are separated by only the 2-mm-thick stripe of the pericardium. When pericardial effusion is present, the subepicardial fat is displaced posteriorly by the higher density fluid, which may be visible as a wide opaque vertical band between the anterior border of the heart and the mediastinum. This "epicardial fat pad sign" is best visualized on the lateral projection and is highly specific for pericardial effusion (Fig. 8-32 *B* and *C*).

ECHOCARDIOGRAPHY (see also Fig. 7-94) .

Echocardiography is the most efficient method for the detection of simple pericardial effusion and/or thickening. A major advantage of echocardiography is that the ultrasound apparatus can be transported to the bedside to examine critically ill patients. The technique is noninvasive and is diagnostically sensitive to fluid-filled structures. When the pericardial fluid volume is small, it appears as an elliptical hypoechoic region behind the left ventricle. When the effusion is large, the pericardial hypoechoic zone expands to surround the right ventricular apex. In some cases, echocardiography may fail to identify pericardial fluid when constriction, neoplasm, or hemorrhage is present.[154] [157] If echocardiography is inconclusive, CT can be helpful in detecting pericardial thickening, diffuse or loculated effusion, calcification, and adjacent mediastinal and pulmonary disease, as well as neoplasm[154] (see Fig. 8-32 *E*). The nature of the fluid may be identified by analysis of CT density numbers. For example, higher CT density values are seen in hemopericardium than in serous effusions. Chylous pericardial effusions may have a lower attenuation value than normal pericardial fluid.[158]

MRI (see also Fig. 10-17) .

MRI can clearly detect pericardial effusion. On T1-weighted images, the pericardial cavity is shown as a dark signal void because of motion of fluid in the pericardial sac. On the other hand, the pericardial effusion is bright on a gradient-echo sequence. Pericardial fibrosis is characterized by a medium-intensity signal on T1-weighted or dark signal on T2-weighted images. Intrapericardial masses, cysts, and diffuse thickening are well demonstrated with MRI. Furthermore, MRI can clearly define pericardial recesses, mediastinal fat, and other anatomical landmarks that may present pitfalls for the echocardiographer.[159]

PERICARDIAL CONSTRICTION.

Pericardial constriction may complicate viral or tuberculous pericarditis, hemopericardium,

Figure 8-32 Pericardial effusion. *A*, The heart assumes a globular shape after development of a pericardial effusion. The normal indentations along the heart borders are effaced, so the cardiac silhouette is smooth and featureless. *B*, The subepicardial radiolucent fat stripe is derived from the subxiphoid fat anterior to a thin, higher density stripe of pericardial fluid (arrowhead). *C*, The pericardial stripe (arrowheads) is wider than in *B* because of a small pericardial effusion. *D*, A large pericardial effusion is present (arrows). *E*, Contrast-enhanced CT shows a large band of nonenhanced water density surrounding the heart that represents pericardial effusion.

pericarditis associated with radiation, and postpericardiotomy syndrome. In patients with chronic pericardial constriction, the overall heart size is large when the pericardium is thickened to 2 cm or more; otherwise, the cardiac silhouette remains normal or small. The right atrial border is flattened, and pulmonary vascular redistribution may be observed.

Small to large pleural effusions are found in 60 percent of patients with pericardial constriction, and enlargement of the azygos vein and left atrium occurs in 20 percent. Pericardial calcification is best appreciated along the anterior and inferior cardiac borders or in the atrioventricular groove. While it is important to appreciate that the presence of pericardial calcification indicates chronic pericarditis, it does not in itself establish a diagnosis of pericardial constriction.

Pericardial constriction is often confused with restrictive cardiomyopathy, and MRI and CT are particularly helpful in differentiating between these entities (see Fig. 10-45) . The pericardium in patients with restrictive cardiomyopathy is normal in thickness, and no calcification is present. In addition, diffuse limitation of global cardiac excursion in systole and diastole is present, together with myocardial thickening in hearts with restrictive cardiomyopathy.[157]

CONGENITAL ABSENCE OF THE PERICARDIUM.

This abnormality may be partial or complete. Complete absence is less common than partial absence and is usually left sided.[160] Partial absence most frequently occurs along the upper border of the pericardium on either side. If the left-sided defect is small, herniation of the left atrial appendage and/or the pulmonary trunk may occur. On the frontal chest film, herniation through a pericardial defect may resemble the appearance of pulmonary stenosis, mitral stenosis, or a mediastinal tumor. When the left

pericardium is completely absent, the aortic knob remains in its usual position, but the remainder of the cardiac silhouette shifts to the left and rotates toward the right so that the right ventricle may become border-forming and the pulmonary artery and left atrial appendage are prominent.[160]

In patients with absence of the left pericardium, a plain film shows the lung interposed between the medial border of the pulmonary artery and the thoracic aorta and outlining the pulmonary artery on both its medial and lateral sides, and aerated lung may be visible between the heart and the diaphragm. CT and MRI demonstrate to best advantage absence of the left anterior pericardium between the ascending aorta and the main pulmonary artery. Displacement of the main pulmonary artery laterally and anteriorly is often a clue to the diagnosis.

PERICARDIAL CYST.

A pericardial cyst generally appears as a smooth convex bulge along the middle or lower right heart border near the cardiophrenic sulcus. However, 20 percent of pericardial cysts lie along the left heart border, sometimes mimicking a prominent left atrial appendage or left ventricular aneurysm.[161] Occasionally, pericardial recess cysts are manifested as a soft tissue mass along the right superior mediastinal border in the area of the superior vena cava[161] (Fig. 8-33) . Pericardial cysts rarely calcify and do not communicate with the pericardial space. Their clinical importance lies in the need to differentiate pericardial cysts from other masses with a similar appearance, such as thymoma, lymphoma, and postoperative hematoma. Pericardial cysts are best diagnosed by echocardiography, CT, or MRI as smoothly marginated, fluid-filled structures adjacent to the right heart border.[58] [59] [60] [61]

Figure 8-33 Pericardial recess cyst. *A*, Posteroanterior chest film showing a mediastinal bulge along the right paratracheal line. *B*, MRI in the sagittal plane shows the cyst as a homogeneous medium-intensity structure behind the superior vena cava.

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Chapter 9 - Nuclear Cardiology

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Myocardial Perfusion Imaging

The regional distribution of coronary myocardial perfusion can be visualized with radiopharmaceuticals that accumulate proportional to regional myocardial blood flow. The first scintigraphic images of myocardial perfusion were acquired in 1964 by Carr and colleagues with cesium-131.[1] Exercise-induced myocardial ischemia was initially visualized with potassium-43 in 1973 by Zaret and coworkers.[2] Thallium-201 (^{201} Tl), a potassium analog, became available in 1974 and has since has been used successfully for over 25 years. In the early 1990s, new technetium-99m (^{99m} Tc)-labeled compounds with better imaging characteristics and novel biological properties were introduced for visualization of myocardial perfusion. [3] Any of these imaging agents can be used to visualize the *relative* distribution of myocardial blood flow. *Absolute* quantification of myocardial blood flow is not yet feasible with single-photon-emitting radioisotopes but can be achieved with positron-emission tomography (PET). State-of-the-art myocardial perfusion imaging with ^{99m} Tc-labeled agents is acquired with electrocardiographically (ECG) synchronized gating and thus provides information on both myocardial perfusion

and function.

The clinically most important application of myocardial perfusion imaging is in conjunction with stress testing for evaluation of ischemic heart disease. Numerous investigators have shown the diagnostic usefulness of exercise myocardial perfusion imaging with either ^{201}Tl or the ^{99m}Tc-labeled imaging agents. Agreement between the results of stress myocardial perfusion imaging and findings on contrast coronary angiography is generally good. More importantly, there is ample evidence that findings on stress myocardial perfusion images reflect the hemodynamic and functional significance of coronary artery stenoses and thus provide important prognostic information. Finally, the information derived from radionuclide myocardial perfusion imaging has independent and incremental value over that derived by other diagnostic methods.

In 1999, approximately 5 million stress myocardial perfusion studies were performed in the United States alone. Sixty-five percent of these studies were performed in conjunction with physical exercise and 35 percent after pharmacological vasodilation. Seventy-five percent of the stress images were acquired with ^{99m}Tc-labeled compounds and 25 percent with ^{201}Tl. Single-photon emission computed tomography (SPECT) was the predominant imaging technique used in over 90 percent of studies. In 1999, planar imaging was rarely used as the primary imaging modality in state-of-art nuclear cardiology laboratories.

RADIOPHARMACEUTICALS

^{99m}Tc-LABELED COMPOUNDS.

A number of ^{99m}Tc-labeled compounds have been developed for myocardial imaging (Table 9-1) . Presently, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are widely used.[3] The ^{99m}Tc label of these agents emits gamma rays at 140 keV and has a physical half-life of 6 hours. Because of the slow body clearance, the biological half-life of sestamibi and tetrofosmin is approximately the same as the physical half-life. The whole-body absorbed radiation dose for these agents is approximately 0.02 rad/mCi. The target organ is the gallbladder, which receives approximately 0.18 rad/mCi.

Because of more favorable dosimetry of the ^{99m}Tc-labeled compounds than ^{201}Tl, up to 30 mCi can be administered per day (see Imaging Protocols). The initial myocardial distribution of ^{99m}Tc-labeled agents is proportional to the regional distribution of myocardial blood flow. After injection, the radiopharmaceutical also accumulates rapidly in the liver and is subsequently cleared into the biliary tract. The net myocardial extraction fraction of ^{99m}Tc-sestamibi is 41 percent and that of ^{99m}Tc-tetrofosmin is 30 percent, which is substantially less efficient than that of ^{201}Tl (see below).[4] Both agents enter the myocyte by passive diffusion and bind stably to intracellular membranes. Because of intracellular retention and additional subsequent myocardial uptake during recirculation, the *absolute net retention* of

TABLE 9-1 -- COMPARATIVE CHARACTERISTICS OF VARIOUS MYOCARDIAL PERFUSION IMAGING AGENTS

CHARACTERISTIC	THALLIUM-201	TECHNETIUM Tc 99m SESTAMIBITECHNETIUM Tc 99m TETROFOSMIN
Energy emission (keV)	69-83 (x-rays) 135, 165, 167 (gamma rays)	140
Physical half-life (hr)	74	6
Biological half-life (hr)	58	6
Heart half-life (hr)	7.5	4.5
Dose (mCi)	2-4.5	30
Radiation dose (rad/mCi)		
Whole body	0.21	0.02
Testes	3.1	0.01
Kidney	1.3	0.06
Intestines	0.54	0.18
Net myocardial extraction fraction (%)	60	41 (Sestamibi) 30 (Tetrofosmin)
Percentage of injected dose to heart	4	1.5
Visualization of		
Blood flow	+	+
Viability	+ (Delayed image)	+
Redistribution	+	Minimal
LVEF (first pass)	-	+
ECG gating	±	+
Imaging time/view (min)		
Planar	10	5
Tomography	21	11

ECG=electrocardiographic; LVEF=left ventricular ejection fraction.

^{99m} Tc-labeled agents several minutes after administration is approximately comparable

to that of ^{201}Tl.

Myocardial Kinetics of ^{99m}Tc-Labeled Agents.

During the first 3 hours after injection, approximately 30 percent of a ^{99m}Tc-labeled myocardial perfusion imaging agent is cleared from the heart (Figs. 9-1 and 9-2) . Although redistribution of sestamibi in ischemic defects has been demonstrated in experimental animals[5] and in selected patients, the degree of redistribution in humans is minimal and does not have clinical significance. Since myocardial distribution of ^{99m}Tc-labeled agents remains relatively fixed over time, the distribution of myocardial blood flow *at the time of injection* is "frozen" over time and can be imaged for several hours. In addition, two separate injections are required to evaluate myocardial uptake at rest and during exercise.

THALLIUM-201.

^{201}Tl is cyclotron produced and emits mercury x-rays at 69 to 83 keV (88 percent) and gamma rays at 135, 165, and 167 keV (12 percent). Its physical half-life is 74 hours; however, its biological half-life is approximately 58 hours (see Table 9-1) . The estimated absorbed radiation dose to the whole body is 0.21 rad/mCi. The target organs are the testes (3.1 rad/mCi), the thyroid (2.3 rad/mCi), and the intestines and kidney, which receive 1.5 rad/mCi. Because of the relatively long half-life of ^{201}Tl, only a relatively small amount of radioactivity can be administered. For planar imaging, usually 2 to 2.5 mCi is administered, whereas for tomographic imaging, 3.0 to 4.5 mCi is given. The 60 percent net myocardial extraction fraction of ^{201}Tl is relatively high.[4] The initial myocardial accumulation of ^{201}Tl is proportional to myocardial blood flow. Once ^{201}Tl has entered the myocyte, continuous exchange of ^{201}Tl takes place across the cell membrane. This

Figure 9-1 ^{99m}Tc-sestamibi organ time activity curves after injection at rest and after exercise in five normal volunteers (mean + SD). The data are normalized at cardiac activity 5 minutes after injection. For clarity, standard deviations are only shown at 5, 60, 120, and 180 minutes. ^{99m}Tc-hexamibi is obsolete nomenclature for ^{99m}Tc-sestamibi. *(From Wackers FJTh, Berman DS, Maddahi J, et al: Technetium-99m hexakis 2-methoxyisobutyl isonitrile: Human biodistribution dosimetry, safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 30:301, 1989. Reprinted with permission from the Society of Nuclear Medicine.)*

Figure 9-2 Planar myocardial perfusion images with ^{99m}Tc-sestamibi. Images of a normal volunteer after exercise were taken with a large-field-of-view camera. Both the right (RV) and left (LV) ventricles are well visualized. The imaging agent initially accumulated in the liver and cleared into the gallbladder (G). After

30 minutes no significant liver accumulation is seen. *(From Wackers FJTh, Berman DS, Maddahi J, et al: Technetium-99m hexakis 2-methoxyisobutyl isonitrile: Human biodistribution dosimetry, safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 30:301, 1989. Reprinted with permission from the Society of Nuclear Medicine.)*

process involves the Na+, K+-ATPase pump. The intrinsic half-life of ^{201}Tl within the myocardial cell is approximately 85 minutes. However, because of continued cellular reaccumulation of ^{201}Tl, the effective half-life of ^{201}Tl in the heart is 7.5 hours. A unique aspect of ^{201}Tl studies is that images obtained *early* and *late* after injection provide different pathophysiological information:

1. Images immediately after injection reflect the flow-dependent initial distribution and thus regional myocardial blood flow.
2. Images taken after a delay of 2 to 24 hours reflect the distribution of the potassium pool and hence myocardial viability.

Myocardial Kinetics of ^{201}Tl.

After injection during peak exercise, ^{201}Tl accumulates rapidly in myocardium supplied by normal coronary arteries and subsequently clears slowly (Fig. 9-3) . In normal patients, washout at 2 hours after injection is approximately 30 percent, and at 4 hours, 35 percent. The rate of ^{201}Tl washout is related to the peak exercise heart rate, exercise duration, and ^{201}Tl blood level. The kinetics of ^{201}Tl in *ischemic myocardium* is variable.[6] When a significant coronary artery stenosis is present, the initial uptake of ^{201}Tl during exercise is lower than in normal myocardium. Subsequently, the washout of ^{201}Tl from ischemic tissue is lower than normal, and accumulation of ^{201}Tl may even occur over time. Thus, an ischemic perfusion defect normalizes, or "fills in," over time. Initial uptake of ^{201}Tl in infarcted or scarred myocardium is considerably lower than in normal myocardium. On planar images, ^{201}Tl clearance from an infarct parallels that of normal myocardium, which is very likely explained by overlap of normal myocardium on planar images.

Technical Considerations

The American Society of Nuclear Cardiology has published standards for the acquisition of nuclear cardiology studies. For a detailed description of the technical and practical aspects of imaging, we refer to these publications.[7]

COMPUTER ACQUISITION.

Radionuclide images are always acquired on computer and stored on computer disk or magnetic tape for data processing. For SPECT myocardial perfusion imaging, a 64 × 64 matrix is commonly used, whereas for planar imaging, acquisition with a 128 × 128 matrix is preferred. Many SPECT studies are acquired with ECG gating. The computer acquires imaging data synchronized with the ECG R wave. The R-R interval is usually divided into eight or sixteen frames.

IMAGING PROTOCOLS.

With the introduction of ^{99m} Tc-labeled agents and new insight in ^{201} Tl biokinetics, several standardized imaging protocols have been developed. Figure 9-4 provides a schematic representation of the most frequently used imaging protocols at the time of this writing. More detailed discussion of variations of standard imaging protocols can be found elsewhere.[8]

For imaging with ^{99m} *Tc-labeled perfusion imaging agents* (Fig. 9-4 *A* to *C*) two separate injections are given: one during exercise and a second at rest. The injections can be administered either on 1 day or on 2 days. With ^{99m} Tc-sestamibi, imaging is started approximately *15 minutes after*

Figure 9-3 Thallium-201 time-activity curves after exercise in normal myocardium (1); transiently ischemic myocardium without visual defect (2); transiently ischemic myocardium with a visible defect (3); and old myocardial infarction (4). Normal myocardium (1) shows a gradual decrease in ^{201} Tl activity over time. After transient ischemia, ^{201} Tl clearance is slower than normal (2), or ^{201} Tl uptake may increase (3) in the myocardium over time. An old infarct area (4) without exercise-induced myocardial ischemia shows a gradual decrease in ^{201} Tl activity over time, similar to that in normal myocardium. The images show an example of a septal defect that gradually fills in over time, except at the apex, where an old scar is present (4).

Figure 9-4 Schematic representation of preferred myocardial perfusion imaging protocols using either ^{201} Tl, ^{99m} Tc-sestamibi (2-day and same-day imaging protocol), or dual isotope imaging (see the text).

injection during exercise and 60 minutes after injection at rest. Since ^{99m} Tc-tetrofosmin clears relatively fast from the liver after injection at rest, rest imaging with this compound can be started earlier than with ^{99m} Tc-sestamibi (approximately *15 minutes after injection*).

^{201} Tl STRESS IMAGING.

For stress imaging (Fig 9-4 *A*), one single dose (3.0 to 4.5 mCi) of ^{201} Tl is injected at peak exercise. Initial stress imaging should be started *within 5 minutes* of the injection. Delayed or redistribution imaging is performed *2 to 4 hours later* (the timing of delayed imaging should be standardized in each laboratory). For complete assessment of viable myocardium, a second injection of ^{201} Tl is administered at rest in selected patients. The repeat rest injection can be given either following redistribution imaging, following

imaging, or on a different day (see viability).

DUAL-ISOTOPE IMAGING.

Dual-isotope imaging (Fig. 9-4 *D*) is a "hybrid" imaging protocol designed to overcome the disadvantage of a relatively lengthy imaging protocol involving two injections of sestamibi.[9] In the dual-isotope protocol, a rest injection of ^{201} Tl (3.5 mCi) is given first, followed by rest ^{201} Tl imaging. The patient is then stressed and injected with 25 to 30 mCi of sestamibi at peak stress, followed after 15 minutes by sestamibi imaging. This imaging protocol can be completed in 1.5 to 2 hours.

PATIENT IMAGING TECHNIQUES

PLANAR IMAGING.

Although SPECT imaging is at present the predominant imaging technique used in clinical nuclear cardiology, the technical basis for good-quality SPECT imaging remains the ability to perform good-quality planar imaging. Moreover, in many countries outside the United States, planar imaging is still commonly performed. To acquire optimal planar myocardial perfusion images, some basic requirements should be met.[10] The most frequent reasons for suboptimal-quality planar images are (1) insufficient count density within the heart, (2) inconsistent *patient positioning and repositioning,* (3) the use of *too large a zoom factor,* and (4) inadequate display of images.

ADEQUATE COUNT DENSITY.

Planar images should have a count of at least 600,000 in the field of view. However, when extracardiac activity is present, e.g., in the lungs or subdiaphragmatic organs, the count density in the field of view does not reflect the count density in the heart. Longer imaging time is needed to obtain adequate counts from the heart. Therefore, it is recommended that images be acquired for a certain *preset time.* For planar ^{201} Tl imaging, 8- to 10-minute acquisitions per view usually result in adequate count density imaging. With ^{99m} Tc-labeled imaging agents, adequate count density is readily achieved since 10 to 30 mC is administered. With the latter agents, a count of 1.5 to 2 million per field of view can be obtained with 5-minute acquisitions per view.

PATIENT POSITIONING.

Planar Imaging is routinely performed in three views. The *left anterior oblique* (LAO) view is usually obtained with the patient lying supine. An optimal LAO is the projection that best shows separation of the right and left ventricular cavity with the septum straight and vertical. This angulation should be used as a reference angle for the other views. The *anterior view* is obtained with the patient lying supine, 45 degrees to the right of the LAO view. For the *left lateral view,* the patient should be turned on the *right side,* with the camera head in the same position as for the anterior view. The detector head should

be angled in such a way that it is as close as possible to the patient's chest wall.

PLANAR IMAGE DISPLAY.

The *display* of planar myocardial perfusion images is of importance for reproducible and consistent interpretation. Planar images should be displayed in a "white-on-black" linear gray scale (see Figs. 9-1 and 9-2) . On these images the heart is white (radioactivity). Color display of *planar* images is discouraged because of exaggeration of nonsignificant differences in radiotracer uptake. The linear gray scale should be normalized to the "hottest pixel" within the heart (Fig. 9-5) . In this manner, the full gray scale is used in representation of the heart, a feature particularly important for display of images acquired with ^{99m} Tc-labeled agents, which may have

Figure 9-5 Normalization of exercise/rest ^{99m} Tc-sestamibi images. Intense subdiaphragmatic activity (arrow) may cause problems with adequate display of the image of the heart. Radionuclide images are usually normalized to the "hottest" area in the field of view. On exercise sestamibi images, the heart is the "hottest" organ. However, on the rest image the gastrointestinal tract is "the hottest" area (arrow). Consequently, when the rest image is normalized to subdiaphragmatic activity, the heart is only faintly visualized (*top*). By using ^{99m} Tc-labeled myocardial perfusion imaging agents, images should be normalized to the heart, as shown in the *bottom panel,* and produce adequate visualization of the heart. *(From Wackers FJTh: Myocardial perfusion imaging. In Sandler MP, Coleman RE, Wackers FJTh, et al: Diagnostic Nuclear Medicine. 3rd ed. Baltimore, Williams & Wilkins, 1995.)*

substantial extracardiac radiotracer accumulation. Exercise and rest/delayed images should be displayed side by side for comparison.

TOMOGRAPHIC (SPECT) IMAGING.

Careful attention to technical details is essential for good-quality SPECT imaging. Energy settings are the same as for planar imaging. During cardiac SPECT imaging, the gamma camera rotates in a circular orbit around the patient. The camera acquires a multitude of planar projection images in a stop-and-shoot or continuous acquisition mode. With ^{99m} Tc-labeled agents, the time for each stop is approximately 25 seconds for a high-dose (20 to 30 mCi) study and 30 seconds for a low-dose (10 mCi) study. For imaging with ^{201} Tl, the duration of each stop is extended to 40 seconds. Extensive recommendations for optimal-quality SPECT imaging can be found in guidelines published by the American Society of Nuclear Cardiology.[7]

The basic principle of tomographic reconstruction involves the acquisition of multiple planar projection images around an object and reconstruction of the three-dimensional object by "filtered backprojection."[11] With ^{99m} Tc-labeled radiotracers and multiheaded gamma cameras, images are usually acquired over a 360- or 180-degree arc. For ^{201} Tl

SPECT imaging, 180-degree anterior image acquisition is preferred. After backprojection, filtering techniques are used to correct for reconstruction artifacts, suppress noise, and enhance image quality. Tomographic slices are generated perpendicular to the anatomical axis of the heart rather than the anatomical axis of the body.

PATIENT POSITIONING

Patient positioning and patient preparation are extremely important for optimal SPECT imaging. Patient motion is a common cause of artifacts on SPECT imaging. Motion may involve movement of the upper half of the patient's body but may also result from a change in position of the heart within the chest. Immediately after exercise, the heart may be in a vertical position because of deeper breathing. While the patient recovers from exercise, the heart may move into a horizontal position. This phenomenon of "upward creep" can cause artifactual inferior wall defects on reconstructed slices and was a problem with ^{201} Tl SPECT since imaging was started as soon as possible after termination of exercise. Artifacts caused by upward creep can be avoided by delaying the start of SPECT imaging for approximately 10 minutes. This delay allows for the acquisition of one *planar* image immediately after exercise, which is useful for evaluation of increased lung uptake. Since SPECT imaging with ^{99m} Tc-labeled agents is not started before 15 minutes after exercise, upward creep is not usually an issue when using these radiotracers.

ADEQUATE COUNT DENSITY.

Adequate count density is a frequently ignored aspect of tomographic perfusion imaging. Poor count density on reconstructed and filtered SPECT images should be suspected when the distribution of radiopharmaceutical appears to occur in multiple "patches" of apparent higher and lower activity, a pattern that does not match the usual anatomy of coronary artery disease.

SPECT ORBIT.

Many cameras provide a choice of various acquisition orbits. The camera may rotate around the patient in a perfect *circle* or may follow the *body contour* of the patient. A body-contour orbit may cause artifacts because of varying gamma camera resolution with varying distance of the detector head from the target organ. These artifacts are characteristic and consist of small 180-degree diametrical defects on the short-axis slices. High-resolution collimation reduces the effect of varying spatial resolution and resulting artifacts. A circular orbit is preferred for cardiac SPECT imaging.

SPECT IMAGE DISPLAY.

Display of reconstructed SPECT slices has been standardized (Fig. 9-6) .[12] [13] Images are preferably displayed on computer screen in "white on black" with a linear gray scale (Fig. 9-7) . In many laboratories, color display is used as well. However, color tends to exaggerate subtle differences in myocardial radiotracer uptake, so images should be

interpreted with caution. Three sets of tomographic slices are reconstructed: short-axis slices, horizontal long-axis slices, and vertical long-axis slices. The exercise and rest (or delayed) images are displayed side by side to facilitate comparison. Because of the multitude of images, it is useful to "condense" all information into one color-coded polar map, or "bull's-eye," image (see Figs. 9-13 *B* and 9-14*B*). For the interpretation of ECG-gated SPECT images, selected slices are displayed in color on computer screen and played as an endless-loop movie. The change in color intensity during the cardiac cycle correlates with regional myocardial thickening.[14]

Normal Planar Myocardial Perfusion Images

In planar imaging, perfusion is visualized as the projection of myocardial radioactivity on a plane parallel to the crystal surface of the gamma camera (see Figs. 9-2 and 9-5) . The "left ventricular cavity" as it appears on planar images is in part an optical illusion.[10] The "horseshoe" appearance of the left ventricle on planar images is a result of attenuation of radiation from the distant myocardial wall by the ventricular blood pool and the relatively greater myocardial mass of the walls perpendicular to the plane of view. The "facing" myocardial wall contains relatively less radiopharmaceutical, which creates the illusion of visualization of the ventricular cavity.

Because of overprojection of myocardial regions in one plane, it is necessary to obtain multiple planar images from different angles to visualize all segments of left ventricular myocardium. The anatomy and standardized nomenclature

Figure 9-6 Standardized display of single-photon emission computed tomographic myocardial perfusion images. The short-axis slices are displayed with the right ventricle to the left and the left ventricle to the right. The short-axis slices are displayed as a horizontal row of images, starting with the apical slice on the left and the basal slices on the right. The vertical long-axis slices are cut from the septum toward the lateral wall and display the septal slices on the left and the lateral slices on the right. The horizontal long-axis slices are cut from the inferior wall toward the anterior wall and display the inferior wall slices on the left and the anterior wall slices on the right. *(From the Cardiovascular Imaging Committee, American College of Cardiology; the Committee on Advanced Cardiac Imaging and Technology, Council of Clinical Cardiology, American Heart Association; and the Board of Directors, Cardiovascular Council Society of Nuclear Medicine: ACC/AHA/SNM Policy Statement: Standardization of cardiac tomographic imaging. J Nucl Cardiol 1:117, 1994.)*

of the heart as projected on various planar views and the various coronary artery territories are shown in Figure 9-8 .[13]

NORMAL VARIATIONS OF PLANAR MYOCARDIAL PERFUSION IMAGES.

There are several variations in the pattern of normal radiotracer uptake on planar

images with which an interpreter should be familiar.[10]

Apex.

Decreased tracer activity at the apex of the left ventricle is normal. In patients with a vertical position of the heart, this feature may be prominent. A typical apical variant appears as a narrow slit or cleft-like area aligned with the long axis of the left ventricle.

Aortic Valve Plane.

On the LAO view, the membranous septum and aortic valve plane are projected at the open end of the horseshoe, which at times may appear to be causing a high septal defect. This variation may be seen prominently in patients with a horizontal position of the heart.

Mitral Valve Plane.

The mitral valve plane is seen as the open end of the horseshoe in all three views.

ARTIFACTS ON PLANAR IMAGES

INFERIOR ATTENUATION.

Attenuation of the inferior left ventricular wall is a common artifact on myocardial perfusion images and occurs in approximately 25 percent of patients.[10] Recognition of this artifact is relevant for an understanding of SPECT imaging. When a patient is imaged in the supine position, planar left lateral images may appear to reveal inferior wall defects. These defects are artifactual and caused by attenuation of inferior wall activity by the left hemidiaphragm. When the patient is turned on the right side, the defect is no longer present (Fig. 9-9) . This disappearance of the defect can be explained by a change in position of the heart and the left hemidiaphragm. By moving to the right side, the heart shifts to a vertical position and the left hemidiaphragm moves caudally, thereby resulting in less attenuation of the inferoposterior wall. Since patients are usually in the supine position for SPECT imaging, inferior attenuation artifacts are common.

OBESITY/LARGE BREASTS.

Attenuation artifacts in obese patients or patients with large pendulous breasts may render planar images almost uninterpretable. These artifactual defects on different planar views are often multiple and occur in a pattern that is inconsistent with known coronary artery territories. Superimposition of breast tissue over the heart may also result in linear areas of relatively increased activity, which is believed to be caused by small-angle scatter from the breast tissue fold. Breast artifacts are the most frequent cause of false-positive planar images. The use of breast markers is an important aid in

correctly interpreting planar images (Fig. 9-10) .[10]

Normal SPECT Myocardial Perfusion Images

SPECT images are reconstructed as multiple slices oriented along the anatomical axis of the left ventricle. For interpretation of short-axis slices, it is convenient to divide the slices into three groups: apical slices, midventricular slices, and basal slices. To avoid apical artifacts from tangential cuts, only apical slices that clearly show the ventricular cavity should by analyzed. When interpreting basal slices, slices showing the membranous septum are excluded.

The standardized nomenclature, segmentation, and coronary territories are shown in Figure 9-11 .

NORMAL VARIATIONS OF SPECT MYOCARDIAL PERFUSION IMAGES.

A useful practical rule of thumb for interpreting a SPECT study is that a perfusion defect should be clearly seen on at least three consecutive slices to be considered a true abnormality. The *vertical long-axis* slices and the *horizontal long-axis* slices contain the same information shown on the short-axis slices. However, the apex and base of the heart can be analyzed in these long-axis slices without partial volume artifacts. Only slices that clearly show the left ventricular cavity should be analyzed. Slightly less inferoseptal uptake can be noted in male patients as a normal variant (see Fig. 9-7) . In females, radiotracer distribution is usually more homogeneous. The basal short-axis slices generally show a septal defect, which is a normal finding and represents the membranous portion of the septum.

ARTIFACTS ON SPECT IMAGES

MOTION ARTIFACTS.

Motion artifacts and how to avoid them have been discussed above (Patient Positioning). Most gamma camera computer systems have motion correction software. Nevertheless, it is better to prevent movement by the patient during imaging than to correct for it later.

ATTENUATION ARTIFACTS.

Attenuation artifacts are the most common source of error in SPECT imaging. The supine position may cause inferior wall defects because of attenuation by the left hemidiaphragm (see Fig. 9-9) . To avoid such artifacts, alternative patient positioning has been proposed. For instance, the patient can be imaged prone (lying on the stomach), turned on the right side, or sitting in an upright position. We recommend repeat imaging in the prone position when inferior attenuation is suspected. Attenuation by breast tissue can cause artifacts on SPECT imaging as well. However, rarely do they render SPECT images uninterpretable as may happen with planar imaging, possibly because SPECT images are acquired and reconstructed from numerous positions

rather than from one single planar projection. Nevertheless, it is important to be aware of the potential presence of artifacts *before* starting interpretation. Careful inspection of the *cinegraphic display of unprocessed projection images* on the computer screen may help anticipate potential attenuation problems. The breast can often be recognized as a "shadow" moving over the heart in certain projections and may therefore cause attenuation artifacts.

All commercial vendors of nuclear imaging equipment are presently developing attenuation correction software. Although the progress is promising, at the time of this writing no attenuation correction system has as yet earned full clinical acceptance.[15] The development of software that accurately corrects for nonuniform attenuation over a wide range of clinical conditions is the single most important challenge that computer scientists face in the field of nuclear cardiology.[16]

QUALITY CONTROL.

Quality control should be performed systematically as a part of *every* interpretation of a SPECT study and should involve the following: (1) The cinegraphic display of all planar projection images should be inspected to assess motion of the patient or the heart and the presence of a breast shadow. (2) Adequate count density should be checked, e.g., a count of *at least 100* within the "hottest" pixel of the heart in one of the unprocessed anterior projection

Figure 9-7 Single-photon emission computed tomographic (SPECT) ^{99m} Tc-sestamibi myocardial images after exercise and at rest in a normal subject showing normal variations of radiopharmaceutical distribution. On the midventricular short-axis slices (*A*) the inferior septal areas (small arrows) have slightly less activity than seen in the lateral wall, which is a normal variation. The hottest area is in the lateral wall. On the basal slices (*B*), an apparent septal defect is present (large arrow) in the membranous portion of the septum. This "septal defect" and normal variation are also seen in the horizontal long-axis slices (*C*), where the septum is shorter (arrow) than the lateral wall. Vertical long-axis slices are shown in *D. (From Wackers FJTh: Artifacts in planar and SPECT myocardial perfusion imaging. Am J Card Imaging 6:42, 1992.)*

images. (3) The presence of diaphragmatic attenuation of the inferoposterior wall should be assessed by comparing a planar left lateral "supine" view with a planar left lateral "right side down" decubitus view (see Fig. 9-9) . When attenuation of the inferior wall is suspected, imaging should be repeated immediately in the prone position. (4) Regional wall motion and thickening should be assessed on cinegraphic display of ECG-gated SPECT images in regions with perfusion defects. A fixed perfusion defect with normal regional wall motion on gated SPECT is very likely an attenuation artifact.

Image Interpretation

Myocardial perfusion images are interpreted qualitatively by visual analysis, often aided by computer quantification. Image interpretation can be described as follows (Fig. 9-12) :

NORMAL.

Homogeneous uptake of the radiopharmaceutical throughout the myocardium is considered normal.

DEFECT.

A defect is a localized myocardial area with relatively less radiotracer uptake than normal. Defects may vary in intensity from slightly reduced activity to almost absent activity.

REVERSIBLE DEFECT.

A defect present on the initial stress images and no longer present or present to a lesser degree on resting or delayed images is a reversible defect. This pattern indicates myocardial ischemia. Improvement over time on ^{201} Tl imaging is referred to as "redistribution." It is not appropriate to use this terminology for ^{99m} Tc-labeled agents.

FIXED DEFECT.

A defect that is unchanged and present on both exercise and rest (delayed) images is a fixed defect. This pattern generally indicates infarction and scar tissue. However, in some patients with fixed ^{201} Tl defects on 2- to 4-hour delayed imaging, improved uptake can be noted on 24-hour redistribution imaging or after a new resting injection (see below).[17] Similarly, a fixed defect with ^{99m} Tc-labeled agents (which involves injection at rest) may at times underestimate myocardial viability.

REVERSE REDISTRIBUTION.

This pattern occurs mainly with ^{201} Tl imaging. However, a "reverse defect" is observed occasionally with ^{99m} Tc-labeled agents. The initial stress images are either normal or show a defect, whereas the delayed or rest images show a new defect or a more severe defect. This pattern is frequently observed in patients with

Figure 9-8 *Top,* Anatomy of the heart as projected on planar views. *Bottom,* Coronary artery territories

on three planar views. The shaded area indicates the facing myocardium overlying the left ventricular cavity. *(From Wackers FJTh: Artifacts in planar and SPECT myocardial perfusion imaging. Am J Card Imaging 6:42, 1992.)*

infarction who are undergoing thrombolytic therapy or percutaneous coronary angioplasty. The phenomenon is thought to be caused by initial *excess* of tracer uptake in a reperfused area with a mixture of scar tissue and viable myocytes. Initial accumulation is followed by rapid clearance from scar tissue. Although the significance of this finding is controversial, it does *not* represent evidence of exercise-induced ischemia. With PET using fluorine-18-labeled fluorodeoxyglucose (FDG), the presence of residual viable myocardium has been demonstrated within areas with reverse redistribution.[18]

RADIOTRACER LUNG UPTAKE.

Normally, no or very little radiotracer is noted in the lung fields on postexercise images. Increased lung uptake can be quantified as a lung/heart ratio (normal, <0.5 for ^{201} Tl, <0.45 for ^{99m} Tc-sestamibi). This abnormal image pattern indicates stress-induced left ventricular dysfunction and severe coronary artery disease,[19] [20] [21] a powerful predictor of adverse outcome.

TRANSIENT LEFT VENTRICULAR DILATION.

Occasionally, the left ventricle can be noted to be larger following exercise than on the rest or delayed image. This pattern of transient dilation probably indicates exercise-induced left ventricular dysfunction. It has been suggested that rather than a true increase in volume of the left ventricle, this image pattern is caused by decreased subendocardial radiotracer uptake and, consequently, apparent thinning of the myocardium on the stress image.

RIGHT VENTRICULAR VISUALIZATION.

Usually, the right

Figure 9-9 Artifactual inferior defect resulting from diaphragmatic attenuation. *Top,* ^{99m} Tc-sestamibi short-axis images acquired in the supine position. A mild inferior myocardial perfusion defect (arrow) is present. Because of a clinically low likelihood of coronary artery disease, imaging was repeated in the prone position (*bottom*). The prone images are normal. The artifactual defect is caused by diaphragmatic attenuation. On the right side are two planar left lateral (LL) images obtained with the patients supine and in a right-sided decubitus position (decub). The planar supine image shows again a posterior wall defect (arrow) caused by diaphragmatic attenuation, whereas the decubitus images are normal. The acquisition of two planar LL images is a simple quality assurance measure that can be performed in every patient.

Figure 9-10 Planar^{201} Tl left anterior oblique (LAO) and anterior (ANT) images in a woman with large breasts (LAO1, ANT1 = exercise images; LAO2, ANT2 = delayed images). The breasts are marked with radioactive line markers (m) in the images on the right. On the LAO exercise images (*top*), a definite attenuation artifact is present (arrow). At delayed imaging, the breast contour is lower and is visualized as a linear area (arrow) with increased activity caused by "small-angle scatter." The exercise anterior view (*bottom*) is normal because the breast did not cover the heart. However, at delayed imaging, the contour of the breast is across the heart and is causing an attenuation artifact (arrow). This example demonstrates how breast attenuation artifacts can vary in the same view with different breast positions. Note that on the delayed LAO image, unequal attenuation mimics an image with increased lung uptake of ^{201} Tl. *(From Wackers FJTh: Artifacts in planar and SPECT myocardial perfusion imaging. Am J Card Imaging 6:42, 1992.)*

Figure 9-11 Left ventricular anatomy and coronary artery territories on single-photon emission computed tomographic slices taken from a 17-segment model. *(Modified from Port SC (ed): Imaging Guidelines for Nuclear Cardiology Procedures, Part 2. J Nucl Cardiol 6:649, 1999.)*

Figure 9-12 Schematic representation of the interpretation of myocardial perfusion images. Shaded areas indicate myocardial perfusion defects.

ventricle is only faintly visualized on rest or stress SPECT myocardial perfusion images. Right ventricular myocardial mass and blood flow are approximately 50 percent less than that of the left ventricle. Marked visualization of the right ventricle at rest is abnormal and in most cases indicates right ventricular hypertrophy. Markedly increased right ventricular uptake on exercise SPECT images is an abnormal pattern that has been associated with severe coronary artery disease.[22]

GLOBAL AND REGIONAL CONTRACTION ON ECG-GATED IMAGES.

The ECG-gated image should be analyzed in color display. Regional myocardial wall thickening can be appreciated as a regional increase in the brightness of color. Wall thickening can be scored subjectively as normal, hypokinetic, or absent.

Visual and Quantitative Image Analysis

Myocardial perfusion images are relatively difficult to interpret. As with visual interpretation of any image data, considerable intraobserver and interobserver variability

in subjective interpretation is noted, even among experienced readers.[23] Reproducibility of interpretation is related to a number of factors: (1) the overall quality of raw data, (2) image display quality, (3) the degree of abnormality, (4) the degree of change between exercise and rest images, and (5) familiarity with normal variations.

SCORING OF SPECT IMAGES

SEMIQUANTITATIVE.

Myocardial perfusion defects may vary in extent and severity. The extent of a defect can be expressed as the number of segments involved with the use of a scheme as shown in Figure 9-11 . Although computer quantification of defect size is preferred, a semiquantitative scoring system using a 5-point score for each segment is well established. For each segment, the severity of reduced radiotracer uptake can be scored subjectively as follows: 0 = normal, 1 = mildly reduced or equivocal, 2 = moderately reduced, 3 = severely reduced, and 4 = absent uptake. From this scoring system a "summed stress score," a "summed rest score," and a "summed reversibility score" can be derived.[24] A summed stress score less than 4 is considered normal, 4 to 8 is mildly abnormal, 8 to 13 is moderately abnormal, and more than 13 is severely abnormal.

QUANTIFICATION OF SPECT IMAGES.

Computer quantification of myocardial perfusion images provides an important means of improving the consistency of image interpretation and decreasing reader variability.[23] Several approaches to image quantification have been described. The output of computer quantification generally consists of

Figure 9-13 Exercise-rest single-photon emission computed tomographic (SPECT) myocardial perfusion imaging with ^{99m} Tc-sestamibi in a normal subject. *A,* Horizontal long-axis, short-axis, and vertical long-axis slices. A normal distribution of ^{99m} Tc-sestamibi is noted. *B,* Exercise and rest polar maps (bull's-eye display) of the tomographic slices in *A.* On both the exercise and rest polar map, the distribution of radiopharmaceutical is approximately homogeneous. Color scale: White represents the area with highest activity; yellow, orange, red, violet, blue, and black indicate gradually decreasing count activity. The coronary artery territories of the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and the right coronary artery (RCA) are indicated. *C,* Circumferential count profiles. The relative activity of sestamibi on the exercise images is displayed as a white line. The relative activity of sestamibi on the rest images is displayed as a black line. The lower limit of normal sestamibi distribution is indicated as the thin white line. Relative radiotracer activity in the anterior (Ant) septum (Sep) and inferior (Inf) and lateral (Lat) wall is shown in representative basal, midventricular, and apical short-axis slices. In this normal subject the relative distribution of sestamibi is above the lower limit of normal distribution, which indicates absence of perfusion defects and thus normal images. *D,* electrocardiographic (ECG)-gated exercise myocardial perfusion images of the same patient. End-diastolic and end-systolic frames of the short-axis slices (SA), horizontal long-axis slices (HLA), and vertical long-axis slices (VLA) are shown. The color coding is the same as in *B.* Comparison of the end-diastolic and end-systolic frames allows assessment of regional wall motion and regional wall

thickening. In this normal subject, wall motion and thickening are homogeneous: The color in the anterior wall, septum, and lateral wall change from yellow to white; in the inferior wall the color changes from orange to yellow. The relatively lesser activity in the inferior wall is caused by diaphragmatic attenuation. *Continued. E,* The left ventricular ejection fraction (LVEF) can be computed from the ECG-gated SPECT slices.

Figure 9-14 *Continued. C,* Circumferential profiles analysis. The relative distribution of radiopharmaceutical is displayed for representative apical, midventricular, and basal short-axis slices. The yellow line represents the exercise study, the orange line represents the rest study, and the thin white line represents the lower limit of normal distribution. The apical slice (*top left*) shows no significant improvement on the resting study. In contrast, septal defect reversibility is demonstrated in the midventricular slice (*top right*) and the basal slice (*bottom left*). The apical defect (*bottom right*) is fixed. Total exercise myocardial perfusion defect size is quantified as 38 percent of the total left ventricle. The rest defect is 24 percent. Defect reversibility is 37 percent. *D,* Electrocardiographic (ECG)-gated exercise SPECT images. End-diastolic and end-systolic frames are shown for the short-axis slices (SA), horizontal long-axis slices (HLA), and vertical long-axis slices (VLA). On the end-diastolic frames an extensive anteroapical and septal myocardial perfusion defect is present. Analysis of wall motion shows absence of thickening in the anteroapical segment on the vertical long-axis and horizontal long-axis slices. On the short-axis slice and horizontal long-axis slice, in spite of the presence of an exercise-induced anteroseptal myocardial perfusion defect, thickening (change from orange and blue to yellow) of the anteroseptal segment can be appreciated. *Continued. E,* The left ventricular ejection fraction (LVEF) is computed from the ECG-gated SPECT images as 40 percent.

the following: (1) graphic or polar map display of the relative myocardial distribution of radiotracer, (2) quantitative comparison of relative radiotracer distribution with a normal reference data base, and (3) quantitative comparison of stress defect size with rest (delayed) defect size and quantification of defect reversibility.

Polar Maps (Bull's-Eye Display).

In SPECT imaging, a multitude of reconstructed images are available for analysis. A typical SPECT study consists of approximately 32 paired (stress and rest) images in short-axis, vertical long-axis, and horizontal long-axis slices (Fig. 9-13 *A* and 9-14 *A*). Computer quantification is usually performed on reconstructed short-axis slices. The most widely used and commercially available approach is that of a polar map, or bull's-eye, display (Fig. 9-13 *B* and 9-14 *B*) The purpose of a polar map is to generate one single image that encompasses the relative radiopharmaceutical distribution in the entire heart. Relative radiopharmaceutical uptake on short-axis images is compressed to color-coded concentric rings, with the apical slice in the center and the basal slices on the periphery of the polar map. It is important to understand that a polar map is *not a true image,* but a simplified color-coded derivative of analog images. The bull's-eye image can be compared with a normal reference polar map. A normal data base is not usually derived from patients with normal coronary arteries, but rather from subjects with a low (<3 percent) likelihood of coronary artery disease. Considerable variation exists with regard to the generation of SPECT normal data bases. In some software packages,

the lower limit is a uniform mean -2 SD. In other approaches, different criteria are applied for each coronary artery territory. Gender-specific data bases have also been recommended.

Areas with a significant myocardial perfusion defect (i.e., relative count distribution below the lower limit of normal) can be highlighted on a polar map as a "blackout area" (Fig. 9-14 *B*). By comparing stress and rest polar maps and image subtraction, the amount of defect reversibility can be visualized and quantified.[25] Although several commercially available software packages exist for the generation of polar maps, manufacturers often do not supply a normal data base. Consequently, in many laboratories, SPECT polar maps are interpreted visually without a normal reference file and without quantification.

Circumferential Profiles.

An alternative approach to the polar map display for quantification of SPECT images is the use of circumferential profiles (Figs. 9-13 *C* and 9-14 *C*). Multiple circumferential profiles are generated over each of the short-axis slices and compared with those of a normal reference data base.[26] In a normal image, all data points of circumferential profiles are above the lower limit of normal (see Fig. 9-13 *C*). In a patient with a myocardial perfusion defect (Fig. 9-14 *C*), the count profile is below the lower limit of normal in the areas corresponding to a visually perceived defect. With circumferential profiles, a defect can be quantified as an integral, i.e., the area below the lower limit of a normal curve proportional to the total potentially visualized normal myocardium.

The total size of a myocardial perfusion defect can be expressed as a percentage of the entire left ventricle. The computed defect size is adjusted for slice thickness and varying diameter of each short-axis slice from base to apex. This approach provides quantification of total exercise defect size, rest defect size, and percent defect reversibility.[26]

Regardless of the quantitative approach used, the advantage of computer quantification is in providing a *graphic display of the relative distribution of radiopharmaceutical uptake in the myocardium and the degree of perfusion abnormality in comparison to a normal reference data base.*

Clinical Use of Quantification of Myocardial Perfusion Imaging

Computer quantification of myocardial perfusion images enhances the overall accuracy of detection of coronary artery disease and also enhances the reproducibility of interpretation.[23] However, quantification should be used astutely. In general, from the standpoint of diagnostic interpretation, quantification should confirm impressions derived from visual analysis of images.[27] If the quantitative information appears to be discordant, one should inspect the images again. Frequently, one may recognize that the quantification was correct. However, sometimes artifacts may cause abnormal quantitative results. The process of integrating visual and quantitative information can be referred to as "quantitative analysis with visual overread." It is important to realize

that artifacts, such as those caused by attenuation from the overlying soft tissue or diaphragm or resulting from patient motion, often have an unpredictable effect on the appearance of reconstructed slices. Although a normal data base, to a certain extent, incorporates normal variations, computer quantification per se should not be expected to be able to distinguish between true perfusion defects and artifacts.

For reasons to be discussed later, it is important that reports to referring physicians describe image abnormalities

TABLE 9-2 -- COMPARATIVE CHARACTERIZATION OF ABNORMAL SPECT RESULTS

CHARACTERISTIC	DEFECT SIZE		
	Small	Medium	Large
Vascular territories	<½ of 1	1	2 or 3
Summed Stress Score	4-8	9-13	>13
Polar maps (% of LV)*	<10	10-20	>20
Circumferential profile (% of LV)	<5	5-10	>10

LV=left ventricle.

Modified from Beller GA, Zaret BL (Program Chairmen): Wintergreen Panel summaries. J Nucl Cardiol 6:93, 1999.

*Compared with gender-matched normal data files and reflects extent only.

Based on Yale-CQ: sum of the defects in 36 interpolated slices. The profiles are compared with normal data files and incorporate both extent and severity.

in terms of "*small, moderate, and large and high or low risk.*" Table 9-2 shows a comparative categorization of myocardial perfusion abnormalities by semiquantitive scoring or computer quantification.[9]

ECG-Gated Myocardial Perfusion Imaging

The high photon flux of ^{99m} Tc-labeled compounds makes it feasible to acquire myocardial perfusion images in an ECG-gated mode.[7] ECG-gated myocardial perfusion images can be displayed as an endless-loop cine on the computer screen. ECG-gated SPECT images allow for assessment of global left ventricular ejection fraction (LVEF) (Figs. 9-13 *E* and 9-14 *E*), regional wall motion, and regional wall thickening.[28] [29] [30] [31] Regardless of whether the injection of radiopharmaceutical was performed during peak

stress or at rest, since the *acquisition* is performed at rest, ECG-gated SPECT images reveal *resting* global function and wall motion and *resting* wall thickening in areas with exercise-induced myocardial perfusion defects. Regional wall thickening on ECG-gated SPECT images can be quantified as "percent wall thickening" in comparison to end-diastole.[30] [31] Commercially available and validated software packages exist for the automatic calculation of resting global LVEF, left ventricular volume, and regional wall thickening from ECG-gated SPECT slices.[28] [29] When eight frames are acquired during the R-R cycle, one should anticipate a slight underestimation of LVEF by approximately 4 percent. In general, LVEF from gated SPECT agrees well with resting LVEF determined by other modalities. Quality assurance is important. LVEF from gated SPECT can be less accurate, even invalidated, by an irregular heart rate, low count density, intense extracardiac radiotracer uptake adjacent to the left ventricle, and small size of the left ventricle.

Combined interpretation of perfusion and function on ECG-gated images substantially increases the confidence of interpretation. Taillefer and associates reported that interpretation of stress *and* rest end-diastolic slices rather than summed ungated slices may enhance the overall sensitivity of detecting mild coronary artery disease.[32] ECG-gated images are also useful for the recognition of artifactual defects caused by attenuation (breast and diaphragm) and thus adds to quality control of SPECT imaging. ECG-gated SPECT imaging is presently considered the state of the art of radionuclide myocardial perfusion imaging.[33]

CLINICAL APPLICATIONS OF MYOCARDIAL PERFUSION IMAGING

Acute Coronary Syndromes

Acute Myocardial Infarction (see also Chap. 35)

DETECTION.

Myocardial perfusion imaging with either ^{201}Tl or ^{99m}Tc-labeled compounds is a very sensitive and reliable means for the early detection of acute myocardial infarction (Fig. 9-15) . The timing of imaging after the onset of acute chest pain is relevant to the results of imaging. Images obtained during the first 6 hours after the onset of myocardial infarction show without exception perfusion abnormalities at the anatomical location of infarction. However, as the time interval after the onset of chest pain increases, some patients may have normal perfusion images. Serial imaging in patients with acute myocardial infarction has revealed that in some patients the size of a myocardial perfusion defect may decrease over time. These observations, initially made in 1976 with ^{201}Tl, are now better understood. Endogenous thrombolysis occurs in approximately 20 percent of patients with acute infarction, which may explain the observed spontaneous improvement in myocardial perfusion images over time. The location and size of myocardial perfusion defects in acute myocardial infarction correlate well with postmortem findings.

THROMBOLYTIC THERAPY.

During the early hours of acute myocardial infarction, serial myocardial perfusion imaging with ^{99m} Tc-labeled compounds can be used to visualize the effectiveness of thrombolytic therapy. Because of the lack of significant redistribution, ^{99m} Tc-labeled compounds can be injected *before* the initiation of thrombolytic therapy, and imaging of myocardial perfusion can be performed later.[34] [35] [35A] [36] [37] Gibbons and coworkers,[34] Wackers and colleagues,[35] and others[36] [37] showed that successful thrombolysis of an infarcted artery can be predicted by a decrease in the size of myocardial perfusion defects on serial ^{99m} Tc-sestamibi imaging (Fig. 9-16) . This imaging modality allows for noninvasive assessment of the area at risk and the amount of salvaged myocardium.

Gibbons and coworkers conducted a series of important clinical studies with ^{99m} Tc-sestamibi in patients with acute infarction that provided unique new insight in the pathophysiology of human acute myocardial infarction. Their experience can be summarized as follows. The myocardial area at risk varies greatly in individual patients,[34] [35] [35A] with little correlation between the extent of the area at risk as demonstrated by sestamibi imaging and the anatomical site of occlusion of the infarcted artery, i.e., distal or proximal.[38] The area at risk in acute anterior myocardial infarction is usually larger than that in acute inferior infarction. Infarct size as measured by sestamibi at hospital discharge is predictive of subsequent remodeling.[39] Patients with collateral coronary circulation to the infarcted artery have a smaller ultimate infarct size than do patients without collateral vessels.[40] [41] A decrease in myocardial perfusion defect size between images obtained before and after thrombolytic therapy reliably predicts subsequent improvement in left ventricular regional wall motion.[42] Serial myocardial perfusion imaging has further shown that in many patients (approximately 40 percent), myocardial perfusion defect size continues to decrease during the days after administration

Figure 9-15 *Top,* Typical singlephoton emission computed tomographic (SPECT) ^{99m} Tc-sestamibi images of acute myocardial infarction in short-axis (SA), horizontal long-axis (HLA), and vertical long-axis (VLA) slices. From top to bottom are shown anterior (ANT), anteroseptal (SEP), lateral (LAT), and inferior (INF) infarctions. Defects are indicated by arrows. *(From Wackers FJTh: Myocardial perfusion imaging. In Sandler MP, Coleman RE, Wackers FJTh (eds): Diagnostic Nuclear Medicine. Baltimore, Williams & Wilkins, 1995.)Bottom,* Quantification of infarct size on SPECT myocardial perfusion images. ^{99m} Tc-sestamibi images in a patient with anteroseptal myocardial infarction are shown. The images on the *left* show horizontal long-axis, short-axis, and vertical long-axis slices. An anterior apical myocardial perfusion defect (arrow) is present. On the *right* is the circumferential profile count distribution. The thin line represents the lower limit of normal distribution of sestamibi. The white data points represent the patient's circumferential profile. The circumferential profile is below the lower limit of normal in the anteroseptal and lateral areas. The defect is quantified as 30 percent of the total left ventricle.

of thrombolytic therapy.[34] [43] Marcassa and colleagues observed the same

phenomenon of continued decreasing resting defect size in stable patients late (7 months) after anterior wall infarction.[44] The pathophysiological basis of this phenomenon remains unclear. Ito and coworkers demonstrated delayed recovery from microvascular damage after acute infarction,[45] which could be a potential explanation for late improvement in defect size.

Serial myocardial perfusion imaging with ^{99m} Tc-labeled myocardial perfusion imaging agents should be viewed as a useful clinical research tool to assess the efficacy of reperfusion strategies in acute myocardial infarction.[46] [47] Patients serve as their own controls, and fewer patients are needed to achieve statistical power in a clinical trial.

EARLY RISK STRATIFICATION.

An inverse relationship exists between the size of a resting myocardial perfusion defect and global LVEF. Not surprisingly, the size of the resting myocardial perfusion defect after acute myocardial infarction correlates with the patient's prognosis. As early as 1980, Silverman and associates showed with planar imaging that patients with large resting myocardial perfusion defects had a significantly poorer prognosis and survival than did patients with small myocardial perfusion defects. This outcome appeared to be independent of other clinical parameters. Similar prognostic value of resting SPECT myocardial perfusion defect size was confirmed by Cerqueira and colleagues after thrombolytic therapy for acute infarction[48] (see Fig. 9-22) . Certain resting image patterns indicate a poor outcome after acute infarction. Visualization of the right ventricle at rest[49] and increased lung uptake of ^{201} Tl at rest in patients with recent infarction [50] are indicators of an unfavorable course after acute myocardial infarction. These image patterns reflect impaired left ventricular function.

Brown and associates demonstrated the value of ^{201} Tl and ^{99m} Tc-sestamibi dipyridamole myocardial perfusion imaging for *early* (days 2 to 4) *risk stratification* of patients with recent acute myocardial infarction.[51] Early vasodilation myocardial perfusion imaging was safe and predicted in-hospital and late cardiac events (cardiac death and recurrent infarction) better than did submaximal exercise imaging at hospital discharge. The ability to perform early risk stratification after infarction with nuclear imaging is of clinical importance. Management decisions regarding discharge or intervention can be made on day 2 after acute infarction rather than on days 5 to 7 at the time of predischarge stress testing with the conventional approach. Such earlier risk stratification may result in the prevention of in-hospital

Figure 9-16 Planar myocardial perfusion imaging with ^{99m} Tc-sestamibi before and after thrombolytic therapy in a patient with an acute anteroseptal myocardial infarct. ^{99m} Tc-sestamibi was injected immediately before initiation of thrombolytic therapy and imaging performed 2 hour later. Because of the lack of significant redistribution of ^{99m} Tc-sestamibi, the distribution of myocardial blood flow at the time of injection is "frozen" in time. The images before thrombolytic therapy show an anteroseptal myocardial

perfusion defect (arrows) that was quantified as 53 percent. The patient was reinjected with ^{99m} Tc-sestamibi when thrombolytic therapy was completed. These images show improved perfusion of the anteroseptal segments, indicative of successful reperfusion of the infarct artery. The size of the perfusion defect after thrombolytic therapy was 35 percent. Therefore, 33 percent of myocardium was salvaged by thrombolytic therapy in this patient. *(From Wackers FJTh, Gibbons RJ, Verani MS, et al: Serial quantitative planar technetium-99m-isonitrile imaging in acute myocardial infarction: Efficacy for noninvasive assessment of thrombolytic therapy. J Am Coll Cardiol 14:861, 1989. Reprinted with permission from the American College of Cardiology.)*

events and will definitely result in shorter in-hospital length of stay. The potential economic impact of this approach still needs to be evaluated.

Unstable Angina (see also Chap. 36)

Patients with unstable angina but without prior myocardial infarction may have abnormal resting myocardial perfusion images. Such resting myocardial perfusion defects are demonstrable not only when the radiopharmaceutical is injected *during* chest pain but also for considerable time *after* the angina has subsided.[52] Resting ^{201} Tl defects in patients with unstable angina are invariably reversible and indicate transient hypoperfusion of viable myocardium. ^{99m} Tc-labeled myocardial perfusion imaging agents that do not redistribute have a particular advantage in patients with unstable angina. The lack of redistribution makes it possible to inject the radiotracer during pain and acquire images at a later time when the patient is pain free and stable. Bilodeau and coworkers studied patients with unstable angina by ^{99m} Tc-sestamibi SPECT imaging.[52] Patients with abnormal ECGs during pain had larger myocardial perfusion defects than did those who did not have abnormal ECGs. The observations with myocardial perfusion imaging in patients with unstable angina imply that impaired regional myocardial blood flow persists longer than can be judged from the clinical status or ECG. Patients with reversible resting myocardial perfusion defects usually have severe multivessel coronary artery disease. Resting myocardial perfusion imaging during pain was more sensitive and more specific for the presence of significant coronary artery disease than the resting ECG was.[52]

Resting imaging in patients with recurrent chest pain after infarction or with unstable angina is useful for objectively demonstrating the presence of transient myocardial hypoperfusion and viable myocardium. This information can be very helpful when myocardial revascularization is considered. In patients with unstable angina who have been stabilized, subsequent exercise myocardial perfusion defect size reliably predicts the extent of coronary artery disease.

Old Myocardial Infarction

Myocardial perfusion imaging with either ^{201} Tl or the ^{99m} Tc-labeled compounds does not differentiate between acute myocardial infarction, acute ischemia, or scar. Nevertheless, a substantial number of patients with presumably old myocardial infarction may have normal or near-normal perfusion images. Frequently, however, prior myocardial infarction can be recognized only as "thinner" myocardial segments, particularly in patients with old inferior wall myocardial infarcts. SPECT imaging may be

more sensitive than planar imaging for the detection of such small myocardial scars.

Myocardial Perfusion Imaging in Emergency Departments and Chest Pain Centers

Since acute myocardial ischemia can be visualized almost instantaneously with ^{201} Tl or ^{99m} Tc-labeled compounds, resting radionuclide myocardial perfusion imaging is increasingly used as a means to triage patients with acute chest pain in emergency departments and chest pain centers.[53] Of the millions of patients who visit emergency departments yearly with complaints of acute chest pain, many have normal or nondiagnostic ECGs. Approximately half of these patients had previously been admitted to a hospital to "rule out acute myocardial infarction." In only a small proportion of these patients (15 to 20 percent) could an acute coronary syndrome be confirmed. In the majority of patients, the chest discomfort was apparently not caused by acute myocardial ischemia and hospitalization was unnecessary.

Wackers and colleagues demonstrated in 1979 the potential value of resting myocardial perfusion imaging in patients with acute chest pain in the emergency room. The presently available ^{99m} Tc-labeled compounds are better suited than ^{201} Tl for acute imaging of patients with chest pain. These compounds can be readily reconstituted when a patient arrives with chest pain. Moreover, the lack of redistribution of these agents provides greater flexibility with regard to the timing of imaging. SPECT imaging also provides useful information relative to the coronary vascular territory involved and, by using ECG gating, allows for assessment of regional and global left ventricular function. Several investigators[53] have shown that acute rest SPECT imaging in the emergency department has high sensitivity for the early detection of acute myocardial infarction. In a total of 1581 patients the sensitivity for acute infarction was 95 percent.[53] Resting myocardial perfusion images are abnormal at a time when enzymes in many patients have not yet risen to diagnostic levels.[54] Furthermore, the negative

predictive value of resting imaging was better than 99 percent. Thus, patients with acute chest pain, a nondiagnostic ECG, and *normal rest* SPECT images have less than a 1 percent chance of having an ongoing acute infarction. The rare patient with acute infarction who was undetected by rest SPECT imaging invariably had small and uncomplicated infarcts.[53] On the other hand, patients with *abnormal* SPECT images had an increased risk of coronary events during hospitalization (death, acute infarction, or revascularization).[53] Patients with normal acute myocardial perfusion images in general had a favorable outcome.[53] Stowers and coauthors reported that acute resting SPECT could be used as a cost-effective means to manage patients with acute chest pain and nondiagnostic ECG.[55] When compared with conventional management, a SPECT imaging-guided approach resulted in fewer cardiac catheterizations and substantial cost savings.

Once acute myocardial infarction has been ruled out in a chest pain center, the evaluation protocol is completed with risk stratification by stress testing. Although most

patients can be evaluated with exercise ECG, a substantial number of patients are not able to perform an adequate level of physical exercise. In these patients, pharmacological vasodilation in conjunction with radionuclide myocardial perfusion imaging is performed. Discriminative use of either resting or stress radionuclide imaging has an important place in the efficient triaging of patients in chest pain centers.

Chronic Coronary Artery Disease (see also Chap. 37)

Stress Testing

In patients with chronic stable coronary artery disease who are capable of physical exercise, myocardial perfusion imaging is used in conjunction with exercise testing. Physical exercise can be performed either on a treadmill, which is most popular in the United States, or on an upright bicycle, which is frequently used in Europe and other countries. Physical exercise has the advantage of providing additional useful clinical and physiological parameters, such as duration of exercise, total workload, maximum heart rate, exercise-induced symptoms, ECG changes, and blood pressure response. However, a substantial number of patients referred for evaluation cannot physically exercise because of orthopedic, neurological, or peripheral vascular problems. In the latter group of patients, pharmacological vasodilatation with dipyridamole or adenosine or pharmacological stress with dobutamine provides useful alternative approaches.

The basic principle of the application of various modes of stress in conjunction with radionuclide myocardial perfusion imaging is used to create *heterogeneity of myocardial blood flow* between vascular territories supplied by normal coronary arteries and that supplied by an artery with significant obstructive coronary artery stenosis (Fig. 9-17) . Heterogeneity in regional myocardial blood flow can be visualized with radionuclide myocardial perfusion agents and is a requirement for abnormal images. However, regional heterogenity does not necessarily imply myocardial ischemia.

PHYSICAL EXERCISE.

Several standardized treadmill exercise protocols exist (see also Chap. 6) . The most widely used protocol was designed by Bruce. Nonimaging endpoints are reproduction of the patient's symptoms, exhaustion, hypotension or a decrease in systolic blood pressure of 20 mm Hg or more, ventricular arrhythmias, or severe ST segment depression on ECG. An intravenous line should be in place in a large antecubital vein for injection of the radiopharmaceutical agent. When the end point of exercise

Figure 9-17 Schematic representation of the principle underlying rest/stress myocardial perfusion imaging. *Top,* Two branches of a coronary artery are schematically shown; the left branch is normal whereas the right branch has a significant stenosis. *Middle,* Myocardial perfusion images of the territories supplied by the two branches. *Bottom,* Schematic representation of coronary blood flow in the branches at rest and during stress. At rest, myocardial blood flow is similar in both coronary artery branches. When a myocardial perfusion imaging agent is injected at rest, myocardial uptake is homogeneous (normal image). During stress, coronary blood flow increases 2.0 to 2.5 times in the normal branch, but not to the same extent in the stenosed branch, thereby resulting in heterogeneous distribution of blood flow. This

heterogeneity in blood flow can be visualized with ^{201} Tl or ^{99m} Tc-sestamibi as an area with relatively decreased radiotracer uptake (myocardial perfusion defect). *(From Wackers FJTh: Exercise myocardial perfusion imaging. J Nucl Med 35:726, 1994. Reprinted with permission from the Society of Nuclear Medicine.)*

is reached, the radiopharmaceutical is injected rapidly through the intravenous line, followed by flushing with saline. The patient is then encouraged to exercise for another 1 to 2 minutes at the same level of exercise. This continuation of exercise after injection of the radiotracer is crucial for diagnostic stress imaging. It is important to maintain the heart rate and thus myocardial blood flow at the peak exercise level to allow for accumulation of the radiotracer during a "steady ischemic state." If the patient is unable to continue exercising at the same level, the speed and grade of the treadmill can be decreased to a lower level.

For bicycle exercise, a similar graded exercise protocol is used. Usually, the patient starts at 25 kpm, and resistance is increased every 3 minutes until an exercise endpoint is reached.

The purpose of exercise is to increase cardiac metabolic demand and to test the ability of the coronary circulation to meet these demands with an appropriate increase in myocardial blood flow. Consequently, myocardial ischemia is frequently provoked with physical exercise.

PHARMACOLOGICAL VASODILATION.

Patients with orthopedic, neurological, or peripheral vascular problems are incapable of exercising adequately on a treadmill or bicycle. These patients can be evaluated for the presence of significant coronary artery disease by the use of pharmacological vasodilatation in combination with radionuclide myocardial perfusion imaging. Furthermore, patients taking

TABLE 9-3 -- REPORTED SIDE EFFECTS (% OF PATIENTS) OF INTRAVENOUS DIPYRIDAMOLE, ADENOSINE, AND DOBUTAMINE MYOCARDIAL PERFUSION IMAGING

SIDE EFFECT	DIPYRIDAMOLE* (RANHOSKY[58])	ADENOSINE* (VERANI [59])	DOBUTAMINE (FLAYS[60])
Cardiac			
Fatal myocardial infarction	0.05	0	0
Nonfatal myocardial infarction	0.05	0	0
Chest pain	19.7	57	31

ST-T changes on ECG	7.5	12	50
Ventricular ectopy	5.2	?	43
Tachycardia	3.2	?	1.4
Hypotension	4.6	?	0
Blood pressure liability	1.6	?	?
Hypertension	1.5	?	1.4
AV block	0	10	0.6
Noncardiac			
Headache	12.2	35	14
Dizziness	11.8	?	4
Nausea	4.6	?	9
Flushing	3.4	29	14
Pain (nonspecific)	2.6	?	7
Dyspnea	2.6	15	14
Paresthesia	1.3	?	12
Fatigue	1.2	?	?
Dyspepsia	1.0	?	?
Acute bronchospasm	0.15	0*	?
AV=atrioventricular; ECG=electrocardiogram.			

*Patients with history of bronchospasm excluded.

Question marks indicate that the side effect was not reported.

beta-blocking medication who are unable to increase their heart rate adequately by physical exercise have been studied successfully with pharmacological coronary vasodilation. In addition, patients with complete left bundle branch block or ventricular pacemakers are preferably studied with vasodilators to avoid artifactual perfusion defects.

Intravenous infusion of dipyridamole blocks the cellular reabsorption of adenosine and thus increases the concentrations of adenosine, an endogenous vasodilator that activates specific receptors. Coronary blood flow is autoregulated by adenosine to meet myocardial metabolic demands.[56] In patients without coronary artery disease, dipyridamole or adenosine infusion creates vasodilatation and increases coronary blood flow three to five times above baseline levels. In patients with significant coronary artery disease, the resistance vessels distal to a stenosis are already dilated, often maximally, to maintain normal resting flow. In these patients, infusion of dipyridamole or adenosine

does not cause further significant vasodilation in the diseased vascular bed. However, in the adjacent myocardium supplied by normal coronary arteries, a substantial increase in myocardial blood flow occurs. In this manner, *heterogeneity in regional myocardial blood flow is created:* Territories supplied by diseased arteries are relatively hypoperfused in comparison to normal regions (see Fig 9-19) . Pharmacological vasodilation by dipyridamole or adenosine infusion does not usually provoke myocardial ischemia. Xanthine derivatives and caffeine block adenosine receptors. Consequently, patients should not be taking these medications and should not drink any caffeine-containing beverages (including caffeine-free drinks and chocolate) the night before testing to avoid false-negative images.[57]

DIPYRIDAMOLE INFUSION PROTOCOL.

Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min)[56] by using an infusion pump or by injection slowly by hand. Approximately 4 minutes after completion of the infusion, the maximal vasodilatory effect is achieved. At this time the radiotracer is injected intravenously. The maximum vasolidatory effect is usually associated with a modest increase in heart rate (10 beats/min) and a slight decrease (10 mm Hg) in systolic blood pressure. In some laboratories, dipyridamole infusion is combined with low-level exercise *after* the completion of dipyridamole infusion. This combination appears to decrease the incidence of side effects in about 50 percent of patients during infusion of dipyridamole. Approximately 20 percent of patients may have ECG changes, and 10 percent may experience angina, although the most frequent complaints consist of headache, flushing, and nausea (Table 9-3) .[58] [61] Ischemia may be caused by "coronary steal." In this situation, the marked increase in blood flow in the *normal* myocardial zones "steals" blood away via collaterals from the vascular bed supplied by significantly diseased coronary arteries. This and other undesirable side effects can usually be reversed quickly by blocking adenosine receptor sites with intravenous aminophylline.

ADENOSINE INFUSION.

Clinical experience with direct intravenous infusion of adenosine (maximum of 140 mug/kg/min) has been comparable to that reported for dipyridamole.[61] [62] Adenosine should be administered only with an infusion pump. It appears that the coronary vasodilatory effect of adenosine is more potent and more consistent than that of dipyridamole. However, side effects are more common and occur in about 75 percent of patients (see Table 9-3) . Approximately 50 percent of patients may have chest pain, and many have headache, nausea, and flushing. The severity of side effects can be limited by simultaneous low-level exercise. In contrast to dipyridamole, the exercise has to be done *during* the infusion of adenosine, which makes it somewhat complicated but still possible. Atrioventricular (AV) conduction abnormalities (second- and third-degree AV block) are not infrequently seen in patients receiving an adenosine infusion, a matter of some concern. However, because of the short half-life (30 seconds) of adenosine, side effects can be reversed almost instantaneously by terminating the infusion of adenosine. Samuels and colleagues observed that adenosine SPECT imaging was well tolerated by patients with moderate to severe aortic valvular stenosis who were

evaluated for coexisting coronary artery disease.[63]

DOBUTAMINE STRESS.

For patients with contraindications to dipyridamole or adenosine infusion, such as those with bronchospastic pulmonary disease, or for patients who are taking xanthine derivatives or who have consumed caffeine, dobutamine infusion offers an alternative diagnostic approach.[60] [64] Dobutamine increases myocardial oxygen demand by increasing myocardial contractility, heart rate, and blood pressure. The increase in coronary blood flow is comparable to that during physical exercise (twofold to threefold) but less than that with adenosine or dipyridamole. Nevertheless, dobutamine infusion should not be considered equivalent to physical exercise. Useful clinical information such as duration of exercise, exercise capacity, and reproduction of symptoms is not obtained. The increase in heart rate is usually lower than that with exercise. Thus, dobutamine pharmacological stress should be considered a last resort in patients who cannot exercise rather than a substitute for exercise.

Dobutamine Infusion Protocol.

Infusion of dobutamine is started

TABLE 9-4 -- SENSITIVITY AND SPECIFICITY FOR DETECTION OF CORONARY ARTERY DISEASE BY QUANTITATIVE PLANAR THALLIUM-201 SCINTIGRAPHY

AUTHOR	PATIENTS (N)	SENSITIVITY (%)	SPECIFICITY (%)
Berger et al.,[66] 1981	140	91	90
Maddahi et al.,[67] 1981	67	93	91
Wackers et al.,[68] 1985	150	89	95
Kaul et al.,[69] 1986	325	90	80
Van Train et al.,[70] 1986	157	84	88
Total/average	*839*	*89*	*89*

with a low dose of 5 mug/kg/min. The dose is increased each 3 minutes if tolerated, to a maximal dose of 40 mug/kg/min. The radiopharmaceutical is injected during infusion of the maximum dose and the infusion continued for 2 to 3 minutes. Table 9-3 shows the incidence of side effects during dobutamine infusion. [60] A similar infusion protocol is used for dobutamine stress echocardiography. In a review of 2942 patients who had dobutamine-atropine stress echocardiography, 9 patients (0.3 percent) had serious cardiac side effects, including 2 nonfatal infarctions, 2 instances of ventricular fibrillation, 2 instances of sustained ventricular tachycardia, 2 patients with severe hypotension, and 1 patient with prolonged severe myocardial ischemia.[65]

Clinical Results of Exercise Testing and Myocardial Perfusion Imaging (see also Chap. 13)

Over the last 25 years the clinical usefulness of stress myocardial perfusion imaging has been well established. During the 1980s, most data in the literature were based on planar ^{201} Tl imaging. Since the early 1990s, numerous reports have confirmed that similar results are obtained with SPECT imaging and with the use of ^{99m} Tc-labeled agents. Presently, ECG gating is an integral part of SPECT myocardial perfusion imaging. Thus, state-of-the-art stress SPECT imaging provides information not only on myocardial perfusion but also on resting left ventricular function.[33]

The introduction of computer processing and quantification of myocardial perfusion images improved the overall detection of coronary artery disease substantially. For instance, the detection of single-vessel disease with ^{201} Tl improved from 55 percent by visual analysis to 84 percent by quantitative analysis (Table 9-4) . Almost all patients with double- or triple-vessel coronary artery disease were detected by quantitative myocardial perfusion imaging[66] [67] [68] [69] [70] (see Table 9-4) .

In 1994, the American Medical Association commissioned a Diagnostic and Therapeutic Technology Assessment (DATTA) review of SPECT myocardial perfusion imaging.[71] This extensive review of the literature revealed sensitivities for planar imaging ranging from 67 to 96 percent and sensitivities for SPECT imaging ranging from 83 to 98 percent. The range of specificities for planar imaging varied from 40 to 100 percent and from 53 to 100 percent for SPECT imaging. The report did not address the potential contribution of image quantification on improvement in diagnostic accuracy. Representative results of qualitative and quantitative SPECT imaging for the detection of coronary artery disease with available radiopharmaceuticals are shown in Table 9-5 . [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83]

The ability to accurately predict coronary disease in specific individual vessels was consistently suboptimal by planar imaging and reflected an inherent limitation of the planar imaging modality. With SPECT imaging, detection of coronary artery disease in individual vessels, in particular, the left circumflex coronary artery, has significantly improved.[73] Consequently, SPECT stress myocardial perfusion imaging is particularly useful to assess patients with known coronary artery disease in whom decisions regarding revascularization are to be made.

VALUE OF ^{99m} Tc-LABELED RADIOPHARMACEUTICALS.

Since the introduction of ^{99m} Tc-sestamibi and ^{99m} Tc-tetrofosmin, many thousands of patients have been evaluated with these agents. Several comparative studies have shown

TABLE 9-5 -- SENSITIVITY, SPECIFICITY, AND NORMALCY RATE FOR DETECTION OF CORONARY ARTERY DISEASE BY THALLIUM-201, TECHNETIUM-99m-SESTAMIBI, AND TECHNETIUM-99m-TETROFOSMIN SPECT IMAGING

AUTHOR	PATIENTS (N)	SENSITIVITY (%)	SPECIFICITY (%)	NORMALCY RATE (%)
Thallium-201				
Maddahi et al.,[72] 1989	110	96	56	86
Fintel et al.,[73] 1989	112	91	90	
Iskandrian et al.,[74] 1989	164	88	62	93
Go et al.,[75] 1990	202	76	80	
Mahmarian et al.,[76] 1990	360	93	87	
Van Train et al.,[77] 1990	242	95	56	
Total/average	*1190*	*90*	*72*	*90*
Technetium-99m-Sestamibi				
Kiat et al.,[78] 1989	36	93	75	100
Iskandrian et al.,[79]	39	82	100	
Kahn et al.,[80] 1989	38	95		
Solot et al.,[81] 1993	128	97	71	
Van Train et al.,[82] 1994	161	89	36	81
Total/average	*402*	*91*	*71*	*91*
Technetium-99m-Tetrofosmin				
Azzarelli et al.,[83] 1999	235	95	77	93

Figure 9-18 Simultaneous assessment of myocardial perfusion and function. ^{99m} Tc-sestamibi imaging in acute myocardial infarction allows assessment of both function and perfusion. In this patient with a large anteroseptal infarction, resting injection of sestamibi was used for first-pass radionuclide angiography (*left*). The end-diastolic and systolic frames are shown. The global left ventricular ejection fraction was severely depressed at 0.33. On the *right* are resting single-photon emission computed tomographic sestamibi images in short-axis and vertical and horizontal long-axis slices. A large anteroseptal

myocardial perfusion defect is present (arrows).

that detection of coronary artery disease with both agents is comparable to that with ^{201}Tl.[3] [84] [85] The relative high dose of ^{99m}Tc administered makes it feasible not only to acquire images in ECG-gated mode but also to perform first-pass radionuclide angiocardiography in combination with myocardial perfusion imaging[28] [79] (Fig. 9-18) . Combined analysis of "still" slices and perfusion wall motion images further improves the accuracy and confidence of interpretation. The clinical importance of acquiring both resting and peak exercise LVEF is discussed elsewhere in this chapter.

The sensitivity and specificity of using pharmacological vasodilation with various myocardial perfusion imaging agents to detect coronary artery disease reportedly resemble those obtained with physical exercise.[86] [87] [88] [89]

REFERRAL BIAS.

As mentioned above, the reported specificity of stress SPECT myocardial perfusion imaging is relatively low, from 53 to 100 percent. This lack of specificity has been partially explained by "referral bias"; that is, since stress myocardial imaging has become accepted in the clinical practice of cardiology, patients with normal stress radionuclide images are no longer referred for cardiac catheterization. Thus, the occasional patient who has normal coronary arteries on angiography is almost always referred because of abnormal stress myocardial perfusion images. The true specificity of stress SPECT imaging can therefore no longer be assessed in patients undergoing coronary angiography because of this referral bias. Specificity should, however, be tested in patients with a low likelihood of coronary artery disease. In such patients, the "normalcy rate" is determined. The normalcy rate of planar imaging with ^{201}Tl was generally over 95 percent. With SPECT imaging, the normalcy rate ranges from 85 percent for ^{201}Tl to 95 to 100 percent for ^{99m}Tc-labeled agents.

NONUNIFORM ATTENUATION.

Although referral bias may be a partial explanation for the less than desirable specificity of SPECT imaging, nonuniform attenuation is a likely culprit as well. In contrast to planar imaging, breast artifacts are not a major cause of suboptimal specificity of SPECT imaging. Of all the projection images acquired, only a few may be sufficiently affected by breast attenuation to create false-positive defects. A mild defect in the anterior wall can be suspected to be a breast artifact if the defect is fixed and wall motion on gated SPECT is normal. The most serious problem on SPECT imaging is that of attenuation of the inferior wall, which occurs frequently because patients are imaged in the supine position. An experienced interpreter is always alert to the possibility of inferior artifacts. Although a number of "tricks" can be used to recognize inferior wall attenuation, such as prone imaging, gated SPECT, and right-side decubitus left lateral images, at best these techniques may lessen or heighten suspicion. Patients with inferior attenuation artifacts may also have right coronary artery disease and vice versa. Only adequately validated attenuation correction devices and software will solve this dilemma and improve the specificity of SPECT imaging. As mentioned above, at the time of this writing, no commercially available attenuation correction system has as yet passed full clinical

testing in a wide range of clinical conditions.[15] [16]

STRESS MYOCARDIAL PERFUSION IMAGING AND PROGNOSIS.

Detection of coronary artery disease is only one aspect of the clinical value of stress myocardial perfusion imaging.[89A] A more important feature is the ability to predict prognosis and identify high- and low-risk patients. The first critical finding on myocardial perfusion images is the presence or absence of defect reversibility, i.e., ischemia. Patients with evidence of transient ischemia on stress myocardial perfusion images have been shown to have a higher incidence of future cardiac events than do patients with fixed scars. In patients with suspected or known chronic coronary artery disease, semiquantitative and quantitative assessment of the number or extent of myocardial perfusion defects, the magnitude of defect reversibility, and poststress LVEF are predictive of cardiac events during follow-up[90] [91] [92] [93] [94] (Fig. 9-19) . Vanzetto and colleagues showed in 1137 patients that the incremental prognostic value of ^{201} Tl exercise SPECT was maintained over a period of 6 years[91] (Fig. 9-20) .

Evidence of transient left ventricular dysfunction during stress (i.e., transient postexercise dilatation and/or increased radiotracer lung uptake) constitutes an important additional scintigraphic marker of adverse outcome.[92] Similarly, increased right ventricular uptake on stress images is another image pattern that indicates severe coronary artery disease. It has been proposed that this increased uptake may be due to acute right ventricular strain and/or right ventricular/left ventricular perfusion imbalance.[22]

DETECTION OF HIGH-RISK CORONARY ARTERY DISEASE.

The greater the functional severity of coronary artery disease, the more abnormal exercise myocardial perfusion images are likely to be. Most patients (approximately 95 percent) with left main coronary disease have abnormal stress myocardial perfusion images. However, the expected typical left main pattern, i.e., defects in the anteroseptal and posterolateral walls, is found in only a minority (approximately 14 percent) of patients with left main coronary artery disease. The majority (approximately 75 percent) of patients nevertheless have multiple perfusion defects and, frequently, abnormally increased lung uptake of ^{201} Tl.

Although most patients with triple-vessel disease have abnormal stress images, only approximately 60 percent have multiple defects in two or more vascular regions. Disease in the left circumflex coronary artery is better detected with SPECT imaging than with planar imaging.[73]

Myocardial perfusion images of a high-risk patient (Fig. 9-21) can be characterized by *one or more* of the following image features: (1) multiple reversible defects in two or more coronary artery territories, (2) quantitatively large

Figure 9-19 Prognostic importance of the size and type of myocardial perfusion abnormality. The data are from 816 patients with stable coronary artery disease enrolled in the Multicenter Study on Silent Myocardial Ischemia (MSSMI). The patients had 26 months' follow-up. All patients had quantitative planar ^{201} Tl stress imaging. The graph relates the size of exercise defects, defect reversibility, and number of abnormal segments to the cardiac death rate during follow-up. The highest cardiac death rate occurred in patients with the most abnormal images. In particular, patients with the greatest defect reversibility had the highest cardiac death rate. *(Modified from Bodenheimer MM, Wackers FJTh, Schwartz RG, et al: Prognostic significance of a fixed thallium defect one to six months after onset of acute myocardial infarction or unstable angina. Am J Cardiol 74:1196, 1994.)*

myocardial perfusion defects,[90] [91] (3) increased pulmonary radiotracer uptake after exercise,[19] [20] [21] (4) transient dilatation of the left ventricle immediately after exercise,[92] (5) depressed resting LVEF on either gated SPECT[93] or first-pass angiography, and (6) increased right ventricular uptake on stress images.[22] This high-risk pattern is highly specific (approximately 95 percent) for multivessel coronary artery disease; however, the sensitivity is only about 70 percent. Therefore, in the absence of the above-mentioned scintigraphic characteristics, multivessel disease cannot be ruled out.

PREDISCHARGE STRESS TESTING AFTER ACUTE INFARCTION (see also Chap. 35) .

Gibson and associates were the first to demonstrate the importance of quantitative planar ^{201} Tl stress imaging at the time of discharge in patients with uncomplicated myocardial infarction. Patients without ischemia at hospital discharge had only a 6 percent cardiac event rate (death, recurrent infarction, or unstable angina), whereas patients who had high-risk findings on predischarge ^{201} Tl stress images (multiple defects in more than one vascular region, abnormal washout, or increased lung uptake) had a 51 percent cardiac event rate. Numerous other investigators have since reported a similar prognostic value of stress myocardial perfusion imaging after myocardial infarction with the use of either physical or pharmacological stress.[95] [96] [97] [98] [99] [100] Brown and colleagues observed that patients with recurrent chest pain after myocardial infarction frequently had ischemia within the infarct region (75 percent of patients), whereas only 25 percent of patients had ischemia at a distance: Patients with evidence of reversibility had a substantially poorer prognosis and higher incidence of revascularization procedures than did patients who did not have demonstrable defect reversibility. Dipyridamole and adenosine myocardial perfusion imaging can be used for very early risk stratification during the first days after the acute event (see Acute Myocardial Infarction above) or at the time of discharge from the hospital. Mahmarian and coworkers demonstrated that at discharge, the absolute extent of stress-induced myocardial ischemia and the resting LVEF were multivariate predictors of future cardiac events[97] (Fig. 9-22) . In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,[100] invasive management (routine angiography) was compared with conservative management (noninvasive testing) in stable survivors of non-Q-wave acute infarctions. Patients in the conservative limb (who had radionuclide stress myocardial perfusion imaging) had significantly less coronary angiography (96 vs.

48 percent) but a higher revascularization rate (42 vs. 68 percent). Importantly, overall infarct-free survival was comparable in both groups. Thus, stress myocardial perfusion imaging at the time of discharge effectively identified high- and low-risk patients.

STRESS MYOCARDIAL PERFUSION IMAGING AFTER THROMBOLYTIC THERAPY.

Early reports on stress testing in patients who had thrombolytic therapy for acute infarction suggested decreased sensitivity of stress myocardial perfusion imaging for predicting multivessel coronary artery disease and cardiac events.[101] [102] It now appears that this observation can be explained on the basis of unintentional bias in patient selection. In the early 1990s, patients who were eligible for thrombolytic therapy constituted a patient cohort at relatively low risk. These patients were generally younger and had fewer prior myocardial infarctions, fewer non-Q-wave infarctions, and less multivessel coronary artery disease than did patients with acute infarction

Figure 9-20 Kaplan-Meier cardiac survival curves according to the number of abnormal segments on ^{201}Tl single-photon emission computed tomography ([201] Tl SPECT). = normal ^{201}Tl SPECT;
= presence of one to two abnormal segments;
= presence of three or more abnormal segments. *(Modified from: Vanzetto G, Ormezzano O, Fogret D, et al: Long term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low-to-intermediate risk patients. Study in 1,137 patients with 6 year follow-up. Circulation 100:1521, 1999. By permission of the American Heart Association, Inc.)*

Figure 9-21 ^{99m}Tc sestamibi single-photon emission computed tomographic images of a high-risk patient. The "raw" planar projection image obtained 15 minutes after termination of stress (*top*) shows increased bilateral lung uptake. The left ventricle is enlarged and dilated. On the resting image the left ventricle is still enlarged but lung uptake is normal. On the reconstructed short-axis slices (*bottom*), the left ventricle is enlarged and shows multiple (anterior and inferior wall) fixed defects. These images are consistent with transient left ventricular dysfunction during stress.

in the prethrombolytic era. Because of the favorable outcome and low mortality in these patients, one would predict, based on bayesian principles, diminished predictive value for stress myocardial perfusion imaging. Dakik and associates recently evaluated the prognostic value of predischarge quantitative ^{201}Tl SPECT in 71 patients who had thrombolytic therapy for acute infarction.[103] They observed that ^{201}Tl SPECT imaging, particularly when combined with assessment of LVEF, continued to provide important incremental and long-term (36 months) prognostic information over other clinical variables, including angiography.

PROGNOSTIC SIGNIFICANCE OF NORMAL STRESS PERFUSION IMAGES.

Normal planar or SPECT stress myocardial perfusion images, even when coronary artery stenosis is angiographically documented, indicate a favorable prognosis with a low subsequent cardiac event rate.[104] [105] [106] Patients with quantitatively normal myocardial perfusion images have a yearly nonfatal myocardial infarction rate of 0.5 to 1 percent per year and a mortality rate of 0 to 0.5 percent per year[107] [108] [109] [110] (Table 9-6) . *The "warranty" for normal stress myocardial perfusion images is believed to expire after 1.5 to 2 years.*[111]

These data on abnormal and normal stress myocardial perfusion images indicate that the extent of myocardial perfusion defects, or the lack thereof, provides significant physiological and prognostic information that surpasses the anatomical information obtained from coronary angiograms. The prognostic predictive value of stress myocardial perfusion imaging is independent of the imaging technique applied (planar or SPECT) or the radiopharmaceutical used ([201] Tl or ^{99m} Tc-labeled agents).

Independent Incremental Value of Stress Myocardial Perfusion Imaging (see also Chap. 13)

In clinical practice, diagnostic tests are generally used in conjunction with each other. The clinician usually has other clinical and diagnostic information available. Evidence for the prognostic value of stress myocardial perfusion imaging as outlined above is compelling. However, if similar information can be derived from other less costly and readily available tests, it may not be cost-effective to perform radionuclide myocardial perfusion imaging. The incremental prognostic value of various diagnostic data obtained in succession (clinical data, exercise ECG, stress ^{201} Tl-myocardial perfusion imaging, and coronary angiography) was first assessed by Pollock and coworkers.[112] The combination of clinical and exercise ^{201} Tl variables provided greater prognostic information than did the combination of clinical and angiographic data alone. Iskandrian and coworkers[113] and others[24] [114] [115] [116] [117] [118] observed similar independent and incremental prognostic information from SPECT stress imaging, even when cardiac catheterization data are available (Fig. 9-23) .

Pursuing the same goal of defining the incremental prognostic value of noninvasive testing, Hachamovitch and colleagues performed a series of large data bank analyses that further clarified the role of stress myocardial perfusion imaging.[106] [116] [117] [118] [119] Patients can be categorized into low, intermediate, and high risk for coronary artery disease on the basis of clinical, historical, and exercise information. In each clinical

Figure 9-22 Cox regression model displaying 1-year risk for a cardiac event after acute myocardial infarction according to rest left ventricular (LV) ejection fraction and total LV ischemia on adenosine ^{201} Tl single-photon emission computed tomography at hospital discharge. Patient risk for cardiac death (triangles) or nonfatal infarction (solid circles) increases as total ischemia increases and the resting LV

ejection fraction decreases. Diagonal lines represent separate clusters of image variables signifying increasing risk for cardiac events, i.e., 10 to 75 percent. Patients with no events are represented by open circles. *(Modified from Mahmarian JJ, Mahmarian AC, Marks GF, et al: Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 25:1333, 1995.)*

risk category, radionuclide imaging can further enhance risk stratification with respect to the occurrence of future cardiac events (Fig. 9-24) . As stated above, in all clinical subgroups, normal perfusion studies were associated with an exceedingly low yearly event rate (<1 percent).

However, the cost for detecting one hard event (death or myocardial infarction) by noninvasive testing varied in each group and was extremely high in the group with low pretest risk ($253,307 per event for the low-risk population vs. $59,096 per event for the high-risk population). It follows that systematic testing is only cost-effective in the group of patients with intermediate and high risk. Hachamovitch demonstrated that incremental value and enhanced risk stratification can be achieved in both men and women and in young and elderly patients.[120]

Several investigators have proposed a strategy of hierarchical testing.[121] [122] [123] Patients with low pretest risk generally do not need testing. Patients with intermediate to high risk for coronary artery disease (and who have a normal resting ECG) should first have an exercise ECG. If the result of exercise ECG is normal, the patient is at low risk and perfusion imaging will not provide additional new information. If the exercise ECG is abnormal and/or the posttest risk is intermediate, stress SPECT imaging is appropriate for further evaluation. In a multicenter data base study, Shaw and coworkers analyzed the cost of two diagnostic approaches in patients referred for the evaluation of chest

Figure 9-23 Independent and incremental prognostic power of clinical, exercise, catheterization, and quantitative ^{201} Tl single-photon emission computed tomographic (SPECT) variables. Data shown represent the global chi-square statistics of various clinical and diagnostic variables. SPECT imaging provides independent and incremental information to identify high-risk patients. Note that angiography (cath) has less incremental value over clinical variables than ^{201} Tl SPECT imaging does. *(From Iskandrian AS, Chae SC, Heo J, et al: Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 22:665, 1993. Reprinted with permission from the American College of Cardiology.)*

pain. [124] One group of 5826 patients first underwent stress SPECT imaging, followed by cardiac catheterization if SPECT images were abnormal, whereas the other group of 5423 patients was directly referred for cardiac catheterization. They found no differences in short- or long-term outcome. However, the total diagnostic cost and the long-term follow-up cost were 30 to 41 percent lower when SPECT imaging was performed as the first step of the evaluation (Fig. 9-25) . Similar cost savings for the noninvasive diagnostic strategy in comparison to the primary invasive diagnostic strategy were reported in the Economics Myocardial Perfusion Imaging in Europe (EMPIRE) Study.[125]

Hachamovitch and associates showed in an observational study of 5183 patients that a

significant association existed between the degree of abnormality on stress SPECT imaging and the occurrence of death or myocardial infarction[106] (Fig. 9-26) . However, in patients with mildly abnormal SPECT images, differential risk was noted. These patients were at a low risk for cardiac death (0.8 percent per year), but intermediate risk for myocardial infarction (2.7 percent per year), which suggests that patients with mildly abnormal myocardial perfusion images are best treated with aggressive risk factor modification. Reports to referring physicians should therefore reflect *the degree of abnormality* observed on stress SPECT images. Bateman and colleagues [126] and Nallamothu and associates[127] showed that categorizing patients in reports as "high" or "low" risk is an effective way to direct appropriate patients for coronary angiography and avoid unnecessary cardiac catheterization. Sharir and coworkers showed that the poststress

TABLE 9-6 -- YEARLY CARDIAC EVENT RATE IN PATIENTS WITH NORMAL MYOCARDIAL PERFUSION IMAGES

AUTHOR	PATIENTS (N)	CARDIAC DEATH (%)	NONFATAL MYOCARDIAL INFARCTION (%)
Thallium-201			
Pamelia et al.,[107]	349	0.5	0.6
Wackers et al.,[108]	95	0	1.0
Wahl et al.,[109]	455	0.2	0.6
Staniloff et al.,[110]	372	0	0.5
Sestamibi			
Brown et al.,[102]	234	0	0.5
Raiker et al.,[103]	208	0	0.5
Hachamovitch et al.,[104]	2946	0.3	0.5

Figure 9-24 Incremental prognostic value obtained by stress myocardial perfusion imaging over and beyond risk stratification in a low-, intermediate-, and high-risk group on the basis of clinical, historical, and exercise information. In each postexercise electrocardiographic risk category, the result of stress myocardial perfusion imaging, i.e., normal, mild, and moderate-severe (MOD-SEV), provides enhanced risk stratification for cardiac events (death and myocardial infarction). *(Modified from Hachamovitch R, Berman DS, Kiat H, et al: Exercise myocardial perfusion SPECT in patients without known coronary artery disease: Incremental prognostic value and impact on subsequent patient management. Circulation 93:905, 1996.)*

LVEF derived from gated SPECT has significant additional incremental value over myocardial perfusion in predicting cardiac death[93] (Fig. 9-27) .

Exercise ECG has been reported to be less accurate in women than in men for the detection of coronary artery disease. This variability can be explained in part by differences in disease prevalence in men and women.[128] Moreover, women more often have an abnormal baseline ECG, which affects accuracy of interpretation of exercise ECGs. Although breast attenuation artifacts may make the interpretation of stress myocardial perfusion images in women more difficult, Desmarais and colleagues demonstrated that experienced interpreters usually recognize artifacts and can avoid false-positive interpretations.[129]

Several investigators have examined the performance of stress myocardial perfusion imaging in women. Although women in general achieve lower exercise workload, the detection of significant coronary artery disease by radionuclide stress perfusion imaging is similar to that in men.[117] [130] [131] [132] [133] [134] Moreover, Chae and coworkers and others showed that low- and high-risk patients are identified without gender differences.[121] [131] [132] [133] [134] [135] Hachamovitch and associates demonstrated that risk stratification by myocardial perfusion imaging was effective in both men and women.[117] In fact, radionuclide stress myocardial perfusion imaging had superior discrimination for high risk in women than men. Irrespective of gender, the long-term outcome for vascular surgery patients could be predicted by dipyridamole ^{201} Tl imaging.[135] The multicenter "Women's Ischemic Syndrome Evaluation" (WISE) Study is ongoing. This study, which incorporates noninvasive stress testing, may further clarify the role of nuclear cardiology studies in women.[136]

Syndrome X (typical exertional angina pectoris, positive ECG response to exercise, and angiographically normal coronary

Figure 9-25 Cost savings (30 to 41 percent) achieved by noninvasive testing (NIVT) and selective catheterization (cath) in comparison to direct cardiac catheterization (direct cath) of patients suspected of having coronary artery disease. The total cost included both initial diagnostic cost and later follow-up cost. *(From Shaw LJ, Hachamovitch R, Berman DS, et al: The economic consequences of available prognostic strategies for the evaluation of stable angina patients: An observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. J Am Coll Cardiol 33:661, 1999. Reprinted with permission from the American College of Cardiology.)*

Figure 9-26 Cardiac event rate as a function of the degree of stress myocardial perfusion abnormalities. The event rate increases as stress single-photon emission computed tomographic images are more abnormal. However, patients with mildly abnormal images have a low risk for cardiac death, but intermediate risk for myocardial infarction (MI). *(From Hachamovitch R, Berman DS, Shaw LJ, et al: Incremental prognostic value of myocardial perfusion single photon emission computed tomography for*

the prediction of cardiac death. Circulation 97:535, 1998. By permission of the American Heart Association, Inc.)

arteries) occurs predominantly in postmenopausal women.[137] These patients, who have a favorable prognosis, generally have normal myocardial perfusion images, although in an occasional patient myocardial perfusion abnormalities have been noted.

DETECTION OF CORONARY ARTERY DISEASE IN DIABETIC PATIENTS (see also Chap. 63) .

Patients with diabetes

Figure 9-27 Cardiac death rate as a function of the degree of stress myocardial perfusion abnormality and poststress left ventricular ejection fraction (EF) by gated single-photon emission computed tomography. Assessment of resting EF in each category provides significant incremental value in predicting cardiac death. Patients with a normal EF have a low cardiac death rate even in the presence of severe perfusion abnormalities. The number of patients in each category is indicated below each column. Abn = abnormal; Mod = moderate. *(From Sharir T, Germano G, Kavanagh PB, et al: Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 100:1035, 1999. By permission of the American Heart Association, Inc.)*

mellitus have an increased risk of coronary artery disease.[138] Moreover, when compared with the nondiabetic population, they have an increased risk for ischemic death, myocardial infarction, and congestive heart failure. Myocardial ischemia is frequently asymptomatic and silent in patients with diabetes. It is not uncommon that an asymptomatic patient with diabetes is referred for stress testing as part of the preoperative evaluation and found to have markedly abnormal myocardial perfusion images. Clearly significant coronary artery disease is detected late in many diabetic patients. Thus far, the value of radionuclide myocardial perfusion imaging has been evaluated only in diabetic patients with *known or suspected* coronary artery disease. As shown in other subgroup analyses, stress perfusion imaging also has important incremental prognostic value in patients with diabetes.[117] However, for any given degree of myocardial perfusion abnormality, the outcome in a diabetic patient was two to three times poorer than in a nondiabetic patient.[139]

The American Diabetes Association published a consensus statement with guidelines for stress testing in diabetic patients without known coronary artery disease.[140] However, these recommendations were based on the clinical judgment of a panel of experts rather than published evidence. Myocardial perfusion imaging can play an important role in the timely detection of coronary artery disease. Observational data are needed in the large cohort of asymptomatic patients with diabetes, as well as characterization of those at highest risk for asymptomatic coronary artery disease.

MYOCARDIAL PERFUSION IMAGING IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK.

In patients with complete left bundle branch block, the conduction abnormality precludes the use of conventional ECG criteria for the diagnosis of infarction or exercise-induced

ischemia. It was expected that myocardial uptake of perfusion imaging agents would be unaffected by the ECG abnormality.[141] Indeed, in patients with left bundle branch block without prior myocardial infarction, *resting* myocardial perfusion images are generally normal. However, the septum is frequently thin, and in older patients the left ventricle is often dilated.

A number of investigators have reported exercise-induced myocardial perfusion defects in anteroapical and anteroseptal areas in patients with complete left bundle branch block and angiographically normal coronary arteries.[142] In some patients, partial or complete reversibility of these defects has been observed. Hirzel and colleagues proposed,

on the basis of experimental animal data with right ventricular pacing, that diminished septal myocardial blood flow during an abnormal sequence of electrical ventricular depolarization caused septal defects. We compared regional myocardial uptake of ^{201} Tl during rapid atrial pacing (normal conduction) with that during rapid right ventricular pacing (left bundle branch block). No significant quantitative difference was observed in regional ^{201} Tl uptake. Thus, it appears that the altered sequence of ventricular depolarization *itself* is not a principal cause for myocardial perfusion defects in left bundle branch block.

We noted a relationship between the presence of exercise-induced myocardial perfusion defects in left bundle branch block and the degree of *left ventricular dilatation* at rest. Patients with left bundle branch block often have clinically unexpected cardiomyopathy with ventricular dilation and a depressed LVEF. Thus, altered geometry with a partial volume effect may be another plausible explanation for the observed defects. Regardless of the cause of abnormal perfusion images in patients with left bundle branch block, patients with abnormal images have a poorer prognosis than do those with normal images.[143] Similar stress-induced false-positive myocardial perfusion abnormalities have been noted in patients with right ventricular pacemakers and paced rhythm during exercise.[144] The use of pharmacological vasodilation with dipyridamole has been shown to reduce the incidence of artifactual perfusion defects in left bundle branch block.[145] It is recommended that patients with left bundle branch block by ECG be evaluated with dipyridamole or adenosine rather than with physical exercise to avoid false-positive results.

MYOCARDIAL PERFUSION IMAGING FOR PREOPERATIVE SCREENING (see also Chap. 60) .

An important clinical application of myocardial perfusion imaging involves the preoperative evaluation of patients undergoing noncardiac surgery. Such perfusion imaging has had its most meaningful application in the study of patients prior to revascularization surgery involving the descending aorta and the lower extremities. This group of patients has a strong likelihood of the coexistence of coronary artery disease. Boucher and colleagues were the first to show that evidence of ischemia on

dipyridamole ^{201} Tl imaging was predictive of subsequent perioperative cardiac events.[146] Preoperative risk assessment has been extended to patients scheduled to undergo major noncardiac surgery.[147] Eagle and coworkers demonstrated that on the basis of simple clinical assessment, patients with high risk of coronary disease and those with very low risk of coronary disease did not require noninvasive testing for appropriate risk stratification.[148] However, the majority of patients consisted of an intermediate clinical risk group and were categorized quite effectively by perfusion studies. The American College of Cardiology/American Heart Association Joint Task Force published guidelines for preoperative risk assessment.[149] Leppo and Dahlberg suggested a shortcut approach based on these guidelines (Table 9-7) for deciding whether a patient needs preoperative testing.[150] If two of the factors listed are present, the guidelines suggest noninvasive testing. In addition to assessing short-term risk, vasodilator myocardial perfusion imaging is also of value in predicting long-term outcome, beyond the perioperative period.[151] [152]

MYOCARDIAL PERFUSION IMAGING BEFORE AND AFTER REVASCULARIZATION.

A main purpose for performing stress myocardial perfusion imaging is not only to detect significant coronary artery disease but also to aid in patient management decisions. Patients with markedly abnormal and high-risk stress myocardial perfusion images will usually be considered candidates for coronary revascularization, either by coronary bypass surgery or by percutaneous transluminal coronary angioplasty and stenting. Myocardial perfusion imaging is not routinely performed after coronary bypass surgery and is only indicated when symptoms recur. Since many patients have nonspecific ST-T segment changes on the baseline ECG after surgery, myocardial perfusion imaging is preferred over exercise ECG to evaluate these patients.[24] [153] Tomographic localization of perfusion abnormalities allows a determination of whether clinical ischemia is likely to be caused by coronary graft closure or by newly developed disease in other coronary arteries. Alazraki and associates monitored 336 patients randomized to

TABLE 9-7 -- SHORTCUT TO NONINVASIVE TESTING IN PREOPERATIVE PATIENTS

Intermediate clinical predictors are present, i.e., Canadian class 1 or 2 angina, prior myocardial infarct based on history or pathological Q waves, compensated or prior CHF, or diabetes
Poor functional capacity, i.e., less than 4 METS
High-risk surgical procedure, i.e., semiemergency major operations; aortic or peripheral vascular repair; prolonged surgical procedures with large fluid shifts and/or blood loss
If two or three factors are present, noninvasive testing is appropriate.
From Leppo JA, Dahlberg ST: The question: To test or not to test in preoperative cardiac risk evaluation. J Nucl Cardiol 5:332, 1998.

coronary bypass graft surgery or coronary angioplasty in the Emory Angioplasty Versus Surgery Trial (EAST) with quantitative ^{201} Tl SPECT imaging.[154] At 1 year after revascularization, stress-induced ischemia occurred more frequently after angioplasty than after surgery (46 vs. 27 percent, $p < 0.001$). Quantitative ^{201} Tl SPECT imaging effectively stratified patients according to the occurrence of subsequent cardiac events at a 3-year follow-up.

Coronary Angioplasty.

Stress myocardial perfusion imaging may be particularly useful after coronary angioplasty in patients with multivessel coronary artery disease. Often, the most severe stenosis in one vessel was dilated and questions remain whether the stenoses in other vessels are of significance. With SPECT imaging, a specified vascular territory can be evaluated readily. The optimal timing of imaging after angioplasty is unclear. Some investigators reported a high incidence of false-positive myocardial perfusion abnormalities early after angioplasty, presumably because of delayed return of coronary flow reserve within the territory of the dilated artery. However, such is not the general experience. Most patients have normal myocardial perfusion images within the first week after successful angioplasty. At approximately 4 weeks after coronary angioplasty, good correlation has been demonstrated between stress-induced myocardial perfusion abnormalities and the presence or absence of restenosis, independent of clinical symptoms.[155] In our own laboratory, we perform ECG treadmill stress testing shortly after angioplasty to assess functional status and exercise-induced symptoms. Stress myocardial perfusion imaging is performed in patients in whom symptoms suggestive of restenosis develop or at 6 months in those who are asymptomatic. SPECT imaging allows one to determine whether clinical ischemia is caused by restenosis at the site of angioplasty and stenting[155A] or by progression of disease in other coronary arteries.

ASSESSMENT OF MYOCARDIAL VIABILITY (see also Chaps. 13 and 37) .

For patients with angina, known coronary artery disease, previous infarction(s), and left ventricular dysfunction, a reliable method for assessing the presence, extent, and location of viable myocardium is of considerable clinical importance. It is well established that global or regional ischemic left ventricular dysfunction is not always an irreversible condition. Approximately 25 to 40 percent of patients have the potential for improvement in function after adequate revascularization. Extensive research has been conducted to establish the relative value of myocardial perfusion imaging with ^{201} Tl[7] [156] [157] [158] [159] and ^{99m} Tc-labeled tracers[160] [161] [162] [163] for predicting myocardial viability. Initially, ^{18} F-FDG regional uptake on positron imaging was used as a reference standard for myocardial viability.[164] [165] Unfortunately, in many later publications only improvement in regional dysfunction on dobutamine echocardiography has been equated with viability.[166] [167] This practice ignores the clinical importance of relieving ischemia in myocardial segments that are unlikely to have improved function after revascularization because of nontransmural

Figure 9-28 [201] Tl-labeled images after exercise (stress), 2.5-hour delayed imaging, and 24-hour delayed imaging and after reinjection of ^{201} Tl at rest. This patient has an apparently fixed defect (arrow) at 2.5-hour delayed imaging. However, on 24-hour redistribution imaging, filling-in of the defect can be appreciated. After reinjection of ^{201} Tl at rest, further normalization of the image can be appreciated. *(From Kayden DS, Sigal S, Soufer R, et al: Thallium-201 for assessment of myocardial viability: Quantitative comparison of 24 hour redistribution imaging with imaging after reinjection at rest. J Am Coll Cardiol 18:1480, 1991. Reprinted with permission from the American College of Cardiology.)*

scarring. [168] Myocardial metabolic activity on positron ^{18} F-FDG imaging is a more appropriate benchmark for viability. [165] [169]

Two important practical issues need to be addressed when evaluating patients with presumed ischemic dysfunction: (1) assessment of the relative regional myocardial uptake of ^{201} Tl (often after rest reinjection [Fig. 9-28]), ^{99m} Tc-sestamibi, or ^{99m} Tc-tetrofosmin [170] (often after rest administration of nitroglycerin[171] [172]). When the resting uptake of radiotracer is greater than 50 percent of normal, one can expect recovery of function after revascularization.[165] [169] (2) Assessment of the presence of demonstrable ischemia (i.e., partially reversible defect) in a myocardial segment with decreased uptake, even if the resting uptake is less than 50 percent.[173]

Bax and colleagues performed a pooled analysis of the various available techniques to predict functional recovery after surgical revascularization by reviewing 37 studies performed between 1980 and 1997.[174] They concluded that the sensitivity for predicting recovery of function was high (86 to 91 percent) for all methodologies analyzed (^{201} Tl rest-redistribution, ^{201} Tl stress-redistribution-reinjection, rest ^{99m} Tc sestamibi, low-dose dobutamine echocardiography, and ^{18} F-FDG PET). However, specificity varied considerably: lowest for ^{201} Tl stress-rest-reinjection (47 percent) and highest for dobutamine echocardiography. These studies were limited since myocardial viability was defined as improvement in regional function on echocardiography. Amanullah and associates observed that contractile reserve on dobutamine echocardiography was more frequently present in segments with normal ^{201} Tl uptake, reversible ^{201} Tl defects, or mild to moderate fixed ^{201} Tl defects than in segments with severely fixed defects.[175] Perrone-Filardi and coworkers showed that the level of resting ^{201} Tl uptake was strongly correlated with the frequency of functional improvement after surgery, consistent with the concept that myocardial viability is a continuum from full-thickness viability without scar to full-thickness scar without viable cells.[176] Patients with larger areas of myocardial viability have improved short- and long-term outcomes when compared with patients with lesser amounts of viable myocardium, which justifies efforts to assess myocardial viability.[177] However, patients with a low myocardial viability index and presumably, less or no improvement in ventricular function also have better survival rates after revascularization than when similar patients are treated medically. Samady and colleagues showed that failure to improve global left ventricular function after bypass surgery was not associated with a worse outcome than seen in patients who

had improved function.[178] Thus, the reported lower specificity of myocardial perfusion imaging for detection of viability may be deceptive because of the use of an inappropriate benchmark.

The experience with ^{201} Tl single-photon imaging for assessment of myocardial viability is extensive. At the time of this writing, resting-4 hour redistribution ^{201} Tl imaging is the preferred protocol for myocardial viability evaluation (see also Chaps. 10 and 13) .

Selection of Patients for Myocardial Perfusion Stress Imaging

Although the sensitivity and specificity of myocardial perfusion imaging for detection of coronary artery disease is better than that of ECG stress testing, false-negative and false-positive results occur. According to Bayes theorem, the clinical utility of test results relates not only to the sensitivity and specificity of a test but also to the prevalence of disease in the population under study.[179] For instance, quantitative ^{99m} Tc-sestamibi stress imaging has a reported sensitivity of approximately 90 percent and a specificity of approximately 80 percent. A positive result obtained in a population with a very low prevalence of coronary disease (e.g., less than 3 percent) will have a predictive value of only 13 percent since a relatively large absolute number of false-positives as compared with expected true-positive results can be anticipated. However, in a patient population with a high prevalence of coronary disease, e.g., 90 percent, a positive result has a predictive value of 99 percent. In this setting, relative to the true-positive results, only a few false-positive results are obtained. On the other hand, in a population with a high prevalence of disease, a relatively large number of false-negative results are also obtained, and the predictive value of a negative test for absence of coronary disease is only 51 percent. Thus, in a population with a low prevalence of coronary disease (such as young asymptomatic subjects or patients in a chest pain center), a positive test is of little predictive value, whereas in a population with a high prevalence of coronary artery disease (50- to 60-year-old men with typical angina pectoris), a negative test is of little practical diagnostic value. The difference between the pretest probability of disease (determined by the patient's age, symptoms, and stress ECG) and posttest probability (determined by the results of myocardial perfusion stress imaging) indicates the practical value of the test. Stress myocardial perfusion imaging has optimal discriminative value in a patient population with a pretest probability of coronary artery disease ranging from about 40 to 70 percent. This population includes patients with atypical chest pain,

asymptomatic patients with major risk factors, and asymptomatic patients with a positive stress ECG.

When a stress test is ordered for diagnostic purposes, the baseline ECG should be considered. In patients with normal baseline ECGs, the ST-T segment response to maximal exercise is of diagnostic value. We and others observed that patients with a normal ST segment response to maximal exercise, almost without exception, also had

normal exercise myocardial perfusion images.[121] [123] Thus, myocardial perfusion imaging *did not provide additional new information.* However, of patients with positive or equivocal exercise ECGs, a substantial number of patients had normal exercise myocardial perfusion images. Thus, in certain patient populations it may be cost-effective to perform exercise ECG as a first test in patients with normal baseline ECGs and repeat the exercise test with added myocardial perfusion imaging only in patients with abnormal exercise ECGs. However, Nallamothu and coworkers showed that in patients with an intermediate to high likelihood of coronary artery disease and normal baseline ECG, SPECT is superior to the ECG response in detecting coronary artery disease.[122]

Stress Myocardial Perfusion Imaging in Non-Coronary Artery Disease

Stress myocardial perfusion imaging has been used in a number of clinical conditions that may be characterized by symptoms of chest pain but angiographically normal epicardial arteries. In a number of these patients, abnormal and "false positive" ^{201} Tl images have been observed. Zeiher and colleagues[180] and others[181] [182] demonstrated abnormal coronary flow reserve in selected patients with such "false-positive" ^{201} Tl images. Cannon and associates found that these patients also had abnormal global and regional systolic and diastolic function.[182] It would appear that at least some of the so-called false-positive ^{201} Tl images in patients with angiographically normal coronary arteries may in fact reveal true abnormalities in endothelial function.

Unique Value of Radionuclide Myocardial Perfusion Imaging in Comparison to Other Diagnostic Modalities

When compared with other diagnostic modalities radionuclide myocardial perfusion imaging has certain distinct characteristics (see also Chap. 13) . (1) An extensive literature has demonstrated that radionuclide myocardial perfusion imaging provides information regarding the pathophysiological significance of disease that surpasses anatomical information. (2) Radionuclide myocardial perfusion imaging provides information that has independent and incremental prognostic value over other clinical and diagnostic information, including the contrast coronary angiogram. (3) Radionuclide myocardial perfusion images are digital count-based images that can be quantified readily. (4) Quantitative radionuclide myocardial perfusion imaging has been shown to be highly reproducible. (5) Diagnostic-quality radionuclide myocardial perfusion images can be acquired in almost all patients, regardless of body habitus or patient cooperation.

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Myocardial Infarct Imaging

From the early days of nuclear cardiology, myocardial infarction was visualized either as a "cold spot" (perfusion defect) or as a "hot spot." Cold spot imaging has been extensively discussed above. When a radiopharmaceutical localizes specifically in an area of recent infarction, the infarct is visualized as a "hot spot." The advantage of hot spot imaging is that it is generally easier to image the presence of a tracer than its absence. The clinical usefulness of infarct imaging still requires clear definition. The diagnosis of acute myocardial infarction in the majority of patients can be readily made on the basis of simple and inexpensive tests such as the ECG and cardiac enzyme analysis.

^{99m} Tc-Sn-PYROPHOSPHATE.

The first clinically useful hot spot imaging of acute infarction was performed with ^{99m} Tc-Sn-pyrophosphate. This imaging agent was very sensitive for detecting acute myocardial infarction from 24 hours to 5 days after the onset of chest pain.[183] The intensity and pattern of ^{99m} Tc-Sn-pyrophosphate uptake were found to be of prognostic significance. At the present time, ^{99m} Tc-pyrophosphate infarct imaging is mainly of historical interest and is performed infrequently in most laboratories.

In occasional patients suspected of having sustained an acute infarction 2 to 3 days prior to hospital admission, ^{99m} Tc-pyrophosphate imaging may be useful to establish the diagnosis at a time when plasma enzymes levels have returned to normal. SPECT imaging appears to be more sensitive than planar imaging. At the present time, cardiac troponins can be used for the same purpose, although the anatomical site is an extent of infarction and cannot be assessed by using these biochemical markers of myocardial

injury.

^{99m} Tc-pyrophosphate is occasionally used to detect cardiac amyloid. For this purpose, ^{99m} Tc-pyrophosphate is a relatively specific, but not very sensitive imaging agent.[184]

INDIUM-111-LABELED ANTIMYOSIN.

The [111] In-labeled murine monoclonal antimyosin binds selectively to irreversibly damaged myocytes. Imaging should be performed 24 hours after injection of the radiopharmaceutical to allow clearance of [111] In from the blood. Typical[111] In-antimyosin images of an acute infarct demonstrate discrete uptake in the myocardium. In addition, substantial liver and spleen uptake may be seen. Clinical studies have shown that ^{111} In-labeled antimyosin is highly specific (100 percent) and sensitive (92 percent) for the detection of acute myocardial necrosis.[185] In addition to positive images in patients with acute myocardial infarction, uptake of ^{111} In-antimyosin has been noted in patients with unstable angina. The intensity and extent of ^{111} In-antimyosin accumulation were of prognostic significance both in patients with acute infarction and in those with unstable angina. Patients with extensive antimyosin uptake, i.e., greater than 50 percent of the myocardium, had a four to nine times increased risk for future cardiac events, i.e., cardiac death and nonfatal myocardial infarction, than did patients with less or no uptake. The positive uptake seen in patients with unstable angina probably represents small clinically undetectable focal areas of necrosis.

In addition to imaging acute myocardial infarction, ^{111} In-antimyosin imaging may have a role in cardiac transplant patients for the detection of cardiac rejection.[186] Furthermore, in patients with active myocarditis, diffuse ^{111} In-antimyosin uptake has been observed.[187] More patients (55 percent) had abnormal ^{111} In-antimyosin images than abnormal endomyocardial biopsies (22 percent). Nearly all patients with abnormal myocardial biopsy findings had abnormal ^{111} In-antimyosin images. More than half of the patients with positive antimyosin images showed improvement in left ventricular function over time, whereas only 18 percent of patients with normal scans improved. This clinical course was independent of the biopsy results. These observations suggest that imaging with ^{111} In-antimyosin provides independent important clinical information in myocarditis. Further studies are needed to define the usefulness of ^{111} In-antimyosin imaging in acute ischemic syndromes and other cardiac diseases associated with cellular necrosis.

Only limited experience exists with ^{99m} *Tc-labeled antimyosin.* [188] The initial clinical results were comparable to those with the ^{111} In label. If this formulation became commercially available, antimyosin imaging might be used more widely for clinical purposes.

^{99m} Tc-GLUCARATE.

^{99m} Tc-glucarate, a glucose analog, accumulates rapidly and specifically in very recent infarctions. This agent is not yet commercially available. In contrast to antimyosin imaging, glucarate imaging can be performed within 30 minutes of injection. Mariani and

colleagues demonstrated a time dependence for positive images.[189] Only patients who were imaged within 9 hours of the onset of chest pain had positive images. If these results can be confirmed, ^{99m} Tc-glucarate imaging could be a very useful imaging agent in selected patients in chest pain centers.

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Assessment of Cardiac Performance

Cardiac performance can be assessed with radionuclide techniques by either of two generic approaches. The first involves analysis of the first transit of a radionuclide bolus through the central circulation (first-pass radionuclide angiocardiogram [FPRNA]). The second, more widely applied method involves analysis following equilibrium intravascular labeling, which allows repeat imaging over several hours (equilibrium radionuclide angiocardiogram [ERNA]).

Variations of each technique involve assessment of the right and left ventricles, diastolic as well as systolic function, regional or global performance, ventricular volume, and adaptations for longer-term or ambulatory monitoring. Although the radionuclide approach for the evaluation of ventricular function has been challenged by echocardiography, these techniques still play a role in the quantitative assessment of cardiac performance. These specific approaches and their clinical implications and applications are discussed below.

EQUILIBRIUM RADIONUCLIDE ANGIOCARDIOGRAPHY

The concept of using a physiological signal such as the ECG to "gate," or physiologically control, the otherwise static imaging of the cardiac blood pool was initially proposed in 1971.[190] The ERNA uses ECG events to define the temporal relationship between the acquisition of nuclear data and the volumetric components of the cardiac cycle. Sampling is performed repetitively over several hundred heartbeats with physiological segregation of nuclear data according to occurrence within the cardiac cycle (Fig. 9-29) . Data are accumulated until the radioactivity count density is sufficient for statistically meaningful analysis. The ECG provides a reasonably sensitive and easily defined physiological signal with which to link the static imaging technique. Data are quantified

and displayed in an endless-loop cinegraphic format for additional qualitative visual interpretation and analysis.

TECHNICAL CONSIDERATIONS.

Because analysis involves the summation of several hundred cardiac cycles, a number of factors must be considered for the study to be deemed adequate. First, the patient must be able to remain relatively still beneath the detector during the period of data acquisition. In general, studies should be obtained with multiple views for interpretation to be complete, including the standard anterior and LAO views, as well as left lateral and/or left posterior oblique views (Fig. 9-30) .

The need for multiple views is inherent in this form of imaging because overlying radioactivity in multiple cardiac and noncardiac structures can obscure a given ventricular region in any one view. In addition, specific abnormalities in regional left ventricular performance, such as ventricular aneurysms or akinesis of the posterobasal segment, may be appreciated only on lateral or posterior oblique views. It is also assumed that cardiac performance remains relatively stable during the entire period of acquisition. Such stability is obviously not the case in the presence of substantial arrhythmia such as atrial fibrillation or frequent premature beats.

The presence of major arrhythmia must be accounted for in interpretation: otherwise, the potential exists for substantially underestimating ventricular performance. Some currently available programs routinely exclude premature beats. Finally, the radionuclide label must also remain stable during the period of analysis, and the interval of data acquisition (framing interval) must be sufficiently short to allow adequate temporal resolution for definition of both systolic and diastolic performance parameters.

PERFORMANCE.

Equilibrium blood pool labeling is achieved by using ^{99m} Tc. The intravascular label is affixed to the patient's own red blood cells by using an in vitro or modified in vitro technique. Unlabeled stannous pyrophosphate is used to facilitate this reaction. The labeling techniques are now well standardized and quality control can be ensured.[191] Following a single labeling procedure, serial studies can be readily obtained for periods ranging from 4 to 6 hours. If necessary, additional labeling can be achieved and the duration of observation extended.

Conventional Anger scintillation cameras are used for these studies. Data are analyzed by computer, generally with some operator interaction. Analysis may be obtained in either the "frame" or "list" mode.[191] Radionuclide data are collected and segregated temporally. In the frame mode, which is used most frequently, the R-R interval of the ECG is divided into 20- to 50-millisecond portions, depending on the patient's intrinsic heart rate and the conditions of the study, i.e., rest or exercise. If one is interested in defining diastolic filling events, a relatively short framing interval is required. The process generally requires 3 to 10 minutes for completion of each view. Following data acquisition, data from the several hundred individual beats are summed, processed, and

displayed as a single "representative cardiac cycle."

Data from the LAO view are also used for qualitative analysis of

Figure 9-29 Diagrammatic representation of the technique for equilibrium radionuclide angiocardiography. Each cardiac cycle is divided into 28 equal segments. For each heartbeat, data are accumulated and then stored in a separate file. To the right, these data for the 28 portions of the cycle are displayed as a single summed ventricular volume curve. The numbers 1 to 28 refer to the temporal sequence within the cardiac cycle. *(From Zaret BL, Berger HJ: Nuclear cardiology. In Hurst JW (ed): The Heart, Arteries and Veins. 7th ed: New York, McGraw-Hill, 1990, p 1899. Copyright © by McGraw-Hill, Inc. Used by permission of McGraw-Hill Book Company.)*

Figure 9-30 Planar and single-photon emission computed tomographic (SPECT) equilibrium radionuclide angiocardiography at rest in a patient with a basal inferior aneurysm after infarction. *Top,* Planar images in the left anterior oblique (LAO), anterior (ANT), and left lateral (LLAT) views. The basal inferior aneurysm is best appreciated in the LLAT view (arrow). *Bottom,* SPECT images of the same patient. Short-axis (SA), vertical long-axis (VLA), and horizontal long-axis (HLA) slices are shown. The basal inferior aneurysm is appreciated on multiple reconstructed slices (arrows). A schematic drawing of the anatomy is shown on the right.

Figure 9-31 Ventricular volume curve derived from an equilibrium radionuclide angiocardiographic study. The raw data have been smoothed with a Fourier filter technique to four harmonics. Note the discrimination of the period of rapid diastolic filling, as well as the atrial contribution to diastolic filling.

global left ventricular function. In this view, overlap of the two ventricles is minimal. In a count-based approach, LVEF and other indices of filling and ejection, are calculated from the left ventricular radioactivity preset at various points throughout the cardiac cycle (Fig. 9-31) . Measurements obtained in this manner correlate well with other defined standards, such as contrast-enhanced left ventricular angiography.

BACKGROUND ACTIVITY.

Because radioactivity is present within the entire intravascular space. It is necessary to correct for the contribution of activity in adjacent intravascular structures to the overall measured left ventricular radioactivity. Major contributions to this "background" come from the lungs and left atrium. Because the left atrium is posterior to the left ventricle in

the LAO view. Its background contribution is substantially attenuated by the more anterior left ventricular blood pool. Semiautomated methods are now routine for determining regions of interest, as well as background zones. With the equilibrium technique, a variable region of interest is used for determining the left ventricular blood pool for each frame of the cardiac cycle. This adaptation is necessary because using a so-called fixed or single region of interest throughout the cardiac cycle introduces error and results in underestimation of the ejection fraction.

INTERPRETATION.

Interpretation of ERNA requires both visual and quantitative analysis. The approximate 45-degree LAO view provides data for quantitative count-based assessment of left ventricular function. In the equilibrium study, quantitative analysis of right ventricular function is difficult because of contamination from overlying anterior right atrial activity. For this reason, right ventricular function is best evaluated by first-pass techniques. The degree of left anterior obliquity must be individualized with consideration of specific patient anatomy and cardiac orientation within the thorax. The degree of obliquity is determined in a manner providing optimal separation of the right and left ventricles ("best septal view"). This relatively straightforward approach can be used by a technologist without physician interaction. The LAO view also provides qualitative information concerning contraction of the septal, inferoapical, and lateral walls. The anterior view provides data concerning regional motion of the anterior and apical segments. The left lateral or left posterior oblique views provide optimal qualitative information concerning contraction of the inferior wall and posterobasal segment.

Ventricular aneurysm can be assessed best in the lateral views as well. Analysis of only the anterior and LAO views may give the false impression of an enlarged, diffusely hypokinetic ventricle, when in fact, additional obscured zones of normally contracting myocardium are present. In addition to a purely visual assessment, a point scoring system can be used for assessing regional function. Each segment is generally graded on a 5-point scale, with specific numerical grades assigned for dyskinesis, akinesis, mild and severe hypokinesis, and normal function.

An advantage of labeling the entire intravascular blood pool involves visualization of all cardiac and vascular structures. Such visual assessment can provide information concerning relative cardiac chamber size and the relative adequacy of contraction of each chamber. In addition, the size, orientation, and pathology of the great vessels can be defined. The relative thickness of the interventricular septum can be appreciated, as can the presence of filling defects representing intracardiac masses such as left atrial myxoma or intraventricular thrombus.

The ERNA can easily be combined with additional physiological stress testing or provocation, which may be in the form of either physiological stress such as exercise, pharmacological stress with positive ionotropic agents such as dobutamine or isoproterenol, or psychological stress.[192] Because equilibrium labeling is stable for the short term, studies can be repeated and can therefore provide multiple stress and control measurements.

VENTRICULAR VOLUMES.

Ventricular volume can also be determined by count-based methods. Because radioactivity at equilibrium is directly proportional to volume, it is straightforward to establish a relationship between volume of a chamber and counts emanating from a region of interest representing that chamber in the two-dimensional display. The study also requires a blood sample to serve as a calibration standard. In addition, radiation attenuation must be accounted for. Attenuation measurement represents the major source of error of the technique. However, volumes measured in this manner correlate well with other analyses. Because the analysis is count based, data are independent of the constraints and errors associated with fitting a deformed left ventricle to a geometrically ideal shape. Count-based approaches are now available to measure volume that do not involve attenuation correction. This innovative new approach substantially simplifies current volumetric analysis.

The ability to measure ventricular volume is quite important because volumetric changes may be critical for analysis of patients with heart failure and severely depressed systolic function. In such individuals, therapeutic benefit may be documented by a reduction in ventricular size while the ejection fraction does not change. Measurement of volume is also key to understanding the process of ventricular remodeling.

QUANTIFICATION OF REGIONAL FUNCTION.

The equilibrium technique has been adapted for quantitative measurement of regional left ventricular function. In the LAO view, measurement is best done by using a regional ejection fraction technique.[193] This technique is based on the same principles used for measuring the global ejection fraction. However, when regional function is assessed, the left ventricular blood pool is divided into several discrete regions with well-established anatomical correlates. The best approach involves division of the left ventricular blood pool into five regions of equal size (Fig. 9-32) . These regions are the upper and lower septal regions and the inferoapical, inferolateral, and posterolateral regions. An upper zone involving the valve planes is excluded.

PHASE ANALYSIS OF CONTRACTION.

Regional function can also be assessed from phase analysis based on the onset, timing, and extent of contraction. The phase and amplitude images can also be used for specific localization of bypass tracts in Wolff-Parkinson-White syndrome, as well as for definition of the site of sustained ventricular ectopy or tachycardia.[194]

OTHER CIRCULATORY BEDS.

With the same study in which an ERNA is obtained, it is also possible to gather quantitative data concerning circulatory beds other than the heart. Since counts are proportional to volume, a relative change in counts provides information concerning

alterations in the volume of various capacitance beds. This approach has been used to assess the effects of exercise and drugs.[195] [196]

Ambulatory Monitoring

Further application of the technique of equilibrium angiocardiography relates to the use of miniaturized equipment suitable for monitoring patients during routine activities. An instrument called the VEST allows for monitoring over several hours following blood pool labeling.[197] It again uses the basic principles of ERNA. The device is worn by patients, so they are fully ambulatory. Radionuclide and ECG data are stored on tape in a manner comparable to use of the Holter monitor for arrhythmia detection. Off-line analysis

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Figure 9-32 A typical regional ejection fraction display obtained from a left anterior oblique equilibrium study. The left ventricle is divided into five sectors. An upper sector involving the valve planes is excluded. These sectors, from upper left to upper right counterclockwise, involve the upper septum, lower septum, apex, and inferolateral and posterolateral segments. In this particular study, regional ejection fraction is decreased in the upper and lower septum, as well as the apex, with maintained contraction of the two lateral segments.

provides trended data concerning ventricular function (Fig. 9-33) . This instrumentation has been validated and standardized in several laboratories and is ready for broader clinical application. A second-generation device with significant technical improvement has recently become available. Initial studies suggest a potential major role for this device in the assessment of silent myocardial ischemia and mental stress.[197] [198]

SPECT Studies

The equilibrium radionuclide technique may also be suitable for application to SPECT studies. At present, work in this area is still relatively early and experimental.[199] This approach may assist in better defining ventricular aneurysms (see Fig. 9-30) . However, tomographic studies may provide optimal radionuclide three-dimensional assessment of global and regional function.[200]

FIRST-PASS RADIONUCLIDE ANGIOCARDIOGRAPHY

FPRNA was the first radionuclide technique applied to the study of cardiac physiology. The initial reports of Blumgart and Weiss appeared in 1927.[201] However, it was not until the early 1970s that the clinical and investigative impact of the measurement was appreciated.[202] The first-pass approach remains a viable alternative to equilibrium studies. At present, it is performed less frequently than ERNA. However, with the recent availability and use of technetium-labeled myocardial perfusion agents, (see p. 273), the

first-pass technique may take on new significance because ventricular function can be assessed by first-pass methods at the time of injection of the perfusion agent before subsequent static perfusion imaging.

TECHNICAL CONSIDERATIONS

The FPRNA technique involves sampling for only seconds during initial transit of the bolus through the central circulation. The high-frequency components of this radioactive passage are recorded and analyzed quantitatively. It is assumed that mixing of the indicator with blood is sufficient that changes in count rates are proportional to volumetric changes. During the initial passage, temporal and anatomical separation of radioactivity within each ventricle should be observed. Therefore, it is possible to analyze right and left ventricular function independently during this brief transit. Regional function can also be assessed from the generated outlines of ventricular silhouettes.

THE SCINTILLATION CAMERA.

In contrast to the equilibrium study, the choice of scintillation camera for the first-pass study is critical. Instrumentation must be used that provides high sensitivity with respect to count rate acquisition. If system linearity is lacking and there are major dead time losses, the data will be inaccurate. For this reason the multicrystal scintillation camera was initially developed. This instrument has since been replaced by second- and third-generation digital cameras that are suitable for rapid acquisition of the high count rate data necessary for first-pass studies.

Several technical issues are relevant to the performance of first-pass studies. First, the injection technique must be impeccable; it is necessary to have a compact radionuclide bolus without streaming. Injections can be made from either the jugular or the antecubital venous systems. Injections at more peripheral sites are not suitable. The presence of major arrhythmia during the evaluation invalidates the data. Because analysis is based on at most 8 to 10 cardiac cycles, the presence of rhythmic irregularity or premature beats negates the validity of the study.

RADIOPHARMACEUTICALS.

^{99m} Tc-labeled radiopharmaceuticals are used for first-pass studies; for the most part, in the past technetium pertechnetate or technetium complexed to either diethylenetriaminepentaacetic acid (DTPA) or sulfur colloid was used. Thus, based on the clearance of individual tracers, multiple injections can be made during a single study. Again, with the advent of technetium-labeled

Figure 9-33 Trended data obtained with the VEST in a patient in whom postmyocardial infarction ischemia is developing. Data for ejection fraction are shown in the *upper panel* and data for relative end-diastolic volume and end-systolic volume are shown in the *lower panel.* Continuous data are shown for a 25-minute period. The times of onset and relief of angina are indicated. The fall in ejection fraction precedes the clinical occurrence of angina. This fall is associated predominantly with a rise in end-systolic

volume, with minimal change in end-diastolic volume. *(From Kayden DS, Wackers FJ, Zaret BL: Silent left ventricular dysfunction during routine activity after thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol 15:1500, 1990. Reprinted with permission of the American College of Cardiology.)*

perfusion agents. It is now also possible to use these perfusion agents for several purposes, including first-pass functional evaluation. In the past, attempts were made to develop additional radiopharmaceuticals suitable for first-pass techniques. However, these short-lived generator systems have been purely investigational and have been used for the most part only in individual laboratories with a specific research interest in their use.

PROCESSING OF FIRST-PASS STUDIES.

The first-pass study is computer processed in frame mode (Fig. 9-34) . Regions of interest are selected over either the right or left ventricle; generally, a fixed region of interest is used. Activity is analyzed only when the initial bolus passes through the specific chamber of interest. This temporal segregation of radioactivity compensates for the potential problem of overlapping regions of interest. Background corrections are necessary, and a variety of approaches have been described. The same approach used for the equilibrium study can be applied to the first-pass technique. In such a manner, global and regional left ventricular performance can be assessed. The first-pass technique is the radionuclide modality of choice for assessing *right* ventricular function.[201] This technique can be carried out in concert with left ventricular analysis as part of a total first-pass evaluation.

GATED FIRST-PASS TECHNIQUE.

Alternatively, a gated first-pass technique can be used at the time of tracer injection for a subsequent equilibrium study. With this latter technique, first-pass data are acquired synchronously with the ECG. They are stored temporally, and several beats are subsequently summed to form a representative cardiac cycle obtained during the right-heart phase. This particular approach provides higher count rate data than could be obtained with simple bolus injection and conventional Anger camera acquisition. The data from this study can also be viewed in an endless-loop cinegraphic format. Unlike the case for the left ventricle, poor contrast-enhanced angiographic standards are available for comparison with right ventricular radionuclide data. For this reason, normal values for the right ventricular ejection fraction have been established independently and the technique standardized. The right ventricular ejection fraction is a highly afterload-dependent measure. The finding of abnormal right ventricular ejection in the absence of intrinsic right ventricular disease is excellent evidence of acquired pulmonary hypertension.[203]

Shunt Studies

The first-pass study can also be used to detect and quantify intracardiac shunts.[204] With this particular approach, a region of interest is selected over the lung field. A pulmonary time-activity curve from the region is analyzed. Normally, a sharp rise and subsequent falloff of radioactivity are observed when the bolus enters and leaves the pulmonary vasculature. A second, lower amplitude peak occurs as a result of normal recirculation of the bolus. In the presence of a significant left-to-right shunt, persistent activity remains

Figure 9-34 Radionuclide time-activity curves obtained from a right ventricular (RV) and left ventricular (LV) region of interest during a first-pass radionuclide angiocardiogram. Each peak plus valley represents a single cardiac cycle. Data from this study are summed to provide RV and LV ejection fractions. *(From Zaret BL, Berger HJ: Nuclear cardiology. In Hurst JW (ed): The Heart, Arteries and Veins. 7th ed. New York, McGraw-Hill, 1990, p 1899. Copyright © by McGraw-Hill, Inc. Used by permission of McGraw-Hill Book Company.)*

in the lungs and washout is relatively slow. Techniques have been developed for applying this approach to quantification of the degree of shunting. The degree of shunting correlates extremely well with oximetry measures of left-to-right shunting. From right-to-left shunting, qualitative assessment demonstrating early appearance of activity in the aorta is often sufficient. Quantitative approaches also exist for defining the degree of right-to-left shunts. At present, this approach has largely been supplanted by Doppler echocardiographic techniques.

Comparison of First-Pass and Equilibrium Techniques

Both the ERNA and FPRNA techniques have advantages and limitations. In addition, any one laboratory should perform the study with which it is most familiar and for which its equipment is optimal. The ERNA has several distinct advantages: (1) Multiple studies can be performed following a single radionuclide injection; (2) regional assessment can be done in as many views as are relevant for analysis: (3) sequential and serial data can be obtained during a variety of control, physiological, and/or pharmacological states; (4) the statistical reliability of high-count rate equilibrium studies is superior to that of the first-pass technique; (5) the entire cardiovascular blood pool may be viewed at equilibrium; and (6) the equilibrium study is less prone to invalidation because of transient arrhythmia than is the first-pass study. On the other hand, additional activity from adjacent or overlying tissue can hinder optimal visualization of a specific ventricular segment in the ERNA. Evaluation of right ventricular performance, as well as shunt detection, is better achieved with the first-pass than the equilibrium technique. While the equipment necessary for performing first-pass studies is more complex, as already stated, first-pass techniques will probably achieve resurgent popularity when combined with perfusion studies involving technetium-labeled agents.

CLINICAL ASSESSMENT OF CARDIAC PERFORMANCE

Diastolic Function (see also Chap. 15)

This function of the ventricles can be evaluated from either an equilibrium or first-pass study, although the former has been more frequently used. A number of indices have been described for assessing diastolic function. The most widely used are the peak filling rate and the time to the peak filling rate. Filling fraction has also been recently studied.[205] High temporal resolution is necessary for performing these studies. Equilibrium studies have often been obtained in list mode so that ectopic or irregular beats can be eliminated from analysis. It is crucial that there be high temporal resolution and reliability of the diastolic filling phase if accurate data are to be obtained. Fourier filtering techniques, in conjunction with polynomial mathematical algorithms, have been applied to volume curves obtained by frame mode equilibrium studies of lower temporal resolution in a manner that provides accurate data.

Assessment of diastolic function has achieved importance with clinical recognition of the entity of congestive heart failure associated with normal systolic and abnormal diastolic function (see Chap. 15) . This complication has been most commonly observed in left ventricular hypertrophy and coronary artery disease, as well as in restrictive cardiomyopathies. Abnormal peak filling rates have been noted in a majority of patients with coronary disease, even in the presence of normal systolic function. Improvement

in filling parameters has been noted following successful coronary angioplasty or after the institution of antianginal therapy. Abnormal diastolic function has been estimated to occur in as many as 30 to 40 percent of patients hospitalized with congestive heart failure.[206]

Follow-up of these patients has indicated substantial cardiovascular morbidity and mortality that is not dissimilar to that of individuals manifesting systolic dysfunction alone.[207] Treatment with verapamil has been shown to improve objective and clinical parameters of heart failure as well as left ventricular filling in such patients.[208] Measurement of diastolic function is an important dimension in the assessment of ventricular performance in patients with heart failure. However, it must be noted that parameters of diastolic filling are age dependent. Abnormal filling proportional to age is noted in the absence of disease.[209]

RESTING VENTRICULAR PERFORMANCE.

Measurement of right and left ventricular performance at rest is clearly of value in the evaluation of patients with congestive heart failure. In the simplest assessment, this particular study can be used to distinguish cardiac from pulmonary or other noncardiac causes of the symptom complex. Resting function is valuable for assessing preoperative surgical risk. The cause of heart failure may be inferred from involvement of the right and/or the left ventricle, as well as the presence of diffuse left ventricular dysfunction as

opposed to regional dysfunction.[191] Systolic versus diastolic heart failure may be differentiated by this study. Relative chamber size may also provide important insight concerning the occurrence of concomitant or primary valvular disease.

Coronary Artery Disease

Perhaps the widest clinical and investigative application of resting radionuclide ventricular function studies has been for the assessment of patients with myocardial infarction. Several reports have documented the importance of prognostic stratification on the basis of global ventricular function as measured by the ejection fraction. The ejection fraction, certainly in the prethrombolytic era, was a key factor in defining prognosis.[210] [211] [212] In the thrombolytic era, the ejection fraction at rest remains an important prognostic index; however, for any level of ejection fraction, mortality is substantially lower than noted in the prethrombolytic period [211] (Fig. 9-35) . The Coronary Artery Surgery Study (CASS) has also shown the importance of prognostic stratification based on the ejection fraction in patients with multivessel disease when survival was compared in patients assigned to surgical as opposed to medical therapy.[213] In patients who have survived out-of-hospital cardiac arrest, the single best prognostic factor has also been the degree of impairment in global function as measured by the ejection fraction.

In addition, the finding of a postinfarction functional left ventricular aneurysm carries further prognostic significance. In one study involving patients with an anterior wall infarction, the finding of aneurysm formation, as defined by nuclear data, provided relevant prognostic information not available from the ejection fraction alone.[214] In the setting of acute infarction, radionuclide studies at rest are also of major value in distinguishing a true aneurysm from a pseudoaneurysm and in distinguishing right from left ventricular infarction.

EXERCISE STUDIES.

Ventricular performance during exercise can be assessed with either equilibrium or first-pass techniques. In general, exercise may be performed in the supine, semisupine, or nearly upright position. A normal exercise response is generally defined by an increment of at least 5 percent (in absolute terms) in the global ejection fraction of both the right and left ventricles. In patients with coronary artery disease, abnormal ventricular reserve is manifested by failure of such augmentation. The finding of a major fall (>5 percent) in the ejection fraction from

Figure 9-35 Relationship of the ejection fraction at rest to cardiac mortality in the Thrombolysis in Myocardial Infarction (TIMI) Phase II study (*black circles*) and Multicenter Postinfarction Research Group Study (MPRG) (*open circles*). Note the comparable shape of both mortality curves and the significantly lower mortality associated with lower ejection fraction levels noted in the TIMI II study. *(From Zaret BL, Wackers FJ, Terrin ML, et al: Value of radionuclide rest and exercise left ventricular ejection fraction to assess survival of patients following thrombolytic therapy for acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II study. J Am Coll Cardiol 26:73, 1995. Reprinted*

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rest to exercise carries with it a poor prognosis. Lee and colleagues have defined the prognostic impact of exercise ejection fraction data.[215] They noted that the exercise ejection fraction itself as an absolute number provides the most relevant prognostic information. The ventricular response to exercise in patients with abnormal resting function may have greater prognostic significance than the extent of coronary disease.[216]

SILENT MYOCARDIAL ISCHEMIA (See also Chap. 37) .

The prognosis associated with ischemia appears to not be affected by the presence or absence of a concomitant pain syndrome.[217] Because it is recognized that radionuclide exercise studies generally add to the sensitivity and specificity of the exercise ECG, it is not surprising that the study of left ventricular function during rest and exercise provides additional information concerning the prognosis in silent ischemia.[218] The ability to detect silent myocardial ischemia during routine activities (as opposed to exercise in the laboratory) is of additional importance. It is within this context that ambulatory ventricular function monitoring has achieved prominence (see Fig. 9-33) . Transient abnormalities in global left ventricular function during routine activity frequently occur silently.

Silent ventricular dysfunction is also relatively common under conditions of mental stress. This phenomenon has been demonstrated in studies using the gamma camera or nuclear probe during several forms of induced mental stress.[191] [198] Regional wall motion abnormalities were readily demonstrated during mental stress in patients with coronary artery disease, with or without an associated abnormal global ejection fraction response. These responses occurred in the absence of major increments in heart rate, which suggests that altered myocardial oxygen supply is the major mechanism. The independent prognostic significance of mental stress-induced ventricular dysfunction has been demonstrated.[219] The major factor involved in triggering an abnormal response appears to be a change in peripheral vascular resistance. In addition, specific patterns of cerebral activation are associated with an abnormal response.[305]

Congestive Heart Failure (see also Chap. 17)

Analysis of left ventricular function is cardinal for the assessment of patients with known or presumed congestive

heart failure. Radionuclide studies provide systolic and diastolic data of relevance. The finding of diastolic dysfunction as the primary pathophysiological abnormality may necessitate the use of a different therapeutic regimen than when systolic dysfunction alone is noted. The radionuclide study can also provide insight into the presence of valvular problems complicating or mimicking heart failure. Serial radionuclide studies provide a basis for monitoring the effects of therapy. In the presence of unexplained

congestive heart failure, the demonstration of intact right ventricular function with abnormal left ventricular function speaks against primary cardiomyopathy as a cause. Generally, the most likely culprits in such a circumstance are coronary artery disease (ischemic cardiomyopathy), hypertensive heart disease, or aortic valvular disease. However, it should be noted that the converse is not necessarily true; secondary pulmonary hypertension and, with this, secondary right ventricular dysfunction may develop in patients with advanced left ventricular dysfunction.

DOXORUBICIN CARDIOTOXICITY (see also Chap. 69) .

A major role for serial radionuclide left ventricular function studies involves the monitoring of patients with neoplastic disease for drug-induced cardiotoxicity. Doxorubicin, a commonly used antineoplastic agent, may be associated with the development of a severe cardiomyopathy that is often both irreversible and ultimately fatal. Radionuclide ventriculography has become established as a means of detecting presymptomatic cardiotoxicity.[220] [221]

Guidelines for patient management with doxorubicin based on resting ejection fraction data have been developed. Retrospective analysis noted marked differences in outcome between individuals who were managed with adherence to the radionuclide guidelines and those who were not. Recent reevaluation of these guidelines has once again demonstrated their utility and clinical relevance.[222]

It appears that the resting ejection fraction provides an optimal means of assessing patients receiving cardiotoxic medication. The addition of exercise stress does not appear to add significantly to this prognostic assessment.

Valvular Heart Disease (see also Chap. 46) .

Rest and exercise ventricular performance studies have been used in the study of valvular heart disease. It has been suggested that left ventricular responses during exercise are of value in patients with aortic and mitral regurgitation with respect to defining the indications for valve replacement, even in the asymptomatic state.[223] At the present time, this general approach is not popular. Resting studies of ventricular performance clearly play a role in the assessment of patients with suspected or known valvular disease in whom surgery is being contemplated. In the context of the mitral regurgitation, such an evaluation may be particularly relevant clinically with respect to the definition of operability.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (see also Chap. 54) .

Patients with chronic obstructive pulmonary disease were studied intensively when radionuclide techniques for assessing the right ventricle were developed initially.[203] It is recognized that the right ventricle is an extremely afterload-dependent structure. The presence of an abnormal right ventricular ejection fraction in such patients strongly suggests the presence of significant pulmonary hypertension. Abnormalities in right ventricular performance can also be related to the degree of ventilatory and

physiological impairment. Right ventricular performance, as measured by the ejection fraction, is responsive to agents that both augment inotropic performance and serve as pulmonary vasodilators.[224]

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Positron-Emission Tomography

PET, long viewed as primarily a research imaging modality, is emerging as a clinically important technique. The uniqueness of PET imaging lies in its ability to image and quantify metabolic processes, receptor occupancy, and blood flow. The main advantages of positron imaging are the ability to label and thus image biologically active compounds and drugs, the higher energy of the positron signal (allowing enhanced count statistics), and the ability to correct for body attenuation, thereby increasing specificity. A major result of these advantages is the ability to derive absolute quantitative measurements with the appropriate kinetic model.

Technical Considerations

Positron-emitting radionuclides are characterized by excess positive charge. This unstable structure results in the emission of a positron (antielectron) from the nucleus, thereby converting a proton to a neutron. The positron travels a few millimeters in tissue; when it encounters an electron, annihilation ensues and results in the release of a photon pair with a characteristic energy of 511 keV. These photon gamma rays travel in opposite directions, 180 degrees apart. Thus, detectors that are placed on opposite sides of a positron decay event should detect each photon emitted at nearly the same time (coincidence). Because the travel of these photon pairs is always 180 degrees apart, when two detectors sense gamma rays coincidentally, the PET camera circuitry records that radioactive decay has occurred somewhere along the line that connects these two detectors. Unlike the collimators used in SPECT imaging, this form of "electronic" collimation, referred to as coincidence detection, increases the sensitivity of the camera and allows more accurate correction for attenuation effects.

While PET images are tomographic, like SPECT, PET cameras are designed to

optimize the detection of high-energy photons (511 keV) and coincident events. PET imaging uses arrays of small stationary crystals/detectors (several thousand detectors are in most cameras) arranged in rings that allow photons to be detected in coincidence. In this manner, multiple tomographic slices are obtained simultaneously in a field of view that can range from 10 to 16 cm.

For most PET systems, attenuation is measured before any radioisotope is injected into the patient by using an external source of radiation, often in the form of a rotating line source. As the source rotates about the patient, PET detectors on the opposite side of the patient measure how much radiation reaches the detector. In this manner, a measurement of the degree of attenuation can be stored, and a correction factor can then be applied to every subsequent emission scan. This technique necessitates that the patient remain in one position during the entire PET study but results in very accurate correction for the effects of attenuation.

PROCEDURES

Current cardiac PET imaging protocols generally follow a prescribed imaging sequence. First, since the field of view of many cameras is relatively small, procedures must ensure that the heart is within the camera's field of view, which can be done by using data from limited transmission scans or by using very small doses of perfusion tracer sufficient to localize the heart. Whenever possible, the patient is positioned with arms above the head since any movement of the arms, if they are within the camera's range, may result in inaccurate attenuation correction. After the patient is made comfortable, a 10- to 30-minute attenuation (transmission) scan is acquired with an external source of radiation. The positron-emitting radionuclide is then injected. The specific imaging protocol depends on the radiotracer used. Allowance must be made for individual variation in the time needed for accumulation and subsequent acquisition of each radiopharmaceutical. For example, metabolic imaging with ^{18} F-FDG requires the injection of 5 to 10 mCi, and 30 to 40 minutes must elapse before FDG image acquisition is initiated. Perfusion tracers, however, do not require such a prolonged period to allow for radiotracer uptake. As noted previously, it is important that the patient not move during the entire study to ensure accurate attenuation correction.

RADIOPHARMACEUTICALS

Positron emitters are unique in several respects. First, the radioisotopes used are naturally occurring, small-atomic weight atoms (carbon [C], nitrogen [N], and oxygen [O]) that are the predominant constituents of organic compounds. Therefore, positron-emitting

TABLE 9-8 -- POSITRON EMITTERS IN CARDIOVASCULAR IMAGING

ISOTOPE	HALF-LIFE	LABELED COMPOUND	APPLICATION
^{18} F	109 min	^{18} F-fluoro-2-deoxyglucose	Carbohydrate metabolism
		^{18} F-fluorodopamine	Adrenergic neuronal imaging
		^{18} F6-fluorometaraminol	Adrenergic neuronal imaging
		^{18} F-misonidazole	Tissue hypoxia
^{13} N	10 min	^{13} N-ammonia	Perfusion
		^{13} N-amino acids (glutamate, alanine, leucine, aspartate)	Amino acid metabolism
^{11} C	20 min	^{11} C-amino acids (alanine, leucine, tryptophan)	Amino acid metabolism
		^{11} C-palmitate	Fatty acid metabolism
		^{11} C-acetate	Myocardial oxygen consumption
		^{11} C-butanol	Perfusion
		^{11} C-hydroxyephedrine	Adrenergic neuronal imaging
		^{11} C-CGP 12177	Muscarinic receptor density
		^{11} C-carazolol	Beta receptor imaging
^{15} O	2 min	^{15} O-oxygen	Oxygen utilization
		^{15} O-water	Blood flow quantification
^{82} Rb	75 sec	^{82} Rb-chloride	Perfusion
^{68} Ga	68 min	^{68} Ga-platelets	Thrombus formation

isotopes of carbon, nitrogen, and oxygen may replace stable counterparts in the synthesis of metabolic substrate, receptor ligands, drugs, and other biologically active compounds without disrupting biochemical properties or activity. ^{18} F is also a suitable substitute for naturally occurring hydrogen because of its strong carbon-fluorine bond and stearic effect similar to that of hydrogen. Secondly, positron-emitting tracers generally have shorter physical half-lives than most single-photon emitters. This property allows for repeat injections as a means of observing rapidly changing events over time. Table 9-8 summarizes the PET radioisotopes, half-lives, and synthesized radiopharmaceuticals suitable for use in cardiovascular medicine.

Clinical Indications

The primary clinical indications for PET studies are for the identification of myocardial viability in patients with established coronary artery disease and regional or global left ventricular dysfunction[225] [226] and for the noninvasive diagnosis of coronary artery disease. In selected patients, the enhanced accuracy of this technique may be clinically important.

Assessment of Myocardial Viability (see also Chap. 37)

As discussed above, accurate assessment of the presence and extent of viable, yet poorly contractile myocardium and its discrimination from purely infarcted tissue are of potential clinical importance. A number of diagnostic techniques are available for assessing myocardial viability. Approaches to viability assessment using radionuclide techniques involve the assessment of myocardial perfusion, cell membrane integrity, or myocardial metabolism. For institutions without PET facilities, myocardial viability is generally assessed with resting ^{201} Tl imaging. Assessment of myocardial viability with ^{99m} Tc-sestamibi is still under active investigation, and results are variable with regard to the assessment of viability.[227] [228] PET imaging is generally regarded as the noninvasive "gold standard" in decisions regarding viability. Identification of viable myocardium with PET is usually based on assessment of metabolism, although certain parameters of perfusion have been shown to be indicators of preserved viability as well. ^{18} F-FDG, a marker of glucose utilization, is the most commonly used metabolic radiotracer. Other metabolic tracers include ^{11} C-acetate and ^{11} C-palmitate as markers of oxidative metabolism.

^{18} F-FLUORODEOXYGLUCOSE.

Metabolism as assessed with FDG traces exogenous glucose uptake. When FDG is exchanged across the cellular membrane in proportion to glucose exchange, it competes for the enzyme hexokinase. The phosphorylated glucose analog FDG 6-phosphate, unlike the native glucose 6 phosphate, is a poor substrate for glycolysis, glycogen synthesis, or the fructose-pentose shunt. It is also relatively impermeable to cell membranes since the enzyme that catalyzes the reverse reaction, glucose-6-phosphatase, is absent or only present in negligible quantities. Therefore, the tracer becomes trapped in the myocardium and its persistent activity reflects regional rates of exogenous glucose uptake and preserved utilization.[229] Viability assessment with FDG is based on the principle that viable myocardium is metabolically active and that ischemic myocardium may in fact have enhanced glucose uptake. Experimental studies have demonstrated that glucose utilization is augmented in segments that are hypoperfused and ischemic but nevertheless viable. During ischemia, energy production is shifted from the oxidation of free fatty acids to that of glucose, and glucose may contribute up to 70 percent of the total energy production. Enhancement of myocardial glucose uptake also occurs in the postprandial state, where insulin levels increase. Clinical assessment of viability with FDG is generally performed in a controlled postprandial state, i.e., after the ingestion of a known quantity of glucose, to promote uniformity of FDG uptake. Since FDG uptake may be abnormally low or abnormally high, it is necessary to have a reference by which to compare its uptake on standard imaging. Thus, assessment of myocardial viability by PET imaging involves a

comparison of regional myocardial perfusion with regional glucose utilization. Myocardial perfusion can be visualized and quantified with flow tracers such as ^{82} Rb, ^{13} N-ammonia, and ^{15} O-water.

The most common PET viability studies are usually performed at rest, with an initial assessment of resting perfusion followed by an assessment of FDG uptake. Since ^{18} F has a relatively long half-life of about 2 hours, imaging does not require an on-site cyclotron. The choice of perfusion tracer may be dictated by the presence or absence of a cyclotron (^{82} Rb is generator produced, whereas ^{13} N-ammonia and ^{15} O-water require an on-site cyclotron). As noted above, subjects are usually given 50 gm of oral glucose just prior to beginning the study to facilitate uniform myocardial FDG uptake. Diabetic patients require glucose monitoring and may need a combination of glucose and/or insulin administration to stimulate myocyte glucose uptake. Initial resting perfusion images are obtained following the intravenous injection of a flow tracer. Then, 5 to 15 mCi of FDG is injected and metabolic images obtained 30 to 50 minutes after injection. Perfusion and FDG images can be analyzed by visual and quantitative activity profile analysis similar to that used in SPECT image processing. Three basic patterns of

Figure 9-36 Three positron-emission tomographic scintigraphic presentations. On each panel, perfusion is represented by NH_3 and glucose metabolism by flourodeoxyglucose (FDG). The *left panel* shows normal homogeneous uptake of NH_3 and FDG. In the *middle panel,* the arrows point to markedly reduced blood flow with preserved glucose uptake in a patient with myocardial viability in an area of an old anterior wall myocardial infarction. On the *right,* the arrows point to concordant reduction in blood flow and FDG in a patient with remote inferior wall myocardial infarction. (Reprinted by permission from Zaret BL, Wackers FJTh: Nuclear cardiology (I). N Engl J Med 329:775, 1993.)

comparative blood flow and distribution of metabolic activity are demonstrable (Fig.9-36). First, there may a match between flow and metabolic activity with homogeneous myocardial distribution of each tracer (normal). Second, regional blood flow may be decreased while glucose utilization in the same area is normal or increased relative to normally perfused myocardium or to the region with reduced blood flow. This pattern of blood flow--metabolism mismatch is the PET scintigraphic signature of myocardial viability in the presence of ventricular dysfunction. Third, regional myocardial blood flow and glucose utilization may be concordantly decreased. This pattern is the marker of myocardial scar and irreversible damage, although mild to moderate degrees of matched defects imply an admixture of viable and scarred myocardium.

CORRELATIONS WITH CLINICAL OUTCOME.

Clinical investigations have consistently demonstrated that preserved viability by PET is associated with improvement in regional wall motion after revascularization, particularly in regions demonstrating flow-metabolism mismatch (diminished flow, increased

glucose uptake).[165] [230] These studies indicate positive and negative predictive accuracies in the 80 to 90 percent range. One of the initial studies that suggested the feasibility of this approach was by Tillisch and colleagues, who evaluated 17 patients with abnormal resting wall motion.[164] Eighty-five percent of myocardial segments that showed preserved glucose uptake in regions of abnormal wall motion improved following bypass surgery. In contrast, 92 percent of segments with depressed glucose uptake in regions with abnormal wall motion did not improve following revascularization. An alternative approach using postexercise FDG PET imaging was used by Marwick and colleagues to determine the spectrum of metabolic responses of hibernating myocardium, as well as predict improvement in exercise capacity after revascularization.[230] Taken together, these studies reinforce the concept that metabolic imaging with PET is a useful tool to predict the reversal of preoperative wall motion abnormalities after successful revascularization.

LIMITATIONS OF FDG IMAGING.

Several limitations of FDG imaging should be mentioned. First, approximately 10 percent of patients with diabetes mellitus will have unreadable studies as a result of inadequate radiotracer uptake. In such patients, an insulin clamp procedure, while technically demanding, may improve the study. In the majority of patients with diabetes, image quality will be good without performing an insulin clamp, and the diagnostic accuracy of the procedure is similar to that in nondiabetics.[231] Second, FDG imaging early (within 1 week) after myocardial infarction is inaccurate, possibly because of the inflammatory response soon after infarction. Finally, although the strength of PET lies in its potential for accurate quantitation of metabolic processes, quantification of regional myocardial glucose uptake with FDG has not been shown to enhance the accuracy of viability assessment over semiquantitative and/or visual assessment.[232] This limitation may in part relate to the fact that differences in FDG uptake versus endogenous glucose uptake may not be accounted for in current techniques.

Studies addressing the ability of modified SPECT camera systems to accept keV photons, specifically, ^{18} F-FDG, have been performed.[233] [234] [235] Such imaging can be accomplished with SPECT technology by using high-energy collimators (single-photon imaging of PET tracers) or with SPECT cameras that have special coincidence circuitry (hybrid PET-SPECT systems). In general, the resolution of SPECT with high-energy collimation is poor, although probably sufficient for clinical cardiac studies. While coincidence detection with hybrid PET-SPECT systems in the practice of nuclear oncology has shown promise, such systems have not been used for cardiac imaging and will probably not be used for this purpose until accurate methods for attenuation correction can be developed. At present, initial studies suggest that FDG SPECT imaging may be a clinically useful and cost-effective means for the metabolic assessment of left ventricular myocardial viability.

Figure 9-37 Static^{11} C-acetate images in a patient within 1 week of an anterior wall myocardial infarction are shown above. The white arrows point to a marked decrease in ^{11} C-acetate in the anteroapical region.

Serial data acquisition over time revealed a marked decrease in ^{11}C-acetate washout in these regions.

Other PET Tracers of Myocardial Metabolism

^{11}C-ACETATE.

Dynamic PET studies of ^{11}C-acetate kinetics provide a noninvasive measurement of regional myocardial oxygen consumption. Unlike FDG PET imaging, the utility of acetate imaging is dependent on accurate quantification of dynamic studies. Also, the short half-life of ^{11}C (20 minutes) necessitates a cyclotron on-site. Therefore, this approach is technically demanding and limited to selected centers. Clearance of ^{11}C-acetate from the myocardium is biexponential. The decay constant of the initial component of the clearance curve is linearly related to myocardial oxygen consumption, and thus analysis of ^{11}C kinetics is thought to accurately reflect myocardial oxygen consumption and thus mitochondrial oxidative flux in human subjects.[236] Furthermore, since initial uptake of acetate is proportional to myocardial blood flow, it may be used to assess perfusion with the same tracer injection.

Despite its complex imaging requirements, the available data on acetate imaging for viability assessment are promising and highlight potential advantages over FDG. Gropler and colleagues quantified myocardial oxidative metabolism by analysis of the rate of myocardial clearance of acetate in 35 patients with ischemic myocardial dysfunction who were undergoing coronary revascularization. Glucose metabolism was assessed preoperatively by analysis of FDG uptake. The predictive value for recovery of regional function was comparable for both techniques, with a trend toward improved accuracy with acetate.[237] The complementary role of ^{11}C-acetate in PET myocardial viability imaging may be its ability to distinguish viable from nonviable myocardium early after acute infarction (Fig. 9-37). In this setting, where myocardial stunning may be predominant, an index of overall oxidative metabolism may be more accurate than FDG.[229] Additionally, because acetate kinetics is not influenced by diabetes, it may be more useful than FDG imaging in diabetic patients with chronic coronary artery disease. Finally, acetate imaging combined with low-dose dobutamine infusion may be more accurate than assessment of oxidative metabolism at rest alone, possibly reflecting the fact that intact "oxidative reserve" may be a useful marker of viability. [238]

^{11}C-PALMITATE.

[11]C-palmitate is a positron-emitting radiopharmaceutical that has been used to characterize fatty acid metabolism experimentally and clinically.[239] Impaired mitochondrial function as a result of ischemia is characterized by slower palmitate clearance and presumably reflects decreased fatty acid oxidation. There is controversy, however, regarding how palmitate kinetics is affected by ischemia, the arterial content of nonesterified fatty acids, and the hormonal milieu. These confounding observations and the observation of increased backdiffusion of altered tracer in myocardial ischemia have limited the usefulness of ^{11}C-palmitate in the evaluation of myocardial ischemia.[240] Currently, this agent is rarely used in PET studies.

PET Perfusion Tracers for Myocardial Viability

The concept that myocardial perfusion tracers alone may be useful in the assessment of myocardial viability rests on several principles. The first principle is that myocardial perfusion and viability are linked and are not independent of each other. In particular, it is understood that myocardial viability is not maintained below a certain threshold of perfusion. Second, as for SPECT perfusion tracers, certain PET perfusion tracers have dual properties, with kinetics that reflects not only perfusion but also cell membrane integrity, a potential marker of viability. Finally, emerging evidence suggests that intact coronary flow reserve may also serve as a useful marker of viability.

PET TRACERS OF MYOCARDIAL PERFUSION.

Myocardial positron-emitting perfusion tracers include ^{82} Rb, ^{13} N-ammonia, ^{15} O-water, and ^{62} Cu-pyruvaldehyde-bis-(*N*-4-methylthiosemicarbazone (PTSM). ^{15} O-water is freely diffusable,[241]

whereas uptake and retention of the other tracers are dependent on both perfusion and cell membrane integrity. ^{82} Rb and ^{62} Cu-PTSM are generator produced and thus do not require a cyclotron. Both agents result in good-quality images for visual and circumferential analysis, although only ^{82} Rb is currently approved by the FDA for this indication. Rubidium is a potassium analog that like thallium, requires the sodium-potassium pump for uptake.[242] Its first-pass extraction is 65 percent.[243] ^{13} N-ammonia is perhaps the most versatile perfusion tracer in that it yields excellent images for visual and circumferential analysis, as well as being quantifiable for analysis of absolute myocardial blood flow and flow reserve. Ammonia has a first-pass extraction rate of 80 percent, and its extraction is in part energy dependent. Finally, ^{15} O-water is an excellent perfusion tracer in theory since its extraction is independent of the metabolic state and its uptake is linear across a wide spectrum of flow values.[244] The requirement for complex analysis to differentiate myocardium from the blood pool and surrounding tissues, however, makes its use more technically challenging.

PARAMETERS OF MYOCARDIAL PERFUSION FOR VIABILITY ASSESSMENT

As noted above, PET perfusion tracers may be used to assess absolute blood flow, flow reserve, or cell membrane integrity. Each of these parmeters has been studied as a potential marker of myocyte viability. Using PET measurements of absolute myocardial blood flow, clinical studies indicate that myocardial regions with blood flow less than 0.25 ml/gm/min are almost always nonviable.[245] [246] Similarly, recent studies have suggested that relative ^{13} N-ammonia activity of less than 40 percent of maximal uptake is associated with nonviable myocardium.[247] [248] While these studies suggest that a certain threshold of flow exists below which viability is not maintained, considerable

overlap is seen in values between viable and nonviable segments in most studies. Also, it is not clear whether the various perfusion tracers exhibit differences in accuracy and whether absolute quantitation of flow is necessary.

More recently, experimental studies have suggested that preserved coronary flow reserve may be a marker of intact myocardial viability.[249] Preliminary clinical studies have likewise demonstrated an association between flow reserve and viability. Marzullo and colleagues compared rest/stress ammonia PET with FDG PET in patients with chronic coronary artery disease and showed that intact coronary flow reserve was associated with preserved metabolic activity on FDG imaging.[250] Similarly, preserved flow reserve has been demonstrated with radiolabeled microspheres even in regions with critical stenosis and left ventricular dysfunction.[251] These data, while preliminary, suggest that intact coronary flow reserve may be an accurate marker of myocardial viability.

Techniques are also available that relate aspects of perfusion tracer kinetics to myocardial viability.[82] Rb is analogous to thallium with regard to uptake and trapping characteristics. Experimental studies indicate that its retention in particular is dependent on intact myocyte viability. Gould and colleagues, who used a background-corrected ratio of early versus late rubidium uptake, demonstrated the feasibility of using assessment of rubidium retention as a marker of viable myocardium. Subsequently, this technique has been shown to correlate well with FDG imaging.[252] Similar preliminary studies have examined how ^{13} N-ammonia kinetics relates to myocardial viability. These studies suggest that measurement of the volume of distribution[253] or late ammonia uptake[254] may enhance viability detection in comparison to perfusion kinetics alone. Therefore, with the development of appropriate analytical methods, it may be feasible to assess both myocardial perfusion and viability with a single injection of a "perfusion" tracer.

PERFUSABLE TISSUE INDEX

The water-perfusable tissue index bases assessment of myocardial viability on the principle that normal or viable myocardium, and not scar, exchanges water rapidly.[255] The technique uses an assessment of the fractional volume of distribution of ^{15} O-water and an estimate of extravascular tissue density derived from from data transmission and ^{15} O-water blood pool images. Preliminary data suggest that measurement of the perfusable tissue index is an accurate predictor of functional recovery both after reperfusion for acute myocardial infarction and after revascularization for chronic coronary artery disease.[255] [256] This technique remains technically demanding and is thus limited to a few academic centers.

PET Imaging for Myocardial Viability in Risk Stratification

Prognostic stratification of patients with coronary artery disease and left ventricular dysfunction has been addressed with metabolic PET imaging. These data are particularly important inasmuch as the preponderance of the literature has used improvement in left ventricular function as a clinical endpoint. Four reports have addressed this issue by performing PET studies of myocardial viability[257] [258] [259] [260]

(Table 9-9) . In each of these studies, patients were characterized as FDG viable or nonviable and then according to treatment with medical therapy or revascularization. Despite methodological differences among studies, the results have been consistent. The mortality rate was significantly lower in patients with a PET mismatch pattern who were revascularized, whereas such patients had very high mortality if medically managed. In contrast, patients with primarily matched perfusion-metabolism defects showed no major differences in outcome whether medically or surgically managed. Thus, these data suggest that intact myocardial viability, in particular, the pattern of flow-metabolism mismatch, is associated with a poor prognosis unless revascularized.

In a related study by Tamaki and colleagues, the prognostic importance of increased FDG uptake was demonstrated in 158 patients with myocardial infarction who were referred for FDG PET and stress ^{201} Tl imaging.[261] Eighty-four patients were monitored for a mean interval of 23 months. This study confirmed that an increase in FDG uptake was the best predictor of future cardiac events when compared with clinical, angiographic, and radionuclide variables. An increase in FDG uptake was also predictive even when a stress ^{201} Tl scan did not show redistribution.

Finally, recent studies suggest that viability assessment with PET may have a significant clinical impact on decisions concerning management in patients with coronary artery disease. In particular, PET imaging may identify a subset of patients with severe ischemic cardiomyopathy who in the presence of a preponderance of viable myocardium may benefit from coronary revascularization rather than transplantation.[257] [262] In one study, one quarter of patients with severe ischemic cardiomyopathy had evidence of viable myocardium in at least five regions.[263] Additional studies are warranted to determine the optimum utilization of PET viability imaging in such patients.

TABLE 9-9 -- POSITRON IMAGING PATTERNS AND MORTALITY IN CORONARY ARTERY DISEASE AND LEFT VENTRICULAR DYSFUNCTION

STUDY	NUMBER OF PATIENTS	VIABLE		NONVIABLE	
		Medical	Revascularization	Medical	Revascularization
Eitzman et al.[257]	83	6/18	1/26	2/24	0/14
DiCarli et al.[258]	93	7/17	3/26	3/33	1/17
Lee et al.[259]	137	10/21	4/49	2/40	2/19
Total	313	23/56	8/101	7/97	3/50
Mortality		41%	8%	7%	6%

Comparison of PET FDG with SPECT Techniques

[201] Tl SPECT.

[201] Tl SPECT is widely used as a means of assessing myocardial viability in centers without access to PET. As previously discussed, modifications to standard stress-redistribution ^{201} Tl imaging have been made to optimize detection of myocardial viability. Early studies showed a consistent underestimation of viability with stress-redistribution ^{201} Tl imaging comparison to FDG PET. Acquisition of late (24-hour) redistribution ^{201} Tl images improves accuracy, but viability is still underestimated in comparison to FDG PET.[264] Two protocols have subsequently proved to be quite accurate for viability assessment: stress-redistribution-reinjection and rest-redistribution imaging.

Several studies have directly compared thallium reinjection and PET FDG imaging in the same patients.[165] [264] [265] [266] Overall, these studies suggest that concordance between these techniques is in the range of 80 percent. A study by Bonow and Dilsizian highlighted the importance of ^{201} Tl defect quantitation to achieve optimal accuracy in comparison to PET. Specifically, the best correlation between FDG was observed in the severest ^{201} Tl defects on reinjection imaging.[165] [266]

Although^{201} Tl imaging appears to be a clinically acceptable substitute for FDG PET, several issues remain unresolved. First, while the concordance of ^{201} Tl imaging is around 80 percent in most series, the potential underestimation of viability even in 10 to 20 percent of patients may not be acceptable in all clinical situations, particularly in patients with very poor left ventricular function. Second, the accuracy of thallium imaging is not likely to improve much further until reliable methods to correct for photon attenuation are developed for SPECT. Third, it is not clear whether gated SPECT imaging will improve the accuracy of viability detection.

^{99m} Tc-SESTAMIBI SPECT.

Studies comparing FDG and ^{99m} Tc-sestamibi SPECT in the assessment of myocardial viability in patients with chronic coronary artery disease have yielded mixed results. Even when quantitative SPECT imaging is used, significant underestimation of myocardial viability has been demonstrated in many studies.[267] [268] [269] [270] [271] In the study by Sawada and colleagues, for example, FDG evidence of viability was present in 47 percent of segments with severe sestamibi defects. Other studies have suggested potential factors that may explain this underestimation. One study revealed that a major portion of the discordance was contributed by the inferior wall myocardial segments, which suggests that inferior wall attenuation may contribute significantly to the underestimation of viability by ^{99m} Tc-sestamibi.[269] [270] Another study compared the two techniques in patients with varying degrees of left ventricular dysfunction and revealed that concordance was worse in patients with severe left ventricular dysfunction than in those with mild to moderate dysfunction.[271] [272] In particular, ^{99m} Tc-sestamibi SPECT

identified only 42 percent of regions with PET flow-metabolism mismatch as viable, which highlights the potential influence of left ventricular dysfunction and/or regional hypoperfusion on the accuracy of sestamibi imaging for viability assessment.[272] Several methods have been proposed to enhance the detection of viable myocardium with ^{99m}Tc-sestamibi, including attenuation correction, administration of nitrates prior to resting imaging, and acquisition of delayed sestamibi images. The degree to which these methods will improve the accuracy of sestamibi imaging in comparison to PET is unclear.

Diagnosis of Coronary Artery Disease

Similar to SPECT imaging, stress-rest PET perfusion imaging may be used for the diagnosis of coronary artery disease and/or the assessment of disease severity in patients with known coronary artery disease. The clinical application of PET in this regard is very similar to that for SPECT; i.e., stress and rest images are obtained with radiotracers that track myocardial perfusion. Although absolute quantification of myocardial perfusion and flow reserve is possible, routine clinical studies for the diagnosis or assessment of coronary artery disease are usually performed with semiquantitative approaches, also similar to SPECT. As noted previously, attenuation correction is always performed with PET imaging, and count statistics are higher than for SPECT. As such, it is theoretically possible to detect smaller and milder defects with PET. Since the patient is required to maintain one position throughout the PET study, however, PET imaging is restricted to the use of pharmacological stressors.

A number of clinical studies have demonstrated that stress-rest PET perfusion imaging has a sensitivity and specificity for the diagnosis of coronary artery disease[75] [273] [274] [275] [276] [277] [278] that generally exceed 90 percent. PET perfusion imaging detects coronary artery disease with similar accuracy in asymptomatic as well as symptomatic subjects,[275] and it is equal to or better than arteriography for monitoring changes in stenosis severity.[243]

While the accuracy of PET perfusion imaging for routine diagnostic imaging is unequivocal, the incremental value of PET over SPECT remains controversial. Certainly, patients likely to have significant attenuation artifacts would be expected to benefit from PET, but this group probably does not represent the majority of patients. Initial studies comparing rest-dipyridamole rubidium PET with ^{201}Tl SPECT demonstrated a significantly higher accuracy of PET for the diagnosis of coronary artery disease.[75] [278] One study suggested improvement in both sensitivity and specificity,[75] while others suggested that the primary benefit of PET over thallium SPECT was increased specificity.[278] Methodological concerns, such as timing of PET versus SPECT acquisitions in relation to stress, and potential referral bias make these studies inconclusive. Studies using ^{13}N-ammonia as the perfusion tracer have likewise demonstrated excellent diagnostic accuracy for the detection of coronary artery disease, but direct comparisons to SPECT imaging are lacking.[275] A major question that remains unresolved is whether the application of quantitative techniques, such as measurement of absolute myocardial blood flow and/or coronary flow reserve (see below), will add incremental diagnostic information to qualitative PET imaging.

Special Applications of PET and Future Directions

The true potential of cardiac PET is its ability to label organic compounds and accurately quantitate radiotracer uptake, thereby allowing assessment of absolute myocardial and brain blood flow, coronary flow reserve, cardiac and brain receptor density, and other potential in vivo markers of cardiac and/or vascular physiology. Cardiac PET has added much to our understanding of a variety of cardiac disorders and will continue to do so with the future development of quantitative techniques. Selected areas in which quantitative cardiac PET may contribute relevant clinical information will be presented.

Coronary Blood Flow and Flow Reserve

The anatomical delineation of coronary artery luminal narrowing by coronary angiography may not accurately reflect the functional significance of coronary artery disease.[279] With stress-rest dynamic PET perfusion imaging, measurements of absolute myocardial blood flow and flow reserve can be determined. The term "flow reserve" is meaningful to the extent that absolute measurement before and after pharmacological intervention is measured. Absolute flow reserve, that is, the difference between stress and rest flow, reflects the cumulative effects of physiological factors such as vasomotor tone, workload, hypertrophy, and coronary stenosis. Relative flow reserve, that is, the ratio of stress to

rest flow, reflects more specifically coronary stenosis independent of these other physiological variables and is thus comparable (with regard to mechanism) to reversible/nonreversible SPECT flow tracers for the assessment of coronary artery disease. In general, stress perfusion imaging is performed after vasodilator hyperemia with either dipyridamole or adenosine. Delineation of absolute myocardial blood flow and determination of flow reserves with PET are powerful noninvasive techniques by which to assess the effects of coronary and other cardiovascular diseases on cardiac physiology.

The contribution of absolute flow measurements with cardiac PET can be demonstrated by several examples. Studies have demonstrated the feasibility of delineating absolute myocardial blood flow in normal individuals[280] and have examined the effects of aging on flow reserve.[281] [282] PET myocardial perfusion imaging using either ^{83} Rb, ^{13} N-ammonia, or ^{15} O-labeled water has identified abnormal perfusion reserve in patients with coronary artery disease.[75] [273] [278] [283] [284] [285] [286] More recently, the performance of quantitative flow measurements for the diagnosis of varying degrees of epicardial coronary stenosis was assessed with dynamic ^{13} N-ammonia PET.[287] Diagnostic accuracy and the sensitivity of coronary flow reserve for the detection of epicardial stenosis greater than 50 percent were high, and specificity was moderately high. Additionally, flow reserve in regions with anatomically normal coronaries in patients with coronary artery disease was lower than that in normal individuals, thus suggesting early

functional abnormalities in vascular reactivity. Abnormalities in coronary flow reserve have also been demonstrated in young patients with insulin-dependent diabetes mellitus despite normal exercise echocardiography and tests of autonomic function,[288] in patients with hypertrophic cardiomyopathy, and in a subset of patients with chest pain and angiographically normal coronary arteries. Taken together, these studies highlight the potential for quantitative perfusion imaging in the assessment of a variety of cardiac disorders.

NONINVASIVE ASSESSMENT OF LIPID LOWERING AND CORONARY PLAQUE REGRESSION

Considerable evidence supports the benefits of aggressive cholesterol lowering in the primary and secondary prevention of coronary events.[289] [290] [291] [292] Initial studies suggest that cardiac PET imaging may be used to assess the effect of therapy on myocardial perfusion in such patients. Longitudinal noninvasive assessment with dipyridamole PET has demonstrated a decrease in the size and severity of perfusion abnormalities in patients with successful vigorous cholesterol lowering during a 90-day intensive cholesterol-lowering treatment plan.[293] These same patients had a final control period without administration of lipid-lowering regimens; repeat rest-dipyridamole PET showed significant increases (worsening) in the size and severity of perfusion abnormalities. PET perfusion imaging has also been used to monitor long-term risk factor modification in patients with established coronary artery disease.[294] In a study of 35 patients, those randomized to risk factor modification that included a very low fat diet, regular exercise, and stress management showed improvement in PET perfusion parameters both during stress and at rest when compared with patients randomized to the usual care. The pathophysiological mechanisms that may account for improved perfusion defects over such a short period of cholesterol lowering are probably not explained by anatomical regression of atherosclerosis but may be more consistent with restoration of endothelium-dependent vasodilatation by a reduction and/or pharmacological manipulation of serum lipids.[295] This concept is supported by observations that coronary flow reserve measured with cardiac PET is abnormal in young patients with familial hypercholesterolemia and is inversely associated with the total serum cholesterol concentration.[296] Similar studies using SPECT imaging to assess the efficacy of lipid-lowering medical therapy are ongoing. These provocative observations provide a basis for future studies with larger populations that would address absolute serial changes in perfusion.

NEUROCARDIAC PET IMAGING

Neurocardiac PET imaging refers to the use of PET to assess either cardiac innervation with specific neuronal radiotracers or central nervous system activation as it relates to the expression of cardiac disease (e.g., chest pain, mental stress-induced ischemia). PET studies of cardiac innervation may include assessment of sympathetic and parasympathetic interactions, neural regulation of the coronary circulation, adrenergic mechanisms in the genesis of arrhythmias, cardiac reflexes, and sympathetic innervation in the failing heart. Visualization of the cardiac sympathetic nervous system has also been performed with ^{11} C-hydroxyephedrine (^{11} C-HED), an analog of norepinephrine. Comparative studies were performed in six normal volunteers and five cardiac transplant patients, the latter representing a model of global cardiac

denervation. The normal volunteers showed homogeneous uptake of ^{11} C-HED and ^{82} Rb. However, the transplant patients, while demonstrating normal blood flow with ^{82} Rb, had markedly reduced uptake of ^{11} C-HED. Subsequently, abnormalities in innervation were associated with abnormalities in coronary blood flow, thus indicating a link between cardiac sympathetic innervation and myocardial blood flow responses.[297] Recently, it has been demonstrated that patients with diabetes exhibit distal dysinnervation with proximal hyperinnervation, potentially indicative of electrical instability in susceptible individuals.[298] These abnormalities have also been associated with abnormalities in myocardial perfusion.[299] Other cardiac neuronal agents that image presynaptic and postsynaptic sympathetic and parasympathetic nerves are under investigation.[300] Furthermore, true postganglionic receptor imaging may be possible with the ongoing development of muscarinic and beta receptor ligands. Assessment of adrenergic receptor density in the myocardium may be of increasing importance in the future. Given the neurohormonal contribution to conditions such as congestive heart failure,[301] acute myocardial infarction,[302] long QT syndrome, [303] and sudden death,[304] PET may play an important role in identifying, stratifying, and monitoring therapy in these patients.

Studies examining the role of the central nervous system in the expression of cardiac disease have focused on two areas: the pathophysiology of mental stress-induced ischemia and silent versus symptomatic demand-induced ischemia. A recent study used PET to measure brain activation during arithmetic mental stress along with simultaneous cardiac echocardiographic monitoring in patients with coronary artery disease and normal subjects. Patients with coronary artery disease had hyperactivation in brain regions that mediate emotion and memory. In addition, the subset of patients with coronary artery disease who became ischemic showed depression of the right hemispheric regions. Furthermore, these mental stress-induced ischemic patients showed bilateral deactivation in the anterior cingulate in the absence of angina. The anterior cingulate has been associated with pain perception. Deactivation of this region may provide insight into the silent nature of mental stress-induced ischemia.[305] Similarly, the absence of angina secondary to demand (dobutamine)-induced ischemia has been investigated. Rosen and colleagues studied two groups of patients with coronary artery disease, one with dobutamine-induced myocardial ischemia *with* angina and the other *without* angina.[306] Patients underwent brain PET imaging at baseline and during dobutamine stress. In both groups of patients, activation of the thalamus occurred during myocardial ischemia, which implies that peripheral nerve dysfunction cannot fully explain differences in pain perception. Subtle differences between groups were noted in cortical activation, possibly indicative of a significant role for central processing of afferent stimuli in the ultimate perception of ischemic pain. The quantification of regional opiate receptors with tracers such as ^{11} C-diprenorphine may deliver important additional insight into silent myocardial ischemia and the central nervous system modulation of specific cardiovascular manifestations.[307]

Future of Clinical Cardiovascular PET Imaging

In institutions in which PET and SPECT are both available, established referral patterns suggest that PET is used in situations where conventional modalities render equivocal results (for example, attenuation artifacts on SPECT imaging or questions about the

presence of viable myocardium). The higher spatial resolution and attenuation correction may justify direct PET referrals when the pretest likelihood of coronary artery disease is low (see also Chap. 13) .[308] Socioeconomic changes have influenced institutions with PET capability to offer PET imaging at a cost competitive with that of SPECT and conventional nuclear cardiology studies. In institutions where SPECT and PET are both available, for reasons stated above, PET viability studies are frequently a final resort for making difficult clinical decisions in high-risk coronary artery disease patients after conventional myocardial perfusion imaging, echocardiography, and coronary angiography have been performed.[228] [258] [309] [310] In the future, cardiac PET may be more widely used if the cost of PET studies declines and regional distribution of PET radiopharmaceuticals or generator-produced radiopharmaceuticals becomes available. These trends are already in place in some locales and may play an important role in the future use of PET in clinical cardiology. Patterson and

colleagues addressed the economic aspects of a multimodality approach to the diagnosis of coronary artery disease with a comparison of stress PET, SPECT, coronary angiography, and stress ECG.[310] Their analysis suggested that stress PET is the most economical, with lowest cost per use in patients with a less than 70 percent pretest likelihood of coronary artery disease. Two future diagnostic indications may provide an expanded role of PET in clinical cardiology: absolute quantification of regional myocardial blood flow and assessment of adrenergic neuronal integrity.

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Special Imaging Techniques

Fatty Acid Imaging

Sixty-eight percent of the adenosine triphosphate (ATP) that is produced within the myocardium under aerobic conditions is derived from fatty acid oxidation. Consequently, for a number of years, efforts have been under way to base imaging of the myocardium on radiolabeled fatty acid uptake to assess myocardial metabolism and viability. The first major efforts involved PET with ^{11}C-palmitate. Because of the rapid turnover of this compound, imaging was difficult and has for the most part been abandoned.

Current efforts focus on radioactive iodine (^{123}I)-labeled fatty acids for imaging purposes.[311] These efforts have achieved the widest use in Japan, as well as in Europe. To date, relatively limited studies have been performed in the United States. Two major types of radiolabeled fatty acids are suitable for imaging. ^{123}I-labeled straight-chain compounds undergo rapid beta oxidation and are then released from the myocardium. Consequently, their turnover rate is relatively rapid. For this reason, compounds of this class are best used for assessing the kinetics of fatty acid washout rather being used to provide static imaging data of the more conventional type iodophenyl pentadecaenoic acid (IPPA).[312] [313] [314] [315] Investigators have demonstrated imaging at rest with associated kinetic evaluation to be of value for assessing viability and functional recovery after revascularization. However, again it must be noted that the rapid washout will present difficulties with respect to high-quality SPECT imaging because of low count statistics.

The second category involves the modified branched-chain fatty acids, which because of the chemical manipulation of their structure, are metabolically trapped within the myocardium. These compounds provide excellent image quality. However, uptake

probably does not reflect beta oxidation. Rather, uptake is based on fatty acid accumulation and the turnover rate of the lipid pool. The compound representing this class is BMIPP, which is 15(*p*-iodophenyl)-3*R,S*-methylpentadecanoic acid. BMIPP is currently the most widely used fatty acid imaging agent. A number of studies have demonstrated disparity between the uptake of a perfusion agent such as thallium or sestamibi and BMIPP, an indication that this tracer is providing information concerning metabolism that is independent of perfusion.[316] [317] [318] [319] [320] BMIPP remains within the myocardium for a protracted period. Only 25 percent is cleared at 2 hours. Sixty-five to 68 percent of the activity remains within the myocyte triglyceride pool. Abnormalities have been seen for a protracted period after an ischemic event, particularly in vasospastic angina, which suggests that delayed imaging with BMIPP may provide a "memory image" of a previously occurring ischemic event that has protracted metabolic consequences. Particularly in Japan, significant work has been done with the use of BMIPP in the setting of coronary artery disease, as well as cardiomyopathy.

Neurotransmitter Imaging

The mammalian heart contains dense adrenergic innervation. On the basis of norepinephrine regional concentrations, a gradient of adrenergic innervation is seen from the atria to the base of the heart, as well as from the base to the apex of both ventricles. In contrast to sympathetic activation, parasympathetic innervation is most evident in the atria, with much less uptake in the ventricular myocardium.

[123] I-metaiodobenzylguanidine (MIBG) has been used most widely to evaluate and image sympathetic innervation patterns.[321] This compound was initially developed for the diagnosis of pheochromocytoma and first used in studies of the human heart in the 1980s. The radiopharmaceutical is an analog of guanethidine and has uptake mechanisms similar to that of norepinephrine at sympathetic nerve terminals. It is transported into cells by uptake 1 and is stored in vesicles but not catabolized. The compound has little pharmacological action. Its uptake within the myocardium correlates with concentrations of norepinephrine in tissue. A problem with MIBG is that it has additional nonspecific uptake (uptake 2) by nonneuronal tissue. Clearance of MIBG from normal human heart is slow (5 to 12 percent in 3 to 4 hours). This rate is consistent with norepinephrine turnover. A significant number of clinical studies using MIBG imaging have been reported in the literature.

Perhaps the most relevant clinical application of myocardial MIBG imaging relates to the study of congestive heart failure.[322] [323] It is well recognized that the adrenergic nervous system plays a major role in the pathophysiology of heart failure, which is also associated with increased plasma norepinephrine levels, reduced cardiac stores of norepinephrine, and desensitization of beta receptors. It is also well recognized that elevated plasma norepinephrine levels have been associated with an unfavorable prognosis in heart failure patients. A number of studies have now demonstrated that an abnormal decrement in cardiac MIBG activity is associated with poor outcome in heart failure. In these studies, myocardial MIBG uptake is expressed as a heart/mediastinal ratio. A ratio of less than 1.2 has been associated with poor prognosis, independent of the ejection fraction.[324] It is likely that MIBG imaging could provide important insight into

the heart failure population, both with ischemic and nonischemic cardiomyopathies.

Abnormal uptake has also been noted in patients with diabetes mellitis. This observation is consistent with altered autonomic innervation in diabetics and could provide at least one explanation for the frequent finding of silent myocardial ischemic in diabetics with coronary disease.[325] Likewise, decreased uptake has been noted following cardiac transplantation.[326] A level of reinnervation is often noted several years after successful transplantation.

In acute myocardial infarction a mismatch has often been noted between perfusion imaging patterns and MIBG patterns, with larger defects noted on MIBG imaging.[327] This finding is consistent with local denervation associated with the ischemic insult. A level of reinnervation has been noted several months after the infarction.

A role for MIBG has also been suggested in certain cardiac arrhythmias. In patients with arrhythmogenic right ventricular cardiomyopathy, abnormal findings on MIBG imaging have frequently been noted in the presence of normal thallium imaging.[328] Additional abnormalities have been noted in patients with prolonged QT syndrome.[329]

The general area of neurotransmitter imaging holds significant potential for studies in patients with cardiac disease. While its major application appears to be in the heart failure population, additional studies in patients with coronary disease, diabetes, and cardiac arrhythmias seem warranted.

Myocardial Imaging with Hypoxia Markers

Imaging of myocardial hypoxia is of significant interest in that such imaging could offer a new approach to the assessment of myocardial ischemia and viability. In addition, an imaging marker for myocardial hypoxia could prove of value in noninvasively defining a regional stimulus for angiogenesis. A good deal of work in this area has derived from tumor imaging. However, major applications have

been made to the study of myocardial hypoxia.[330] [331] Imaging is based on use of a radiolabeled compound that incorporates the nitroimidazole moiety. Recent studies have involved ^{99m}Tc-labeled nitroimidazoles. Two technetiumlabeled compounds have been studied. One represents a class of technetium (V) oxopropylene-amneoxime (PnAO) complexes that is called (BMS-181321).[332] Another recently studied compound is derived from removal of the 2-nitroimidazole moiety from a nitroimidazole-containing ligand. This compound is 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione (^{99m}Tc-HL91).[333] [334]

The nitroimidazoles are believed to diffuse passively across the cell membrane. Once in the cytoplasm of the myocardial cell, nitroreduction occurs with formation of an R-NO_2

radical ion, which is an oxygen-independent step. In the presence of normoxia, the radical interacts with oxygen to yield superoxide and noncharged nitroimidazole. The free radical anion formation is then reversed in the presence of oxygen. The noncharged compound diffuses back out of the cell. Under hypoxic conditions, the radical anion is reduced further and yields a nitroso compound. The reduced metabolites of the nitroimidazole have lower permeability and are retained within the hypoxic cell. The additionally formed hydroxylamines also bind to intracellular macromolecules and are trapped within the cell. As a result, areas of hypoxia are visualized as zones of increased radionuclide uptake. These agents have been tested in pilot experiments both in isolated heart preparations and in canine models of experimental ischemia.[335] [336] [337] Agents also appear to have a threshold level of hypoxemia below which retention will be demonstrated.[338] Issues relating to the target-background ratio and uptake in adjacent organs may at this time limit clinical applicability with the first-generation compounds. However, this new class of compounds presents potential excitement for studying ischemia, regional hypoxia, and angiogenesis.

Molecular Imaging

As nuclear cardiology moves forward into new areas, fundamental advances continue to be made with respect to applying the principles of molecular and cellular biology to myocardial and vascular nuclear imaging. The development of such approaches will ultimately have meaning in assessing diagnosis and prognosis in coronary artery disease, as well as in various forms of myocardial disease and heart failure. Issues relating to the presence of significant atherosclerosis in its earliest phases, vulnerability of arterial plaque, myocardial necrosis, apoptosis, receptor affinity, upregulation and downregulation of receptors, monitoring of endogenous gene expression, and modalities for assessing the efficacy of gene therapy should all be readily achieved in the next era of modern nuclear cardiology techniques. [339]

Vascular Imaging

A significant challenge to nuclear cardiology and to the field of cardiology in general involves the ability to image the components of the vascular wall. In so doing one should be able to define the two extremes of the pathological process: (1) atherosclerosis at its earliest stages, when recognition of the problem could lead to aggressive intervention prior to major cardiovascular events, and (2) plaque vulnerability prior to the development of thrombosis and total occlusion. The issue of imaging the vascular wall will require major innovation with respect to both new radiopharmaceuticals and new instrumentation. In general, it is anticipated that one will be defining areas of interest involving enhanced radiopharmaceutical uptake, which will allow specific issues relating to target size, target-to-background ratio, and system resolution to be appropriately modulated such that reasonable results can be obtained with external imaging. Alternatively, because of the small size and geometry of the lesion, it may become necessary to develop intravascular probes or imaging devices, akin to intravascular ultrasound, to evaluate this emerging area of interest.[340] [340A] This requirement would be particularly true for defining plaque vulnerability.

A number of different targets have already been studied as prototypes for imaging the vascular wall. Initial targets have focused on proliferating smooth muscle cells, macrophages, and lipid pools. One of the newer approaches involves using a radiolabeled murine monoclonal antibody (Z2D3) generated against homogenized human atherosclerotic plaque; the antibody appears to be specific for antigenic components of proliferating smooth muscle cells. To date, the nature of the actual antigen(s) has not been defined biochemically. In the rabbit aorta atherosclerosis model, Narula and associates demonstrated increased uptake of the radiolabeled antibody, which could be imaged in vivo by using relatively simple planar imaging techniques[341] (Fig. 9-38) . The significant increase in uptake was also readily noted on ex vivo imaging and macro-autoradiography. This work has since been extended by Carrio and colleagues, who demonstrated that the radiolabeled antibody could also be used to image atherosclerotic plaque in human carotid arteries[342] (Fig. 9-39) . These investigators used both planar and SPECT techniques in patients who were about to undergo carotid endarterectomy procedures. This study is the first to demonstrate the feasibility of targeting atherosclerotic lesions with a specific radiolabeled antibody against a significant component of the vascular wall.

Figure 9-38 Left lateral oblique scintillation camera images of rabbits injected with ^{111} In-labeled conventional Z2D3 (*A*) and nonspecific antibody (*B*) for visualization of experimental lesions in the atherosclerotic aortic of a rabbit 48 hours after injection. Focal accumulation of Z2D3 is seen (solid arrows) between the vertebral activity (open arrow) and the kidney activity (bottom K). No localization is noted with the nonspecific antibody (open arrow). The in vivo localization of Z2D3 for the animal in figure *A* is seen in the ex vivo image (*C*). The nonspecific antibody does not show localization in the ex vivo image (*D*). *(From Narula J, Petrov A, Bianchi C, et al: Noninvasive localization of experimental atherosclerotic lesions with mouse/human chimeric Z2D3 F(ab)$_2$ specific for the proliferating smooth muscle cells of human atheroma: Imaging with conventional and negative charge-modified antibody fragments. Circulation 92:474, 1995. By permission of the American Heart Association, Inc.)*

Figure 9-39 Scintigraphy with ^{111} In-labeled Z2D3 antibody before carotid endarterectomy. The planar images demonstrate a diffuse increase in antibody uptake in the affected left carotid artery (*A*) as compared with a normal study (*B*). The walls of the arteries are indicated with the arrows. The carotid angiogram revealed 80 percent stenosis of the left carotid artery. *(From Carrio I, Pieri PL, Narula J, et al: Noninvasive localization of human atherosclerotic lesions with indium 111-labeled monoclonal Z2D3 antibody specific for proliferating smooth muscle cells. J Nucl Cardiol 5:551, 1998.)*

Elmaleh and associates applied the concept that ATP and its analogs are significant inducers of aortic medial smooth muscle cell proliferation in cell culture to the development of an imaging approach to the vessel wall.[343] It was hypothesized that ^{99m} Tc-labeled diadenosine polyphosphate could be used for the noninvasive imaging of active atherosclerotic lesions. This radiopharmaceutical was then tested in the same

rabbit aortic atherosclerosis model used by Narula and coworkers for the study of Z2D3. The authors noted significant uptake of the technetium-labeled diadenosine tetrophosphate in vivo as well as ex vivo.

Additional vascular imaging studies have used the principle that endothelin receptors are present on the surface of smooth muscle cells.[344] Since the atherosclerosis is characterized by proliferation and migration of smooth muscle cells, it was believed that imaging with radiolabeled endothelin derivatives could play a role in vascular imaging. A ^{99m} Tc-labeled endothelin analog has been developed and tested in the rabbit atherosclerosis model. Imaging of the atherosclerotic aorta has been demonstrated in vivo and confirmed by tissue counting and ex vivo imaging. Additionally, the degree of uptake of the radiolabeled endothelin derivative correlated directly with the number of smooth muscle cells present in the vascular wall, but it did not correlate with either the amount of macrophages present or the area of maximal plaque thickness.

Atherosclerotic plaque contains large amounts of lipid and cholesterol. Consequently, the lipid pool would also represent an appropriate imaging target. Initial attempts designed to capitalize on this strategy were not successful. However, recently, Tsimikas and coworkers demonstrated the feasibility of this approach and used a radiolabeled monoclonal antibody against oxidized low-density lipoprotein cholesterol as a means of imaging atherosclerotic lesions.[345] In vivo scintigraphy demonstrated significant uptake in the rabbit aorta. In addition, histological and histochemical studies demonstrated uptake predominately in lipid-laden legions of the rabbit aorta; uptake was also greatest in areas with abundant foam cells and in the lipid-rich necrotic core areas of lesions. Such an approach, after appropriate development and calibration, might also provide a means for directly assessing the efficacy of aggressive lipid-lowering therapy on specific atherosclerotic lesions.

Other appropriate targets for vascular imaging obviously include the endothelium, macrophages or monocyte products or attractants, and antigens specific for neovascularization and angiogenesis.[346] With respect to the endothelium, antibodies against adhesion molecules have already been studied with in vitro systems and should ultimately be applicable to nuclear imaging strategies.[347] Nonimaging probe studies with FDG have demonstrated increased uptake at the site of active atherosclerotic lesions, presumably caused by enhanced metabolic activity of the macrophages present in the lesion.[348] Magnetic resonance imaging in experimental tumor angiogenesis has demonstrated that $alpha_V$ $beta_3$ activity can be imaged as an index of angiogenesis in experimental tumors.[349] A similar conceptual approach using nuclear imaging strategies could be readily adapted to the study of angiogenesis.

Apoptosis

Recently, it has been demonstrated that it is possible to image the process of programmed cell death, apoptosis,

Figure 9-40 Imaging cardiac allograft rejection with radiolabeled annexin V. Representative images of an

abdominal cardiac ACI rat isograft and a PVG allograft in ACI host rats 5 days after transplantation are shown. Rats were imaged after injection of technetium-99m and annexin V. Locations of the transplanted hearts are marked by arrows. Intense uptake of annexin V was observed in the cardiac allograft animal (right) versus the lack of visualization of the syngeneic cardiac isograft (left). *(From Blankenberg FG, Katsikis PD, Tait JF, et al: In vivo detection and imaging of phosphatidyl-serine expression during programmed cell death. Proc Natl Acad Sci U S A 95:6349, 1998.)*

with nuclear imaging techniques. Blankenberg and coworkers reported imaging apoptosis based on the principle that annexin V, an endogenous human protein with a high affinity for membrane-bound phosphatidyl serine, can be used in vitro to detect apoptosis before other changes are noted.[350] ^{99m} Tc-labeled annexin V was used to image apoptosis in a number of experimental models in vivo, including

Figure 9-41 Positron-emission tomographic (PET) imaging for detecting the location, magnitude, and persistence of HSV1-tk reporter gene expression. Adenoviral-mediated delivery of the HSV1-tk reporter gene followed by subsequent ^{18} F-fluoroganciclovir ([F-18]FGCV) PET reporter probe trapping is used. Transcription and translation of HSV1-tk lead to the production of HSV1-tk enzyme, which can phosphorylate and thereby trap [F-18]FGCV. *(From Gambhir SS, Barrio JR, Herschman HR, Phelps ME: Imaging gene expression: Principles and assays. J Nucl Cardiol 6:219, 1999.)*

Figure 9-42 Transverse sections through the myocardium of a 300-gm rat injected with 2 mCi of fluorine-18 imaged with a micro-positron-emission tomographic scanner. Imaging time was 30 minutes and reconstructed resolution is 1.8 mm. Notice the clear definition of myocardium from the blood pool. *(From Weber DA, Ivanovic M: Ultra-high-resolution imaging of small animals: Implications for preclinical and research studies. J Nucl Cardiol 6:332, 1999.)*

rejecting cardiac allografts in the rat (Fig. 9-40) . Histological correlation of the presence of apoptosis in regions with increased annexin V uptake was noted. This new technique presents significant opportunities to use concepts of modern cell biology for imaging important pathophysiological processes. By studying both apoptosis and conventional necrosis in myocardium associated with heart failure, insight into potential new therapy can probably be achieved.

Imaging Gene Expression

One of the most exciting new directions in nuclear imaging involves the ability to directly visualize gene expression.[351] This new area of nuclear imaging has enormous potential. As yet, the technology has not been applied to direct study of the heart. However, the principles developed are readily applicable to any organ. Two general approaches have been used. One involves using reporter gene/reporter probe systems to image the expression of endogenous or exogenous genes. The second involves the use of antisense oligodeoxynucleotides that are radionuclide labeled and targeted to a specific

mRNA of a particular gene radiolabeled antisense oligodeoxynucleotide (RASON). Both techniques are still in early phases of study, and both have been applied to in vivo imaging in small animals (mice and rats). One such system using PET involves the herpes simplex virus type I thymidine kinase gene (HSV-1tk) and ^{18} F-ganciclovir (Fig. 9-41) . In this setting, thymidine kinase serves as the reporter gene, which is introduced with any other gene used in a therapeutic manner, and ^{18} F-ganciclovir serves as the reporter probe, which will allow imaging.[352] This imaging probe serves as a substrate for thymidine kinase, which phosphorylates the imaging probe and thereby results in intracellular trapping of the fluorinated marker and consequently the ability to detect the location, magnitude, and persistence of reporter gene expression with PET imaging. Preliminary results are extremely exciting and offer a genetic approach applicable to both PET and ultimately to conventional SPECT technology. While initial studies have focused on exogenous genes, subsequent studies will also involve the imaging of endogenous gene expression.

Many such studies involve mice, in which direct gene manipulation is routine. Consequently, the availability of high-resolution instruments capable of imaging small animals is mandatory. Systems to meet this need have already been designed and developed for both PET and SPECT technologies[353] (Fig. 9-42) . Micro-PET and micro-SPECT systems will shortly be available for widespread use and will probably have a major impact on fundamental scientific and pharmacological approaches that extend far beyond the scope of cardiology.

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Instrumentation

Acquisition and display of a nuclear image are dependent on the detection of radiation emitted from the patient after administration of a radionuclide. In radionuclide cardiac imaging, the radionuclides are either extracted by myocardium or remain in the cardiac blood pool. Several components are required to acquire gamma rays and produce an image, including a scintillation device such as the sodium iodide crystal, which absorbs the gamma rays and generates photons that are converted to an electrical signal by photomultiplier tubes. The electric signal is then amplified and accelerated such that the energy of the gamma ray initially absorbed by the crystal is directly proportional to the height of the generated electrical pulse. Different radionuclides emit at different energies, which allows discrimination between photons from the target and scatter.

Scintillation (Gamma) Camera

The acquisition of nuclear cardiology images is performed with a scintillation camera interfaced with a computer. Radionuclide images are the result of gamma rays passing through several principal camera components: a collimator (for single-photon imaging), a large sodium iodide crystal, and a hexagonal array of photomultiplier tubes.[354] The gamma camera provides an image of the location and intensity of a radiopharmaceutical in the heart. The image is the result of interaction between gamma rays and the camera crystal, which converts part of this energy into light (scintillation). The photomultiplier tubes translate these scintillations into voltage pulses, which are measured as an electrical signal that defines the position at which gamma rays

and the crystal interact. Such localization is accomplished by electronic circuits that compute *x* and *y* coordinates of crystal interaction and display this interaction in a two-dimensional matrix anatomically analogous to the site of occurrence within the patient. A multichannel analyzer (pulse height analyzer) defines the appropriate energy of the event; thus, low-energy (Compton) scatter events are not accepted. Most cameras have the capability of selecting more than one energy window, potentially allowing simultaneous dual-energy acquisition (a single isotope with more than one gamma emission or two isotopes with different gamma emissions). A crucial part of quality control involves periodic "balancing" of the photomultiplier tubes to ensure uniformity of the amplification and resultant image.

Characteristics that influence overall performance of the gamma camera are spatial resolution, sensitivity, maximum count rate, and field of view. Spatial resolution is the ability of the camera to differentiate two sources of activity in space. It is measured in terms of "full width at half maximum" (FWHM) and expression of the amount of blur. Typical gamma camera resolution is 4 to 5 mm without collimation and 6 to 10 mm with collimation. Sensitivity refers to the ability of the camera to detect incident photons. Intrinsic sensitivity reflects the sensitivity of the gamma camera itself and is dependent on crystal structure, crystal thickness, and the energy of the incident photons. Extrinsic sensitivity reflects the sensitivity of the system with a collimator and is much lower than intrinsic sensitivity. Crystals of most gamma cameras are composed of 1/4- to 5/8-inch-thick NaI. Cameras specifically designed to image high-energy photons (e.g., ^{18}F) may have thicker crystals at a minor loss of spatial resolution. The maximum count rate refers to the camera's ability to record counts over time. Most general-purpose gamma cameras have maximum count rates in the range of 300,000 counts per second, and multicrystal cameras have significantly higher count rate capabilities.

COLLIMATION

For single-photon imaging, collimation is important for appropriate localization of the radioactive event in space and serves as the primary means to reject scatter. A collimator is composed of lead channels designed in either a parallel, convergent, or diverging manner. Gamma rays must pass through the collimator before reaching the crystal. The purpose of the collimator is to approximate the origin of the photon emission within the patient to an analogous location within the crystal. Parallel-hole collimators are of either the high-resolution or high-sensitivity variety. A high-resolution collimator permits better spatial resolution (the ability of the detector source to discriminate between neighboring sources of activity and visually resolve various components within the field of view), but with a loss of count sensitivity (the number of counts acquired per unit time). Alternatively, a high-sensitivity collimator maximizes count sensitivity at the expense of spatial resolution. A compromise between the two types of collimators is the low-energy all-purpose or general all-purpose collimator, which is intermediate with respect to sensitivity and resolution. The thickness of the crystal and the type of collimation determine the sensitivity of a gamma camera. The type of collimation used for a particular study is based on these simple concepts. For instance, a parallel-hole

high-sensitivity collimator would be appropriate for rapidly acquired studies such as first-pass blood pool studies.

COMPUTING

The computer is a principal component of all nuclear imaging systems. These data processing systems are interfaced with the gamma camera. The routine use of computers makes radionuclide imaging intrinsically quantitative. The computers have software containing algorithms for quantification of both static and dynamic digital images. The principal hardware components of the computer include an analog-digital converter, central processing unit, image memory, mass storage, an array processor, and a display monitor. The scintigraphic matrix is generally 64 × 64 or 128 × 128 pixels (picture elements).

Single-Photon Emission Computed Tomography (SPECT)

SPECT acquisition is the most widely used imaging technique in cardiovascular nuclear medicine imaging. Planar images, however, are still routinely used for equilibrium gated blood pool imaging. With SPECT, a series of planar images are obtained over a 180- to 360-degree arc around the patient's thorax.[11] Transaxial images are re-created by using a technique called filtered backprojection, although iterative reconstruction, which may be better suited to nuclear imaging, is currently being developed. These transaxial images are reconstructed into short-axis and horizontal and vertical long-axis orientations relative to the anatomical axis of the heart. The overall result is an improvement in anatomical contrast up to five to eight times that of a planar image, but at the expense of some decrease in spatial resolution. SPECT imaging requires diligent attention to detail with regard to the parameters set for acquisition and more stringent quality control measures. The most important parameters for SPECT imaging are the number of views obtained, the number of counts, and pixel size. Also, it should be emphasized that patient movement during the scan will significantly degrade the image.

Although the first SPECT camera systems used single heads, i.e., one gamma camera, most systems sold today have multiple (two or three) heads. The addition of more heads increases sensitivity and decreases imaging time. Some dual-headed camera systems also have movable heads that allow a configuration either 90 or 180 degrees apart. Cardiac SPECT acquisitions can be obtained over 180- or 360-degree orbits and with circular or noncircular orbits. The relative merits of each of these approaches remain a subject of study.

TECHNICAL ADVANCES

GATED SPECT.

Gated SPECT imaging is now routinely performed in many laboratories and allows for simultaneous measurement of both left ventricular perfusion and function. Using the same principle as for equilibrium gated blood pool imaging, SPECT acquisition is gated to the ECG, and the cardiac cycle is sampled over 8 to 16 frames. It is crucial that the

patient be in a regular rhythm during the acquisition of a gated SPECT study. Arrhythmias have a serious degrading effect and make assessment of left ventricular function unreliable. Images are then displayed in a cinegraphic mode to allow visual analysis of ventricular wall motion, and methods have been developed to determine LVEF from these digital images.[28] [29] [30] Gated studies are preferably performed with ^{99m} Tc-based perfusion tracers because the high photon flux ensures good-quality images.

ATTENUATION CORRECTION.

One of the major limitations of SPECT imaging in clinical practice is suboptimal specificity, which is probably caused by attenuation artifacts from the breast or diaphragm. Attenuation artifacts are often recognized by their characteristic[355] [356] appearance and location, but such methods are subjective and may not reliably distinguish artifactual defects from real defects. Normal data bases for circumferential profile analysis and gated SPECT imaging have been used to enhance specificity. Ideally, however, unique nonuniform attentuation masks are computed to correct for attenuation in each individual patient. A variety of investigational methods using fixed and moving line sources, various collimator configurations, and reconstruction algorithms have been developed for measurement and correction for attenuation. Clinical results, however, remain mixed, and the methodology requires further development.

Scattered photons are perhaps the major source of degraded image quality.[192] Accurate scatter correction would signify a major improvement in radionuclide image quality. Methods are under development to correct for scatter by using techniques such as convolution subtraction (from emission data) and transmission-based approaches. Recently, a combined attenuation and scatter correction transmission-based method was evaluated in a multicenter trial of patients with and without coronary artery disease.[15] Although normalcy rates improved with attenuation/scatter correction, overall receiver operator characteristic curves were no different, and the ability to detect multivessel disease was reduced.

QUANTIFICATION.

Quantification of SPECT myocardial perfusion images is generally performed by assessing the count in a given region relative to the maximum count in the image. Short-axis slices are generally used, and counts are sampled over evenly spaced angles. The maximum or mean count values then can be plotted against the angle at which they were encountered, and circumferential profiles can be generated.[26] This approach has several advantages. First, the profiles can be used as a more quantitative confirmation of what is seen by visual analysis alone. Second, profiles can be created for normal populations and can then serve as normal data bases. Third, the profiles can be used to assess both the severity and size of a perfusion defect in quantitative terms. Fourth, use of such quantitative analysis in concert with normal data bases reduces interobserver variability and thus improves the consistency of test performance. A variety of programs have been developed that are based on these circumferential profile-based concepts. Some programs display selected short-axis slices and graphs of

profiles, while others display polar maps ("bull's-eye" images) for an overall overview of perfusion in a single image.[25]

TELEMED/NETWORK.

Advances in network-based telemedicine initiatives will probably develop into a useful tool for the nuclear medicine community. Applications of such technology include improvement in access to diagnostic imaging services in remote areas,

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facilitation of consultation with expert readers, and development of an almost unlimited data base for teaching cases.

MICROIMAGING.

Small animals are often used for initial experimental studies in areas such as vascular biology, genetics, biochemistry, and metabolism. The development of imaging systems tailored specifically for small animals (e.g., mice, rats) may open new possibilities in the research of novel imaging applications. Recently, a PET scanner dedicated to the imaging of small animals has been developed.[357] This system uses lutetium oxyorthosilicate crystals arranged in a 17.2-cm diameter ring. The usable resolution for this system is in the range of 2 to 2.5 mm with typical filtered backprojection and a potential resolution of 1.2 mm with newer reconstruction algorithms.[358]

IMAGING OF POSITRON-EMITTING RADIOISOTOPES WITH SPECT SYSTEMS.

Primarily driven by the clinical impact of FDG imaging in the area of oncology, considerable interest has been expressed in developing techniques to image FDG with modified SPECT cameras. Initial studies have relied on the use of high-energy collimators and increased shielding of detector heads. Although the spatial resolution of such a system is poor, this approach has been shown to be feasible for myocardial viability assessment.[359] Recently, extensive research and development have been devoted to dual-purpose camera systems that can function as SPECT cameras but also have coincidence detection capability and thus function as "part-time" PET cameras. These systems tend to have resolution approaching that of dedicated PET systems, albeit with substantially reduced sensitivity. Methods for attenuation correction are not yet fully developed for these dual systems.

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GUIDELINES
CARDIAC RADIONUCLIDE IMAGING

Thomas H. Lee

Guidelines for the use of cardiac radionuclide imaging have been difficult to develop and apply for several reasons. As is true for most diagnostic tests, there have been no randomized trials comparing outcomes for patients who did and did not undergo nuclear cardiology tests; nor have there been large trials comparing these tests with competing technologies. Furthermore, there has been rapid evolution in radionuclide imaging technologies, in which both the number and the complexity of choices for clinicians have increased.

An American College of Cardiology/American Heart Association (ACC/AHA) task force issued guidelines for use of cardiovascular nuclear imaging tests in 1995.[1] These guidelines are relatively old in comparison with other ACC/AHA guidelines, but the themes of the ACC/AHA guidelines for nuclear imaging have not been contradicted by subsequent guidelines. As with most ACC/AHA guidelines, this task force designated some indications for cardiac radionuclide imaging as generally appropriate (Class I) and generally inappropriate (Class III). Equivocal indications for nuclear cardiology tests are divided into two groups: Class IIa (weight of evidence in favor of usefulness) and Class IIb (can be helpful but are not well established by evidence).

Acute Myocardial Infarction

The ACC/AHA guidelines indicate that nuclear cardiology tests have a limited role in the diagnosis of acute myocardial infarction and should be used only when the history,

electrocardiogram, and chemistry test results are less reliable. Technetium-99m pyrophosphate scanning was considered potentially useful (Class IIa) for patients who presented more than 24 hours and less than 7 days after the onset of symptoms, and radionuclide angiography can be used to support the diagnosis of right ventricular infarction by demonstrating a reduced right ventricular ejection fraction and right ventricular asynergy. However, nuclear tests were considered inappropriate for routine use for diagnosis.

For evaluation of prognosis *after* acute myocardial infarction, stress myocardial perfusion imaging was considered appropriate (Class I) to assess whether further myocardium is in jeopardy (Table 9-G-1) . The method used to provoke ischemia can be physical exercise or pharmacological, although these guidelines noted that the safety of dipyridamole and adenosine testing that is performed 2 to 3 days after admission "remains to be established." The guidelines do not address settings in which radionuclide imaging would be preferred over standard exercise electrocardiography. However, as described in guidelines to Chapters 6 , 35 , and 36 , other, more recent guidelines from ACC/AHA task forces have concluded that exercise electrocardiography should be the first-line test for patients who can exercise and whose electrocardiograms lend themselves to interpretation with stress testing.

Radionuclide angiography was considered useful for assessment of ventricular function after acute myocardial infarction and also can help detect aneurysms and mechanical complications such as an infarct-related ventricular septal defect. However, the ACC/AHA guidelines imply that for assessment of mechanical complications, nuclear cardiology testing is a second-choice technology that should be used when echocardiography is not available or definitive.

Unstable Angina

The ACC/AHA task force identified two principal issues for which radionuclide imaging techniques are potentially useful in patients with unstable angina: assessment of myocardial viability and prediction of future cardiac events in patients whose angina is successfully stabilized with medical therapy. Therefore, the two indications that were considered clearly appropriate (Class I) were use of stress myocardial perfusion imaging to detect ischemia and use of radionuclide angiography to assess baseline left ventricular function. Myocardial perfusion imaging was also considered potentially useful (Class IIa) for patients with ongoing ischemia who undergo imaging at rest. The use of rest myocardial perfusion imaging was considered less definitive (Class IIb) in patients in whom the diagnosis of myocardial ischemia was unreliable after consideration of routinely available clinical data.

Chronic Ischemic Heart Disease

The ACC/AHA guidelines considered exercise or pharmacological myocardial perfusion imaging to be appropriate (Class I) for identification of the extent and severity of ischemia and localization of ischemia in patients with chronic ischemic heart disease. The guidelines considered thallium-201 and technetium-99m to be sufficiently similar to

be used interchangeably in this patient population. Review of data on the three most commonly used agents in pharmacological perfusion imaging (dipyridamole, adenosine, and dobutamine) led the ACC/AHA writing committee to conclude that their diagnostic performances were in the same range as exercise testing.

Asymptomatic Patients

The ACC/AHA guidelines did *not* consider cardiac radionuclide imaging an appropriate routine test for diagnosis of coronary artery disease

TABLE 9-9-G-1 -- ACC/AHA GUIDELINES FOR USE OF EXERCISE OR PHARMACOLOGICAL MYOCARDIAL PERFUSION IMAGING

Class I (Appropriate)

1. Prognostic stratification after acute myocardial infarction.
2. Identification of ischemia in patients with unstable angina.
3. Identification of extent and severity of ischemia in symptomatic patients and selected patients with asymptomatic myocardial ischemia.
4. Planning PTCA--identifying lesions causing myocardial ischemia if not otherwise known.
5. Risk stratification for selected patients before noncardiac surgery.
6. Assessment for restenosis after PTCA for symptomatic patients.
7. Assessment of ischemia in symptomatic patients after CABG.
8. Assessment of selected asymptomatic patients after PTCA of CABG, such as patients with an abnormal electrocardiographic response to exercise or those with rest electrocardiographic changes precluding identification of ischemia during exercise.

Class IIa

1. Identification of severity/extent of disease in patients whose angina is satisfactorily stabilized with medical therapy.
2. Diagnosis of anomalies of coronary circulation in adults with congenital heart disease.
3. Detection and assessment of functional significance of concomitant coronary artery disease in patients with valvular heart disease.

Class IIb

1. Assessment of drug therapy upon myocardial perfusion.
2. Assessment of coronary arteriopathy after cardiac transplantation.

Class III (Inappropriate)

1. Screening of asymptomatic patients with low likelihood of ischemic heart disease.

ACC/AHA = American College of Cardiology/American Heart Association; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angiography.

From Guidelines for Clinical Use of Cardiac Radionuclide Imaging. A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Committee on Nuclear Imaging). J Am Coll Cardiol 25:521-547, 1995.

in patients who are not symptomatic. However, a stress radionuclide test (either perfusion imaging or radionuclide angiography) can be useful for determining the need for coronary angiography for asymptomatic patients with positive exercise electrocardiography tests. The use of a stress radionuclide test can also be valuable in asymptomatic patients with known coronary artery disease to determine the presence and severity of inducible ischemia.

Before Noncardiac Surgery

Several studies have demonstrated that abnormal dipyridamole- or adenosine-thallium-201 scintigraphy identifies patients at increased risk for cardiovascular complications associated with noncardiac surgery (see Chap. 61) . Most of these investigations have focused on vascular surgical procedures, but some data indicate that these tests can also be expected to help stratify patients according to risk associated with other types of major operations. However, because the overall risk involved in elective noncardiac surgery is low, the positive predictive value of abnormal tests is only between 15 percent and 30 percent. Therefore, the ACC/AHA guidelines concluded that noninvasive testing is not needed in most patients undergoing nonvascular surgery because their cardiac risk is low.

Before and After Revascularization Interventions

Myocardial perfusion imaging can be useful in planning percutaneous coronary interventions (PCI) procedures by providing insight into the functional impact of single or multiple coronary artery stenoses. This type of imaging can also be used after PCI to assess whether restenosis has occurred and for patients who become symptomatic after coronary artery bypass graft (CABG) surgery, to determine whether grafts may have occluded. However, the ACC/AHA guidelines on nuclear imaging did *not* endorse routine testing for patients who are asymptomatic after PCI or CABG because of the lack of data that outcomes are improved with this approach. These conclusions are consistent with more recent guidelines from the ACC/AHA on exercise testing.[2]

Myocarditis and Cardiomyopathies

With the exception of assessment of ventricular function with radionuclide angiography, there were no indications for the use of nuclear cardiology tests in patients with

myocarditis and cardiomyopathies that were considered clearly appropriate (Class I) by the ACC/AHA task force. Thallium-201 scintigraphy was believed to be potentially useful (Class IIa) for the purpose of differentiating ischemic and dilated cardiomyopathy and assessment of myocardial ischemia in patients with hypertrophic cardiomyopathy. Other indications for testing in patients with myocarditis or cardiomyopathies, such as gallium-67 imaging to demonstrate myocardial inflammation, were considered possibly useful but unproven (Class IIb).

Other Conditions

Echocardiography is the imaging technology of choice for patients with congenital heart disease, but first-pass radionuclide angiography and lung perfusion scanning can be used to detect, localize, and quantitate shunts. For patients who have undergone cardiac transplantation, the use of radionuclide tests to detect rejection or coronary arteriopathy is not well established (Class IIb). Similarly, cardiac nuclear tests are not directly useful for assessment of patients with valvular heart disease, except for assessment of left ventricular function.

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Chapter 10 - Newer Cardiac Imaging Modalities: Magnetic Resonance Imaging and Computed Tomography

CHARLES B. HIGGINS

MAGNETIC RESONANCE IMAGING OF THE HEART

Magnetic resonance imaging (MRI) has several important attributes that make it intrinsically advantageous for cardiovascular diagnosis. First, a high natural contrast exists between the blood pool and the cardiovascular structures because of the lack of signal from flowing blood with the spin-echo MRI technique or the bright signal from blood with the gradient-echo (cine MRI) technique. When the spin-echo technique is used, blood appears black on images; therefore, internal structures of the heart can be visualized within the signal void of the cardiac chambers. With the use of the gradient-echo technique, the blood pool appears white and has substantially higher signal than the myocardium, again providing good edge definition of the endocardial margin. Consequently, contrast medium is not required for discrimination of the blood pool, making MRI an entirely noninvasive imaging technique. Second, a wide range of soft tissue contrast provides the potential for the characterization of myocardial tissue. This contrast among tissues depends on proton (hydrogen nuclei) density, magnetic

relaxation times of the protons, and magnetic susceptibility effects. Myocardial tissue characterization is improved with the use of MR contrast media. Third, imaging can be done in any plane, including those parallel and perpendicular to the major axis of the ventricles. Fourth, blood flow can be measured in any cardiac chamber or blood vessel using velocity encoded MR.

MAGNETIC RESONANCE GLOSSARY

Brief descriptions of the MRI process, general imaging techniques, and specific imaging techniques for the heart are given here, along with some useful terminology for MRI. A more detailed description of the principles underlying MRI is available elsewhere.[1]

ECHO-PLANAR IMAGING (EPI).

A method for obtaining MR images in 30 to 50 milliseconds. Multiple lines of the image matrix are acquired after the initiating radiofrequency (RF) pulse. In EPI, a very rapid series of echoes is generated by rapidly switching a strong phase-encoding gradient in the presence of a weaker read gradient. Data for all points in the image matrix can be obtained with a single pulse repetition (single PR). Image quality is increased by acquiring every second (or third or fourth) line of the image matrix with each initiating RF pulse. This sequence is called interleaved EPI.

FREE INDUCTION DECAY (FID).

The signal produced by the release of energy absorbed by the nuclei from a previously applied RF pulse. The FID is the signal analyzed in MRI and spectroscopy. The signal obtained with FID is related to field inhomogeneities.

GRADIENT-ECHO IMAGING SEQUENCE.

A method by which images are acquired more rapidly than with spin-echo imaging by substantially reducing the repetition time (TR). The technique uses a flip angle of 90 degrees or less and a short TR. This reduction is achieved by switching the read gradient to focus the signal rather than by a time-consuming refocusing RF pulse. Contrast on these images is very different from that for spin-echo images. A major difference is that blood flow produces a strong signal and appears bright.

HYDROGEN DENSITY (SPIN DENSITY, PROTON DENSITY).

Density of protons at a site in a sample that is resonating as part of the MR process. From the point of view of quantum mechanics, these are the protons making transitions from high-energy states to lower-energy ones and vice versa, when energy just equal to the difference between these two states is applied.

MAGNETIC MOMENT.

Intensity and direction of the net magnetic field of spinning nuclei. In a magnetic field, nuclei align to produce a net magnetic moment parallel to the field.

MAGNETIC RESONANCE IMAGING (MRI).

Spatial two- or three-dimensional map of nuclei resonating at a characteristic frequency when placed in a magnetic field and subjected to intermittently applied RF pulses.

MAGNETIC RESONANCE SIGNAL.

During relaxation after cessation of an RF pulse, energy absorbed from this pulse is released and provides an RF signal.

MAGNETIC RESONANCE SPECTROSCOPY.

Spectrum of resonant frequencies of a specific nucleus contained within a sample. This spectrum results from the chemical shift of a nucleus caused by the influence of the local chemical environment. Consequently, the resonant frequency of phosphorus in the inorganic state is slightly different from its frequency in creatine phosphate. MR spectroscopy detects and maps these chemical shifts of a nucleus.

MULTINUCLEAR MRI.

Imaging using nuclei other than hydrogen, such as sodium-23 and phosphorus-31.

PROTON MRI.

Imaging dependent on the concentration and relaxation time of hydrogen nuclei.

PROTON SPECTROSCOPY.

Spectrum of resonant frequencies of hydrogen nuclei (protons) in relation to the chemical environment. Proton spectroscopy can define chemical peaks representative of substances such as fats, water, lactic acid, choline, and carnitine.

PARAMAGNETIC SUBSTANCES.

Substances that alter the natural relaxation times of nuclei undergoing the MR process. These are usually molecules with unpaired electrons that reduce the relaxation times of resonating nuclei. These substances are being used and developed as contrast media

for MRI.

RELAXATION.

Return of nuclei to the original state of alignment with a magnetic field after having been tilted by an RF pulse.

RELAXATION TIMES.

Relaxation of nuclei undergoing the MR process has two components, called T1 and T2 relaxation times. These relaxation times are time constants, measured as the magnetization vector processes into alignment with the magnetic field after perturbation by an RF pulse.

RESONANT FREQUENCY.

Each nucleus that is sensitive to the MR process must be tilted in the magnetic field by a specific frequency (resonant frequency) to induce resonance. When this frequency is applied, the nucleus is rotated away from its equilibrium alignment with the magnetic field. When the RF pulse ceases, the nucleus realigns with the magnetic field through a process of magnetic relaxation.

SEGMENTED CINE GRADIENT-ECHO IMAGING.

Multiple image lines are obtained during a phase of a cardiac cycle using a gradient-echo sequence. It is done to permit a cine gradient-echo acquisition during breath holding.

SPIN-ECHO IMAGING SEQUENCE.

Images are produced by sampling the signal after an initial 90-degree RF pulse, followed by one or more 180-degree pulses. The 180-degree pulse refocuses spins and thereby enhances the signal from them. A signal is sampled some time after the 180-degree pulse. The signal is usually lost from the flowing blood, producing low signal from the blood pool.

SURFACE COILS.

RF receiver coils placed upon the surface of the subject or upon an organ of interest to detect the MR signal. These coils increase the efficiency and signal strength for both MRI and spectroscopy.

T1 RELAXATION TIME.

Also called spin-lattice or longitudinal relaxation time. T1 relaxation is a measure of the

exponential rate of growth of the magnetization vector along the direction of the external magnetic field after the nuclei have been tilted (flipped) by an RF pulse. T1 values vary with the magnetic field strength.

T1-WEIGHTED IMAGE.

Image in which the intensity of image voxels depends greatly on the T1 relaxation time of tissues. For the spin-echo technique, this is done with a short TR and echo delay time (TE). T1 weighting is done by setting TR
T1 of tissue and TE
T2 of tissue.

T2 RELAXATION TIME.

Also called spin-spin or transverse relaxation time. Immediately after cessation of a 90-degree RF pulse, the nuclei process in phase, resulting in a magnetization vector in the transverse plane. There is gradual dephasing of nuclei, leading to cancellation of the magnetization vector in the transverse plane.

T2-WEIGHTED IMAGE.

Image in which the intensity of image voxels depends heavily on the T2 relaxation time of tissues. For the spin-echo technique, this is done with a long TR and TE. T2 weighting is accomplished by setting TR
T1 of tissue and TE
T2 of tissue.

TE.

Echo delay time. Time between the initiation of a pulse sequence (90-degree pulse) and the sampling of the spin-echo signal. For the spin-echo sequence, this sampling is done after the 180-degree pulse. For example, the first spin-echo signal is sampled at a time that is twice the duration between the initial 90-degree pulse and the 180-degree refocusing pulse.

TR.

Pulse repetition time. The interval between sets of RF pulses that are used to acquire the necessary lines of the image matrix. For the standard spin-echo and gradient-echo sequence one line is acquired for each TR. With fast sequences, multiple lines of the image matrix are acquired within each TR.

TECHNICAL ASPECTS

Atomic nuclei with a net charge have a magnetic moment. A net charge exists when a nucleus contains unpaired (an odd number) protons, neutrons, or both. The hydrogen

nucleus contains only a proton; it is positively charged and has a strong magnetic moment. The magnetic properties of nuclei are expressed when they are placed in an external magnetic field. When protons or other nuclei with magnetic moment lie within a magnetic field and are then exposed to electromagnetic radiation (RF waves), energy is absorbed and subsequently emitted. This absorption and release of energy causes resonance-nuclear MR. The RF necessary to induce resonance has to be proportional to the local magnetic field (H_L) and a constant (magnetogyric ratio [g]) related to the specific nucleus involved. The relationship between frequency (f) and magnetic field is expressed by the following equation:
$f=gH_L /2pi$

When nuclei at equilibrium in a magnetic field are irradiated at the resonant frequency, they attain a higher energy state. When they return to equilibrium, they emit energy at the same frequency if the magnetic field remains constant. If the magnetic field changes between the time of excitation and emission, then the emission occurs at a frequency corresponding to the new field strength as expressed by this equation. The physics and techniques of MRI are discussed in greater detail elsewhere.[1]

Localization of Magnetic Resonance Signal

Magnetic resonance imaging depends on the reception of the emitted RF signal from resonating nuclei and on the capability of locating these nuclei in space. Location of the resonating nuclei can be achieved by spatially varying the field strength in a known manner. Because resonance frequency of a nucleus at a specific site is related to local field strength, the emitted frequency characterizes the spatial location of the nucleus when a magnetic gradient exists in one or more planes.

Selection of a transverse section for imaging is done by applying a magnetic gradient along the Z axis (long axis of the body). In such a gradient, each transverse plane (XY plane) has a specific and different resonant frequency. If the body is irradiated with a 90-degree RF pulse consisting of a narrow range of frequencies corresponding to the resonance frequency of a single plane, only the nuclei in that plane resonate *selective irradiation* and the image plane is delineated.

Once a plane is excited by selective irradiation, spatial localization is attained in that plane by another gradient oriented parallel to that plane. After the selective 90-degree RF pulse is applied, a magnetic field gradient is produced in the X or Y direction. Nuclei at the stronger end of the field gradient resonate at a higher frequency than those at the weaker end of the gradient. This provides spatial localization within the selected plane.

MAGNETIC RESONANCE SIGNAL INTENSITY

The magnetic signal from a sample undergoing MRI is detected by an RF receiver coil. The intensity of the signal at foci in the imaging plane depends on the concentration of resonating nuclei at the site and the magnetic relaxation times of the nuclei. The relaxation times are measures of the interaction of the resonating protons with the static

magnetic field and the intermittently applied RF pulses.

The net magnetic moment of nuclei at any site can be expressed as a vector with length (intensity) and direction. At equilibrium, the vector points along the main static magnetic field. The vector can be tipped 90 degrees by the application of an RF pulse. The component of the net magnetic moment that points along the main magnetic field is called *longitudinal magnetization.* The component at 90 degrees to the main field is the *transverse magnetization.* The component at 90 degrees to the main field is fully aligned with the magnetic field (equilibrium); the vector varies continuously between longitudinal and transverse magnetization and gradually approaches full longitudinal magnetization.

MAGNETIC RELAXATION TIMES

After the application of a 90-degree RF pulse, net magnetization is rotated from the longitudinal direction (ZY plane) into the transverse direction (XY plane). At this instant, transverse magnetization is maximum

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and longitudinal magnetization is zero. Immediately after this, longitudinal magnetization recovers toward its equilibrium value. This exponential growth has a time constant called *T1*. Likewise, after the 90-degree pulse, transverse magnetization exponentially decays; the time constant is called *T2*. In tissues, T2 is much shorter than T1. These relaxation times are related to several characteristics of tissues, including temperature. Tissues have different relaxation times, and these differences contribute to contrast among tissues during imaging. Contrast between two tissues can be accentuated by sampling signal at an instant when the difference between the relaxation times of the two tissues is maximal. Another term, T2*, is the effective T2 relaxation time, which is much more rapid due to movement of spins in static gradient fields. This value is greatly influenced by spatial inhomogeneity of the magnetic field and substances including contrast media, which induce local macroscopic and microscopic susceptibility variations in tissue.

IMAGING, TR, AND TE.

The MR image is produced by applying the sets of RF pulses many times over several minutes; generally, 128 to 512 pulse sequences are used. The time between application of sets of RF pulses is called the *repetition time* (TR). Depending on the technique employed for imaging, each set consists of one or more RF pulses. The time between the initial pulse in a sequence and the instant when a signal is acquired from the sample is called the *echo delay time* (TE). It is possible to alter the pulse sequences in such a way that differences in T1 and T2 relaxation times among the tissues can be accentuated to produce contrast among these tissues. This is referred to as *T1* or *T2 weighting of the images.* T1-weighted images have short TR and TE intervals, whereas T2-weighted images have long TR and TE intervals when using the spin-echo technique. T1 and T2 weighting for new fast-imaging techniques is achieved to some

extent by variations in the flip angles induced in the nuclei by the initial RF pulses.

EFFECTS OF MOVING BLOOD.

During an imaging sequence, the motion of nuclei through the region that is being imaged greatly influences signal intensity. Although the influence of blood flow on MR images is complex, motion of the excited nuclei causes either a loss or an increase of signal intensity, depending on the RF pulse sequence employed. For the spin-echo sequence, moving blood in the lumina of vessels appears dark (no signal), providing considerable natural contrast for visualization of the internal surfaces of the blood vessels and walls of the cardiac chambers (Fig. 10-1) . Because contrast medium is not required to mark the blood pool, MRI is a totally noninvasive technique for cardiovascular diagnosis. When blood velocity is such that protons move through the thickness of the tomogram (usually 5 to 10 mm) in the time between the 90-degree and 180-degree pulses of the spin-echo sequence, signal is lost from the blood. When using standard spin-echo sequences, this time (TE/2) is usually 5 to 15 milliseconds for the first such image. Any residual signal in the blood flow can be nulled on spin-echo images by applying a preparatory (inversion) pulse with the spin-echo technique to create black blood images (Fig. 10-1) . For the gradient-echo pulse sequence, signal is received from blood flowing at normal velocities in the cardiac chambers and all blood vessels. The signal of flowing blood increases in proportion to the rate of flow (velocity) over a moderate range of velocities until a plateau of nearly constant signal is reached. In this circumstance, blood appears substantially brighter (white) than the cardiac walls (Fig. 10-2) . With jet flow at very high velocities, signal is lost. This loss of signal from high-velocity disturbed flow in jets can be minimized by the use of short TE (5 milliseconds). High-velocity jets produced by flow across stenotic or regurgitant valves can be recognized as a signal void within the signal-filled cardiac chambers (Fig. 10-3) .

Cardiovascular Imaging Techniques

Cardiac imaging usually requires some form of physiological gating of the imaging sequence. Acquisition of MR signals of the thorax without gating results in poor cardiac images, owing to loss of the signal from moving structures and to the variable position of the cardiac structure relative to imaging pixels when data are acquired indiscriminately throughout the cardiac cycle.

Figure 10-1 Fast spin-echo image in the short-axis plane. The blood pool is black (signal void), producing sharp demarcation of the endocardium. *(Courtesy of Kevin King, General Electric Medical Systems.)*

GATING WITH MRI.

Gating during MRI presents unique challenges. Sensors, wire leads, and transducers are usually composed of ferromagnetic materials, which can generate noise or may grossly distort the images within the RF-shielded room containing the MRI device. Consequently, gating with MRI requires the use of a nonferromagnetic physiological

signal-sensing circuit. An electronically isolated electrocardiogram (ECG) electrode-lead circuit containing very little metal has been used for repetitive synchronization (i.e., ECG gating) of pulse sequences to fixed segments of the cardiac cycle. ECG gating is done prospectively for some sequences (spin-echo) or retrospectively for others (cine gradient-echo).

ECG-GATED SPIN-ECHO IMAGING.

The techniques used in MRI of the heart depend on the primary goals of the procedure. When the evaluation of anatomical abnormalities is paramount, the use of the ECG-gated spin-echo technique provides static images with high signal-to-noise ratios. The spin-echo technique is used with prospective ECG gating; each R wave initiates a new 90-degree pulse. Thus, the TR is equal to the RR interval. The signal is sampled at the TE time. In the center of each TE interval, a 180-degree refocusing RF pulse is applied to accentuate the signal. With standard spin-echo imaging, one line of the image matrix is acquired at each anatomical level for each RR interval. This sequence usually displays flowing blood as black on the image (signal void) (see Fig. 10-1) . Another approach is to acquire multiple echoes from the same anatomical level during each RR interval. This decreases the time for acquisition of an image and is called fast spin-echo imaging.

ECG-REFERENCED GRADIENT ECHO (CINE MRI).

Cine MRI is important for the evaluation of ventricular and valvular functions. This technique uses narrow flip angles (<90 degrees) and gradient-refocused echoes. Because the TR and TE values are 5 to 30 milliseconds and 1 to 15 milliseconds, respectively, the cardiac cycle can be divided into about 16 time-frame slices. Lacing these slices together in a cinematic format permits construction of tomograms of the beating heart. The blood pool has bright signal on cine MR images (see Fig. 10-2) .

The cine MRI techniques is used to measure ventricular volumes and ejection fraction and for quantification of regional contraction. It also provides identification of abnormal flow across valves, cardiac defects, and vascular stenoses.

Figure 10-2 A series of gradient echo (cine MR) images in the short-axis plane acquired at end-diastole extending from the base *(top left)* to the apex *(bottom right)* of the heart. The blood pool is white, producing sharp demarcation of the endocardium. This three-dimensional data set can be used to measure directly ventricular volumes and mass. a=aorta; la=left atrium; lv=left ventricle; P=pulmonary artery; ra=right atrium; rv=right ventricle. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

It permits identification of valvular stenosis and regurgitation (see Fig. 10-3) .

BREATH-HOLD (SEGMENTED) CINE MRI.

Fast gradient-echo imaging techniques are important for MRI of the heart. For conventional spin-echo and gradient techniques, one line of the imaging matrix (usually 128 to 256 lines compose the imaging matrix) is acquired for each TR interval (RR interval for gated acquisitions). With fast gradient-echo imaging, multiple lines (usually eight) are acquired for each RR interval. This reduces the acquisition time by a factor that equals number of lines acquired, so that a cine acquisition can be done in a breath-hold period of 12 to 14 seconds (breath-hold cine MR imaging).[2]

CONTRAST-PREPARED FAST GRADIENT-ECHO IMAGING.

This fast imaging method uses very short TR and TE intervals for gradient-echo acquisition with a course matrix (64 to 128 lines) to produce low spatial resolution images in about 600 to 2000 milliseconds. These are sometimes called fast gradient-echo or turbo gradient-echo images. These can be weighted for T1 and T2 contrast by applying a preparation pulse before the imaging sequence, such as an inversion recovery (180 degree) pulse before the image sequence to produce T1 weighting. These sequences have been initially applied to provide 1- to 2-second monitoring of the initial passage of injected contrast medium through the central circulation and myocardium to evaluate regional myocardial perfusion.[3] [4]

VELOCITY-ENCODED CINE MRI.

Blood flow volume and flow velocity can be quantified using velocity-encoded cine MRI (velocity flow mapping).[5] This technique provides a velocity image (velocity map or phase image) at evenly spaced intervals, usually 16, throughout the cardiac cycle. Analysis of the velocity image can be done to measure peak velocity or average velocity in any selected region of interest across the vascular lumen or flow channel. Velocity-encoded sequences can be used with either standard cine MRI or breath-hold cine MRI. Using the multiple phase images collected over the cardiac cycle, flow- or velocity-versus-time curves can be made.

ECHO-PLANAR IMAGING (EPI).

EPI is the fastest MRI technique. It can provide an image in an acquisition time of 40 to 50 milliseconds (Fig. 10-4) . The acquisition can be done so that all lines in the image matrix or K space are acquired in a single TR interval (single-shot EPI) or in a few (usually two to four) sequential TR intervals (multishot or interleaved EPI).[6] EPI sequences can be either spin-echo EPI or gradient-echo EPI. In addition, preparatory pulses can be used to increase the T1 weighting of the imaging; inversion recovery EPI is very sensitive to T1-contrast effects, such as those produced by low doses of MR contrast medium.[7]

MAGNETIC RESONANCE ANGIOGRAPHY (MRA).

MRA employs a variety of flow-sensitive MR sequences in an

Figure 10-3 Cine MR image in the coronal plane at mid diastole. There is aortoannular ectasia with an aneurysm of the ascending aorta and aortic insufficiency (flow void emanating from the closed aortic valve). *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

attempt to maximize the signal from flowing blood and suppress the signal of surrounding tissue.[8] One type depends on the inflow of blood into a slice or a volume that is continuously exposed to repetitive RF pulses. The repetitive RF pulse depletes the signal of stationary tissue while the inflowing blood retains signal, causing high contrast between the vessels and surrounding tissue. This is called the time-of-flight technique. Another type depends on the difference in the change of phase of spins in motion compared with stationary spins during the RF pulse sequence. This is called the phase contrast technique. With either type, the data can be collected from multiple adjacent slices in a sequential manner (two-dimensional [2D]) or

Figure 10-4 Echoplanar images (interleaved acquisition) at end diastole *(left)* and end systole *(right)* in the short-axis plane. Note the sharp contrast between the blood pool and myocardium, permitting accurate measurement of ventricular volumes and regional wall thickening.

Figure 10-5 Contrast medium-enhanced three-dimensional MR angiogram of the chest. Maximum intensity projection image is shown in coronal plane.

simultaneously from a specified volume of tissue (three-dimensional [3D]). Thus, the MRA methods are 2D time-of-flight, 3D time-of-flight, 2D phase contrast, and 3D phase contrast techniques. At the current time, the most popular techniques are the time-of-flight methods.

The use of 3D time-of-flight method in the chest requires the use of MR contrast media. Moreover, data collection is done during a breath-hold period to avert breathing artifacts. The imaging data are acquired during the time of peak opacification of the arterial structures of interest. Acquisition of the 3D data set in a breath-hold period is realistic for most patients (15 to 25 seconds) and is accomplished by employing very short TR (5 seconds or less). This technique can provide exquisite images of the

thoracic aorta and pulmonary artery (Figs. 10-5 and 10-6).

IMAGING PLANES.

Imaging can be done in any plane desired. The plane is specified before imaging, and the tomograms

Figure 10-6 Contrast medium-enhanced three-dimensional MR angiogram of the chest in the coronal plane demonstrates partial anomalous pulmonary venous connection from left upper lobe to a vertical vein (arrow) connecting to the left brachiocephalic vein. A=ascending aorta; S=superior vena cava.

are produced in the specified plane. As opposed to some techniques, such as computed tomography (CT), the images obtained in the sagittal and coronal planes are directly acquired rather than reconstructed planes; there is no loss of spatial resolution in these planes in comparison to the transverse plane. Most MRI studies of the heart have been done in the transverse plane, with supplemental studies obtained in the coronal and sagittal planes in some instances. However, these three planes are orthogonal to the body as a reference structure but produce oblique sections of the heart, because the heart is oriented in the thorax at approximately a 45-degree angle to the sagittal plane. Consequently, images parallel (long axis) or perpendicular (short axis) to the long axis of the heart are sometimes needed. Preliminary images, usually in the transverse or coronal plane, are done to calculate the angle of the slice-selective gradient needed for acquiring short- or long-axis images (see Figs. 10-2 and 10-7).

EVALUATION OF SPECIFIC CARDIOVASCULAR DISEASES BY MRI

The clinical use of MRI has been primarily for the demonstration of pathological anatomy. However, in the past few years MRI has been used for the quantification of global and regional function of the right and left ventricles, for the quantification of valvular heart disease, for the measurement of blood flow in the heart and great arteries, and for the assessment of myocardial perfusion and even coronary blood flow. MRI also offers several approaches to evaluation of myocardial viability. Precise demonstration of anatomical abnormalities has been useful for the evaluation of patients with ischemic heart disease, cardiomyopathies, pericardial disease, neoplastic disease, right ventricular dysplasia, congenital heart disease, and thoracic aortic disease.

Figure 10-7 Cine MR images acquired in vertical long axis *(left)* and horizontal long-axis *(right)* planes.

Ischemic Heart Disease

Recent advances in technology provide capabilities by which MRI could evolve as a comprehensive imaging technique for ischemic heart disease (see also Chap. 13) .[9] In this regard, morphology can be assessed with the ECG-gated spin-echo and cine MRI techniques, permitting determination of the extent of wall thinning caused by previous infarctions and depiction of complications of infarctions, such as true and false aneurysms. Segmental myocardial function can be quantified by measuring the extent of regional wall thickening or wall motion on standard or breath-hold cine MRI. Moreover, regional myocardial ischemia can be demonstrated by analysis of regional myocardial wall thickening in the basal state and during pharmacological stress induced by dipyridamole or dobutamine.[10] [11] NMR spectroscopy may furnish a noninvasive way to evaluate myocardial ischemia due to microvascular disease in individuals with chest discomfort but lacking significant epicardial coronary artery disease.[11A] By using a variety of approaches, breath-hold cine MRI can produce images of the major coronary arteries. Breath-hold velocity-encoded techniques can be applied for measuring coronary blood flow or velocity at rest and during interventions intended to test coronary flow reserve.[12] [13] Finally, contrast-prepared fast gradient-echo imaging can be used to evaluate myocardial perfusion in the basal and vasodilated states to identify myocardium jeopardized by coronary arterial stenosis.[14] [15]

MORPHOLOGY.

MRI provides direct visualization of the myocardium with excellent delineation of the epicardial and endocardial interfaces. Consequently, it can define accurately segmental wall thinning that indicates previous myocardial infarction. In some patients with a history of transmural infarction, residual myocardium can be demonstrated at the site of the infarction. In others, MRI shows virtually complete absence of remnant muscle. Direct visualization of the myocardium can be used to determine whether sufficient residual myocardium remain in the region jeopardized by a coronary arterial lesion to warrant a bypass graft. Regional wall thickening can also be assessed. It has been shown that a wall thickness of less than 6 mm at end diastole and wall thickening of less than 1 mm

Figure 10-8 Gradient echo image in an oblique coronal plane demonstrates the small ostium (arrow) connecting the large false aneurysm (A) with the left ventricular chamber. Note the severe wall thinning in the posterior and diaphragmatic regions of the left ventricle. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

indicate myocardial scar when compared with uptake of technetium-99m sestamibi single-photon emission tomography, positron emission tomography, and recovery of region function after myocardial revascularization.[16] [17] [18] [19]

The recognition of decreased signal intensity of the myocardial wall at the site of old myocardial infarction suggests that MRI can identify the replacement of myocardium by fibrous scar. Gated MRI has also demonstrated complications of myocardial infarctions, such as left ventricular thrombus and aneurysms (Fig. 10-8) . Transverse or short-axis tomography facilitates the recognition of the small ostium connecting the left ventricular chamber and the false aneurysm (see Fig. 10-8); this is a distinguishing feature of the false compared with the true left ventricular aneurysm.

Acute myocardial infarctions have been demonstrated by gated MRI. The region of ischemically damaged myocardium

Figure 10-9 Coronal T1-weighted spin-echo images in the coronal plane before *(left)* and after *(right)* injection of a gadolinium chelate contrast medium in a patient with a recent infarction of the diaphragmatic wall of the left ventricle. The infarcted region is indiscernible before contrast medium. The infarcted myocardium (arrow) enhances to a greater degree than normal myocardium after contrast medium, resulting in demarcation of the infarcted region. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

Figure 10-10 Sets of short-axis cine MRI image acquired in the basal state *(left, A)* and after "pharmacological stress" induced by dipyridamole *(right, B).* In each set, images are shown at end diastole *(upper left),* early, mid, and late systole *(lower right).* In the basal state wall thickening is normal in all regions. After dipyridamole, there is markedly reduced wall thickening in the diaphragmatic region (open arrow). *(From Baer FM, et al: Coronary artery disease: Findings with cine GRE and Tc99m methoxy-isonitrile SPECT during simultaneous stress. Radiology 193:203, 1994.)*

displays increased signal intensity compared with normal myocardium.[20] [21] Contrast between infarcted and normal myocardium increases on images with greater T2 contribution to signal intensity. Administration of MR contrast medium (gadolinium chelates) with T1-weighted spin-echo images causes greater enhancement of infarcted than of normal myocardium[22] [23] (Fig. 10-9) .

Regional Contraction Abnormalities.

The major role of noninvasive imaging techniques in ischemic heart disease is the detection of ischemic myocardium and other features indicative of the presence of obstructive coronary arterial disease. Ischemic myocardium can be demonstrated directly or indirectly by MRI. Indirectly, it is shown by demonstrating a regional contraction abnormality, usually by wall thickening measurement, at rest or during pharmacological stress (Fig. 10-10) . Cine MRI in the basal state and during pharmacological intervention with dobutamine or dipyridamole has correlated closely

with nuclear perfusion imaging and/or coronary arteriography for demonstrating potentially ischemic myocardial segments.[10] [11] Directly, the monitoring of the first-pass distribution of MR contrast medium with T1-sensitive fast gradient-echo imaging in

Figure 10-11 Two-dimensional MR angiogram of the right coronary artery (arrow). The distal right coronary artery and part of the posterior descending artery (arrow) can be visualized. *(Courtesy of Kevin King, General Electric Medical Systems.)*

Figure 10-12 *A,* Short-axis magnitude *(left)* and phase *(right)* images from breath-hold velocity-encoded cine MRI acquisition in baseline state and vasodilated state induced by dipyridamole. The left anterior descending (LAD) artery (arrow) is imaged perpendicular to the direction of blood flow. *B,* Velocity-versus-time curve of the LAD artery in baseline and vasodilated states. Peak diastolic velocity increased by a factor of more than 3, indicating normal vasodilator reserve. RV=right ventricle; LV=left ventricle; ECG=electrocardiogram. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

basal and vasodilated states has shown regions of decreased myocardial perfusion in association with coronary arterial stenosis.[14] [15]

Visualization of Coronary Arteries.

Among noninvasive imaging modalities used in ischemic heart disease, MRI promises to visualize the major coronary arteries, using newly developed MR angiographic techniques[24] [25] [26] (Fig. 10-11) . An early report has shown approximately 90 percent correlation between coronary MRA and coronary x-ray angiography for identifying hemodynamically significant coronary arterial stenoses or occlusions.[24] Subsequently, reports have shown variable sensitivities and specificities.[25] [26] [27] Coronary MRA has been improved in recent years by using respiratory motion compensation techniques such as navigators[26] and blood pool MR contrast media. Recent reports have suggested the feasibility of visualizing coronary atherosclerotic plaques using high-resolution MRI afforded by stronger magnetic gradients and focused fields of view.[28] Equally intriguing is the possibility of measuring volume or velocity of flow in the major coronary arteries using breath-hold gradient-echo or echo-planar velocity-encoded techniques[12] [13] (Fig. 10-12) . These techniques have already been used in human subjects to document an increase in volume flow or flow velocity in response to vasodilators; the exclusion or confirmation of coronary arterial disease by the noninvasive assessment of coronary flow may be an important future application of MRI in ischemic heart disease.

CORONARY ARTERY BYPASS GRAFTS.

Gated MRI has been used to evaluate the patency of bypass grafts. Because blood usually flows rapidly through the grafts, they appear as small circular structures with absence of a luminal signal. For visualization of grafts, ECG-gated images are acquired to minimize the effect of motion of the grafts. Generally, images are acquired at each anatomical level during multiple phases of the cardiac cycle to ensure that an image is acquired at a phase when the rate of flow through the graft is rapid. High flow rate in the graft produces a flow void in the lumen of the graft using spin-echo MRI and thus indicates patency of the graft. With the cine (gradient-echo) MRI and MRA techniques, flowing blood causes bright signal intensity; therefore, bright signal rather than flow void indicates graft patency with this technique. MRI has an accuracy of 80 to more than 90 percent for defining

graft patency.[29] [30] [31] [32] Phase-contrast gradient-echo techniques have been used to demonstrate flow and to estimate flow velocity in coronary bypass conduits[31] [33] [34] (Fig. 10-13) . Contrast medium-enhanced MRA acquired during breath-holding or with respiratory compensation using navigators with and without electrocardiographic gating have provided imaging of the entire or major segments of vein grafts and internal mammary arteries bypass[32] (Fig. 10-14) . The MR angiogram permits the identification of stenoses as well as merely indicating patency.

MYOCARDIAL PERFUSION.

Fast gradient-echo imaging or EPI is used to monitor the signal intensity changes of the myocardium during the first pass of MR contrast media to assess regional myocardial perfusion. Monitoring of the first-pass distribution of MR contrast medium with T1-sensitive fast gradient-echo imaging in basal and vasodilated states has shown regions of decreased perfusion in association with coronary arterial stenosis.[14] [15] [35] [36] [37] Methods have been developed and validated for quantifying regional perfusion using these MR techniques.[35] The detection and assessment of coronary artery disease may be improved by

Figure 10-13 *A,* Phase image of a breath-hold cine MRI acquisition in a patient with bilateral internal mammary artery--coronary conduits. Left internal mammary artery is indicated by arrow. *B,* Velocity-versus-time curve for the left internal mammary artery conduit. Note the greater flow in diastole characteristic of unimpeded flow in the artery. ECG=electrocardiogram.

quantifying regional contractile function and perfusion during the same study.[37]

DETERMINATION OF MYOCARDIAL VIABILITY.

Several promising MR approaches to determining viability of hibernating and stunned

myocardium have been pursued in recent years[19] [38] (see also Chap. 13) . They can be conveniently divided into two groups: assessment of contractile reserve in response to inotropic stimulation (low dose dobutamine)[16] [17] [18] [19] and tissue characterization using various MR contrast media.[38] [39] [40] [41] [42] The first MR approach for defining myocardial viability simulates techniques used with echocardiography by demonstrating residual contractile response to inotropic drugs in an ischemically injured or chronically ischemic region. This approach to predicting viability not only assesses contractile response but also incorporates the precise measurement of wall thickness afforded by MRI as an additional parameter. MRI-defined diastolic wall thickness (5.5 mm) and dobutamine-induced systolic wall thickening (2 mm) have been shown to predict contractile recovery after myocardial revascularization.[17] [18] [19] With the use of ^{19}F-fluorodeoxyglucose positron emission tomography as the determinant of residual viability (see also Chap. 9) , dobutamine transesophageal echocardiography and dobutamine cine MRI have been compared in patients with prior myocardial infarction.[16] Sensitivity and specificity of dobutamine transesophageal echocardiography and cine MRI for positron emission tomography-defined viability were 77 percent versus 81 percent and 94 percent versus 100 percent, respectively.

A potential advantage of MRI over echocardiography is that it is fully quantitative; the excellent edge definition of the epicardial and endocardial borders permits precise measurement of regional wall thickening (see also Chap. 13) . Recently, this edge definition has been improved by the use of double inversion pulses to completely null the signal of intracavitary blood producing black blood images. The precision of the assessment of regional functional reserve has been augmented by the use of myocardial tagging.[43] [44] Dobutamine cine MRI with myocardial tagging was found to have a sensitivity of 89 percent and a specificity of 93 percent for defining residual viability, as shown by recovery of segmental function after revascularization.[43] Myocardial tagging has also been used to demonstrate residual viability of subepicardial myocardium in putative transmural myocardial infarction that predicted subsequent improvement of regional and global left ventricular function[43] (see p. 343 for discussion of myocardial tagging).

A second MRI approach for determining myocardial viability in a region of ischemic injury uses MR contrast media to provide tissue characterization. Most MR contrast media have a molecular size such that they freely exit the vascular space and rapidly distribute in the extracellular space. Gadolinium (Gd)-based contrast media, such as gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) usually increase the MRI signal of tissues. These contrast media have extracellular distribution and are excluded from myocardial cells with intact membranes. Recent reports have used this approach to estimate the distribution volume of Gd chelates in normal and ischemically injured myocardium.[39] [40] Under optimal circumstances, measurement of the distribution volume of Gd chelates provides an index of the percentage of necrotic myocardial cells within a zone of ischemic injury.[39] [40] At equilibration, the relative concentration of Gd chelate in myocardium and blood is determined by the relative distribution volume in the tissue of interest. The distribution volume in ischemically injured myocardium is slightly expanded by interstitial edema but very substantially increased by loss of myocardial cellular membrane integrity, permitting entrance of the indicator, which can act on intracellular water.

Recent studies in rats with reperfused myocardial infarctions have shown that the distribution volume of both Gd chelates (Gd-DTPA-Boyden

Figure 10-14 Contrast medium-enhanced three-dimensional MR angiogram of the chest demonstrates a stenosis of a bypass graft to the right coronary artery. Stenosis is displayed on the maximum intensity projection *(left)* and on an individual partition *(right)* in the sagittal plane. *(Courtesy of Dr. Gus Bis)*

microchamber assay [BMA]) and ^{99} Tc-DTPA was 90 to 100 percent of the tissue space, indicating entrance of the indicators into all myocardial cells in the infarcted region.[39] [40] It has been proposed that this technique for estimating distribution volume of MR contrast media might be used to estimate the percentage of nonviable cells in a region of reperfused ischemic injury. Viability of ischemically injured tissue can also be assessed using MR contrast media that accumulate in necrotic tissue. The first of these necrosis-specific MR contrast media, gadophyrin 2, is a Gadodiamid-labeled porphyrin compound. In an experimental model of reperfused infarction, this agent precisely defined the volume of the infarcted myocardium.[41]

Another potential approach for defining myocardial viability involves the use of an MR contrast agent that enters and is retained in normal myocardial cells. Such an agent is manganese DPDP (MnDPDP, Teslacon), which mimics the characteristics of thallium-201 in that normal membrane integrity is a requisite for entering myocardial cells. In experimental animals with reperfused myocardial infarctions, MnDPDP gradually accumulated in normal myocardial cells while it cleared from the infarcted region at the same rate as it cleared from blood.[42] This viability agent produced sharp demarcation of the ischemically injured myocardium at 4 hours after administration.

The standard MR contrast medium, Gd-DTPA, has also been used to distinguish between viable and nonviable myocardial segments in patients with chronic coronary artery disease and left ventricular dysfunction.[45] Hyperenhancement was observed 3 to 15 minutes after administration of Gd more frequently in myocardial segments judged to be nonviable by thallium-201 scans and by dobutamine echocardiography compared with viable segments.[45] The absence of delayed hyperenhancement in regions with resting contractile dysfunction correlated with radionuclide and echocardiographic determinants of viability (see also Chap. 13) .

PROGNOSIS FOR FUNCTIONAL RECOVERY AFTER INFARCTION.

The contrast enhancement pattern of acute myocardial infarctions provides insight into the severity of the infarction. Wu and associates[46] reported greater postinfarction complications, morbidity, and mortality in patients with an enhancement pattern consisting of hyperenhancement of the periphery and lack of enhancement of the core

of the infarction in comparison with patients with homogeneous enhancement of the entire infarction after administration of Gd-DTPA. Rodgers and coworkers[47] also showed prognostic significance to the enhancement pattern produced by Gd-DTPA using both early and delayed image acquisitions. A perfusion deficit with first-pass dynamic imaging and delayed hyperenhancement usually predicted poor recovery of regional function at 7 weeks after infarction. There is some controversy regarding the interpretation of hyperenhancement of the injured region on images acquired at several minutes after contrast medium administration; contrast media at this time reaches a pseudoequilibrium state in the myocardium but can be influenced by delayed washout kinetics. Some studies[46] have concluded that delayed hyperenhancement with Gd-DTPA indicates irreversible injury (infarction), whereas others indicate recovery of function in part of the hyperenhanced region.[47] The latter notion is supported by observation in experimental animals showing that the size of the hyperenhanced region demarcated by Gd-DTPA, a nonspecific MR contrast medium, was significantly larger than the area enhanced by a necrosis-specific MR contrast medium, a Gd porphyrin compound.[48]

IMAGING OF ATHEROSCLEROTIC PLAQUES.

The feasibility of MRI for imaging and characterizing atherosclerotic plaque has been shown.[49] [50] This has been done using both intravascular coils and surface coils.

Cardiomyopathies (See also Chap. 48)

HYPERTROPHIC CARDIOMYOPATHIES.

MRI has been used to define the presence, distribution, and severity of the left and right ventricular hypertrophy in hypertrophic cardiomyopathies.[51] [52] It has displayed the extent of septal involvement and has been particularly useful for identifying the unusual distribution of hypertrophy in the variant forms of hypertrophic cardiomyopathy[51] (Fig. 10-15) . Left ventricular and right ventricular mass and wall thickness can be quantified precisely using spin-echo and cine MRI. Substantial right ventricular hypertrophy has been shown by MRI measurements in patients with hypertrophic cardiomyopathy. Cine MRI has also been used to assess ventricular diastolic parameters by constructing volume-time curves during the cardiac cycle; reduced filling rate and time to peak filling have been demonstrated in patients with hypertrophic cardiomyopathy.[52] Measurement of coronary sinus flow using breath-hold velocity-encoded MRI has disclosed abnormal coronary flow reserve in hypertrophic cardiomyopathy.[53]

DILATED CARDIOMYOPATHY.

MRI has depicted the morphological and functional alterations in congestive (dilated) cardiomyopathy.[54] [55] [56] Cine MRI has been used to quantify left ventricular volume and systolic wall stress in patients with congestive cardiomyopathies.[54] [55] Cine MRI has also been performed sequentially to monitor the effect of drug therapy in patients with congestive cardiomyopathy; it has demonstrated significant decreases in left ventricular volume, mass, and systolic wall stress during 3 months of treatment with an

angiotensin-converting enzyme inhibitor.[55] Because MRI provides excellent discrimination of the edges of the myocardium, it can also assess myocardial mass and wall thickness in patients with cardiomyopathies; several studies have indicated the accuracy of MRI for quantifying myocardial mass in both normally and abnormally shaped left ventricles.[56] [57] Cine MRI has also been

Figure 10-15 Spin-echo MR image in the coronal plane displays severe symmetrical hypertrophy in a patient with hypertrophic cardiomyopathy. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

found to be highly reproducible in measuring left ventricular mass and volumes between two studies in the same subject.[56] [57] The interstudy variability of mass measurements is less than 5 percent.[56] Cine MRI has demonstrated considerable increase in left ventricular mass and markedly elevated end-systolic wall stress in patients with dilated cardiomyopathy.[54] [55] [56] Cine MRI has demonstrated both a decrease in the extent of wall thickening and a change in the regional pattern of wall thickening in patients with dilated cardiomyopathy compared with normal subjects.

Quantification of ventricular volumetric changes during the cardiac cycle by cine MRI and volume flow across the atrioventricular valve during diastole by velocity-encoded cine MRI have demonstrated abnormal diastolic filling parameters in the right and/or left ventricle in patients with hypertrophic,[52] congestive,[58] and restrictive[59] cardiomyopathies.

RESTRICTIVE CARDIOMYOPATHY.

ECG-gated spin-echo MRI has displayed features considered to be characteristic for restrictive cardiomyopathy.[60] There is substantial enlargement of the atria and the inferior vena cava, with usually less prominent ventricular enlargement. Because of resistance caused by the noncompliant ventricles with atrial emptying during diastole, prominent signal is observed in the atrial blood. Such intraatrial signals originate from slowly moving blood on spin-echo MR images. The major contribution of MRI to establishing the diagnosis of restrictive cardiomyopathy is the demonstration of normal pericardial thickness, which essentially excludes the alternate diagnosis of constrictive pericarditis.

In *amyloid heart disease,* MRI has demonstrated thickened myocardial walls and diminished wall thickening during the cardiac cycle.[61] [62] Thickening of the right atrial wall and atrial septum on MR images is highly suggestive of this disease. Cine MRI indicates apparent hypertrophy of the left ventricle with normal or decreased left ventricular contraction rather than hypercontractile left ventricle expected in left ventricular hypertrophy. MRI has also demonstrated granulomatous involvement of the

myocardium in sarcoidosis.[63] [64] It has been used to monitor the cardiac response to therapy for sarcoidosis.[64] Abnormally low signal of the myocardium on T2-weighted spin-echo and gradient-echo images due to high iron content of the myocardium is a characteristic feature of myocardial involvement by hemochromatosis.[65]

RIGHT VENTRICULAR DYSPLASIA.

Right ventricular dysplasia is represented pathologically by variable replacement or infiltration of right ventricular myocardium by fatty or fibrous tissue. Aside from suggestive clinical and electrophysiological features, the diagnosis has been definitively established by tissue examination after endomyocardial biopsy. The major differential diagnoses for ventricular arrhythmias of right ventricular origin in the presence of a grossly normal right ventricle are right ventricular dysplasia and right ventricular outflow tract tachycardia. ECG-gated spin-echo MRI has been used to identify transmural or focal fat in the right ventricular free wall to establish the diagnosis of right ventricular dysplasia.[66] Focal or generalized wall thinning of the right ventricle is also consistent with this diagnosis.[66] Cine MRI demonstrates focal dyskinesis or aneurysm at sites of wall thinning. Focal wall thinning and focal bulging (aneurysm) of the right ventricular outflow tract have been shown also on MRI in right ventricular outflow tract tachycardia.[67] One report has shown that MRI actually demonstrates fat in the right ventricular free wall in less than half of patients with right ventricular dysplasia, but a regional contractile abnormality is demonstrated by cine MRI in a majority.[68] The sensitivity of MRI for the diagnosis of right ventricle dysplasia has not been established. Transmural fat in the right ventricular free wall occurs in the absence of this disease; this entity has been referred to as benign fatty infiltration of the right ventricle. [69]

MYOCARDITIS.

MRI has demonstrated abnormal signal intensity of the myocardium in acute myocarditis.[70] [71] In acute and subacute myocarditis, there is high signal of the myocardium at the site of inflammation displayed on Gd-enhanced T1-weighted spin-echo images[71] and on nonenhanced T2-weighted images. High signal intensity foci[72] in the myocardium have also been demonstrated in Chagas disease[72] and Lyme myocarditis. [73]

Pericardial Disease (See also Chap. 50)

Gated MRI provides direct visualization of the pericardium[74] (see also Chap. 50) . It has been effective for the assessment of patients with suspected pericardial disease. Normal pericardium is composed primarily of fibrous tissue and has low MRI signal intensity. The thickness of pericardial line measured in normal subjects was 1.5 ± 0.4 mm (SD) with a range from 0.8 to 2.6 mm. A variation of thickness of the low-intensity line has been observed during the cardiac cycle in normal subjects. These latter observations, along with information from postmortem studies, indicate that the normal pericardium measures less than 3.0 mm and suggest that the low-intensity pericardial line consists of pericardium and some adherent pericardial fluid. A thickness of 4 mm or greater is abnormal. This is probably responsible for the pericardial line observed on CT as well, because normal CT measurements of pericardial thickness are similar to MRI

measurements. On spin-echo MR images, pericardial effusion causes a low signal intensity space separating the heart and pericardium (Fig. 10-16) . The distinction between the pericardium itself and pericardial fluid can also be achieved on cine MR images, on which the fluid has bright signal and the pericardium is a dark line (Fig. 10-17) . MRI can establish the diagnosis of congenital absence of the left pericardium.[75] Pericardial thickening and effusions are characteristic features of acute pericarditis.

Gated MRI has been useful for demonstrating pericardial thickness in patients with suspected constrictive pericarditis.[76] [77] The signal intensity of the thickened pericardium is variable. The purely fibrous or calcified pericardium in chronic constrictive pericardial disease has low signal intensity. However, in subacute forms of constrictive pericarditis caused by irradiation, surgical trauma, or uremia, the thickened pericardium has moderate to high intensity on spin-echo images. The effusive-constrictive form of pericardial disease has thickened pericardium and pericardial effusion. One study[77] has demonstrated a diagnostic accuracy of 93 percent for MRI in distinguishing between constrictive pericarditis and restrictive cardiomyopathy by demonstrating thickened pericardium (>4 mm) in the former disease.

MRI demonstrates even the small amount of pericardial fluid present in normal subjects. Fluid in the superior pericardial recesses is commonly seen even when fluid is not evident posterior to the left ventricle. The appearance of pericardial fluid is different on spin-echo and cine MRI (gradient-echo) images (see Fig. 10-17) . Nonhemorrhagic fluid shows low intensity on short-TR, short-TE sequences (T1-weighted) and has high intensity on long-TR, long-TE sequences (T2-weighted). On the other hand, pericardial hematoma has high intensity on T1-weighted images (Fig. 10-18) and may have high intensity on T2-weighted images, depending on the age of the hematoma and the magnetic field strength of the imager. On cine MRI, the nonhemorrhagic effusion is bright and the hemorrhagic one may be low intensity.

Figure 10-16 ECG-gated spin-echo images in coronal *(left)* and transverse *(right)* planes of a patient with constrictive pericarditis. The pericardium is substantially thickened. Thick pericardium can be visualized extending over the pulmonary artery on the coronal image.

In pericardial disease the role of MRI must be considered in the light of the established effectiveness of echocardiography. An advantage of MRI over echocardiography is the capability to differentiate pericardial hematoma from other types of effusions. Because of the wide field of view, MRI seems to be useful in locating loculated effusions. Determination of pericardial thickening seems to be a clear indication for the use of MRI.

Neoplastic Disease (See also Chaps. 49 and 69)

Several reports have documented the clinical utility of gated MRI for the evaluation of intracardiac and paracardiac masses.[78] [79] [80] [81] Because of the unequivocal delineation of the pericardium, myocardial walls, and chambers of the heart on MR images, the precise relationship of tumors to cardiovascular structures can be defined. Tumors within the myocardial wall may be identified by virtue of a difference in signal intensity (usually higher) compared with the myocardium. In this regard, MR contrast media can be used in an attempt to accentuate differences in signal intensity between tumor and myocardium (Fig. 10-19) .[80]

Secondary cardiac involvement by tumors is about 40 times more frequent than primary tumors (see also Chap. 49) . Secondary involvement occurs by three routes: (1) direct extension from the mediastinum and lungs, (2) metastases to the pericardium or cardiac chambers, and (3) direct extension of upper abdominal tumors through the inferior vena cava or lung tumors through the pulmonary veins. MRI appears to be superior to CT for assessing the extent and effect of mediastinal masses adjacent to cardiovascular structures. MRI is the imaging procedure of choice for identifying paracardiac masses, defining their nature, and determining invasion of the pericardium. The intensity on spin-echo images can differentiate such masses from innocuous lipomas, the pericardial fat pad, pericardial cysts, loculated pericardial effusions, and unusual enlargement or displacement of cardiac chambers.

Intracardiac tumors can be clearly identified within the signal void of the cardiac blood pool (Fig. 10-20) . Because of its wide field of view, MRI is ideal for defining both the intracardiac and extracardiac extent of masses. For the evaluation of intracardiac masses, it is advisable to acquire spin-echo and gradient-echo MR images and to obtain images with at least two planes perpendicular to each other. Intracardiac or intravascular tumors can be distinguished from thrombus using cine MRI in most instances[81] (Fig. 10-21) . Tumors are represented by medium signal (higher signal or similar signal compared with myocardium), whereas thrombus produces very low signal (less than myocardium). This low signal is due to elements in the thrombus, e.g., hemosiderin, deoxyhemoglobin, that induce a magnetic susceptibility effect and vitiate signal from the region. The cine MRI sequence is very sensitive to this effect. Some myxomas contain a considerable amount of iron and can show the same effect, so confident distinction between myxoma and clot may not always be possible. Differentiation between tumor and thrombus has not been possible using the ECG-gated spin-echo sequence. Differentiation between tumor and blood clots can also be done using MR contrast media. The contrast medium enhances the signal of tumor but not that of clots.[80]

Valvular Heart Disease (See also Chap. 46)

Magnetic resonance imaging can be used to identify the presence of valvular stenosis and regurgitation.[82] [83] [84] [85] [86] [87] [88] [89] [90] [91] This is done using cine MRI to depict the signal void caused by

Figure 10-17 Spin-echo *(left)* and gradient-echo (cine MR) *(right)* images of a patient with a large pericardial effusion.

Figure 10-18 ECG-gated spin-echo images show a pericardial hematoma (H). The hemorrhagic pericardial effusion causes bright signal intensity on the T1-weighted (TE=30 msec) image. The right atrium and right ventricle are compressed by the hematoma. Pericardium (arrow) is thickened. R=right ventricle; shaded letters indicate right (R) and left (L) for orientation.

high velocity jet flow across a narrow valvular orifice associated with the opened valve in stenosis and the incompletely closed valve in regurgitation. The high velocity jet causes a signal void that is projected into the ascending aorta in systole with aortic stenosis and into the left ventricle during diastole in aortic regurgitation (see Fig. 10-3). Mitral regurgitation produces a signal void in the left atrium during systole whereas mitral stenosis causes a signal void emanating from the mitral valve into the left ventricle during diastole (Fig. 10-22) .

Velocity-encoded cine MRI has been employed to measure the volume of valvular regurgitation.[84] [85] [86] [87] [88] [89] [90] This technique typically provides images corresponding to 16 phases of the cardiac cycle. These images can distinguish between antegrade and retrograde flow. Thus, measurement of retrograde flow in the ascending aorta and pulmonary artery during diastole can be used to quantify the volume of aortic and pulmonary regurgitation, respectively (Fig. 10-23) . The same approach has been applied at the level of the mitral and tricuspid annuli to quantify mitral and tricuspid regurgitation, respectively. This approach is sometimes problematic for quantifying atrioventricular valvular regurgitation, owing to directional unpredictability of the regurgitant jet

Figure 10-19 ECG-gated spin-echo images before *(left)* and after *(right)* injection of gadolinium chelate in a patient with a sarcoma of the ventricular septum. A fat saturation technique was used after contrast medium to accentuate the effect of the contrast medium. The tumor is enhanced to a greater degree than myocardium.

Figure 10-20 Spin-echo image demonstrates an angiosarcoma of the right atrium with extension (arrow) through the right atrial wall.

into the left atrium. Another approach is to measure the systolic outflow from the left ventricle by velocity-encoded cine MRI at the level of the ascending aorta and the diastolic inflow to the left ventricle by velocity-encoded cine MRI at the level of the mitral annulus; the difference between the two is a measure of the volume of mitral

regurgitation[89] (Fig. 10-24) .

Velocity-encoded cine MRI has also been used to measure the peak flow velocity (V_p) across aortic and mitral stenoses. [86] [88] [91] Similar to the echo Doppler echocardiographic approach, the transvalvular pressure gradient is estimated by the modified Bernoulli equation ($DeltaP=4V_p^2$). The MR measurement is subject to several potential inaccuracies related to marginal temporal resolution, slice thickness, and signal loss. The accuracy of this measurement can be improved by using small voxels, thin slices, and very short echo delay time.

Cine MRI can be employed for the evaluation and monitoring of ventricular function, mass, and wall stress in patients with valvular heart disease.[84] [86] Because of the excellent interstudy reproducibility of the 3D data set provided by cine MRI for quantifying ventricular volumes and mass, it is an attractive method for evaluating the effect of therapy.

Figure 10-21 Gradient-echo (cine MR) images in two patients with intracardiac masses. *Left,* Metastatic tumor in the right ventricle has medium intensity. *Right,* Thrombus at the left ventricular apex has low intensity. *(From Higgins CB, Hricak H, Helms C: MRI of the Body. 2nd ed. New York, Raven Press, 1992.)*

Figure 10-22 Cine MR image in the transaxial plane during diastole displays a signal void emanating from the mitral valve (arrows) caused by the high velocity "jet" flow of mitral stenosis. *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

In addition, velocity-encoded cine MRI has been used to document the efficacy of angiotensin-converting enzyme inhibitors for decreasing the volume of aortic regurgitation.[85]

Congenital Heart Disease (See also Chaps. 43 and 44)

Magnetic resonance imaging has multiple capabilities for the evaluation of congenital heart disease.[92] Morphological information is provided by ECG-gated spin-echo and cine MRI. Ventricular volumes, mass, and function can be obtained using cine MRI. The volumes of shunts, valvular function, and pressure gradients across valves and conduits can be estimated using velocity-encoded cine MRI (velocity-flow mapping). However, the clinical use of these capabilities is influenced by the widespread application of echocardiography and Doppler techniques for many of these same purposes. Consequently, the current clinical role of MRI is to supplement the information acquired

by echocardiography.

Figure 10-23 *A,* Magnitude *(above)* and phase *(below)* images in systole *(left)* and diastole *(right)* of a patient with aortic regurgitation on phase images. Bright signal in the ascending aorta in systole represents antegrade flow. In diastole, dark signal in the ascending aorta represents retrograde flow due to aortic regurgitation. *B,* Flow-versus-time curve in a patient with aortic regurgitation. Reverse flow in diastole represents aortic insufficiency. The area under this curve provides a direct measurement of the volume of aortic regurgitation. *(From Higgins CB, Caputo GR: MRI of valvular heart disease. In Pohost GM [ed]: Cardiovascular Applications of Magnetic Resonance. Mt. Kisco, NY, Futura Publishing, 1993.)*

Figure 10-24 *A,* Magnitude and phase images at the level of the mitral annulus. The phase image is used to measure mitral inflow. *B,* Magnitude *(left)* and phase *(right)* images at the level of the proximal aorta. *C,* Flow-versus-time curve for mitral inflow and aortic outflow in a normal subject. *D,* Flow-versus-time curve in a patient with mitral regurgitation. By using phase images, flow is calculated as the spatial average velocity in the region of interest (i.e., aorta) and the cross-sectional area of the region of interest. The areas under the two curves in *C* are nearly equal. In *D,* the area under the mitral inflow curve is considerably greater than the area of the aortic outflow curve. The difference between the two areas is the volume of mitral regurgitation. *(From Fujita N, Chazouilleres AF, Hartiala JJ, et al: Quantification of mitral regurgitation by velocity-encoded cine magnetic resonance imaging. J Am Coll Cardiol 23:951-958, 1994.)*

Reports from several centers indicate the effectiveness of MRI for the evaluation of both children and adults with congenital heart disease.[92] [93] [94] [95] [96] [97] [98] [99] [100] [101] In several studies in which the results of MRI were corroborated by angiography and/or 2D echocardiography, accurate anatomical diagnosis of anomalies was achieved by MRI in more than 90 percent of patients.[97] [98] [99] MRI has also shown substantial capability for anatomical and functional evaluation of congenital heart disease after palliative and total correction.[95] [101] [102]

Visceroatrial situs, the type of ventricular loop, and the relationship of the great vessels can be identified in all patients in whom studies encompassing the entire heart were done.[99] The diagnostic accuracy of MRI exceeded 90 percent for abnormalities of arterioventricular connections,

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Figure 10-25 Transverse *(left)* and coronal *(right)* spin-echo images of a patient with transposition of the great arteries, pulmonary atresia, and ventricular septal defect. The transverse image acquired at the base of the heart shows only the aortic valve (A). Coronal image shows the right subclavian to pulmonary

arterial anastomosis (curved arrow). The right pulmonary artery is aneurysmal while the left pulmonary artery is absent. The heart is shifted to the left, owing to decreased size of the left lung. AA=aortic arch; I=innominate artery; RP=right pulmonary artery.

great vessel anomalies such as coarctation and vascular rings, ventricular and atrial septal defects, and abnormalities of venous connections.[99] Likewise, determination of visceroatrial situs and type of ventricular loop reached an accuracy of nearly 100 percent with MRI.[99]

Much of the diagnostic information provided by MRI can also be shown by 2D echocardiography. The role of MRI must therefore be considered in respect to the established role of echocardiography. Among noninvasive modalities, the unique capabilities of MRI in congenital heart disease are visualization of the central pulmonary arteries in cases of pulmonary atresia[92] [98] [103] (Fig. 10-25) and assessment of anomalies of the thoracic aorta[92] [99] ; complete definition of complex anomalies involving both the great vessels and ventricles[92] [96] [100] ; and the postoperative evaluation of patients who have undergone complicated supracardiac operations for cyanotic congenital heart disease.[95] [101] [102] [103] [104] [105] [106] MRI has been shown to be reliable for both preoperative and postoperative evaluation of coarctation of the aorta; angiography can be obviated in most patients. Several reports[95] [101] [102] [103] [104] [105] [106] [107] have shown the effectiveness of MRI for the postoperative evaluation of the Fontan, Rastelli, Norwood, Damus, Glenn, and Jatene procedures. MRI has been used to quantitatively monitor the size of the pulmonary arteries after surgical procedures that either involve the pulmonary arteries or are intended to increase their size by altering pulmonary blood flow.[106] [108] A comparative study between echocardiography and MRI for the evaluation of the pulmonary arteries after surgery showed that MRI was superior for the evaluation of right and left pulmonary stenoses and dimensions (Fig. 10-26) .[108] MRI has been used to monitor pulmonary arteries through multiple-staged surgeries such as the Fontan[106] and Norwood[104] procedures. Velocity-encoded MRI has been effective for estimating and monitoring the gradient across Rastelli conduits.[107]

In postoperative patients, velocity-encoded cine MRI has been useful for measuring blood flow to each lung in patients with residual unilateral pulmonary stenosis (Fig. 10-27) and for measuring retrograde flow in conduits or reconstructed outlet regions to quantify the volume of pulmonary regurgitation.[95]

MRA has been shown in recent years to be valuable for depicting thoracic aortic anomalies, pulmonary arterial stenoses, and connections of pulmonary veins. Contrast medium-enhanced MRA is additive to spin-echo MRI for unraveling the anatomy of unusual coarctations (Fig. 10-28) . This technique is likely the most sensitive for the identification of partial anomalous pulmonary venous connections (see Fig. 10-6 .)

The capability of MRI in congenital heart disease has been extended by cine MRI and velocity-encoded cine MRI. The former technique can provide multiple images per cardiac cycle so that ventricular function can be evaluated, whereas the latter technique permits measurement of blood flow and velocity in the aorta and pulmonary artery and across valves and conduits. Functional evaluation of congenital heart disease using MR

techniques is discussed later.

Diseases of the Thoracic Aorta (See also Chap. 40)

MRI and CT are now the procedures most frequently used for the diagnosis and monitoring of thoracic aortic diseases.

Figure 10-26 Oblique coronal spin-echo image in a patient after repair of tetralogy of Fallot. There is dilatation of the right ventricular outlet tract (open arrow) and stenosis (solid arrow) of the proximal right pulmonary artery.

Figure 10-27 *A,* Systolic *(above)* and diastolic *(below)* images at the level of the right pulmonary artery (RPA) in a patient after repair of tetralogy of Fallot. The systolic image shows a flow void due to high-velocity jet flow through the stenosis in the RPA. *B,* Flow-versus-time curve for the main, right, and left pulmonary arteries derived from the phase images in each of 16 evenly spaced intervals of the cardiac cycle. Flow in the RPA is severely reduced by the stenosis. MPA=main pulmonary artery; LPA=left pulmonary artery.

The roles of these noninvasive tomographic techniques have rapidly evolved in the past decade and have replaced x-ray aortography for the definitive diagnosis of thoracic aortic diseases.[109] [110] For a number of thoracic abnormalities, especially aortic dissection, transesophageal echocardiography has been used frequently and is competitive with these tomographic imaging modalities.

A number of MRI sequences have been used in the evaluation of aortic diseases (see Figs. 40-12 , 40-13 , and 40-14). These include ECG-gated spin-echo MRI; standard cine MRI; segmented K space (breath-hold) cine MRI; and contrast medium-enhanced 3D time-of-flight MRA. The introduction of breath-hold cine MRI and contrast medium-enhanced MRA has permitted rapid imaging of thoracic aortic emergencies.

A number of reports attest to the effectiveness of MRI for the evaluation of aortic dissection, true and false aneurysms, periaortic abscess, aortic arch anomalies, and coarctation of the aorta.[109] [110] [111] [112] [113] In aortic dissection, MRI can depict the intimal flap and the proximal extent of the dissection, and it can distinguish true from false channels (Fig. 10-29) . On spin-echo MRI images, intraluminal signal is usually seen in the false channel as a result of thrombus, slow blood flow, or both. Differentiation between slow flow and thrombus is evident on cine MRI (gradient-echo) images because the former produces high or moderate intraluminal signal whereas thrombus causes low signal on this type of image. Velocity-encoded cine MRI provides a measurement of the differential flow velocity in the true and false channels. By using multiple images per cardiac cycle, a velocity-time curve can be generated to display the

disparate flow pattern in the two channels.

MRI has been very effective for identifying intramural hematoma, which is dissection without intimal rupture.[114] [115] Spin-echo MR images display wall thickening due to the intramural hematoma. It is confined to the descending aorta in type B and involves the ascending aorta in type A. The hematoma usually shows high intensity on T1=weighted images and sometimes very low intensity on gradient-echo images (cine MR). MRI can monitor the resolution or detect recurrence of intramural hemorrhage.[114]

A report[110] has shown high sensitivity for transesophageal echocardiography, CT, and MRI for the diagnosis of aortic dissection. However, the specificity of CT and MRI was significantly better than that of transesophageal echocardiography. The wide field of view of CT and MRI is an additional advantage for showing the extent of the dissection. On the other hand, transesophageal echocardiography has the important advantage of portability.

MRI has been used to monitor the size of the thoracic aorta in patients with Marfan syndrome and to exclude the presence of an occult dissection[116] (see also Chaps. 40 and 56) . An aortic diameter of greater than 4 cm is considered enlarged, and a diameter exceeding 5 cm is considered aneurysmal. Because MRI is a completely noninvasive technique, it is ideal for monitoring patients with aortic diseases and patients who have undergone surgical or medical treatment of aortic dissection.[117] [118]

MRI has been used to detect periaortic abscess complicating bacterial endocarditis. The 3D tomographic nature of the technique permits precise localization of these abscesses.

MRI and MRA are now employed to monitor patients with thoracic aortic dissection and aneurysms.[117] [118] [119] It is recognized that the false channel remains patent distal to the ascending aortic graft after surgical repair of type A dissections. [117] , [118] Because most patients with type B dissection are managed medically, the false channel frequently persists in these patients as well. The complications caused by long-term patency of the false channel are aneurysm of the false channel (Figs. 10-30 and 10-31) and obstruction of aortic branches by the intimal flap. Consequently, noninvasive imaging studies are necessary to monitor the status of the false channel and intimal flap.

MRI and MRA are also used to monitor the maximum diameter and extent of the thoracic aortic aneurysms; a maximum diameter exceeding 6 cm indicates the need for surgical repair.[120] Regular monitoring is also important in patients with Marfan syndrome and other conditions associated with progressive aortic dilatation. Because MRI and MRA are noninvasive and provide images along both the short and long axis of the thoracic aorta, they are now the preferred method for follow-up of thoracic aortic diseases. MRA in the sagittal plane is very effective for depicting the origins of the arch branches

Figure 10-28 Three-dimensional reconstruction of a contrast medium-enhanced MR angiogram of the thoracic aorta displays a severe juxtaductal coarctation of the aorta.

and visceral arteries of the abdominal aorta and their relationship to the aneurysm.

Velocity-encoded cine MRI can be used in thoracic aortic disease to quantify the volume of concomitant aortic regurgitation in patients with aortoannular abnormalities (see Fig. 10-3) . It can also measure the velocity and volume of flow in the true and false channels.

Figure 10-29 Spin-echo image in type A aortic dissection demonstrates the intimal flap in the aorta (solid arrows) and innominate artery (open arrow).

Evaluation of Cardiovascular Function (See also Chap. 15)

A variety of MRI techniques has been employed for the evaluation of several aspects of cardiovascular function. These include standard cine MRI for the quantitation of global and regional contraction of the left and right ventricles. The cine MRI technique usually produces gradient-echo images at 16 to 30 evenly spaced intervals through the cardiac cycle (Fig. 10-32) . With standard cine MRI, the data acquisition period occupies 256 cardiac cycles. A fast version can be performed in only 16 cardiac cycles and has been called breath-hold cine MRI or segmented fast cine gradient-echo imaging.[2]

Blood flow volume and flow velocity can be quantified using velocity-encoded cine MRI (velocity flow mapping).[5] [121] [122] [123] This technique provides a velocity image (velocity map, phase image) at evenly spaced intervals, usually 16, throughout the cardiac cycle. Analysis of the velocity image can be done to measure peak velocity or average velocity in any selected region of interest in the flow channel. Velocity-encoded sequences can be coupled with either standard cine MRI or breath-hold cine MRI. Using the multiple phase images collected over the cardiac cycle, flow- or velocity-versus-time curves can be made.

ECHO-PLANAR IMAGING.

The most attractive technique for evaluating cardiovascular function is EPI, which essen

Figure 10-30 Spin-echo images early *(left)* and late *(right)* after repair of type A aortic dissection depict interval development of an aneurysm of the persistently patent false channel (F). *(From Higgins CB, Hricak H, Helms C [eds]: MRI of the Body. 3rd ed. Philadelphia, Lippincott-Raven, 1998.)*

Figure 10-31 Sagittal partition (3 mm thickness) from a three-dimensional MR angiogram in the sagittal plane in a patient after repair of type A aortic dissection. The intimal flap (arrow) separates the dilated false channel from the compressed true channel in the descending aorta. After repair, the diameter of the ascending aorta is normal.

tially constitutes real-time MRI. It can be used in "single shot" or "multishot" modes.[6] [124] [125] The "single-shot" mode acquires the entire image in about a 40- to 80-millisecond interval of a single heartbeat. The "multishot" mode acquires the image in 20- to 40-millisecond intervals of two to four consecutive heartbeats (see Fig. 10-4) . Thus, a cine version of EPI can be done during a single cardiac cycle or acquired over two to four cardiac cycles. Velocity-encoded EPI can also be done. Thereby, analysis of contractile function of the ventricles and blood flow quantification are possible in essentially real time and on a nearly beat-to-beat basis using cine and velocity-encoded cine versions of EPI.

Because MRI is a 3D imaging technique, it can provide direct measurements on which the clinical evaluation of global left ventricular function has been based. By using sets of images encompassing the left ventricle, it is possible to calculate end-diastolic, end-systolic, and stroke volumes and ejection fraction. This can be done directly and does not depend on the geometric assumptions used for such measurements from echocardiograms and x-ray angiograms. Moreover, MRI provides a 3D direct visualization of the myocardium with excellent mural edge discrimination, thereby allowing quantitation of a left ventricular mass.[55] [56] [57] MRI measurements have correlated closely with postmortem measurements of left ventricular mass. Measurements of volumes and mass using a single MR image acquired in the long-axis plane of the left ventricle or in two perpendicular long- or short-axis planes, assuming various geometric models, have been validated.[126]

RIGHT VENTRICULAR FUNCTION.

Because MRI also defines the right ventricular myocardium, it may serve as the preferred technique for the accurate determination of right ventricular mass.[127] Reasonable accuracy has been shown for the measurement of right ventricular end-diastolic, end-systolic, and stroke volumes as well as ejection fraction.[128] [129] Moreover, comparison of right and left ventricular stroke volumes has been used to estimate the regurgitant fraction in patients with aortic and mitral regurgitation.

MYOCARDIAL TAGGING.

Myocardial tagging is the most useful method for quantitation of myocardial motion with MRI.[130] [131] [132] Specified regions of the myocardium can be labeled by restricted localized RF pulses; these are placed perpendicular to the myocardial wall. These RF pulses are followed by a conventional imaging sequence after a short, specified delay.

The labeled or "tagged" myocardial regions can be tracked precisely during systolic contraction. Myocardial motion occurring between RF excitation of the tag and image formation can be expressed as the displacement and distortion of the tagged regions, which appear as dark stripes (Fig. 10-33) .

The extent of the displacement of the tagged myocardium can be measured as the distance between a given tag and its original position at end diastole. Heterogeneous myocardial motion among various segments of the left ventricle has been shown in normal subjects. The longitudinal displacement of the tag during systole is significantly greater at the basal layer than at the mid or apical layers of the left ventricle. Short-axis images with tagging showed heterogeneous rotation of the wall with an increasing degree of counterclockwise rotation from the base to the apex. This technique has been used to characterize abnormal contraction and twisting of various myocardial regions in hypertrophic cardiomyopathy.[131] It has also demonstrated tethering and compensatory regional contraction of normal myocardial segments after acute myocardial infarction.[132] This technique provides the first noninvasive method for quantitating the complex multidirectional motion of myocardial segments.

Quantification of Valvular Regurgitation (See also Chap. 46)

Accurate determination of the severity of valvular regurgitation is important for the evaluation of medical therapy and timing of surgical interventions. Among various methods, Doppler echocardiography has been used as the main diagnostic tool to detect valvular regurgitation because of its high sensitivity and specificity. However, quantification of severity has been less successful. Mapping of the spatial extent of the disturbed flow in the regurgitant chamber with pulse Doppler or color Doppler is useful for routine serial evaluation but provides only a semiquantitative estimate of the severity of valvular regurgitation. In this regard, cine MRI provides several methods for quantifying the extent of

Figure 10-32 Cine MR images in the short-axis plane acquired at end diastole (ED) and end systole (ES) near the base *(upper panels),* middle *(middle panels),* and apex *(lower panels)* of the left ventricle. These images demonstate symmetrical wall thickening of the left ventricle. From such images encompassing the length of both ventricles, measurement of ventricular volume and global function can be made.

Figure 10-33 Composite of six short-axis views of the left ventricle (LV) from end diastole *(upper left)* to end systole *(lower right)* in a patient with left ventricular hypertrophy. The pattern of diagonal lines is a saturation grid created in the tissue with spatial modulation of magnetization (SPAMM). Initially the grid moves with the underlying tissue, enabling analysis of regional wall motion within separate delineated elements of the wall. *(Courtesy of Dr. Leon Axel, University of Pennsylvania Medical School.)*

valvular regurgitation, including measurement of signal void on cine MRI and determination of the difference in stroke volumes of the two ventricles.[83] [84] In addition, velocity-encoded cine MRI can be used to measure the volume of retrograde flow in the ascending aorta or pulmonary artery in aortic and pulmonary regurgitation, respectively.[84] [87] [93] [95]

The difference between end-diastolic and end-systolic volume for a ventricle with a regurgitant valve includes both the forward stroke volume and the regurgitant volume. Because the forward or net stroke volume is equal to the volume ejected from normal ventricle, the difference in stroke volumes between a regurgitant ventricle (e.g., left ventricle with aortic and mitral regurgitation) and normal ventricle (e.g., right ventricle) is the regurgitant volume. The sum of the forward and regurgitant volume is called total stroke volume of the regurgitant ventricle.

Ventricular volume can be accurately measured from cine MRI images. In the absence of regurgitation, the stroke volumes of the right and left ventricle are nearly equal. However, in patients with aortic and/or mitral regurgitation, the stroke volume of the left ventricle exceeds that of the right ventricle by a value equivalent to the regurgitant volume. The regurgitant fraction can be calculated as the regurgitant volume divided by the total stroke volume of the regurgitant ventricle. The stroke volume ratio can also be calculated from the stroke volumes of the two ventricles. These measurements derived from cine MRI have distinguished patients with mild, moderate, and severe left-sided regurgitant lesions, as shown by independent imaging techniques.[82] [84]

The major limitation of utilizing stroke volume difference for quantification of regurgitation is in the presence of multiple valve disease. If both aortic and mitral regurgitation are present, the calculation determines only the total volume of regurgitation. If regurgitation coexists on both sides of the heart, this calculation is not meaningful.

The most effective MR technique for quantifying valvular function is velocity-encoded cine MRI or velocity-flow mapping. It has been used to quantify the volumes of aortic[84] [85] [86] [87] and mitral[89] [90] and pulmonic regurgitation[93] [94] and to estimate the pressure gradients in aortic[88] and mitral[88] [91] stenosis.

QUANTIFICATION OF AORTIC REGURGITATION.

This has been accomplished by velocity-encoded cine MRI in two ways.[84] [85] [86] [87] Measurement of blood flow in the ascending aorta and main pulmonary artery provides stroke volume for the left and right ventricles, respectively. The difference between the two stroke volumes is the aortic regurgitant volume. Moreover, because retrograde as well as antegrade flow can be determined from the instantaneous flow changes throughout the cardiac cycle using velocity-encoded cine MRI, the volume of aortic regurgitation or pulmonary regurgitation can be measured directly by the time integration of diastolic regurgitant flow (see Fig. 10-23) .

QUANTIFICATION OF MITRAL REGURGITATION.

This has been quantified by measuring diastolic inflow to the left ventricle by a velocity-encoded cine MR acquisition in a short-axis plane positioned at the level of the mitral annulus and systolic outflow by a velocity-encoded cine MR acquisition positioned at the level of the proximal ascending aorta (Fig. 10-24) . The difference between the two volumes is the volume of mitral regurgitation.[89]

Measurement of Blood Flow

Measurement of blood flow velocity with MRI has been done using a technique under several names, including phase contrast MRI, velocity flow mapping, and velocity-encoded cine MRI. This method is principally based on the phase shifts of moving spins in the magnetic field gradient.[5] The extent of phase shifts of moving spins is proportional to velocity along the velocity-encoding direction. Velocity encoding is performed by using bipolar gradient pulses. The direction of velocity encoding can be done in any orthogonal or oblique axis of the body.

Velocity encoding of blood flow in each pixel provides 2D quantitative velocity mapping of the vascular system (see Figs. 10-23 , 10-24 , and 10-34). The instantaneous flow in the ascending aorta can be determined by the product of the cross-sectional area and mean velocity of the blood within the aorta. The integration of the instantaneous flow at the base of the aorta through the cardiac cycle provides a measure of left ventricular stroke volume, and the same done at the proximal pulmonary artery is a measure of right ventricular stroke volume. The stroke volumes measured in this manner have correlated well with ventricular stroke volumes measured by planimetry of the multiple adjacent cine MR images. Measurement of flow by velocity-encoded cine MRI should be very accurate provided that the flowing blood generates enough signal to calculate phase; the velocity phase-encoding gradients are accurately calibrated; and the correct range of velocity in the vessels being interrogated has been selected.

VELOCITY-ENCODED CINE MRI.

Measurement of flow by velocity-encoded MRI has been tested for an array of applications, including measurement of stroke volume of both ventricles, quantification of valvular regurgitation[84] [85] [86] [87] (see Figs. 10-23 and 10-24), estimation of the gradient across valvular and vascular stenoses,[88] [91] and measurement of the volume of left-to-right shunts[133] (see Fig. 10-34) . Velocity encoding can be used with the breath-hold cine MRI sequence[12] [13] (see Fig. 10-12) and with EPI. Some pitfalls accompany the use of the velocity-encoded cine MRI technique for measuring blood flow. These include aliasing due to setting of the maximum velocity range to less than the actual velocity. The finite slice thickness also results in volume averaging, causing underestimation of peak velocity. Furthermore, orientation may not provide optimal interrogation of the jet, so that velocity is underestimated.

Velocity-encoded cine MRI can be used to measure flow in the ascending aorta and

pulmonary artery simultaneously to quantify the volume of some left-to-right shunts and to calculate the pulmonary-to-systemic flow ratio (Qp/Qs) of cardiovascular shunts (see Fig. 10-34) . The MR measurement of Qp/Qs has correlated closely with that derived from oximetric data acquired during cardiac catheterization in patients with atrial septal defects.[133] Measurement of blood flow separately in the right and left pulmonary arteries can be used to quantify the distribution of pulmonary blood flow in lesions causing unequal flow. This technique can also be applied to estimate the gradient across pulmonary vascular stenosis, stenosis of branches of the pulmonary artery, coarctation of the aorta, and Rastelli conduits.

Velocity-encoded cine MRI has been used to provide an estimate of the collateral circulation in coarctation.[134] In healthy subjects the total flow in the distal part of the descending aorta is slightly decreased compared with the flow in the proximal part of the descending aorta because of runoff through the intercostal arteries. In patients with hemodynamically significant coarctation, the MR measurements have revealed a substantial increase in flow in the distal compared with the proximal part of the descending aorta. This increase in flow is presumably due to retrograde flow in the branches of the descending aorta.

Figure 10-34 *A,* Phase image at level of ascending aorta and main pulmonary artery. Flow is calculated as the spatial average velocity of the vessel and the cross-sectional area of the vessel. *B,* Flow-versus-time curves for the aorta and pulmonary artery. The difference in area under the two curves is the volume of the left-to-right shunt in a patient with an atrial septal defect.

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COMPUTED TOMOGRAPHY

TECHNICAL ASPECTS

Computed tomography of the heart usually requires modification of the standard CT techniques used for investigating other parts of the body. For some purposes, such as evaluation of thoracic aortic disease, pericardial disease, paracardiac and intracardiac tumors, and patency of coronary arterial bypass grafts, newer spiral and multiple array CT scanners with exposure times of less than 1 second are usually adequate. Continuously rotating (spiral) CT scanners have an exposure time of 1 second or less for each image with no interscan delay between images at sequential anatomical levels, producing images of the entire heart in 12 to 20 seconds. Multiple-array CT scanners can acquire images of the entire heart and proximal aorta in several seconds. Although adequate anatomical depiction of cardiovascular anatomy is attained with spiral and multidetector CT scanners, scans corresponding to precise phases of the cardiac cycle cannot be obtained. For the assessment of cardiac dimensions and function in addition to morphology, millisecond CT scanners are required.[135] [136] [137] [138] The evolution of CT of the heart in the early stages also involved ECG gating of CT data acquisition. However, such gating techniques proved to be cumbersome and never received clinical acceptance. The use of ECG triggering of the acquisition is now being used again with the new multiple array (multislice) CT scanner.

SPIRAL CT SCANNING.

CT scans at multiple adjacent anatomical levels are obtained during a breath-hold period. Each CT scan is acquired in approximately 1 second. This is accomplished by multiple rotations of the CT scanner gantry while the table is continuously moved through the gantry. This permits multiple transaxial scans, 3 to 10 mm in thickness, of

most or the entire thorax during a single breath-hold period at the time of peak contrast medium enhancement of the cardiovascular structures. Eighty to 100 ml of contrast medium at a rate of 2 to 3 ml/sec is injected intravenously, and CT acquisition is started at 15 to 30 seconds after the start of the injection (circulation time).

Electron-Beam (Cine, Ultrafast) CT Scanner

The electron-beam (EB) CT scanner employs a scanning focused x-ray beam that provides complete cardiac imaging in 50 milliseconds without the need for electrocardiographic gating (Fig. 10-35) . This CT scanner is not limited by the inertia associated with moving mechanical parts. It uses a focused electron beam that is successively swept across four cadmium tungstate target arcs at the speed of light. Each of the four targets generates a fan beam of photons that pass from beneath the patient to a bank of photon detectors arranged in a semicircle above the patient.

The EBCT scanner can be operated in three different modes: (1) the *cine mode* is used to assess global and regional myocardial function. The scans are obtained at an exposure time of 50 milliseconds and at a rate of 17 scans per second[135] (Fig. 10-36) . The *triggered mode,* used for flow analysis, employs a series of 20 to 40 successive scans in which each 50-millisecond exposure is triggered at a specific phase of the cardiac cycle of successive heartbeats or every other heartbeat. From such a series of scans, time-density curves can be constructed for specific regions of interest in the cardiac chamber or myocardium, providing an estimate of transit time, perfusion, or blood flow.[140] The *volume mode* provides eight scans by the use of all four target arcs in an imaging period of approximately 200 milliseconds. These eight transverse scans can sometimes encompass the entire left ventricular chamber and thereby provide an estimate of left ventricular volume and mass. Usually 10 to 12 tomographic levels are needed to entirely encompass the heart.

Because multiple images can be acquired at multiple levels, EBCT permits the acquisition of images at end diastole and end systole because both are approximately 60 milliseconds in duration. Real-time sequential imaging is accomplished within a single heartbeat at multiple levels, and these images can then be displayed in a close-loop cine format (cine CT display).

CONTRAST ENHANCEMENT.

For nearly all purposes, intravenous injection of iodinated contrast medium is used to

Figure 10-35 Diagram of cine CT scanner. Electron gun produces a stream of electrons that are magnetically focused and directed onto four tungsten target rings. Each target ring emits two fan beams of x-ray. Transmission of x-rays through the subject is registered by detectors arranged over a

180-degree arc.

delineate the blood pool on CT scans. The contrast medium can be given as an intravenous bolus injection or a rapid infusion. For evaluation of the heart and great vessels, contrast medium is usually delivered in a bolus over several seconds and in a volume of 40 to 80 ml. Scans are exposed at the estimated time of peak enhancement of the structure of interest. To identify the time of arrival of contrast medium in the left-sided cardiac chamber and aorta, a preliminary bolus injection of a small volume of contrast medium or indocyanine green dye can be given to define circulation time. This time is then used to specify the time of acquisition of the series of EBCT scans. Scans are sometimes obtained without contrast medium to identify calcification of cardiac structures.

Figure 10-36 Series of CT scans of the same anatomical level acquired every 50 msec during a single cardiac cycle in a patient with hypertrophic cardiomyopathy. These are 9 of 17 scans acquired in approximately one cardiac cycle. Frame at upper left is near end diastole (ED) and middle frame is near end systole (ES). Note the change in ventricular volumes during the cardiac cycle and wall thickening during systole. *(Courtesy of J. Rumberger, PhD, MD, Mayo Clinic.)*

EVALUATION OF CARDIAC DIMENSIONS AND FUNCTION (See also Chap. 15)

Computed tomography has the capability of identifying not only the inner endocardial wall but also the epicardial surface. Wall thickness and myocardial mass have been estimated accurately with EBCT.[138] A close correlation has been found between CT measurements and postmortem anatomical measurements of wall thickness and mass.[138] It has also been employed to estimate right ventricular mass by measuring the mass of the free wall.[142] [143] Right ventricular mass was demonstrated to be substantially increased in patients with pulmonary arterial hypertension compared with measurements in normal subjects.[143]

CT can be used in the assessment of the dynamics of *regional myocardial wall thickening* (see Fig. 10-36) . [142] [144] A series of tomograms in a short-axis plane acquired during multiple phases of the cardiac cycle permits measurement of area ejection fraction and wall thickening at various levels of the left ventricle, extending from the base to the apex. In normal human subjects, a variation in both regional ejection fraction and extent of wall thickening has been defined; a gradient in both area ejection fraction and extent of wall thickening increases progressively from basal to apical layers.[141] Cine CT has demonstrated dysfunction of wall thickening and wall motion in global and regional myocardial abnormalities.[136] [145] [146]

Left ventricular volumes and *ejection fraction* can be estimated by contrast angiography, echocardiography, and gated blood pool nuclear images. Whereas the quantitation of ventricular volumes and ejection fraction by EBCT is not a unique capability, the accuracy of CT can potentially exceed that of the other techniques. Other cardiac imaging techniques such as echocardiography and left ventricular angiography estimate left ventricular volume, making geometric assumptions from measurements performed in one or two planes. These assumptions lead to inaccuracies of volume measurement

in the presence of left ventricular conformational abnormalities. EBCT directly measures chamber volumes by planimetry of the cardiac blood pool on each tomogram, allowing precise volume determination. Left ventricular volume, ejection fraction, and stroke volume can be acquired by EBCT with high accuracy and close reproducibility among observers and among studies on different occasions in the same subject.[147] [148] In normal subjects the stroke volumes of the right and left ventricle as measured by ultrafast CT were equal.[148]

EBCT provides a measurement of total ventricular *stroke volume.* If an independent technique is used for the measurement

of forward (effective) stroke volume, then these measurements can be combined to estimate regurgitant volume; regurgitant volume is the difference between total stroke volume and forward stroke volume. EBCT can also be applied for the simultaneous quantification of the right and left ventricular stroke volumes.[148] [149] The difference in the stroke volume between the ventricles is equal to the total regurgitant volume of valves on one side of the heart. The method is not relevant for circumstances in which valvular regurgitation is present in both the right and left ventricles.

EVALUATION OF SPECIFIC CARDIAC DISEASES

Ischemic Heart Disease

After myocardial infarction, CT can be used to demonstrate regional wall thinning and complications of infarction, such as left ventricular aneurysm (Figs. 10-37 and 10-38) and mural thrombus (see also Chap. 35) . EBCT demonstrates reduced wall thickening and wall motion as evidence of left ventricular segmental dysfunction in ischemic heart disease.[150] EBCT has also been used to monitor left ventricular remodeling after acute myocardial infarction[151]

CT provides unequivocal spatial separation between various regions of the left ventricle, enabling better localization and estimation of the extent of wall thinning after infarction compared with projectional techniques such as left ventriculography and most scintigraphic techniques. Likewise, the site and extent of anterior and posterior aneurysms of the left ventricle can be well demonstrated (see Figs. 10-37 and 10-38). The differentiation by CT between true aneurysm and pseudoaneurysm depends on the identification of the small ostium connecting the left ventricular cavity and the aneurysm. False aneurysms are usually substantially larger than true aneurysms and frequently arise from the posterior or inferior wall of the left ventricle.

CT has been found to be as accurate as 2D echocardiography

Figure 10-37 Cine (ultrafast) CT images at four adjacent anatomical levels (cranial [*upper left*] to cranial [*lower right*]) in a patient with inferior left ventricular aneurysm. The CT images demonstrate the location and extent of the aneurysm. *(Courtesy of Imatron, Inc.)*

Figure 10-38 Cine (ultrafast) CT images at four adjacent anatomical levels (cranial [*upper left*] to cranial [*lower right*]) demonstrate an anterior left ventricular aneurysn. There is severe thinning of the anteroseptal and anterior walls and bulging of the left ventricle anteriorly. *(Courtesy of Imatron, Inc.)*

for identifying left ventricular *mural thrombus.*[152] Moreover, comparative studies have shown greater accuracy of CT compared with 2D echocardiography in demonstration of thrombus in the left atrium.[153] The comparative accuracy of CT and transesophageal echocardiography has not been established.

REGIONAL WALL MOTION.

For the evaluation of regional myocardial function, the cine mode of the ultrafast CT scanner is used to acquire images at 17 scans per second at the time of peak opacification of the left ventricle. Quantitation of systolic myocardial wall thickening appears to be a particularly useful technique for evaluating regional myocardial contractile function in patients with ischemic heart disease. Identification of regional contraction abnormalities in patients with hemodynamically significant stenoses has been done using EBCT performed at rest and during exercise.[146]

MYOCARDIAL PERFUSION.

EBCT may also be able to provide an indication of *regional myocardial perfusion.*[139] [140] [154] [155] Estimates of myocardial perfusion are obtained by drawing regions of interest over various sites of the myocardium displayed on the transverse CT scans. The density of the myocardial regions is measured on sequential 50-millisecond scans acquired during an appropriate duration of the myocardial contrast medium-enhancement phase. From these measurements, time-density curves are constructed; analyses of these curves in regard to contrast appearance and washout are used to estimate regional myocardial perfusion. Thus, EBCT has the potential of providing both regional function and perfusion in a single study. Experiments have shown that flow can be reliably estimated under variable physiological (vasodilatation) and pathological (stenosis) states in comparison to radiolabeled microspheres.[140] [155] Measurements of regional flow in response to a vasodilator can be used to test coronary flow reserve in various regions and to identify a region served by an artery with a critical stenosis by failure of flow to rise in response to a vasodilator.

DETECTION OF MYOCARDIAL ISCHEMIA.

EBCT can be used to detect regional myocardial dysfunction or a regional

Figure 10-39 *Left,* Sequential cine CT scans show patent bypass grafts (arrows) to the left anterior descending artery and acute diagonal. *Right,* Graft to the obtuse marginal branch of the circumflex artery (arrow). Note that the grafts opacify simultaneously with the ascending aorta. Each set of four images was obtained at the same anatomical level. The images were done with the passage of contrast medium through the central circulation. Early images *(A, B)* show contrast in the pulmonary artery and later images *(C, D)* show contrast in the aorta and bypass grafts.

myocardial perfusion deficit caused by ischemia. Thus, this technique has the capability of combining functional and perfusion approaches for the detection of regional myocardial ischemia. It has improved edge definition compared with echocardiography, permitting measurement of wall thickening before and after pharmacological stress. It also has considerably better spatial resolution than radionuclide imaging.

PATENCY OF CORONARY ARTERY BYPASS GRAFTS (CABG).

Several reports have indicated high accuracy of EBCT for defining the patency of coronary artery bypass grafts.[156] [157] [158] The diagnostic accuracy of EBCT for defining the patency of saphenous grafts and internal mammary bypasses has been shown to be greater than 90 percent in a multicenter study.[156] High accuracy was shown for defining patency of grafts to the left anterior descending, circumflex branches, and right coronary arterial branches.

The site of the bypass graft on contrast medium-enhanced CT scans can be related to a clock. The grafts to the right coronary artery are situated between 9 and 11 o'clock; grafts to the left anterior descending artery system are situated at 12 to 2 o'clock; and the grafts to the circumflex coronary system are located at 2 to 4 o'clock (Fig. 10-39) . Diagnostic confidence is enhanced by visualizing the grafts at two adjacent anatomical levels and by showing contrast medium enhancement of the graft with aortic opacification.

CORONARY ARTERIAL CALCIFICATION (See also Chap. 8) .

Calcification in the coronary arteries usually indicates the presence of atherosclerosis. Although the early stages of atherosclerosis exist without calcification and calcification occurs in the coronary arteries in the absence of hemodynamically significant arterial obstruction, the detection of calcification increases the likelihood of significant coronary arterial obstructive disease in a specified population of patients. Older studies[159] [160] [161] have revealed that in patients being studied by coronary arteriography, the absence of fluoroscopically detectable coronary arterial calcification is usually associated with no significant arterial stenoses and the presence of calcification with significant stenoses (50 percent reduction in luminal diameter).

EBCT has been used in the past few years for the detection of calcification in the

coronary arteries. It can be performed more rapidly than can fluoroscopy, without the presence of a physician, which potentially makes it feasible as a low-cost screening test. It is more sensitive than fluoroscopy in detecting calcification, with excellent intraobserver and interobserver and interstudy reproducibility.[141] [162] Several studies using excised hearts or excised coronary arteries have shown a nearly one-to-one correlation between sites of coronary calcification depicted by EBCT and postmortem histomorphometry.[163] [164] [165] [166] The total volume of calcification by EBCT correlates more closely with total burden of atherosclerotic plaque than lumen stenosis.[167]

A close correlation has been found between the total mass of calcium in the coronary arteries as reflected in the calcium score (area of calcium on scan times density of calcium as expressed by the range of CT density numbers) and the total mass of atherosclerotic plaques, numbers of arterial segments with stenosis, and numbers of arteries and segments with greater than 75 percent reduction in luminal diameter.[163] [164] [165] [166] [167] In one postmortem study, greater than 97 percent of arterial segments without calcification were free of hemodynamically significant stenosis (<75 percent area stenosis) and no hemodynamically significant stenosis was shown in any vessel without calcification in any segment.[163] Thus, EBCT examination of postmortem specimens shows that the technique detects coronary calcification when it is present and can accurately quantify the mass of calcium in the coronary arteries. The mass of the calcium as measured by EBCT is closely related to the number of arterial segments and number of arteries containing nonobstructive and obstructive atherosclerotic plaques and the total atherosclerotic burden of the coronary arterial system.

PREDICTION OF PRESENCE OF CORONARY STENOSIS.

The presence of coronary arterial calcification, the number of coronary arteries with calcification, and the total mass of coronary calcification in the coronary circulation have been used to predict the presence of any degree of coronary arterial stenosis and hemodynamically significant stenosis compared with coronary arteriography.[168] [169] [170] The sensitivity for predicting any degree of stenosis or hemodynamically significant stenosis has been high, usually exceeding 90 percent, but the specificity is only fair. The mass of calcium is quantified by calculating the calcium score (total area of calcium×density weighting) (Fig. 10-40) .[162]

The prevalence of coronary arterial calcification detected by EBCT in women is half that of men until the age of 60; the distribution of calcium scores of men between the ages 40 and 69 years was nearly identical to that of women between ages 50 and 79.[170] Because the presence of coronary calcification and the calcium score increase with age,[162] the usefulness of EBCT for identifying patients at a higher risk for significant coronary arterial disease decreases with increasing age (Fig. 10-41) . Although the sensitivity remains high even in patients younger than age 50 years, the specificity for predicting significant stenosis is still only fair.[171]

In one report,[167] investigators found that coronary calcium quantification by EBCT is an effective method for defining atherosclerotic burden at individual arterial sites and the total amount of calcium correlates with the atherosclerotic burden in the coronary

arteries. Rumberger and associates[172] have proposed coronary artery calcium

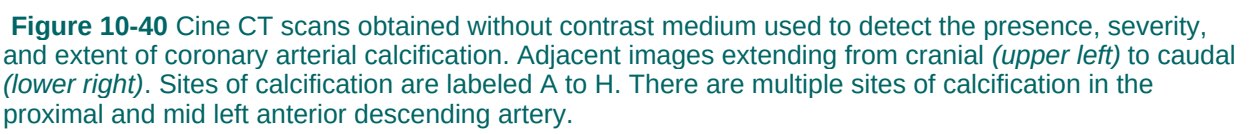

Figure 10-40 Cine CT scans obtained without contrast medium used to detect the presence, severity, and extent of coronary arterial calcification. Adjacent images extending from cranial *(upper left)* to caudal *(lower right)*. Sites of calcification are labeled A to H. There are multiple sites of calcification in the proximal and mid left anterior descending artery.

scores (CAC scores) for individual coronary arteries that maximize the sensitivity and specificity for predicting the severity of coronary arterial stenosis on coronary angiography (Fig. 10-42) . A calcium score of 80 predicts a 50 percent stenosis with a sensitivity and specificity of 84 percent.

Coronary arterial calcium quantification has been compared with electrocardiographic and thallium exercise testing for predicting stenoses in 251 consecutive patients before elective coronary arteriography.[173] A cut-off score of total coronary arterial calcium was at least as useful and better in some patient groups for predicting stenoses compared with the other two tests. Coronary arterial calcium scoring has also been found to be a reliable test for distinguishing between patients with ischemic and nonischemic cardiomyopathies.[174]

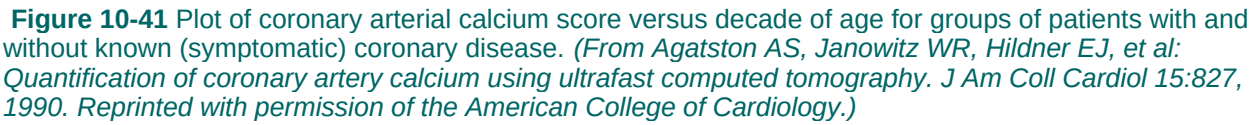

Figure 10-41 Plot of coronary arterial calcium score versus decade of age for groups of patients with and without known (symptomatic) coronary disease. *(From Agatston AS, Janowitz WR, Hildner EJ, et al: Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 15:827, 1990. Reprinted with permission of the American College of Cardiology.)*

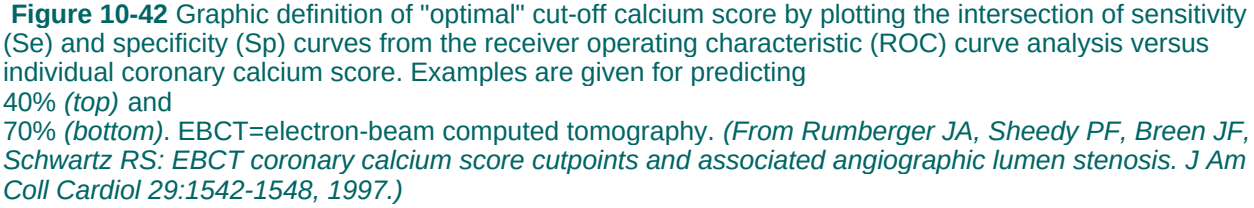

Figure 10-42 Graphic definition of "optimal" cut-off calcium score by plotting the intersection of sensitivity (Se) and specificity (Sp) curves from the receiver operating characteristic (ROC) curve analysis versus individual coronary calcium score. Examples are given for predicting
40% *(top)* and
70% *(bottom)*. EBCT=electron-beam computed tomography. *(From Rumberger JA, Sheedy PF, Breen JF, Schwartz RS: EBCT coronary calcium score cutpoints and associated angiographic lumen stenosis. J Am Coll Cardiol 29:1542-1548, 1997.)*

Because an absolute correspondence has not been shown for calcification and an obstructive lesion at a specific site, this test cannot be substituted for coronary arteriography. Consequently, the additive value of EBCT in symptomatic patients in the era of cost containment has been questioned. The role of EBCT for detecting calcification in asymptomatic patients is also still controversial, although it is being performed with increasing frequency. A number of studies have shown significant correlations between several risk factors for coronary artery disease and the presence

and amount of coronary artery calcium defined by EBCT in asymptomatic patients. Coronary artery calcification has been related to age, gender, cigarette smoking, hypertension, diabetes, and hypercholesterolemia. EBCT-defined calcification was found in high-risk asymptomatic adults to be about equivalent to but no better than risk factors assessment in identifying patients who will incur coronary events over a 3- to 4-year follow-up period.[175] Some studies also suggest that coronary events in both symptomatic patients referred for coronary arteriography [176] and asymptomatic individuals[177] [178] could be related to coronary artery calcification score.

The role of EBCT in identifying patients at higher risk for the development of symptomatic coronary arterial disease, cardiac morbidity, and death remains somewhat controversial. As a potential screening test, it does have high sensitivity and can be performed rapidly, inexpensively, and noninvasively. Perhaps its role at the current time is to indicate patients with some degree of atherosclerotic coronary arterial disease who should enter strict risk-reduction programs. The absence of coronary arterial calcification by EBCT makes the presence of significant coronary arterial disease very unlikely. However, it does not exclude such disease.

EBCT CORONARY ARTERIOGRAPHY.

In the past few years, contrast medium-enhanced EBCT has been shown to be effective for visualizing the lumen of the major coronary arteries.[179] [180] [181] [182] [183] This is done by acquiring contiguous or overlapping

Figure 10-43 Electron-beam CT coronary angiography sliding slab reconstruction of four 3-mm slices through the proximal portion of the coronary arteries during peak opacification of the coronary arteries after intravenous injection of contrast medium. The proximal left and right arteries are shown. *(From Chernoff D, Ritchie CT, Higgins CB: Evaluation of electron beam CT coronary angiography in healthy subjects. AJR Am J Roentgenol 169:93, 1997.)*

thin CT scans at the same phase of diastole during breath holding (Fig. 10-43) . From this 3D data set, projectional images can be produced that display the major coronary arterial branches (Fig. 10-44) . Postprocessing of the data set can be done to subtract the heart from the image and thereby provide an isolated projectional image of the coronary arteries.

EBCT coronary arteriography in normal volunteers has shown the capability of the technique for displaying about 8 cm of the three major coronary arteries with good contrast-to-noise ratio.[179] Several studies[180] [181] [182] [183] have now shown a sensitivity of 74 to 92 percent and specificity of 79 to 94 percent for identifying hemodynamically significant coronary arterial stenosis as defined by selective coronary arteriography.

Pericardial Disease (See also Chap. 50)

Computed tomography provides distinct visualization of the pericardium in most patients. Discrimination of the pericardial line from the myocardium depends on the presence of some epicardial and pericardial fat; it has been reported to be visible on CT scans of 95 percent of normal subjects.[184] Although visible over the right atrium and ventricle in most subjects, it is frequently not detectable on the lateral and posterior walls of the left ventricle. The mean width of the line in normal subjects is 2.2 mm at its thinnest portion and is always less than 4 mm. Pericardial thickness is usually normal near its diaphragmatic attachments. CT also frequently demonstrates the superior recesses of the pericardium extending over the ascending aorta and lateral to the main pulmonary artery. These recesses may be distended in the presence of a pericardial effusion.

2D echocardiography is an extremely effective technique for the diagnosis of pericardial abnormalities and is the primary modality for evaluation of suspected pericardial disease (see also Chap. 7) . Although it is extremely sensitive for the detection of pericardial effusion, it has some limitations in defining loculated effusions, hemorrhagic effusions, and especially pericardial thickening. CT is especially effective in depicting these features.[185] [186] Consequently, it is complementary to echocardiography in the diagnosis and assessment of pericardial disease.

CONGENITAL ABNORMALITIES AND CYSTS OF THE PERICARDIUM.

Congenital abnormalities, such as absence of the pericardium[187] and pericardial cyst[185] [186] can be well demonstrated by CT. The pericardial defect (usually partial or complete absence of left-sided pericardium) is recognized on CT by the discontinuity of the pericardial line over the left aspect of the heart, with shift of the heart leftward or bulging of the left atrial appendage through the defect. CT demonstrates interposition of a tongue of lung tissue between the proximal ascending aorta and main pulmonary artery at the base of the heart in the absence of the left-sided pericardium.

A pericardial cyst appears as a paracardiac mass with a thin capsule that is occasionally partially or completely calcified and has a homogeneous internal density nearly equivalent to that of water. However, rarely the cyst contains mucoid material, causing the density to be higher than water; such a cyst usually cannot be reliably distinguished from a solid mass. *Thymic* and *bronchogenic cysts,* which may be adjacent to the pericardium, also may show homogeneous water density on CT densitometry and may be indistinguishable from pericardial cysts.

PERICARDIAL FLUID.

Fluid in the pericardial space may be reliably detected by CT.[185] [188] This technique can also provide an accurate estimate of the volume of this fluid.[188] Although 2D echocardiography is sufficient and, for economic and logistic reasons, more clinically efficacious for the primary evaluation of most pericardial effusions, CT is indicated in

some special situations. Loculated effusions (especially anterior loculations), which may pose difficulty

Figure 10-44 Elecron-beam CT coronary angiography. Shaded surface displays three-dimensional reconstruction of the left coronary artery. The reconstruction is done from 3-mm transaxial CT scans. LAD=left anterior descending artery; LCX=left circumflex artery.

Figure 10-45 Calcific constrictive pericarditis. Cine CT scans at the base of the heart *(left)* and at mid ventricular level *(right)*. Note the heavy calcification at multiple sites of the pericardium and extending into the posterior atrioventricular grove. *(Courtesy of Imatron, Inc.)*

for echocardiography, are readily demonstrated on CT because of the wide field of view provided and the potentially 3D nature of the technique.[186] CT can be effective not only for diagnosing loculated effusions but also for guiding pericardiocentesis.[189] CT density measurements provide some degree of characterization of pericardial fluid. Density numbers (Hounsfield numbers) exceeding water density (water density=0 to 12 units) are suggestive of hemopericardium, purulent exudate, or effusions associated with hypothyroidism. Low-density pericardial effusions have been reported in the presence of chylopericardium.[188]

CONSTRICTIVE PERICARDITIS.

The establishment of the diagnosis of constrictive pericarditis can be substantially aided by CT.[185] [186] Because CT shows the pericardium, it can document pericardial thickening, defined as thickness greater than 4 mm. Focal plaques of thickening or the greater thickness of the pericardium near the diaphragm should not be confused with the more extensive pericardial thickening associated with constrictive pericarditis. However, the pericardial thickening may be limited to the right side of the heart, a form that appears to be more prevalent in patients who have undergone coronary arterial bypass surgery.

The documentation of pericardial thickening is the major discriminatory feature between constrictive pericarditis and restrictive cardiomyopathy (Fig. 10-45) . However, thickened pericardium per se is not indicative of constrictive disease. Pericardial thickening without constriction is frequently observed in the early postoperative period and may persist for several months after operation in patients with the postpericardiotomy syndrome.[185] Thickened pericardium without constriction has also been observed in association with inflammation of the pericardium caused by a variety of conditions, including uremia, rheumatic heart disease, rheumatoid arthritis, sarcoidosis, and postmediastinal irradiation. Pericardial thickening may also be caused by metastatic carcinoma, thymoma, and lymphoma and mesothelioma. These conditions are usually associated

with effusion. Likewise, primary sarcoma of the heart and mediastinal and lung malignant tumors extending to the pericardium produce local or diffuse pericardial thickening and loculated or generalized pericardial effusion. Moreover, thickened pericardium is to be expected in many patients for several weeks after cardiac surgery. It may be present for a prolonged period in patients afflicted by the postpericardiotomy syndrome.

EFFUSIVE-CONSTRICTIVE PERICARDITIS.

This condition is demonstrated by an effusion in association with thickened pericardium; however, it may not always be possible to distinguish a small effusion from thickened pericardium.[185] Pericardial thickening alone usually measures between 5 and 20 mm, whereas greater thickening generally indicates associated effusion or effusion alone. Contrast medium enhancement of the thickened pericardium is indicative of pericardial inflammation[190] (Fig. 10-46) . Additional CT findings in constrictive pericarditis often reflect the anatomical and physiological consequences of the thickened pericardium on the cardiac chambers.[191] [192] [193] CT shows substantial dilatation of the inferior vena cava and some enlargement

Figure 10-46 Cine CT scans at the levels of the right pulmonary artery *(A)* and at the ventricles *(B)* in a patient with a pericardial inflammation and large effusion. The effusion extends over the pulmonary artery as well as the ventricles. There is contrast enhancement of the pericardium (arrows), suggesting pericardial inflammation. *(Courtesy of Imatron, Inc.)*

of the atria, especially the right atrium (see Fig. 10-45) . The ventricles tend to have a small volume and a narrow tubular configuration.[192] In some cases, a sigmoid-shaped ventricular septum or prominent leftward convexity of the septum has been observed. Unusual contours, such as straightening or focal indentation of the free wall of either the right or left ventricle, have been noted on CT.[192]

The density resolution of CT makes it the most sensitive technique for identifying pericardial calcification. Pericardial calcific deposits are usually residuals of pericardial inflammation and are most commonly found in the visceral layer along the atrioventricular and interventricular grooves. Extensive calcification of the pericardium suggests but does not prove the presence of cardiac constriction.

Paracardiac, Pericardial, and Cardiac Masses

Computed tomography is useful for the evaluation of pericardial and paracardiac masses. CT and, more recently, MRI have emerged as the preferential techniques for defining the site and extent of such masses and in some cases even indicate their nature.[185] [186] CT may show the water density of pericardial cysts; this is an especially

useful finding when the cyst is located in an unusual mediastinal location or when it protrudes inwardly, displacing the atrial wall. CT and MRI are currently the best techniques for defining the extension of mediastinal neoplasms (including lymphoma) and of carcinoma of the lung into the pericardium. Metastatic involvement of the pericardium is suggested by the CT findings of effusion with an irregularly thickened pericardium or the actual demonstration of a mass involving the pericardium. An effusion with high CT density (hemopericardium) along with pericardial thickening also suggests metastatic pericardial involvement.[186]

CT sometimes provides insight into the nature of the mass by demonstrating the shape, defining the density measurements, or showing multiple masses. The CT demonstration of multiple pericardial nodules suggests metastatic tumor or, rarely, multicentric mesothelioma. Pericardial cysts have water density, whereas lipomas have a very low density value (-55 or fewer Hounsfield units). Demonstration of calcium or bone and fat in a paracardiac mass by CT suggests teratoma.

Intracardiac masses can be detected very well by echocardiography and angiography. However, CT not only can detect masses within the cardiac chambers but also can define fully their extent (Fig. 10-47) . CT can demonstrate components of the mass within the myocardial wall and extending outside of the heart. The contrast resolution of CT may provide some insight into the composition of the mass, such as demonstrating the presence of fat or calcium. CT readily demonstrates simple intracardiac masses such as atrial myxoma and complex masses involving the myocardial wall with extracardiac extension. Finally, by defining clearly the myocardial wall, CT can demonstrate an extracardiac location of tumors that produce compression and invagination of cardiac walls, simulating an intracardiac origin.[194]

INTRACARDIAC THROMBUS.

The most frequent intracardiac mass is a thrombus. Intracardiac thrombi are usually located in the left atrium in patients with mitral valve disease or patients with atrial fibrillation from any cause and in the left ventricle in patients with recent myocardial infarction or patients with dilated (congestive) cardiomyopathy. Although transthoracic echocardiography is usually the initial study used to detect intracardiac thrombi or an intracardiac source of peripheral embolism, recent studies have revealed that CT is as sensitive but more specific for identifying ventricular thrombus[152] and more sensitive for defining left atrial thrombus.[153] Thrombi in the left atrial appendage and lateral wall of the atrium are more readily detected with MRI and CT than with transthoracic echocardiography. MRI and CT are very effective techniques for the detection of intracardiac thrombus; however, their accuracy compared with transesophageal echocardiography has yet to be systematically evaluated.

Congenital Heart Disease (See also Chaps. 43 and 44)

Standard CT, EBCT, and MRI are useful noninvasive techniques for the visualization of cardiovascular anatomy in patients with congenital heart disease. EBCT and MRI can also provide assessment of cardiovascular function in these patients. MRI appears to be the most suitable of these techniques for assessing congenital heart disease. The x-ray

exposure, contrast media requirement, and inability to image in multiple plane are limitations of CT for the evaluation of congenital heart disease.

STANDARD CT.

This technique has been found to be useful for evaluation of suspected *anomalies of the aortic arch.* [195] [196] Contrast medium-enhanced CT is usually required to show the vascular tissue surrounding the trachea in the presence of double aortic arch and the retroesophageal vascular structure indicating anomalous origin of the subclavian artery. Double arch is also suggested by the presence of four paratracheal vessels arranged symmetrically at the cervicothoracic junction.

EBCT.

At a few centers EBCT has also been tested for its potential for the evaluation of congenital heart disease.[197] [198] EBCT accurately defined systemic and pulmonary venous connections. Likewise, it has demonstrated atrial and ventricular septal defects. Transverse tomograms provide clear spatial separation of the inflow and outflow portions of the ventricular septum. This permits localization of defects and facilitates the detection of multiple ventricular septal defects. In addition, an assessment of the hemodynamic effects of septal defects (and of other lesions) can be made by evaluation of chamber dimension and wall thickness. Because of the absence of overlying structures defined on CT

Figure 10-47 Cine CT scans of left atrial myxoma. *Left,* The attachment of the myxoma to the atrial septum and prolapsing across the mitral valve are shown. *Right,* Malignant tumor invading the left atrium.

Figure 10-48 Type A aortic dissection, cine CT scans at level of right pulmonary artery *(left)* and 1 cm caudal *(right)* demonstrate intimal flap in ascending and descending aorta. Note also the pericardial effusion, indicating probable leakage from the false channel. *(Courtesy of Imatron, Inc.)*

scans and the 3D nature of CT acquisition, the size of the ventricles can be measured.

Normal and abnormal atrioventricular valves can be demonstrated by EBCT,[197] [198] which can be used to diagnose both tricuspid and mitral atresia. It can also demonstrate the size of the atrium above the atretic valve. EBCT has been effective for demonstrating abnormal arterioventricular connections, including transposition complexes and double-outlet right ventricle.[197] [198] Abnormalities of the pulmonary arteries, such as congenital absence, peripheral coarctations, and hypoplasia, have been demonstrated by this technique. However, EBCT is not recommended for this

purpose because multiplanar MRI has been shown in recent years to be the most effective technique for assessing pulmonary arterial anomalies.

Congenital anomalies of the coronary arteries have been demonstrated very well using EBCT scans positioned at the base of the heart.[199] Ectopic origin of coronary arteries and coronary arteriovenous fistulas have been effectively demonstrated by this technique. Contrast medium-enhanced EBCT and MRI are probably the noninvasive procedures of choice for the diagnosis and exclusion of major or minor anomalies of origin and course of the coronary arteries. They can display both the anomalous origin and course of coronary arteries. This is especially important for showing a course in the ventricular septum or between the base of the aorta and pulmonary artery when the left anterior descending branch arises from the right coronary artery.

EVALUATION OF CARDIAC FUNCTION IN CONGENITAL HEART DISEASE.

This can be accomplished in patients with congenital heart disease by EBCT, which, along with cine MRI, may be the best technique for quantitating right ventricular volumes and ejection fraction. In addition, EBCT can be used to estimate the volume of shunts. This is accomplished by measuring density of contrast medium within a cardiac chamber receiving shunt flow on sequential CT scans obtained during passage of contrast medium through the central circulation. A density-versus-time curve can be generated for such a region of interest. The normal curve is unimodal as contrast medium enters and leaves a cardiac chamber. A bimodal time-density curve may be generated from the region-of-interest cursor placed over any chamber involved in a shunt. By using a gamma variate fit method, the areas under the primary and secondary portions of the curve can be measured to calculate pulmonary-to-systemic flow ratios.

Another method for calculating the net shunt is to compare the difference in stroke volume between the two ventricles. For a left-to-right shunt at the ventricular level, the difference between the larger left ventricular stroke volume and right ventricular stroke volume indicates the net shunt value. Such an approach can be used also to calculate net volume and fraction of regurgitant lesions.

EBCT appears to be an excellent technique for the evaluation of both right and left ventricular function in surgically corrected congenital heart disease. Because volumes and mass of both ventricles can be measured accurately by CT, this technique can be used to evaluate the expected regression of ventricular dilatation and hypertrophy after corrective procedures.

Figure 10-49 Thoracic aortic aneurysm and type A dissection, cine CT scans at the level of the sinus of Valsalva *(left)* and distal ascending aorta *(right)*. There is aneurysmal dilatation of the sinuses of Valsalva and ascending aorta. Note also the intimal flap in the ascending aorta. There is no dissection of the descending aorta. *(Courtesy of Imatron, Inc.)*

Figure 10-50 Ultrafast CT scans of pulmonary arteries demonstrate a thrombus in the central right pulmonary artery *(left)* and extending into the descending branch of the right pulmonary artery *(right)*. *(Courtesy of Imatron, Inc.)*

Disease of the Thoracic Aorta (See also Chap. 40)

Computed tomography has been shown to be extremely accurate for the diagnosis of thoracic aortic aneurysm, aortic dissection, intramural hematoma, and atherosclerotic ulcerating plaque.[110] [200] [201] [202] [203]

AORTIC DISSECTION.

CT has an accuracy of greater than 95 percent and is equivalent to MRI and better than x-ray angiography for the diagnosis of a variety of diseases of the thoracic aorta.[110] A study comparing CT, MRI, and transesophageal and transthoracic echocardiography has shown greater diagnostic accuracy of CT and MRI than of the echocardiographic techniques.[110] However, some instances of false-negative CT examination in aortic dissection have been reported. Diagnosis of dissection requires the demonstration of the intimal flap, appearing as a lucency within the lumen of the contrast-enhanced aortic lumen on CT scans (Fig. 10-48) . Supportive findings for the diagnosis of aortic dissection are differential temporal enhancement of the true and false aortic channels or compression of the opacified true lumen by a thrombosed false channel. Inward displacement of calcium in the aortic wall is also a sign of aortic dissection. CT can distinguish between dissections that involve the ascending aorta and those that are limited to the descending aorta. In the former, the intimal flap can be demonstrated in the ascending aorta. It may be difficult to differentiate a dissection with thrombus of the false channel from an aortic aneurysm with mural thrombus. A dissection is more likely when CT scans at multiple levels show the thrombus extending for more than 10 cm longitudinally. Also, dissection usually results in a compressed true aortic lumen whereas aneurysm has a normal or increased lumen (see Figs. 40-13 and 40-14).

Intramural hematoma has been reported as a feature of aortic dissection without entry into the lumen of the aorta.[202] It is likely that this is an early stage of some acute dissections, but not all intramural hematomas progress to the typical feature of acute dissection.[202] [204]

CT also may be used for following the course of thoracic aortic dissections after initial treatment.[205] [206] [207] [208] After surgical placement of an ascending aortic graft, the false channel beyond the distal anastomosis of the graft frequently remains patent. Sequential CT studies have also revealed persistent patency of the false channel after medical as well as surgical therapy. Eventual thrombosis of the false channel or even its disappearance is seen in some patients.[207] [208] CT has also been used to follow the

alterations in the false channel of untreated type B dissections; in a minority of patients the aorta reverts to a normal appearance after months to years.[206]

AORTIC ANEURYSM.

This is characterized by an increase in aortic diameter and by outward displacement of calcium of the aortic wall (Fig. 10-49) . CT is an effective method for defining the maximum diameter of the aneurysm and monitoring the diameter over time. A diameter exceeding 4 cm is considered aneurysmal, and one exceeding 6 cm is usually an indication for surgery of thoracic aortic aneurysm.[120]

PULMONARY EMBOLISM.

EBCT[209] and spiral[210] [211] [212] CT have been used in recent years for establishing or excluding the diagnosis of pulmonary embolism (Fig. 10-50) . Both techniques have been shown to provide high diagnostic accuracy for this purpose. It has been proposed that CT scanning be used to confirm the diagnosis of pulmonary embolism in patients with intermediate likelihood of the diagnosis by nuclear pulmonary perfusion scans. At some centers, EBCT or spiral CT has replaced x-ray angiography and nuclear perfusion imaging for the definitive diagnosis of pulmonary embolism.

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Chapter 11 - Cardiac Catheterization

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INDICATIONS FOR DIAGNOSTIC CARDIAC CATHETERIZATION

As with any procedure, the decision to recommend cardiac catheterization is based on an appropriate risk-benefit ratio. In general, diagnostic cardiac catheterization is recommended whenever it is clinically important to define the presence or severity of a suspected cardiac lesion that cannot be adequately evaluated by noninvasive techniques. Intracardiac pressure measurements and coronary arteriography are procedures that, as of this writing, can be performed only by catheterization, although some intracardiac pressures and rudimentary coronary artery anatomy can be evaluated with echocardiography and magnetic resonance imaging, respectively (see Chaps. 7 and 10) . Because the mortality from cardiac catheterization is approximately 0.1 percent in most laboratories, there are few patients who cannot be studied safely in an active laboratory.

The guidelines for diagnostic coronary angiography have been reported by a joint task force of the American College of Cardiology and the American Heart Association.[1] These guidelines describe a three-tiered priority classification for specific disease

states. Class I applications exist for those conditions about which there is general agreement that coronary angiography is justified, although this may not be the only appropriate diagnostic procedure. Class II indications apply to those conditions in which coronary angiography is frequently performed but about which there is divergence of opinion with respect to justification of the usefulness or efficacy of the procedure. Class IIa applies to situations in which the weight of evidence is in favor of usefulness. Class IIb indications are less well established by evidence or opinion. Class III conditions are those about which there is general agreement that cardiac catheterization is not ordinarily useful or effective and in some cases may be harmful. Diseases are grouped under several categories: known or suspected coronary heart disease, atypical chest pain, acute myocardial infarction, valvular heart disease, congenital heart disease, and other conditions. Table 11-1 summarizes the Class I and IIa recommendations of the task force.

The indications for cardiac catheterization are changing and are likely to continue to evolve. A trend has been in two divergent directions. In one, many critically ill and hemodynamically unstable patients are being studied during acute myocardial ischemia and/or severe heart failure. At the other end of the spectrum, an increasing number of studies are being performed in an outpatient setting. The result has been the expansion of traditional indications for cardiac catheterization to include both critically ill patients and ambulatory patients.

Cardiac catheterization should be considered to be a diagnostic test for use in combination with complementary noninvasive tests in cardiology. For example, cardiac catheterization in patients with valvular or congenital heart disease is best done with full echocardiographic knowledge and any other functional information. Then, catheterization can be directed and simplified without obtaining redundant anatomical information.

Identification of coronary artery disease and assessment of its extent and severity are the most common indications for cardiac catheterization in adults. The information obtained by catheterization is crucial to optimize the care of patients with various chest pain syndromes. In addition, the presence of dynamic coronary vascular lesions, such as spasm or thrombosis, may be identified. The consequences of coronary heart disease, such as ischemic mitral regurgitation or left ventricular dysfunction and aneurysm, can be defined. In the current era of acute catheter intervention for acute coronary syndromes, patients may be studied during myocardial infarction or unstable angina or in the early period after acute myocardial injury. The aggressiveness of individual centers in approaching such patients depends on local facilities and treatment philosophies as well as the availability of appropriate therapy and surgical support.

In patients with myocardial disease, cardiac catheterization may provide critical information. It can exclude coronary artery disease as the cause of symptoms and evaluate left ventricular dysfunction in patients with cardiomyopathy. Cardiac catheterization also permits quantification of the severity of both diastolic and systolic dysfunction (see Chap. 15) , differentiation of myocardial restriction from pericardial constriction, assessment of the extent of valvular regurgitation, detection of active myocarditis by endomyocardial biopsy, and observation of the cardiovascular response

to acute pharmacological intervention.

In patients with valvular heart disease, cardiac catheterization provides data both confirmatory and complementary to noninvasive echocardiography and nuclear studies. Roberts[2] and Rahimtoola[3] have emphasized that the risk-benefit ratio of preoperative cardiac catheterization is weighted heavily in favor of the cardiac catheterization. Catheterization may be unnecessary in some preoperative situations, such as in patients with an atrial myxoma or young patients with endocarditis or acute mitral or acute aortic regurgitation. Nevertheless, additional confirmation of the severity of the valvular lesion, identification of associated

TABLE 11-1 -- INDICATIONS FOR CORONARY ANGIOGRAPHY

KNOWN OR SUSPECTED CORONARY DISEASE (Known: previous myocardial infarction, or coronary bypass surgery or PTCA. Suspected: rest- or exercise-induced ECG abnormalities suggesting silent ischemia)

Asymptomatic or Stable Angina

Class I

1. Evidence of high risk on noninvasive testing.
2. Canadian Cardiovascular Society (CSS) class III or IV angina on medical treatment.

Class IIa

1. CCS class III or IV angina that improves to class I or II on medical therapy.
2. Serial noninvasive testing showing progressive abnormalities.
3. Patient with disability or illness that cannot be stratified by other means.
4. CCS Class I or II with intolerance or failure to respond to medical therapy.
5. Individuals whose occupation involves safety of others (e.g., pilots, bus drivers) with abnormal stress test results or high-risk clinical profile.

Nonspecific Chest Pain

Class I

High-risk findings on noninvasive testing.

Class IIa

None.

Class IIb

Recurrent hospitalizations for chest pain with abnormal or equivocal noninvasive test results.

UNSTABLE CORONARY SYNDROMES

Class I

1. High or intermediate risk for adverse outcome in patients with unstable angina refractory to initial adequate medical therapy, or recurrent symptoms after initial stabilization. Emergent catheterization is recommended.
2. High risk for adverse outcome in patients with unstable angina. Urgent catheterization is recommended.
3. High- or intermediate-risk unstable angina that stabilizes after initial treatment.
4. Initially low short-term-risk unstable angina that is subsequently high risk on noninvasive testing.
5. Suspected Prinzmetal's variant angina.

Class IIa

None.

PATIENTS WITH POSTREVASCULARIZATION ISCHEMIA

Class I

1. Suspected abrupt closure or subacute stent thrombosis after percutaneous revascularization.
2. Recurrent angina or high-risk criteria on noninvasive evaluation within 9 mo of percutaneous revascularization.

Class IIa

1. Recurrent symptomatic ischemia within 12 mo of CABG.
2. Noninvasive evidence of high-risk criteria occurring at any time postoperatively.
3. Recurrent angina inadequately controlled by medical means after revascularization.

DURING THE INITIAL MANAGEMENT OF ACUTE MI (MI SUSPECTED AND ST SEGMENT ELEVATION OR BUNDLE BRANCH BLOCK PRESENT)

Coronary Angiography Coupled with the Intent to Perform Primary PTCA

Class I

1. As an alternative to thrombolytic therapy in patients who can undergo angioplasty of the infarct-related artery within 12 hr of the onset of symptoms or beyond 12 hr if ischemic symptoms persist, *if performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in an appropriate laboratory environment.*
2. In patients who are within 36 hr of an acute ST elevation/Q wave or new LBBB MI who develop cardiogenic shock, who are younger than 75 years, and in whom revascularization can be performed within 18 hr of the onset of the shock.

Class IIa

As a reperfusion strategy in patients who are candidates for reperfusion but who have a contraindication to fibrinolytic therapy, if angioplasty can be performed as outlined earlier in class I.

Early Angiography in the Patient With Suspected MI (ST Segment Elevation or Bundle Branch Block Present) Who Has Not Undergone Primary PTCA

Class I

None

Class IIa

Cardiogenic shock or persistent hemodynamic instability.

Early Angiography in Acute MI (MI Suspected But No ST Segment Elevation)

Class I

1. Persistent or recurrent (stuttering) episodes of symptomatic ischemia, spontaneous or induced, with or without associated ECG changes.
2. The presence of shock, severe pulmonary congestion, or continuing hypotension.

Class II

None

Coronary Angioplasty During the Hospital Management Phase (Patients with Q Wave and Non-Q-Wave Infarction)

Class I

1. Spontaneous myocardial ischemia or myocardial ischemia provoked by minimal exertion, during recovery from infarction.
2. Before definitive therapy of a mechanical complication of infarction such as acute mitral regurgitation, ventricular septal defect, pseudoaneurysm, or left ventricular aneurysm.
3. Persistent hemodynamic instability.

Class IIa

1. When MI is suspected to have occurred by a mechanism other than thrombotic occlusion at an atherosclerotic plaque (e.g., coronary embolism, arteritis, trauma, certain metabolic or hematologic diseases or coronary spasm).
2. Survivors of acute MI with left ventricular EF
0.40, CHF, prior revascularization, or malignant ventricular arrhythmias.
3. Clinical heart failure during the acute episode, but subsequent demonstration of preserved left ventricular function (left ventricular EF > 0.40).

During the Risk-Stratification Phase (Patients With All Types of MI)

Class I

Ischemia at low levels of exercise with ECG changes (
1-mm ST segment depression or other predictors of adverse outcome) and/or imaging abnormalities.

Class IIa

1. Clinically significant CHF during the hospital course.
2. Inability to perform an exercise test with left ventricular EF
0.45.

PERIOPERATIVE EVALUATION BEFORE (OR AFTER) NONCARDIAC SURGERY

Class I: Patients with suspected or known CAD

1. Evidence for high risk of adverse outcome based on noninvasive test results.
2. Angina unresponsive to adequate medical therapy.
3. Unstable angina, particularly when facing intermediate- or high-risk noncardiac surgery.
4. Equivocal noninvasive test result in high-clinical-risk patient undergoing high-risk surgery.

Class IIa

1. Multiple-intermediate-clinical risk markers and planned vascular surgery.
2. Ischemia on noninvasive testing but without high-risk criteria.
3. Equivocal noninvasive test result in intermediate-clinical-risk patient undergoing high-risk noncardiac surgery.
4. Urgent noncardiac surgery while convalescing from acute MI.

PATIENTS WITH VALVULAR HEART DISEASE

Class I

1. Before valve surgery or balloon valvotomy in an adult with chest discomfort, ischemia by noninvasive imaging, or both.
2. Before valve surgery in an adult free of chest pain but with many risk factors for CAD.
3. Infective endocarditis with evidence of coronary embolization.

Class IIa

None.

PATIENTS WITH CONGENITAL HEART DISEASE

Class I

1. Before surgical correction of congenital heart disease when chest discomfort or noninvasive evidence is suggestive of associated CAD.
2. Before surgical correction of suspected congenital coronary anomalies such as congenital coronary artery stenosis, coronary arteriovenous fistula, and anomalous origin of the left coronary artery.
3. Forms of congenital heart disease frequently associated with coronary artery anomalies that may complicate surgical management.
4. Unexplained cardiac arrest in a young patient.

Class IIa

Before corrective open heart surgery for congenital heart disease in an adult whose risk profile increases the likelihood of coexisting CAD.

PATIENTS WITH CHF

Class I

1. CHF due to systolic dysfunction with angina or with regional wall motion abnormalities and/or scintigraphic evidence or reversible myocardial ischemia when revascularization is being considered.
2. Before cardiac transplantation.
3. CHF secondary to postinfarction ventricular aneurysm or other mechanical complications of MI.

Class IIa

1. Systolic dysfunction with unexplained cause despite noninvasive testing.
2. Normal systolic function, but episodic heart failure raises suspicion if ischemically mediated left ventricular dysfunction.

OTHER CONDITIONS

Class I

1. Diseases affecting the aorta when knowledge of the presence or extent of coronary artery involvement is necessary for management (e.g., aortic dissection or aneurysm with known CAD).
2. Hypertrophic cardiomyopathy with angina despite medical therapy when knowledge of coronary anatomy might affect therapy.
3. Hypertrophic cardiomyopathy with angina when heart surgery is planned.

Class IIa

1. High risk for CAD when other cardiac surgical procedures are planned (e.g., pericardiectomy or removal of chronic pulmonary emboli).
2. Prospective immediate cardiac transplant donors whose risk profile increases the likelihood of CAD.
3. Asymptomatic patients with Kawasaki's disease who have coronary artery aneurysms on echocardiography.
4. Before surgery for aortic aneurysm/dissection in patients without known CAD.
5. Recent blunt chest trauma and suspicion of acute MI, without evidence of preexisting CAD.

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; ECG = electrocardiographic; EF = ejection fraction; LBBB = left bundle branch block; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

From Scanlon PJ, Faxon DF, Auden AM, et al. ACC/AHA guidelines for coronary angiography: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 33(6):1756-1824, 1999.

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coronary disease, quantification of the hemodynamic consequences of the valvular lesions (such as pulmonary hypertension), and occasionally the acute hemodynamic response to pharmacological therapy all provide useful preoperative information that fully defines the operative risk and permits a more directed surgical approach.

The current role of cardiac catheterization in certain congenital disease states is less well defined, as echocardiography, Doppler techniques, and cardiac magnetic resonance imaging have improved in accuracy and image quality (see Chaps. 7 and 10) . Because gross cardiac anatomy can generally be well defined by these methods, catheterization is required only if certain hemodynamic information (e.g., shunt size or pulmonary vascular resistance) is important in determining the indications for surgical procedures, if catheter interventional methods are contemplated, or if coronary anomalies are suspected.

COMPLICATIONS ASSOCIATED WITH CARDIAC CATHETERIZATION (Table 11-2)

Cardiac catheterization is a relatively safe procedure but has a well-defined risk of morbidity and mortality.[4] [5] [6] [7] [8] The potential risk of major complications during cardiac catheterization may be difficult to ascertain owing to the confounding aspects of

comorbid disease and disparities in methods used to collect complication data. Advances including the use of low-osmolar contrast media, lower profile diagnostic catheters, and extensive operator experience all serve to reduce further the incidence of complications. Several large trials including the American Heart Association's Cooperative Study on cardiac catheterization,[4] the Society for Cardiac Angiography's Registry,[6] [8] and others[5] [6] [7] permit insight into the incidence of major events and delineate patient cohorts that are at increased risk. Two studies

TABLE 11-2 -- RISK GROUPS FOR CARDIAC CATHETERIZATION

	MORTALITY RATE (%)
Overall mortality	0.14
Age-related mortality	
Less than 1 yr	1.75
More than 60 yr	0.25
Coronary artery disease	
One-vessel disease	0.03
Three-vessel disease	0.16
Left main disease	0.86
Coronary heart failure	
NYHA functional Class I or II	0.02
NYHA functional Class III	0.12
NYHA functional Class IV	0.67
Valvular heart disease	
PATIENTS AT HIGHEST RISK FOR COMPLICATIONS AND UNSUITABLE FOR CATHETERIZATION IN AN AMBULATORY SETTING	
Coronary artery disease	
Unstable or progressive angina	
Recent myocardial infarction (<7 days)	
Pulmonary edema thought due to ischemia	
High risk for left main disease by noninvasive testing	
Congestive heart failure	
NYHA functional Class III or IV	

Severe right heart failure	
Valvular heart disease	
Suspected severe aortic stenosis	
Suspected severe aortic regurgitation (pulse pressure 80 mm Hg)	
Congenital heart disease	
Suspected severe pulmonary hypertension	
Severe right heart failure	
PATIENTS WHO REQUIRE PROLONGED MONITORING AFTER CARDIAC CATHETERIZATION AND MAY BE UNSUITABLE FOR AMBULATORY CARDIAC CATHETERIZATION	
Severe peripheral vascular disease	
General debility, mental confusion, or cachexia	
Need for continuous anticoagulation or a bleeding diathesis	
Uncontrolled systemic hypertension	
Poorly controlled diabetes mellitus	
Recent stroke (<1 mo)	
Renal insufficiency (creatinine 2 mg/dl)	

Adapted from ACC/AHA Ad Hoc Task Force on Cardiac Catheterization: Guidelines for cardiac catheterization and cardiac catheterization laboratories. J Am Coll Cardio 84:2213-2247, 1991.
Modified from Bashore TM: Traditional and nontraditional cardiac catheterization laboratory settings. In Pepine CJ, Hill JA, Lambert CR: Diagnostic and Therapeutic Cardiac Catheterization. 2nd ed. Baltimore, Williams & Wilkins, 1994, pp 18, 19.

evaluating the specific risk of coronary angiography are also available--a survey of 46,904 patients[9] and the report from the Collaborative Study of Coronary Artery Surgery that included 7553 patients who were studied prospectively.[5]

Death due to diagnostic cardiac catheterization occurs in 0.14 to 0.75 percent of patients, depending on the population studied. Data from the Society for Cardiac Angiography identified subsets of patients with an increased mortality rate.[6] These include patients with greater than 50 percent stenosis of the left main coronary artery (0.94 percent), left ventricular ejection fraction less than 30 percent (0.54 percent). New York Heart Association (NYHA) functional Class III or IV heart failure (0.24 percent), age greater than 60 years (0.23 percent), aortic valvular disease (0.23 percent), and three-vessel coronary artery disease (0.13 percent).[10] In an analysis of 58,332 patients, multivariate predictors of significant complications were moribund status, advanced NYHA functional class, hypertension, shock, aortic valve disease, renal insufficiency,

unstable angina, mitral valve disease, acute myocardial infarction within 24 hours, congestive heart failure, and cardiomyopathy.[8] The risk of cardiac catheterization appears to be further increased in octogenarians,[11] in whom overall mortality is approximately 0.8 percent and the risk of nonfatal major complications, which are primarily peripheral vascular, is about 5 percent.

The risk of myocardial infarction varies from 0.07 to 0.06 percent, cerebrovascular accidents from 0.03 to 0.2 percent, and significant bradyarrhythmias or tachyarrhythmias from 0.56 to 1.3 percent. Reports of the incidence of major vascular complications have varied widely, with most series suggesting a slightly higher frequency when the brachial approach is used. The incidence of major vascular complications has been reported at approximately 0.40 percent.[8] Major vascular complications include occlusion requiring arterial repair or thrombectomy, retroperitoneal bleeding, hematoma formation, pseudoaneurysm, arteriovenous fistula formation, and infection. The risk of requiring surgical repair for vascular injury is related to advanced age, congestive heart failure, and larger body surface area.[12]

Systemic complications can vary from mild vasovagal responses to severe vagal reactions that lead to cardiac arrest. Prolonged hypotension during the procedure may also occur as a result of various mechanisms that include the vasodepressor vagal response, contrast medium-induced vasodilation or osmotic diuresis, cardiac tamponade due to myocardial perforation or coronary laceration, myocardial infarction, and an acute anaphylactoid reaction to the contrast media. Minor complications occur in approximately 4 percent of patients undergoing routine cardiac catheterization.[13] The most common untoward effects are transient hypotension and brief episodes of angina lasting less than 10 minutes. With the use of low-osmolar contrast media, however, bradycardia is infrequent and usually responds to cough. Rarely, administration of intravenous atropine is necessary.

After the procedure, diuresis from the radiographic contrast load and subsequent hypotension can be common. Intravenous hydration given before and after the procedure can usually restore the intravascular volume to compensate for the anticipated diuresis. A prospective trial evaluated the effects of saline, mannitol, and furosemide in preventing acute decreases in renal function due to contrast media-induced nephrotoxicity.[14] The researchers concluded that saline alone was most effective in reducing the acute increase in serum creatinine level. The incidence of acute renal dysfunction in patients with baseline renal insufficiency was 28 and 40 percent with mannitol and furosemide, respectively, compared with 11 percent with saline hydration alone.

Controversy surrounds the use of low-osmolar nonionic or hemionic versus high-osmolar ionic contrast media for routine cardiac catheterization and angiography. Consensus about the types of patients in whom use of low-osmolar contrast agents should be considered is growing (Table 11-3) . Several reviews have suggested that contrast media-related toxicity occurs in 1.4 to 2.3 percent of patients receiving ionic contrast media.[15] [16] High-osmolar ionic contrast media produce various adverse hemodynamic and electrophysiological effects during coronary angiography. Most of these adverse events are clearly related to the osmolality, sodium content, and

calcium-binding characteristics of the ionic contrast solutions. In addition, myocardial depression, peripheral vasodilation, and increased coronary blood flow occur.[17] Nonionic low-osmolar contrast agents clearly reduce acute adverse hemodynamic and electrophysiological reactions.[18] They appear to release less histamine from mast cells and potentially reduce allergic reactions.[19] Clinical studies suggest no advantage of low-osmolar contrast over ionic contrast media in the prevention of nephrotoxicity in patients with normal renal

TABLE 11-3 -- INDICATIONS FOR USE OF LOW OSMOLAR CONTRAST AGENTS

Unstable ischemic syndromes
Congestive heart failure
Diabetes mellitus
Renal insufficiency
Hypotension
Severe bradycardia
History of contrast allergy
Severe valvular heart disease
Internal mammary artery injection

Data from Hill JA, Lambert CR, Pepine CJ: Radiographic contrast agents. In Pepine CJ, Hill JA, Lambert CR: Diagnostic and Therapeutic Cardiac Catheterization. 2nd ed. Baltimore, Williams & Wilkins, 1994, p 192.

function.[13] [20] Other data, however, indicate that the risk of contrast media-induced nephropathy is reduced in patients with baseline renal insufficiency with or without diabetes mellitus, if nonionic contrast medium is used.[21]

Baseline renal insufficiency has been consistently shown to be an independent predictor of subsequent contrast nephrotoxicity.[13] Contrast media-induced renal dysfunction can be minimized if the dose of contrast medium is kept below 30 ml for the entire study.[22] The question of some inherent thrombogenicity of nonionic low-osmolar agents has also been raised,[23] and this possibility may relate to the formation of "thin" fibrin in the thrombus.[24] A prospective multicenter trial has demonstrated that an isosmolar nonionic contrast agent produced fewer major adverse cardiac events during percutaneous transluminal coronary angioplasty (PTCA) when compared with low-osmolar ionic contrust media.[25] Because a substantial difference in costs exists between ionic and nonionic media, the controversy about the exclusive use of nonionic contrast media for routine diagnostic cardiac catheterization is unresolved.

TECHNICAL ASPECTS OF CARDIAC CATHETERIZATION

CATHETERIZATION LABORATORY FACILITIES

Cardiac catheterization facilities have evolved to include traditional hospital-based laboratories with in-house cardiothoracic surgical programs, hospital-based laboratories without on-site surgical programs, free-standing laboratories, and mobile laboratories. The relative merits of each type of facility have been discussed in detail by a task force of the American Heart Association and the American College of Cardiology,[26] and guidelines for development of a mobile facility have been outlined by the Society for Cardiac Angiography and interventions.[27] The goals of the free-standing and mobile cardiac catheterization facilities are to reduce cost while offering services in a convenient location for low-risk patients. In one study evaluating the safety of mobile catheterization involving 1001 low-risk patients, no patient died, 0.9 percent required urgent referral for clinical instability, 0.6 percent had major complications, and 27 percent required further referral to a tertiary site for additional diagnostic or therapeutic procedures.[28] The issue of cost-saving potential of mobile and free-standing laboratories, as well as quality of patient care and ethical issues, remains unresolved. Because the majority of patients in the United States live within 30 to 60 minutes of a hospital-based facility,[26] It is generally recommended that catheterization be performed in traditional settings.

Because of cost containment considerations and the documented safety of diagnostic cardiac catheterization, there has been increasing pressure to perform catheterization on an ambulatory outpatient basis.[29] [30] Medicare data indicate that in 1986, 5 percent of total cases were performed on an outpatient basis. This rose to 23 percent in 1993.[1] Criteria for ambulatory catheterization have been reported.[26] [31] In general, patients who are not appropriate candidates for ambulatory catheterization include those with severe peripheral vascular disease, mechanical prosthetic valves, severe congestive heart failure, bleeding disorders, severe ischemia during stress testing, ischemia at rest, known or highly suspected severe left main or proximal three-vessel disease, critical aortic stenosis, and severe comorbid disease. Despite careful screening for low-risk patients, 12 percent of patients may require hospitalization.[32]

PERSONNEL

Personnel in the catheterization laboratory include the director, physicians, nurses, and radiological technologists. All members should be trained in cardiopulmonary resuscitation and preferably in advanced cardiac life support. It is desirable for facilities to be associated with a cardiothoracic surgical program. In general, high-risk diagnostic studies and all elective percutaneous interventions should be performed in laboratories with on-site surgical facilities. The American College of Cardiology/American Heart Association task force assessment of diagnostic and therapeutic cardiovascular procedures suggests that PTCA in high-risk patients with acute myocardial infarction may be performed by trained physicians without on-site surgical back-up if the patient

cannot be transferred to a more traditional setting without additional risk.[32A]

In order to maintain proficiency, laboratories for adult studies should perform a minimum of 300 procedures per year, and physicians performing diagnostic catheterization should perform a minimum of 150 procedures per year.[26] [33] Regular evaluation of laboratory and physician performance is also mandatory.[34]

EQUIPMENT

The physical requirements for the catheterization facility have been described in detail elsewhere.[26] Necessary equipment includes the radiographic system, physiological data monitoring and acquisition instrumentation, sterile supplies, and an emergency cart. Also included is support equipment consisting of a power injector, cineangiographic film or digital archiving, film processors, and viewing equipment.

RADIOGRAPHIC EQUIPMENT.

High-resolution x-ray imaging is required for optimal performance of catheterization procedures. The necessary equipment includes a generator, x-ray tube, image intensifier, video system, and either digital archiving or a cinecamera.[35] Although many facilities continue to use traditional film-based cineangiography, other laboratories have made the transition to using digital technology, thus becoming "cinefilm-less" laboratories.[36] The advantages of digital acquisition and archiving include the ability to have immediate on-line review, quantitative computer analysis of high-quality images, image manipulation capabilities, and flicker-free images at very low frame rates, thereby minimizing radiation exposure. Using these technologies, transfer of images between cardiac catheterization laboratories, hospitals, and physician offices can be accomplished using a common network.[37] The development of digital imaging and communication (DICom) standards for cardiac angiography has allowed compatability among different systems. Digital image quality is improved over videotape, and increased computer storage capabilities have allowed quick access to more than 2000 cases.

PHYSIOLOGICAL MONITORS.

Continuous monitoring of blood pressure and the electrocardiogram (ECG) is required during cardiac catheterization. Systemic, pulmonary, and intracardiac pressures are generally recorded using fluid-filled catheters connected to strain-gauge pressure transducers and then transmitted to a monitor. Equipment for determination of cardiac output and blood gas determination, as well as a standard 12-lead ECG machine, are necessary.

RADIATION SAFETY

The patient and catheterization laboratory personnel must be protected from the harmful effects of radiation. Installing and maintaining optimal x-ray imaging equipment will reduce unnecessary radiation exposure. The amount of radiation exposure to the

patient can be reduced by limiting fluoroscopic and image acquisition time, collimation of the beam to the anatomical region of interest, using low-intensity fluoroscopy, acquiring images at lower frame rates (i.e., 15 frames/sec), maintaining a minimum distance between the image intensifier and the x-ray tube, and using lead shielding when appropriate. Personnel in the laboratory can limit radiation exposure by minimizing acquisition and fluoroscopy times and by using low-dose fluoroscopy and 15 frames/sec acquisition rates. The most important factors are maximizing distance from the source of x-rays and using appropriate shielding (lead aprons, lead thyroid collars, lead eyeglasses, and movable leaded glass barriers). A method for measuring radiation exposure for personnel is required. The maximum allowable radiation dose per year for those working with radiation is 5 roentgen-equivalents-man (rem). A full discussion of radiation safety has been presented by the Society for Cardiac Angiography and interventions and others.[26] [38] [39]

Catheterization Laboratory Protocol

PREPARATION OF THE PATIENT FOR CARDIAC CATHETERIZATION.

Before arrival in the catheterization laboratory, the cardiologist responsible for the procedure should fully explain to patients the procedure including its risk and

benefits and answer questions that the patient and/or family may have. Precatheterization evaluation includes a patient history, physical examination, laboratory evaluation (complete blood count, platelet count, and determinations of serum creatinine, serum electrolytes, blood glucose, prothrombin time, and partial thromboplastin time), and ECG. Important components of the history that need to be addressed include possible insulin-dependent diabetes mellitus, renal insufficiency, long-term anticoagulation, and peripheral vascular disease, as well as previous contrast media reactions. Full knowledge of any prior procedures, including prior cardiac catheterizations, percutaneous interventions, and cardiac surgery, is necessary before the procedure. Patients should be fasting, and an intravenous line should be established. Oral or intravenous sedation should usually be administered (e.g., benzodizepine). Some laboratories routinely premedicate patients with antihistamines such as diphenhydramine (25 mg intravenous push) to decrease allergic reactions and prolong mild sedation.

CATHETERIZATION PROTOCOL.

Each physician should develop a routine for performing diagnostic catheterization to ensure efficient acquisition of all pertinent data. The particular technical approach and necessary procedures should be individualized for each patient so that the specific clinical questions can be addressed (Table 11-4) . In general, hemodynamic measurements and cardiac output determination should be made before angiography to reflect basal conditions most accurately and to guide angiography. When angiography is

performed, the vessel or chamber with most clinical importance should be visualized first, in case an untoward reaction to the contrast media or another complication of the procedure should occur.

Controversy exists about whether right-heart catheterization should be performed in *all* patients undergoing routine coronary angiography. Some physicians believe that right-heart catheterization including screening oximetric analysis, measurement of right-heart pressures, and determination of cardiac output should be performed in every patient because the risks are limited and potential benefits exist (uncovering an unsuspected problem). A prospective study evaluated 200 patients undergoing left-heart catheterization for suspected coronary artery disease; data from right-heart catheterization were not considered necessary for clinical treatment of these patients before the procedure.[40] The right-heart catheterization took approximately 6 additional minutes of procedure time and 86 seconds of fluoroscopy time. Treatment was altered in only 1.5 percent of patients as a result of the data obtained by right-heart catheterization. Although routine right-heart catheterization does not appear necessary for patients undergoing routine coronary angiography, it is clearly indicated when the clinical question cannot be answered by isolated left-heart catheterization or when a patient has left ventricular dysfunction, congestive heart failure, complicated acute myocardial infarction, valvular disease, suspected pulmonary hypertension, a congenital anomaly, or pericardial disease.[26]

Although the use of a temporary pacemaker is not indicated for routine cardiac catheterization, operators should understand the techniques for proper insertion and setting of the pacemaker if needed (see Chap. 24) . Even in patients with isolated left bundle branch block, right-heart catheterization can generally be safely performed with balloon flotation catheters without causing additional conduction disturbance.

CATHETERS AND ASSOCIATED EQUIPMENT.

Physicians performing cardiac catheterization should be familiar with technical aspects of the equipment used during the procedure.[41] Catheters used for cardiac catheterization come in various lengths, sizes, and shapes. The widely used balloon flotation catheter (Swan-Ganz) is shown in Figure 11-1. Typical catheter lengths vary between 50 and 125 cm, with 100 cm being the most commonly used length for adult left-heart catheterization via the femoral approach. The outer diameter of the catheter is specified using French units, where one French unit (F) = 0.33 mm. The inner diameter of the catheter is smaller than the outside diameter owing to the thickness of the catheter material. Guidewires used during the procedure must be small enough to pass through the inner diameter of both the introducer needle and the catheter. Guidewires are described by their length in centimeters, diameter in inches, and tip conformation. A commonly used wire is a 150-cm, 0.035-inch J-tipped wire. The introducer sheaths are specified by the French number of the largest catheter that passes freely through the inner diameter of the sheath, rather than its outer diameter. Therefore, a 7F introducer sheath accepts a 7F catheter but has an outer diameter of more than 7F or 2.31 mm.

The choice of the size of the catheters to be used is made by balancing the need to opacify the coronary arteries and cardiac chambers adequately, to have adequate

catheter

TABLE 11-4 -- CATHETERIZATION PROTOCOL

CLINICAL ISSUE	LHC	RHC	CORO	LV	AO	RV	PA	BX	PROVO	IABP	PTCA
Known or suspected coronary artery disease											
Stable angina											
Positive stress test result											
Preoperative evaluation											
Atypical chest pain									±		
Unstable or new-onset angina											±
Acute myocardial infarction				±						±	±
Failed thrombolysis				±						±	±
Postinfarction angina				±						±	±
Cardiogenic shock				±						±	±
Mechanical complications										±	±
Sudden cardiac death											
Valvular heart disease											
Myocardial disease								±			
Pericardial disease											
Congenital heart disease					±	±	±				
Aortic dissection		±		±							

Pulmonary disease						±	±				

AO=aortogram; BX=biopsy; CORO=coronary angiography; IABP=intraaortic balloon pump; LHC=left heart catheterization, including measurement of left ventricular end-diastolic pressure and aortic valve gradient; LV=left ventriculography; PA=pulmonary angiography or wedge pulmonary angiography; PROVO=provocative challenge (i.e., ergot alkaloids, acetylcholine); PTCA=percutaneous transluminal coronary angioplasty; RHC=right heart catheterization including pressure measurement, determination of cardiac output, oximetric analysis; RV=right ventriculography;
=appropriate; ±=may be appropriate in certain clinical circumstances.

Figure 11-1 Typical Swan-Ganz catheter. Proximal ports, left to right, are balloon inflation valve with syringe, distal lumen hub, thermistor connector, and proximal injector hub. The distal end of the catheter has a balloon and a distal lumen. The proximal injectate port exits at 30 cm from the distal lumen (arrow). The thermistor lies just proximal to the ballon.

manipulation, to limit vascular complications, and to permit early ambulation. Although the larger catheters (7F and 8F) allow greater catheter manipulation and excellent visualization, the smaller catheters (5F and 6F) permit earlier ambulation after catheterization. Catheter technology has advanced such that 5F or 6F systems can be used for routine angiography without significant compromise of angiographic quality.[42] Even 4F catheters have been used from both the femoral artery and radial artery approaches. Use of the smaller catheters requires greater technical skill of manipulation to achieve adequate angiography and thus may be less appropriate for training students of catheterization. The 6F diagnostic catheter is most widely used for routine angiography because this size catheter appears to balance most appropriately the needs outlined earlier. The relationship between sheath size and vascular complications is not clear. Rather, anticoagulation status and operator experience are more important factors related to vascular complications.[43]
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Techniques

Right-Heart Catheterization

Right-heart catheterization allows for measurement and analysis of right-heart, pulmonary artery, and pulmonary capillary wedge pressures; measurement of cardiac output by thermodilution; screening for intracardiac shunts; temporary ventricular pacing; assessment of arrhythmias; and pulmonary wedge angiography.[44] Right-heart catheterization is performed antegrade through either the inferior vena cava (IVC) or

superior vena cava (SVC). Percutaneous entry is achieved via the femoral, subclavian, jugular, or antecubital vein. The anatomy of the major arteries and veins used for cardiac catheterization is shown in Figures 11-2 (Figure Not Available) and 11-3 . In the cardiac catheterization laboratory, the femoral venous access is used most often because the Judkins technique of left-heart catheterization is performed concurrently.

BALLOON FLOTATION CATHETERS.

Balloon flotation catheters are the simplest and most widely used (see Fig. 11-1 . If thermodilution cardiac outputs must be determined, catheters that contain thermistors, such as Swan-Ganz catheters, should be used. These catheters have balloon tips, proximal and distal ports, and thermistors. Therefore, intracardiac pressures and oxygen saturation to evaluate intracardiac shunts can be obtained. These catheters

Figure 11-2 (Figure Not Available) Principal arteries used for access during cardiac catheterization. Only the superficial veins are shown on the forearm. (Modified from Anthony CP: Textbook of Anatomy and Physiology. 11th ed. St. Louis, CV Mosby, 1983.)

Figure 11-3 Anatomy relevant to percutaneous catheterization of the femoral artery and vein. The right femoral artery and vein pass underneath the inguinal ligament, which connects the anterior-superior iliac spine and pubic tubercle. The arterial skin nick (indicated by X) should be placed approximately 1 1/2 to 2 fingerbreaths (3 cm) below the inguinal ligament and directly over the femoral artery pulsation. The venous skin nick should be placed at the same level, but approximately 1 fingerbreadth medial. (From Baim DS, Grossman W: Percutaneous approach including transseptal and apical puncture. *In* Baim DS, Grossman W [eds]: Cardiac Catheterization, Angiography, and Intervention. 5th ed. Philadephia, Lea & Febiger, 1996.)

are both flexible and flow directed, but when the femoral approach is used, fluoroscopic guidance is almost always necessary to cannulate the pulmonary artery and to obtain pulmonary capillary wedge position. Although most right-heart catheters have a J-shaped curvature distally to facilitate passage from the SVC to the pulmonary artery, a catheter with an S-shaped distal end has been designed for femoral insertion. Although manipulation is limited, the balloon flotation catheters are the safest and most rapid method for obtaining right-heart pressures and blood samples. Other balloon flotation end-hole catheters that are stiffer and therefore allow better manipulation are available for right-heart catheterization. These lack the ability to obtain thermodilution cardiac outputs but yield better pressure fidelity owing to less catheter whip artifact and a larger end hole.

There are two methods for advancing a balloon flotation catheter from the femoral vein. On many occasions, the catheter can be advanced directly through the right atrium and across the tricuspid valve. Once in the right ventricle, the catheter is manipulated to point superiorly and directly into the right ventricular outflow tract. This can usually be achieved while the catheter is advanced with slight clockwise rotation. Once in the

outflow tract, the balloon tip should allow flotation into the pulmonary artery and wedge positions. When necessary, deep inspiration or cough can facilitate this maneuver and assist in crossing the pulmonic valve. If the catheter continues to point inferiorly toward the right ventricular apex, another technique should be used, because further advancement can risk perforation of the right ventricular apex.

One such additional technique for performing right-heart catheterization with a balloon flotation catheter is shown in Figure 11-4 . A loop is formed in the right atrium, with the catheter tip directed laterally. The loop can be created by hooking the catheter tip on the hepatic vein or by advancing the catheter while it is directed laterally in the right atrium. Once the loop is formed, the catheter should be advanced farther; this directs the tip inferiorly and then medially across the tricuspid valve. Antegrade blood flow should then direct the catheter into the pulmonary artery. After the catheter is placed into the wedge position, the redundant loop should be removed by slow withdrawal. Screening blood samples for oximetric analysis should be obtained from the SVC and the pulmonary artery to evaluate for intracardiac shunts. Cardiac output can also be determined by thermodilution techniques.

NONFLOTATION CATHETERS.

When an end-hole catheter that does not have a balloon tip is used, the technique for cannulating the pulmonary artery is markedly different. Manipulation and torquing of the nonflotation catheter are necessary to advance into the pulmonary artery. The catheter should be directed inferiorly across the tricuspid valve and then superiorly into the right ventricular outflow tract. It is generally recommended that one attempt to form a loop in the right atrium before advancement into the right ventricle in order to lessen the risk of perforation. These stiffer catheters can often prolapse into the left atrium with mild pressure against the interatrial septum in patients with a probe-patent foramen ovale. Left atrial position can be verified by the pressure waveform, by blood samples demonstrating arterial saturation, or by hand contrast injection.

COMPLICATIONS.

The most common complications of right-heart catheterization are nonsustained atrial and ventricular arrhythmias. Major complications associated with right-heart catheterization are infrequent. These include pulmonary infarction, pulmonary artery or right ventricular perforation, and infection. Pulmonary artery rupture can be avoided by combined use of fluoroscopic guidance and constant evaluation of the pressure waveform. Confusion about the location of the distal end of the catheter may arise in the setting of large v waves in the pulmonary capillary wedge pressure tracing; the operator may mistake these for a pulmonary artery waveform (Fig. 11-5) . Careful attention

Figure 11-4 Technique of right-heart catheterization from the femoral approach. *A,* The catheter is advanced through the inferior vena cava. *B,* A loop is created in the catheter by hooking on the hepatic vein or lateral right arterial wall. *C,* Clockwise rotation and advancement of the catheter cross the tricuspid valve. *D,* Additional rotation and withdrawal straightens the catheter and directs it superiorly so that it may

be advanced through the right ventricular outflow tract. (Copyright 1984 Mayo Foundation.)

Figure 11-5 Acute mitral regurgitation with poor left atrial compliance. The left ventricle (LV) pressure versus the pulmonary capillary wedge (PCW) is shown on left. A large regurgitant v wave is seen. This v wave is transmitted through the pulmonary bed to the pulmonary arterial (PA) tracing and is superimposed in the right panel. (From Bashore TM, Harrison JK, Davidson CJ: Cardiac catheterization, angiography, and interventional techniques in valvular and congenital heart disease. *In* Sabiston DC, Spencer FC [eds]: Surgery of the Chest. 6th ed. Philadelphia, WB Saunders, 1995.)

to the timing of the peak pulmonary artery systolic pressure and the v wave with respect to the ECG, along with the use of fluoroscopy, prevents inadvertent inflation of the balloon in the wedged position, which can cause pulmonary artery rupture.

Left-Heart Catheterization and Coronary Arteriography

THE JUDKINS TECHNIQUE.

Because of its relative ease, speed, reliability, and low complication rate,[5] the Judkins technique has become the most widely used method of left-heart catheterization and coronary arteriography in the United States. After local anesthesia with 1 percent lidocaine (Xylocaine), percutaneous entry of the femoral artery is achieved by puncturing the vessel 1 to 3 cm (or 1 to 2 fingerbreadths) below the inguinal ligament. The ligament can be palpated as it courses from the anterior superior iliac spine to the superior pubic ramus. This ligament, not the inguinal crease, should be used as the landmark; use of this crease is misleading. A transverse skin incision is made over the femoral artery with a scapel. Using a modified Seldinger's technique (Fig. 11-6) , an 18-gauge thin-walled needle (Fig. 11-7) (Figure Not Available) is inserted at a 30- to 45-degree angle into the femoral artery, and a 0.035- or 0.038-inch J-tip Teflon-coated guidewire is advanced through the needle into the artery. The wire should pass freely up the aorta. After arterial access is obtained, a sheath at least equal in size to the coronary catheter is usually inserted into the femoral artery. It is generally recommended that the patient receive 3000 to 5000 units of heparin after access is obtained. The technique of coronary arteriography using this approach is described in Chapter 12.

Left ventricular systolic and end-diastolic pressures can be obtained by advancing a pigtail catheter into the left ventricle (Fig. 11-8) . In assessing valvular aortic stenosis, left ventricular and aortic pressures should be recorded simultaneously. In suspected mitral stenosis, left ventricular and wedge or left atrial pressures should be obtained simultaneously. Left ventriculography is performed in the 30-degree right anterior oblique and 45- to 50-degree left anterior oblique views. A pigtail catheter is most commonly used for this purpose. Power injection of 30 to 50 ml of contrast medium into the ventricle is used to assess left ventricular function and the severity of mitral

regurgitation. After ventriculography, pressure measurements may be repeated and the systolic pressure should be recorded as the catheter is withdrawn from the left ventricle into the aorta. If an aortic transvalvular gradient is present, recording these pressures detects it. For measurement of suspected intraventricular gradients, a multipurpose catheter with an end hole is desirable to localize the gradient in the left ventricle. Pigtail catheters contain side holes, which obscure the capacity to define whether the gradient is intraventricular or transvalvular.

After coronary arteriography and left-heart catheterization have been completed, the catheters are removed and firm pressure is applied to the femoral area for 15 to 20 minutes, either by hand or by a mechanical clamp. The patient should be instructed to lie in bed for several hours, with the leg remaining straight to prevent hematoma formation. With 5F catheters, 2 hours of bed rest is usually sufficient, whereas use of 6F catheters usually involves at least 3 to 4 hours. Alternatively, closure devices may be used. Two types are currently available. These are collagen plugs and suture closure. Both allow for earlier ambulation of the patients. However, none has been shown to lower vascular complication rates compared with hand compression.[45]

The main advantage of the Judkins technique is the speed and ease of selective catheterization. These attributes do not, however, preclude the importance of extensive operator experience to ensure quality studies with acceptable safety. The main disadvantage of this technique is its use in patients with iliofemoral atherosclerotic disease, in whom retrograde passage of catheters through areas of extreme narrowing or tortuosity may be difficult or impossible.

BRACHIAL ARTERY TECHNIQUE--SONES TECHNIQUE.

Sones and colleagues introduced the first technique for coronary artery catheterization by means of a brachial artery cutdown. The Sones technique is still popular in many centers and is described in Chapter 12 .

PERCUTANEOUS BRACHIAL ARTERY TECHNIQUE

A modification of Sones technique is the percutaneous brachial artery technique using preformed Judkins catheters. This technique uses Seldinger's method of percutaneous brachial artery entry. A 5F or 6F sheath is placed into the brachial artery, and 3000 to 5000 units of heparin is infused into the side port. A guidewire is then advanced to the ascending aorta under fluoroscopic control. Number 5F or 6F left, right, and pigtail catheters are passed over the guidewire for routine arteriography and ventriculography. The guidewire may occasionally be necessary to direct the left coronary catheter into the left sinus of Valsalva and the ostium of the left main coronary artery.

The main advantage of the percutaneous brachial technique is that it avoids a brachial artery cutdown and repair. The main disadvantage is that manipulation of catheters can be difficult. When this technique was compared with the femoral technique, patients' comfort, hemostasis time, and time to ambulation favored the brachial

Figure 11-6 Modified Seldinger's technique for percutaneous catheter sheath introduction. *A,* Vessel punctured by needle. *B,* Flexible guidewire placed into the vessel via the needle. *C,* Needle removed, guidewire left in place, and the hole in the skin around the wire enlarged with a scalpel. *D,* Sheath and dilator placed over the guidewire. *E,* Sheath and dilator advanced over the guidewire and into the vessel. *F,* Dilator and guidewire removed while the sheath remains in the vessel. (From Hill JA, Lambert CR, Vlietstra RE, Pepine CJ: Review of general catheterization techniques. *In* Pepine CJ, Hill JA, Lambert CR [eds]: Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore, Williams & Wilkins, 1998, p 107.

technique, whereas procedural efficiency, time of radiation exposure, and diagnostic film quality were more favorable with the femoral approach.[46] Complication rates appear similar.

PERCUTANEOUS RADIAL ARTERY TECHNIQUE

Left-heart catheterization via the radial artery approach was developed as an alternative to the percutaneous transbrachial approach in

Figure 11-7 (Figure Not Available) Two most commonly used needle types for vascular access. On the left, a single-piece, thin-walled "front-wall needle"; on the right, a two-component, thin-walled Seldinger needle. (From MacDonald RG: Catheters, sheaths, guidewires, needles, and related equipment. *In* Pepine CJ, Hill JA, Lambert CR [eds]: Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore, Williams & Wilkins, 1998, p 130.)

an attempt to limit vascular complications.[47] The inherent advantages of the transradial approach are that the hand has a dual arterial supply connected via the palmar arches and that there are no nerves or veins at the site of puncture. In addition, prolonged bed rest is unnecessary after the procedure, thus allowing for more efficient outpatient angiography.

The procedure requires a normal Alien's test result: After manual compression of both the radial and ulnar arteries during fist clenching, normal color returns to the opened hand within 10 seconds after releasing pressure over the ulnar artery, and significant reactive hyperemia is absent on releasing pressure over the radial artery.[48]

The arm is abducted, and the wrist hyperextended over a gauze roll. Routine skin anesthesia is used, a small incision is made just proximal to the styloid process of the radius, and the subcutaneous tissue is tunneled using forceps. An 18-gauge needle is introduced at a 45-degree angle and an exchange-length 0.035- or 0.038-inch J-tip guidewire is inserted. A 23-cm long 4F or 5F sheath is then introduced. Heparin, 5000 units, is administered through the side arm of the sheath. Coronary catheters are then advanced over the exchange wire into the ascending aorta. The left coronary artery is intubated using a left 4-cm tip Judkins (JL 4.0), a left Amplatz, or a brachial Castillo type II catheter. The right coronary artery is intubated using a 4-cm right Judkins (JR 4.0), a

left Amplatz, or a multipurpose catheter. Left ventriculography can be performed using a multipurpose catheter with side holes or a pigtail catheter. Exchanges are best performed over the guidewire. Hemostasis is obtained at the end of the procedure after sheath removal using direct pressure. It is recommended that the arterial puncture site be allowed to bleed for several beats before maintaining direct pressure. The radial pulse should be monitored regularly for several hours after the procedure.

The potential limitations of this procedure include the inability to cannulate the radial artery owing to its smaller size and propensity to develop spasm, poor visualization of the coronary arteries resulting from the small caliber catheters with limited manipulation potential, and risk of arterial occlusion caused by dissection or thrombus formation, in addition, when right-heart catheterization is required, other approaches are necessary. Although there is little debate that the femoral approach is the simplest and probably the safest technique for left-heart catheterization, the transradial approach for left-heart catheterization has gained in popularity with refinements in technique and equipment.

Figure 11-8 Technique for retrograde crossing of an aortic valve using a pigtail catheter. The upper row shows the technique for crossing a normal aortic valve. In the bottom row, the use of a straight guidewire and pigtail catheter in combination is shown. Increasing the length of protruding guidewire straightens the catheter curve and causes the wire to point more toward the right coronary ostium; reducing the length of protruding wire restores the pigtail contour and deflects the guidewire tip toward the left coronary artery. Once the correct length of wire and the correct rotational orientation of the catheter have been found, repeated advancement and withdrawal of catheter and guidewire together will allow retrograde passage across the valve. In a dilated aortic root, the angled pigtail catheter is preferable. In a small aortic root (*bottom row, right*), a right coronary Judkins catheter may have advantages. (From Baim DS, Grossman W: Percutaneous approach including transseptal and apical puncture. *In* Baim DS, Grossman W [eds]: Cardiac Catheterization, Angiography, and Intervention. 5th ed. Philadelphia, Lea & Febiger, 1996.)

Transseptal Catheterization

This procedure has received renewed interest with the growth of percutaneous balloon mitral commissurotomy as a viable option to surgical commissurotomy (see Chap. 46) , with electrophysiologic procedures requiring access to pulmonary veins, and with increasing use of disc valves in the aortic position (Fig. 11-9) . These mechanical prosthetic valves cannot be crossed safely and prohibit retrograde left-heart catheterization.

The original technique of transseptal heart catheterization has been well described,[49] and various techniques currently exist. The transseptal catheter is a short, curved catheter with a tapered tip and side holes. One commonly used approach is to place a 0.032-inch guidewire via the femoral vein through the right atrium and into the SVC. A Mullins transseptal sheath and dilator are then advanced over the wire into the SVC. The guidewire is removed and replaced with a Brokenbrough's needle, and the distal port is connected to a pressure manifold. With the needle tip just proximal to the Mullins

sheath tip, the entire catheter system is withdrawn. The catheter is simultaneously rotated from a 12 o'clock to a 5 o'clock position. The operator experiences two abrupt rightward movements of the catheter. The first occurs as the catheter descends from the SVC to the right atrium. The second occurs as the Mullins dilator tip passes over the limbic edge into the fossa ovalis. The curve of the sheath and needle should be oriented slightly anteriorly. The dilator and needle can then be advanced gently as a unit. Steady pressure often is adequate to advance the system into the left atrium. If not, the needle should be advanced across the interatrial septum while holding the Mullins sheath in place.

Left atrial position can be confirmed by the increase in pressure with left atrial a and v waveforms, hand injection of contrast medium, or measurement of arterial oxygen saturation. Once position is confirmed, the dilator and sheath can be safely advanced 2 to 3 cm into the left atrium. The sheath is held firmly, and the dilator and needle are removed. Left atrial pressure measurements may then be repeated. If measurement of left ventricular pressure and/or left ventriculography is necessary, the catheter can usually be advanced easily into the left ventricle after slight counterclockwise rotation. The risk of major morbidity with skilled operators should be less than 2 percent.[50] The major risk of transseptal catheterization lies in inadvertent puncture of atrial structures, such as the atrial free wall or coronary

Figure 11-9 Transseptal catheters. *A,* Distal catheter. *B,* Proximal catheter. *Left,* Mullins transseptal sheath. *Middle,* Introducer (dilator) that is placed inside sheath to add stiffness to the catheter. *Right,* Brockenbrough transseptal needle that is placed inside the sheath and is used to penetrate the septum.

sinus, or entry into the aortic root or pulmonary artery.

DIRECT TRANSTHORACIC LEFT VENTRICULAR PUNCTURE

The sole indication for direct left ventricular puncture is to measure left ventricular pressure and to perform ventriculography in patients with mechanical prosthetic valves in both the mitral and aortic positions, thus preventing retrograde arterial and transseptal catheterization. Crossing tilting disc valves with catheters should be avoided because this may result in catheter entrapment, occlusion of the valve, or possible dislodgement of the disc with embolization.

The procedure is performed after localizing the left ventricular apex via palpation or preferably using echocardiography.[51]

After local anesthesia is administered, a 3 1/2-inch-long 18-gauge needle is inserted at the upper rib margin and directed slightly posteriorly and toward the right shoulder. An 0.035-inch J-tip guidewire is introduced into the ventricle under fluoroscopic guidance,

followed by a 4F dilator and then a 4F pigtail catheter.[52]

The risks of this procedure include cardiac tamponade, hemothorax, pneumothorax, laceration of the left anterior descending coronary artery, embolism of left ventricular thrombus, vagal reactions, and ventricular arrhythmias. The risk of pericardial tamponade, however, is limited in patients who have undergone prior cardiac surgery because mediastinal fibrosis is present. With the advent of transesophageal echocardiography, this procedure is now infrequently performed.

Endomyocardial Biopsy (See also Chaps. 20 and 48)

This procedure can be performed using various bioptomes. The most common devices in use include the stiff-shaft Caves-Schulz Stanford bioptome[53] and the floppy-shaft King's bioptome.[54] Right ventricular biopsy may be performed using the internal jugular vein,[53] [55] the subclavian vein,[56] or the femoral vein.[57] Left ventricular biopsy may be performed using the femoral arterial approach.[54]

For performing right ventricular biopsy via the right internal jugular vein, a 7-9F sheath is introduced using the usual Seldinger's technique. A 7-9F bioptome is advanced under fluoroscopic guidance to the lateral wall of the right atrium. Using counterclockwise rotation, the device is advanced across the tricuspid valve and toward the interventricular septum. Position of the bioptome against the interventricular septum is confirmed using 30-degree right anterior oblique and 60-degree left anterior oblique fluoroscopic projections. Alternatively, two-dimensional echocardiography has been used to guide the position of the bioptome with good results.[58] Contact with the myocardium is confirmed by the presence of premature ventricular contractions, lack of further advancement, and transmission of ventricular impulse to the operator. The bioptome is then slightly withdrawn from the septum, the forceps jaws are opened, the bioptome is readvanced to contact the myocardium, and the forceps closed. A slight tug is felt on removal of the device. Approximately four to six samples of myocardium are required for adequate pathological analysis. Consultation with a pathologist should be obtained to ensure appropriate specimen collection and processing.

Right or left ventricular biopsy from the femoral vein or artery requires insertion of a long 6F or 7F sheath directed toward the portion of the ventricle to be sampled. The sheath used for right ventricular biopsy has a 45-degree angle on its distal end to allow for easier access to the right ventricle. An angled pigtail catheter and long guidewire system are used to enter the right ventricle. The sheath is then advanced over the pigtail catheter into the right ventricle, the catheter is withdrawn, the sheath is flushed, and pressure is measured. The bioptome is advanced through the sheath. Samples of myocardium are taken in a manner similar to that described earlier. If left ventricular biopsy is to be performed, the biopsy sheath is generally positioned over a multipurpose or pigtail catheter that has been positioned in the ventricle. The sheath is advanced below the mitral apparatus and away from the posterobasal wall. The catheter is then withdrawn, and either a long King's bioptome or the Stanford left ventricular bioptome is inserted. Care must be taken when left ventricular biopsy is performed to prevent air embolism while introducing the bioptome into the sheath. A constant infusion of flush

solution through the sheath minimizes the risk of air or thrombus embolism.

Complications of endomyocardial biopsy include cardiac perforation with cardiac tamponade (see Chap. 50) , emboli (air, tissue, or thromboembolus), arrhythmias, electrical conduction disturbances, injury to heart valves, vasovagal reactions, and pneumothorax.[59] The overall complication rate is between 1 and 2 percent, with the risk of cardiac perforation with tamponade generally reported in less than 0.05 percent.[60] Systemic embolization and ventricular arrhythmias are more common with left ventricular biopsy. Left ventricular biopsy should generally be avoided in patients with right bundle branch block because of the potential for developing complete atrioventricular block, as well as in patients with known left ventricular thrombus.

The indications for endomyocardial biopsy remain controversial.[61] [62] [63] Generally agreed is that endomyocardial biopsy is indicated to monitor cardiac allograft rejection and that it may also be useful to monitor for anthracycline cardiotoxicity.[61] However, considerable persistent controversy surrounds the use of endomyocardial biopsy to evaluate the cause of dilated cardiomopathy.[61] [64] Other possible indications for endomyocardial biopsy include differentiation between restrictive and constrictive myopathies,[65] [66] determination of whether myocarditis is the cause of ventricular arrhythmias,[61] [63] and assessment of patients with left ventricular dysfunction associated with human immunodeficiency virus infection.[67] [68]

Percutaneous Intraaortic Balloon Pump (IABP) Insertion (See also p. 159)

The intraaortic balloon counterpulsation devices available for adult use are positioned in the descending thoracic aorta. They have a balloon volume of 30 to 50 ml, use helium as the inflation gas, and are timed to inflate during diastole and deflate during systole. Details of the technique of balloon insertion have been well described.[69] Briefly, the device is inserted via the femoral artery using the standard Seldinger's technique. The device is placed such that the tip is just below the level of the left subclavian artery. Optimal positioning requires fluoroscopic guidance. Timing of the balloon is adjusted during 1:2 pumping such that inflation of the balloon occurs at the aortic dicrotic notch and deflation occurs immediately before systole to ensure maximal augmentation of diastolic flow and maximal systolic unloading.

Favorable hemodynamic effects include reduction in left ventricular afterload and improvement in myocardial oxygenation.[70] [71] Therefore, IABP insertion is indicated for patients with angina refractory to medical therapy, cardiogenic shock, or mechanical complications of myocardial infarction (see Chap. 35) (including severe mitral regurgitation, ventricular septal defect) or for those who have severe left main coronary artery stenosis and who will be undergoing cardiac surgery. IABP may also be valuable in patients undergoing high-risk angioplasty and after primary angioplasty in the setting of acute myocardial infarction.[72] [73] IABP insertion is contraindicated in patients with moderate or severe aortic regurgitation, aortic dissection, aortic aneurysm, patent ductus arteriosus, severe peripheral vascular disease, bleeding disorders, or sepsis.

Complications of IABP insertion include limb ischemia requiring early balloon removal or vascular surgery, balloon rupture, balloon entrapment, hematomas, and sepsis.[74] [75]

The incidence of vascular complications ranges from 12 percent to greater than 40 percent.[74] Most patients who develop limb ischemia after insertion of a balloon pump device have resolution of the ischemia on balloon removal and do not require surgical intervention (thrombectomy, vascular repair, fasciotomy, or amputation). The risk of limb ischemia is heightened in patients with diabetes or peripheral vascular disease, in women, and in patients with a postinsertion ankle-brachial index of less than 0.8.[74] With the development of smaller catheters (8.5F to 9.5F) and the advent of the sheathless insertion techniques, vascular complications have been reduced.[75] [76]

HEMODYNAMIC DATA

The hemodynamic component of the cardiac catheterization procedure focuses on pressure measurements, the measurement of flow (cardiac output, shunt flows, flow across a stenotic orifice, regurgitant flows, coronary blood flow, and so on), and the determination of vascular resistances. Simply stated, flow through a blood vessel is determined by the pressure difference within the vessel and the vascular resistance as described by Ohm's law: Q = DeltaP/R.

Pressure Measurements

Accurate recording of pressure waveforms and correct interpretation of physiological data derived from these waveforms are major goals of cardiac catheterization. A pressure wave is the cyclical force generated by cardiac muscle contraction, and its amplitude and duration are influenced by various mechanical and physiological parameters. The pressure waveform from a particular cardiac chamber is influenced by the force of the contracting chamber and its surrounding structures including the contiguous chambers of the heart, the pericardium, the lungs, and the vasculature. Physiological variables of heart rate and the respiratory cycle also influence the pressure waveform. An understanding of the components of the cardiac cycle is essential to the correct interpretation of hemodynamic data obtained in the catheterization laboratory (see Fig. 14-22) .

PRESSURE MEASUREMENT SYSTEMS.

Intravascular pressures are typically measured using a fluid-filled catheter that is attached to a pressure transducer. The pressure wave is transmitted from the catheter tip to the transducer by the fluid column within the catheter. The majority of pressure transducers used currently are disposable electrical strain gauges. The pressure wave distorts the diaphragm or wire within the transducer. This energy is then converted to an electrical signal proportional to the pressure being applied using the principle of the Wheatstone bridge. This signal is then amplified and recorded as an analog signal.[77]

There are a number of sources of error when pressures are measured using a fluid-filled catheter/transducer system[78] (see Fig. 15-4) . Distortion of the output signal occurs as a

result of the frequency response characteristics and damping characteristics of the system. The frequency response of the system is the ratio of the output amplitude to input amplitude over a range of frequencies of the input pressure wave. The natural frequency is the frequency that the system oscillates when it is shock excited in the absence of friction. If the energy of the system is dissipated, such as by friction, this is called *damping.* To ensure a high-frequency response range, the pressure measurement system should have the highest possible natural frequency and optimal damping. Optimal damping dissipates the energy gradually, thus maintaining the frequency response curve as close as possible to an output/input ratio of 1 as it approaches the system's natural frequency. This is achieved by using a short, wide-bore, noncompliant catheter/tubing system that is directly connected to the transducer using a low-density liquid from which all air bubbles have been removed.[77]

The pressure transducer must be calibrated against a known pressure, and the establishment of a zero reference must be undertaken at the start of the catheterization procedure. To "zero" the transducer, the tranducer is placed at the level of the heart, which is approximately midchest. If the transducer is attached to the manifold and is therefore at variable positions during the procedure, a second fluid-filled catheter system should be attached to the transducer and positioned at the level of the heart. All transducers being used during the procedure should be zeroed and calibrated simultaneously.

Other sources of error include catheter whip artifact (motion of the tip of the catheter within the measured chamber), end pressure artifact (an end-hole catheter measures an artificially elevated pressure on account of streaming or high velocity of the pressure wave), catheter impact artifact (when the catheter is impacted by the walls or valves of the cardiac chambers), and catheter tip obstruction within small vessels or valvular orifices occurring because of the size of the catheter itself. The operator must be aware of the many sources of potential error, and when there is a discrepancy between the observed data and the clinical scenario, the system should be examined for errors or artifacts.

MICROMANOMETER CATHETERS.

The use of these catheters, which have the pressure transducer mounted at their tip, greatly reduces many of these errors in measurement. However, their utility is limited by the additional cost and time needed for properly calibrating and using the system. These catheters have higher natural frequencies and more optimal damping characteristics because the interposing fluid column is eliminated. In addition, there is a decrease in catheter whip artifact. The pressure waveform is less distorted and is without the 30- to 40-msec delay seen in the fluid-filled catheter/transducer system. Commercially available high-fidelity micromanometer systems (Millar Instruments, Houston, TX) have both an end hole and side holes to allow for an over-the-wire insertion into the circulation while also permitting angiography. Catheters that have two transducers separated by a short distance are useful for accurate measurement of gradients across valvular structures and within ventricular chambers. The micromanometer system has been used for research purposes to measure the rate of ventricular pressure rise (dP/dt), wall stress, the rate of ventricular pressure decay (-dP/dt), and the time

constant of relaxation, and to determine ventricular pressure-volume relationships.[79]

The micromanometer catheter systems have several disadvantages, including their expense, fragility, added procedural time, and the need for sterilization between uses. In addition, the zero level of these systems may drift after the pressure is zeroed to the fluid-filled lumen within the catheter.

Normal Pressure Waveforms

An understanding of the normal pressure waveform morphologies is necessary to comprehend the abnormalities that characterize certain pathological conditions. Normal pressures in the cardiac chambers and great vessels are listed in Table 11-5 . Simply stated, whenever fluid is added to a chamber or compressed within a chamber, the pressure usually rises; conversely, whenever fluid exits from a chamber or the chamber relaxes, the pressure usually falls. One exception to this rule is the early phase of ventricular diastolic filling, when ventricular volume increases after mitral valve opening but ventricular pressure continues to decrease because of active relaxation.[80] Examples of normal pressure waveforms are shown in Figure 11-10) (Figure Not Available) .

ATRIAL PRESSURE.

The *right atrial pressure waveform* has three positive deflections, the a, c, and v waves. The a wave is due to atrial systole and follows the P wave of the ECG. The height of the a wave depends on atrial contractility and the resistance to right ventricular filling. The *x* descent follows the a wave and represents relaxation of the atrium and downward pulling of the tricuspid annulus by right ventricular contraction. The *x* descent is interrupted

TABLE 11-5 -- NORMAL PRESSURES AND VASCULAR RESISTANCES

PRESSURES	AVERAGE (mm Hg)	RANGE (mm Hg)
Right atrium		
a wave	6	2-7
v wave	5	2-7
mean	3	1-5
Right ventricle		
peak systolic	25	15-30
end-diastolic	4	1-7
Pulmonary artery		

peak systolic	25	15-30
end-diastolic	9	4-12
mean	15	9-19
Pulmonary capillary wedge		
mean	9	4-12
Left atrium		
a wave	10	4-16
v wave	12	6-21
mean	8	2-12
Left ventricle		
peak systolic	130	90-140
end-diastolic	8	5-12
Central aorta		
peak systolic	130	90-140
end-diastolic	70	60-90
mean	85	70-105
VASCULAR RESISTANCES	**MEAN (dyne-sec^{-1} cm^{-5})**	**RANGE (dyne-sec^{-1} cm^{-5})**
Systemic vascular resistance	1100	700-1600
Total pulmonary resistance	200	100-300
Pulmonary vascular resistance	70	20-130

by the c wave, which is a small positive deflection due to protrusion of the closed tricuspid valve into the right atrium. Pressure in the atrium rises after the *x* descent owing to passive atrial filling. The atrial pressure then peaks as the v wave, which represents right ventricular systole. The height of the v wave is related to atrial compliance and the amount of blood returning to the atrium from the periphery. The right atrial v wave is generally smaller than the a wave. The *y* descent occurs after the v wave and reflects tricuspid valve opening and right atrial emptying into the right ventricle. During spontaneous respiration, right atrial pressure declines during inhalation as intrathoracic pressure falls. Right atrial pressure rises during exhalation as intrathoracic pressures increase. The opposite effect is seen when patients are mechanically ventilated.

The *left atrial pressure waveform* is similar to that of the right atrium, although normal left atrial pressure is higher, reflecting the high pressure system of the left side of the heart. In the left atrium, as opposed to the right atrium, the v wave is generally higher than the a wave. This occurs because the left atrium is constrained posteriorly by the pulmonary veins, whereas the right atrium can easily decompress throughout the IVC and SVC. The height of the left atrial v wave most accurately reflects left atrial

compliance.

PULMONARY CAPILLARY WEDGE PRESSURE.

The pulmonary capillary wedge pressure waveform is similar to the left atrial pressure waveform but is slightly damped and delayed as a result of transmission through the lungs. The a and v waves with both *x* and *y* descents are visible, but c waves may not be seen. In the normal state, the pulmonary artery diastolic pressure is similar to the mean pulmonary capillary wedge pressure because the pulmonary circulation has low resistance. In certain disease states that are associated with elevated pulmonary vascular resistance (hypoxemia, pulmonary embolism, and chronic pulmonary hypertension), and occasionally after mitral valve surgery, the pulmonary capillary wedge pressure may overestimate true left atrial pressure, and in this circumstance accurate measurement of mitral valve gradient may require obtaining direct left atrial pressure.

VENTRICULAR PRESSURE.

Right and left ventricular waveforms are similar in morphology. They differ mainly with respect to their magnitudes. The durations of systole and isovolumic contraction and relaxation are longer, and the ejection period shorter in the left than in the right ventricle. There may be a small (
5 mm Hg) systolic gradient between the right ventricle and the pulmonary artery. Ventricular diastolic pressure is characterized by an early rapid filling wave during which most of the ventricle fills, a slow filling phase and the a wave denoting atrial systolic activity. End-diastolic pressure is generally measured at the C-point, which is the rise in ventricular pressure at the onset of isovolumic contraction (see Fig. 14-22) . When the C-point is not well seen, a line is drawn from the R wave on the simultaneous ECG to the ventricular pressure waveform, and this is used as the end-diastolic pressure.

GREAT VESSEL PRESSURES.

The contour of the *central aortic pressure* and the *pulmonary artery pressure* tracing consists of a systolic wave, the incisura (indicating closure of the semilunar valves), and a gradual decline in pressure until the following systole. The pulse pressure reflects the stroke volume and compliance of the arterial system. The mean aortic pressure more accurately reflects peripheral resistance. As the systemic pressure wave is transmitted through the length of the aorta, the systolic wave increases in amplitude and becomes more triangular, while the diastolic wave decreases until it reaches the midthoracic aorta and then increases. The mean aortic pressures, however, are usually similar, with the mean *peripheral arterial pressure* typically equal to or less than 5 mm Hg lower than the mean central aortic pressure. The difference in systolic pressures between the central aorta and the periphery (femoral, brachial, or radial arteries) is greatest in younger patients owing to their increased vascular compliance. These

Figure 11-10 (Figure Not Available) Normal right- and left-heart pressure recorded from fluid-filled catheter systems in a human. (From Pepine C, Hill JA, Lambert CR [eds]: Diagnostic and Therapeutic

potential differences between proximal aorta and peripheral artery must be considered in order to measure and interpret the peak systolic pressure gradient between the left ventricle and systemic arterial system in patients with suspected aortic stenosis.

ABNORMAL PRESSURE CHARACTERISTICS.

Abnormal pressure waveforms may be diagnostic of specific pathological conditions. Although these conditions are discussed in greater detail elsewhere in this book, Table 11-6 summarizes the more commonly encountered waveforms.

TABLE 11-6 -- PATHOLOGICAL WAVEFORMS

I. Right atrial pressure waveforms

A. Low mean atrial pressure
1. Hypovolemia
2. Improper zeroing of the transducer

B. Elevated mean atrial pressure
1. Intravascular volume overload states
2. Right ventricular failure due to valvular disease (tricuspid or pulmonic stenosis or regurgitation)
3. Right ventricular failure due to myocardial disease (right ventricular ischemia, cardiomyopathy)
4. Right ventricular failure due to left heart failure (mitral stenosis/regurgitation, aortic stenosis/regurgitation, cardiomyopathy, ischemia)
5. Right ventricular failure due to increased pulmonary vascular resistance (pulmonary embolism, chronic obstructive pulmonary disease, primary pulmonary hypertension)
6. Pericardial effusion with tamponade physiology
7. Obstructive atrial myxoma

C. Elevated a wave (any increase to ventricular filling)
1. Tricuspid stenosis
2. Decreased ventricular compliance due to ventricular failure, pulmonic valve stenosis, or pulmonary hypertension

D. Cannon a wave
1. Atrial-ventricular asynchrony (atria contract against a closed tricuspid valve, as during complete heart block, following premature ventricular contraction, during ventricular tachycardia, with ventricular pacemaker)

E. Absent a wave
1. Atrial fibrillation or atrial standstill
2. Atrial flutter

F. Elevated v wave
1. Tricuspid regurgitation
2. Right ventricular heart failure
3. Reduced atrial compliance (restrictive myopathy)

E. Absent a wave
1. Atrial fibrillation or atrial standstill
2. Atrial flutter
F. Elevated v wave
1. Tricuspid regurgitation
2. Right ventricular heart failure
3. Reduced atrial compliance (restrictive myopathy)
G. a wave equal to v wave
1. Tamponade
2. Constrictive pericardial disease
3. Hypervolemia
H. Prominent *x* descent
1. Tamponade
2. Subacute constriction and possibly chronic constriction
3. Right ventricular ischemia with preservation of atrial contractility
I. Prominent *y* descent
1. Constrictive pericarditis
2. Restrictive myopathies
3. Tricuspid regurgitation
J. Blunted *x* descent
1. Atrial fibrillation
2. Right atrial ischemia
K. Blunted *y* descent
1. Tamponade
2. Right ventricular ischemia
3. Tricuspid stenosis
L. Miscellaneous abnormalities
1. Kussmaul's sign (inspiratory rise or lack of decline in right atrial pressure): constrictive pericarditis, right ventricular ischemia
2. Equalization (
5 mm Hg) of mean right atrial ventricular diastolic, pulmonary artery diastolic, pulmonary capillary wedge, and pericardial pressures in tamponade
3. M or W patterns: right ventricular ischemia, pericardial constriction, congestive heart failure
4. Ventricularization of the right atrial pressure: severe tricuspid regurgitation
5. Sawtooth pattern: atrial flutter
6. Dissociation between pressure recording and intracardiac electrocardiogram: Ebstein's anomaly

II. Left atrial pressure/pulmonary capillary wedge pressure waveforms

A. Low mean pressure

1. Hypovolemia
2. Improper zeroing of the transducer

B. Elevated mean pressure

1. Intravascular volume overload states
2. Left ventricular failure due to valvular disease (mitral or aortic stenosis or regurgitation)
3. Left ventricular failure due to myocardial disease (ischemia or cardiomyopathy)
4. Left ventricular failure due to systemic hypertension
5. Pericardial effusion with tamponade physiology
6. Obstructive atrial myxoma

C. Elevated a wave (any increase to ventricular filling)

1. Mitral stenosis
2. Decreased ventricular compliance due to ventricular failure, aortic valve stenosis, or systemic hypertension

D. Cannon a wave

1. Atrial-ventricular asynchrony (atria contract against a closed mitral valve, as during complete heart block, following premature ventricular contraction, during ventricular tachycardia, with ventricular pacemaker)

E. Absent a wave

1. Atrial fibrillation or atrial standstill
2. Atrial flutter

F. Elevated v wave

1. Mitral regurgitation
2. Left ventricular heart failure
3. Ventricular septal defect

G. a wave equal to v wave

1. Tamponade
2. Constrictive pericardial disease
3. Hypervolemia

H. Prominent *x* descent

1. Tamponade
2. Subacute constriction and possibly chronic constriction

I. Prominent *y* descent

1. Constrictive pericarditis
2. Restrictive myopathies
3. Mitral regurgitation

J. Blunted*x* descent

1. Atrial fibrillation
2. Atrial ischemia K. Blunted *y* descent
1. Tamponade
2. Ventricular ischemia
3. Mitral stenosis

L. Pulmonary capillary wedge pressure not equal to left ventricular end-diastolic pressure

1. Mitral stenosis
2. Left atrial myxoma
3. Cor triatriatum
4. Pulmonary venous obstruction

L. Pulmonary capillary wedge pressure not equal to left ventricular end-diastolic pressure
1. Mitral stenosis
2. Left atrial myxoma
3. Cor triatriatum
4. Pulmonary venous obstruction
5. Decreased ventricular compliance
6. Increased pleural pressure7. Placement of catheter in a nondependent zone of lung

III. Pulmonary artery pressure waveforms
A. Elevated systolic pressure
1. Primary pulmonary hypertension
2. Mitral stenosis or regurgitation
3. Congestive heart failure
4. Restrictive myopathies
5. Significant left-to-right shunt
6. Pulmonary disease (pulmonary embolism, hypoxemia, chronic obstructive pulmonary disease)
B. Reduced systolic pressure
1. Hypovolemia
2. Pulmonary artery stenosis
3. Subvalvular or supravalvular stenosis
4. Ebstein's anomaly
5. Tricuspid stenosis
6. Tricuspid atresia
C. Reduced pulse pressure
1. Right heart ischemia
2. Right ventricular infarction
3. Pulmonary embolism
4. Tamponade
D. Bifid pulmonary artery waveform
1. Large left atrial v wave transmitted backward (i.e. MR)
E. Pulmonary artery diastolic pressure greater than pulmonary capillary wedge pressure
1. Pulmonary disease
2. Pulmonary embolus
3. Tachycardia

IV. Ventricular pressure waveforms
A. Systolic pressure elevated
1. Pulmonary or systemic hypertension
2. Pulmonary valve or aortic valve stenosis
3. Ventricular outflow tract obstruction
4. Supravalvular obstruction
5. Right ventricular pressure elevation with significant:
a. Atrial septal defect
b. Ventricular septal defect
6. Right ventricular pressure elevation due to factors that increase pulmonary vascular resistance (see factors that increase right atrial pressure)
B. Systolic pressure reduced
1. Hypovolemia
2. Cardiogenic shock
3. Tamponade
C. End-diastolic pressure elevated
1. Hypervolemia

B. Systolic pressure reduced
1. Hypovolemia
2. Cardiogenic shock
3. Tamponade
C. End-diastolic pressure elevated
1. Hypervolemia
2. Congestive heart failure
3. Diminished compliance
4. Hypertrophy
5. Tamponade
6. Regurgitant valvular disease
7. Pericardial constrictoin
D. End-diastolic pressure reduced
1. Hypovolemia
2. Tricuspid or mitral stenosis
E. Diminished or absent a wave
1. Atrial fibrillation or flutter
2. Tricuspid or mitral stenosis
3. Tricuspid or mitral regurgitation when ventricular compliance is increased
F. Dip and plateau in diastolic pressure wave
1. Constrictive pericarditis
2. Restrictive myopathies
3. Right ventricular ischemia
4. Acute dilatation associated with:
a. Tricuspid regurgitation
b. Mitral regurgitation
G. Left ventricular end-diastolic pressure > right ventricular end-diastolic pressure
1. Restrictive myopathies

V. Aortic pressure waveforms
A. Systolic pressure elevated
1. Systemic hypertension
2. Arteriosclerosis
3. Aortic insufficiency
B. Systolic pressure reduced
1. Aortic stenosis
2. Heart failure
3. Hypovolemia
C. Widened pulse pressure
1. Systemic hypertension
2. Aortic insufficiency
3. Significant patent ductus arteriosus
4. Significant ruptures sinus of Valsalva aneurysm
D. Reduced pulse pressure
1. Tamponade
2. Congestive heart failure
3. Cardiogenic shock
4. Aortic stenosis
E. Pulsus bisferiens
1. Aortic insufficiency
2. Obstructive hypertrophic cardiomyopathy
F. Pulsus paradoxus
1. Tamponade
2. Chronic obstructive airway disease
3. Pulmonary embolism

1. Aortic insufficiency
2. Obstructive hypertrophic cardiomyopathy

F. Pulsus paradoxus
1. Tamponade
2. Chronic obstructive airway disease
3. Pulmonary embolism

G. Pulsus alternans
1. Congestive heart failure
2. Cardiomyopathy

H. Pulsus parvus et tardus
1. Aortic stenosis

I. Spike-and-dome configuration
1. Obstructive hypertrophic cardiomyopathy

Cardiac Output Measurements

There is no totally accurate method of measuring cardiac output, but it can be estimated on the basis of various assumptions. The two most commonly used methods are the Fick method and thermodilution method. For comparison among patients, cardiac output is often corrected for the patient's size based on the body surface area and expressed as cardiac index.

INDICATOR-DILUTION TECHNIQUES.

The indicator-dilution method has been used to measure cardiac output since its introduction by Stewart in 1897 and subsequent modification by Hamilton and associates in 1932. The basic equation, commonly referred to as the Stewart-Hamilton equation, follows:

The assumption is made that after the injection of a certain quantity of an indicator into the circulation, the indicator appears and disappears from any downstream point in a manner commensurate with the cardiac output. For example, if the indicator rapidly appears at a specific location downstream and then washes out quickly, the assumption is that the cardiac output is high. Although variation can occur, the site of injection is usually a systemic vein or the right side of the heart, and the sampling site is generally a systemic artery. The normal curve itself has an initial rapid upstroke followed by a slower downstroke and eventual appearance of recirculation of the tracer (Fig. 11-11) . In practice, this recirculation creates some uncertainty on the tail of the curve, and assumptions are required to correct for this distortion. Because the indicator concentration declines exponentially in the absence of recirculation, the initial data points from the descending limb are used to extrapolate the remainder of the descending limb. The area under both the ascending and descending limbs is then determined along with the total curve duration. The area of the curve is assumed to be a function of the mean indicator concentration. Both variables can be substituted in the Stewart-Hamilton equation to calculate the cardiac output.

There are several sources of error in this determination. Because the dye is unstable over time and can be affected by light, fresh preparations of indocyanine green dye are necessary.`The exact amount of dye must be accurately measured, as it is crucial to the performance of the study. It is generally administered through a tuberculin syringe and

injected rapidly as a single bolus. After injection, the indicator must mix well before reaching the sampling site, and the dilution curve must have an exponential decay over time so that extrapolation can be performed. If, for example, there is severe valvular regurgitation or a low cardiac output state in which the washout

Figure 11-11 Thermodilution Cardiac Output Curves. A normal curve has a sharp upstroke following an injection of saline. A smooth curve with mildly prolonged downslope occurs until back to baseline. The area under curve is inversely related to the cardiac output. At low cardiac output, a prolonged period is required to return to baseline. Therefore, there is a larger area under the curve. In a high cardiac output state, the cooler saline injectate moves faster through the right side of the heart and temperature returns to baseline more quickly. The area under curve is smaller and the output is higher.

of the indicator is prolonged and recirculation begins well before an adequate decline in the indicator curve occurs, determinations will be erroneous. Intracardiac shunts may also greatly affect the shape of the curve.

THERMODILUTION TECHNIQUES.

Because of the rather tedious and time-consuming nature of the indicator-dilution method, it has been replaced by thermodilution techniques in many laboratories. The development of balloon flotation (e.g., Swan-Ganz) catheters with a proximal port and distal thermistor (see Fig. 11-1) has greatly expanded the ability to obtain thermodilution cardiac outputs in many clinical settings.

The thermodilution procedure requires injection of a bolus of liquid (saline or dextrose) into the proximal port of the catheter. The resultant change in temperature in the liquid is measured by a thermistor mounted in the distal end of the catheter. The change in temperature versus time can be plotted in a manner similar to the dye-dilution method described earlier (in which the indicator is now the cooler liquid). The cardiac output is then calculated using an equation that considers the temperature and specific gravity of the injectate and the temperature and specific gravity of the blood, along with the injectate volume. A calibration factor is also used. The cardiac output is inversely related to the area under a thermodilution curve, plotted as a function of temperature versus time, with a smaller area indicative of a higher cardiac output.

The thermodilution method has several advantages. It obviates the need for withdrawal of blood from an arterial site and is less affected by recirculation. Perhaps its greatest advantage is the rapid display of results using computerized methods (see Fig. 11-11) . Computers use the washout rate represented by the downslope of the curve to obtain a decay constant to correct the descending limb and compute the cardiac output.

Thermodilution cardiac output measurements are susceptible to pitfalls similar to those encountered with indicator-dilution methods using indocyanine green. Because the data

represent right-sided heart output, tricuspid regurgitation can be a particular problem as the bolus of saline is subsequently broken up. The thermodilution method tends to overestimate cardiac output in low-output states, because the dissipation of the cooler temperature to the surrounding cardiac structures results in reduction in the total area under the curve, causing a falsely elevated cardiac output value. Other difficulties include fluctuations in blood temperature during respiratory or cardiac cycles and the warming of the temperature of the injectate before its injection into the catheter. Because of these possible limitations, the general practice is to calculate the average of several (usually three to five) cardiac output determinations.

From a practical viewpoint, thermodilution cardiac output measurements have become standard practice. Their variability can be relatively large; thus, small changes should not be overinterpreted. Practically, cardiac output data can be defined only to within a 15 percent range.[81]

FICK TECHNIQUE.

The Fick principle, first described by Adolph Fick in 1870, assumes that the rate at which oxygen is consumed is a function of the rate of blood flow times the rate of oxygen pick-up by the red blood cells. The basic assumption is that the flow of blood in a given period is equal to the amount of substance entering the stream of flow in the same period divided by the difference between the concentrations of the substance in the blood upstream and downstream from its point of entry into the circulation[82] (Fig. 11-12) . The same number of red blood cells that enter the lung must leave the lung, if no intracardiac shunt is present. Thus, if certain parameters were known (the number of oxygen molecules that were attached to the red blood cells entering the lung, the number of oxygen molecules that were attached to the red blood cells leaving the lung, and the number of oxygen molecules consumed during travel through the lung), then the rate of flow of these red blood cells as they pass through the lung could be determined. This can be expressed in the following terms:

Measurements must be made in steady state. Automated methods can accurately determine the oxygen content within the blood samples. Thus, the greatest source of measurement variability is that of the oxygen consumption. In traditional Fick determinations, expiratory gas samples

Figure 11-12 Schematic illustration of flow measurement using the Fick principle. Fluid containing a known concentration of an indicator (C_{in}) enters a system at flow rate, Q. As the fluid passes through the system, indicator is continuously added at rate V, raising the concentration in the outflow to C_{out} . In a steady state, the rate of indicator leaving the system (QC_{out}) must equal the rate at which it enters (QC_{in}) plus the rate at which it is added (V). When oxygen is used as the indicator, cardiac output can be determined by measuring oxygen consumption (VO_2), arterial oxygen content ($C_A O_2$), and mixed venous oxygen content ($C_v O_2$). (From Winniford MD, Kern MJ, Lambert CR [eds]: Blood flow

measurement. *In* Pepine CJ, Hill JA, Lambert CR [eds]: Diagnostic and Therapeutic Cardiac Catheterization. 3rd ed. Baltimore, Williams & Wilkins, 1998, p 400.)

were collected in a large bag over a specified period. By measuring the expiratory oxygen concentration and by knowing the concentration of oxygen in room air, the quantity of oxygen consumed over time could be determined. In newer techniques that allow for measurement of expired oxygen, concentration is quantified by using a polarigraph. This device can be connected to the patient by use of a plastic hood or by a mouthpiece and tubing.

The advantage of the Fick method is that it is the most accurate method in patients with low cardiac output and thus is preferred over the thermodilution method in these circumstances. It is also independent of the factors that affect curve shape and cause errors in thermodilution cardiac output. The Fick method suffers primarily from the difficulty in obtaining accurate oxygen consumption measurements and the inability to obtain a steady state under certain conditions. Because the method assumes mean flow over a period of time, it is not suitable during rapid change in flow. It requires considerable time and effort on the part of the catheterization laboratory to obtain the appropriate data. Many laboratories use an "assumed" Fick method in which oxygen consumption index is assumed on the basis of the patient's age, gender, and body surface area or an estimate made (125 ml/$m^{[2]}$) on the basis of body surface area. The inaccuracy of oxygen consumption measurements results in up to 10 percent variability in the calculated cardiac output, which may be even greater when assumed oxygen consumption, rather than measured oxygen consumption, is used.

ANGIOGRAPHIC CARDIAC OUTPUT.

Angiographic stroke volume can be calculated from tracing the end-diastolic and end-systolic images. Stroke volume is the quantity of blood ejected with each beat. End-diastolic volume is the maximum left ventricular volume and occurs immediately before the onset of systole. This occurs immediately after atrial contraction in patients in sinus rhythm. End-systolic volume is the minimum volume during the cardiac cycle. Calibration of the images with calibrated grids or ventricular phantoms is necessary to obtain accurate ventricular volumes. Angiographic cardiac output and stroke volume are derived from the following equations:

where EDV = end-diastolic volume and ESV = end-systolic volume. The inherent inaccuracies of calibrating angiographic volumes often make this method of measurement unreliable. In cases of valvular regurgitation or atrial fibrillation, angiographic cardiac output does not accurately measure true systemic outputs. However, the angiographic cardiac output is preferred over the Fick or thermodilution output for calculation of stenotic valve areas in patients with significant aortic or mitral regurgitation.

DETERMINATION OF VASCULAR RESISTANCE.

Vascular resistance calculations are based on hydraulic principles of fluid flow, in which resistance is defined as the ratio of the decrease in pressure between two points in a vascular segment and the blood flow through the segment. Although this straightforward analogy to Ohm's law represents an oversimplification of the complex behavior of pulsatile flow in dynamic and diverse vascular beds, the calculation of vascular resistance based on these principles has proved to be of value in a number of clinical settings.

Determination of the resistance in a vascular bed requires measurement of the mean pressure of the proximal and distal ends of the vascular bed and accurate measurement of cardiac output. For this purpose, measurement of cardiac output by the Fick, the indicator-dilution, or the thermodilution method is preferred. Vascular resistance (R) is usually defined in absolute units (dyne-sec cm^{-5}) and is defined as R = [mean pressure gradient (dyne/cm^{2})]/[mean flow (cm^{3} /sec)]. Hybrid units (Wood units) are less often used.[83]

Systemic vascular resistance in absolute units is calculated using the following equation:

where AO_m and RA_m are the mean pressures (in mm Hg) in the aorta and right atrium, respectively, and Q_s is the systemic cardiac output (in liters/min). The constant 80 is used to convert units from mm Hg/liters/min (Wood units) to the absolute resistance units dyne-sec cm^{-5} . If the right atrial pressure is not known, the term RA_m can be dropped, and the resulting value is called the *total peripheral resistance* (TPR).

Similarly, the pulmonary vascular resistance is derived from the following equation:

where PA_m and LA_m are the pulmonary artery and left atrial pressures, respectively, and Q_p is the pulmonary blood flow. Mean pulmonary capillary wedge pressure is commonly substituted for mean left atrial pressure if the latter has not been measured directly.[84] In the absence of an intracardiac shunt, Q_p is equal to the systemic cardiac output.

Normal values are listed in Table 11-5 .

Elevated resistances in the systemic and pulmonary circuits may represent reversible abnormalities or may be fixed owing to irreversible anatomical changes. In several clinical situations, such as congestive heart failure, valvular heart disease, primary

pulmonary hypertension, and congenital heart disease with intracardiac shunting, determination of whether elevated systemic or pulmonary vascular resistance can be lowered transiently in the catheterization laboratory may provide important insights into potential management strategies. Interventions that may be used in the laboratory for this purpose include administration of vasodilating drugs (e.g., sodium nitroprusside), exercise, and (in patients with pulmonary hypertension) oxygen inhalation.

Vascular impedance measurements account for blood viscosity, pulsatile flow, reflected waves, and arterial compliance. Hence, vascular impedance has the potential to describe the dynamic relation between pressure and flow more comprehensively than is possible using the simpler calculations of vascular resistance. However, because the simultaneous pressure and flow data required for the calculation of impedance are complex and difficult to obtain, the concept of impedance has failed to gain widespread acceptance, and vascular impedance has not been adopted as a routine clinical index in most laboratories.

Evaluation of Valvular Stenosis (See also Chap. 46)

Determining the severity of valvular stenosis on the basis of the pressure gradient and flow across the valve is one of the most important aspects of evaluating patients with valvular heart disease. In most patients, the magnitude of the

pressure gradient alone is sufficient to distinguish clinically significant from insignificant valvular stenosis.

DETERMINATION OF PRESSURE GRADIENTS.

In patients with *aortic stenosis,* the transvalvular pressure gradient should be measured, whenever possible, with a catheter in the left ventricle and another in the proximal aorta. Although it is convenient to measure the gradient between the left ventricle and the femoral artery, downstream augmentation of the pressure signal and delay in pressure transmission between the proximal aorta and femoral artery may alter the pressure waveform substantially and introduce errors into the measured gradient.[85]

Left ventricular-femoral artery pressure gradients may suffice in many patients as an estimate of the severity of aortic stenosis to confirm the presence of a severely stenotic valve. If the side port of the arterial introducing sheath is used to monitor femoral pressure, the inner diameter of the sheath should be 1F size larger than the outer diameter of the catheter being used. The left ventricular-femoral artery pressure gradient may not always be relied on in the calculation of valve orifice area in patients with equivocal valve gradients. A careful single catheter pull-back from left ventricle to aorta is often preferable to simultaneous measurement of left ventricular and femoral artery pressures. Alternatively, a single catheter with distal and proximal lumina or a micromanometer catheter with distal and proximal transducers may be used for

simultaneous measurement of left ventricular pressure and central aortic pressure. Another method is to place two catheters, one in the aorta and the second in the left ventricle. However, this requires two punctures of the femoral artery and is rarely used.

In patients with very severe aortic stenosis, the left ventricular catheter itself may reduce the effective orifice area, resulting in an artifactual increase in the measured pressure gradient.[86] This overestimation of the severity of aortic stenosis is rarely an important issue, because the diagnosis of severe aortic stenosis is usually already apparent in such patients.

The mean pressure gradient across the aortic valve is determined by planimetry of the area separating the left ventricular and aortic pressures using multiple beats (Fig. 11-13) , and it is this gradient that is applied to calculation

Figure 11-13 Various methods of describing an aortic transvalvular gradient. The peak-to-peak gradient (47 mm Hg) is the difference between the maximal pressure in the aorta (Ao) and the maximal left ventricle (LV) pressure. The peak instantaneous gradient (100 mm Hg) is the maximal pressure difference between the Ao and LV when the pressures are measured in the same moment (usually during early systole). The mean gradient (shaded area) is the integral of the pressure difference between the LV and Ao during systole (60 mm Hg). (From Bashore TM: Invasive Cardiology: Principles and Techniques. Philadelphia, BC Decker, 1990.)

Figure 11-14 Pressure gradient in a patient with mitral stenosis. The pressure in the left atrium (LA) exceeds the pressure in the left ventricle (LV) during diastole, producing a diastolic pressure gradient (shaded area). (From Bashore TM: Invasive Cardiology: Principles and Techniques. Philadelphia, BC Decker, 1990.)

of the valve orifice area. The peak-to-peak gradient, measured as the difference between peak left ventricular pressure and peak aortic pressure, is commonly used to quantify the valve gradient, because this measurement is rapidly obtained and can be estimated visually. There is no physiological basis for the peak-to-peak gradient, however, because the maximum left ventricular and aortic pressures rarely occur simultaneously. The peak-to-peak gradient measured in the catheterization laboratory is generally lower than the peak instantaneous gradient measured in the echocardiography laboratory. This is because the peak instantaneous gradient represents the maximum pressure difference between the left ventricle and aorta when measured simultaneously. This occurs on the upslope of the aortic pressure tracing (Fig. 11-13) . Mean aortic transvalvular gradient and aortic valve area are well correlated with both techniques (r = 0.86 - 0.90 and r = 0.88 - 0.95, respectively).[87]

In patients with *mitral stenosis,* the most accurate means of determining mitral valve gradient is measurement of left atrial pressure using the transseptal technique with simultaneous measurement of left ventricular pressure and with planimetry of the area bounded by the left ventricular and left atrial pressures in diastole using several cardiac cycles (Fig. 11-14) . In most laboratories, the pulmonary capillary wedge pressure is

substituted for the left atrial pressure, as the pulmonary wedge pressure is more readily obtained. The pulmonary wedge pressure tracing must be realigned with the left ventricular tracing for accurate mean gradient determination. Although it has been generally accepted that pulmonary capillary wedge pressure is a satisfactory estimate of left atrial pressure,[84] some studies indicate that the pulmonary wedge pressure may systematically overestimate the left atrial pressure by 2 to 3 mm Hg, thereby increasing

the measured mitral valve gradient.[88] In addition, accurate wedge tracings may be difficult to obtain in patients with mitral stenosis because of pulmonary hypertension or dilated right-sided heart chambers. Improperly wedged catheters, resulting in damped pulmonary artery pressure recordings, further overestimate the severity of mitral stenosis. If there is doubt about the accurate position of the catheter in the wedge position, the position can be confirmed by slow withdrawal of blood for oximetric analysis. An oxygen saturation equal to that of the systemic circulation confirms the wedge position.

In *pulmonic stenosis,* the valve gradient is usually obtained by a catheter pull-back from the pulmonary artery to the right ventricle, although multilumen catheters are available for simultaneous pressure recordings. *Tricuspid valve gradients* should be assessed with simultaneous recording of right atrial and right ventricular pressures.

CALCULATION OF STENOTIC VALVE ORIFICE AREAS.

The stenotic orifice area is determined from the pressure gradient and cardiac output using the formula developed by Gorlin and Gorlin from the fundamental hydraulic relationships linking the area of an orifice to the flow and pressure drop across the orifice.[89] Flow (F) and orifice area (A) are related by the fundamental formula

where V is velocity of flow and c is a constant accounting for central streaming of fluid through an orifice which tends to reduce the effective orifice size. Hence,

Velocity is related to the pressure gradient through the relation V=k sqrt(2gDeltaP), where k is a constant accounting for frictional energy loss, g is the acceleration due to gravity (980 cm/sec[2]) and DeltaP is the mean pressure gradient (mm Hg). Substituting for V in the orifice area equation and combining c and k into one constant C,

Gorlin and Gorlin determined the value of the constant C by comparing the calculated valve area with actual valve area measured at autopsy or at surgery in 11 mitral valves. The maximal discrepancy between the actual mitral valve area and calculated values was only 0.2 cm[2] when the constant 0.85 was used. No data were obtained for aortic

valves, a limitation noted by the Gorlins, and a constant of 1.0 was assumed. Because flow across the aortic valve occurs only in systole, the flow value for calculating aortic valve area (cm^2) is the cardiac output in ml/min divided by the systolic ejection period (SEP) in seconds/beat times the heart rate (HR) in beats/min. The systolic ejection period is defined from aortic valve opening to closure. Hence, the aortic valve area is calculated from the Gorlin formula using the following equation:

Similarly, as mitral flow occurs only in diastole, the cardiac output is corrected for the diastolic filling period (DFP) in seconds/beat in the equation for mitral valve area, where the diastolic filling period is defined from mitral valve opening to mitral valve closure:

The normal aortic valve area is 2.6 to 3.5 cm^2 in adults. Valve areas of 0.8 cm^2 or less represent severe aortic stenosis. The normal mitral valve area is 4 to 6 cm^2 , and severe mitral stenosis is present with valve areas less than 1.3 cm^2 .

The calculated valve area often is crucial in management decisions in patients with aortic stenosis or mitral stenosis. Hence, it is essential that accurate and simultaneous pressure gradient and cardiac output determinations be made, especially in patients with borderline or low pressure gradients.

LIMITATIONS OF THE ORIFICE AREA FORMULA.

As the square root of the mean gradient is used in the Gorlin formula, the valve area calculation is more strongly influenced by the cardiac output than the pressure gradient. Thus, errors in measuring cardiac output may have profound effects on the calculated valve area, particularly in patients with low cardiac outputs, in whom the calculated valve area is often of greatest importance.

The Fick method of determining cardiac output is the most accurate for assessing cardiac output, especially in low-output states. As noted previously, both the dye-dilution technique and the thermodilution technique may provide inaccurate cardiac output data when cardiac output is reduced or when concomitant aortic, mitral, or tricuspid regurgitation is present. In patients with mixed valvular disease (stenosis and regurgitation) of the same valve, the use of forward flow as determined by the Fick method or thermodilution technique overestimates the severity of the valvular stenosis. This is because the Gorlin formula depends on total forward flow across the stenotic valve, not net forward flow. If valvular regurgitation is present, the angiographic cardiac output is the most appropriate measure of flow. If both aortic and mitral regurgitation are present, flow across a single valve cannot be determined and neither aortic valve area nor mitral valve area can be assessed accurately.

Other potential errors and limitations are inherent in the use of the Gorlin formula,[90] [91]

related both to inaccuracies in measurement of valve gradients and to more fundamental issues regarding the validity of the assumptions underlying the formula. In low-output states, the Gorlin formula may systematically predict smaller valve areas than are actually present. Several lines of evidence indicate that the aortic valve area by the Gorlin formula increases with increases in cardiac output.[92] [93] [94] Although this may represent an actual greater opening of stenotic valves by the higher proximal opening pressures that result from increases in transvalvular flow, the flow dependence of the calculated valve area may also reflect inherent errors in the assumptions underlying the Gorlin formula, particularly with respect to the aortic valve.[90] [95]

A study was performed to compare simultaneous aortic valve area determinations by transesophageal echocardiographic planimetry and the Gorlin formula.[96] This demonstrated that with increases in transvalvular flow, the Gorlin valve area also increased. This was not associated with alterations in direct planimetry of the aortic valve area. These results suggest that flow-related variation in the Gorlin aortic valve area is due to disproportional flow depedence of the formula and not a true change in the valve area.

Cannon and colleagues[93] demonstrated in valves of fixed orifice size that the constant in the Gorlin formula is actually not constant but varies with the square root of the mean pressure gradient (C=k sqrt(mean gradient)). This concept would transform the Gorlin formula such that the square root disappears and the valve area varies inversely with the mean gradient:

This concept has particular implications in aortic stenosis, in which the higher valve gradients have a greater effect on the Gorlin constant than the considerably smaller gradients encountered in mitral stenosis. The constant h was added to correct for a small offset between predicted and measured valve areas. The values of the new constants K and h have not been fully validated, and the complete independence of these constants from transvalvular flow has not been well investigated.

Other alternative formulas for determining valve areas have been proposed. Hakki[97] observed empirically that the effects of the systolic ejection period and the diastolic filling period were relatively constant at normal heart rates and proposed eliminating this term from the equation. This assumes that (HR × SEP × 44.3)
1000 in most circumstances. In this modified and simplified approach, the aortic valve area would be determined by the following formula:

Angel and colleagues[98] tested this approach at various heart rates and proposed adding an empirical constant for heart rates less than 75 beats/min for mitral stenosis and more than 90 beats/min for aor

tic stenosis. As is the case with Cannon's modification of the Gorlin formula, this alternate approach to determining valve area has not been fully validated.

One approach to patients with a low aortic transvalvular gradient and low cardiac output is to calculate the aortic valve resistance using the following formula:

where HR is heart rate, SEP is systolic ejection period, and valve resistance is expressed in dyne-sec cm^{-5} . [94] [99] The limited data available using aortic valve resistance suggest that this measure may be a helpful adjunct in distinguishing those patients with borderline aortic valve areas (0.6 to 0.8 cm^2) who have severe versus mild aortic stenosis.

Measurement of Intraventricular Pressure Gradients

The demonstration of an intracavitary pressure gradient is among the most interesting and challenging aspects of diagnostic catheterization. Simultaneous pressure measurements are usually obtained in the central aorta and from within the ventricular cavity. Pull-back of the catheter from the ventricular apex to a posterior position just beneath the aortic valve demonstrates an intracavitary gradient. An erroneous intracavitary gradient may be seen if the catheter becomes entrapped by the myocardium.

The intracavitary gradient is distinguished from aortic valvular stenosis due to the loss of the aortic-left ventricular gradient when the catheter is still within the left ventricle yet proximal to the myocardial obstruction (see Fig. 48-12) (Figure Not Available) . In addition, careful analysis of the upstroke of the aortic pressure waveform will distinguish a valvular from a subvalvular stenosis, as the aortic pressure waveform demonstrates a slow upstroke in aortic stenosis. Other methods to localize intracavitary gradients include the use of a dual-lumen catheter or a double-sensor romanometer catheter, or placement of an end-hole catheter in the left ventricular outflow tract while a transseptal catheter is advanced into the left ventricle, with pressure measured simultaneously. An intracavitary gradient may be increased by various provocative maneuvers including the Valsalva maneuver, inhalation of amyl nitrate, introduction of a premature ventricular beat, or isoproterenol infusion (see Physiological and Pharmacological Maneuvers).

Assessment of Valvular Regurgitation

VISUAL ASSESSMENT OF REGURGITATION.

Valvular regurgitation may be assessed visually by determining the relative amount of radiographic contrast medium that opacifies the chamber proximal to its injection. The estimation of regurgitation depends on the regurgitant volume as well as the size and

contractility of the proximal chamber. The original classification scheme devised by Sellers and colleagues remains the standard in most catheterization laboratories:[100]

+++

Minimal regurgitant jet seen. Clears rapidly from proximal chamber with each beat

++++

Moderate opacification of proximal chamber, clearing with subsequent beats

++++

Intense opacification of proximal chamber, becoming equal to that of the distal chamber

++++

Intense opacification of proximal chamber, becoming more dense than that of the distal chamber. Opacification often persists over the entire series of images obtained

REGURGITANT FRACTION.

A gross estimate of the degree of valvular regurgitation may be obtained by determining the regurgitant fraction (RF). The difference between the angiographic stroke volume and the forward stroke volume can be defined as the regurgitant stroke volume. The RF is that portion of the angiographic stroke volume that does not contribute to the net cardiac output.

Forward stroke volume is the cardiac output determined by the Fick or thermodilution method divided by the heart rate. Thermodilution cardiac output cannot be used if there is significant concomitant tricuspid regurgitation.

As detected visually, 1+regurgitation is roughly equivalent to an RF less than or equal to 20 percent; 2+ regurgitation to an RF of 21 to 40 percent; 3+41 to 60 percent; and 4+ to more than 60 percent.

The assumption underlying the determination of RF is that the angiographic and forward cardiac outputs are accurate and comparable, a state requiring similar heart rates, stable hemodynamic states between measurements, and only a single regurgitant valve. Given these conditions, the equation yields only a gross approximation of regurgitant flow.

Shunt Determinations

Normally, pulmonary blood flow and systemic blood flow are equal. With an abnormal communication between intracardiac chambers or great vessels, blood flow is shunted either from the systemic circulation to the pulmonary circulation (left-to-right shunt), from the pulmonary circulation to the systemic circulation (right-to-left shunt), or in both directions (bidirectional shunt). Although many shunts are suspected before cardiac catheterization, physicians performing the procedure should be vigilant in determining the cause of unexpected findings. For example, an unexplained pulmonary artery oxygen saturation exceeding 80 percent should raise the operator's suspicion of a left-to-right shunt, whereas unexplained arterial desaturation (<93 percent) may indicate a right-to-left shunt.[101] Arterial desaturation commonly results from alveolar hypoventilation and associated "physiological shunting," the causes of which include oversedation from premedication, pulmonary disease, pulmonary venous congestion, pulmonary edema, and cardiogenic shock. If arterial desaturation persists after the patient takes several deep breaths or coughs or after administration of 100 percent oxygen, a right-to-left shunt must be highly suspected.

Several noninvasive and invasive methods are available for detection of intracardiac shunts. Noninvasive methods include echocardiographic, radionuclide, and magnetic resonance imaging techniques. The most commonly used method in the cardiac catheterization laboratory is the oximetric method.

OXIMETRIC METHOD.

The oximetric method is based on blood sampling from various cardiac chambers for the determination of oxygen saturation. A left-to-right shunt is detected when a significant increase in blood oxygen saturation is found between two right-sided vessels or chambers.[102]

A screening oxygen saturation measurement for any left-to-right shunt should be performed with right heart catheterization by sampling blood in the SVC and the pulmonary artery. If the difference in oxygen saturation between these

samples is 8 percent or more, a left-to-right shunt may be present, and a full oximetry "run" should be performed.[101] This includes obtaining blood samples from all right-sided locations including the SVC, IVC, right atrium, right ventricle, and pulmonary artery. In cases of interatrial or interventricular shunts, it may be helpful to obtain multiple samples from the high, middle, and low right atrium or the right ventricular inflow tract, apex, and outflow tract in order to localize the level of the shunt. One may miss a small left-to-right shunt using the right atrium for screening purposes rather than the SVC because of incomplete mixing of blood in the right atrium, which receives blood from the IVC, SVC, and coronary sinus. Oxygen saturation in the IVC is higher than in the SVC because the kidneys use less oxygen relative to their blood flow than do other organs, whereas coronary sinus blood has very low oxygen saturation. Mixed venous saturation is most

accurately measured in the pulmonary artery after complete mixing has occurred.

A full saturation run involves obtaining samples from the high and low IVC; high and low SVC; high, mid, and low right atrium; right ventricular inflow and outflow tracts and midcavity; main pulmonary artery; left or right pulmonary artery; pulmonary vein and left atrium if possible; left ventricle; and distal aorta. When a right-to-left shunt must be localized, oxygen saturation samples must be taken from the pulmonary veins, left atrium, left ventricle, and aorta. Although the major weakness of the oxygen step-up method is its lack of sensitivity, clinically significant shunts are generally detected by this technique. Another method of oximetric determination of intracardiac shunts uses a balloon-tipped fiberoptic catheter that allows for continuous registration of oxygen saturation as it is withdrawn from the pulmonary artery through the right heart chambers into the SVC and IVC.

SHUNT QUANTIFICATION.

The principles used to determine Fick cardiac output are also used to quantify intracardiac shunts. To determine the size of a left-to-right shunt, pulmonary blood flow (PBF) and systemic blood flow (SBF) determinations are required. PBF is simply oxygen consumption divided by the difference in oxygen content across the pulmonary bed, whereas SBF is oxygen consumption divided by the difference in oxygen content across the systemic bed. The effective blood flow (EBF) is the fraction of mixed venous return received by the lungs without contamination by the shunt flow. In the *absence* of a shunt, PBF, SBF, and EBF all are equal. These equations are shown below:

where P bar(v)$_{O_2}$, Pa$_{O_2}$, Sa$_{O_2}$, and M bar(v)$_{O_2}$ are the oxygen contents (in milliliters of oxygen per liter of blood) of pulmonary venous, pulmonary arterial, systemic arterial, and mixed venous bloods, respectively. The oxygen content is determined as outlined in the section on Fick cardiac output.

If a pulmonary vein is not sampled, systemic arterial oxygen content may be substituted, assuming systemic arterial saturation is 95 percent or more. As discussed earlier, if systemic arterial saturation is less than 95 percent, a right-to-left shunt may be present. If arterial desaturation is present but not secondary to a right-to-left shunt, systemic arterial oxygen content is used. If a right-to-left shunt is present, pulmonary venous oxygen content is calculated as 98 percent of the oxygen capacity.

The mixed venous oxygen content is the average oxygen content of the blood in the chamber proximal to the shunt. When assessing a left-to-right shunt at the level of the right atrium, one must calculate mixed venous oxygen content on the basis of the contributing blood flow from the IVC, SVC, and coronary sinus. The most common formula used is Flamm's formula.[103]

Assuming conservation of mass, the size of a left-to-right shunt, when there is no associated right-to-left shunt, is simply

When there is evidence of a right-to-left shunt in addition to a left-to-right shunt, the approximate left-to-right shunt size is

while the approximate right-to-left shunt size is

The flow ratio PBF/SBF (or QP/QS) is used clinically to determine the significance of the shunt. A ratio of less than 1.5 indicates a small left-to-right shunt; a ratio of 1.5 to 2.0, a moderate-sized shunt. A ratio of 2.0 or more indicates a large left-to-right shunt and generally requires repair to prevent future pulmonary and/or right ventricular complications. A flow ratio of less than 1.0 indicates a net right-to-left shunt. If oxygen consumption is not measured, the pulmonic/systemic blood flow ratio may be calculated as follows:

where Sa_{O_2} , $M\ bar{(v)}_{O_2}$, $P\ bar{(v)}_{O_2}$, and Pa_{O_2} are systemic arterial, mixed venous, pulmonary venous, and pulmonary arterial blood oxygen saturations, respectively.

INDICATOR-DILUTION METHOD

Although the indicator-dilution method is more sensitive than the oximetric method in detection of small shunts, it cannot be used to localize the level of a left-to-right shunt (Fig. 11-15) . An indicator such as indocyanine green dye is injected into a proximal chamber while a sample is taken from a distal chamber using a densitometer, and the density of dye is displayed over time. To detect a left-to-right shunt, dye is injected into the pulmonary artery and sampling is performed in a systemic artery. Presence of a shunt is indicated by early recirculation of the dye on the downslope of the curve.[104] The presence of aortic or mitral regurgitation may distort the downslope of the curve, thereby yielding a false-positive result. In adults, the indocyanine green method provides estimates of shunt magnitude that are somewhat smaller than those of the oximetric method, although they are in general agreement with one another concerning the PBF/SBF.[105] [106] To detect a right-to-left shunt, dye is injected into the right heart proximal to the presumed shunt and sampling is performed in a systemic artery. If there is a right-to-left shunt, a distinct early peak is seen on the upslope of the curve.[107] The level of the right-to-left shunt may be localized by injecting more distally until the early peak disappears. Shunts may also be quantified using this technique.

A sensitive method for detection and localization of a left-to-right shunt is to check systematically within the various right heart chambers for the early appearance of an indicator that is injected distal to the presumed shunt. Indicators that have been used for this purpose include indocyanine green dye, inhaled hydrogen, hydrogen dissolved

Figure 11-15 Left-to-right shunt (increased pulmonic flow). Indicator is not cleared rapidly but recirculates through the central circulation via a defect. Based on magnitude of shunt, a constant fraction leaves the central pool with each circulation. Maximal deflection is reduced, and the disappearance is prolonged as a result of slow clearance. Right-to-left shunt (decreased pulmonic flow). A portion of the indicator passes directly to the arterial circulation via the defect without passing through the lungs and arrives at the arterial sampling site before the portion that did traverse the pulmonary circulation. (From Kern MJ, Deligonul U, Donohue T, et al: Hemodynamic data. *In* Kern MI [ed]: The Cardiac Catheterization Handbook. 2nd ed. St. Louis, Mosby-Year Book, 1995, p 142.)

in saline, and ascorbic acid. Platinum-tipped electrodes are used for detection when hydrogen and ascorbic acid are used. These techniques may also be used to detect small right-to-left shunts by altering the sites of injection and sampling.

Selective injection of radiographic contrast (angiocardiography) can detect both left-to-right and right-to-left shunts, although these cannot be quantified. Angiocardiography is a useful adjunct to transesophageal echocardiography as part of a preoperative evaluation. It is also useful in detecting pulmonary arteriovenous fistulas that may not be detected by other methods.

Physiological and Pharmacological Maneuvers

Potentially significant cardiac abnormalities may be absent in the resting condition but may be unmasked by stress. Therefore, if the cause of a patient's symptoms cannot be assessed at rest, various physiological and pharmacological maneuvers can be considered.

DYNAMIC EXERCISE.

Dynamic exercise in the catheterization laboratory is most commonly performed using supine bicycle ergometry, although straight leg raises or arm or upright bicycle exercise may be used. Upright treadmill exercise may also be performed outside the catheterization laboratory, using a balloon flotation catheter inserted through an antecubital vein to measure pulmonary artery and wedge pressure and cardiac output. The associated changes in the heart rate, cardiac output, oxygen consumption, and

intracardiac pressures are monitored at steady state during progressive stages of exercise. Normally, the increased oxygen requirements of exercise are met by an increase in cardiac output and an increase in oxygen extraction from arterial blood.[108] Patients with cardiac dysfunction are unable to increase their cardiac output appropriately in response to exercise and must meet the demands of the exercising muscle groups by increasing the extraction of oxygen from arterial blood, thereby increasing the arteriovenous oxygen difference. Dexter and colleagues found that the relationship between cardiac output and oxygen consumption was linear and that a regression formula may be used to calculate the predicted cardiac index at a given level of oxygen consumption.[109] The actual cardiac index divided by the predicted cardiac index is defined as the *exercise index.* A value of 0.8 or more indicates a normal cardiac output response to exercise.[108] The *exercise factor* is another method of describing the same relationship between the cardiac output and oxygen consumption. The exercise factor is the increase in cardiac output divided by the increase in oxygen consumption. Normally, for every 100 ml/min increase in oxygen consumption with exercise, the cardiac output should increase by at least 600 ml/min. Therefore, a normal exercise factor should be 0.6 or more.[108]

Supine exercise normally causes a rise in mean arterial and pulmonary pressures. There is a proportionately greater decrease in systemic vascular resistance compared with pulmonary vascular resistance and an increase in heart rate. Myocardial contractility increases owing to both increased sympathetic tone and the increase in heart rate. Left ventricular ejection fraction rises. During early levels of exercise, increased venous return augments left ventricular end-diastolic volume, leading to an increase in stroke volume.[110] At progressively higher levels of exercise, both left ventricular end-systolic and end-diastolic volumes decrease such that there is a negligible rise in stroke volume. Thus, the augmentation in cardiac output during peak supine exercise in the catheterization laboratory is generally caused by an increase in heart rate. For this reason, all agents that may impair the chronotropic response should be discontinued before catheterization if exercise is contemplated during the procedure.

Exercise may provoke symptoms in a patient who had been found to have valvular disease of borderline significance in the resting state. Exercise increases the gradient across the mitral valve in mitral stenosis and may provoke symptoms not experienced at rest. The hemodynamic response to exercise is also useful in evaluating regurgitant valvular lesions. Clinically important valvular regurgitation exists if an increase occurs in left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, and systemic vascular resistance, in conjunction with a reduced exercise index and abnormal exercise factor. Simultaneous echocardiographic data may also be useful in equivocal cases. Patients with myocardial disease, ischemic or otherwise,

may have pronounced increases in left ventricular end-diastolic pressure with exercise.[111]

ISOMETRIC EXERCISE.

Isometric handgrip exercise causes an increase in heart rate, mean arterial pressure, and cardiac output. Because the systemic vascular resistance does not increase, the elevation in arterial pressure is due to the rise in cardiac output rather than a vasoconstrictor response. Patients with left ventricular dysfunction respond abnormally to isometric exercise (i.e., significant increase in left ventricular end-diastolic pressure, a failure to increase stroke work appropriately, and a blunted rise in left ventricular peak dP/dT).[108]

PACING TACHYCARDIA.

Rapid atrial or ventricular pacing increases myocardial oxygen consumption and myocardial blood flow.[112] In distinction to dynamic or isometric exercise, left ventricular enddiastolic volume decreases with pacing and there is little change in cardiac output.[113] This method may be used to determine the significance of coronary artery disease or valvular abnormalities. For example, the gradient across the mitral valve increases with rapid atrial pacing owing to the increase in heart rate. Pacing has the advantage of allowing for greater control and rapid termination of the induced stress.

PHYSIOLOGICAL STRESS.

Various physiological stresses alter the severity of obstruction in hypertrophic cardiomyopathy (see Chap. 48) . The *Valsalva maneuver* (forced expiration against a closed glottis) increases the systolic subaortic pressure gradient in the strain phase, during which there is a decrease in venous return and decreased left ventricular volume. This maneuver is often abnormal in patients with heart failure.[114] *Mueller's maneuver* (forced inspiration against a closed glottis) causes the opposite effect. Another useful maneuver in patients with hypertrophic obstructive cardiomyopathy is the introduction of a *premature ventricular beat* (Brockenbrough's maneuver). Premature ventricular contractions normally increase the pulse pressure of the subsequent ventricular beat. In obstructive hypertrophic cardiomyopathy, the outflow gradient is increased during the postpremature beat with a decrease in the pulse pressure of the aortic contour. A premature ventricular beat may also accentuate the spike-and-dome configuration of the aortic pressure waveform.

Rapid volume loading may reveal occult pericardial constriction, when atrial and ventricular filling pressures are relatively normal under baseline conditions owing to hypovolemia,[115] and may help distinguish pericardial constriction from myocardial restriction. *Kussmaul's sign* occurs in pericardial constriction (see Chap. 50) . This is demonstrated when, with inspiration, right atrial pressure fails to decrease or actually increases in relation to impaired right ventricular filling. *Cold pressor testing,* in which a patient's forearm is exposed to ice water, may induce coronary vasoconstriction in patients with coronary artery disease.[116]

PHARMACOLOGICAL MANEUVERS.

Isoproterenol infusion may be used to simulate supine dynamic exercise, although untoward side effects may limit its applicability. This drug's positive inotropic and chronotropic effects may increase the gradients in obstructive hypertrophic cardiomyopathy and mitral stenosis. *Nitroglycerin* and *amyl nitrate* decrease preload and accentuate the systolic gradient in patients with obstructive hypertrophic cardiomyopathy. Amyl nitrate is generally inhaled, and its onset of action is very rapid. Agents that increase systemic vascular resistance, such as *phenylephrine,* reduce the gradient in obstructive hypertrophic cardiomyopathy. Infusion of *sodium nitroprusside* may improve the cardiac output and filling pressures in patients with dilated cardiomyopathies and in patients with mitral regurgitation by lowering systemic and pulmonary vascular resistances. A favorable response to sodium nitroprusside infusion may predict a good clinical outcome.

Methylergonovine maleate has replaced ergonovine as a safer and more specific provocation test for coronary artery spasm (see Chap. 37) . Small intracoronary increments of 5 to 10 mug are given. Total dose should not exceed 50 mug. Intracoronary acetylcholine is also as effective and safe as methylergonovine.[119]

CORONARY BLOOD FLOW DETERMINATIONS

Five methods are available for measuring human coronary blood flow in the cardiac catheterization laboratory: thermodilution, digital subtraction angiography, electromagnetic flow meters, Doppler velocity probes, and pressure wires. Although most current methods measure relative changes in coronary blood flow, useful information about the physiological significance of stenosis,[120] cardiac hypertrophy, [121] and pharmacological interventions[122] can be obtained from these measurements.

Ganz and colleagues[123] introduced thermodilution methods for measuring coronary sinus flow (Fig. 11-16) . This inexpensive, widely available technique is the most frequently applied method for measuring global coronary blood flow in humans.[124] By injecting iced saline in the distal end of the catheter placed in the coronary sinus and measuring the temperature change from a proximal thermistor, the rate of change in temperature can be used to define coronary flow. The frequency response of this system is sufficient to measure flow changes that occur in 2 to 3 seconds and exceed 30 percent.[123] This technique has several limitations, however.[124] Although the method has been validated in vitro with the thermodilution catheter attached to the coronary sinus,[123] weaker correlations have been shown when the thermodilution catheter is allowed to move within the coronary sinus.[125] No studies have clearly demonstrated the accuracy of this method in patients with severe coronary artery disease or myocardial infarction. Other limitations include the fact that (1) rapid changes in flow cannot be assessed because of the slow time constant of the technique, (2) right atrial and ventricular perfusion cannot be evaluated because the venous drainage does not occur via the coronary sinus, and (3) regional flow and specifically transmural coronary flow cannot be assessed.

To measure coronary flow with digital subtraction angiography, contrast medium is power injected into a coronary artery at a rate sufficient to replace blood within the artery completely. It is assumed that the contrast bolus is undiluted until the peak concentration has been imaged distally in the arterial segment. Regional flow reserve can be calculated in a number of ways, including the use of downstream appearance time and maximal contrast concentration before and during reactive hyperemia.[126] The assumption is that transit time within a region is inversely proportional to coronary blood flow in that region. This is true if the volume of distribution is constant. The technique is limited by a slow time constant and the inability to measure absolute flow. Evaluation of coronary flow reserve

Figure 11-16 Schematic illustration of venous thermodilution method for measurement of coronary blood flow. The thermal indicator (injectate) at temperature T_1 is infused at a constant rate (e.g., 15 ml/min). Turbulence causes mixing of the injectate with coronary venous blood at temperature T_B , resulting in a blood-injectate mixture at temperature. T_M . The catheter tip thermistor monitor T_B and T_M , while an internal thermistor monitors T_1 , and these are recorded continuously on a uniform temperature scale *(lower left)*. Because heat loss by blood is gained by injectate, coronary venous flow is calculated using the measured temperatures, the rate of indicator injection, and the constant derived from the specific heats of blood and injectate. (From Bradley AB, Baim DS: Measurement of coronary blood flow in man: Methods and implications for clinical practice. Cardiovasc Clin 14:67, 1984.)

by this method has been validated in dogs by comparing digital flow ratio estimates with electromagnetic flow ratio measurements.[127] In humans, flow reserve has been shown to be abnormal in stenosed coronary arteries and bypass grafts and after coronary angioplasty.[128] Further validation in humans is necessary.

The electromagnetic flow meter is based on Faraday's induction law, which states that a conductor moving in an electric field produces current. A major advantage of electromagnetic flow meters is the high-frequency response.[121] Although these flow meters have been used to measure aortic blood flow velocity in humans,[129] they have not been developed to the point at which they are useful for measuring coronary blood flow at catheterization, in part because most methods require placement directly around the coronary artery. Electromagnetic flow meters are still in occasional use intraoperatively to evaluate flow in aortocoronary bypass grafts.

The Doppler flow meter is based on the principle of the Doppler effect (Fig. 11-17) (see also Chap. 7) . It is the most widely applied technique for measurement of coronary flow in humans. High-frequency sound waves are reflected from moving red blood cells and undergo a shift in sound frequency that is proportional to the velocity of the blood flow. In pulsed-wave Doppler methods, a single piezoelectric crystal can both transmit and receive high-frequency sound waves. These methods have been applied successfully in humans by using miniaturized crystals fixed to the tip of catheters. Technological

developments have further miniaturized steerable 12-mHz Doppler guidewires to 0.014inch in diameter. Therefore, flow can be assessed distal and proximal to a stenosis. The Doppler guidewire measures phasic flow velocity patterns and tracks linearly with flow rates in small, straight coronary arteries.[130] It has been advocated for use in determining the severity of intermediate stenosis (40 to 60 percent) and in evaluating whether normal blood flow has been restored after PTCA. Validation studies have been performed to compare Doppler flow probes with labeled microspheres[131] and electromagnetic flow probes. [132] This method has been validated both in vitro and in vivo.[133] The use of this technique for assessment of lesion severity has been reported.[134] It has the advantage of permitting repeated sampling and at high frequency, thus allowing measurements after physiological or pharmacological interventions. The use of smaller Doppler catheters allows selective coronary artery flow velocity to be measured. By noting the increase in flow velocity following a strong coronary vasodilator, such as papaverine,

Figure 11-17 Schematic diagram of the distal portion of a 3F intracoronary Doppler catheter with side-mounted piezoelectric crystal. The copper wires attached to the crystal exit from the proximal end of the catheter and are connected to a 20-mHz pulsed Doppler velocimeter. The catheter is advanced into the coronary artery over an 0.014-inch angioplasty guidewire. O.D. = outer diameter. (Modified from Wilson RF, Laughlin DE, Ackell PH, et al: Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 72:82, 1985. Copyright 1985 American Heart Association.)

the coronary flow reserve (CFR) can be defined. CFR provides an index of the functional significance of coronary lesions that obviates some of the ambiguity of anatomical description.[134]

Animal data indicate that stenosis exceeding 50 percent is associated with a reduction in absolute flow reserve (see Chap. 34) . It has been suggested that stenosis flow reserve (SFR) is a more reliable method of evaluating functional severity.[135] For a fixed arterial dimension and stenosis geometry, directly measured arterial CFR can be zero if no aortic perfusion is present or may change with other physiological conditions. Thus, CFR can be broken into its component parts of SFR (i.e., the flow reserve of the proximal arterial stenosis) and myocardial perfusion reserve (MPR), the flow reserve of the distal vascular bed. SFR is defined by geometric quantitative coronary dimensions using standard physiological conditions. MPR is directly or indirectly measured and is affected by geometric as well as physiological variables. The equation relating pressure change across a lesion and flow is

where DeltaP is the translesional gradient, Pc is distal coronary pressure, Pa is aortic pressure, Q and Qrest are flow and rest flow, and A and B are related to lesion geometry. A and B are defined by lesion length, minimal cross-sectional area of the lesion and reference segment, and blood viscosity.

The limitation of the current Doppler probe method is that only changes in flow velocity,

rather than absolute velocity or volumetric flow, are measurable. The change in flow velocity is directly proportional to changes in volumetric flow only when vessel dimensions are constant at the site of the sample volume. Other factors including left ventricular hypertrophy and myocardial scar can also affect CFR.[126] Furthermore, a concern is that changes in luminal diameter and arterial cross-sectional area during interventions are not reflected in measurements of flow velocity, thus potentially causing underestimation of the true volume flow.[126]

The measurement of pressure gradients across coronary stenoses was originally advocated to assess the results of coronary angioplasty. Owing to the large profile of catheters used, this technique was never widely applied. However, new technology using small (0.018-inch) guidewires to assess pressure gradients across stenoses has been introduced.[136] [137] [138] Myocardial fractional flow reserve (FFR) has been used as an index of functional severity of coronary artery stenosis.

Pressure gradients are determined by measuring the ratio of the mean pressure distal to a coronary stenosis compared with that proximal to the stenosis. The proximal stenosis is measured through the tip of the guiding catheter, and distal pressure is measured through the tip of the guidewire. Maximal vasodilatation is induced by intracoronary administration of either adenosine or papaverine. FFR is calculated from the ratio of the mean pressure distal to a coronary stenosis to the mean aortic pressure during maximal hyperemia. If the FFR is less than 0.75, there is at least 80 percent sensitivity and 85 percent specificity for an abnormal exercise test result. Pressure wire measurement has been less well validated than Doppler flow reserve measurement. However, early studies indicate improved clinical utility owing to the ease of use and reproducibility of re

Figure 11-18 Electromechanical mapping of patient with significant left anterior descending artery stenosis. *A,* Demonstrates normal left ventricular endocardial voltage map (blue, green, yellow). *B,* Demonstrates abnormal mechanical activity or shortening of the anterior wall (blue). LA=left atrium; RA=right atrium.

sults.[139]

LEFT VENTRICULAR ELECTROMECHANICAL MAPPING

Advances in catheter design and navigational technology have resulted in catheter-based three-dimensional mapping systems for evaluating regional and global left ventricular function. By integrating measurements of local endocardial electrical activity and wall motion during the cardiac cycle, the electromechanical mapping system provides information about myocardial ischemia and viability (Fig. 11-18) . The ability of the electromechanical left ventricular maps to distinguish viable from nonviable myocardium and ischemic from nonischemic myocardium has been validated in animal models of myocardial ischemia and infarction.[140] [141] [142] The clinical experience with this system is limited at this time. However, the preliminary data from these studies

indicate that the mapping system has promise in differentiating normal myocardium from myocardial fibrosis[142] and may also distinguish ischemic from infarcted myocardium.[143] In addition to identifying infarcted myocardium and zones of viable but ischemic myocardium, this technology has the potential to guide accurate, direct transendocardial administration of drug or gene therapies targeted at specific myocardial regions identified during the mapping process.

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Chapter 12 - Coronary Angiography and Intravascular Ultrasonography

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GLOSSARY

ACC/AHA=American College of Cardiology/American Heart Association
AP=anteroposterior
CABG=coronary artery bypass graft surgery
CAD=coronary artery disease
CCS=Canadian Cardiovascular Society
EKG=electrocardiogram
Fr=French size
GEO=gastroepiploic artery
IMA=internal mammary artery
LMCA=left main coronary artery
LAD=left anterior descending artery
LAO=left anterior oblique

LCA=left coronary artery
LCx=left circumflex coronary artery
MI=myocardial infarction
PCI=percutaneous coronary intervention
RAO=right anterior oblique
RCA=right coronary artery
SVG=saphenous vein bypass graft

Coronary arteriography remains the "gold standard" for identifying the presence or absence of stenoses due to coronary artery disease (CAD) and provides the most reliable anatomical information for determining the appropriateness of medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery in patients with ischemic CAD. First performed by Sones in 1959,[1] coronary arteriography has subsequently become one of the most widely used invasive procedures in cardiovascular medicine. It is performed by directly injecting radiopaque contrast material into the coronary arteries and recording radiographic images on 35-mm cinefilm or digital recordings.[2] More than 2 million patients will undergo coronary arteriography in the United States this year alone. Coronary arteriography is now performed in 25 percent of acute care hospitals in this country.

The methods used to perform coronary arteriography have evolved substantially since 1959. Smaller (5-6 French), high-flow injection catheters have replaced larger (8 Fr), thick-walled catheters, and the reduced sheath size has allowed same-day coronary arteriography, ambulation, and discharge. Complication rates associated with coronary arteriography have been reduced with a better understanding of the periprocedural management of patients undergoing cardiac catheterization. The number of "filmless" digital laboratories increases steadily, based on recent advances in digital image acquisition, storage, and data transfer. New adjunct imaging modalities performed at the time of coronary arteriography, such as intravascular ultrasonography (IVUS), have also been developed to give the clinician more precise characterization of the vessel wall and extent of atherosclerosis.

In this chapter we review the indications and techniques of coronary arteriography, the cineangiographic x-ray imaging and digital storage systems, the normal coronary anatomy and pathological coronary variants, the qualitative and quantitative angiography techniques for the assessment of stenoses severity and risk stratification, and the advantages and limitations of IVUS for the diagnosis and treatment of CAD.

INDICATIONS FOR CORONARY ARTERIOGRAPHY

Coronary arteriography is used to establish the presence or absence of coronary stenoses, define therapeutic options, and determine prognosis in patients with symptoms or signs of ischemic CAD.[2] Coronary arteriography can also be used as a research tool to evaluate serial changes that occur after PCI or pharmacological therapy or assess dynamic changes in arterial tone based on evaluations of endothelial tone. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force has established indications for coronary arteriography in patients with known or

suspected CAD (Table 12-1) .[2]

Patients with suspected CAD who are asymptomatic or have stable angina should undergo coronary arteriography if their angina is severe (Canadian Cardiovascular Society [CCS] Class III-IV) or there are "high-risk" criteria for adverse outcome on noninvasive testing. High-risk features include severe resting left ventricular dysfunction (left ventricular ejection fraction [LVEF]<35 percent) or a standard exercise treadmill test demonstrating hypotension or 1 to 2 mm or more ST segment depression associated with decreased exercise capacity[3] or an exercise-induced LVEF less

TABLE 12-1 -- INDICATIONS FOR CORONARY ARTERIOGRAPHY

CLASS I	CLASS IIA	CLASS IIB	CLASS III
Asymptomatic or Stable Angina			
CCS Class III and IV on medical therapy High-risk criteria on noninvasive testing irrespective of angina Successfully resuscitated from sudden cardiac death with sustained monomorphic VT or nonsustained polymorphic VT	CCS Class III or IV that improves to Class I or II with medical therapy Worsening noninvasive testing Patients with angina and severe illness that precludes risk stratification CCS Class I or II angina with intolerance to medical therapy Individuals whose occupation affects the safety of others	CCS Class I or II angina with demonstrable ischemia but no high-risk criteria on noninvasive testing Asymptomatic men or postmenopausal women with >2 major clinical risks with low-risk noninvasive testing and no CAD Asymptomatic patients with prior MI, normal LV function, and not-high-risk noninvasive testing	Angina in patients who prefer to avoid revascularization Angina in patients who are not candidates for revascularization or in whom it will not improve QOL As a screening test for CAD After CABG when there is no evidence of ischemic on noninvasive testing Coronary calcification on fluoroscopy or EBCT
Unstable Angina			

High or intermediate for adverse outcome in patients refractory to medical therapy High or intermediate risk that stabilizes after initial treatment Initially low short-term risk that is high risk on noninvasive testing Suspected Prinzmetal variant angina	None	Low short-term-risk unstable angina without high-risk criteria on noninvasive testing	Recurrent chest discomfort suggestive of unstable angina, but without objective signs of ischemia and with a normal coronary angiogram within the past 5 years Unstable angina in patients who are not candidates for revascularization

Post-Revascularization Ischemia

Suspected abrupt closure or subacute stent thrombosis after PCI Recurrent angina and high-risk criteria on noninvasive evaluation within 9 months of PCI	Recurrent symptomatic ischemia within 12 months of CABG Noninvasive evidence of high-risk criteria occurring at any time post CABG Recurrent angina inadequately controlled by medications	Asymptomatic post-PCI patient suspected of having restenosis with the first months after PCI because of an abnormal but not high-risk noninvasive test Recurrent angina without high-risk criteria on noninvasive testing occurring >1 year postoperatively Asymptomatic post-CABG in whom a deteriorating noninvasive test is found	Symptoms in a post-CABG patient who is not a candidate for revascularization Routine angiography after PCI or CABG unless part of an approved research protocol

After QWMI or NQWMI

Spontaneous myocardial ischemia or ischemia provoked with minimal exertion Before surgical therapy for acute MR, VSD, true or pseudoaneurysm Persistent hemodynamic instability	Suspected MI due to coronary embolism, arteritis, trauma, certain metabolic diseases, or coronary spasm Survivors of acute MI with LVEF<0.40, CHF, prior PCI or CABG, or malignant ventricular arrhythmias	For a suspected persistant occlusion of the IRA to perform delayed PCI Coronary arteriography performed without risk stratification to identify the presence of left main or three-vessel CAD All patients after NQWMI Recurrent ventricular tachycardia despite antiarrhythmic therapy without ongoing ischemia	Patients who are not a candidate for or refuse revascularization
Nonspecific Chest Pain			
High risk features on noninvasive testing	None	Patients with recurrent hospitalizations for chest pain who have abnormal or equivocal findings on noninvasive testing	All other patients with nonspecific chest pain

Class I: conditions for which there is agreement that the procedure is useful and effective; Class IIa: weight of the evidence is in favor of usefulness and efficacy; Class IIb: weight of the evidence is less well established by evidence and opinion; Class III: conditions for which there is general agreement that the procedure is not useful and effective and in some cases may be harmful.

CABG=coronary artery bypass graft surgery; CAD=coronary artery disease; CCS=Canadian Cardiovascular Society; CHF=congestive heart failure; EBCT=electron beam computed tomography; IRA=infarct-related artery; LV=left ventricular; MI=myocardial infarction; MR=mitral regurgitation; NQWMI=non-Q-wave MI; PCI=percutaneous coronary intervention; QOL=quality of life; VSD=ventricular septal defect; VT=ventricular tachycardia.

From Scanlon P, Faxon D, Audet A, et al: ACC/AHA guidelines for coronary angiography. J Am Coll Cardiol 33:1756-1824, 1999.

than 35 percent.[2] Stress imaging that demonstrates a large perfusion defect (particularly in the anterior wall), multiple defects, a large fixed perfusion defect with left ventricular dilatation or increased thallium-201 lung uptake, or extensive stress or dobutamine-induced wall motion abnormalities also indicate high risk for an adverse outcome.[2] [4] Patients resuscitated from sudden cardiac death, particularly those with residual ventricular arrhythmias, are also candidates for coronary arteriography, given the favorable outcomes associated with revascularization in these patients.[2]

Patients with unstable angina who develop recurrent symptoms despite medical therapy or are at "intermediate" or "high" risk of subsequent death or myocardial infarction (MI) are also candidates for coronary arteriography.[2] [5] [6] High-risk features include prolonged ongoing (>20 minutes) chest pain, pulmonary edema, or worsening mitral regurgitation, dynamic ST segment depression of 1 mm or more, or hypotension.[2] Intermediate-risk features include angina at rest (>20 minutes) relieved with rest or sublingual nitroglycerin, angina associated with dynamic electrocardiographic changes, recent-onset angina with a high likelihood of CAD, pathological Q waves or ST segment depression less than 1 mm in multiple leads, or age older than 65 years.[2]

Patients with Q-wave or non-Q-wave MI who develop spontaneous ischemia or with ischemia at a minimal workload or who have MI complicated by congestive heart failure (CHF), hemodynamic instability, cardiac arrest, mitral regurgitation, or ventricular septal rupture should undergo coronary arteriography. Patients with angina or provocable ischemia after MI should also undergo coronary arteriography, because revascularization may reduce the high risk of reinfarction in these patients.[7]

Patients presenting with chest pain of unclear etiology, particularly those who have high-risk criteria on noninvasive testing, may benefit from coronary arteriography to diagnose or exclude the presence of significant CAD.[2] Patients who have undergone prior revascularization should undergo coronary arteriography if there is suspicion of abrupt vessel closure or when recurrent angina develops with high-risk noninvasive criteria in patients who have undergone PCI within the past 9 months.

Coronary arteriography should be performed in patients scheduled to undergo noncardiac surgery who develop high-risk criteria on noninvasive testing, have angina unresponsive to medical therapy, develop unstable angina, or who have equivocal noninvasive test results and are scheduled to undergo high-risk surgery. Coronary arteriography is also recommended for patients scheduled to undergo surgery for valvular heart disease or congenital heart disease, particularly those with multiple cardiac risk factors and those with infective endocarditis and evidence of coronary embolization.[2]

Coronary arteriography should be performed annually in patients after cardiac transplantation in the absence of clinical symptoms because of the diffuse and asymptomatic nature of graft atherosclerosis.[8] Coronary arteriography is useful in potential donors for cardiac transplantation whose age or cardiac risk profile increases

the likelihood of CAD. The arteriogram often provides important diagnostic information about the presence of CAD in patients with intractable arrhythmias before electrophysiological testing or in patients who present with a dilated cardiomyopathy of unknown etiology.

CONTRAINDICATIONS.

There are no absolute contraindications for coronary arteriography.[2] Relative contraindications include unexplained fever, untreated infection, severe anemia with hemoglobin less than 8 g/dl, severe electrolyte imbalance, severe active bleeding, uncontrolled systemic hypertension, digitalis toxicity, previous contrast allergy but no pretreatment with corticosteroids, and ongoing stroke. Other relative contraindications include acute renal

TABLE 12-2 -- PATIENTS AT INCREASED RISK FOR COMPLICATIONS AFTER CORONARY ARTERIOGRAPHY

Increased General Medical Risk
Age>70 years
Complex congenital heart disease
Morbid obesity
General debility or cachexia
Uncontrolled glucose intolerance
Arterial oxygen desaturation
Severe chronic obstructive lung disease
Renal insufficiency with creatinine greater than 1.5 mg/dl
Increased Cardiac Risk
Three-vessel coronary artery disease
Left main coronary artery disease
Functional Class IV
Significant mitral or aortic valve disease or mechanical prosthesis
Low ejection fraction less than 35 percent
High-risk exercise treadmill testing (hypotension or severe ischemia)
Pulmonary hypertension
Pulmonary artery wedge pressure greater than 25 mm Hg
Increased Vascular Risk
Anticoagulation or bleeding diathesis
Uncontrolled systemic hypertension
Severe peripheral vascular disease
Recent stroke
Severe aortic insufficiency

failure, decompensated CHF, severe coagulopathy, and active endocarditis.[2] Risk factors for significant complications after catheterization include advanced age, as well as several general medical, vascular, and cardiac characteristics (Table 12-2) . Patients with these characteristics should be monitored closely for a minimum of 18 to 24 hours

after coronary arteriography. Coronary arteriography performed under emergency conditions is associated with a higher risk of procedural complications. Careful discussion of the risks and benefits of the procedure, and its alternatives, should be reviewed with the patient and family in all circumstances before coronary arteriography is performed.

TECHNIQUE OF CORONARY ARTERIOGRAPHY

PREPARATION OF THE PATIENT.

Elective coronary arteriography should be performed, alone or in conjunction with right-sided heart catheterization or contrast medium-enhanced left ventriculography (see Chap. 11) , when comorbid conditions, such as CHF, diabetes mellitus, or renal insufficiency, are stable. A baseline electrocardiogram (ECG), electrolyte and renal function tests, complete blood cell count, and coagulation parameters should be reviewed before coronary arteriography. Patients who may undergo PCI should receive aspirin, 80 to 325 mg, at least 2 hours before the procedure. Warfarin sodium should be discontinued 2 days before elective coronary arteriography, and the international normalized ratio (INR) should be less than 2.0 before arterial puncture. Patients at increased risk for systemic thromboembolism on withdrawal of warfarin, such as those with atrial fibrillation, mitral valve disease, or a prior history of systemic thromboembolism, may be treated with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin in the periprocedural period.

VASCULAR ACCESS.

A variety of vascular approaches are available for coronary arteriography. The selection of the vascular access will depend on operator and patient preferences, anticoagulation status, and presence of peripheral vascular disease.

Femoral Artery Approach.

The right or left femoral arteries are the most commonly used access sites for coronary arteriography. The anterior wall of the common femoral artery should be punctured several centimeters below the inguinal ligament but proximal to the bifurcation of the superficial femoral and profunda arterial branches. The common femoral artery courses across the junction between the middle and medial thirds of the femoral head and can be localized by fluoroscopy before arterial puncture. If the puncture site is proximal to the inguinal ligament, hemostasis after the procedure may be difficult with manual compression, leading to an increased risk of retroperitoneal hemorrhage. If the puncture site is at or distal to the femoral bifurcation, there is a higher risk of pseudoaneurysm formation after sheath removal.

Brachial and Radial Artery Approaches.

Access to the brachial and radial arteries is obtained percutaneously in most cases, although access to the brachial artery can also be obtained using a "cutdown" with blunt dissection and direct visualization. These approaches are preferred in the presence of severe peripheral vascular disease. Whereas saphenous vein grafts (SVGs) can be engaged using either brachial artery, cannulation of the internal mammary artery (IMA) is best performed from the ipsilateral brachial or radial artery. Contralateral catheterization of the left internal mammary artery from the right brachial or radial artery is technically challenging and may require the use of a "headhunter" catheter for selective entry into the left subclavian artery. The brachial artery will easily accommodate an 8-Fr (1 Fr=0.33 mm in diameter) sheath, whereas the radial artery is smaller and generally limited to 6-Fr catheters. Before radial artery access is attempted, an Allen test should be carried out to ensure that the ulnar artery is patent in the event of radial artery occlusion.

CATHETERS.

A number of injection catheters have been developed to perform coronary arteriography from the femoral, brachial, and radial approaches. These catheters are generally constructed of polyethylene or polyurethane with

Figure 12-1 Right (R) and left (L) Judkins catheters. The primary (straight arrow) and secondary (curved arrow) curves of the left Judkins catheter are shown. (Courtesy of Cordis Corporation.)

a fine wire braid within the wall to allow advancement and directional control (torque ability) and prevent kinking. The outer diameter size of the catheters ranges from 4 to 8 Fr, but 5 and 6 Fr catheters are used most commonly for diagnostic arteriography.

Judkins Catheters.

The left Judkins catheter is preshaped to allow entry into the left coronary ostia from the femoral approach with minimal catheter manipulation (Figs. 12-1 and 12-2) . A preformed left Judkins catheter

Figure 12-2 Tip configurations for several catheters useful in coronary arteriography. JR=Judkins right; JL=Judkins left; AR=Amplatz right; Mod=modified; AL=Amplatz left; MP=multipurpose; PIG=pigtail; LCB=left coronary bypass graft; SON=Sones; CAS=Castillo; NIH=National Institutes of Health; RCB=right coronary bypass graft; CB=coronary bypass catheter; IM=internal mammary; LUM=lumen. (Courtesy of Cordis Corporation.)

can also be used from the left brachial or radial artery, but a catheter with 0.5 cm less curvature than required for the femoral approach is generally needed. The right Judkins catheter is shaped to permit entry into the RCA with a small amount of rotational catheter manipulation from any vascular approach.

Selection of Judkins catheter shape is based on the body habitus of the patient and size of the aortic root. The left coronary artery (LCA) is easily engaged with the Judkins left 4.0 catheter from the femoral approach in most patients, whereas patients with a dilated ascending aorta (e.g., in the setting of congenital aortic stenosis and post-stenotic dilatation) may require the use of a Judkins left 5.0 or 6.0 catheter. Patients with large ascending aortic aneurysms may require arteriography with heat-modified catheters to achieve Judkins left 7.0 to 10.0 shapes. Use of a Judkins shape that is too small for the ascending aorta often leads to folding of the catheter within the aortic root. The best technique for removing a folded Judkins left catheter from the body involves withdrawing the folded catheter into the descending aorta and advancing a guidewire anterograde in the contralateral common iliac artery. On withdrawal of the catheter and guidewire together, the catheter will straighten and can be removed safely from the body without disrupting the arterial access site.

Amplatz Catheters.

Amplatz catheters can be used for the femoral or brachial approach to coronary arteriography (Fig. 12-3) . [9] The Amplatz catheters are an excellent alternative in cases in which the Judkins catheter is not appropriately shaped to enter the coronary arteries. The Amplatz L-1 or L-2 catheter may be used for coronary angiography from the right brachial or radial approaches.

Other Catheters.

Other catheters used for coronary arteriography include the Sones catheter and a variety of catheter shapes for engagement of SVGs, including the multipurpose catheter (Fig. 12-4) and Hockey stick catheters, among others**.** Specially designed catheters for engagement of the coronary arteries from the radial artery have been developed.

Drugs Used During Coronary Arteriography

ANALGESICS.

The goal of analgesic use is to achieve a state of conscious sedation, defined by a minimally depressed level of consciousness that allows a patient to respond appropriately to verbal commands and to maintain a patent airway.[10] Several different sedation regimens are recommended, but depending on patient comorbid conditions,

most use diazepam, 2.5 to 10 mg orally, and diphenhydramine,

Figure 12-3 Right (R) and left (L) Amplatz catheters. (Courtesy of Cordis Corporation.)

Figure 12-4 Multipurpose A, B, and C type catheters. (Courtesy of Cordis Corporation.)

25 to 50 mg orally, 1 hour before the procedure. Intravenous midazolam, 0.5 to 2 mg, and fentanyl, 25 to 50 mug, are useful agents to provide sedation during the procedure. Patients undergoing conscious sedation should have continuous hemodynamic, ECG, and oximetry monitoring and access to oxygen and suction ports and a resuscitation cart.[11]

ANTICOAGULANTS.

Intravenous unfractionated heparin is no longer required during routine coronary arteriography.[12] Patients at increased risk for thromboembolic complications, including those with severe aortic stenosis, critical peripheral arterial disease, or arterial atheroembolic disease, or those undergoing procedures in which there is a need for prolonged (>1 to 2 minutes) use of guidewires in the central circulation, may be given intravenous heparin, 3000 to 5000 units. Patients undergoing brachial or radial artery catheterization may also be given intraarterial unfractionated heparin, 2000 to 5000 units. Frequent (every 30-60 seconds) flushing of catheters with contrast medium or heparinized saline will avoid the formation of microthrombi within the catheter tip.

The anticoagulant effect of unfractionated heparin can be reversed with protamine, 1 mg for every 100 units of heparin. Protamine may cause anaphylaxis or serious hypotensive episodes in approximately 2 percent of patients. Protamine should not be administered to patients with prior exposure to NPH insulin, owing to an excess risk of adverse effects, or in patients with a history of unstable angina or high-risk coronary anatomy or those patients who have undergone coronary arteriography by means of the brachial or radial arteries. Femoral sheaths can be removed after the anticoagulant effect of heparin has dissipated (activated clotting time<150-180 seconds).

TREATMENT OF PERIPROCEDURAL ISCHEMIA.

Patients may develop angina during coronary arteriography, owing to ischemia induced by tachycardia, hypertension, contrast agents, microembolization, coronary spasm or enhanced vasomotor tone, or dynamic platelet aggregation. Sublingual (0.3 mg), intracoronary (50 to 200 mug), or intravenous (25 mug/min) nitroglycerin can be given in patients with a systolic blood pressure greater than 100 mm Hg. Patients without contraindications to beta blockers, such as bradycardia, bronchospasm, or left ventricular dysfunction, can be given

TABLE 12-3 -- CHARACTERISTICS OF RADIOCONTRAST AGENTS

COMPOUND	BRAND NAME	OSMOLALITY mOsm/kg H_2O	VISCOSITY AT 37° C	IODINE (mg/ml)	SODIUM (mEq/liter)	ADDITIVES
Ionic Agents						
Sodium diatrizoate	Hypaque	1690	9.0	370	160	Calcium disodium EDTA
Sodium meglumine diatrizoate	Renografin	1940	8.4	370	160	Sodium citrate, disodium EDTA
Nonionic or Low Osmolar						
Sodium meglumine ioxaglate	Hexabrix	600	7.5	320	150	Calcium disodium EDTA
Iohexal	Omnipaque	844	10.4	350	5	Tromethamine calcium disodium EDTA
Iopamidol	Isovue	790	9.4	370	2	Tromethamine calcium disodium EDTA
Ioversol	Optiray	702	5.8	320	2	Tromethamine calcium disodium EDTA
Iodixanol	Visipaque	290	11.8	320	19	Tromethamine calcium disodium EDTA+0.15 mEq/L calcium

Modified from Hill J, Lambert C, Pepine C: Radiographic contrast agents.*In* Pepine C, Hill J, Lambert C (eds): Diagnostic and Therapeutic Cardiac Catheterization. Baltimore, Williams & Wilkins, 1994, pp 182-194.

intravenous metoprolol, 2.5 to 5.0 mg, or propranolol, 1 to 4 mg. Intraaortic balloon counterpulsation is also a useful adjunct in patients with coronary ischemia and left main coronary artery disease, cardiogenic shock, or refractory pulmonary edema.

Contrast Agents

All radiographic contrast agents contain iodine, which effectively absorbs x-rays in the energy range of clinical imaging systems.[13] Radiographic contrast agents currently used for coronary arteriography produce a number of adverse hemodynamic, electrophysiological, and renal effects. These agents differ in their ionic content, osmolality, viscosity, side-effect profile, and cost (Table 12-3) .

IONIC CONTRAST AGENTS.

Monomeric ionic contrast agents used historically for coronary arteriography were the high-osmolar meglumine and sodium salts of diatrizoic acid. These substances dissociate into cations and iodine-containing anions,[14] resulting in a serum osmolality greater than 1500 mOsm/kg H_2O (vs. 300 mOsm/kg H_2O in human plasma). The hypertonicity of these compounds produced sinus bradycardia, heart block, QT interval and QRS prolongation, ST segment depression, giant T wave inversion, decreased left ventricular contractility, decreased systolic pressure, and increased left ventricular end-diastolic pressure, owing, in part, to the calcium-chelating properties of these agents. Ventricular tachycardia and fibrillation occur in 0.5 percent of cases and may develop more often when ionic contrast agents are injected into a damped coronary catheter or are given too rapidly or in too great a volume.

NONIONIC AND LOW OSMOLAR CONTRAST AGENTS.

Nonionic agents do not ionize in solution and provide more iodine-containing particles than ionic agents per milliliter of contrast.[13] Their osmolality is substantially reduced (<850 mOsm/kg H_2O) because these agents go into solution as single neutral molecules and do not contain calcium-chelating agents, potentially leading to fewer side effects. It is estimated that nonionic agents are used in 60 to 70 percent of current coronary arteriographic procedures.[15]

SIDE EFFECTS.

Toxic reactions may also occur after radiocontrast use, relating, in part, to the hyperosmolality of these agents[13] (Table 12-4) . Toxic reactions include hot flushing, nausea, vomiting, and arrhythmia. When hypotension occurs after contrast medium administration, it may be due to an anaphylactoid reaction, a direct toxic effect, or a vasovagal reaction.[13] Whereas ionic radiocontrast agents inhibit clot formation when mixed with blood, nonionic agents exhibit less of this inhibitory effect, and clots may form when low ionic contrast agents and blood are in direct contact with one another. The clinical effects of this finding are not known.[15A] Low-osmolality ionic dimer

methylglucamine-sodium ioxaglate retains most of the anticoagulant properties of diatrizoate sodium.[14] [16] [17] [18] [163A]

Nephrotoxicity may occur after contrast agent administration, particularly in those patients with prior renal insufficiency, diabetes mellitus, dehydration before the procedure, CHF, larger volumes of contrast, and those with recent (<48 hour) contrast agent administration.[19] [20] Oliguria generally occurs within the first 24 hours after contrast exposure and generally lasts for 2 to 4 days after the procedure.[13] The creatinine reaches its peak 3 to 5 days after contrast agent administration and returns to baseline in the majority of cases.[13] In patients with baseline renal insufficiency (creatinine > 1.5 mg/dl), use of nonionic contrast agents is associated with a lower incidence of contrast nephropathy.[21] [21A]

TABLE 12-4 -- TOXICITIES ASSOCIATED WITH RADIOCONTRAST AGENTS

Hypersensitivity (Anaphylactoid) Reactions
Grade I: Single episode of emesis, nausea, sneezing, or vertigo Grade II: Hives, multiple episodes of emesis, fevers, or chills Grade III: Clinical shock, bronchospasm, laryngospasm or edema, loss of consciousness, hypotension, hypertension, cardiac arrhythmias, angioedema, or pulmonary edema
Cardiovascular Toxicity
Electrophysiological
Bradycardia (asystole, heart block)
Tachycardia (sinus, ventricular)
Ventricular fibrillation
Hemodynamic
Hypotension (cardiac depression, vasodilatation) Heart failure (cardiac depression, increased intravascular volume)
Nephrotoxicity **Discomfort**
Nausea, vomiting Heat and flushing
Hyperthyroidism

Adequate fluid hydration before the procedure was the only method shown to reduce the frequency of contrast medium-induced nephropathy in a randomized study.[22]

CONTRAST REACTION PROPHYLAXIS.

Allergic reactions to radiocontrast agents can classified as mild (grade I: single episode of emesis, nausea, sneezing, or vertigo), moderate (grade II: hives, multiple episodes of emesis, fevers, or chills), or severe (grade III: clinical shock, bronchospasm, laryngospasm or edema, loss of consciousness, hypotension, hypertension, cardiac arrhythmias, angioedema, or pulmonary edema).[23] Although mild or moderate reactions occur in approximately 9.0 percent of patients, severe reactions are uncommon (0.15-0.7 percent).[19] [20] Contrast reactions may be more difficult to manage in patients receiving beta-blocker therapy. Recurrence rates may approach 50 percent on reexposure to contrast agents, and prophylactic use of H_1 and H_2 histamine blocking agents and aspirin therapy has been advocated.[13] Patients treated with corticosteroids (methylprednisolone, 32 mg) 12 hours and 2 hours before contrast agent exposure had a lower (6.4 percent) incidence of allergic reactions than patients treated with a single dose of methylprednisolone 2 hours before contrast agent exposure (9.4 percent) or placebo (9.0 percent) (p<0.001). [23] Based on these findings, patients with a prior history of radiocontrast allergy should be treated with two doses of prednisone, 60 mg (or its equivalent), on the night before and 2 hours before the procedure. Diphenhydramine, 50 mg, and cimetidine, 300 mg, may also be given before the procedure.[13]

CONTRAST AGENT SELECTION.

A number of randomized studies have shown that side effects occur less often with nonionic contrast agent use than with conventional ionic agents.[13] The major drawback of the nonionic contrast agents was their 10- to 20-fold increase in cost relative to the ionic agents. Although these differences have been narrowed with the availability of lower cost nonionic agents, nonionic or low osmolar agents may be particularly useful in patients with severe bradycardia (<55 to 60 beats/min), diabetes mellitus, baseline renal insufficiency, hypotension, unstable angina, acute MI, renal failure, age older than 65 to 70 years, CHF, valvular heart disease, internal mammary injection, or a previous reaction to contrast agents.[13] When ionic agents are selected, additional precautions are needed to avoid complications. Patients should be "coached" about coughing before the first selective coronary arteriogram is performed, and use of the minimal amount of contrast agent to fill the entire coronary artery for two cardiac cycles and allow brief reflux of contrast agent into the aortic root is needed.

CINEANGIOGRAPHIC IMAGE TECHNOLOGY

The basic principle of radiographic coronary imaging is that radiation produced by the x-ray tube is attenuated as it passes through the body and is detected by the image intensifier. Iodinated contrast medium injected into the coronary arteries enhances the absorption of x-rays and produces a sharp contrast with the surrounding cardiac tissue.[24] The x-ray shadow is then converted to a visible light image by an image detector, then displayed on fluoroscopic monitors, and stored on 35-mm cinefilm or

digital storage systems.[24]

Cineangiographic Equipment

There are several important parts of the x-ray imaging system that are required for image generation, review, and storage (Fig. 12-5) .

X-RAY GENERATOR.

The x-ray generator produces the power that accelerates electrons within the x-ray tube.[24] Constant-potential and multipulse generators are both suitable for coronary imaging. X-ray generators should provide a voltage range between 40 and 150 kVp, a

Figure 12-5 Cineangiographic equipment. The major components include a generator, x-ray tube, image intensifier attached to a positioner such as a C-arm, optical system, cine camera, video camera, videocassette recorder (VCR), analog-to-digital converter (ADC), and television monitors. The x-ray tube is the source of the x-ray beam, which passes superiorly through the patient.

current that reaches a maximum of 600 mA, a cine pulse system that provides individual exposure times ranging from 5 to 8 milliseconds to optimize image quality, and power output that is 100 kW at 80 kVp.[24] Longer exposures times are associated with motion artifact, whereas shorter exposure times may require increased voltage, which results in decreased image resolution. Automatic exposure control maintains the optimal brightness level of the image intensifier by varying voltage, current, and exposure duration.

X-RAY TUBE.

The x-ray tube is responsible for the conversion of electrical energy to x-radiation. Newer ceramic and graphite tubes are more expensive than conventional tubes but provide a longer half-life and higher heat load capacity. Focal spots should vary between 0.5 mm and 1.0 mm. Smaller (0.2-0.3) focal spots increase image resolution at the expense of more heat production. X-ray pulsing using carbon grid switching is more efficient compared with secondary electronic switching methods that have long radiation decay and more radiation scatter.

IMAGE INTENSIFIER.

The image intensifier converts an x-ray image into a visible light image. The image intensifier is generally a bell-shaped glass tube that contains an input and output phosphor.[24] X-ray photons that have passed through the patient produce visible light photons by interacting with the input phosphor.[24] An electronic image is produced by the interaction of the light photons with the photocathode tube.[24] These electrons are then accelerated toward the output phosphor, where they create a bright replica of the x-ray pattern. A dual- or triple-mode cesium iodide image intensifier with a resolution

capability of approximately 5 line pairs per millimeter, a contrast ratio of greater than 15:1, and a conversion factor of greater than 50 for the small mode is recommended for coronary arteriography.[24] The intensifier should have at least two modes, with the large mode approximating 9 inches to be able to image large ventricles and a small mode (magnified mode) of 6 inches or less for coronary imaging.[24]

OPTICAL SYSTEM.

The objective and the camera lenses gather light generated in the image intensifier and focus it onto the image detector.[24] The output screen of the image intensifier is located at the focal spot of the objective lens, which then emits parallel light rays from the image intensifier.[24] The camera lens then collects the parallel light rays and forms an image at its focal plane.[24] The focal length of the camera lens should allow the proper degree of overframing, which is used to increase the image magnification.[24] Apertures ranging from f-20 to f-75 are generally used for cardiac imaging.

VIDEO SYSTEMS.

Permanent recording of angiographic images historically utilized 35-mm film, using a cine camera capable of operating at 15 to 60 frames per second with low vibration levels. A partially-silvered mirror splits the image and diverts 10 percent of the light to a television system that allows real-time viewing. The television system must have excellent image clarity and minimal lag. A high-quality 525-line or 1023-line television camera and monitor with a signal-to-noise ratio of at least 45 dB is suggested.[11] The 1023-line television system results in reduced raster line artifact.

Image Recording and Storage

While 35-mm cine film has been the preferred medium for recording and storage of coronary arteriograms or Digital Imaging and COMmunication standard (DICOM3) compatible digital storage has become a prevalent alternative. Despite its relative expense, 35-mm cinefilm currently meets the desirable criteria of exchangeability, adherence to a standard format, a medium with high resolution, the need for a

permanent record, and suitability for quantitative analysis. With adequate quality control in film development, no other recording medium can compete with the spatial resolution or the dynamic contrast range of 35-mm cinefilm. Optimal radiographic imaging is critical to the success of coronary arteriography. Under ideal circumstances, modern radiographic imaging techniques provide spatial resolution of 5 line pairs per millimeter, a level of resolution that must be considered of borderline adequacy for imaging coronary vessels as small as 1 millimeter.

Use of 35-mm cinefilm does have certain drawbacks, including cost, delay in access,

and inability for processing of data directly on film. Digital imaging and storage modalities are now available as possible replacements for cinefilm.[25] Because spatial resolution is lost in the transfer of digital to analog images, the earlier practice of using Super-VHS videotapes as the storage medium, analog videotape cannot be recommended as a replacement for cinefilm at the current time.[26] [27]

Digital Imaging

The American College of Cardiology, American College of Radiology, and the National Electronic Manufacturer's Association (NEMA) have recommended that interinstitutional transfer of digital images be performed using the DICOM3 standard as the exchange medium. Long-term storage can be performed using 2:1 JPEG lossless compression onto DLT tapes or magnetooptical disc for storage without loss of information. Requirements for storage are substantial (approximately 400 megabytes-1 gigabyte per study).[26]

ANATOMY AND VARIATIONS OF THE CORONARY ARTERIES

The major epicardial branches and their second and third order branches are visualized using coronary arteriography. The networks of smaller intramyocardial branches are generally not visualized because of their size, cardiac motion, and limitations in resolution of cineangiographic systems. These "resistance" vessels play a major role in autoregulation of coronary blood flow, may limit myocardial perfusion during stress, and contribute to ischemia in patients with left ventricular hypertrophy or systemic hypertension.

ARTERIAL NOMENCLATURE AND EXTENT OF DISEASE.

The Coronary Artery Surgery Study (CASS) Investigators established the most commonly used nomenclature to describe the coronary anatomy, defining 27 segments in three major coronary arteries (Table 12-5) .[28] The Bypass Angioplasty Revascularization Investigators modified these criteria by addition of two segments for the ramus intermedius and the third diagonal branch.[29] In this system, the three major coronary arteries include the left anterior descending (LAD), left circumflex (LCx), and right coronary arteries (RCA) with a right-dominant, balanced, or left dominant circulation (see later). CAD is defined as a more than 50 percent diameter stenosis in one or more of these vessels, although it is clear that stenoses of less than 50 percent have major prognostic implications because these lesions most commonly lead to plaque rupture and acute myocardial infarction. Subcritical stenoses of less than 50 percent are best characterized as nonobstructive CAD. CAD is classified as one-, two-, or three-vessel disease.

A number of "jeopardy scores" have been used to quantitate plaque burden and predict patient-based clinical outcomes[30] and to identify risk factors for the presence of atherosclerosis and its progression.[31] The Califf scoring system divided the coronary circulation into 6 segments with 2 points allotted for each coronary stenosis of 75 percent or more (score range: 0-12).[32] The Gensini scoring system used an ordinal

ranking based on stenosis severity in 11 coronary segments (score range: 0-72).[33] The Candell-Riera scoring system used an ordinal ranking (from 1 to 5) of 13 coronary segments (score range: 0-65).[34] One comparative study found that 80 percent of the prognostic information in one jeopardy index was obtained with other indices using subtly different methodologies.[30] In the Coronary Artery Surgery Study (CASS), the major determinants of 6-year outcome included the number of diseased vessels, the number of diseased proximal segments, and the global left ventricular function; these three factors alone accounted for 80 percent of the prognostic information obtained in this study.[30]

ANGIOGRAPHIC PROJECTIONS.

The major coronary arteries traverse the interventricular and atrioventricular grooves, aligned with the long and short axes of the heart, respectively. Because the heart is oriented obliquely in the thoracic cavity, the coronary circulation is generally visualized in the right anterior oblique (RAO) and left anterior oblique (LAO) projections (Figs. 12-6 and 12-7) , but these views are limited by vessel foreshortening and superimposition of branches.[35] [36] Simultaneous rotation of the x-ray beam in the sagittal plane provides a better view of the major coronary arteries and their branches. A simple nomenclature has evolved for the description of these sagittal views, which characterizes the relationship between the image intensifier and the patient. Assuming that the x-ray tube is under the patient table and the image intensifier is over the patient table, the projection is referred to as the "cranial" view if the image intensifier is tilted toward the head of the patient. The projection is referred to as "caudal" if the image intensifier is tilted down toward the feet of the patient.

It is difficult to predict which angulated views will be most useful in any given patient, because the "optimal" angiographic projection depends largely on body habitus, variation in the coronary anatomy, and location of lesions. It is recommended that the coronary arteries be visualized in both the LAO and RAO projections using both cranial and caudal angulation.

TABLE 12-5 -- CLASSIFICATION SYSTEM FOR CORONARY SEGMENTS

NUMBER	MAP LOCATION	NUMBER	MAP LOCATION	NUMBER	MAP LOCATION
Right Coronary Artery		**Left Main Coronary Artery**		**Left Circumflex**	
1	Proximal RCA	11	Left main coronary artery	18	Proximal LCx
2	Mid RCA			19	Distal LCx
		Left Anterior Descending			
3	Distal RCA	12	Proximal LAD	20	1st obtuse marginal

4	Right posterior descending branch	13	Mid LAD	22	Third obtuse marginal
5	Right posterior atrioventricular	14	Distal LAD	23	LCx atrioventricular groeve
6	First right posterolateral	15	1st diagonal	24	1st left posterolateral branch
7	Second right posterolateral	16	2nd diagonal	25	2nd left posterolateral branch
8	Third right posterolateral	17	LAD septal perforators	26	3rd left posterolateral branch
9	Posterior descending septals	28	Ramus intermedius	27	Left posterior descending branch
10	Acute marginal segment	29	3rd diagonal		

Coronary Artery Surgery Study: National Heart, Lung, and Blood Institute Coronary Artery Surgery Study: A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease and a registry of consecutive patients undergoing coronary arteriography. Circulation 63 (Suppl I): I81, 1981. Copyright 1981, American Heart Association.

Figure 12-6 Angiographic views of the left coronary artery. The approximate position of the x-ray tube and image intensifier are shown for each of the commonly used angiographic views. The 60-degree left anterior oblique view with 20 degrees of cranial angulation (LAO cranial) shows the ostium and distal portion of the left main coronary artery (LMCA), the middle and distal portions of the left anterior descending artery (LAD), septal perforators (S), diagonal branches (D), and the proximal left circumflex (LCx) and superior obtuse marginal branch (OMB). The 60-degree left anterior oblique view with 25 degrees of caudal angulation (LAO caudal) shows the proximal LMCA and the proximal segments of the LAD and LCx. The anteroposterior projection with 20 degrees of caudal angulation (AP caudal) shows the distal LMCA and proximal segments of the LAD and LCx. The anteroposterior projection with 20 degrees of cranial angulation (AP cranial) also shows the midportion of the LAD and its septal (S) branches. The 30-degree right anterior oblique projection with 20 degrees of cranial angulation (RAO cranial) shows the course of the LAD and its septal (S) and diagonal branches. The 30-degree right anterior oblique projection with 25 degrees of caudal angulation (RAO caudal) shows the LCx and obtuse marginal branches (OMB).

Figure 12-7 Angiographic views of the right coronary artery. The approximate position of the x-ray tube and image intensifier are shown for each of the commonly used angiographic views. The 60-degree left anterior oblique view (LAO) shows the proximal and midportions of the right coronary artery (RCA) as well as the acute marginal branches (AMB) and termination of the RCA in the posterior left ventricular branches (PLV). The 60-degree left anterior oblique view with 25 degrees of cranial angulation (LAO cranial) shows the midportion of the RCA and the origin and course of the posterior descending artery (PDA). The 30-degree right anterior oblique view (RAO) shows the midportion of the RCA, the conus branch, and the course of the PDA.

Left Coronary Artery

CANNULATION.

The Judkins left coronary catheter is used most often to engage the LCA (Fig. 12-8) . If the catheter begins to turn out of profile (so that one or both curves of the catheter are no longer visualized *en face*), it can be rotated very slightly and advanced slowly to enter the left sinus of Valsalva, permitting the catheter tip to engage the ostium of the LCA. In conditions of a large ascending aorta, advancement of the Judkins left coronary catheter is associated with the formation of an acute secondary angle. Further advancement should be avoided, because this would distort the catheter shape and prevent catheterization of the LCA. In the presence of a mildly dilated ascending aorta, the guidewire can be temporarily reinserted into the catheter to straighten the secondary bend and permit the catheter to be advanced to the left sinus of Valsalva. If the ascending aorta is significantly dilated, the catheter should be exchanged for a larger size (e.g., Judkins left 5.0 or 6.0). If the tip of the Judkins left catheter advances beyond the ostium of the LCA without engagement, the primary bend of the catheter can be reshaped within the patient's body by further careful advancement and prompt withdrawal of the catheter, allowing the tip to "pop into" the ostium of the LCA. This maneuver, along with gentle clockwise or counterclockwise rotation, frequently permits selective engagement of the LCA when the initial attempt has failed.

To cannulate the LCA with the Amplatz catheter, the broad secondary curve of the appropriately sized left Amplatz catheter is positioned so that it rests on the right aortic cusp with its tip pointing toward the left aortic cusp. Alternating advancement and retraction of the catheter with slight clockwise or counterclockwise rotation allows the catheter tip to enter the left coronary ostium. Once the tip enters the ostium, the position of the catheter can usually be stabilized with slight retraction. After the left coronary ostium has been cannulated, the pressure at the tip of the catheter should be checked immediately to ensure that there is no damping or "ventricularization" of the pressure contour. If a damped or ventricularized pressure tracing is obtained, the catheter should be removed immediately from the LCA and an attempt at repositioning should be made. If abnormal pressure recording persists, the catheter should be withdrawn from the coronary artery and a nonselective injection

Figure 12-8 Push-pull technique for catheterizing the left coronary artery with the Judkins left catheter. In the left anterior oblique view, the coronary catheter is positioned in the ascending aorta over a guidewire and the guidewire is removed. The catheter is advanced so that the tip enters the left sinus of Valsalva. If the catheter does not selectively engage the ostium of the left coronary artery, further slow advancement into the left sinus of Valsalva imparts a temporary acute angle at the catheter. Prompt withdrawal of the catheter allows easy entry into the left coronary artery.

of contrast medium into the LCA should be performed in the anteroposterior (AP) view to evaluate the left main coronary artery (LMCA). If the pressure measured at the catheter tip is normal, and a test injection of contrast agent suggests the absence of LMCA disease, left coronary arteriography is then performed using standard techniques.

LEFT MAIN CORONARY ARTERY.

The LMCA arises from the superior portion of the left aortic sinus, just below the sinotubular ridge of the aorta, which defines the border separating the left sinus of Valsalva from the smooth (tubular) portion of the aorta. The LMCA ranges from 3 to 6 mm in diameter and 0 to 10 mm in length. The LMCA courses behind the right ventricular outflow tract and usually bifurcates into the LAD artery and LCx branches. The LMCA is best visualized in the AP projection with slight (0-20°) caudal angulation, but it should be viewed in several projections with the vessel off the spine to exclude LMCA stenosis (Figs. 12-9 and 12-10) .[37]

LEFT ANTERIOR DESCENDING ARTERY.

The LAD courses along the epicardial surface of the anterior interventricular groove toward the cardiac apex. In the RAO projection, it extends along the anterior aspect of the heart; and in the LAO projection, it passes down the cardiac midline, between the right and left ventricles (see Fig. 12-6) .

The major branches of the LAD are the septal and diagonal branches. The septal branches arise from the LAD at approximately 90-degree angles and pass into the interventricular septum, varying in size, number, and distribution. In some cases there is a large first septal branch that is vertically oriented and divides into a number of secondary "pitchforking" branches that ramify throughout the septum. In other cases a more horizontally oriented, large first septal branch is present that passes parallel to the LAD itself within the myocardium. In still other cases a number of septal arteries are roughly comparable in size. These septal branches interconnect with similar septal branches passing upward from the posterior descending branch of the RCA to produce a network of potential collateral channels. The interventricular septum is the most

densely vascularized area of the heart.

The diagonal branches of the LAD pass over the anterolateral aspect of the heart. Although virtually all patients have a single LAD in the anterior interventricular groove, there is wide variability in the number and size of diagonal branches. Most (90 percent) patients have one to three diagonal branches,[38] and acquired atherosclerotic occlusion of the diagonal branches should be suspected if no diagonal branches are seen, particularly if there are unexplained contraction abnormalities of the anterolateral left ventricle. Visualization of the origin of the diagonal branches often requires very steep (50-60 degrees) LAO and angulated cranial (20-40 degrees) skews.

In some (37 percent) patients the LMCA trifurcates into the LAD, LCx, and ramus intermedius.[38] In these cases the ramus intermedius arises between the LAD and LCx arteries. This vessel is analogous to either a diagonal branch or an obtuse marginal branch, depending on its anterior or posterior course along the lateral aspect of the left ventricle. In most (78 percent) patients the LAD courses around the left ventricular apex and terminates along the diaphragmatic aspect of the left ventricle. In the remaining (22 percent) patients the LAD fails to reach the diaphragmatic surface, terminating instead either at or before the cardiac apex.[39] In these cases the posterior descending branch (PDA) of the RCA is larger and longer than usual and supplies the apical portion of the ventricle.

The best angiographic projections for viewing the course of the LAD are the cranially angulated LAO, AP, and RAO views. The LAO cranial view displays the midportion of the LAD and separates the

Figure 12-9 Missed left main coronary artery (LMCA) stenosis. *A-C,* Left coronary arteriography in the standard right anterior oblique, left anterior oblique, and right anterior oblique caudal views fails to demonstrate significant stenoses of the LMCA or left anterior descending (LAD) artery. *D,* Left anterior oblique cranial view shows severe stenosis (curved arrow) for the LAD (L) immediately beyond the origin of the diagonal branch. *E,* Right anterior oblique cranial view shows the LAD stenosis (curved arrow) but also shows a severe stenosis of the LMCA (straight arrow) at its bifurcation.

Figure 12-10 Difficulty in detecting ostial left main coronary artery (LMCA) stenosis. *A,* Shallow right anterior oblique views of the left anterior descending artery with the catheter not well seated in the vessel results in poor visualization of the ostial stenosis of the LMCA. *B,* Left anterior oblique cranial view shows the catheter tip selectively positioned in the LMCA without reflux of contrast medium around the tip.

diagonal and septal branches. The RAO cranial view displays the proximal, mid, and distal segment of the LAD and allows separation of the diagonal branches superiorly and the septal branches inferiorly. The AP view requiring cranial (20 to 40 degrees)

skew will often project the midportion of the LAD, separating the vessel from its diagonal and septal branches. The LAO caudal view will also display the origin of the LAD in a horizontally oriented heart, and the AP caudal or shallow RAO caudal view will visualize the proximal LAD as it arises from the LMCA. The RAD caudal projection is also useful for visualizing the distal LAD and its apical termination.

Some patients have no LMCA but separate ostia for the LAD and LCx. In general, the LAD has a more anterior origin than the LCx. The LAD can be engaged with the left Judkins catheter in this setting with paradoxical counterclockwise rotation, which rotates the secondary bend of the catheter to a posterior position in the aorta and turns the primary bend and tip of the catheter to an anterior position. The opposite maneuver may be used to engage the LCx selectively in the setting of separate LAD and LCx ostia. A Judkins catheter, such as Judkins left 5.0 with a larger curve, will selectively engage the downward coursing LCx, and a catheter with shorter curve, such as a Judkins left 3.5, will tend to selectively engage the more anterior and superior LAD.

LEFT CIRCUMFLEX ARTERY.

The LCx artery originates from the LMCA and courses within the posterior (left) atrioventricular groove toward the inferior interventricular groove (see Fig. 12-6). The LCx artery is the dominant vessel in 15 percent of patients, supplying the left PDA from the distal continuation of the LCx. In the remaining vessels, the distal LCx varies in its size and length, depending on the number of posterolateral branches supplied by the distal RCA. The LCx usually gives off one to three large obtuse marginal branches as it passes down the atrioventricular groove. These are the principal branches of the LCx, because they supply the lateral free wall of the left ventricle. Beyond the origins of the obtuse marginal branches, the distal LCx tends to be small. The actual position of the LCx can be determined on the late phase of a left coronary injection, when the coronary sinus becomes opacified with diluted contrast material.

The RAO caudal and LAO caudal projections are best for visualizing the proximal and mid LCX and obtuse marginal branches. The AP (or 5- to 15-degree RAO) caudal projections also show the origins of the obtuse marginal branches. More severe rightward angulation often superimposes the origins of the obtuse marginal branches on the LCx. If the LCA is dominant, the optimal projection for the left PDA is the LAO cranial view. The LCx also gives rise to one or two left atrial circumflex branches. These branches supply the lateral and posterior aspects of the left atrium.

Right Coronary Artery

Cannulation of the origin of the RCA is also performed in the LAO position but requires different maneuvers than cannulation of the LCA. Whereas the left Judkins catheter naturally seeks the ostium of the LCA, the right coronary catheter must be rotated to engage the vessel. This usually is accomplished by first passing the catheter to a point just superior to the aortic valve in the left sinus of Valsalva and then rotating the catheter clockwise, which forces the tip to move anteriorly from the left sinus of Valsalva to the right sinus of Valsalva along the sinotubular ridge. Sudden rightward and downward movement of the catheter tip signifies the entry into the right coronary ostium. If the

ostium of the RCA is not easily located, the most common reason is that the ostium has a more superior and anterior origin than anticipated. Repeat attempts to engage the RCA should be made at a level slightly more distal to the aortic valve. Nonselective contrast agents injections in the right sinus of Valsalva may reveal the site of the origin of the RCA. Positioning an Amplatz catheter in the ostium of the RCA requires a technique similar to that used with the right Judkins catheter. If a gentle attempt to withdraw the Amplatz catheter results in paradoxical deep entry into the coronary artery, removal of the catheter can be achieved by clockwise or counterclockwise rotation and advancement to prolapse the catheter into the aortic sinus.

An abnormal pressure tracing showing dampening or ventricularization may suggest the presence of an ostial stenosis or spasm, selective engagement of the conus branch, or deep intubation of the right coronary artery. If an abnormal pressure tracing has been encountered, the catheter tip should be gently rotated counterclockwise and withdrawn slightly in an effort to free the tip of the catheter. If persistent damping occurs, a very small amount of contrast medium (<1 ml) can be injected carefully and the catheter immediately withdrawn in a "shoot-and-run" maneuver, which may allow the cause of damping to be identified. If the pressure tracing is normal on entry into the RCA, the vessel should be imaged in at least two projections. The

initial injection should be gentle, because of the possibility that forceful injection through a catheter whose tip is immediately adjacent to the vessel wall may lead to dissection.

ANGIOGRAPHIC PROJECTIONS.

The ideal angiographic projections for evaluating the RCA are the LAO cranial, AP cranial, and RAO views. The ostium of the RCA is best evaluated in the LAO view, with or without cranial angulation. The origin of the PDA is evaluated in the LAO cranial view, whereas the midportion of the RCA occasionally requires the left lateral view. The ostium of the RCA is best viewed in the LAO projection, occasionally with caudal angulation.

The RCA originates from the right anterior aortic sinus somewhat inferior to the origin of the LCA (see Fig. 12-7). It passes along the right atrioventricular groove toward the crux (a point on the diaphragmatic surface of the heart where the anterior [right] atrioventricular, the posterior [left] atrioventricular groove, and the inferior interventricular groove coalesce). The first branch of the RCA is generally the conus artery, which arises at the right coronary ostium or within the first few millimeters of the RCA in 50 percent of patients. The Judkins right coronary catheter may engage the conus artery subselectively, producing a damped or ventricularized pressure tracing. Gentle withdrawal and further clockwise rotation may allow the catheter to enter the true RCA. In the remaining patients, the conus artery arises from a separate ostium in the right aortic sinus just above the right coronary ostium.[40] The second branch of the RCA usually is the sinoatrial node artery. It has been found that this vessel arises from the

RCA in 59 percent of patients, from the LCx in 38 percent, and from both arteries with a dual blood supply in 3 percent.[41] The midportion of the RCA usually gives rise to one or several medium-sized acute marginal branches. These branches supply the anterior wall of the right ventricle and may provide collateral circulation in patients with LAD occlusion.

RCA DOMINANCE.

The RCA is dominant in 85 percent of patients, supplying the PDA and at least one posterolateral branch (right dominant) (Figs. 12-11 , 12-12 , and 12-13). The PDA courses in the inferior interventricular groove and gives rise to a number of small inferior septal branches, which pass upward to supply the lower portion of the interventricular septum and interdigitate with superior septal branches passing down from the LAD. After giving rise to the PDA, the dominant RCA continues beyond the crux as the right posterior atrioventricular branch along the distal portion of the posterior (left) atrioventricular groove, terminating in one or several posterolateral branches that supply the diaphragmatic surface of the left ventricle. The RCA is nondominant in 15 percent of patients. One half of these patients have a left PDA and left posterolateral branches that are provided by the distal LCx artery (left dominant circulation). In these cases, the RCA is very small, terminates before reaching the crux, and does not supply any blood to the left ventricular myocardium. The remaining patients have a RCA that gives rise to the PDA with the

Figure 12-11 Strongly dominant right coronary artery (RCA). *A* and *B,* Left anterior oblique and right anterior oblique views of the RCA show that the distal segment (arrows) extends to the left atrioventricular groove. After giving rise to the posterior descending artery, the RCA gives rise to multiple posterior left ventricular branches. *C,* A variation in the origin of the posterior descending artery, which originates early from the RCA, runs parallel to it and enters the posterior interventricular groove. *D,* Right anterior oblique right coronary arteriogram showing the posterior descending artery (P) arising from a right ventricular branch of the RCA. E, Left anterior oblique right coronary arteriogram showing duplicated posterior descending arteries (arrows). (From Levin DC, Baltaxe HA: Angiographic demonstration of important anatomic variations of the posterior descending artery. AJR Am J Roentgenol 116:41, 1972.)

Figure 12-12 Weakly dominant right coronary artery (RCA). *A* and *B,* Left anterior oblique and right anterior oblique views of the RCA. Both the conus and sinoatrial node artery arise from the RCA. The distal portion of the RCA beyond the origin of the posterior descending artery is short and gives rise to a single small posterior left ventricular branch. *C-E,* Left coronary artery in the right anterior oblique, left anterior oblique, and left lateral projections. Note that the circumflex artery gives rise to four obtuse marginal branches, the most distal of which (arrow) supplies some of the diaphragmatic surface of the left ventricle. The left anterior descending artery gives rise to two small and one medium-sized diagonal branches. C=conus branch; L=left anterior descending artery; P=posterior descending artery; S=sinoatrial nodal artery.

LCx artery providing all the posterolateral branches (balanced or codominant circulation). In about 25 percent of patients with RCA dominance, there are significant anatomical variations in the origin of the PDA. These variations include partial supply of the PDA territory by acute marginal branches, double PDA, and early origin of the PDA proximal to the crux. At or near the crux, the dominant artery gives rise to a small atrioventricular node artery, which passes upward to supply the atrioventricular node.

CORONARY BYPASS GRAFTS.

Selective cannulation of bypass grafts may be more challenging than cannulation of the native coronary arteries because the locations of graft ostia are more variable, even when surgical clips or ostia markers are used. Knowledge of the number, course, and type of bypass grafts obtained from the operative report is invaluable for the identification of the location of the bypass grafts during arteriography.

SAPHENOUS VEIN GRAFTS.

SVGs from the aorta to the distal RCA or PDA originate from the right anterolateral aspect of the aorta approximately 5 cm superior to the sinotubular ridge. SVGs to the LAD originate from the anterior portion of the aorta about 7 cm above the superior to the sinotubular ridge. SVGs to the obtuse marginal branches arise from the left anterolateral aspect of the aorta 9 to 10 cm superior to the sinotubular ridge. In most patients, all SVGs can be engaged with a single catheter, such as a Judkins right 4.0 (JR-4.0) or a modified Amplatz right 2.0 (AR-2.0). Other catheters useful for engaging SVGs include the right and left bypass graft catheters. Amplatz left 1.0 to 2.0 catheters are useful for superiorly oriented SVGs (see Fig. 12-3) . A multipurpose catheter may also be useful for the cannulation of the SVG to the RCA or PDA.

Viewed in the LAO projection, the JR-4.0 or AR-2.0 catheters will rotate anteriorly from the leftward position as the catheter is rotated in a clockwise direction at the level of the femoral artery or manifold. The relation between the movement of catheter shaft at the femoral artery and the response of catheter tip on fluoroscopy immediately indicates whether the catheter tip is anteriorly positioned in the aorta and likely to enter an SVG ostium or posteriorly positioned and unlikely to engage a SVG. Steady advancement and withdrawal of the catheter tip proximal and distal in the ascending aorta, 5 to 10 cm above the sinotubular ridge, with varying degrees of rotation, usually results in entry into the SVG. Entry into the SVG is associated with abrupt outward motion of the tip of the catheter. When this occurs, a small test injection of contrast material verifies that the catheter is in the SVG. A well-circumscribed "stump" is almost always present if the SVG is occluded. Each SVG or stump must be viewed in nearly orthogonal views. The

Figure 12-13 Dominant left coronary system. *A,* The left anterior oblique projection shows that the right

coronary artery is small and terminates before reaching the crux. *B-D,* The right anterior oblique, left anterior oblique, and left lateral projections show that the left circumflex artery is large and gives rise to the posterior descending artery at the crux of the heart and to several posterior descending arteries.

relation between the origin of the SVGs and surgical clips confirms whether all targeted SVGs have been visualized. If neither a patent SVG nor stump can be located, it may be necessary to perform an ascending aortogram (preferably in biplane) in an attempt to visualize all SVGs and their course to the coronary arteries.

The goal of SVG angiography is to provide an assessment of the ostium of the SVG, its entire course, and the distal insertion site at the anastomosis between the bypass SVG and the native coronary vessel. The ostium of a SVG must be evaluated by achieving a coaxial engagement of the catheter tip and the origin of the SVG. The midportion (body) of the SVG must be evaluated with complete contrast filling of the SVG, because inadequate opacification produces an angiographic artifact suggestive of friable filling defects. It is critical to assess the SVG insertion or anastomotic site in full profile without any overlap of the distal SVG or the native vessel. Angiographic assessment of the native vessels beyond SVG anastomotic sites requires views that are conventionally used for the native segments themselves.

INTERNAL MAMMARY ARTERY.

The left IMA arises inferiorly from the left subclavian artery approximately 10 cm from its origin. Catheterization of the left IMA is performed with a specially designed J-tip IMA catheter (see Fig. 12-2, bottom row). The catheter is advanced into the aortic arch distal to the origin of the left subclavian artery in the LAO projection, and the catheter is rotated counterclockwise and is gently withdrawn with the tip pointing in a cranial direction, allowing entry into the left subclavian artery (Fig. 12-14). A 0.035 "J" or angled Terumo guidewire is advanced to the left subclavian artery under fluoroscopy, and the catheter is advanced into the subclavian artery. The RAO or AP projections can then be used to selectively cannulate the IMA by withdrawing and slightly rotating the catheter anteriorly (counterclockwise) with tip down. The right IMA can also be cannulated with the IMA catheter. The innominate artery is entered in the LAO projection, and the guidewire is advanced cautiously to avoid entry into the right common carotid artery. Once the guidewire is positioned in the distal right subclavian artery, the IMA catheter is advanced to a point distal to the expected origin of the right

Figure 12-14 Catheterization of the left internal mammary artery. The internal mammary catheter is positioned in the aortic arch and visualized in the left anterior oblique position. The catheter tip is rotated so that it engages the origin of the left subclavian artery immediately subjacent to the head of the clavicle *(A).* This is followed by gentle advancement of the guidewire into the left subclavian artery to a point distal to the origin of the left internal mammary artery. After the guidewire is removed, the left subclavian artery is visualized in the right anterior oblique projection, the catheter is withdrawn, and the catheter tip engages the ostium of the left internal mammary artery selectively *(B).* (From Judkins MW: Coronary

arteriography. *In* Douglas JS Jr, King SB III [eds]: Coronary Arteriography and Intervention. New York, McGraw-Hill, 1985, p 231.)

IMA. The catheter is withdrawn in the LAO view and rotated to cannulate the right IMA. Selective catheterization of the IMAs may be difficult due to tortuosity of the subclavian arteries. In this circumstance, the Headhunter catheter may be used to enter the left subclavian or the innominate artery.

The IMA itself is rarely affected by atherosclerosis, which may be attributable to preserved endothelial properties of anticoagulation, vasodilatation, and growth inhibition, as compared with SVGs and native coronary arteries.[42] Angiographic studies of the IMAs should assess not only the patency of the graft itself but also the distal anastomosis, where most of IMA graft compromise occurs.[43] Whereas the LAO cranial view may be limited in demonstrating the anastomosis of the IMA with the LAD because of overlap, the left lateral or AP cranial project may be useful in visualizing the anastomotic site. The risk of catheter-induced dissection of the origin of the IMA can be reduced by careful manipulation of the catheter tip and avoidance of forceful advancement without the protection of the guidewire. If the IMA cannot be selectively engaged because of tortuosity of the subclavian artery, nonselective arteriography can be enhanced by placing a blood pressure cuff on the ipsilateral arm and inflating it to a pressure above systolic arterial pressure. The occurrence of IMA spasm can be treated with 50 to 200 mug of intraarterial nitroglycerin or 50 to 100 mug of intraarterial verapamil.

GASTROEPIPLOIC ARTERY.

The right gastroepiploic artery (GEA) is the largest terminal artery of the gastroduodenal artery. The other terminal branch of the gastroduodenal artery is the superior pancreaticoduodenal artery. The gastroduodenal artery arises from the common hepatic artery in 75 percent of cases, but it may also arise from the right or left hepatic artery or the celiac trunk. Catheterization of the right GEA is carried out by first entering the common hepatic artery with a Cobra catheter (Fig. 12-15) . A torquable, hydrophilic-coated guidewire is advanced to the gastroduodenal artery and then to the right GEA. The Cobra catheter is then exchanged for a multipurpose or Judkins right coronary catheter, which will then permit selective arteriography of the right GEA.

STANDARDIZED PROJECTION ACQUISITION.

General recommendations about routine views can be made for most patients, although tailored views may be needed to accommodate variations in patient anatomy. Each coronary artery should be visualized in multiple projections (Figs. 12-16 , 12-17 , and 12-18). During coronary arteriography, an AP view with shallow caudal angulation is often performed first to evaluate the possibility of LMCA disease. Other important views include the LAO view with cranial angulation to evaluate the LAD. This view should have sufficient leftward positioning of the image intensifier to allow separation of the LAD, diagonal, and septal branches. This is followed by the LAO caudal view to evaluate the proximal segment of the LCx, RAO view with caudal angulation to assess the LCx and marginal branches, and shallow RAO or AP cranial view to evaluate the midportion of

the LAD.

Complications of Coronary Arteriography

Major complications are uncommon (<2 percent) after coronary arteriography (Table 12-6) . [44] In two large registries of patients undergoing femoral artery catheterization, death occurred in 0.10 to 0.14 percent, MI in 0.06 to 0.07 percent, cerebral ischemia or neurological complications in 0.07 to 0.14 percent, contrast agent reactions in 0.23 percent, and local vascular complications in 0.24 to 0.46 percent.[45] [46] Complications occurred more often in patients whose brachial artery was treated.[45] [47]

The incidence of death during coronary arteriography is higher in the presence of LMCA disease (0.55 percent), with a left ventricular ejection fraction less than 30 percent (0.30 percent), and with New York Heart Association functional Class IV disease (0.29 percent). More recent registries have identified equivalent complication rates despite increasing age and acuity of illness.[47] The risk of clinically significant coronary air embolus during diagnostic coronary arteriography is low, occurring in less than 0.1 percent of cases. If the syndrome of coronary air embolus and air lock does occur, 100 percent oxygen should be administered, which allows resorption of smaller amounts of air within 2 to 4 minutes. Morphine sulfate may be given for pain relief. Ventricular arrhythmias associated with air embolus can be treated with lidocaine and direct current cardioversion.

Figure 12-15 Catheterization of the right gastroepiploic artery (GEA) graft. The celiac trunk (CT) is selectively engaged with a cobra catheter, and a guidewire is gently advanced to the gastroduodenal artery (GDU) and the GEA. The catheter is advanced over the guidewire for selective arteriography of the GEA graft. CHA=common hepatic artery; RCA=right coronary artery; SA=splenic artery.

Figure 12-16 Importance of orthogonal projections. Each vascular segment of the coronary artery must be recorded in two orthogonal or nearly orthogonal views to avoid missing important diagnostic information about eccentric stenoses. In plane A the image is associated with a 75 percent stenosis, but in plane B the image results in 10 percent stenosis. (Modified from Miller SW, Wilson CL: Cardiac Angiography. Boston, Little, Brown, 1984, p 87.)

Figure 12-17 Superimposition of branches. *A* and *B,* Left anterior oblique and right anterior oblique views of the left coronary arteriogram show that the left anterior descending artery (LAD) is totally occluded, although the point of occlusion is not visualized. There is a large diagonal branch (black arrows) that closely parallels the LAD in both projections and could be mistaken for the LAD. Late-phase frames from a right anterior oblique *(C)* and left anterior oblique *(D)* right coronary arteriogram show filling of the LAD

(white arrows) by means of septal collaterals.

Figure 12-18 Septal branch mimicking the left anterior descending (LAD) artery. *A,* Left anterior oblique left coronary arteriogram shows an enlarged septal branch (arrowhead) occupying the expected course of the LAD. *B,* The right anterior oblique view shows that the LAD is totally occluded (white arrowhead). The septal branch (black arrowhead) runs in a course approximately parallel to the LAD but below it and within the interventricular septum. (From Levin DC, Baltaxe HA, Sos TA: Potential sources of error in coronary arteriography: II. Interpretation of the study. AJR Am J Roentgenol 124:386, 1975.)

CONGENITAL ANOMALIES OF THE CORONARY CIRCULATION

Anomalies that Cause Myocardial Ischemia

CORONARY ARTERY FISTULAE.

Coronary artery fistulae are the most common abnormality of the coronary arteries that are hemodynamically significant.[48] Although half the patients with a coronary artery fistula remain asymptomatic, the other half develop CHF, infective endocarditis, myocardial ischemia, or rupture of an aneurysm.[48] Fistulae arise from the RCA or its branches in about 50 percent of cases; the remaining fistulae arise from the LAD or LCx arteries or their branches, or they have multiple origins (Fig. 12-19). Drainage occurs into the right ventricle in 41 percent, right atrium in 26 percent, pulmonary artery in 17 percent, left ventricle in 3 percent, and superior vena cava in 1 percent.[48] A left-to-right shunt exists in more than 90 percent. Coronary arteriography is the best method of demonstrating the origin of these fistulae.

ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY.

Most patients with the origin of the LCA from the main pulmonary artery manifest congestive heart failure and myocardial ischemia in the first 4 months of life.[48] About 25 percent survive to adolescence or adulthood

TABLE 12-6 -- RISK OF CARDIAC CATHETERIZATION

	SCAI REGISTRY (%)
Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident	0.07
Arrhythmias	0.38

Vascular complications	0.43
Contrast reaction	0.37
Hemodynamic complications	0.26
Perforation of heart chamber	0.03
Other complications	0.28
Total of major complications	1.70

but develop mitral regurgitation, angina, or CHF.[49] Aortography typically shows a large RCA with absence of a left coronary ostium in the left aortic sinus. During the late phase of the aortogram, patulous LAD and LCx branches fill by means of collateral circulation from RCA branches. Still later in the filming sequence, retrograde flow from the LAD and LCx opacifies the LMCA and its origin from the main pulmonary artery (Fig. 12-20) . The clinical course of the patient tends to be more favorable if extensive collateral circulation exists. In rare instances, the RCA rather than the LCA may arise from the pulmonary artery.

CONGENITAL CORONARY STENOSIS OR ATRESIA.

Congenital stenosis or atresia of a coronary artery can occur as an isolated lesion or in association with other congenital diseases, such as calcific coronary sclerosis, supravalvular aortic stenosis, homocystinuria, Friedreich's ataxia, Hurler's syndrome, progeria, and rubella syndrome.[48] In these cases, the atretic vessel usually fills by means of collateral circulation from the contralateral side.

ANOMALOUS ORIGIN OF EITHER CORONARY ARTERY FROM THE CONTRALATERAL SINUS.

Origin of the LCA from the proximal RCA or the right aortic sinus with subsequent passage between the aorta and the right ventricular outflow tract has been associated with sudden death during or shortly after exercise in young persons[50] [51] [52] [53] [54] (Fig. 12-21) . The increased risk of sudden death may be due to a slitlike ostium with acute takeoff angles of the aberrant coronary arteries or possible compression between the pulmonary trunk and aorta. After its aberrant origin, the LCA takes an abrupt leftward turn and tunnels between the aorta and the right ventricular outflow tract. Sudden death is thought to result from transient occlusion of the anomalous LCA, caused by an increase in blood flow through the aorta and pulmonary artery that occurs during exercise and creates either a kink at the sharp leftward bend or a pinchcock mechanism in the tunnel. Origin of the RCA from the LCA or left aortic sinus with passage between the aorta and the right ventricular outflow tract is somewhat less dangerous. This anomaly, however, has also been associated with myocardial ischemia or sudden death, presumably through the same mechanism.[52] [53] [55] In rare cases of anomalous origin of the LCA from the right aortic sinus, myocardial ischemia may occur even if the LCA passes anterior to the right ventricular outflow tract or posterior to the aorta (i.e., not through a tunnel between the two great vessels).[56]

The course of the anomalous coronary arteries is easily assessed by angiography in the

RAO view (Fig. 12-22) . There are four common courses for the anomalously arising LCA from the right sinus of Valsalva, one common course for the anomalous RCA arising from left sinus of Valsalva, and one common course for the anomalous LCx arising from the right sinus of Valsalva. The anomalous LCA arising from the right sinus of Valsalva may take either a septal, anterior,

Figure 12-19 Congenital fistula. *A,* Right anterior oblique cranial view of the left coronary arteriogram shows a congenital fistula (arrow) arising from branches of both the left anterior descending and left circumflex arteries and draining into the left ventricle. *B,* Left anterior oblique view of the left coronary arteriogram shows the fistula (arrow).

Figure 12-20 Anomalous origin of the left coronary artery (LCA) from the pulmonary artery. *A-C,* The thoracic aortogram shows a large right coronary artery (RCA) and no antegrade filling of the LCA. The LCA fills primarily through extensive collaterals from the RCA to the LAD (white arrows). The anomalous origin of the LCA from the pulmonary artery is demonstrated in late phases of the aortogram (*C,* curved arrow).

Figure 12-21 Anomalous origin of the right coronary artery (RCA). Right anterior oblique coronary arteriogram shows an anomalous RCA arising from left sinus of Valsalva. The origin of the aberrantly arising artery, which is engaged with a left Judkins catheter, arises immediately anterior to the origin of the left coronary artery (not shown in the arteriogram). The anomalous right coronary follows an interarterial course opposite but analogous to that for the anomalous left coronary artery arising from the right sinus of Valsalva.

Figure 12-22 Anomalous origin of the left coronary artery from the right sinus of Valsalva. Each panel includes a caudocranial cross-sectional schematic representation at the level of the semilunar valves, showing the course of the anomalous coronary. The right anterior oblique angiograms and bitmaps show examples of each of the four most common courses of the anomalous left coronary artery aberrantly arising from the right sinus of Valsalva: posterior (retroaortic), interarterial, anterior, and septal (subpulmonic) courses.

interarterial, or posterior course.[57] The posterior course of the anomalous LCA arising from the left sinus of Valsalva is similar to the course of the anomalous LCx arising from the right sinus of Valsalva (Fig. 12-23) , whereas the common interarterial course of the anomalous RCA from the left sinus of Valsalva is similar to the interarterial course of the

anomalous LCA arising from the right sinus of Valsalva.

When either the LCA or the LAD arises anomalously from the right aortic sinus, another angiographic method to identify the course of the anomalous vessel is to first pass a catheter into the main pulmonary artery and then perform an arteriogram of the aberrant coronary artery in the steep AP caudal projection. This places the aberrant coronary artery, the rightward and anterior pulmonary valve, and the

Figure 12-23 Anomalous origin of the left circumflex. The caudocranial cross-sectional view at the level of the semilunar valves shows the common course of the left circumflex coronary artery aberrantly arising from the right sinus of Valsalva. The left circumflex artery passes behind the aortic root and runs to the left atrioventricular groove following an initial course identical to that for the anomalous left coronary artery arising from the right sinus of Valsalva that follows a posterior, retroaortic course.

leftward and posterior aortic valve all in one plane (see Fig. 12-22) . From this "laid-back aortogram," which can be used even in mapping the course of anomalous coronary arteries in transposition of the great vessels, it is usually possible to confirm whether the course of the aberrant coronary artery is between the great vessels. Although angiography is useful for establishing the presence of anomalous coronary arteries, transesophageal echocardiography may also be an important adjunctive diagnostic tool for establishing the course of the vessels.[58]

SINGLE CORONARY ARTERY.

Although there are numerous variations of this anomaly,[59] it assumes hemodynamic significance when a major branch passes between the aorta and the right ventricular outflow tract.

Anomalies Not Causing Myocardial Ischemia

In this category of anomalies, the coronary arteries originate from the aorta, but their origins are in unusual locations. Although myocardial perfusion is normal, cannulation of the origin of these vessels may be problematic. These anomalies occur in about 0.5 to 1.0 percent of adult patients undergoing coronary arteriography.[60]

ORIGIN OF THE LEFT CIRCUMFLEX ARTERY FROM THE RIGHT AORTIC SINUS.

Anomalous origin of the circumflex artery from the right aortic sinus is the most common of these anomalies (see Fig. 12-23). In a series of nearly 3000 patients, this anomaly was found in 0.67 percent.[61] The anomalous LCx generally arises posterior to the right coronary artery and courses inferiorly and posteriorly to the aorta to enter the left atrioventricular groove. An interarterial course for an anomalous LCx originating from

the right sinus of Valsalva is extremely uncommon.

ORIGIN OF ALL THREE CORONARY ARTERIES FROM EITHER RIGHT OR LEFT AORTIC SINUSES VIA MULTIPLE SEPARATE OSTIA.

This rare anomaly is similar to single coronary artery. There is absence of a coronary ostium in either the left or right aortic sinus. The missing vessels arise in the contralateral aortic sinus, but instead of arising as a single coronary artery they arise through two or even three separate ostia.

HIGH ANTERIOR ORIGIN OF THE RIGHT CORONARY ARTERY.

This anomaly is commonly encountered but of no hemodynamic significance. The inability to engage the ostium of the RCA selectively from conventional catheter manipulation raises the question of this superior origin of the RCA above the sinotubular ridge. Forceful, nonselective injection contrast medium into the right sinus of Valsalva may reveal the anomalous take-off of the RCA, which can then be selectively engaged with a Judkins right 5.0 catheter or Amplatz left 1.0 or 1.5 catheter.

CORONARY ARTERY SPASM (See also Chap. 37.)

In 1959, Prinzmetal and colleagues[62] described an unusual or variant form of angina in which the onset of chest pain was not provoked by the usual factors, such as exercise, emotional upset, cold, or ingestion of a meal. Patients considered to have variant angina are those in whom chest pain commences at rest or both at rest and during exertion,[63] occurs in a cyclical pattern at the same time every day, and is accompanied by ST segment elevation if an ECG is recorded. Although the ST segment elevation often is striking, it rapidly reverts to normal when the pain disappears spontaneously or is terminated by the administration of nitroglycerin and may be accompanied by atrioventricular block, ventricular ectopic activity, ventricular tachycardia, or ventricular fibrillation.[62]

Coronary arteriography plays an important role in understanding the pathophysiology and clinical consequences of coronary artery spasm.[64] Angiographic studies have shown that although spasm usually was superimposed on areas of fixed stenosis, it often occurred in segments of coronary arteries that appeared angiographically normal. Intravenous ergonovine maleate was used in the late 1970s to provoke spasm in patients with suspected variant angina who were undergoing coronary arteriography.[64] In a series of 1089 consecutive patients undergoing coronary arteriography for chest pain, coronary artery spasm was found in 12 percent of patients after ergonovine provocation.[65] Coronary spasm occurred with angiographic evidence of a coronary stenosis in 59 percent and in the absence of a demonstrable coronary lesion in 41 percent. Although ergonovine-induced spasm occurred rarely (<5 percent) in patients with atypical chest pain and exertional angina, it occurred in 14 percent of patients with symptoms of both exertional and resting angina. Ergonovine-induced coronary spasm was seen in 85 percent of patients with primarily rest angina who were observed to have episodes of ST segment elevation. Coronary angiography is also useful in these patients to exclude the diagnosis of fixed CAD. Accordingly, the diagnosis of coronary

artery spasm must rely instead on clinical features and response to treatment with nitrates and calcium channel blockers.

MORPHOLOGY OF ATHEROSCLEROTIC LESIONS

Characterization of lesion morphology based on the coronary arteriogram has been used to assess the chance of success and risk for complications associated with PCI.[66] [67] Criteria established by a joint ACC/AHA task force (Table 12-7) [68] were prospectively tested in a series of 350 patients undergoing multivessel PCI, which found that procedural success and complication rates were 92 percent and 2 percent, respectively, for type A lesions; 76 percent and 10 percent, respectively, for type B lesions; and 61 percent and 21 percent, respectively, for type C lesions. Lesions with two or more type B lesion characteristics (modified ACC/AHA B2) had an intermediate risk between lesions with one type B characteristic (modified ACC/AHA B1) and type C lesions.[66] Certain lesion characteristics were associated

TABLE 12-7 -- CHARACTERISTICS OF TYPE A, B, AND C CORONARY LESIONS

Type A Lesions (high success, >85%; low risk)	
Discrete (<10 mm)	Little or no calcium
Concentric	Less than totally occlusive
Readily accessible	Not ostial in locations
Nonangulated segment, <45 degrees	No major sidebranch involvement
Smooth contour	Absence of thrombus
Type B Lesions (moderate success, 60-85%; moderate risk)	
Tubular (10 to 20 mm length)	Moderate to heavy calcification
Eccentric	Total occlusions >3 months old
Moderate tortuosity of proximal segment	Ostial in location
Moderately angulated segment, 45 degrees, <90 degrees	Bifurcation lesion requiring double guidewire
Irregular contour	Some thrombus present
Type C Lesions (low success, <60%; high risk)	

Diffuse (2 cm length)	Total occlusion >3 months old
Excessive tortuosity of proximal segment	Inability to protect major sidebranches
Extremely angulated segments, 90 degrees	Degenerated vein grafts with friable lesions

From Ryan T, Faxon D, Gunnar R, et al: Guidelines for percutaneous transluminal coronary angioplasty: A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 12:529-545, 1988.

with higher risk, including chronic total occlusions, high-grade stenoses, stenoses on a bend of 60 degrees or more, and lesions located in vessels with proximal tortuosity[66] (Fig. 12-24) .

With advances in operator experience, availability of coronary stents, and the use of glycoprotein IIb to IIIa inhibitors (see Chap. 38) , higher (>90 percent) procedural success rates have been reported with complex type B and C lesions.[69] It is now recognized that the ACC/AHA classification system is limited by the subjectivity of the criteria,[66] [66A] [70] variable risk with the individual criteria,[71] and the demonstration that some criteria are associated with a risk for failure but low risk for complications, whereas others are associated with a higher risk for both failure and complications.[69]

Specific Lesion Characteristics

Estimation of procedural risk may be more useful based on the presence of one or more specific adverse morphological features rather than use of a composite scoring system (see Chap. 38) (Table 12-8).

IRREGULAR LESIONS.

Lesion irregularity, including those lesions with ulceration, aneurysm formation, a "sawtooth" pattern, or an intimal flap, suggests a friable surface, correlating pathologically with plaque fissuring, rupture, and platelet and fibrin aggregation.[72] Complex, irregular plaques have been associated with unstable coronary syndromes[72] and progression to total occlusion,[73] whereas smooth lumen contours are more suggestive of stable angina.[72] Other surface morphology features associated with unstable angina and infarction include lesions with sharply angulated leading or trailing

borders, multiple serpiginous channels, and discrete intraluminal filling defects.[74]

Semiquantitative measurements of lesion irregularity have obtained in patients with unstable coronary syndromes.[75] By using curvature analysis of the arterial contour in one study, lesion irregularity was quantified by measuring the number and magnitude of the peaks and

Figure 12-24 Examples of the ACC/AHA lesion complexity score. A concentric stenosis (arrow) is identified in the proximal segment of the proximal right coronary artery (type A lesion, *A*). A calcified, ostial lesion of the left anterior descending artery (arrow) is shown (type B2 lesion, *B*). A long (35 mm) diffuse narrowing (arrow) in the midsegment of the left anterior descending artery is demonstrated (type C lesion, *C*).

TABLE 12-8 -- DEFINITIONS OF PREPROCEDURAL LESION MORPHOLOGY*

FEATURE	FREQUENCY (%)	DEFINITION
Eccentricity	48.0	Stenosis that is noted to have one of its luminal edges in the outer one fourth of the apparent normal lumen.
Irregularity	17.9	Characterized by lesion ulceration, intimal flap, aneurysm, or "sawtooth" pattern
Ulceration	12.1	Lesions with a small crater consisting of a discrete luminal widening in the area of the stenosis
Intimal flap	3.22	A mobile, radiolucent extension of the vessel wall into the arterial lumen
Aneurysm	5.49	Segment of arterial dilatation larger than the dimensions of the normal arterial segment
"Sawtooth"	0.84	Multiple, sequential stenosis irregularities
Length		Measured "shoulder-to-shoulder" in an unforeshortened view
Discrete	55.0	Lesion length <10 mm
Tubular	34.8	Lesion length 10-20 mm
Diffuse	10.2	Lesion length >20 mm
Ostial location	10.0	Origin of the lesion within 3 mm of the vessel origin
Angulation		Vessel angle formed by the center line through the lumen proximal and distal to the stenosis

Moderate	15.3	Lesion angulation 45 degrees
Severe	0.93	Lesion angulation 90 degrees
Bifurcation stenosis	6.05	Stenosis involving the parent and daughter branch if a medium or large branch (>1.5 mm) originates within the stenosis and if the side branch is completely surrounded by stenotic portions of the lesion to be dilated
Proximal tortuosity		
Moderate	15.3	Lesion is distal to two bends 75 degrees
Severe	NR	Lesion is distal to three bends 75 degrees
Degenerated SVG	7.1	Graft characterized by luminal irregularities or ectasia comprising >50% of the graft length
Calcification	34.3	Readily apparent densities noted within the apparent vascular wall at the site of the stenosis
Total occlusion	6.4	TIMI 0 or 1 flow
Thrombus	3.4	Discrete, intraluminal filling defect is noted with defined borders and is largely separated from the adjacent wall. Contrast staining may or may not be present.

SVG=saphenous vein graft; NR=not reported.

From Popma JJ, Lansky AJ: Qualitative and quantitative angiography. In Topol EJ (ed): Textbook of Interventional Cardiology 3rd ed. Philadelphia, WB Saunders, 1999.

troughs of the lumen contour. The number of peaks per centimeter, summed maximum errors per centimeter, integrated errors per centimeter, and features per centimeter were higher in patients with unstable angina than in those with stable angina.[75] Clinical application of this technique has been limited owing to the sophisticated software and time required for its routine use.

LESION LENGTH.

Estimates of axial lesion length have been obtained using a number of methods, including the measurement of the "shoulder-to-shoulder" extent of atherosclerotic narrowing more than 20 percent or by the lesion length with a more than 50 percent visual diameter stenosis.[76] In clinical practice, the lesion length is often estimated by the distance between the proximal and distal angiographically "normal" segments. The ACC/AHA criteria categorize lesions as discrete (<10 mm), tubular (10-20 mm), and diffuse (> 20 mm). Diffuse lesions are associated with reduced procedural success.[77] Lesion length is also an important predictor of restenosis after PCI,[67] [69] potentially

relating to the more extensive plaque burden in long lesions.

OSTIAL LOCATION.

Ostial lesions are defined as those arising within 3 mm of origin of the vessel or branch. Balloon PTCA of aortoostial lesions and ostial lesions of LAD or LCx coronary arteries has been associated with a reduced procedural success and high recurrence rates,[78] [79] potentially owing to smooth muscle and eccentric intimal proliferation noted pathologically in ostial lesions. Technical factors may also account for the suboptimal success rates, such as difficulty with guide catheter support, lesion inelasticity precluding maximal balloon inflation, and the need for multiple balloon exchanges. Although directional and rotational atherectomy improve the procedural success rates in patients with ostial lesions, late clinical recurrence remains high.[80] [81] [82] Coronary stents have improved the late recurrence rates by reducing the degree of arterial recoil.

ANGULATED LESIONS.

Balloon PTCA of highly angulated (
45 degrees) lesions carries an increased risk of procedural complications (13 percent versus 3.5 percent in nonangulated stenoses; $p<0.001$). [83] Complications are most often due to coronary dissection, with the risk of dissection related to the severity of the angulation.[66] Vessel curvature should be measured in the most unforeshortened projection using a length of curvature that approximates the balloon or stent length used for coronary dilatation. Those devices that are relatively rigid (e.g., directional atherectomy) are less useful in angulated lesions. Coil stents appear better able to conform to an angulated segment than tubular slotted or multicellular designs.

BIFURCATION LESIONS.

The risk of sidebranch occlusion ranges from 14 to 27 percent in bifurcation lesions, relating to the extent of atherosclerotic involvement within the origin of the sidebranch.[67] [84] The risk of sidebranch compromise has been reduced using advanced angioplasty methods, including guidewire protection, "kissing balloon" techniques, branch vessel stent placement,[85] and lesion angulation, but calcification or vessel size may preclude adequate sidebranch protection in some cases. Sidebranch occlusion during PCI is a frequent cause of periprocedural cardiac enzyme elevation.

DEGENERATED SVGs.

The procedural success rate after balloon angioplasty of SVG lesions ranges from 84 to 92 percent,[86] [87] [88] depending, in part, on the presence of SVG friability or degeneration, lesion location, and SVG age of 36 months or more.[86] Few criteria have been proposed for classifying the degree of SVG degeneration, although such a definition should include an estimate of the percentage of SVG irregularity and ectasia, friability, presence of thrombus,

Figure 12-25 Intracoronary thrombus in acute myocardial infarction. In the setting of acute MI, this right anterior oblique caudal left coronary arteriography shows an eccentric lesion (arrowhead) in the proximal left anterior descending artery, immediately followed by a globular filling defect (arrow) surrounded by contrast media on all sides.

and number of discrete or diffuse lesions (>50 percent stenosis) located within the SVG. The major periprocedural risk for PCI is the occurrence of distal embolization of thrombus and plaque contents.

LESION CALCIFICATION.

Coronary artery calcium is an important marker for coronary atherosclerosis. With IVUS as a reference standard, conventional angiography is moderately sensitive for the detection of extensive lesion calcium (sensitivity, 60 percent and 85 percent for three- and four-quadrant calcium, respectively) but is less sensitive for the presence of milder degrees of lesion calcification.[89]

The presence of angiographic coronary artery calcium has also been related to reduce procedural success rates after balloon PTCA and DCA.[67] [90] Higher (90 percent) procedural success rates have been reported after rotational atherectomy in heavily calcified lesions.[91]

Figure 12-26 Intracoronary thrombus in unstable angina. This left anterior oblique right coronary arteriogram shows a severe stenosis in the midportion of the right coronary artery (arrowhead), followed by a large filling defect surrounded by contrast medium on all sides (arrows).

Figure 12-27 Total occlusion with blunt appearance. The left anterior oblique right coronary arteriogram shows a blunt total occlusion (arrow) of the midportion of the right coronary artery associated with a sidebranch. The blunt appearance and the presence of the sidebranch are characteristics that angioplasty may be unsuccessful.

THROMBUS.

Conventional angiography is a relatively insensitive method to detect coronary thrombus,[92] although complex lesion morphology has been associated with clinical findings of "high-risk" unstable angina.[93] When it is present, angiographic thrombus, defined as discrete, intraluminal filling defects within the arterial lumen, has also been associated with a variably higher (range: 6-73 percent) incidence of ischemic complications after PCI[94] [95] (Figs. 12-25 and 12-26). Large, intracoronary thrombi may

be treated with a combination of pharmacological agents (e.g., glycoprotein IIb-IIIa inhibitors) and mechanical devices (e.g., rheolytic thrombectomy) (see Chap. 38) .

Figure 12-28 Total occlusion with taper. The left anterior oblique right coronary arteriogram shows a total occlusion (arrow) of the midportion of the right coronary artery, but the smoothly tapering appearance of the site of total occlusion suggests that attempt with angioplasty may be successful.

TABLE 12-9 -- THROMBOLYSIS IN MI (TIMI) FLOW

Grade 3 (complete reperfusion)	Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.
Grade 2 (partial reperfusion)	Contrast material flows through the stenosis to opacity the terminial artery segment. However, contrast material enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis, noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
Grade 1 (penetration with minimal perfusion)	A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
Grade 0 (no perfusion)	No contrast flow through the stenosis.

Modified from Sheehan F, Braunwald E, Canner P, et al: The effect of intravenous thrombolytic therapy on left ventricular function: A report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI) Phase I trial. Circulation 72:817-829, 1987. Copyright 1987, American Heart Association.

TOTAL OCCLUSION.

Total coronary occlusion is identified on the cineangiogram as an abrupt termination of the epicardial vessel; anterograde and retrograde collaterals may be present and are helpful in quantifying the length of the totally occluded segment (Fig. 12-27). Primary success rates for balloon angioplasty of total occlusions remains suboptimal (66-83 percent),[67] [69] [96] lower than the 94.2 percent primary success rates for subtotal

occlusions.[69] The risk of an unsuccessful procedure depends on the duration of the occlusion[69] and certain lesion morphological features, such as bridging collaterals, occlusion length greater than 15 mm, and the absence of a "nipple" to guidewire advancement (Fig. 12-28) .

CORONARY PERFUSION.

Perfusion distal to a coronary stenosis can occur anterograde by means of the native vessel, retrograde through collaterals, or through a coronary bypass graft.[29] The rate of anterograde coronary flow is influenced by both the severity and complexity of the stenosis and the status of the microvasculature. The Thrombolysis in Myocardial Infarction (TIMI) study group established criteria to assess the degree of anterograde coronary reperfusion in patients with acute MI[97] (Table 12-9) . Successful reperfusion was present with TIMI flow 2 or 3, whereas TIMI 0 or 1 flow was deemed failed reperfusion. It is now clear that TIMI 2 flow may also be insufficient for myocardial perfusion, associated with increased mortality in patients with acute MI compared with those with normal TIMI 3 perfusion.[98] [99] The TIMI frame count was subsequently introduced to quantifying the coronary artery perfusion rates in patients with acute MI.[100] With this method, the number of cinefilm frames required for opacification of the involved vessel are counted by means of an automated frame counter, which is present on most cine projectors. Flow delayed more than 60 frames (approximately two cardiac cycles at 30 frames/second) and 90 frames (approximately three cardiac cycles at 30 frames/second) may be associated with increased risks for cardiac morbidity.[100]

Coronary Collateral Circulation

In the normal human heart, networks of tiny anastomotic branches interconnect the major coronary arteries and are precursors for the collateral circulation.[101] These anastomotic arteries cannot be visualized in patients with normal or mildly diseased coronary arteries because they carry only minimal flow and their small (<200 mum) caliber is well beyond the spatial resolution capabilities of cine imaging systems. As a coronary artery obstruction forms, a pressure gradient develops within anastomotic vessels connecting the distal hypoperfused segment with the proximal artery or the adjacent anastomotic channels of other vessels. The trans-stenosis pressure gradient facilitates blood flow through the anastomotic vessels, which progressively dilate and eventually become angiographically visible as collateral channels.

Although it is not entirely clear why some patients develop effective collateral vessels distal to a severe stenosis and others do not, a gradual rate of obstruction formation may allow enlargement of preexisting channels or growth of new ones by angiogenesis. This may allow the development of a "protected" region of myocardial perfusion. Coronary collaterals are usually not visualized until the coronary obstruction is larger than 90 percent.[101] [102] The temporal sequence of collateral development has been studied in patients who show persistent occlusion of the IRA after acute MI.[103] Among patients studied within 6 hours of infarction, about half demonstrated angiographically visible collateral vessels. Among those studied more than 24 hours after infarction, virtually all had visible collaterals. This suggests that collateral flow may develop more rapidly than previously recognized and may potentially develop within hours after total

occlusion. It thus appears that collateral circulation does not represent the formation of new vessels but rather the utilization of vessels that already exist but carry little blood flow because distal perfusion was not compromised. Other factors that affect collateral development are patency of the arteries supplying the collateral and the size and vascular resistance of the segment distal to the stenosis.[104] A classification system for the grading of coronary collaterals has been proposed (Table 12-10) . A wide variety of collateral pathways exist in patients with severe CAD (Figs. 12-29 (Figure Not Available) to 12-31) .

FUNCTION OF COLLATERAL VESSELS.

Coronary collateral vessels have a number of functional roles. In patients with total occlusions, regional

TABLE 12-10 -- PERFUSION GRADES DISTAL TO A CORONARY STENOSIS

GRADE	TIMI	COLLATERAL FLOW	RENTROP COLLATERAL GRADE
3	Prompt anterograde flow and rapid clearing	Excellent	Complete perfusion. Contrast material enters and completely opacifies the target epicardial vessel.
2	Slow distal filling, but full opacification of distal vessel	Good	Partial collateral flow. Contrast material enters but fails to opacify the target epicardial vessel completely.
1	Small amount of flow, but incomplete opacification of distal vessel	Poor	Barely detectable collateral flow. Contrast medium passes through collateral channels but fails to opacify the epicardial vessel at any time.
0	No contrast flow	No visible flow	No collaterals present.

Modified from Alderman E, Stadius M: The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. Coron Artery Dis 3:1189-1207, 1992.

Figure 12-29 (Figure Not Available) Coronary collaterals seen with right coronary artery occlusion and common collateral pathways seen with right coronary artery occlusion. The arrows point to the site of obstruction. The small tortuous channels represent the collateral connections. Numbers in parentheses refer to the frequency with which each pathway was visualized in a series of 200 patients with significant coronary disease. RC=right coronary artery; C=circumflex artery; OM=obtuse marginal branch of the circumflex artery; PD=posterior descending branch of the RCA; AM=acute marginal branch of the RCA; A-V=artery to the atrioventricular node. (From Levin DC: Pathways and functional significance of the

coronary collateral circulation. Circulation 50:831, 1974. Copyright 1974, American Heart Association.)

left ventricular contraction is better in segments supplied by adequate collateral circulation than in those segments supplied by inadequate or no collateral circulation.[101] In patients with acute MI undergoing emergency coronary arteriography without antecedent thrombolytic therapy, those with adequate collaterals had significantly lower left ventricular end-diastolic pressures, higher cardiac index, higher ejection fraction, and lower percentage of area dyssynergy than patients without collaterals.[105] Patients with severe coronary obstruction without collateral circulation were found to have a significantly higher incidence of thallium-201 myocardial perfusion defects than those with an intact collateral circulation.[106] With balloon inflation during PTCA, patients with well-developed collateral vessels experienced less pain, have less left ventricular asynergy, and have less summed ST segment elevation than those with poorly developed collateral vessels.[107] Distal coronary perfusion pressure during balloon inflation is higher in patients with well-developed collaterals than in those with poorly developed collateral circulation.[108] [109] [110]

Angiographic Findings After Percutaneous Coronary Intervention

A number of angiographic complications have been characterized after PCI, based on their risk for early complications and late restenosis. Pathological studies have demonstrated that plaque fracture and dissections are integral components of PCI,[111] occurring after 32 to 41 percent of balloon procedures[112] [113] [114] (Figs. 12-32 and 12-33). A scoring system for the severity of the dissection was proposed by the National Heart, Lung, and Blood Institute (NHLBI) PTCA Registry investigators (Table 12-11) . The immediate prognostic importance of a coronary dissection depends on its extent into the medial and adventitia, axial length, presence of contrast staining, and effect on coronary perfusion.[112] [115] [116] Dissections involving more than 50 percent of the vessel circumference or extending more than 10 mm in axial length are associated with a worse prognosis. [111] Plaque rupture, fissure, intimal flaps, and nonocclusive thrombus formation may also be manifest angiographically as intraluminal haziness, obscuring arterial borders and making visual and quantitative estimates of residual coronary dimensions difficult.

Embolic complications may also be identified during PCI. Distal embolization is defined as the migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches. "No reflow" is defined as a reduction in anterograde flow without a demonstrable residual stenosis at the treatment site. These complications occur during 1 to 2 percent of PCI procedures.[117] [118] [119] Coronary perforation is defined as the extravasation of contrast material outside the vessel lumen and classified as localized (confined to the pericardial space immediately surrounding the artery) or nonlocalized (extending diffusely within the pericardial space). Coronary perforation may develop more often in patients treated with new devices compared with balloon PTCA.[120]

Quantitative Angiography

Quantitative angiographic methods, including automated arterial contour-detection, videodensitometry, and digital parametric algorithms, have been used to assess

procedural outcome after PCI. These methods have been developed based on the recognized limitations of visual estimation of stenosis severity, which include observer variability,[121] overestimation of the stenosis severity before PCI and underestimation of the stenosis severity after PCI,[122] and provision of some visual estimates (>90 percent) that are physiologically untenable.[123] It does seem clear that once the inherent limitations of visual estimation of stenosis severity are understood that the clinician's eye can become "retrained," and one series has shown that visual estimates by experienced observers may correlate more closely with quantitative measurements.[124]

DIGITAL CALIPERS.

Digital calipers provide a more quantitative estimate of stenosis severity than visual estimates, and, when properly applied, this method appears to correlate

Figure 12-30 Common collateral pathways seen with left anterior descending artery occlusion. (See Figure 12-29 (Figure Not Available) for abbreviations.) (From Levin DC: Pathways and functional significance of the coronary collateral circulation. Circulation 50:831, 1974. Copyright 1974, American Heart Association.)

with automated-edge detection algorithms.[125] With the use of digital calipers, cineangiograms are magnified and projected onto a wall or flat surface using this method. Calibration is performed by measuring the known dimensions of the diagnostic or guiding catheter. The lumen border is measured using the caliper, and a calibration factor is obtained to determine quantitative dimensions.[29] Notably, if the caliper measurements are obtained from nonmagnified images, the correlation with automated edge-detection algorithms is less favorable (r=0.72).[126]

AUTOMATED EDGE DETECTION ALGORITHMS.

Based on early work using hand-drawn arterial contours that corrected for pincushion distortion and reconstructed a three-dimensional representation of the arterial contour,[127] computer-assisted methods for automated arterial contour detection were developed. These computer-assisted techniques have been applied to directly acquired digital images or to 35-mm cinefilm digitized using a cinevideo converter. Examples of such systems include the Cardiovascular Angiographic Analysis System (CAAS),[128] ARTREK,[129] Cardiovascular Measurement System (CMS),[130] and the Duke University Quantitative/Qualitative Evaluation System,[131] among others.[132] [133]

Quantitative angiographic analysis is divided into several distinct processes, including film digitization, image calibration, and arterial contour detection. A cine-video converter is used to digitize 35-mm cineframes into a 512×512 (or 480)×8 bit pixel matrix. Magnification of the image results in an effective pixel matrix of approximately

2458×2458.[129] The contrast agent-filled diagnostic or guiding catheter can be used as a scaling device for determining absolute vessel dimensions, yielding a calibration factor in millimeters per pixel. Catheter and arterial contours are obtained by drawing a center line through the segment of interest. Linear density profiles are then constructed perpendicular to the center line, and a weighted average of the first and second derivative function is used to define the catheter or arterial edges. Individual edge points are then connected using an automated algorithm, and outliers are discarded and the edges are smoothed. The automated algorithm is then applied to a selected arterial segment, and absolute coronary dimensions and percent diameter stenosis are obtained.

Important differences exist in the various quantitative coronary angiographic systems with respect to the calibration method, identification of the arterial edge, use of minimal cost or "smoothing" algorithms for contour construction, and identification of the normal "reference" segment. These systematic differences may affect the accuracy and precision of the quantitative coronary angiographic measurements, and system-to-system variability may be substantial.[134] For most angiographic systems, interobserver variabilities are 3.1 percent for diameter stenosis and 0.10 to 0.18 mm for minimal lesion diameter.

VIDEODENSITOMETRY.

This technique has also been used to evaluate changes in stenosis severity before and after PCI.[135] With this method, the contrast density of a selected reference segment is compared with the contrast density in the region of a stenosis. The major advantage of videodensitometry is that lesion eccentricity and irregularity, typically manifest as haziness within a single projection, can be accounted for without the need for multiple image projections. The primary limitation of videodensitometry is that vessel overlap with other anatomical structures (e.g., diaphragm, ribs) and image overpenetration make precise determination of the reference vessel area problematic in some vessels.

Figure 12-31 Common collateral pathways seen with left circumflex artery occlusion. (See Figure 12-19 for abbreviations.) (From Levin DC: Pathways and functional significance of the coronary collateral circulation. Circulation 50:831, 1974. Copyright 1974, American Heart Association.)

Figure 12-32 Moderately severe coronary dissection. This left anterior oblique cranial left coronary arteriogram shows a large intramural collection of contrast medium (arrows) at the site of angioplasty in the proximal left anterior descending artery. Although contrast medium cleared rapidly from artery itself, contrast medium persisted within the dissection, thus meeting criteria for a type C dissection.[120] [121]

The accuracy and reproducibility of quantitative angiography are dependent on a

number of factors that add error to the precision of the measurements.[136] The total variance associated with the measurement of the minimal lumen and reference diameters within a study is affected by (1) the biological differences among lumen dimensions (e.g., intrinsic arterial size, vasomotor tone, thrombus); (2) inconsistencies in radiographic image acquisition parameters (e.g., quantum mottling, out-of plane magnification, foreshortening); and (3) angiographic measurement variability (e.g., frame selection, factors affecting the edge-detection algorithm) (Table 12-12) . It is essential that these factors be minimized during image acquisition, particularly in prospectively designed research protocols.[137]

Although analysis of two or more "orthogonal" projections has been recommended to allow a more accurate assessment of the physiological significance of lesion severity,[138] [139] a second, technically suitable projection may not be available in many (14-53 percent) angiographic cases, owing to vessel foreshortening, overlap, and poor image quality.[140] If orthogonal projections are not available, analyses of the "worst-view" projection may provide sufficiently accurate information.[140]

Figure 12-33 Spiral dissection. This left anterior oblique right coronary arteriogram shows evidence of a vessel dissection emanating from the site of angioplasty in the midportion of the right coronary artery (arrowhead) and extending to the distal right coronary artery (arrow), thus meeting criteria for a severe type D dissection.[112] [113]

TABLE 12-11 -- STANDARDIZED CRITERIA FOR POSTPROCEDURAL LESION MORPHOLOGY

FEATURE	DEFINITION
Abrupt closure	Obstruction of contrast flow (TIMI 0 or 1) in a dilated segment with previously documented anterograde flow
Ectasia	A lesion diameter greater than the reference diameter in one or more areas
Luminal irregularities	Arterial contour that has a "sawtooth pattern" consisting of opacification but not fulfilling the criteria for dissection or intracoronary thrombus
Intimal flap	A discrete filling defect in apparent continuity with the arterial wall
Thrombus	Discrete, mobile angiographic filling defect with or without contrast medium staining
Dissection,* A	Small radiolucent area within the lumen of the vessel
B	Linear, nonpersisting extravasation of contrast medium
C	Extraluminal, persisting extravasation of contrast medium
D	Spiral-shaped filling defect
E	Persistent lumen defect with delayed anterograde flow

F	Filling defect accompanied by total coronary occlusion
Dissection, length (in mms)	Measure end-to-end for type B through F dissections
Dissection, staining	Persistence of contrast medium within the dissection after washout of contrast medium from the remaining portion of the vessel
Perforation, localized	Extravasation of contrast medium confined to the pericardial space immediately surrounding the artery and not associated with clinical tamponade
Nonlocalized	Extravasation of contrast medium with a jet not localized to the pericardial space, potentially associated with clinical tamponade
Side branch loss	TIMI 0, 1, or 2 flow in a side branch >1.5 mm in diameter that previously had TIMI 3 flow
Distal embolization	Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches
Coronary spasm	Transient or permanent narrowing >50% when a <25% stenosis has been previously noted

Modified from Popma JJ, Lansky AJ: Qualitative and quantitative angiography. In Topol EJ (ed): Textbook of Interventional Cardiology, 3rd ed. Philadelphia, WB Saunders, 1999.

*National Heart, Lung, and Blood Institute classification system for coronary dissection.

TABLE 12-12 -- CORRECTABLE SOURCES OF IMAGING ERROR DURING ACQUISITION AND ANALYSIS

SOURCE OF ERROR	POTENTIAL CORRECTIONS
Biologic Variation in Lumen Diameter	
Vasomotor tone	Nitroglycerin, 200 mug IC every 10 minutes
Variations in image acquisition	
Single Studies	
Vessel motion Cardiac	End-diastolic/end-systolic cineframe
Respiration	Breath holding
Vessel foreshortening	Obtain multiple angiographic projections

Insufficient contrast injection	Use 7-8 Fr large, high flow catheters
Branch vessel overlap	Obtain multiple angiographic projections
Pincushion distortion	Image objects in center of image
Sequential Studies	
X-ray generator (pulse width/dose/beam quality)	Repeat study in same imaging laboratory
X-ray tube (focal spot/shape/tube current)	As above
Image intensifier (magnification/resolution)	As above
Differences in angles and gantry height	Record gantry height/angle/skew on worksheet
Image calibration	Use measured catheter diameter
Errors in Image Analysis	
Electronic noise	Recursive digitization and frame averaging
Quantum noise	Spatial filtering of digital image data
Automated edge detection algorithm	Minimize observer interaction
Selection of reference positions	Interpolated or averaged normal segment
Identification of lesion length	Use of sidebranches, other landmarks
Frame selection	End-diastolic frame showing "worst" view

Pitfalls of Coronary Arteriography

A systematic approach based on a few, common-sense principles is needed to avoid pitfalls in the performance and interpretation of coronary arteriography. It should be recalled that the normal coronary artery tapers gradually from proximal to distal and has smooth walls completely free of irregularities. Several factors may affect the quality of the angiographic interpretation.

INADEQUATE OPACIFICATION.

Inadequate filling of the coronary artery with contrast medium may result in streaming of contrast medium and give the impression of ostial stenoses, missing sidebranches, or thrombus. Superselective injection of contrast medium into the LCx through short LMCA may give the impression of total occlusion of the LAD. Adequate filling of the coronary arteries and bypass grafts is required to overcome the native flow of unopacified blood and produce high-quality coronary arteriograms. Streaming of contrast medium, admixed with unopacified blood, leads to artifactual impression of filling defects and incomplete assessment of stenosis severity. The causes of incomplete filling include competition from increased native coronary blood flow in the setting of left ventricular hypertrophy associated with aortic insufficiency or anemia and inadequate placement of

the diagnostic catheter with subselection of the LCx through a short LCMA. The problem of underfilling can be overcome by more forceful contrast agent injection so long as catheter tip position and pressure recording confirm the safety of such a maneuver. Under some conditions, switching to an angioplasty-guiding catheter with soft, short tip and a larger lumen than a diagnostic catheter may allow for more complete opacification of the target coronary artery or bypass graft.

ECCENTRIC STENOSES.

Coronary atherosclerosis more often leads to eccentric or slitlike atherosclerotic narrowings than concentric narrowings. If the long axis of the lumen is projected, the vessel may appear to have a normal or near-normal caliber. Only if the short axis of the stenotic lumen is projected will the narrowing be visible. For this reason, coronary arteries must be viewed in at least two projections approximately 90 degrees apart.

A related problem is that of the bandlike or membranous stenosis. Lesions such as this may be exceedingly difficult to detect. It is not clear whether these peculiar lesions represent pure atherosclerotic stenosis or are caused in some instances by congenital membranous bands. Aside from the difficulty in detecting these lesions, it is difficult to ascertain their hemodynamic significance. Measurement of the pressure gradient across the lesion through a small inner catheter inserted through the angiographic catheter may be useful in this regard.

UNRECOGNIZED OCCLUSIONS.

Flow disturbances associated with branch points predispose to the development of atherosclerosis and total occlusions of major arteries at this location. Because of this fact and the variability in the number and distribution of side branches in the normal coronary circulation, it is possible for occlusions at branch origins to escape detection. In some cases, occlusion of a branch can be recognized only by late filling of the distal segment of this branch by means of collateral circulation.

SUPERIMPOSITION OF BRANCHES.

Superimposition of major branches of the left coronary tree in the LAO and RAO projections can result in failure to detect stenoses or total occlusions of these branches. Although this problem most commonly affects the LAD and parallel diagonal branches, it is alleviated by the use of cranial and caudal angulation. Septal branches may mimic the LAD in the LAO cranial projection. When the LAD is occluded beyond the origin of the first septal branch, this branch often becomes quite enlarged in an attempt to provide collateral circulation to the vascular bed of the distal LAD.

MYOCARDIAL BRIDGING.

The major coronary arteries pass over the epicardial surface of the heart. In some

cases,

however, short segments descend into the myocardium for a variable distance. This occurs in 5 to 12 percent of patients and is almost always confined to the LAD. Because a "bridge" of myocardial fibers passes over the involved segment of the LAD, each systolic contraction of these fibers can cause narrowing of the artery. Myocardial bridging has a characteristic appearance on cineangiography. The bridged segment is of normal caliber during diastole but abruptly narrows with each systole. Systolic narrowing caused by myocardial bridging should not be confused with an atherosclerotic plaque. Although bridging is not thought to have any hemodynamic significance in most cases, some have suggested that when it produces severe systolic narrowing, ischemia or infarction may result. The presence of myocardial bridging has important implications for interventional cardiovascular therapy, because bridges do not respond to balloon dilatation or other interventions.

RECANALIZATION.

Although a narrowed segment of a coronary artery seen on arteriography usually is considered a "stenosis," such lesions may actually be a segment that was once totally occluded but has recanalized. Pathological studies suggest that approximately one third of totally occluded coronary arteries ultimately recanalize. The arteriographic appearances of stenosis and recanalization may be indistinguishable. Recanalization usually results in the development of multiple tortuous channels, which are quite small and close to one another, creating an impression on cineangiography of a single, slightly irregular channel. It is unlikely that the spatial resolution of cineangiography is sufficient to demonstrate this degree of detail in most patients with recanalized total occlusions, but this has important implications for interventional cardiovascular treatments because they are unlikely to be successful in the setting of multiple microscopic channels.

INTRAVASCULAR ULTRASONOGRAPHY (See also Chap. 7.)

Contrast coronary arteriography is limited in its ability to quantitate the extent or distribution of atherosclerosis[141] or to identify changes within the vessel wall over time.[142] [143] IVUS is a safe,[144] accurate,[145] and reproducible[146] [147] method of detecting vessel wall pathology[148] and lends insight into the dynamic changes before, after, and late after PCI.[149] [150] The two-dimensional tomographic images provided by IVUS also permits 360-degree characterization of arterial lumen dimensions in regions that are difficult to assess using conventional angiography, such as the LMCA and the ostii of the LAD, LCx, and RCA.[151]

TECHNICAL ISSUES.

IVUS has evolved substantially since the early 1990s, resulting in the commercial

availability of rapid exchange, mechanical or dynamic array imaging catheters,[152] ranging in size from 2.6 to 3.2 Fr, compatible with 6- to 7-Fr guiding catheters, and yielding a 30-MHz imaging frequency for enhanced tissue characterization.[153] Longitudinal or three-dimensional display of the arterial wall is best performed using an automated pullback device,[154] [155] which uses sidebranches and other anatomical landmarks to ascertain the plaque location along the axial length of the vessel.[156]

VESSEL WALL COMPOSITION.

In nondiseased arteries, IVUS differentiates the vessel wall into three components: (1) the intimal, which is composed of endothelial cells, subintimal smooth muscle cells, and fibroblasts, is 150 to 200 mum in diameter and is partitioned from the media by the internal elastic lamina; 2) the media, which is composed of smooth muscle cells, elastin, and collagen, is 100 to 350 mum in diameter and is encircled by the external

Figure 12-34 Intravascular ultrasonographic examples of plaque morphology. A longitudinal pullback in the left anterior descending artery using intravascular ultrasonography shows concentric calcification of the left anterior descending artery with echo dropout *(A).* A normal vessel wall is demonstrated in *B.* A thick fibrous cap is shown in *C* (arrow). A soft, echolucent plaque with a rupture of the fibrous cap is shown in *D* (arrow). (Courtesy of Gary S. Mintz, MD.)

Figure 12-35 Discordance between angiographic and intravascular ultrasonographic findings. The proximal and distal regions of the right coronary artery have only minor lumen irregularities by conventional angiography (arrows, *A*). The corresponding intravascular sonogram demonstrates significant plaque burden proximal (71 percent plaque burden, *B*) and distal (63 percent plaque burden, *C*) within the vessel. (Courtesy of Gary S. Mintz, MD.)

elastic membrane (EEM); and (3) the adventitia, which contains fibrous tissue, is 300 to 500 mum in diameter and is encased by perivascular stroma and epicardial fat.[157] Differences in acoustic impedance between the cell layers generally account for the "three-layer" appearance seen in the normal vessel wall of most patients by IVUS.[158] A "two-layer" coronary artery is seen in some patients, depending on the IVUS transducer frequency (<30 MHz), intimal thickness (<160 mum), and collagen content of the media.[158]

In diseased arteries, the differentiation between vessel wall components becomes more obscure, and, depending on the cellular composition of the atherosclerotic plaque, at least three plaque types can be described.[157] Hypoechoic, or soft, plaques are echolucent compared with the EEM and indicate a high lipid content and presence of fatty pools[157] (Fig. 12-34) . Thrombus within the vessel lumen can often be mistaken for soft plaque, but it can be distinguished from soft plaque by its mobility, lobular edges,

and movement away from the vessel wall during the cardiac cycle.[157] Fibrous plaques have similar brightness as the adventitia and indicate a higher content of collagen and elastin.[157] Calcified plaques are identified by their bright, echogenic components with acoustic shadowing of the underlying vascular structures.[157] A calcified plaque may be characterized as superficial or deep and quantified by its circumferential extent (from 0 to 360 degrees) and by its axial length (in millimeters)**.** [157] [159] Comparative studies with IVUS show that fluoroscopy is relatively insensitive for the detection of vessel wall calcium.[159] In one study of 110 patients undergoing PCI, IVUS detected calcium in 76 percent of target lesions, whereas fluoroscopy identified calcium in only 48 percent (p<0.001). Detection of fluoroscopic calcium increased to 74 percent in lesions with two or more quadrants of calcium by IVUS and 86 percent in lesions with calcium of 6 mm or more in length or with a circumferential arc of calcium 180 degrees or more by IVUS.[160] The presence of lesion calcification has also been correlated with the overall plaque burden.[160]

IVUS studies in patients undergoing PCI have also demonstrated that coronary atherosclerosis is more diffuse than appreciated using conventional angiography[161] (Fig. 12-35). In an IVUS series of 884 angiographically "normal" reference segments, only 6.8 percent were free of atherosclerosis; with an average 51 percent cross-sectional plaque area found proximal or distal to the target lesion.[161] IVUS studies have also confirmed an earlier pathological finding,[162] suggesting that the coronary artery undergoes "adaptive" remodeling, or vessel expansion, in most patients in the early stages of atherosclerosis, maintaining a nonobstructive coronary lumen diameter (Fig. 12-36). Once the EEM has expanded by 40 percent, further accumulation of plaque encroaches on the arterial lumen.[161] Arterial constriction has also been seen in some patients, particularly diabetics, owing to "negative" arterial remodeling.[163]

IVUS USE DURING PCI.

IVUS may be used for several purposes during PCI: (1) to characterize baseline plaque composition, vessel size, and lesion accessibility, to select the best single device, or combination of devices, for PCI; (2) to confirm (or refute) angiographic estimates of stenosis severity, particularly in regions difficult to visualize using conventional methods; and (3) to assess anatomical results and detect complications, including dissections and residual minimal cross-sectional area, after PCI.[163A] IVUS has also been used after stent placement to ensure full strut apposition against the vessel wall, symmetrical and complete stent expansion compared with the contiguous reference vessel, and absence of significant "margin" dissections adjacent to the stent. The Angiography Versus Intravascular Ultrasound-Directed (AVID) study, a randomized comparison of 759 patients assigned to angiography-guided or IVUS-guided (<10 percent area stenosis, absence of dissections, full stent apposition) stent placement, showed similar (p=0.22) rates of target lesion revascularization (TLR) in the IVUS-guided (8.7 percent) and angiography-guided (6.2

Figure 12-36 Characterization of the plaque burden using intravascular ultrasonography. A cross-section of a diseased artery is demonstrated in *A.* The external elastic membrane (EEM) cross-sectional area (CSA) is demonstrated in *B.* The lumen CSA is shown in *C.* The area between the lumen and the EEM

contains the plaque and the media, comprising atherosclerotic plaque. (Courtesy of Gary S. Mintz, MD.)
from sudden cardiac death
Individuals whose occupa-
function, and not-high-risk
prefer to avoid revascular-

percent) groups, despite a larger initial lumen cross-sectional area in the IVUS-guided lesions (7.54 mm^2 versus 6.94 mm^2 in angiography-guided lesions; $p<0.01$). [164] For vessels less than 3.25 mm, however, the TLR rate was 7.9 percent in the IVUS-guided group and 14.6 percent in the angiography-guided group ($p=0.04$), suggesting a potential benefit for IVUS-guided stent placement in smaller vessels.[164]

VESSEL WALL CHANGES AFTER PCI.

IVUS provides unique insight into the dynamic changes that occur within the vessel wall after PCI.[165] [166] Sequential IVUS studies show that lumen renarrowing after balloon PTCA and atherectomy relates both to arterial remodeling and, to a lesser extent, to intimal hyperplasia.[165] The Serial Ultrasound Restenosis (SURE) Trial, a registry of 61 lesions treated with balloon PTCA or DCA, performed angiography and IVUS at baseline, after PCI, and 24 hours, 1 month, and 6 months later.[165] Lumen cross-sectional area by IVUS improved from 6.81 mm^2 after PCI to 8.22 mm^2 at 1 month ($p=0.0001$) but decreased to 4.88 mm^2 6 months later ($p=0.0001$). Vessel, or EEM, cross-sectional area enlarged from 17.32 mm^2 after PCI to 19.39 mm^2 at 1 month ($p=0.0001$) but decreased to 16.33 mm^2 at 6 months ($p=0.0001$). Intimal hyperplasia, as assessed by the plaque+media cross-sectional area, increased from 10.51 mm^2 after PCI to 10.96 mm^2 at 24 hours ($p=0.001$) and 11.45 mm^2 ($p=0.03$) 6 months later.[165] Changes in lumen cross-sectional area in each study interval correlated more closely with changes in vessel cross-sectional area than with changes in intimal hyperplasia cross-sectional area.[165] In contrast to these findings, IVUS studies have also shown that lumen renarrowing after stent implantation is virtually all due to intimal hyperplasia within the axial length of the stent or its border.[167] [168]

LIMITATIONS OF IVUS.

A number of factors have limited the widespread use of IVUS during PCI, including its cost, its cumbersome set-up for occasional IVUS users, steep "learning curve" for "online" IVUS interpretation, and the improved outcomes associated with routine use of stents. Current catheter-based IVUS systems are also limited by their inability to assess lumen diameters less than 1.0 mm, owing to the catheter size and "ring-down artifact[26] [27] ; and the limited spatial resolution of a 30-MHz imaging transducer (theoretical spatial resolution, 80 mum; usual spatial resolution, 120-150 mum) makes IVUS detection of a "vulnerable" plaque somewhat problematic. Nevertheless, IVUS will remain useful in lesions difficult to assess using conventional angiography as these limitations are addressed with newer IVUS designs.

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Chapter 13 - Relative Merits of Cardiovascular Diagnostic Techniques

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THE SPECTRUM OF CARDIOVASCULAR DIAGNOSTIC PROCEDURES

A variety of noninvasive and invasive techniques can be used for the diagnostic and prognostic assessment of patients with cardiovascular disease. The technologies supporting these techniques vary widely, and all require significant training of physicians who supervise and interpret test results. The confidence of requesting physicians who order these tests relates predominantly to their experience regarding the accuracy of test results in their patient populations from the laboratories to which such patients are referred. Although one test modality may have higher specificity for the detection of disease than a competing test aimed at identifying the same pathophysiology as reported from specialized centers of excellence, the specificity advantage may not apply in other settings because of local differences in quality control and/or experience of the test interpreter. Therefore, it is always difficult to definitively declare superiority of one diagnostic test over another since local equipment and expertise can influence their results substantially.

Most of the diagnostic tests presently available to cardiovascular specialists are based on assessment of regional and global function (echocardiography [see Chap. 7], radionuclide angiography [see Chap. 9], magnetic resonance imaging [MRI] [see Chap. 10]), myocardial perfusion (myocardial scintigraphy, contrast echocardiography, contrast MRI), myocardial metabolism (positron-emission tomography [PET] [see Chap. 9]), or coronary anatomy (coronary angiography [see Chap. 12]) under resting conditions, stress conditions, or both. The cardiovascular system can be stressed by either exercise or pharmacological means, such as the infusion of a vasodilator or an inotropic agent. The principle underlying all of the noninvasive stress tests that can be performed for diagnosing coronary artery disease (CAD) is uncovering abnormal flow reserve or an ischemic response in patients with physiologically significant luminal narrowing of one or more coronary arteries. The ischemic response can be identified as flow heterogeneity represented by a "defect" on a perfusion scan, abnormal regional systolic thickening or abnormal wall motion, or abnormal regional metabolism. Regional myocardial perfusion and metabolism are simultaneously assessed for the detection of myocardial viability in ischemic cardiomyopathy. Various other techniques used to distinguish viable from nonviable myocardium are inotropic reserve as assessed with dobutamine echocardiography or MRI, determination of the integrity of the microcirculation as evaluated with contrast echocardiography, or evaluation of myocardial membrane transport as determined from imaging a radiolabeled monovalent cation such as thallium-201 (^{201} Tl).

Diagnostic techniques such as electron beam computed tomography[1] and measurement of carotid intimal-medial thickness have emerged in recent years and are used for detecting asymptomatic coronary or carotid atherosclerosis, respectively. These technologies are not aimed at identifying an ischemic response but at detecting occult vascular disease in the coronary or peripheral circulation. The precise clinical role of these imaging methodologies is yet to be determined.

Sources of Bias when Evaluating and Comparing Diagnostic Techniques

The "gold standard" used for comparing the sensitivity and specificity of the various noninvasive techniques for detecting CAD remains the coronary angiogram, which can be obtained only with invasive means (see also Chap. 12) . However, the coronary angiogram can at times be misleading, and it often underestimates disease severity, particularly in segments with crescentic lumina and in the presence of diffuse disease rendering the reference diameter misleading. A high degree of intraobserver and interobserver variability in visually interpreting the degree and significance of coronary stenosis is well known. Quantitative angiography for measuring the minimal luminal diameter of a coronary lesion has greater predictive physiological significance with less intraobserver and interobserver variability. In recent years, the amount of information that can be obtained at the time of coronary angiography regarding the extent and severity of CAD has increased (see also Chap. 12) . Assessment of coronary flow reserve with Doppler-tipped

catheters in conjunction with vasodilator stress adds value to the mere assessment of coronary anatomical findings. The use of intravascular ultrasound has also provided important additional diagnostic and prognostic information in comparison with contrast angiography alone. Presently, the noninvasive techniques aimed at diagnosing CAD and assessing its functional and prognostic severity are being compared with physiological data obtained at cardiac catheterization and not with the degree of coronary anatomical narrowing alone.

Another significant limitation in determining the specificity of noninvasive techniques for detection of CAD is that most patients with normal noninvasive study findings (e.g., a normal stress perfusion scan or normal stress echocardiogram) are not referred for coronary angiography. Patients are referred for coronary angiography most often because of abnormal noninvasive test results, which leads to a posttest referral bias whereby predominantly patients with true-positive or false-positive noninvasive test results (an abnormal perfusion scan or abnormal echocardiogram and normal coronary arteries) undergo angiography. Patients with true-negative noninvasive test results are not sent to cardiac catheterization. This trend has led to use of the normalcy rate as a surrogate for specificity in evaluating the accuracy of a noninvasive test for CAD diagnosis. The normalcy rate represents the percentage of normal scans in patients who have less than a 5 percent posttest likelihood of CAD when taking into account clinical information, the resting electrocardiogram (ECG), and exercise treadmill test results. This posttest referral bias tending to lower the specificity if a normal coronary angiogram is required as the "gold standard" for a normal test result should be kept in mind when reviewing the literature, particularly with reports following the introduction of a new test.

A critical observer should bear in mind that the sensitivity and specificity of a test for detecting a cardiovascular abnormality (e.g., significant CAD, resting left ventricular [LV] dysfunction) are always very high in the first few reports that are published for a newly introduced imaging methodology. These initial good results relate to many variables, including the inclusion of a highly selected patient population that may include normal volunteers on one end of the spectrum and patients with severe disease at the other end.

When evaluating the worth of a test for diagnosing cardiovascular disease or a complication of disease, cost should now also be considered.[2] [3] One test may have a few percentage points higher sensitivity than another test to which it is being compared, but the cost may be twice as high. Thus, the cost/benefit ratio should also be weighed when comparing the worth of two or more tests that are developed for the same clinical application. A good example is the noninvasive assessment of myocardial viability with PET imaging versus resting and delayed ^{201} Tl perfusion imaging and low-dose dobutamine echocardiography. PET imaging for viability assessment may be slightly more accurate than the two competing technologies[4] but at a substantially higher cost.

Table 13-1 summarizes the major clinical indications for noninvasive and invasive

testing and lists various techniques applicable to each of these clinical indications. The remainder of this chapter will sequentially address the headings provided in this table.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION AT REST

Echocardiography (see also Chap. 7)

Of all the noninvasive techniques available for the assessment of regional and global LV function at rest, echocardiography

TABLE 13-1 -- CLINICAL APPLICATIONS OF NONINVASIVE AND INVASIVE TECHNIQUES IN CARDIOVASCULAR DISEASE

ASSESSMENT OF LEFT VENTRICULAR FUNCTION
Echocardiography
Radionuclide angiography
Gated SPECT
Gated MRI
Contrast ventriculography
DETECTION OF CORONARY ARTERY DISEASE AND ASSESSMENT OF PROGNOSIS
Exercise electrocardiographic stress testing
Exercise or pharmacological stress SPECT myocardial perfusion imaging
Exercise or dobutamine echocardiography
Pharmacological stress MR perfusion imaging
Dobutamine stress MRI
MR angiography
Coronary angiography, intravascular ultrasound, and measurement of flow reserve
ASSESSMENT OF MYOCARDIAL VIABILITY
Resting SPECT perfusion imaging
Low-dose dobutamine echocardiography
Positron-emission tomography
Low-dose dobutamine MRI
MRI=magnetic resonance imaging; SPECT=single-photon emission computed tomography.

is the most versatile overall, provides the most ancillary information, and has the lowest cost.[5] Two-dimensional echocardiography provides excellent images of the heart and great vessels, but it depends on obtaining satisfactory windows from the body surface to

the area of interest in the heart. When good windows are obtained, echocardiography is superbly well suited for the evaluation of global and regional LV systolic function because of its high spatial and temporal resolution and its ability to define both regional wall thickening and inward endocardial excursion. When compared with all other techniques, it should be the preferred initial test to diagnose heart muscle diseases of yet unknown etiology. These disease entities include ischemic cardiomyopathy, nonischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive myocardial disease. Resting echocardiographic technology not only allows a thorough assessment of cardiac morphology and function but also permits the simultaneous assessment of valvular, pericardial, intramyocardial, and extracardiac abnormalities.

Echocardiography has an advantage over other techniques for assessing LV function in its ability to accurately assess regional myocardial thickening, which is not influenced by either cardiac translation or the center of reference used. Regional thickening is a better marker of regional function than is regional wall motion. Regional thickening abnormalities cannot be well identified by radionuclide angiography or contrast ventriculography. The only other technique that perhaps permits a more accurate assessment of regional systolic thickening is gated MRI. The latter, however, is currently more expensive than two-dimensional echocardiography and cannot be performed at the bedside in critically ill patients. The advent of small portable echocardiographic apparatus will enhance only the bedside utility of this technique. A limitation of resting echocardiography in gauging the severity of regional or global LV dysfunction is the lack of a reproducible quantitative technique to measure the LV ejection fraction. A quantitative ejection fraction is better obtained by using alternative approaches such as LV contrast angiography, radionuclide angiography, and gated single-photon emission computed tomography (SPECT) imaging.

Echocardiography is invaluable in assisting in the detection

of acute myocardial infarction and such mechanical complications as right ventricular infarction, acute mitral regurgitation from papillary muscle rupture or dysfunction, ventricular septal defect, a true or false LV aneurysm, or pericardial effusion (Chap. 35) . Thus, it is the noninvasive technique of choice for the comprehensive evaluation of regional and global LV dysfunction and associated abnormalities in the setting of acute myocardial infarction. Transesophageal echocardiography can be performed at the bedside in an acutely ill patient with shock in the intensive care unit setting to help identify the etiology of the hemodynamic disturbance. Echocardiography can also be performed in the emergency room in patients with chest pain and a possible acute ischemic syndrome. A defined regional wall motion abnormality lends support to a presumptive diagnosis that regional ischemia may be the cause of the chest pain syndrome.

Echocardiography is more sensitive than ECG for detecting LV hypertrophy[6] and is an excellent technique for estimating LV mass, which has been shown to independently predict cardiovascular morbidity and mortality.[7] [7A] The variability in LV mass

measurements and the reliability of serial measurements to assess regression of hypertrophy[8] have been reduced by the substitution of linear measurements of LV wall thickness and internal dimension from the two-dimensional parasternal long-axis view whenever the two-dimensional directed M-mode beam is not ideally oriented for measuring thickness and cavity dimensions[9] (see also Chap. 7) . Further improvements in the echocardiographic measurement of LV mass may be offered by three-dimensional localization of imaging slices.[10]

Radionuclide Angiography (see Chap. 9)

First-pass radionuclide angiography and gated equilibrium blood pool radionuclide angiography are nuclear cardiology techniques that use a gamma camera and ECG gating for determining the changes in radioactivity in the left and right ventricular chambers over the cardiac cycle by generating time-activity curves. Quantitative ejection fraction measurements from both the right and left ventricles are highly accurate. Ventricular and pulmonary blood volumes and regional ventricular wall motion can also be assessed. As with echocardiography, resting radionuclide angiography is clinically useful for prognostication: the lower the resting LV ejection fraction or the more global the LV dysfunction, the worse the subsequent outcome with respect to survival. An advantage of radionuclide angiography over echocardiography is its ability to accurately quantitate the left and right ventricular ejection fractions by using a "count-based" technique and to obtain data in virtually all patients. Patients with arrhythmias can undergo radionuclide angiography since windows for cycle length can be preset and all beats falling outside the window are rejected.

Chemotherapy with anthracycline agents can result in a dose-dependent deterioration in LV function because of the toxic effects of the drug on cardiac myocytes (see also Chap. 69) . Radionuclide angiography is ideally suited to provide serial quantitative LV ejection fraction measurements in patients who have received or are receiving doxorubicin therapy. If doxorubicin administration is continued after objective evidence of reduced systolic function, significant symptomatic congestive heart failure and irreversible LV dysfunction may ensue. Resting radionuclide angiography may provide a more quantitative assessment of LV dysfunction after myocardial infarction, but it cannot provide other important information such as the extent of infarction expansion, presence of LV thrombus, development of mitral regurgitation, and extent of regional systolic thickening abnormalities.

Gated SPECT Imaging (see Chap. 9)

The emergence of technetium-99m (^{99m}Tc)-labeled myocardial perfusion agents led to the development of gated ^{99m}Tc-SPECT imaging,[11] which permits simultaneous evaluation of regional systolic thickening, global LV function, and myocardial perfusion (see also Chap. 9) . The introduction of gated ^{99m}Tc-SPECT imaging significantly enhanced the specificity of SPECT for detection of CAD in patients with chest pain,[12] [13] [14] [120A] [120B] [120C] [120D] [120E] [131A] increased the detection rate of viable myocardium by demonstration of preserved systolic thickening corresponding to preserved tracer uptake,[15] and improved the ability to risk-stratify patients by providing information relevant to the global LV ejection fraction.[16] New techniques using technology similar to

that used for gated equilibrium blood pool imaging allow for automated determination of the LV ejection fraction.[17] [18] Thus, a quantitative global ejection fraction and percent thickening in various regions of the left ventricle can be reported with results of myocardial perfusion analysis under resting and stress conditions.

Severe perfusion abnormalities can limit quantitation of the LV ejection fraction by the gated SPECT technique by interfering with detection of endocardial edges along the whole LV volume on SPECT tomograms. Manrique and colleagues found that gated SPECT underestimated the LV ejection fraction when compared with equilibrium radionuclide angiography in patients with LV dysfunction and large perfusion defects.[19] Others have reported accurate LV ejection fraction measurements by gated SPECT in the presence of large perfusion defects.[20] Count-based techniques for assessing regional systolic thickening are not as adversely influenced by low regional radioactive counts in areas of severe defects.[17] Gated ^{99m} Tc-tetrofosmin SPECT imaging compared favorably with cine-MRI with respect to grading regional wall motion abnormalities in patients with an acute myocardial infarction.[21] Exact agreement in wall motion scores between gated SPECT and MRI was 92 percent (kappa=0.82). Gated ^{99m} Tc-sestamibi SPECT assessment of regional function also correlates well with echocardiography.[22]

Gated SPECT can also be performed with ^{201} Tl. He and associates[20] reported similar LV ejection fraction measurements for ^{201} Tl-gated SPECT (54 ± 15 percent) and ^{99m} Tc-gated SPECT (54 ± 16 percent) in 63 patients who had LV ejection fractions also determined by first-pass radionuclide angiography (54 ± 12 percent). ^{99m} Tc-gated SPECT is preferred to ^{201} Tl-gated SPECT because of better image quality and better interobserver agreement.[23] Patient obesity significantly reduces the accuracy of quantitative SPECT ^{201} Tl perfusion imaging.[23A]

Magnetic Resonance Imaging (see Chap. 10)

MRI systems have recently become more available for cardiovascular imaging.[24] Regional and global cardiac function can be evaluated at rest and under pharmacological stress with MRI,[25] and high-speed MRI techniques allow for the simultaneous assessment of myocardial perfusion with magnetic resonance (MR) contrast agents.[26] MRI is superior to other noninvasive imaging modalities in diagnosing congenital heart disease,[27] aortic disease, anomalous coronary arteries, and right ventricular dysplasia. The role of MRI in evaluation of CAD is still in the early stages. At present, nuclear cardiology techniques and echocardiographic techniques have cost/benefit characteristics superior to those of MRI for assessing regional and global function. The major strength of MRI is its ability to provide high-resolution detail of cardiovascular anatomy. It can yield three-dimensional information on anatomy, function, and blood flow. It is accurate in determining wall thickness and may be the best technique for quantitating overall LV mass. MRI tagging is an imaging modality that uses a grid overlying the full thickness of the myocardium on tomographic slices for assessment of progressive thickening of endocardial, midwall, and epicardial layers during the cardiac cycle. This technique measures intramyocardial function, which enhances measurement of the degree of regional myocardial dysfunction. Serial assessment of LV mass and volume is important in monitoring LV remodeling after

myocardial infarction, and this technique is being used in clinical trials to test certain pharmacological interventions for their effect on remodeling.

Contrast Left Ventriculography (see Chap. 15)

Left ventriculography has been available for many years for the assessment of LV function in a variety of pathological

disorders. It has been used as the "gold standard" to which noninvasive techniques have been compared. Abnormal wall motion, but not abnormal thickening, can be assessed by contrast left ventriculography and quantitative measurements of LV ejection fraction, and absolute volumes are highly reproducible and perhaps yield the most precise quantitative measurements of global function of all the noninvasive techniques discussed above. Limitations of contrast ventriculography include its invasive nature, high cost, potential nephrotoxicity of the dye, and the need to trace endocardial contours to quantitate ejection fraction and volume. LV hypertrophy and LV mass are better quantitated by echocardiography or MRI. An advantage of contrast ventriculography is its ability to simultaneously measure intracavitary pressure and other hemodynamic variables such as stroke and end-diastolic volume, as well as performance of coronary angiography during the same cardiac catheterization procedure. Differentiation between dilated and ischemic cardiomyopathy can easily be made, and associated valvular lesions such as mitral regurgitation can be simultaneously diagnosed and semiquantitated. Left-to-right shunts at the atrial and ventricular levels are most accurately quantitated by cardiac catheterization measurements, although echocardiography and MRI can precisely localize atrial and ventricular septal defects.

The Utility of Different Approaches to the Assessment of Left Ventricular Function

Overall, when all factors are considered, two-dimensional echocardiography with Doppler remains the most effective approach to assessment of resting LV function. Its major limitation is an inability to visualize all regions of the left ventricle in every patient, and poor-quality images are acquired in certain patients, such as those with severe chronic obstructive pulmonary disease. The lack of a highly accurate and reproducible method for deriving a quantitative measurement of LV ejection fraction also limits the utility of echocardiography. Contrast echocardiography improves visualization of myocardial walls and shows promise for the simultaneous assessment of regional perfusion at rest and during stress. Gated ^{99m} Tc-SPECT and gated MRI provide precise determinations of regional myocardial thickening and LV ejection fraction, and MRI also allows for simultaneous assessment of perfusion by using a contrast agent. Visualization of the coronary arterial tree is one of the ultimate goals of MRI, and progress has been made in this application, although it is not ready for clinical use. Table 13-2 summarizes the strengths and limitations of the various techniques for

assessment of regional and global LV function.

DETECTION OF CORONARY ARTERY DISEASE

A number of noninvasive techniques are available to the clinician for detection of CAD in patients with chest pain. The techniques vary greatly in methodology but have as a fundamental principle the detection of myocardial ischemia or flow heterogeneity with exercise or pharmacological stress. The variables indicative of myocardial ischemia differ considerably and are specific for the test under consideration. The advent of myocardial imaging techniques using radionuclide, echocardiographic, or MRI methodology has provided enhanced accuracy for detection of CAD but at a higher cost than for the standard exercise treadmill test. The strengths and limitations of the various noninvasive techniques used for the detection of CAD are described in the sections to follow.

TABLE 13-2 -- STRENGTHS AND LIMITATIONS OF THE VARIOUS DIAGNOSTIC TECHNIQUES FOR ASSESSMENT OF LEFT VENTRICULAR FUNCTION

ECHOCARDIOGRAPHY
Strengths: Portability; immediately available; repeatability; provides ancillary structural and physiological information; high spatial and temporal resolution; accurately measures regional systolic thickening; sensitive for detecting LV hypertrophy and measuring LV mass; good for RV function assessment; excellent for detection of diastolic dysfunction; no ionizing radiation or contrast material needed; low cost
Limitations: Poor acoustic windows in some patients; lack of quantitative ejection fraction; high operator dependence
RADIONUCLIDE ANGIOGRAPHY
Strengths: Accurate measurement of LV and RV ejection fractions; reproducible; little operator dependency; serial monitoring of patients receiving cancer chemotherapy
Limitations: Regional systolic thickening not evaluated; radiation exposure; ancillary anatomical information not obtained; difficult to detect LV hypertrophy
GATED ^{99m} TC SPECT IMAGING
Strengths: Assessment of systolic thickening; global LV ejection fraction accurately measured; simultaneous evaluation of perfusion and function; viability assessment
Limitations: Decreased accuracy of LV ejection fraction assessment with large defects; lack of portability; LV hypertrophy and mass not measured; no ancillary structural information obtained; lower spatial resolution than ultrasound
MAGNETIC RESONANCE IMAGING

Strengths: Best technique for diagnosing congenital heart disease; high-resolution anatomical detail; excellent for measuring wall thickness and LV mass; provides functional images in any desired imaging plane; can accurately assess regional and global LV function; 3-dimensional information; proximal coronary arteries visualized; myocardial tagging permits analysis of subendocardial, midwall, and subepicardial function; high-speed MRI permits perfusion imaging

Limitations: Lack of portability; cannot monitor ST segments during imaging; claustrophobia in some patients; need to correct for cardiac and respiratory motion; patients with pacemakers excluded

LV=left ventricular; RV=right ventricular; SPECT=single-photon emission computed tomography.

Exercise Electrocardiography (see also Chap. 6)

A review of the literature concerning the diagnostic accuracy of the standard exercise test was published by Gibbons and colleagues[28] and used as a basis for formulating guidelines for exercise testing by the American College of Cardiology/American Heart Association Practice Guidelines Task Force. Meta-analysis showed that the sensitivity and specificity of the exercise ECG stress test for the detection of CAD were 68 and 77 percent, respectively, in 147 consecutively published reports of patients who underwent both angiography and exercise testing.[29] However, bias from the selection of patients who agreed to undergo both treadmill testing and coronary angiography at the outset led to a 45 percent sensitivity for 1.0 mm of horizontal or downward ST segment depression but an 85 percent specificity.[30] Even when studies that included patients with resting ST segment depression were excluded, the sensitivity and specificity of the exercise test were only 67 and 84 percent, respectively.[28]

SENSITIVITY.

The sensitivity of exercise ECG is very dependent on the level of exercise achieved. Sensitivity is reduced in patients who fail to achieve 85 percent of the age-adjusted maximum predicted heart rate or greater. Specificity of the ST segment depression response is markedly affected by variables such as LV hypertrophy, hyperventilation, digoxin therapy, intraventricular conduction disturbances, preexcitation syndrome, hypokalemia, severe hypertension, and resting ST segment depression from a variety of causes. Many patients are precluded from undergoing treadmill testing alone because

of nonspecific resting ST or T wave abnormalities, conduction abnormalities, or claudication. Interestingly, however, the specificity of the exercise test was only 69 percent in an analysis of 10 studies totaling 3548 patients who underwent exercise testing without digitalis therapy. Similarly, the specificity of the exercise test in studies excluding LV hypertrophy only increased to 77 percent, which was just 8 percent higher

than the 69 percent specificity of the ST segment response for CAD detection when studies including LV hypertrophy were analyzed.

SPECIFICITY.

The specificity of the exercise ECG response is also suboptimal in women,[31] particularly those who are in the premenopausal age group with a low to intermediate pretest likelihood of CAD. In contrast, the negative predictive value of a normal exercise ECG response in women for excluding CAD is high. Women with a normal baseline resting ECG who achieve greater than 85 percent of the maximum predicted heart rate for age and have a normal peak stress ECG have an excellent prognosis and a low prevalence of underlying CAD. The negative predictive value of the exercise ECG response appears to be lower in men than in women, whereas the positive predictive value of the ST segment depression response is higher in men than women.[32] [33] Heart rate adjustment for the ST segment response may improve diagnostic accuracy of the exercise ECG.[34]

EXTENT OF CAD.

The extent of CAD affects the sensitivity of the exercise ECG. Its sensitivity is less than 50 percent for patients with single-vessel disease but exceeds 85 percent for patients with three-vessel disease. Horizontal or downsloping ST segment depression at low exercise heart rates has a higher positive predictive accuracy for CAD than does ST segment depression at very high heart rates or workloads. The administration of beta-blocking drugs certainly influences exercise test results since they prevent the patient from attaining the desired heart rate-blood pressure product at which ischemic ST segment depression would appear. This effect leads to an increased prevalence of false-negative responses. In addition, other antianginal drugs, such as nitrates given before testing, may prevent the appearance of abnormal ST segment changes. Slow upsloping ST segment depression has occasionally been used to increase the criteria for a positive test. Although such responses may enhance the sensitivity of the exercise ECG, specificity is lowered.[35]

In summary, although the exercise ECG is the least expensive of the noninvasive tests for detecting CAD, it has limited sensitivity and specificity in certain patient populations. Its main value may be as the initial test for excluding CAD in patients with a low pretest likelihood of CAD based on age and gender, in those who have a normal resting ECG, and in patients with nonanginal or very atypical chest pain. If such patients achieve their maximum exercise heart rates with no ST segment depression and with normal hemodynamic responses, significant stenoses would not be likely to be the cause of their atypical chest pain syndrome. However, in most other populations, the exercise ECG is limited by suboptimal sensitivity and specificity for diagnosing CAD for the reasons outlined above.

Stress Radionuclide Myocardial Perfusion Imaging (see also Chap. 9)

Exercise or pharmacological stress ^{201}Tl or ^{99m}Tc-sestamibi SPECT imaging in patients

with chest pain yields a sensitivity for detecting CAD in the 85 to 90 percent range.[36] Specificity for excluding CAD is in the 90 percent range when gated SPECT imaging is used.[13] Exercise SPECT imaging and pharmacological SPECT imaging both yield sensitivities and specificities for coronary artery detection that are superior to those of exercise ECG testing alone.[37] [38] Radionuclide stress perfusion imaging has particular value when compared with exercise ECG testing alone in (1) patients with resting ECG abnormalities, such as those seen with LV hypertrophy, digitalis effect, preexcitation, and intraventricular conduction abnormalities, and (2) patients who fail to achieve greater than 85 percent of the maximum predicted heart rate and have no ST segment depression. Patients who fail to achieve a target heart rate and stop exercising at submaximal exercise levels demonstrate a higher sensitivity for CAD detection than when exercise ECG testing is performed alone[39] because myocardial perfusion abnormalities in response to stress appear earlier during the course of graded exercise stress. The ST segment depression response appears to require a higher rate-pressure product to induce flow heterogeneity, which is demonstrated as a perfusion defect on scintigraphy. Figure 13-1 shows an example of a reversible inferior wall perfusion defect on exercise ^{99m} Tc-sestamibi SPECT in a patient with a normal exercise ECG.

The addition of stress perfusion imaging to the exercise ECG stress test greatly assists in differentiating true-positive from false-positive exercise ST segment depression responses. In patients with a low to intermediate pretest likelihood of CAD, approximately 40 percent with ST segment depression have no evidence of CAD (false-positive findings). Quantitative analysis of SPECT has resulted in a higher sensitivity and specificity than merely visual evaluation of SPECT images. The single-vessel disease detection rate with stress SPECT imaging is approximately 25 percent higher than the rate achieved with exercise ECG testing alone. The sensitivity for detecting three-vessel disease with exercise SPECT is in the range of 95 to 100 percent.

LIMITATIONS.

The major limitation of using ^{201} Tl as a tracer for myocardial perfusion imaging is the high false-positive rate observed in many laboratories. This high rate is predominantly attributed to image attenuation artifacts that are interpreted as defects secondary to CAD. Although quantitation of ^{201} Tl images improves specificity, the false-positive rate remains higher than desirable, particularly with imaging of obese persons and women, who may demonstrate defects reflecting breast attenuation artifacts. Such artifacts are sometimes difficult to distinguish from myocardial perfusion abnormalities caused by inducible ischemia or from myocardial scarring (see also Chap. 9) . In the past decade, new ^{99m} Tc-labeled perfusion agents introduced into clinical practice have enhanced the specificity of SPECT.[14] The quality of images obtained with ^{99m} Tc-labeled radionuclides is superior to that of images obtained with ^{201} Tl because

Figure 13-1 Representative short-axis and vertical long-axis stress and rest ^{99m} Tc-sestamibi images showing a reversible inferior defect consistent with significant stenosis in the right coronary artery. The sensitivity for detecting single-vessel disease is substantially greater with stress myocardial perfusion

imaging than with stress electrocardiography. This patient had a normal ST segment response to exercise stress.

of the more favorable physical characteristics of ^{99m} Tc for imaging with a gamma camera.[37] The feasibility of using^{99m} Tc doses approximately 10 to 20 times higher than the doses used with ^{201} Tl permits the acquisition of images with higher count density, less scatter and attenuation, and fewer artifacts than seen with ^{201} Tl imaging. Perhaps most importantly, ^{99m} Tc-sestamibi or ^{99m} Tc-tetrofosmin imaging facilitates gated acquisition, thereby allowing simultaneous evaluation of regional systolic thickening, global LV ejection fraction, and myocardial perfusion.[40]

ECG-gated SPECT yields important information about regional and global LV function that could previously only be obtained with a second test, such as radionuclide angiography, echocardiography, or contrast ventriculography. The ability to accurately measure the resting LV ejection fraction with ^{99m} Tc-sestamibi or ^{99m} Tc-tetrofosmin adds supplementary value to the detection of perfusion abnormalities alone.

Women with chest pain who are referred for exercise or pharmacological stress testing benefit most from the enhanced test accuracy of ^{99m} Tc-gated SPECT imaging. Taillefer and coworkers prospectively evaluated the diagnostic accuracy of ^{201} Tl SPECT and ^{99m} Tc-sestamibi SPECT perfusion imaging for detection of CAD in women.[13] The greater than 70 percent overall sensitivity for detecting stenoses was similar for ^{201} Tl SPECT and ^{99m} Tc SPECT; the specificity, however, was only 67 percent for ^{201} Tl SPECT but increased to 92.2 percent when gated ^{99m} Tc-sestamibi images in the same women were analyzed (Fig. 13-2) . Since soft tissue attenuation causes nonuniformity of photon activity in the myocardium that results in artifacts often perceived as perfusion defects, attempts have been made to correct for attenuation by using certain algorithms emerging from advances in gamma camera instrumentation and software development.[41] [42] Specificity for CAD detection can be improved by the use of such approaches for correction of nonuniform photon attenuation. In one multicenter study, attenuation and scatter correction of ^{99m} Tc-sestamibi SPECT increased the normalcy rate from 86 to 96 percent in patients with a low pretest likelihood of CAD.[43] Caution, however, should be exercised when using currently available attenuation correction techniques since enhanced specificity may be offset by a decrease in multivessel disease identification[42] and a decrease in the detection of left anterior descending CAD.[43]

Some patients are less than ideal candidates for treadmill testing alone, and pharmacological stress with vasodilators such as dipyridamole or adenosine or an inotropic agent such as dobutamine is an alternative to exercise for detecting physiologically significant coronary artery stenosis. The basis for vasodilator perfusion imaging relates to the concept of coronary flow reserve. When coronary blood flow is maximally increased with an intravenously administered vasodilator, an impairment in flow reserve capacity in a stenotic artery simultaneous with a large flow increase in a

normal vascular bed results in relative inhomogeneity of myocardial perfusion between normal and stenotic beds. If tracers such as ^{201} Tl or ^{99m} Tc-sestamibi are injected during peak vasodilation in the presence of a hemodynamically significant coronary stenosis with reduced flow reserve, heterogeneity in tracer uptake will be observed as defects on post-stress images acquired soon after tracer injection. Sensitivity and specificity for coronary artery detection are comparable for dipyridamole and adenosine. Dobutamine stress is preferred in patients who have bronchospasm or a history of asthma or in those who have consumed caffeine before testing. Dipyridamole or adenosine administration in such patients could result in severe bronchospasm. Vasodilator imaging is the scintigraphic method of choice for detection of CAD in patients with complete left bundle branch block.[44] Such patients will be unable to undergo diagnostic exercise ECG testing alone.

Today, most laboratories use ^{99m} Tc perfusion imaging agents for detection of CAD in conjunction with exercise or pharmacological stress because of enhanced specificity for CAD detection and the ability to gate the images to the ECG

Figure 13-2 Specificity of ^{201} Tl stress single-photon emission computed tomographic (SPECT) imaging (open bars), ^{99m} Tc-sestamibi SPECT (crosshatched bars), and gated ^{99m} Tc-sestamibi SPECT (stippled bars) for detection of coronary artery disease in women. The specificities are for criteria of 50 percent or greater or 70 percent or greater stenosis representing significant coronary artery disease. Note that the specificity was only 67 percent for ^{201} Tl SPECT versus 92 percent for gated ^{99m} Tc SPECT in women evaluated for the presence of coronary artery disease when 70 percent or greater stenosis was used as the criteria. (From Taillefer R, DePuey EG, Udelson JE, et al: Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging [perfusion and ECG-gated SPECT] in detecting coronary artery disease in women. J Am Coll Cardiol 29:69, 1997. Reprinted with permission from the American College of Cardiology.)

to view regional systolic thickening. Mild nonreversible defects that represent attenuation artifacts usually show preserved systolic thickening, whereas if such areas of diminished tracer uptake represent scar, abnormal systolic thickening is observed.

Exercise and Dobutamine Stress Echocardiography (see also Chap. 7)

Stress echocardiography can be performed either with treadmill, upright bicycle, or supine bicycle exercise or by using pharmacological stressors such as dobutamine or dipyridamole. Dobutamine stress has a higher sensitivity than vasodilator stress does.[45] A pooled analysis of data in the literature pertaining to the diagnostic value of exercise or dobutamine stress echocardiography was recently published by Cheitlin and colleagues in the summary of the American College of Cardiology/American Heart Association Guidelines for Clinical Application of Echocardiography.[5] For the same reasons as outlined above for SPECT perfusion imaging, stress echocardiography is more sensitive and specific for detecting inducible ischemia than is exercise ECG

testing alone. The sensitivity of exercise stress echocardiography in 21 studies gleaned from the literature averaged 84 percent (71 to 97 percent), with a specificity of 86 percent (64 to 100 percent).[5]

These published studies reveal a rather marked variation in the sensitivity of exercise and dobutamine echocardiography for detecting angiographically documented CAD.[5] [46] This large variability may be related to patient selection, including the percentage of patients in each study with previous infarction and/or multivessel disease, the definition of what constitutes a new stress-induced wall motion abnormality (a new wall motion abnormality vs. failure to demonstrate hyperkinesis), the use of beta blockers during testing, and pretest referral bias.[47] The sensitivity of exercise echocardiography may be diminished if submaximal exercise heart rates are attained. Marwick and coauthors reported that when exercise heart rates were less than 85 percent of the maximum predicted heart rate, the sensitivity of exercise echocardiographic tests was only 42 percent.[48] Also, like stress SPECT imaging, stress echocardiography is more sensitive in detecting stenoses larger than 70 percent than in detecting vessels with 50 to 70 percent narrowing. It is also more sensitive in detecting CAD in patients with multivessel disease than with single-vessel disease[46] (Fig. 13-3) .

The sensitivity of exercise echocardiography is approximately 10 percent lower in women than men, with comparable specificities. [49] This decreased sensitivity for CAD detection in women has been reported for ECG treadmill testing,[50] radionuclide perfusion imaging, radionuclide angiography, and dobutamine echocardiography.[51]

Dobutamine stress echocardiography was often found to be negative in women with single-vessel stenosis.[52] The overall sensitivity of dobutamine stress echocardiography for detecting 50 percent or greater coronary narrowing in women was 40 percent. In women with two- or three-vessel disease, the sensitivity increased to 60 percent. The sensitivity of dobutamine stress echocardiography in women without a baseline wall motion abnormality was 21 percent overall and 33.3 percent in patients with two- or three-vessel disease. The explanation for the poor overall sensitivity of dobutamine stress echocardiography in this group of women relates, in part, to the relatively low overall prevalence of severe coronary artery narrowing. This lower sensitivity for detection of single-vessel disease has been reported by most investigators and is in the 50 to 80 percent range.[53] [54] [55] [56] [57] Another reason for a lower sensitivity of dobutamine stress echocardiography in the detection of single-vessel disease or mild stenoses is premature termination of the test because of side effects. Secknus and Marwick reported premature termination of dobutamine stress echocardiography in 15 percent of 3000 patients.[58] Most of the episodes of premature test termination were due to cardiovascular side effects, including ventricular and supraventricular arrhythmias, severe hypertension, hypotension, severe ischemia by echocardiography, or severe chest pain.

To acquire images at peak stress and thus enhance the sensitivity of the test, some have proposed that supine bicycle echocardiography be the stress technique of choice for the ultrasound modality. Although treadmill exercise yields higher maximal heart rates, systolic

Figure 13-3 Sensitivity of dobutamine stress echocardiography for detection of coronary artery disease by the number of diseased vessels. (From Geleijnse ML, Fioretti PM, Roelandt JR: Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 30:595, 1997. Reprinted with permission from the American College of Cardiology.)

blood pressure is higher with supine bicycle exercise, so a similar double product is seen with the two techniques. With respect to detection of CAD, Badruddin and colleagues reported an 82 percent sensitivity for supine bicycle exercise versus 75 percent for upright treadmill echocardiography with a somewhat lower specificity for supine bicycle exercise (80 vs. 90 percent).[59] Several other studies have shown that imaging at peak exercise is approximately 8 to 9 percent more sensitive than acquiring images after bicycle exercise.[60] [61]

Comparison of Exercise SPECT Perfusion Imaging and Exercise Echocardiography

Stress echocardiography and stress perfusion imaging share common positive features that deserve emphasis before comparing the value and limitations of each technique. First, both are associated with a higher sensitivity and specificity for CAD detection than is exercise ECG testing alone. Second, both noninvasive techniques provide *functional* information for risk stratification, assessment of the area at risk, and determination of myocardial viability that is superior to that obtained with coronary angiography (see below).

ADVANTAGES OF STRESS ECHOCARDIOGRAPHY.

When compared with radionuclide perfusion imaging, advantages of stress echocardiography include the following: (1) The technique is totally noninvasive, safe, and repeatable; (2) no radiation exposure is involved; (3) the time to complete a full examination is short; (4) the technique is portable and requires no highly sophisticated instrumentation; (5) the cost is relatively low; (6) it has the ability to identify structural abnormalities of the heart, including coexisting valvular disease, LV hypertrophy, and pericardial abnormalities; and (7) ultimately, contrast echocardiography will be used with conventional stress echocardiography to allow for simultaneous assessment of regional myocardial perfusion and regional systolic function. Contrast echocardiography performed in association with vasodilator stress is still in the preliminary phases of testing. The addition of contrast should enhance the diagnostic accuracy and value of the technique.

LIMITATIONS OF STRESS ECHOCARDIOGRAPHY.

Limitations include the following: (1) Images are difficult to acquire at peak exercise because of exertional hyperpnea and

cardiac excursion; (2) an ischemic response is required for the elucidation of regional abnormal wall motion; (3) rapid recovery of wall motion abnormalities can be seen with mild ischemia, particularly with single-vessel disease, which may lead to a false-negative test result if the images are not acquired rapidly postexercise; (4) detection of residual ischemia within an infarct zone is difficult because of resting akinesis; (5) the technique is highly operator dependent for data collection and image analysis, and considerable interindividual variability in interpreting stress echocardiograms has been reported[62] ; (6) good-quality, complete images are acquired in only 70 percent of patients. An inability to image all of the LV myocardium occurs in a substantial number of patients. In four studies involving a total of 418 patients, the echocardiography investigators determined that visualization of all myocardial segments was inadequate in 37 percent of patients[63] ; (7) a long training period is required to gain experience; and (8) quantitative assessment of inducible wall motion abnormalities and LV ejection fraction is operator dependent.

ADVANTAGES OF EXERCISE PERFUSION IMAGING.

When compared with exercise echocardiography, the following advantages of exercise myocardial perfusion imaging for detection of CAD may be listed: (1) Myocardial perfusion imaging detects abnormal flow reserve and does not require an ischemic response for a positive test result; (2) data relevant to abnormal myocardial perfusion are obtained at peak stress with treadmill exercise rather than after exercise as required for echocardiography; (3) the sensitivity for detecting CAD is slightly higher (8 to 10 percent) with exercise perfusion imaging, chiefly because the sensitivity for detecting single-vessel disease and mild stenoses of 50 to 70 percent narrowing is rather low with exercise echocardiography; (4) perfusion imaging appears to identify more ischemic regions than stress echocardiography does,[64] [65] [66] [67] perhaps because mere flow heterogeneity and not true ischemia causing systolic myocardial dysfunction produces defects on stress scintigrams[68] ; (5) infarct zone ischemia is more easily identified with perfusion imaging by demonstration of a partial reversible defect in an area that contains a mixture of scar and viable myocardium; (6) operator dependency is not nearly as much a factor with SPECT perfusion imaging for the acquisition of images as it is with echocardiography; (7) virtually 100 percent of patients can undergo adequate SPECT perfusion imaging in which all areas of the myocardium are visualized; (8) with ^{99m} Tc-sestamibi, simultaneous assessment of myocardial perfusion and function can be obtained, and recent data show that the resting LV ejection fraction can be accurately measured from gated ^{99m} Tc SPECT; and (9) vasodilator stress SPECT imaging has a significantly higher sensitivity for CAD detection than does vasodilator stress echocardiography, whereas dobutamine stress echocardiography is associated with a significantly higher sensitivity and specificity for CAD detection than is vasodilator echocardiography.

LIMITATIONS OF STRESS PERFUSION IMAGING.

When compared with stress echocardiography, the limitations of stress SPECT imaging are (1) longer imaging protocols, which may take many hours; (2) greater equipment expense and the necessity of injecting radiopharmaceuticals with exposure to radiation; (3) less than desirable specificity in many laboratories because of failure to distinguish attenuation artifacts from scarring; (4) inability to visualize the heart in a real-time approach; (5) lower spatial resolution than seen with echocardiography; and (6) higher cost to patients.

COMPARATIVE STUDIES OF STRESS ECHOCARDIOGRAPHY VERSUS PERFUSION IMAGING

In seven comparative studies,[69] the overall sensitivity of myocardial perfusion imaging was 80 percent versus 74 percent for stress echocardiography. In contrast, the specificity for stress echocardiography was higher than that of myocardial perfusion imaging (88 vs. 78 percent). When single-vessel disease detection was analyzed separately, the sensitivity of myocardial perfusion imaging was 76 percent as compared with 67 percent for stress echocardiography. Another review of the literature by O'Keefe and colleagues that involved 11 studies and 808 patients reported an overall sensitivity and specificity for stress echocardiography of 78 and 86 percent, respectively, as compared with 83 and 77 percent for myocardial perfusion imaging.[70] Thus, sensitivity is lower and specificity higher for stress echocardiography.

Fleischmann and associates reviewed 44 articles to compare the diagnostic performance of exercise echocardiography and exercise SPECT imaging for CAD detection.[71] These authors concluded that when exercise echocardiography was compared with exercise SPECT via a receiver operating characteristic model, exercise echocardiography yielded significantly better discriminatory power when adjusted for age, publication year, and a setting including known CAD than did SPECT studies. This review did not include some of the more recent studies using gated ^{99m} Tc SPECT in which the specificity for detection of CAD is higher than the specificity with ^{201} Tl.[13] Also, the posttest referral bias may have been greater in the nuclear studies examined. Both exercise echocardiography and exercise SPECT performed significantly better than exercise testing alone.

Few studies have compared multiple diagnostic techniques for CAD detection in the same patient population. In one study, 60 patients being evaluated for the first time for chest pain underwent exercise stress testing, dipyridamole and dobutamine stress echocardiography, and dipyridamole and dobutamine ^{99m} Tc-sestamibi imaging.[72] With greater than 70 percent coronary stenosis used as the criteria for CAD, the sensitivity was 58 percent for exercise ECG testing, 55 percent for dipyridamole echocardiography, 61 percent for dobutamine echocardiography, 97 percent for dipyridamole ^{99m} Tc-sestamibi, and 91 percent for dobutamine ^{99m} Tc-sestamibi. The specificities for these tests were 67, 96, 96, 89, and 81 percent, respectively. All tests yielded higher sensitivity values for multivessel disease than for single-vessel disease. Although dobutamine echocardiography had a lower sensitivity than reported by other groups, this result agrees with the observation in another study that approximately 25 percent of patients manifested dobutamine-induced perfusion abnormalities without

reversible wall motion abnormalities on dobutamine echocardiography.[73]

MAGNETIC RESONANCE CORONARY ANGIOGRAPHY.

This technique is under development and can now depict the major coronary arteries.[74] [75] [76] [77] Obstacles to its clinical use include correction for cardiac and respiratory motion, need for millimeter spatial resolution, and suppression of signal from adjacent epicardial fat and myocardium.[77] Avoiding the need for breath-holding with real-time tracking of diaphragmatic motion would be advantageous. Three-dimensional navigator-gated (to compensate for respiratory motion in the foot-to-head direction) and prospectively corrected free-breathing coronary MR angiography can provide more favorable signal-to-noise ratios but is limited by poor contrast between coronary blood and myocardium. Botnar and colleagues overcame this problem by combining three-dimensional MR angiography with a T2 preparatory prepulse for myocardial suppression and a shorter acquisition window[77] (Fig. 13-4). (Figure Not Available) This maneuver improved the contrast-to-noise ratio by 123 percent and yielded better coronary edge definition, thereby permitting good agreement between x-ray angiography and MR coronary angiography regarding vessel anatomy. The proximal left anterior descending and left circumflex coronary arteries were visualized on reconstructed images.

MRI offers the advantage of potentially examining the atheromatous lesion as well as the lumen.[77A] However, traditional selective x-ray coronary angiography currently offers higher resolution (0.1 mm).

New approaches introduced into the cardiac catheterization laboratory that provide additional anatomical and functional information for assessing coronary stenoses include quantitative angiography, intravascular ultrasound, coronary flow reserve measurements with a Doppler-tipped wire, and measurement of stenosis gradients with a pressure wire (see Chaps. 12 and 34) .

ASSESSMENT OF PROGNOSIS OF PATIENTS EVALUATED FOR CORONARY ARTERY DISEASE (see also Chap. 37)

One of the chief applications of noninvasive stress testing in patients with suspected or known CAD is the identification of patients at either high or low risk for future ischemic cardiac events.[5] [28] [37] Prognostication using noninvasive stress ECG testing or stress imaging technology is based on the rationale that physiological alterations under stress conditions predict events better than does knowledge of coronary artery anatomy. Accurate risk stratification contributes

Figure 13-4 (Figure Not Available) Reconstructed magnetic resonance angiographic images that were reformatted for length quantification. The paths of the left anterior descending (LAD) and the left circumflex (LCX) coronary arteries are visualized. The left main (LM) coronary artery is also identified.

(From Botnar RM, Stuber M, Danias PG, et al: Improved coronary artery definition with T2-weighted, free-breathing, three-dimensional coronary MRA. Circulation 99:3139, 1999. By permission of the American Heart Association, Inc.)

importantly to clinical decision-making. For example, patients who are identified as being at low risk for future cardiac events on the basis of noninvasive test variables can be spared unnecessary or premature referral for invasive strategies unless symptoms are not adequately alleviated by antiischemic drugs. Conversely, patients with high-risk ECG stress test and/or imaging variables may benefit from early referral for invasive strategies, including revascularization, even if symptoms are mild.

Treadmill ECG Stress Testing for Evaluation of Prognosis (see also Chap. 6)

Treadmill exercise ECG stress testing alone without the addition of an imaging procedure is useful for differentiating low- and high-risk patients with chest pain (see also Chap. 6) . The demonstration of 1.0 mm or more of horizontal or downsloping ST segment depression at low exercise heart rates or workloads is a significant predictor of an adverse outcome when using exercise ECG testing for prognostication. Perhaps the most powerful predictive variable on treadmill testing for identifying high-risk patients is functional capacity reflected by workload achieved.[78] [79] Patients who failed to achieve at least 6 metabolic equivalents (METs) of estimated work during symptom-limited exercise had a significantly higher mortality rate over the next 2.5 years than did patients who exceeded 6 METs of work[78] (Fig. 13-5) . Similarly, chronotropic incompetence, identified as an attenuated heart rate response to exercise, predicts increased mortality.[80] [81] In the latter study, chronotropic incompetence independently predicted all-cause mortality, even after considering ^{201} Tl perfusion defects. Failure to reach 85 percent of the age-predicted maximum heart rate was associated with an increased risk of death (adjusted relative risk, 1.85). Poor exercise tolerance can be observed in patients with depressed resting LV function with or without superimposed transient exercise-induced ischemia.

A treadmill score has been proposed for better separating high- and low-risk patients undergoing ECG stress testing. Perhaps the most popular of these scores, derived by the Duke University group, relies on the duration of exercise, the maximal ST segment deviation, and a treadmill angina index.[82] Data from the literature suggest that the extent of inducible hypoperfusion on poststress SPECT perfusion images provides superior stratification of patients with stable chest pain attributed to known or suspected CAD into low- and high-risk groups than does the Duke treadmill score.[83] [84] [85] [86] In a recent follow-up study from the Duke group, patients with a low-risk Duke treadmill score who were treated medically had a 3.1 percent 5-year mortality rate. Those deemed at high risk by the Duke treadmill score criteria had a 35 percent 5-year mortality rate. The low-risk group, which represented 36 percent of the cohort, had a 40 percent prevalence of any CAD and a 9 percent prevalence of severe CAD determined angiographically. The high-risk group, which represented only 9 percent of

Figure 13-5 Cumulative mortality rates for patients who failed to achieve at least 6 metabolic equivalents (METs) of estimated work during symptom-limited exercise are compared with those of patients who

exceeded 6 METs of work on stress testing. (From Snader CE, Marwick TH, Pashkow FJ, et al: Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: Report of 3,400 patients from a single center. J Am Coll Cardiol 30:641, 1997. Reprinted with permission from the American College of Cardiology.)

the entire cohort, had a 74 percent incidence of severe CAD, and all patients had at least one or more coronary stenoses.

The practical problem with the Duke treadmill score is that a substantial proportion of patients are classified as having intermediate or moderate risk after exercise ECG treadmill testing. In a study by Shaw and associates, 55 percent of the patients were classified as having moderate risk by the Duke treadmill score, and they had a 9.5 percent 5-year mortality rate and a 31 percent prevalence of severe CAD.[83] Perfusion imaging variables are useful in further risk-stratifying patients with intermediate-risk Duke treadmill scores.[84] A substantial number of these patients can be deemed to be at low risk if they show normal perfusion or only a mild postexercise defect.

LIMITATIONS.

Exercise ECG stress tests have other important limitations in assessing prognosis. First, a strongly positive exercise ECG, which is defined as an early or low ischemic threshold, significant horizontal ST segment depression, and a prolonged ST depression recovery time, does not necessarily signify more severe CAD by either angiographic or scintigraphic criteria.[87] The extent of exercise ST segment depression poorly predicts the extent of CAD, and the maximum ST segment depression achieved at peak exercise correlated poorly with the extent of stress-induced hypoperfusion by scintigraphy. Also, a considerable portion of patients have an uninterpretable exercise ECG response.[88] Several studies have established substantial incremental prognostic value of exercise SPECT in patients with nondiagnostic or positive ECG stress tests.[88] [89] In these studies, imaging variables provided substantial supplementary prognostic information over ECG stress test variables. Patients with normal scans have an excellent outcome even if the ECG stress test is nondiagnostic or abnormal.

Exercise ECG testing alone has particular utility in the risk assessment of patients with a normal resting ECG who have nonanginal or very atypical chest pain. If these patients achieve an adequate exercise heart rate or workload without significant ST segment depression, the prognosis during follow-up is excellent. However, for improved diagnostic and prognostic value, an imaging technique should be performed in conjunction with treadmill testing in patients with an intermediate or a high pretest likelihood of CAD on the basis of age, gender, and type of chest pain.

Stress Myocardial Perfusion Imaging for Evaluation of Prognosis (see also Chap. 9)

The prognostic value of exercise and pharmacological stress myocardial perfusion imaging has been established in thousands of patients evaluated in multiple clinical studies.[90] [91] The major prognostic variables on stress perfusion images predictive of future cardiac events are (1) a large defect size (>20 percent of the left ventricle); (2) multiple perfusion abnormalities in two or more coronary supply regions suggestive of multivessel CAD; (3) defect reversibility reflective of inducible ischemia in multiple myocardial scan segments, even in the distribution of one major coronary artery; (4) a large number of nonreversible defects; (5) transient LV cavity dilation from stress to rest images; (6) increased lung ^{201} Tl uptake best assessed by quantitating the lung/heart ^{201} Tl ratio; and (7) a resting LV ejection fraction of less than 40 percent measured on gated SPECT.[40] [90] [91] [92] Perhaps one of the most valuable features of exercise or pharmacological stress perfusion imaging with either ^{201} Tl or ^{99m} Tc-sestamibi is the ability to predict a low mortality and subsequent myocardial infarction rate in patients with a totally normal scan. Patients with normal tracer uptake at peak stress have less than a 1 percent combined annual mortality and nonfatal infarction rate and are thus often spared unnecessary invasive evaluation for assessment of their symptoms.[84] [88] [93] [94] [95] With respect to experience with exercise ^{99m} Tc-sestamibi perfusion imaging, Iskander and Iskandrian analyzed 14 prognostic studies consisting of more than 12,000 patients with respect to the prognostic value of normal and abnormal SPECT images.[95] A normal ^{99m} Tc-sestamibi study was associated with an average annual hard cardiac event rate of 0.6 percent. Patients with abnormal images had a 12-fold higher event rate at 7.4 percent annually.

INCREMENTAL VALUE OF PERFUSION IMAGING OVER ECG STRESS TESTING.

Numerous studies have shown that additional prognostic information is obtained when variables from stress myocardial perfusion imaging are added to information obtained from the clinical and ECG stress test variables.[84] [85] [88] [89] [93] [94] [95] Figure 13-6 shows the incremental value of SPECT in patients with a low, intermediate, or high likelihood of CAD after exercise ECG stress testing.[88] Patients with a high postexercise ECG stress test likelihood of CAD and a normal scan had a 0 percent event rate during follow-up. Those with an abnormal scan had a 10.8 percent event rate (death or myocardial infarction). In one study, when the stepwise Cox proportional hazards model and receiver operating characteristic curve analysis were used, nuclear testing added incremental prognostic value after inclusion of the most predictive clinical and exercise ECG stress test variables.[84] In addition, some studies have shown that when clinical, ECG stress test, and scintigraphic variables are known, little incremental prognostic information is gained by the addition of coronary angiographic variables, such as the number of vessels with significant stenoses.

The greater the number of perfusion defects on postexercise SPECT perfusion images, the greater the subsequent cardiac mortality rate with medical therapy.[89] [93] Figure 13-7 shows cardiac event-free survival curves according to the extent of hypoperfused myocardium on ^{201} Tl SPECT imaging in the study of Vanzetto and colleagues.[89] The extent of hypoperfusion could be an important variable in the selection of patients whose initial management approach would be aggressive medical therapy versus revascularization. In an observational retrospective review, Hachamovitch and

associates found a low annual cardiac event rate (0.8 percent per year) in patients with mildly abnormal normal stress perfusion scans receiving medical therapy as

Figure 13-6 Incremental value of exercise ^{99m} Tc-sestamibi myocardial perfusion imaging in patients who had either a low, intermediate, or high postexercise treadmill test likelihood of coronary artery disease (POST-ETT LK CAD). Note that patients with an abnormal scan (solid bars) had a significantly higher cardiac death or nonfatal myocardial infarction rate than did patients who had normal scan (crosshatched bar) results *p<0.05 for all abnormal versus normal scan results. (From Berman DS, Hachamovitch R, Kiat H, et al: Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: A basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 26:639, 1995. Reprinted with permission from the American College of Cardiology.)

Figure 13-7 Cardiac event-free survival over 7 years of follow-up after exercise ^{201} Tl single-photon emission computed tomographic (SPECT) imaging according to the extent of hypoperfused myocardium. Note that patients with three or more abnormal SPECT segments had a significantly worse event-free survival rate than did patients with more mild defects and patients who had a normal perfusion scan. (From Vanzetto G, Ormezzano O, Fagret D, et al: Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients. Study in 1137 patients with 6-year follow-up. Circulation 100:1521, 1999. By permission of the American Heart Association, Inc.)

compared with an annual cardiac death rate of 0.9 percent in patients with mildly abnormal scans who were referred for initial revascularization.[93] In contrast, patients with moderately abnormal or severely abnormal scans had a better outcome with revascularization early after nuclear testing than with medical therapy.

INCREMENTAL VALUE OF FUNCTIONAL VARIABLES OVER SPECT PERFUSION IMAGING ALONE

More recent studies have demonstrated incremental prognostic value of the poststress LV ejection fraction and LV volume determined on gated ^{99m} Tc-sestamibi SPECT over perfusion variables alone. [16] The poststress ejection fraction and end-systolic volume by gated ^{99m} Tc-sestamibi SPECT had incremental prognostic value over prescan and perfusion imaging information in predicting cardiac death. For example, patients with a resting SPECT ejection fraction of 45 percent or greater had mortality rates of less than 1 percent per year despite severe perfusion abnormalities, whereas patients with an ejection

Figure 13-8 Incremental prognostic value of the left ventricular ejection fraction on gated ^{99m} Tc single-photon emission computed tomographic imaging in relation to the myocardial perfusion findings. The ejection fraction calculated on the poststress images had incremental value over perfusion imaging

information for predicting cardiac death. Patients with an ejection fraction of less than 45 percent (crosshatched bars) had a significantly higher annual mortality rate than did patients with an ejection fraction of 45 percent or greater. (Adapted from Sharir T, Germano G, Kavanagh PB, et al: Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 100:1035, 1999. By permission of the American Heart Association, Inc.)

fraction of less than 45 percent had high mortality rates, even with only mild to moderate perfusion abnormalities (9.2 percent per year) (Fig. 13-8) . Good exercise tolerance on treadmill testing is associated with a favorable prognosis. Nevertheless, myocardial perfusion imaging provides additional prognostic information for subsequent cardiac death, nonfatal infarction, or revascularization in patients who reach stage IV of the Bruce protocol.[96]

COST-EFFECTIVENESS OF SPECT IMAGING.

The use of myocardial perfusion imaging as an initial evaluation in patients with stable chest pain is highly cost-effective when compared with an initial invasive strategy. A large observational study consisting of 11,372 consecutive stable angina patients referred for stress myocardial perfusion SPECT imaging or direct catheterization revealed that costs were higher for the initial invasive strategy in clinical subsets with a low, intermediate, or high pretest likelihood of disease.[97] Diagnostic and follow-up costs of care were 30 to 41 percent higher for patients undergoing direct cardiac catheterization without any reduction in mortality or infarction. The diagnostic costs were $1320, $1275, and $1229 greater for low-, intermediate-, and high-risk patients undergoing initial cardiac catheterization than for those having stress perfusion imaging as the initial test for CAD detection. The cardiac death rate and nonfatal infarction rate in the 5826 patients undergoing initial stress perfusion imaging for assessment of stable angina were both 2.8 percent as compared with 3.3 and 3.0 percent, respectively, for the 5423 patients who were referred directly for cardiac catheterization as the initial diagnostic strategy. The cost of screening women with myocardial perfusion imaging was shown in a separate analysis to be considerably lower than the cost of direct coronary angiography in a similar type of analysis[98] (Fig. 13-9) . Thus, stress myocardial perfusion imaging undertaken as the initial step in diagnosis and assessment of prognosis yields comparable outcomes at a lower cost than does direct referral for cardiac catheterization. This noninvasive strategy is "ischemia driven" and should be applicable even to patients with angiographic disease and normal scans, since this group also has an excellent prognosis.[99]

CONCLUSIONS.

Thus, taken together, data reported from the literature demonstrate that patients with normal myocardial perfusion scans have an excellent prognosis whereas patients with abnormal scans have an increased rate of cardiac death and nonfatal infarction during follow-up. The greater the extent of stress-induced hypoperfusion and reversibility, the greater the probability of an event. It is apparent from multiple studies cited above that myocardial perfusion imaging variables provide supplementary prognostic information to exercise ECG testing alone, particularly in patients who have an intermediate risk of an adverse outcome estimated by clinical variables and exercise stress testing. Stress

perfusion imaging variables appear to be equal or even superior to mere knowledge of coronary anatomical variables for assessing prognosis because the extent of hypoperfusion during stress and the magnitude and extent of stress-induced ischemia better predict subsequent cardiac death than does demonstration of the presence of one-, two-, or three-vessel disease alone. In fact, patients with three-vessel disease on angiography can be further risk-stratified by myocardial perfusion imaging performed

Figure 13-9 Composite cost of diagnostic screening and follow-up cost in patients referred directly to cardiac catheterization as the initial diagnostic strategy for evaluation of chest pain in comparison to the cost of undergoing stress perfusion imaging as the initial test for coronary artery disease detection in women. Note that for patients with either a low, intermediate, or high pretest likelihood of coronary artery disease, total cost was significantly greater in patients referred directly to cardiac catheterization as the initial test for chest pain evaluation. The cardiac death or subsequent myocardial infarction rate was comparable in the two groups. (From Shaw LJ, Heller GV, Travin MI, et al: Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis [END] study group. J Nucl Cardiol 6:559, 1999.)

after catheterization into low-, intermediate-, and high-risk groups.

Echocardiographic Assessment of Prognosis

Evaluation of LV function on the resting echocardiogram obtained before commencing the stress portion of the protocol offers considerable prognostic information by itself. A resting wall motion abnormality has proved to be most useful in predicting future cardiac events in patients who undergo dobutamine stress echocardiography.[100] The presence of a resting wall motion abnormality in combination with a positive dobutamine echocardiogram resulted in a 34 percent incidence of any cardiac event versus an incidence of 18 percent when the stress echocardiogram was negative. After it was known that resting wall motion was normal, the second best predictor of a cardiac event was the patient's age.

Reports of the relative ability of stress echocardiography to predict the extent of CAD vary widely.[51] [101] For the most part, the sensitivity of stress echocardiography for identifying patients with severe CAD is good.

Heupler and coauthors reported that detection of exercise-induced wall motion abnormalities independently predicted cardiac events in 508 women monitored for 41 ± 10 months after exercise echocardiography.[102] Evidence of ischemia by echocardiography foretold future cardiac events better than did exercise capacity or inducible ST segment depression. The prognostic data provided by the exercise echocardiogram added to that provided by clinical and exercise ECG variables in patients with both undiagnosed and known CAD. In a study from the same institution consisting of both men and women, the presence of ischemia on exercise

echocardiography predicted future cardiac events well. In the multivariate model in that study, the presence of ischemia during exercise echocardiography was the strongest independent predictor of cardiac death, myocardial infarction, or unstable angina.[103]

COMPARISON WITH PERFUSION IMAGING

Few studies in the literature have compared exercise echocardiography with exercise perfusion imaging for long-term prediction of prognosis. Olmos and colleagues compared clinical, exercise, echocardiographic, and SPECT ^{201} Tl variables in 248 patients who underwent both stress imaging modalities simultaneously.[104] The clinical models characterized by exercise echocardiography with exercise ECG testing and ECG ^{201} Tl SPECT with exercise ECG were comparable in the prediction of cardiac events. For the exercise echocardiography model, the exercise wall motion score index and induction of ischemia were the strongest predictors of events, with odds ratios of 2.63 per unit increment. For the model with exercise ^{201} Tl SPECT, the strongest predictor was the extent of the ischemic perfusion defect, with an odds ratio of 4.93. Of interest, for the prediction of ischemic events and/or cardiac death, echocardiographic and ^{201} Tl variables were the only predictive variables. Figure 13-10 shows the event-free survival for cardiac death with the use of quantitative exercise ^{201} Tl and exercise echocardiography in this study.

One reason for the failure to predict some events by stress echocardiography is the inability to attain an adequate heart rate response.[105] This limitation agrees with the finding of compromised sensitivity of stress echocardiography for detecting ischemia in the setting of inadequate heart rate responses.[48] Therefore, patients who are deemed unable to exercise adequately should undergo dobutamine stress echocardiography for both diagnosis and prognosis indications.

With respect to the comparison of dobutamine echocardiography and simultaneously performed ^{99m} Tc-sestamibi SPECT imaging, Geleijnse and coauthors reported that any abnormality or ischemia on echocardiography or scintigraphy was associated with cardiac events.[106] Dobutamine-atropine echocardiography and ^{99m} Tc-sestamibi imaging provided comparable prognostic information. With respect to the negative predictive value of a normal study, patients with normal studies had equally very low event rates (0.4 percent by echocardiography and 0.5 percent by ^{99m} Tc-sestamibi).

Although earlier studies[91] showed a higher event rate for patients with a normal stress echocardiogram than for those with a normal stress SPECT study, later studies have shown almost comparable, very low event rates for patients with a normal stress echocardiogram and normal stress SPECT.[107] [108]

In the study by Poldermans and colleagues of 1737 patients with known or suspected CAD who underwent dobutamine-atropine stress echocardiography, a normal echocardiographic study was associated with an annual event rate of cardiac death or infarction of 1.3 percent over a 5-year period.[109] In that study, the rate of cardiac death or myocardial infarction in patients with new wall motion abnormalities or extensive resting wall motion abnormalities increased 3.6- and 2.5-fold, respectively. A negative

echocardiographic response to pharmacological stress in women was associated with a less than 1 percent hard cardiac event rate over 3 years of follow-up.[110] Echocardiographic evidence of ischemia was found as the only independent predictor of hard cardiac events (odds ratio, 27.5) in this study.

Few studies have directly compared vasodilator stress and inotropic stress with echocardiography for risk stratification. High-dose dipyridamole echocardiography (up to 0.84 mg/kg over a 10-minute period) with atropine (up to 1 mg over a 4-minute period) and dobutamine-atropine echocardiography yielded comparable risk stratification on the basis of the presence, severity, and extent of induced wall motion abnormalities in a prospective, multicenter study.[111] By stepwise analysis, the wall motion score index at the peak dipyridamole dose was the most important predictor (relative risk, 7.4). Most laboratories currently prefer dobutamine stress for detection of CAD and prognostication.

PREDICTION OF PERIOPERATIVE ISCHEMIC EVENTS.

A meta-analysis of 15 studies demonstrated the prognostic value of dipyridamole ^{201} Tl imaging and dobutamine echocardiography for predicting perioperative ischemic events in patients undergoing risk stratification before vascular surgery[111A] (see also Chap. 61) . For dipyridamole ^{201} Tl studies, the cardiac death rate or myocardial infarction rate was 1, 7, and 9 percent for normal results, fixed defects, and reversible defects, respectively. For patients with a dobutamine-induced new or worsening wall motion response, 23.1 percent had a perioperative ischemic event as compared with 0.37 percent of patients with a normal stress echocardiographic response. Summary odds ratios were greater for dobutamine echocardiography than for dipyridamole ^{201} Tl, but the 95 percent confidence intervals were wider with echocardiography because of a smaller sample size.

Conclusions: Stress Perfusion Imaging Versus Stress Echocardiography

In summary, both stress perfusion imaging and stress echocardiography provide prognostic information supplemental to that of clinical and exercise ECG stress test variables.

Figure 13-10 Event-free survival for ischemic events and cardiac death with the use of quantitative parameters of exercise ^{201} Tl and echocardiography. Note that for both exercise ^{201} Tl single-photon emission computed tomographic imaging and exercise echocardiography (performed in the same patients), those with a low-risk finding had a significantly better outcome than did patients demonstrating high-risk imaging variables. ExWMS=exercise wall motion score; PDS=perfusion defect size. (From Olmos LI, Dakik H, Gordon R, et al: Long-term prognostic value of exercise echocardiography compared with exercise ^{201} Tl, ECG, and clinical variables in patients evaluated for coronary artery disease.

Circulation 98:2679, 1998. By permission of the American Heart Association, Inc.)

Both techniques have excellent negative predictive value for identifying low-risk patients. Such patients with either a normal perfusion study at peak stress or normal regional function have an excellent outcome with a cardiac death or infarction rate of less than 1 percent per year. The negative predictive value of a normal study is perhaps slightly better with perfusion imaging than echocardiography because of its slightly higher sensitivity for identifying mild CAD. Patients with high-risk stress imaging findings on either perfusion imaging or echocardiography have a worse outcome with medical therapy, and the greater the degree of regional abnormalities (either perfusion or function), the higher the event rate. Either technique is superior to exercise ECG test variables alone. An abnormal workload and a suboptimum heart rate response are excellent prognostic variables derived from the ECG stress test for identifying high-risk patients. Ischemia occurring at low exercise heart rates and workloads should prompt evaluation with coronary angiography. Pharmacological stress imaging provides comparable prognostic information to exercise imaging for both nuclear cardiology and echocardiographic techniques, and either can be used for preoperative risk stratification in intermediate- or high-risk patients scheduled for vascular surgical procedures. A limitation of both stress perfusion imaging and stress echocardiography is a low positive predictive value with regard to future ischemic events. That is, the percentage of patients who die or suffer a nonfatal infarction with abnormal imaging studies is fairly low. The negative predictive value of normal studies is much better and exceeds 95 percent.

Magnetic Resonance Perfusion or Function Imaging (see also Chap. 10)

MR perfusion imaging performed with gadolinium-based contrast agents and a stressor such as dipyridamole is an alternative approach to detecting CAD. The technique is still investigational, but early results appear promising. Dipyridamole MR perfusion imaging and ^{99m} Tc-sestamibi SPECT were shown to have comparable sensitivity for detecting single-vessel disease.[112] Dipyridamole stress MRI had 85 percent agreement with ^{201} Tl scintigraphy in detection of CAD and a correlation of 0.86 in sizing perfusion defects.[113] Dobutamine MRI for the detection of induced wall motion abnormalities is an alternative stress MRI approach for CAD detection. Early studies show sensitivities comparable to those of SPECT imaging.[114] [115] [116] [117]

Stress MRI with contrast may ultimately be very clinically useful in that the technique provides high spatial resolution and has the capability of imaging in any desired plane without ionizing radiation. Images can be acquired with reproducible quality that is operator independent. Since no imaging window is required, images can be obtained in virtually all patients, including those with emphysema. The endocardial border can easily be defined and separated from the cavity blood volume.

A major competing technology will be contrast echocardiography using microbubbles with dipyridamole or adenosine stress or dobutamine echocardiography. Nagel and associates reported that high-dose dobutamine stress MRI using short breath-holds and a gradient-echo technique in 208 consecutive patients had higher sensitivity (86.2 vs. 74.3 percent) and specificity (85.7 vs. 69.8 percent) than did dobutamine stress

echocardiography. [117] Dobutamine stress examinations were feasible in 89.4 percent of patients with both echocardiography and MRI. Interestingly, insufficient image quality was the major reason for exclusion from dobutamine stress echocardiography, whereas claustrophobia was the major reason for exclusion from stress MRI. Other disadvantages of stress MRI techniques are an inability to image patients with pacemakers and implanted cardioverter-defibrillators and the need for prolonged breath-holding.

Table 13-3 summarizes the major strengths and limitations of the various techniques used for detection of CAD and assessment of prognosis.

TABLE 13-3 -- MAJOR STRENGTHS AND LIMITATIONS OF VARIOUS TECHNIQUES FOR DETECTING CORONARY ARTERY DISEASE AND ASSESSING PROGNOSIS

EXERCISE ECG

Strengths: Low cost; short duration; functional status evaluated; high sensitivity in 3-vessel or left main CAD; provides useful prognostic information (e.g., ischemia at low workload)

Limitations: Suboptimal sensitivity; low detection rate of 1-vessel disease; nondiagnostic with abnormal baseline ECG; poor specificity in certain patient populations (e.g., premenopausal women); need to achieve 85% of maximum heart rate for maximizing accuracy

EXERCISE/PHARMACOLOGICAL SPECT PERFUSION IMAGING

Strengths: Simultaneous evaluation of perfusion and function with gated SPECT; higher sensitivity and specificity than exercise ECG; high specificity with ^{99m} Tc-labeled agents; studies can be performed in almost all patients; significant additional prognostic value; comparable accuracy with pharmacological stress; viability and ischemia simultaneously assessed; quantitative image analysis

Limitations: Suboptimal specificity with ^{201} Tl; long procedure time with ^{99m} Tc-labeled agents; no routine correction for attenuation and scatter; higher cost than exercise ECG; radiation exposure; poor-quality images in obese patients

EXERCISE/PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY

Strengths: Higher sensitivity and specificity than exercise ECG; additional prognostic value; comparable value with dobutamine stress; time to complete examination short; identification of coexisting structural cardiac abnormalities (e.g., valvular disease); simultaneous evaluation of perfusion with contrast agents; relatively lower cost than other techniques; no radiation

Limitations: Decreased sensitivity for detection of 1-vessel disease or mild stenosis with postexercise imaging; inability to image all of the left ventricle in some patients; highly operator dependent for image analysis; no quantitative image analysis; poor acoustic window in some patients (e.g., chronic obstruction lung disease); infarct zone ischemia less well detected

CAD=coronary artery disease; ECG=electrocardiogram; SPECT=single-photon emission computed tomography.

NONINVASIVE ASSESSMENT OF MYOCARDIAL VIABILITY (see also Chap. 37)

Regional and global LV dysfunction leading to depressed LV ejection fractions in patients with CAD can result from (1) myocardial necrosis or scarring, (2) postischemic stunning, or (3) myocardial hibernation. Hibernation is defined as the state in which myocytes are chronically hypoperfused but in which flow is sufficient to sustain structural integrity. Hibernating myocardium, by definition, demonstrates improved systolic function with improved resting perfusion after coronary revascularization.

An accurate noninvasive determination of myocardial viability that is capable of distinguishing irreversible myocardial cellular injury from hibernation is critically important for the clinical decision-making process. It allows for improved selection of patients with CAD and resting LV dysfunction who will benefit most from revascularization strategies. It plays a major role in the triage of patients with severe ischemic cardiomyopathy to transplantation versus revascularization. Patients with substantial zones of myocardial viability in asynergic myocardium reflective of hibernation demonstrate better function and overall improved outcomes after revascularization than do patients with LV dysfunction predominantly caused by myocardial scarring.

Techniques Used for Myocardial Viability Assessment

Thallium-201 Imaging (see also Chap. 9)

^{201}Tl rest and delayed redistribution imaging is the most commonly used radionuclide imaging modality for the assessment of myocardial viability (see also Chap. 9) . It is used for this purpose because the initial uptake of ^{201}Tl is related to both blood flow and myocardial membrane integrity. Myocardial stunning or hibernation does not result in impaired ^{201}Tl extraction as long as the sarcolemmal membrane transport system for monovalent cations does not have irreversible ischemic damage.[118] [119] Several groups have shown that approximately 60 to 70 percent of asynergic myocardial segments showing greater than 50 percent ^{201}Tl uptake on resting ^{201}Tl scintigraphy will show improved systolic function after revascularization.[120] The most likely reason for the lack of enhanced systolic function after revascularization in zones judged to be viable before revascularization is the presence of subendocardial scar. That is, certain segments showing 20 to 30 percent subendocardial scarring may not demonstrate improved systolic thickening after revascularization, even if greater than 50 percent ^{201}Tl uptake

is seen in those regions. However, such patients may benefit from revascularization by reducing stress-induced ischemic dysfunction or reinfarction.

^{99m} Technetium-Labeled Agents (see also Chap. 9)

^{99m} Tc-labeled perfusion agents do not show significant redistribution over time after being injected at rest intravenously. However, several studies have shown comparable sensitivity and specificity for viability detection between these agents and ^{201} Tl.[120a--c] It is thought that this similarity is due to high extraction of ^{99m} Tc-sestamibi or ^{99m} Tc-tetrofosmin in regions of low flow. These agents bind to the mitochondrial membrane and can identify stunned or hibernating myocardium as long as the mitochondria are not irreversibly damaged. The advantage of ^{99m} Tc-labeled agents is less attenuation or less scatter than noted with ^{201} Tl, which produces higher quality images. In addition, gated SPECT imaging can be undertaken with ^{99m} Tc-sestamibi or ^{99m} Tc-tetrofosmin to allow for simultaneous assessment of regional systolic thickening in myocardial perfusion. Demonstration of intact thickening at rest or when images are acquired during dobutamine infusion indicates viability.

Positron-Emission Tomography (see also Chap. 9)

PET is considered by many to be the standard of reference for the noninvasive detection of myocardial viability by nuclear cardiology techniques because PET imaging can simultaneously assess myocardial perfusion and metabolism.[120D] Nitrogen-13-labeled ammonia is the most often used perfusion tracer, and fluorine-18-labeled fluorodeoxyglucose (FDG) is the metabolic tracer for assessing glucose utilization. Patients with a mismatch pattern between perfusion and FDG uptake will show improved regional and global LV function after revascularization, whereas patients demonstrating a concordant reduction in perfusion and FDG uptake (a "match" pattern) have predominantly myocardial scar as the cause of asynergy, and segments showing this pattern have a significantly lower chance of improved function after revascularization. Preserved myocardial oxygen consumption estimated by carbon 11 (^{11}C)-acetate PET imaging is found in myocardial regions that are hibernating.[11] ^{11}C-Acetate PET imaging is an alternative to FDG-PET imaging for detection of viability.

Dobutamine Echocardiography (see also Chap. 7)

Low-dose dobutamine echocardiography is another useful modality for assessment of viability. The rationale for inotropic

stress is the identification of contractile reserve in zones of severe myocardial asynergy. This technique furnishes an alternative noninvasive approach to resting SPECT perfusion imaging or PET imaging. Enhanced systolic thickening with low-dose dobutamine predicts functional recovery well. A biphasic response in which systolic

thickening increases at low doses and then deteriorates at high doses indicates both viability and ischemia. It is the most sensitive criterion for improved function after revascularization. End-diastolic wall thickness is also an important marker of myocardial viability in patients with suspected hibernation and has been shown to predict recovery of function in a manner similar to that of ^{201} Tl scintigraphy after revascularization.[120E]

STRENGTHS AND WEAKNESSES OF VARIOUS MODALITIES FOR ASSESSING VIABILITY

When compared with ^{201} Tl or ^{99m} Tc-sestamibi, dobutamine echocardiography is more specific but less sensitive. The positive predictive value of inotropic reserve for predicting improved systolic function with dobutamine echocardiography after revascularization is higher than the positive predictive value for predicting improvement in regional function with ^{201} Tl scintigraphy when greater than 50 percent ^{201} Tl uptake is used as the criterion for myocardial viability. Studies that have compared ^{201} Tl SPECT imaging and dobutamine echocardiography[121] [122] [123] [124] [125] [126] have consistently demonstrated that the number of asynergic segments exhibiting preserved ^{201} Tl uptake or showing rest ^{201} Tl redistribution significantly exceed the number of segments with residual capacity for systolic thickening as determined by dobutamine infusion. Similarly, studies that have compared PET imaging using FDG with dobutamine echocardiography[127] [128] [129] [130] [131] have shown results similar to those comparing^{201} Tl SPECT and dobutamine echocardiography in that the number of severely asynergic segments with preserved FDG uptake significantly exceeds these segments with residual inotropic reserve.

The sensitivity of dobutamine echocardiography and the negative predictive value in regard to failure to improve after revascularization are lower than the sensitivity and negative predictive value of SPECT imaging because certain regions that are severely underperfused and are akinetic at rest and supplied by severely stenotic vessels but are viable may not demonstrate enhanced systolic thickening, even with the lowest doses of dobutamine. Such segments have no flow reserve with the increased oxygen demand because of inotropic stress and therefore become ischemic immediately.

The degree of residual stenosis may significantly influence the response of ischemic myocardium to dobutamine. To have improvement in systolic wall thickening with inotropic stress, myocardial oxygen delivery must increase in proportion to oxygen demand, which at any given dose of dobutamine is influenced by the amount of viable myocardium. In the absence of stenosis, regional blood flow will increase in proportion to oxygen demand, but if a limiting stenosis is present, ischemia will occur with even very low doses of dobutamine despite the presence of significant viable myocardium.

Combined Modalities for Viability Assessment

If techniques are combined, regions with preserved FDG uptake and hypoperfusion by ^{13} N-ammonia, and with inotropic reserve by dobutamine echocardiography, have limited myocardial scarring or irreversible myocardial injury and a substantial chance of improved regional and global function after revascularization. When metabolic imaging and dobutamine echocardiographic results agree regarding the lack of substantial

myocardial viability, extensive myocardial scarring most likely exists, and revascularization will seldom yield any functional benefit or even survival over medical therapy. In one study in which both PET imaging and dobutamine echocardiography were performed in patients with CAD and severe LV dysfunction, the overall rates of accuracy of PET and dobutamine echocardiography for predicting postoperative improvement in function were similar.[131A] However, the strongest predictor of improvement was a preoperative increase of LV ejection fraction with low-dose dobutamine infusion. When SPECT or PET imaging indicates the presence of viable myocardium but dobutamine echocardiography shows an absence of systolic thickening, the most likely scenario is severe resting hypoperfusion with exhausted flow reserve, subendocardial fibrosis, or a combination of these factors. Recovery of resting function after revascularization would be quite unpredictable. This viability pattern has been reported to occur in about 20 to 45 percent of segments that show viability by PET imaging and contributes to the lower sensitivity and higher specificity of dobutamine echocardiography.[132] Cornel and coauthors reported that although 94 percent of myocardial asynergic segments that were nonviable on ^{201} Tl SPECT did not show contractile reserve by low-dose dobutamine echocardiography, the disagreement between SPECT and dobutamine echocardiography was caused mainly by the absence of contractile reserve in 27 percent of the segments that were viable by ^{201} Tl scintigraphy.[133]

Summary of Approaches to Assessment of Viability

Taken together, all of the techniques for the assessment of myocardial viability described have high accuracy in the noninvasive assessment of myocardial viability. All provide value in decision-making that is supplementary to clinical and coronary angiographic information alone with respect to the worth of coronary revascularization in patients with ischemic cardiomyopathy. All the techniques show that the greater the number of viable segments preoperatively, the greater the improvement in ejection fraction and exercise tolerance after revascularization. Pagley and colleagues found that the mortality rate after revascularization over a 5-year follow-up was significantly higher in patients with lesser degrees of preoperative viability as assessed by quantitative ^{201} Tl scintigraphy [134] (Fig. 13-11) . Similarly, using dobutamine echocardiography, Afridi and coworkers found that in patients with CAD and severe LV dysfunction who demonstrated myocardial viability during dobutamine echocardiography, revascularization improved survival when compared with medical therapy and when compared with revascularized patients with poor viability preoperatively.[135] Myocardial contractile reserve significantly predicts survival in patients undergoing revascularization for

Figure 13-11 Survival free of cardiac death or cardiac transplantation relative to the extent of preoperative myocardial viability assessed by resting ^{201} Tl scintigraphy in patients with coronary artery disease and a depressed left ventricular ejection fraction who underwent coronary artery bypass graft surgery. The designation of greater or lesser viability was made on the basis of a quantitative viability index determined by the extent of ^{201} Tl uptake in multiple myocardial segments. Note that patients with lesser viability had significantly worse event-free survival than did patients with greater viability. (Adapted from Pagley PR, Beller GA, Watson DD, et al: Improved outcome after coronary bypass surgery in

patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 96:793, 1997. By permission of the American Heart Association, Inc.)

CAD and LV dysfunction.[136] Survival was greater with revascularization than with medical therapy in patients showing substantial myocardial contractile reserve. Among patients with myocardial contractile reserve in five or more segments, the survival rate was 93 ± 6 percent at 3 years versus 49 ± 15 percent in patients treated medically. Similarly, Bax and colleagues found that in patients with substantial viability on dobutamine stress echocardiography, the LV ejection fraction and New York Heart Association functional class improved after revascularization.[137] A combination of imaging modalities appears to provide even greater accuracy in noninvasive assessment of viability than do the individual technologies.[132]

MAGNETIC RESONANCE IMAGING.

Few studies have examined the value of MRI in the assessment of myocardial viability in patients with chronic CAD and LV dysfunction.[138] [139] [140] Markers of viability on MRI include increased signal intensity, preservation of end-diastolic thickness, systolic wall thickening at rest, and contractile reserve during dobutamine infusion.[24] When end-diastolic wall thickness is 5.5 mm or greater, the probability of viability is high.[138] When PET imaging with FDG was used as the "gold standard," this criterion had a sensitivity of 72 percent and specificity of 89 percent for viability detection. Dobutamine MRI had a sensitivity of 89 percent and specificity of 94 percent for prediction of functional recovery after revascularization.[141] A lower accuracy of 80 percent for dobutamine MRI was reported by Dendale and coauthors.[142] Thus, although a promising alternative to dobutamine echocardiography for viability assessment in chronic ischemic cardiomyopathy, further studies comparing the sensitivity, specificity, and cost-effectiveness of this approach are needed. Myocardial viability can be assessed with MRI and gadolinium contrast enhancement after acute myocardial infarction. Hypoenhancement or diminished signal intensity on delayed contrast-enhanced imaging is a marker of large infarct size and a worse prognosis.[143] [144] Nonviability can also be predicted by using first-pass and delayed MRI in that myocardial regions showing hypoenhancement with contrast injection on both first-pass and delayed imaging predict a lack of functional improvement after myocardial infarction.[145] Regions showing normal signal intensity on first-pass and increased intensity on delayed imaging exhibit significant functional improvement.

Table 13-4 summarizes the strengths and limitations of the various noninvasive techniques for detection of myocardial viability. All have been shown to be clinically useful in identifying which patients with ischemic cardiomyopathy have the greatest chance of enhancement of regional and global LV function, as well as improved survival, after revascularization.

A PERSPECTIVE ON THE FUTURE OF CARDIAC IMAGING

The future appears bright for further progress in technology and clinical application of noninvasive imaging techniques. Advances in instrumentation and the emergence of new imaging agents will permit enhanced diagnostic and prognostic value of the methodologies reviewed in this chapter. With respect to nuclear cardiology, the development of transmission-emission SPECT instrumentation will provide attenuation and scatter correction reconstruction algorithms leading to fewer imaging artifacts and enhanced specificity for CAD detection. Another expected advance in instrumentation will be the capability to image PET tracers with SPECT cameras that have special collimators or specially designed coincidence detecting software. New radiopharmaceuticals on the horizon will allow molecular imaging of gene expression by using reporter gene/reporter probe systems to image the expression of endogenous or exogenous genes (see also Chap. 9) . Micro-PET and micro-SPECT systems are being designed for imaging small animals such as mice. Imaging of the various stages of the atherosclerotic

TABLE 13-4 -- STRENGTHS AND LIMITATIONS OF NONINVASIVE TECHNIQUES FOR ASSESSMENT OF MYOCARDIAL VIABILITY

SPECT IMAGING
Strengths: High sensitivity for predicting improved function after revascularization; uses quantitative objective criteria (e.g., 60% segmental uptake); FDG imaging with special collimator; LVEF quantitated on ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin imaging; predictive of clinical outcomes in a large number of studies
Limitations: Reduced spatial resolution and sensitivity in comparison to PET; less quantitative than PET; areas of attenuation (e.g., inferior wall on ^{99m}Tc-sestamibi scans) misconstrued as nonviability; cannot differentiate endocardial from epicardial viability; no absolute measurement of blood flow; lower specificity than dobutamine echocardiography for predicting improved function after revascularization
PET IMAGING
Strengths: Simultaneous assessment of perfusion and metabolism; more sensitive than other techniques; good specificity; no attenuation problems; absolute blood flow can be measured; predictive of outcomes
Limitations: Lower specificity than dobutamine echocardiography or MRI; cannot separate endocardial from epicardial viability; high cost and highly sophisticated technology; limited availability
DOBUTAMINE ECHOCARDIOGRAPHY
Strengths: Higher specificity than nuclear techniques; viability assessed at low doses and ischemia at higher doses; evaluation of mitral regurgitation on baseline echocardiography; good spatial resolution; predictive of clinical outcomes; widely available; lower cost than dobutamine MRI

Limitations: Poor windows in 30% of patients; lower sensitivity than nuclear techniques; viable regions with absent flow reserve will not show increased thickening during dobutamine stimulation; reliance on visual assessment of wall thickening

CONTRAST ECHOCARDIOGRAPHY

Strengths: Microcirculatory integrity evaluated as well as systolic thickening; better estimation of extent of viability than functional assessment alone; precise delineation of area of necrosis; good spatial resolution permitting endocardial vs. epicardial perfusion; viability assessed in presence of total coronary occlusion; use of very long pulsing intervals; pulse inversion, power pulse inversion, and power modulation reduce attenuation artifacts

Limitations: Difficult windows in 30% of patients; attenuation problems; scant clinical data available

DOBUTAMINE MRI

Strengths: Separately evaluate inotropic reserve in endocardium with tagging; measurement of wall thickness more accurate than with TTE; better image quality than echocardiography for assessment of contractile reserve; simultaneous assessment of perfusion using contrast enhancement; good sensitivity and specificity for viability detection; good imaging windows in all patients

Limitations: Higher cost than echocardiography; limited availability; need better, faster automated techniques; less sensitive than nuclear techniques but may be more specific; imaging information not available in real time; lack of clinical research studies; patients with pacemakers or ICDs cannot be imaged

FDG=[18] F-fluorodeoxyglucose; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; PET=positron-emission tomography; SPECT=single-photon emission computed tomography; TTE=transesophageal echocardiography.

process in the vascular wall is also potentially feasible, as is imaging sites of apoptosis.

With respect to contrast echocardiography, progress in microbubble contrast agents and imaging technology to enhance the microbubble signal-to-noise ratio will enable better assessment of myocardial perfusion and viability with intravenous injection of contrast. Accurate infarct sizing with second-generation contrast agents and intermittent harmonic imaging should emerge. Imaging of myocardial inflammation will be permissible since lipid microbubbles can persist in the microcirculation during injury by means of attachment to activated leukocytes.[146] Microbubbles adhere to damaged endothelial cells and may thus furnish a way to assess areas of microvascular endothelial dysfunction in vivo. Microbubbles may ultimately prove useful for local drug delivery since such bubbles can be destroyed in tissue by ultrasound in vivo. Finally, there is a potential for quantifying myocardial blood flow by using a constant venous infusion and subsequent ultrasound destruction of microbubbles, with microbubble

destruction and replenishment occurring at predetermined intervals.[147]

We can expect great advances in the field of cardiac MRI in the ensuing years. With the advent of new developments such as high-speed imaging, improved surface coils, and emergence of suitable contrast agents, MR coronary angiography could become a useful screening tool for noninvasive imaging of the proximal coronary vessels. Imaging of coronary plaque by MRI and spectroscopic techniques may allow differentiation between stable and unstable plaque, which could be a great contribution to the evaluation of patients with asymptomatic CAD. Arterial remodeling in atherosclerosis might also be assessed by MRI in either native disease or after a percutaneous intervention.[148] Finally, phosphorus-31 nuclear magnetic resonance spectroscopy, which can directly measure high-energy phosphates in the myocardium, may prove useful for noninvasively identifying metabolic evidence of stress-induced ischemia.[149]

These examples illustrate how we can look forward to further advances in the field of noninvasive cardiovascular imaging as a result of progress in instrumentation, enhanced computer processing of images, and new imaging agents for new applications.

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Part III - NORMAL AND ABNORMAL CARDIAC FUNCTION

Chapter 14 - Mechanisms of Cardiac Contraction and Relaxation

LIONEL H. OPIE

MICROANATOMY OF CONTRACTILE CELLS AND PROTEINS

Ultrastructure of Contractile Cells

The major function of myocardial muscle cells *(cardiomyocytes)* is in the cardiac contraction-relaxation cycle. The contractile proteins of the heart lie within these myocytes, which constitute about 75 percent of the total volume of the myocardium,

although only about one third in number of all the cells. About half of each ventricular cell is occupied by myofibers and about one fourth to one third by mitochondria (Table 14-1) .[1] A *myofiber* is a group of myocytes (Fig. 14-1) (Figure Not Available) held together by surrounding collagen connective tissue. Further strands of collagen connect myofibers to each other.[2] Excess collagen, one cause of left ventricular diastolic dysfunction, may accumulate in left ventricular pressure but not volume overload.[3]

The individual contractile muscle cells that account for more than half of the heart's weight are roughly cylindrical (Fig. 14-2) . Those in the atrium are quite small, being less than 10 mum in diameter and about 20 mum in length. Relative to atrial cells, human ventricular myocytes are large, measuring 17 to 25 mum in diameter and 60 to 140 mum in length (see Table 14-1) .

When examined under the light microscope, the atrial and ventricular muscle cells have cross striations and are branched.[4] Each cell is bounded by a complex cell membrane, the *sarcolemma* (*sarco,* "flesh"; *lemma,* "thin husk") and is filled with rodlike bundles of *myofibrils* (see Fig. 14-1) (Figure Not Available) . The latter are the contractile elements. The sarcolemma of the myocyte invaginates to form an extensive tubular network (the *T tubules*) that extends the extracellular space into the interior of the cell (see Figs. 14-1 (Figure Not Available) and 14-2) . The nucleus, which contains almost all of the cell's genetic information, is often centrally located. Some myocytes have several nuclei. Interspersed between the myofibrils and immediately beneath the sarcolemma are many mitochondria, the main function of which is to generate the energy in the form of adenosine triphosphate (ATP) needed to maintain the heart's contractile function and the associated ion gradients. Of the other organelles, the *sarcoplasmic reticulum* (SR) is most important (see Fig. 14-1) (Figure Not Available) . From the SR is discharged, in response to the wave of electrical excitation, the calcium that triggers contraction; and when the calcium is once again taken up into the SR, relaxation ensues.

Anatomically, the SR is a fine network spreading throughout the myocytes, demarcated by its lipid bilayer, which is rather similar to that of the sarcolemma. Parts of

TABLE 14-1 -- CHARACTERISTICS OF CARDIAC CELLS, ORGANELLES, AND CONTRACTILE PROTEINS

	MICROANATOMY OF HEART CELLS		
	Ventricular Myocyte	**Atrial Myocyte**	**Purkinje Cells**
Shape	Long and narrow	Elliptical	Long and broad
Length (mum)	60-140	About 20	150-200
Diameter (mum)	About 20	5-6	35-40

Volume (mum^3)	15,000-45,000	About 500	135,000-250,000
T tubules	Plentiful	Rare or none	Absent
Intercalated disc	Prominent end-to-end transmission	Side-to-side as well as end-to-end transmission	Very prominent abundant gap junctions. Fast; end-to-end transmission
General appearance	Mitochondria and sarcomeres very abundant. Rectangular branching bundles with little interstitial collagen	Bundles of atrial tissue separated by wide areas of collagen	Fewer sarcomeres, paler

COMPOSITION AND FUNCTION OF VENTRICULAR CELL

Organelle	**% of Cell Volume**	**Function**
Myofibril	About 50-60	Interaction of thick and thin filaments during contraction cycle.
Mitochondria	16 in neonate 33 in adult rat 23 in adult man	Provide adenosine triphosphate chiefly for contraction
T system	About 1	Transmission of electrical signal from sarcolemma to cell interior
Sarcoplasmic reticulum (SR)	33 in neonate 2 in adult	Takes up and releases Ca^{2+} during contraction cycle
Terminal cisternae of SR	0.33 in adult	Site of calcium storage and release
Rest of network of SR	Rest of volume	Site of calcium uptake en route to cisternae
Sarcolemma	Very low	Control of ionic gradients; channels for ions (action potential); maintenance of cell integrity; receptors for drugs and hormones
Nucleus	About 5	Protein synthesis
Lysosomes	Very low	Intracellular digestion and proteolysis
Sarcoplasm (= cytoplasm) (+ nuclei + other structures)	About 12 in adult rat 18 in humans	Provides cytosol in which rise and fall of ionized calcium occurs; contains other ions and small molecules

the SR lie in very close apposition to the T tubules.[4] Here the tubules of the SR expand into bulbous swellings, which are still hollow and lie along the inner surface of the sarcolemma or are wrapped around the T tubules (see Fig. 14-1) (Figure Not Available) . These expanded areas of the SR have several names: *subsarcolemmal cisternae* (from the Latin and meaning "boxes or baskets") or *junctional SR*. Sometimes the cisternae occur in pairs (*dyads*) lying astride the T tubule, the whole having the appearance of *triads*. Their major function is to release calcium from the *calcium release channel* (also called the ryanodine receptor) to initiate the contractile cycle.

The second part of the SR, the *longitudinal or network SR*, consists of ramifying tubules (see Fig. 14-1) (Figure Not Available) and is concerned with the uptake of calcium that initiates relaxation. This uptake is achieved by the ATP-requiring calcium pump, also called *SERCA* (SarcoEndoplasmic Reticulum Ca^{2+} -ATPase), that increases its activity in response to beta-adrenergic stimulation. Calcium taken up into the SR is then stored at high concentration in a number of storage proteins, including *calsequestrin,* before being released again.

The *cytoplasm* is the intracellular fluid and proteins therein contained within the sarcolemma but excluding the contents of organelles such as mitochondria and the SR. The fluid component of the cytoplasm, minus the proteins, is called the *cytosol*. It is in the cytosol that the concentrations of calcium ions rise and fall to cause cardiac contraction and relaxation. The proteins of the sarcoplasm include many enzymes that act to accelerate the conversion of one chemical form to another, thereby eventually producing energy.

SUBCELLULAR COMPARTMENTATION.

Increasingly there is evidence that the cytosol is not uniform in its composition. There may be a subsarcolemmal space from where calcium ions may preferentially exchange with the extracellular space. Also, the molecular signal systems that convey messages from surface receptors to intracellular organelles may be directed to specific sites by molecules that "anchor" components of the internal messenger chain to specific organelles, as when the beta-adrenergic chain must link up with the calcium pump of the sarcoplasmic reticulum (see p. 452). Another example is the local unloading of ATP where it is needed, by the exact cellular location of the enzyme creatine kinase that converts creatine phosphate to ATP. "In the world of intracellular real estate, location, location, and location are the key determinants of in vivo function."[5]

Contractile Proteins

The major molecules involved in the contraction-relaxation cycle are the two chief contractile proteins: the thin actin filament and the thick myosin filament (Fig. 14-3). Calcium ions initiate the contraction cycle by interacting with troponin C to relieve the inhibition otherwise exerted by troponin I. Titin is a large elastic molecule that supports myosin (Fig. 14-4). During contraction, the filaments slide over each other without the individual molecules of actin or myosin actually shortening. This interaction of the myosin heads with actin filaments is called *cross-bridge cycling.* As they slide, they pull

together the two ends of the fundamental contractile unit called the *sarcomere*. On electron

Figure 14-1 (Figure Not Available) Cardiac myofiber (top), detailed structure of myocyte and sarcomere (center), and contracted proteins (bottom). The crux of the contractile process lies in the changing concentrations of Ca^{2+} ions in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions "trigger" the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually, the small amount of calcium that has entered the cell will leave predominantly by a Na^{+} /Ca^{2+} exchanger, with a lesser role for the sarcolemmal calcium pump. The varying actin-myosin overlap is shown for systole, when calcium ions arrive, and diastole, when calcium ions leave. The myosin heads, attached to the thick filaments, interact with the thin actin filaments, as shown in Figure 14-6. For the role of titin, see Figure 14-4 . The top panel shows the difference between the myocardial cell, or myocyte, and the myofiber, composed of many myocytes. (Top panel from Braunwald E, et al: Mechanisms of Contraction of the Normal and Failing Heart. 2nd ed. Boston, Little, Brown, 1976. The other panels are reprinted with permission and copyright L. H. Opie, © 2001.)

microscopy, the sarcomere is limited on either side by the *Z line* (Z, abbreviation for German *Zuckung*, "contraction") to which the actin filaments are attached (see Fig. 14-2). Conversely, the myosin filaments extend from the center of the sarcomere in either direction toward but not actually reaching the Z lines (see Fig. 14-1 (Figure Not Available)).

As the actin filaments move inward toward the center of the sarcomere, they draw the Z lines closer together, so that the sarcomere shortens (see Fig. 14-3) . The energy for this shortening is provided by the breakdown of ATP, chiefly made in the mitochondria.

TITIN.

Titin (also called *connectin*) is the largest protein molecule yet described. It is an extraordinarily long, flexible, and slender myofibrillar protein (see Fig. 14-4) . Titin acts as a third filament to provide elasticity.[6] Being between 0.6 and 1.2 mum in length, the titin molecule extends from the Z line, stopping just short of the M line (see Fig. 14-1) (Figure Not Available) . It has two distinct segments: an inextensible anchoring segment and an extensible elastic segment that stretches as sarcomere length increases.[7] Titin has two functions. It tethers the myosin molecule to the Z line, and as it stretches its elasticity explains the stress-strain relation of cardiac and skeletal muscle.[6] [7] As the sarcomere length of cardiac muscle is increased, the enfolded part of the titin molecule straightens, and beyond 2.0 mum the elastic part of the molecule is stretched. These changes explain, at least in part,

Figure 14-2 The sarcomere is the distance between the two Z lines. Note the presence of numerous mitochondria (mit) sandwiched between the myofibrils and the presence of T tubules (T), which penetrate

into the muscle at the level of the Z lines. This two-dimensional picture should not disguise the fact that the Z line is really a "Z disc," as is the M line (M), also shown in Figure 14-1. (Figure Not Available) H=central clear zone containing only myosin filament bodies and the M line; A=band of actin-myosin overlap; I=band of actin filaments, titin, and Z line; g=glycogen granules. ×32,000 rat papillary muscle. (Courtesy of Dr. J. Moravec, Dijon, France.)

Figure 14-3 The major molecules of the contractile system. The contractile cycle consists of interactions between the thin actin filament and the myosin heads *(A)*. The myosin head (*B)* undergoes a series of cyclical interactions with the thin actin filament (*A*), when Ca^{2+} ions arrive at troponin C *(C).* A complex interaction between troponin C (TnC) and the other troponins moves tropomyosin to "uncover" an actin site to which a myosin head can attach (*D*). The molecular aspects are as follows. *B*, The myosin head is composed of heavy and light chains. The heavy head chain in turn has two major domains: one of 70 kDa that interacts with actin at the actin cleft and has an ATP-binding pocket; and the "neck" domain of 20 kDa, also called the "lever arm," an elongated alpha helix that extends and bends and has two light chains surrounding it as a collar. The essential light chain is part of the structure. The other regulatory light chain may respond to phosphorylation to influence the extent of the actin-myosin interaction. *A,* Details of the thin filament, showing the calcium-binding troponin (TnC); the inhibitory troponin I (TnI); and troponin T, with a newly described role in the contractile cycle. *D,* Calcium binding to TnC induces a conformational change in TnC that elongates (compare systole with diastole). TnI closes up to TnC, and the normal inhibition of TnI on actin-tropomyosin is lessened. There is a strengthening of the interaction between TnC and TnT. These changes allow repositioning of tropomyosin in relation to actin, with lessening of its normal inhibitory effects, as shown in the bottom panel. Now the contractile cycle (see Fig. 14-6) can start. (From Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001. *D* modified from Solaro RJ, Van Eyk J: Altered interactions among thin filament proteins modulate cardiac function, J Mol Cell Cardiol 28:217-230, 1999.)

Figure 14-4 Titin is the very large elongated protein with elasticity that binds myosin to the Z line. It may act as a bidirectional spring that develops passive forces in stretched sarcomeres and resting forces in shortened sarcomeres.[6] As the sarcomere is stretched to its maximum physiological diastolic length of 2.2 mum (see Fig. 14-25), titin first undergoes straightening (up to 2 mum) and then elongation, the latter rapidly increasing the passive forces generated. At low sarcomere lengths, when sarcomeres are slack at about the diastolic limit of 1.85 mum (see Fig. 14-25), the mechanically active elastic domain is folded on top of itself. At even shorter lengths, which may not be physiological in the intact heart, there are substantial restoring forces generated. For differences between cardiac and skeletal titin, see the work of Trombitas and colleagues.[7] (Modified from Trombitas K, Jian-Ping J, Granzier H: The mechanically active domain of titin in cardiac muscle. Circ Res 77:856-861, 1995. Copyright 1995, American Heart Association; and Helmes M, Trombitas K, Granzier H: Titin develops restoring force in rat cardiac myocytes. Circ Res 79:619-626, 1996. Copyright 1996, American Heart Association.)

the development of passive forces (which contrasts to active force development by the cross bridges). Therefore, titin may be the length sensor.[8] Conversely at short

sarcomere lengths, the elastic domain is folded on itself to generate restoring forces (see Fig. 14-3) . Thus, changes in titan help to explain the *series elastic element* that postulates that there is elasticity in series between the contractile elements and the ends of the muscle.

STRONG AND WEAK BINDING STATES.

Although at a molecular level the events underlying the cross-bridge cycle are exceedingly complex, one simple current hypothesis is that the cross bridges exist in either a strong or a weak binding state (Fig. 14-5) .[9] The arrival of calcium ions at the contractile proteins is a crucial link in the series of events known as *excitation-contraction coupling.* The ensuing interaction of calcium with troponin C and the deinhibition of troponin I puts the cross bridges in the strong binding state. As long as enough calcium ions are present, the strong binding state potentially dominates (Fig. 14-6) . If, however, the strong binding state were continuously present, then the contractile proteins could never relax. Thus, the proposal is that the binding of ATP to the myosin head puts the cross bridges into a weak binding state even when calcium is high.[9] Conversely, when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (P_i), the strong binding state again predominates (see Fig. 14-5) . Thus, the ATP-induced changes in the molecular configuration of the myosin head result in corresponding variations in the physical properties (a similar concept is common in metabolic regulation). Length activation also promotes the strong binding state. Conversely, the weak binding state predominates when cytosolic calcium levels fall at the start of diastole. As the calcium ions leave troponin C, a master switch is turned off and tropomyosin again assumes the inhibitory configuration.

ACTIN AND TROPONIN COMPLEX.

Although calcium ions provide the essential switch-on signal to the cross-bridge cycle by binding to troponin C, current evidence suggests more than an "on-off" signaling process. Rather the arrival of calcium initiates a series of interactions between the troponin components of the thin filament, to allow movement of the tropomyosin molecule that in turn promotes the strong binding state (see Fig. 14-5) so that contraction takes place. To understand the role of calcium, a brief description of the molecular structure of actin and the troponin complex is first required. Thin filaments are composed of two actin units, which intertwine in a helical pattern, both being carried on a heavier tropomyosin molecule that functions as a "backbone" (see Fig. 14-3 *A*). At regular intervals of 38.5 nm along this twisting structure is a closely bound group of three regulatory proteins called

Figure 14-5 Hypothesis for cross bridge cycle based on concepts of Brenner.[11] Strong cross bridges are required for the power stroke (see Fig. 14-6) . The probability of such cross bridges forming is decreased by troponin I. When Ca^{2+} interacts with troponin C, there is a physical interaction between troponin C and troponin I (see Fig. 14-3 *D*), with de-inhibition from the influence of tropomyosin so that stronger cross bridges form more easily. Adenosine triphosphate, when attached to the myosin head, causes the strong binding state to change to the weak state and, therefore, inhibits rigor formation (see Fig. 14-6). During force generation, the molecular force generators (myosin cross bridges) cycle between weak and strong

states with apparent rate constants, f and g. (Copyright L. H. Opie, © 2001.)

Figure 14-6 Cross-bridge cycling model updated by the present author from the Rayment[12] five-step model for interaction between the myosin head and the actin filament, taking into account other recent models.[14] [15] [219] The cross bridge (only one myosin head depicted) is pear shaped and consists of the catalytic motor domain that interacts with the actin molecule and an extended alpha-helical "neck region" acting as a lever-arm.[14] The nucleotide pocket receiving and binding adenosine triphosphate (ATP) is a depression near the center of the catalytic domain (see Fig. 14-3 *B*). The actin-binding cleft bisects the catalytic motor domain. During the cross-bridge cycle, the width of the actin binding cleft changes in size although details remain controversial. Starting with the rigor state *(A)* the binding of ATP to the pocket *(B)* is followed by ATP hydrolysis *(C)* that partly closes the actin-binding cleft. The cleft opens when phosphate is released (through the cleft rather than through the pocket), and the myosin head strongly attaches to actin to induce the power stroke (*D* and *E*). During the power stroke the latter rotates about a fulcrum in the region where the helix terminates within the catalytic motor domain.[14] As the head flexes, the actin filament is displaced by about 10 nm *(E)*. In the process, adenosine diphosphate is also released so that the binding pocket becomes vacant. Finally, the rigor state is reached again *(A)* when the myosin head is again ready to receive adenosine triphosphate to reinitiate the cross-bridge cycle. Throughout, the actin monomer with which the myosin head is interacting is dotted. (Professor J. C. Ruegg of Heidelberg University, Germany, is thanked for valuable comments.)

the *troponin complex*. Of these three, it is troponin C that responds to the calcium ions that are released in large amounts from the SR to start the cross-bridge cycle.

When the cytosolic calcium level is low, the tropomyosin molecule is twisted in such a way that the myosin heads cannot interact with actin (see Fig. 14-3 *D*). Therefore, most cross bridges are in the "blocked position," although some are still in the weakly bound state.[10] As calcium ions increasingly arrive and interact with troponin C, then the activated troponin C binds tightly to the inhibitory molecule, troponin I. The latter moves to a new position on the thin filament, thereby weakening the interaction between troponin T and tropomyosin (see Fig. 14-3 *D*). Ultimately, tropomyosin is repositioned on the thin filament,[10] therefore removing most of the inhibition exerted by tropomyosin on the actin-myosin interaction. Thus, weakly bound or blocked cross bridges enter the strongly bound state and the cross-bridge cycle is initiated. As the strong cross bridges form, they activate "near neighbors" and thereby spread the activation process.[10] They also promote further tropomyosin movement to cause more forceful cross-bridge interaction.[11]

MYOSIN AND MOLECULAR BASIS OF MUSCULAR CONTRACTION.

Each myosin head is the terminal part of a heavy chain. The bodies of two of these chains intertwine, and each terminates in a short "neck" that carries the elongated myosin head (see Fig. 14-3 *B*). According to the "Rayment model," it is the base of the head, also sometimes called the neck, that changes configuration in the contractile cycle.[12] Together with the "bodies" of all the other heads, the myosin thick filament is formed. Each lobe of the bilobed head has an *ATP binding pocket* (also called

nucleotide-pocket) and a narrow cleft that extends from the base of this pocket to the actin-binding face.[12] ATP and its breakdown products ADP and P_i bind to the nucleotide pocket in close proximity to the myosin ATPase activity that breaks down ATP to its products (see Fig. 14-6) . Currently, there is controversy about the role in the contractile cycle of the narrow *actin binding cleft* that splits the central 50-kDa segment of the myosin head. According to the revised Rayment model,[13] this cleft responds to the binding of ATP or its breakdown products to the nucleotide pocket in such a way that the conformational changes necessary for movement of the head are produced. According to Dominguez and associates,[14] the cleft is closed in the weakly attached states before the power stroke (see Fig. 14-6 *B* and *C*) but opens when P_i is released through the cleft, whereupon the myosin head attaches strongly to actin to induce the power stroke (see Fig. 14-6 *D* and *E*).

Starting with the rigor state (see Fig. 14-6 *A*), the binding of ATP to its pocket changes the molecular configuration of the myosin head so that the head detaches from actin to terminate the rigor state (see Fig. 14-6 *B*). Next the ATPase activity of the myosin head splits ATP into ADP and P_i and the head flexes (see Fig. 14-6 *C*). As ATP is hydrolyzed, the myosin head binds to an adjacent actin

unit. Then P_i is released from the head through the cleft and there is strong binding of the myosin head to actin (see Fig. 14-6 *D*). Next, the head extends (i.e., straightens). A power stroke takes place, the actin molecule moves by about 10 nm,[14] and the myosin head is now in the rigor state. The pocket then releases ADP and is ready for acceptance of ATP and repetition of the cycle. According to the Rayment model,[12] it is straightening and not flexion of the light chain region of the head (i.e., the "neck") that produces the power stroke. According to the "swinging lever-arm hypothesis,"[15] the arm rotates so that its end moves by about 10 nm as the power stroke occurs.[14] The lever "arm" is the "neck" shown in Figure 14-6 *B*. Thus, positional changes of the essential light chain, part of the "neck," are used experimentally to monitor movement of the "arm."

Myosin ATPase activity normally responds to calcium in such a way that an increase of calcium ion concentration from 10^{-7} M to 5×10^{-5} M results in a fivefold increase in activity.[16] Similar calcium concentrations are associated with contraction in the whole heart (Fig. 14-7) .

Myosin heavy chain isoforms help regulate myosin ATPase activity. Each myosin filament consists of two heavy chains, the bodies of which are intertwined and each ending in one head, and four light chains, two in apposition to each head. The heavy chains, containing the myosin ATPase activity on the heads, occur in two isoforms, beta and alpha of the same molecular weight but with substantially different ATPase activities. The beta-heavy chain (beta-MHC) isoform has lower ATPase activity and is the predominant form in the adult human. In small animals, the faster alpha-MHC form

changes to a predominant beta-MHC pattern in experimental heart failure.

The significance of the double-headed structure of myosin has now been clarified by comparison with single-headed variants. *Double-headed myosin* is required to produce the full displacement of actin, about 10 nm, versus only 6 nm with single-headed myosin.[17]

The *myosin neck* is chiefly formed by a long alpha helix (see Fig. 14-3 *C*), surrounded by two *light chains* (four per bilobed head) that act as a cervical collar. The light chain that is more proximal to the myosin head, the *essential light chain* (MLC-1), appears to inhibit the contractile process by interaction with actin.[18] The other *regulatory light chain* (MLC-2) is a potential site for phosphorylation, for example in response to beta-adrenergic stimulation. Such phosphorylation (i.e., the gaining of a phosphate grouping) may promote cross-bridge cycling by increasing the affinity of myosin for actin.[9] [10] Mutation of this light chain in one type of human cardiomyopathy impairs the contractile response to tachycardia.[19] In vascular smooth muscle, the phosphorylation that occurs under the influence of the enzyme myosin light chain kinase (MLCK) is an obligatory step in the initiation of the contractile process.

Graded Effects of Increased Cytosolic Calcium Levels on Cross-Bridge Cycle

Calcium ions play a crucial role in linking external neurohumoral control of the heart to stimulation of the contractile process. These ions act at multiple control sites.[9] [10] [20] [21] Their interaction with troponin C is essential for cross-bridge

Figure 14-7 The proposed explanation for the Starling effect, whereby a greater end-diastolic fiber length develops a greater force. The left panel shows how the steep ascending limb of the cardiac force-length curve is explained by an interaction between sarcomere length and calcium ions. Light lines show a family of hypothetical force-length curves for increasing free Ca^{2+} concentrations each drawn on the assumption that the shape of the curve is determined solely by the degree of overlap of thin and thick filaments (see Fig. 14-1) (Figure Not Available) . It is postulated that an increase in end-diastolic fiber length (a) at any given free Ca^{2+} concentration would increase force by a small amount on the basis of the change in filament overlap. In addition, length-dependent activation explains how the sarcomere can "upgrade itself" (b) to a higher force-length curve. The middle panel proposes that the effects of Ca^{2+} and length can be explained by the properties of troponin C (TnC) and the binding of calcium to TnC. As more Ca^{2+} ions bind to TnC in a skinned fiber preparation, more force is developed. There is a steep relation, similar to that shown in the left panel. When the fiber is stretched and the sarcomere length is increased, it is postulated that for any given number of Ca^{2+} ions binding to TnC there is a greater force development. The right panel shows how the Ca^{2+} concentration influences the development of tension at long (solid black dots) and shorter (open circles) sarcomere lengths. (Left panel modified from Fuchs F: Mechanical modulation of the Ca^{2+} regulatory protein complex in cardiac muscle. NIPS 10:6-12, 1995. Middle panel modified from Solaro RJ, Wolska BM, Westfall M: Regulatory proteins and diastolic relaxation. *In* Lorell BH, Grossman W [eds]: Diastolic Relaxation of the Heart. Norwell, MA, Kluwer Academic Publishers, 1994, pp 53-53. Right panel modified from Cazorla O, Vassort G, Garnier D, LeGuennec J-Y: Length modulation of active force in rat cardiac myocytes: Is titin the sensor? J Mol Cell Cardiol 31:1215-1227, 1995.)

cycling. It has been held that the calcium concentration acts as an on-off switch to regulate the total number of cycling cross bridges. According to this proposal, the enhanced force development in response to a greater calcium ion concentration must be due to recruitment of additional cross bridges.[22] Alternatively, to explain the graded model,[21] there may be (1) a graded response of troponin C to calcium ions, including altered rates of calcium binding and release[10] ; (2) a graded response of myosin ATPase to calcium[16] ; (3) "near neighbor" self-activation whereby actin-myosin interaction activates additional cross bridges even in the absence of increased binding of calcium to the troponin C of those cross bridges[10] ; or (4) alterations in the extent of myosin light chain phosphorylation.[9] Of specific interest is the proposal that tightly bound cross bridges act to spread activation on the thin filament to near-neighbor units to achieve full activation.[10] By such mechanisms, one calcium-troponin complex could turn on as many as 14 actin molecules, in contrast to the expected number of 7.

Length-Dependent Activation

Besides the cytosolic calcium concentration, the other major factor influencing the strength of contraction is the length of the muscle fiber at the end of diastole, just before the onset of systole. Starling observed that the greater the volume of the heart in diastole, the more forceful is the contraction. The increased heart volume translates into an increased muscle length, which acts by a length-sensing mechanism (see Fig. 14-7) . Previously, this relation was ascribed to a more optimal overlap between actin and myosin. The current view is that an increased sarcomere length leads to greater sensitivity of the contractile apparatus to the prevailing cytosolic calcium.[9] [10] The mechanism for this regulatory change, although not yet clarified, may reside in the interfilament spacing.[10] As the heart muscle is stretched, the interfilament distance decreases; and, hypothetically, there is an increased rate of transition from the weak to the strong binding state (see Fig. 14-5) . Alternatively, sarcomere stretch increases the passive forces built up by titin,[8] which in turn could hypothetically influence the position of myosin heads. Another proposal, that troponin C is the length sensor, is currently less favored.[10]

Cross-Bridge Cycling Versus Cardiac ContractionRelaxation Cycle

The cardiac cycle of Wiggers (see p. 462) must be distinguished from the cross-bridge cycle. The former reflects the overall pressure changes in the left ventricle, whereas the later cycle is the repetitive interaction between myosin heads and actin. According to the 5-step model, the binding of ATP or ADP regulates in part whether the cross bridges would be weak or strong (see Figs. 14-5 and 14-6) . So long as enough calcium ions are bound to troponin C, many repetitive cycles of this nature occur. Thus, at any given moment, some myosin heads are flexing or flexed, some are extending or extended, some are attached to actin, and some are detached from actin. Numerous such cross-bridge cycles, each lasting only a few microseconds, actively move the thin actin filaments toward the central bare area of the thick myosin filaments, thereby shortening the sarcomere. The sum total of all the shortening sarcomeres leads to systole, which is

the contraction phase of the cardiac cycle. When calcium ions depart from their binding sites on troponin C, cross-bridge cycling cannot occur and the diastolic phase of the cardiac cycle sets in.

Myofilament Response to Hemodynamic Demands

Solaro and Rarick[10] have hypothesized that myofilament activity is coupled to the prevailing hemodynamic demands of the circulation. Besides length-dependent activation, there are two chief mechanisms. First, there may be variable rates of calcium binding and release from troponin C (as discussed in the previous section). Second, phosphorylation and dephosphorylation of the contractile proteins may help to control the extent of activation of the myofilaments. Conflicting evidence suggests that increased beta-adrenergic dependent phosphorylation of troponin I *reduces* the myofilament sensitivity to calcium and thereby leads to an *increased* rate of relaxation during beta-adrenergic stimulation. Hypothetically, this mechanism enhances the relaxant (lusitropic) effect of increased uptake rates of calcium into the sarcoplasmic reticulum. The effects of phosphorylation of other proteins such as the myosin essential light chains and C protein, still imperfectly understood, may also be important.[10]

Contractile Proteins and Cardiomyopathy

Abnormalities of the contractile proteins, especially myosin, are known to underlie a variety of genetic-based cardiomyopathies. Hypertrophic cardiomyopathy is, in general, linked to mutant genes that cause abnormalities in the force-generating system, such as beta-myosin heavy chain (see Chap. 48) .[23] Less commonly, there may be defects in the genes encoding myosin light chain isoforms, troponin I and C isoforms, myosin-binding protein C, and alpha-tropomyosin. In contrast, dilated cardiomyopathy can be related to mutations in non-force-generating cytoskeletal proteins, such as dystrophin and actin.[24] [25] Actin abnormalities are of special interest. When the contractile part of actin is involved, then the proposal is that hypertrophic cardiomyopathy results.[26] When the non-force-generating part is involved, then the hypothesis is that dilated cardiomyopathy follows.[26] *Dystrophin* is a large protein that links intracellular

Figure 14-8 Dystrophin is a large intracellular protein that links the contractile system by means of actin to the sarcolemma and thence to the extracellular matrix. Experimentally, dystrophin is cleaved in enterovirus myocarditis. Abnormalities of dystrophin also appear to explain the cardiomyopathies of Duchenne's dystrophy and X-linked cardiomyopathy. The dystrophin-associated protein complex is represented by alpha and beta, whereas $alpha_1$ and $beta_1$ are the syntrophins.[27] (Modified from Bardoff C, Lee G-H, Lamphear BJ, et al: Enteroviral protease 2A cleaves dystrophin: Evidence of cytoskeletal disruption in an acquired cardiomyopathy. Nat Med 5:320-326, 1999.)

actin to the extracellular matrix through a sarcolemmal dystrophin-associated-protein complex (Fig. 14-8). Experimental virus myocarditis cleaves dystrophin (see Fig. 14-8), thereby causing dilated cardiomyopathy.[27]

CALCIUM ION FLUXES IN CARDIAC CONTRACTION-RELAXATION CYCLE

Calcium Movements and Excitation-Contraction Coupling

Despite the crucial role of calcium in regulating the contraction and relaxation phases of the cardiac cycle, the exact details of the associated calcium ion fluxes that link contraction to the wave of excitation (*excitation-contraction coupling*) are still not yet fully clarified. The generally accepted hypothesis is based on the crucial role of calcium release from the SR.[28] Relatively small amounts of calcium ions actually enter and leave the cell during each cardiac cycle, whereas much larger amounts move in and out of the SR (Fig. 14-9) . *Calcium-induced calcium release* explains most of the current available data.[28] The basic proposal is that the SR releases relatively large amounts of calcium ions into the cytosol in response to the much smaller amounts entering the cardiac myocyte with each wave of depolarization.[29] This process elevates by about tenfold the concentration of calcium ions in the cytosol. The result is the increasing interaction of calcium ions with troponin C to trigger the contractile process. This theory has received strong support from several sources: (1) the molecular characterization of the ryanodine receptor on the SR (see later) that releases calcium[28] ; (2) the electrophysiological evidence closely linking the duration of the action potential with the extent of Ca^{2+} release[29] ; and (3) the close proximity of the ryanodine receptors to the sarcolemmal L-type calcium channels (see Figs. 14-9 and 14-10) .[28]

The rise of cytosolic calcium that triggers contraction comes to an end as the wave of excitation passes, no more calcium ions enter, and the release of calcium from the SR ceases. The latter event could be explained by one or more of several mechanisms, namely, (1) that the cytosolic calcium ion concentration has risen high enough to inhibit the process of calcium-induced calcium release, perhaps acting through calmodulin[28] ; (2) the release of calcium from the SR is linked tightly to opening of the calcium channel, so that when the latter closes the release of calcium from the SR ceases[30] ; (3) the rising cytosolic calcium ion concentration activates the calcium uptake pump of the SR[31] ; or (4) calcium release from the SR continues only for the duration of the action potential duration.[29] The overall effect of these mechanisms is that the cytosolic calcium ion concentration starts to fall and diastole is initiated. As the cytosolic calcium decreases, binding with troponin C lessens, tropomyosin again starts to inhibit the interaction between actin and myosin, and relaxation proceeds.

To balance the small quantity of calcium ions entering the heart cell with each depolarization, a similar quantity must leave the cell by one of two processes. First, calcium can be exchanged for sodium ions entering by the Na^{+} /Ca^{2+} exchange, and, second, an ATP-consuming sarcolemmal calcium pump can transfer calcium into the extracellular space against a concentration gradient.

CALCIUM SPARKS.

Calcium sparks are the very small quantities of calcium that can be spontaneously released and locally released from the SR even in the absence of L-channel opening. Hypothetically, the spark represents the spontaneous opening of one or at the most a cluster of calcium release channels.[28] [32] There is so little calcium diffusing

Figure 14-9 Calcium fluxes in the myocardium. Crucial features are (1) entry of Ca^{2+} ions through the voltage-sensitive L-type Ca^{2+} channels, acting as a trigger to the release of Ca^{2+} ions from the sarcoplasmic reticulum (SR), as shown in Figure 14-10; (2) the effect of beta-adrenergic stimulation with adenylate cyclase forming cyclic adenosine monophosphate, the latter both helping to open the Ca^{2+} channel and to increase the rate of uptake of Ca^{2+} into the SR; and (3) exit of Ca^{2+} ions chiefly through the Na^{+} /Ca^{2+} exchange, with the sodium pump thereafter extruding the Na^{+} ions thus gained. The latter process requires adenosine triphosphate. Note the much higher extracellular (10^{-3} M) than intracellular Ca^{2+} values and a hypothetical mitochondrial value of about 10^{-6} M. The mitochondria can act as a buffer against excessive changes in the free cytosolic calcium concentration. MITO=mitochondria. (From Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

Figure 14-10 In the *myocardium* (left side of figure), calcium is released from the sarcoplasmic reticulum (SR) through the calcium release channel (part of the ryanodine receptor), chiefly in response to calcium that has entered during voltage depolarization. Calcium is taken up again by the calcium pump of the longitudinal SR to interact with the storage protein calsequestrin (CS), thence to be released again. In contrast, in *vascular smooth muscle*, stimulation of vasoconstrictor receptors, such as angiotensin II (AII), $alpha_1$ -adrenergic receptors, and endothelin (ET), leads to release of inositol triphosphate (IP_3), which acts on its receptor to release calcium from the SR. In the myocardium, IP_3 does not have a major physiological role, yet in heart failure (HF) its receptor on the SR may be upregulated. (Modified with permission from Opie LH: The Heart, Physiology, from Cell to Circulation, Lippincott-Raven, Philadelphia, 1998. Figure copyright L. H. Opie, © 2001.)

away from a spark that it fails to activate the neighboring calcium release channels and contraction is not initiated. Calcium sparks can be activated by calcium ions, so that a summation of sparks could produce a normally propagating calcium wave that triggers excitation-contraction coupling. One model predicts that the graded response in calcium release can be explained by both an increased number of channels that are opened and an increased amount of calcium released by each channel.[33] When the SR is overloaded with calcium as in pathological conditions such as catecholamine toxicity or during early reperfusion, then calcium sparks can lead to propagated calcium waves with risk of serious arrhythmias or impaired contractile activity.

Calcium Release Channels of the Sarcoplasmic Reticulum

RYANODINE RECEPTORS.

Each L-type calcium channel of the sarcolemma controls a cluster of four to ten SR release channels.[28] [34] There is a close anatomical proximity of the calcium channels on the T tubules, to the calcium release channels, situated on the SR. The calcium release channel is part of the complex structure known as the *ryanodine receptor*, so-called because it coincidentally binds the potent insecticide ryanodine.[31] Part of this receptor extends from the membrane of the SR toward the T tubule to constitute the *foot structure* or *junctional channel complex* that bridges the gap between the SR and the T tubule. After the wave of depolarization has reached the T tubule and induced the voltage-operated calcium channels to open, the calcium ions enter the cardiac myocyte to reach the foot regions of the ryanodine receptors (see Fig. 14-10) . The result is a change in the molecular configuration of the ryanodine receptor that opens the calcium release channel of the SR to discharge calcium ions, probably into the subsarcolemmal space between the foot and the T tubule and thence into the cytosol.

IP_3 -INDUCED RELEASE OF CALCIUM FROM SARCOPLASMIC RETICULUM.

A totally different calcium release signal system may also be involved. In addition to the ryanodine receptor, there is also a second receptor on the SR, that for inositol triphosphate (IP_3) (see Fig. 14-10) . This IP_3 receptor has a high degree of molecular homology with the ryanodine receptor, although it is only about half its size. IP_3 is one of the messengers of the phosphatidylinositol pathway, responding to certain agonists with vasoconstriction as their major physiological role, namely, $alpha_1$ -adrenergic stimulation, angiotensin II, and endothelin. [35] Calcium released from the SR by IP_3 may stimulate Na^+ /Ca^{2+} exchange directly. In vascular smooth muscle, this IP_3 messenger system is of fundamental importance in regulating the release of calcium from the SR and thereby regulating arterial tone. In cardiac muscle, the function of IP_3 is still sufficiently controversial to question its role in the inotropic response. An attractive proposal is that in human heart failure the IP_3 receptor becomes upregulated in relation to the ryanodine receptor, [36] perhaps contributing to calcium overload. Upregulation of IP_3 may promote apoptosis in response to activation of the Fas pathway, again perhaps mediated by an increased cytosolic calcium.[37]

Calcium Uptake by the Calcium ATPase of the Sarcoplasmic Reticulum

Calcium ions are taken up into the SR by the activity of the calcium pump called SERCA (sarcoendoplasmic reticulum Ca^{2+} ATPase) that constitutes nearly 90 percent of the protein component of the SR.[38] [39] Its molecular weight is about 115 kDa, and it straddles the SR membrane in such a way that part of it actually protrudes into the cytosol. It exists in several isoforms, of which the dominant cardiac form is SERCA 2a.[38] [40] For each mole of ATP hydrolyzed by this enzyme, two calcium ions are taken up to accumulate within the SR (Fig. 14-11) .

Phospholamban, which means "phosphate receiver," is the major regulator of this calcium uptake pump and plays a crucial role in the beta-adrenergic response of the myocardium.[41] Phospholamban is a pentamer protein consisting of five subunits, each with a molecular weight of 6 kDa, found in a 1:1 molar ratio to the ATPase of the calcium pump. The activity of phospholamban is governed by its state of phosphorylation, a process that alters the molecular configuration of the calcium pump (see Fig. 14-11) . There are two major protein kinases involved, the one activated by calcium ions and the other by cyclic adenosine monophosphate (AMP). Phospholamban responds to beta-adrenergic stimulation of the cardiac myocyte by enhancing (de-inhibiting) the uptake of calcium by SERCA into the SR to increase the rate of relaxation.[39] The further proposal is that the increased store of calcium in the SR is then released by the subsequent waves of depolarization with an increased rate and force of contraction. This sequence is strongly supported by the transgenic mouse model, totally deficient in phospholamban, in which rates of contraction and relaxation

Figure 14-11 Calcium uptake into the sarcoplasmic reticulum (SR) by the energy-requiring calcium pump, SERCA 2a. Phospholamban can be phosphorylated (P) to remove the inhibition exerted by its dephosphorylated form (positive charges) on the calcium pump. Thereby, calcium uptake is increased either in response to an enhanced cytosolic calcium or in response to beta-adrenergic stimulation. Thus, there are two phosphorylations activating phospholamban at two distinct sites and their effects are additive. An increased rate of uptake of calcium into the SR enhances the rate of relaxation (*lusitropic effect*). (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

are maximal and do not vary in response to added beta-adrenergic stimulation by isoproterenol.[39]

Calcium, taken up into the SR by the calcium uptake pump, is stored within the SR before further release. The highly charged storage protein, *calsequestrin*, is found in that part of the SR that lies near the T tubules. Calcium stored with calsequestrin is thought to become available for the release process as calsequestrin discharges Ca^{2+} into the inner mouth of the calcium release channel. This process replaces those calcium ions liberated from the outer mouth into the cytosol. *Calrectulin* is another Ca^{2+} -storing protein, very similar in structure to calsequestrin and probably similar in function.[31] Hypothetically, calsequestrin and two other proteins located in the SR membrane (junctin and triadin) may help regulate the properties of the ryanonide receptor.[28]

Role of Sarcoplasmic Reticulum in Heart Failure (See also Chap. 16)

In heart failure, the force of cardiac contraction is reduced and there is an abnormal delayed pattern of cardiac relaxation. There is general agreement that the rate of

calcium uptake by SERCA 2a is depressed in the failing human heart,[42] but the mechanisms remain controversial. One hypothesis is that abnormal calcium handling by the SR of the failing myocardium is due to impaired expression of the genes encoding these specific SR proteins. The messenger RNAs (mRNAs) for the ryanodine receptor, the calcium uptake pump, and phospholamban are all abnormally deficient.[43] Yet other data suggest that the poor function of SERCA 2 cannot be explained by defects in protein expression but rather that the regulation of SERCA 2a is upset in the failing human heart, perhaps at the level of phosphorylation.[42]

SARCOLEMMAL CONTROL OF CALCIUM AND SODIUM IONS

Calcium Channels

All current models of excitation-contraction coupling ascribe a crucial role to the voltage-induced opening of the sarcolemmal L-type long-lasting calcium channels in the initiation of the contractile process.[29] Channels are pore-forming macromolecular proteins that span the sarcolemmal lipid bilayer to allow a highly selective pathway for ion transfer into the heart cell when the channel changes from a closed to an open state.[44] [45] Ion channels have two major properties: gating and permeation. Guarding each channel are two or more hypothetical gates that control its opening. Ions can permeate through the channel only when both gates are open. In the case of the sodium and calcium channels, which are best understood, the activation gate is shut at the normal resting membrane potential and the inactivation gate is open, so that the channels are *voltage gated.* Depolarization opens the activation gate.

MOLECULAR STRUCTURE OF L-TYPE CALCIUM CHANNELS.

There is a superfamily of voltage-gated ion channels that includes both the sodium and calcium channels and some of the potassium channels (see also Chap. 22) .[28] The potassium channels have the simpler structure, from which it is thought that the more complex sodium and calcium channels evolved. Both sodium and calcium channels contain a major alpha subunit with four transmembrane subunits or domains, very similar to each other in structure. In addition, both sodium and calcium channels include in their overall structure a number of other subunits whose function is less well understood, such as the alpha subunit. Each of the four transmembrane domains of the alpha subunit is made up of six helices and is folded in on itself, so that the four S5-S6 spans structurally combine to form the single functioning *pore* of each calcium channel (Fig. 14-12) .[46] Activation is now understood in molecular terms as the change in charge on the fourth transmembrane segment, S4, called the *voltage sensor*, of each of the four subunits of the sodium or calcium channel.[47] *Inactivation* is the process whereby the current initially elicited by depolarization decreases with time despite continuation of the original stimulus.[47] The alpha subunit acts to enhance the calcium current flow through the beta-subunit pores.[48] Channels are not simply open or closed. Rather, the open state is the last of a sequence of many molecular states, varying from a fully closed to a fully open configuration. Therefore, it is more correct to speak of the *probability of channel opening*.

CALCIUM CHANNEL PHOSPHORYLATION.

The $alpha_1$ subunit (the organ-specific subunit) of the sarcolemmal calcium channel can be phosphorylated at several sites especially in the C-terminal tail.[28] During beta-adrenergic stimulation, cyclic AMP increases within the cell and phosphate groups are transferred from ATP to the $alpha_1$ subunit. Thereby, the electrical charges near the inner mouth of the nearby pores are altered to induce changes in the molecular conformation of the pores, so that there is an increased probability of opening of the calcium channel.[45]

T- AND L-TYPE CALCIUM CHANNELS.

There are two major subpopulations of sarcolemmal calcium channels relevant to the cardiovascular system, namely, the T channels and the L channels.[49] The T (transient) channels open at a more negative voltage, have short bursts of opening, and do not interact with conventional calcium antagonist drugs.[49] The T channels presumably account for the earlier phase of the opening of the calcium channel, which may also give them a special role in the early electrical depolarization of the sinoatrial node and, hence, of initiation of the heartbeat. Although T channels are found in atrial cells, their existence in normal ventricular cells is controversial. Nonetheless, the T channel from the human heart has been cloned,[50] and presumably most of the tissue was ventricular in origin. The sarcolemmal L (long-lasting) channels are the standard calcium channels found in the myocardium. They are involved in calcium-induced calcium release, and are inhibited by calcium channel blockers such as verapamil, diltiazem, and the dihydropyridines.

Figure 14-12 Simplified model of Ca^{2+} channel showing the $alpha_1$ subunit (a_1) forming the central pore, the regulatory beta-subunit (b), and $alpha_2$ and delta subunits of unknown function. Beta-adrenergic stimulation, by means of cyclic adenosine monophosphate, promotes phosphorylation (P) and the opening probability of the Ca^{2+} channel. The proposal is that four domains, each similar to that shown in the right panel and composed of six spanning segments, combine to form the $alpha_1$ subunit. Segment S4 is thought to respond to voltage depolarization (+=positive charges) by altering the molecular configuration of the loop between S5 and S6 (part of the pore), so that there is a greater probability of Ca^{2+} ions entering (channel opens). (Top panel modified from Varadi G, et al: Molecular determinants of Ca^{2+} channel function and drug action. Trends Pharmacol Sci 16:43-49, 1995, with permission of the authors and Elsevier Science Ltd. Bottom panel modified from Tomaselli GF, et al: Molecular basis of permeation in voltage-gated ion channels. Circ Res 72:491-496, 1993. Copyright 1993, American Heart Association.)

Ion Exchangers and Pumps

Sodium-Calcium Exchanger

During relaxation the sarcoplasmic calcium uptake pump and the Na^+ /Ca^{2+} exchanger in the sarcolemma compete for the removal of cytosolic calcium, with the SR pump normally being dominant.[51] Restitution of calcium balance takes place by the activity of a series of transsarcolemmal exchangers, the chief of which is the Na^+ /Ca^{2+} exchanger (Fig. 14-13) .[52] The exchanger (molecular weight of 108 kDa) consists of 970 amino acids and does not have substantial homology to any other known protein.[52] Specific inhibitory peptides have been identified.[53] The direction of ion exchange is responsive to the membrane potential and to the concentrations of sodium and calcium ions on either side of the sarcolemma. Because sodium and calcium ions can exchange either inward or outward in response to the membrane potential, there must be a specific membrane potential, called the reversal or equilibrium potential, at which the ions are so distributed that they can move as easily the one way as the other.[52] The reversal potential may lie about halfway between the resting membrane potential and the potential of the fully depolarized state. Changing the membrane potential from the resting value of -85 mV to +20 mV in the phase of rapid depolarization of the action potential may therefore briefly reverse the direction of Na^+ /Ca^{2+} exchange.[52] A major unsolved problem in relation to the activity and direction of the Na^+ /Ca^{2+} exchanger is the true value of the internal sodium or calcium ion concentrations, which may differ in the subsarcolemmal "*fuzzy space*" from the bulk cytosol (Fig. 14-14) .

REVERSE MODE Na^+ /Ca^{2+} EXCHANGE.

During depolarization the charge on the inner side of the sarcolemma becomes positive, which will tend to hinder the entrance of sodium ions with their positive charge. Thus, the sodium ions that have just entered during the opening of the sodium channel will tend to leave and calcium ions will tend to enter. This process, thought to occur more in larger mammals with slow heart rates and long action potential durations, contrasts to the standard "forward mode" (Na^+ in, Ca^{2+} out) (compare Figs. 14-13 and 14-14) . Such transsarcolemmal calcium entry during reversed mode exchange may participate in calcium-induced calcium release.[54] In myocytes from the failing human heart, enhanced reversed exchange contributes to the slow decline of the Ca^{2+} transient[55] that may explain delayed diastolic relaxation (see p. 470). After ischemia, and possibly in heart failure, reverse mode exchange may predispose to afterdepolarizations and arrhythmias.[37]

HEART RATE AND Na^+ /Ca^{2+} EXCHANGE.

This exchanger may participate in the force-frequency relationship (Treppe or Bowditch phenomenon).[56] According to the "sodium pump lag" hypothesis, the rapid accumulation of calcium ions during fast stimulation of the myocardium outstrips the ability of the Na^+ /Ca^{2+} exchanger and the sodium pump to achieve return to ionic normality. The result is an accumulation of calcium ions within the SR and an increased force of contraction.[57] Prolonged calcium overload, the result of this process, may

contribute to the cardiomyopathy of tachycardia.

Sodium Pump (Na^+ ,K^+ -ATPase)

The sarcolemma becomes highly permeable to Na^+ only during the opening of the Na^+ channel during early depolarization. Some Na^+ will also enter during the exit of Ca^{2+} by Na^+ /Ca^{2+} exchange. Most of this influx of Na^+ across the sarcolemma must be corrected by the activity of the Na^+ /K^+ pump, also called the Na^+ /K^+ -ATPase or simply the Na^+ pump.[58] The pump is activated by internal Na^+ or external K^+ .[58] One ATP molecule is used per transport cycle. The ions are first secluded within the pump protein and then extruded to either side. Although there has been some dispute about the exact ratio of Na^+ to K^+ that are pumped, a generally accepted model is that for each three Na^+ exported, two K^+ are imported. During this process, one positive charge must leave the cell. Hence, the pump is electrogenic and is also called the electrogenic Na^+ pump.[58] The current induced by sustained activity of the pump may contribute about -10 mV to the resting membrane potential.[58] Because the pump must extrude Na^+ ions entering by either Na^+ /Ca^{2+} exchange or by the Na^+ channel, its sustained activity is essential for the maintenance of normal ion balance (see Fig. 14-13) .

RECEPTORS AND SIGNAL SYSTEMS

The autonomic nervous system can initiate signal systems that profoundly alter the fluxes of calcium and other ions and thereby the contraction and relaxation of the myocardium. The sum total of these processes converting an extracellular hormonal or neural stimulus to an intracellular

Figure 14-13 Regulation of Ca^{2+} balance within the myocardial cell, showing role of sarcoplasmic reticulum (SR) in contraction-relaxation cycle. There is a balance between the Ca^{2+} ions entering on depolarization (right) and those leaving the cell by the Na^+ /Ca^{2+} exchange mechanism. A smaller number of Ca^{2+} ions leave by an adenosine triphosphate (ATP)-dependent sarcolemmal Ca^{2+} pump. Ion gradients for Na^+ and K^+ are maintained by the operation of the sodium pump (Na^+ ,K^+ -ATPase). The Ca^{2+} in the subsarcolemmal "fuzzy space" may be different from that in the free cytosol. An increased internal Ca^{2+} concentration after Ca^{2+} release from the SR is reduced by competition among one of three routes: uptake into the sarcoplasmic reticulum (SR), Na^+ /Ca^{2+} exchange, and outward pumping by the membrane Ca^{2+} -ATPase. The dominant uptake mechanism for Ca^{2+} is into the SR, followed by the exchanger, followed by the membrane pump. (From Opie LH: The Heart, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

physiological change is called *signal transduction*, which typically starts with the agonist binding to a receptor site.[35] Thus, adrenergic or cholinergic stimulation of the sarcolemmal receptors inaugurates the activity of a complex system of sarcolemmal and cytosolic messengers.[59] Occupancy of the beta-adrenergic receptor is coupled by a

G-protein complex (Fig. 14-15) to activation of a sarcolemmal enzyme, adenylate cyclase, that sets in motion a series of signals that terminate with activation of certain crucial proteins, such as those of the calcium channel (Fig. 14-16). Other cardiac receptors, such as the alpha-adrenergic receptor,

Figure 14-14 Proposal for "reverse mode" Na^+ /Ca^{2+} exchange in the direction of calcium entry after accumulation of sodium ions in the "fuzzy space." According to this proposal, the Na^+ /Ca^{2+} exchange may play a role in the liberation of calcium involved in the cardiac contractile cycle. (From Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

have an alternate dual messenger system involving IP_3 and diacylglycerol, with the latter activating protein kinase C (PKC).[35] [60] Such signals are of established importance in controlling calcium flux in vascular smooth muscle, thereby regulating vascular tone and indirectly the blood pressure. In the case of cardiac myocytes, it is now appreciated that receptors coupled to PKC, such as angiotensin II, may play a major role in the regulation of cardiac myocyte growth and sometimes have inotropic effects. Yet other messenger systems exist to convey different signals. For example, in blood vessels, nitric oxide formed in the inner endothelial layer stimulates the formation of cyclic guanosine monophosphate (GMP) in the smooth muscle layer, thereby causing relaxation (vasodilation).

Beta-Adrenergic Receptors and G Proteins

Cardiac beta-adrenergic receptors are chiefly the $beta_1$ subtype, whereas most noncardiac receptors are $beta_2$. About 20 percent of the total beta-receptor population is in the left ventricle and about twice as high a percentage is in the atria. These $beta_2$ receptors appear to have greater efficacy in their capacity to activate the G protein/adenylate cyclase system than do the $beta_1$ receptors.[61] The receptor site is highly stereospecific, the best fit among catecholamines being obtained with the synthetic agent isoproterenol (ISO) rather than with the naturally occurring catecholamines norepinephrine (NE) and epinephrine (E). In the case of $beta_1$ receptors, the order of agonist activity is ISO > E=NE, whereas in the case of $beta_2$ receptors, the order is ISO > E > NE. Human $beta_1$ and $beta_2$ receptors have now both been cloned. [62] The transmembrane domains are held to be the site of agonist and antagonist binding, whereas the cytoplasmic domains interact with G proteins. One of the phosphorylation sites on the terminal COOH tail may be involved in desensitization (see next section).

ADENYLATE CYCLASE.

Adenylate cyclase is a transmembrane enzyme system, also called adenylyl or adenyl cyclase,

Figure 14-15 G proteins and their role in signal transduction in response to beta-adrenergic stimulation. Steps in G_s protein cycle: (i) inactive beta-receptor, inactive G_s protein (alpha+beta+gamma); (ii) beta-receptor occupancy, guanosine triphosphate (GTP) binds to alpha subunit of G_s ($alpha_s$) to displace GDP; (iii) the G subunits dissociate. Affinity of receptor for agonist decreases. $alpha_s$ -GTP stimulates activity of adenylate cyclase with formation of cyclic adenosine monophosphate (AMP); (iv) GTPase becomes active and converts GTP to guanosine diphosphate (GDP), and $alpha_s$ -GDP re-forms. This is the end of the activation cycle. The inactive state is resumed. $alpha_s$ =stimulatory alpha subunit of G protein; beta=beta subunit of G protein; gamma=gamma subunit of G protein; G_s =stimulatory G-protein. (Modified with permission from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

that responds to input from G proteins. G_s is the stimulatory sarcolemmal G protein complex that passes on the signal from the beta receptor to adenylate cyclase.[63] In the sinus node, a similar messenger system increases the heart rate. Adenylate cyclase, stimulated by G_s , produces the second messenger, cyclic AMP, which then acts through a further series of intracellular signals and specifically the third messenger protein kinase A, to increase cytosolic calcium transients. In contrast, cholinergic stimulation exerts inhibitory influences, largely on the heart rate, but also on atrial contraction, acting at least in part by decreasing the rate of formation of cyclic AMP.[59]

THE STIMULATORY G PROTEIN (G_s).

G proteins are a superfamily of proteins that bind guanine triphosphate (GTP) and other guanine nucleotides. G proteins are crucial in carrying the signal onward from the first messenger and its receptor, to the activity of the membrane-bound enzyme system that produces the second messenger (see Figs. 14-15 and 14-16) .[64] The triple combination of the beta receptor, the G protein complex, and adenylate cyclase is termed the *beta-adrenergic system*.[65] The G protein itself is a heterotrimer composed of G_{alpha} , G_{beta} , and G_{gamma} , which on receptor stimulation splits into the alpha subunit that is bound to GTP, and the beta-gamma subunit.[66] Either of these subunits may regulate differing effectors such as adenylate cyclase, phospholipase C, and ion channels. The activity of adenylate cyclase is controlled by two different G-protein complexes, namely G_s , which stimulates, and G_i , which inhibits.[67] The alpha subunit of G_s ($alpha_s$) combines with GTP and then separates off from the other two subunits to enhance activity of adenylate cyclase. The beta and gamma subunits (beta-gamma) appear to be linked structurally and in function.

THE INHIBITORY G PROTEIN (G_i).

In contrast, a second trimeric GTP-binding protein, G_i , is responsible for inhibition of adenylate cyclase.[66] During cholinergic signaling, the muscarinic receptor is stimulated

and GTP binds to the inhibitory alpha subunit ($alpha_1$).[68] The latter then dissociates from the other two components of the G-protein complex, which are, as in the case of G_s , the combined beta-gamma subunits. Whereas the role of $alpha_i$ is not clear, the beta-gamma subunits act as follows. By stimulating the enzyme GTPase,[69] they break down the active $alpha_s$ subunit ($alpha_s$ -GTP), so that the activation of adenylate cyclase in response to $alpha_s$ stimulation becomes less. Furthermore, the beta-gamma subunit activates the K_{ACh} channel,[70] which, in turn, can inhibit the sinoatrial node to contribute to the bradycardiac effect of cholinergic stimulation. The $alpha_i$ subunit activates another potassium channel (K_{ATP}) [70] whose physiological function in the myocardium is still under discussion. Pathophysiologically, preconditioning may link to this channel (see later). In heart failure, $beta_2$ receptors may act via G_i to limit apoptosis (see later).

THE THIRD G PROTEIN (G_q).

This links a group of heptahelical (*hepta*="seven") myocardial receptors, including the alpha-adrenergic receptor and those for angiotensin II and endothelin, to another membrane-associated enzyme, phospholipase C, and thence to PKC (see later). G_q has at least four isoforms, of which two have been found in the heart. This G protein, unlike G_i , is not susceptible to inhibition by the pertussis toxin. Overexpression of Gq in mice induces a dilated cardiomyopathy,[71] which is of interest because angiotensin II and endothelin are known to be overactive in human heart failure. The initial phases may involve myocyte hypertrophy and apoptotic signaling.[72] Experimentally, increased cardiac-directed expression of adenylate cyclase counters this dilated cardiomyopathy.[71]

Role of Cyclic Adenosine Monophosphate

Adenylate cyclase is the only enzyme system producing cyclic AMP and that specifically requires low concentrations of ATP (and magnesium) as substrate. Surprisingly, the proposed molecular structure resembles that of certain channel proteins, such as the calcium channel. Most of the adenylate cyclase protein is located on the cytoplasmic side, the presumed site of interaction with the G protein. Cyclic AMP is the second messenger of beta-adrenergic receptor activity (see Fig. 14-16) , whereas another cyclic nucleotide, cyclic GMP, acts as a second messenger for some aspects of vagal cholinergic activity. In vascular smooth muscle, cyclic GMP is the second messenger of the nitric oxide messenger system. These messenger chemicals are present in the heart cell in minute concentrations, that of cyclic AMP being roughly about 10^{-9} M and that of cyclic GMP about 10^{-11} M.[73] Cyclic AMP has a very rapid turnover as a result of a constant dynamic balance between its formation by adenylate cyclase and removal by another enzyme, phosphodiesterase. In general, directional changes in

Figure 14-16 Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of beta-adrenergic stimulation. When the beta-adrenergic agonist interacts with the beta receptor, a series of G protein-mediated changes (see Fig. 14-15) leads to activation of adenylate cyclase and formation of cyclic adenosine monophosphate (cAMP). The latter acts by means of protein kinase A to stimulate metabolism (on left) and to phosphorylate the calcium channel protein. The result is an enhanced opening probability of the calcium channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma (SL) of the T tubule. These Ca^{2+} ions release more calcium from the sarcoplasmic reticulum (SR) (see Fig. 14-11) to increase cytosolic calcium and to activate troponin C. Calcium ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (P_i). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining the increased peak force development. An increased rate of relaxation is explained because cyclic AMP also activates the protein phospholamban, situated on the membrane of the SR, which controls the rate of uptake of calcium into the SR (see Fig. 14-11). The latter effect explains enhanced relaxation (lusitropic effect). AKAP=A-kinase anchoring proteins. P=phosphorylation; PL=phospholamban; SL=sarcolemma; SR=sarcoplasmic reticulum; TnI=troponin I. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

the tissue content of cyclic AMP can be related to directional changes in cardiac contractile activity. For example, beta-adrenergic stimulation increases both, whereas beta blockade inhibits the increases induced by beta agonists. *Forskolin*, a direct stimulator of adenylate cyclase, increases cyclic AMP and contractile activity. Adenosine, acting through A_1 -receptors, inhibits adenylate cyclase, decreases cyclic AMP, and lessens contractile activity. A number of hormones or peptides can couple to myocardial adenylate cyclase independently of the beta-adrenergic receptor. These are glucagon, thyroid hormone, prostacyclin (PGI_2), and the calcitonin gene-related peptide.

INHIBITION OF CYCLIC AMP FORMATION.

The major physiological stimulus to G_i is thought to be vagal muscarinic receptor stimulation. In addition, adenosine, by interaction with A_1 -receptors, couples to G_i to inhibit contraction and heart rate.[74] The adenosine A_2 -receptor paradoxically increases cyclic AMP. The latter effect, only of ancillary significance in the myocardium, is of major importance in vascular smooth muscle where it induces vasorelaxation.[74] Pathologically, inhibitory G_i is increased in experimental postinfarct heart failure[75] and in donor hearts before cardiac transplantation.[76]

CYCLIC AMP-DEPENDENT PROTEIN KINASES.

It is now clear that most of the effects of cyclic AMP are ultimately mediated by the protein kinases that phosphorylate various important proteins and enzymes.[77] [78] Phosphorylation is the donation of a phosphate group to the enzyme concerned, acting as a fundamental metabolic switch that can extensively amplify the signal.

Each protein kinase is composed of two subunits: regulatory (R) and catalytic (C). When

cyclic AMP interacts with the inactive protein kinase, it binds to the R subunit to liberate the active kinase that is the C subunit:

At a molecular level, this active kinase catalyzes the transfer of the terminal phosphate of ATP to serine and threonine residues of the protein substrates, leading to phosphorylation and modification of the properties of the proteins concerned, thereby promoting further key reactions. *Protein kinase A (PKA)* occurs in different cells in two isoforms: PKA-II predominates in cardiac cells.[78] The proposed anchorage of this kinase by *A-kinase anchoring proteins* (AKAPs) to specific organelles such as the SR explains the phenomenon of cyclic AMP compartmentation.[79] The G-protein system may not be evenly spread throughout the sarcolemma but localized to certain focal areas.[66] Thus, it is very likely that there is only a specific subcompartment of cyclic AMP available to increase contractile activity.[80]

Physiological Beta$_1$ -Adrenergic Effects

The probable sequence of events describing the positive inotropic effects of catecholamines is as follows (see Fig. 14-16) .
Catecholamine stimulation
beta receptor
molecular changes
binding of GTP to alpha$_s$ subunit of G protein
GTP alpha$_s$ subunit stimulates adenylate cyclase
formation of cyclic AMP from ATP
activation of cyclic AMP-dependent protein kinase, locally bound by an A-kinase anchoring protein
phosphorylation

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of a sarcolemmal protein p27
increased entry of calcium ion through increased opening of the voltage-dependent L-type calcium channels
greater calcium-induced calcium release through ryanodine receptor of sarcoplasmic reticulum, coupled with phosphorylation of the ryanodine receptor
greater and more rapid rise of intracellular free calcium ion concentration
increased calcium-troponin C interaction with deinhibition of tropomyosin effect on actin-myosin interaction
increased rate and number of cross bridges interacting with increased myosin ATPase activity
increased rate and peak of force development.

The increased *lusitropic (relaxant)* effect is the consequence of increased protein kinase A-mediated phosphorylation of phospholamban (see p. 452). Also, increased

phosphorylation of troponin I may help to desensitize the contractile apparatus to calcium ions (see Fig. 14-16) .

Physiological Switch-off, betaARK, and Arrestin

SHORT-TERM INHIBITORY MECHANISMS.

There is a potent feedback mechanism whereby the degree of postreceptor response to a given degree of beta-adrenergic receptor stimulation can be muted (Fig. 14-17) . This physiologically decreased response in which the beta-receptor signal is terminated within minutes to seconds is called *desensitization of the beta receptor* (see Fig. 14-17) . The key event is that sustained beta-agonist stimulation rapidly induces the activity of the beta-agonist receptor kinase (betaARK) that is involved in the transfer of the phosphate group to the phosphorylation site on the terminal COOH tail of the receptor.[81] Next, betaARK increases the affinity of the beta receptor for another protein family, the *arrestins.* [81] [82] Hypothetically, arrestins change the molecular configuration of the receptor in such a way that the G proteins cannot interact optimally with it. This disconnection of receptor stimulation from the activity of adenyl cyclase is called *uncoupling.* A back-up mechanism for desensitization is mediated by protein kinase A,[82] activated by cyclic AMP. This process also phosphorylates the beta receptor within minutes, providing a direct feedback mechanism to prevent adverse effects of excess cyclic AMP elevation and protein kinase A activation. *Resensitization* of the receptor occurs when the phosphate groups are split off the beta receptor by a phosphatase, so that the receptor may then again readily be linked to G_s .[83] Resensitization, like desensitization, occurs rapidly. Such short-term changes probably occur whenever there is

Figure 14-17 Mechanisms of beta-adrenergic receptor desensitization and internalization. Note newly described links of the internalized receptor complex with growth stimulation through mitogen activated protein (MAP) kinase. (Modified from Hein L, Kobilka BK: Adrenergic receptors: From molecular structures to in vivo function. Trends Cardiovasc Med 7:137-145, 1997.)

an emotional crisis or a burst of exercise, to fine tune the effects of beta-adrenergic stimulation and to prevent the risks of excess such as severe and potentially lethal arrhythmias.[84]

LONG-TERM INHIBITORY MECHANISMS.

Prolonged desensitization during sustained excess beta-adrenergic receptor stimulation, as during long infusions of sympathomimetic agents, may be explained by receptor sequestration, *internalization,* [82] and even lysosomal degradation.[85] In addition, the internalized receptor can participate in growth signaling, because arrestin forms a complex with the beta receptor and with tyrosine kinases, thereby ultimately linking to mitogen-activated protein (MAP) kinase.[86] Thus, prolonged beta-receptor stimulation may have growth as an end result while losing physiological effects such as positive

inotropic and lusitropic stimulation.

The overall picture is that of a reciprocal effect of beta-adrenergic receptor stimulation by the catecholamine beta agonists, soon followed by self-desensitization of the beta receptor by the betaARK/arrestin and protein kinase A mechanisms.[87] Long-term stimulation of the beta-adrenergic receptor increases the mRNA for betaARK, whereas beta blockade decreases the expression of betaARK, to enhance receptor signaling. Also, arrestin formation and receptor internalization may promote increased cardiac growth. Although the beta-arrestin effects are best described for $beta_2$ receptor, they also occur to a lesser extent with the $beta_1$ receptor.[88] These changes in postreceptor signaling may help to explain pathological alterations in the beta-receptor signaling system in heart failure.

Comparison of $Beta_2$ -Adrenergic Effects with $Beta_1$ -Adrenergic Effects

In the normal ventricle, about 20 percent of the receptors are $beta_2$ in nature; yet in heart failure this percentage can double. Whereas the postreceptor signaling sequence of the $beta_1$ receptor is well understood, that of the cardiac $beta_2$ receptor is still not fully clarified. Although $beta_2$ receptors link efficiently by means of G_s to adenyl cyclase, they may also couple to the inhibitory G_I proteins, at least in isolated murine myocytes.[89] In whole hearts, the inhibitory path seems latent, judging by data from studies in dogs.[90] In humans, the positive inotropic response to $beta_2$ stimulation by salbutamol occurs at least in part through $beta_2$ receptors on the terminal neurones of the cardiac sympathetic nerves, thereby releasing norepinephrine, which in turn exerts dominant $beta_1$ effects.[91] Thus, the overall evidence is that $beta_2$ -receptor stimulation has similar inotropic and lusitropic effects to $beta_1$ -receptor stimulation, even though the precise mechanisms and signal systems may differ.[90]

Cholinergic Receptors

In the case of the parasympathetic system, signaling is again an extracellular first messenger (acetylcholine), a receptor system (the muscarinic receptor), and a sarcolemmal signaling system (the G-protein system). The myocardial *muscarinic receptor* (M_2) is associated specifically with the activity of the vagal nerve endings. Receptor stimulation produces a negative chronotropic response that is inhibited by atropine.

Regarding the *negative inotropic effect of vagal stimulation* (Fig. 14-18) , the mechanism is multiple, including (1) heart rate slowing (negative Treppe phenomenon); (2) an inhibition of the formation of cyclic AMP; and (3) a direct negative inotropic effect mediated by cyclic GMP. Ventricular tissue is much less responsive to muscarinic agonists than atrial tissue, although the receptor populations are similar in density.[59] Thus, there must be postreceptor differences between atrial and ventricular tissue, probably in the degree of G-protein coupling. In general, the negative inotropic effect of vagal stimulation has been best observed in the presence of beta stimulation (Table

14-2) when vagal effects counteract those of prior beta stimulation. [59] [92] The proposal is that muscarinic stimulation acting through G_i inhibits the G_s activation that results from beta-receptor occupation. Physiologically, stimulation of G_i may give better protection

Figure 14-18 Interaction between parasympathetic and sympathetic systems at a cellular level may involve two opposing cyclic nucleotides: cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP). Many effects of vagal stimulation could best be explained by the inhibitory effect on the formation of cyclic AMP, including formation of inhibitory G protein (G_i) in response to M_2 -receptor stimulation (see Fig. 14-19) . NO=nitric oxide. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

from the arrhythmogenic than the inotropic effects of beta stimulation.[93]

Cyclic GMP acts as a second messenger to vagal stimulation just as cyclic AMP does to beta-adrenergic stimulation. Thus, the vagus may have a dual effect on second messengers, inhibiting the formation of cyclic AMP and increasing that of cyclic GMP,[94] thereby providing one of several explanations for *sympathetic-parasympathetic interaction*. In the sinus node, formation of cyclic GMP may occur not only by guanyl cyclase (see Fig. 14-18) but also by a muscarinic-mediated formation of nitric oxide.[95] Cyclic GMP may in turn inhibit the activity of the L-calcium channel by a cyclic GMP-dependent kinase (Gkinase).[96] Favoring this view is the finding that cell-permeable analogs of cyclic GMP have antiadrenergic effects. The problem with this hypothesis is the inconstant increase in ventricular cyclic GMP in response to vagal stimulation. The explanation could lie in cell compartmentation of cyclic GMP, as postulated for cyclic AMP. Also the effects of cyclic GMP on contractility may be more subtle than changes in the pattern of peak force development. Rather, there may be decreased sensitivity of the myofilaments to Ca^{2+} and earlier relaxation.[97]

Yet another mechanism for parasympathetic modulation of sympathetic interaction lies at the level of the sympathetic terminal neurones, where a *presynaptic muscarinic M_2 receptor* inhibits the release of norepinephrine.[59] Additionally, both adrenergic and cholinergic stimuli exert complex and potentially important effects on ion channels that can be translated into opposing effects on cardiac function (see Table 14-2) . The presence of such multiple mechanisms for the inhibitory effects of vagal stimulation on the heart rate, the inotropic state, and arrhythmogenicity suggest that "braking" of beta-adrenergic stimulation is desirable. Otherwise, the risk may be that intense beta-adrenergic stimulation would excessively increase the heart rate or inotropic state or provoke potentially fatal arrhythmias.

Phospholipase C-Protein Kinase C

There is an important group of receptors previously thought to act chiefly on the

myocardium at the presynaptic level to enhance release of norepinephrine and on postsynaptic vascular receptors to cause vasoconstriction. Such receptors include those for alpha$_1$ -adrenergic catecholamines, angiotensin II, and endothelin. They are all linked to phospholipase C by a G protein, G_q (Fig. 14-19) . Currently, two aspects of their action are under intense focus. First, the signaling system involved is clearly different from that involved in beta-adrenergic effects.[35] Second, these receptors have been identified in ventricular myocytes, posing the question of their physiological role--a problem that is still not fully clarified.[60]

PHOSPHOLIPASE C.

When any of these agonists (alpha$_1$ -adrenergic catecholamines, angiotensin I, and endothelin) occupies its receptor, then the link to phospholipase C is by one of the G-protein family, namely G_q . Phospholipase C is the "common route for the action of many hormones" in noncardiac cells.[98] The exact steps involved are not as well understood as is the coupling of the beta receptor to adenylate cyclase, but similar components of the G-protein complex appear to be involved.[99] First G_q activates phospholipase C to split the compound phosphatidyl inositol bisphosphate (PIP_2), part of the membrane phospholipid system, into two second messengers: IP_3 and 1,2-diacylglycerol (DAG). IP_3 is the natural ligand for the IP_3 receptors on the SR, stimulating the slow release of calcium and increasing calcium oscillations.[100] This calcium is unlikely to play a major role in the regulation of contraction, but it contributes to the excess calcium oscillations that underlie reperfusion arrhythmias.[101] Physiologically, calcium released by IP_3 acts on the next messenger in the system, PKC, by promoting the translocation of this enzyme from cytosol to sarcolemma.[102] Once translocated, PKC becomes activated by DAG, the other second messenger of phospholipase C activity. DAG, being highly lipophilic, stays in the cell membrane and, together with a resident serine component of the membrane lipids, stimulates PKC into activity by reducing the calcium requirement of the PKC to micromolar values.[78]

PROTEIN KINASE C.

This key kinase has multiple functions. First, it is linked to the phospholipase signaling system, of prime importance in vascular contraction, and possibly acting as an inotropic back-up system in the myocardium (see Fig. 14-19) . Second, PKC may be a key molecular switch in the "hypertrophic signal system," responding to stretch and to neurohormonal input.[103] Third, it plays a pivotal role in preconditioning, receiving stimuli from a number of G protein-linked

TABLE 14-2 -- IONIC EFFECTS OF ADRENERGIC AND CHOLINERGIC STIMULATION: RELATION TO HEART RATE AND CONTRACTILE ACTIVITY

AGONIST	IONIC CURRENT	EFFECT

Beta-adrenergic stimulation*	I_{Ca} increased I_k increased I_{to} increased I_f increased I_{Na} increased	+ Inotropic - Inotropic - Inotropic Heart rate Contraction Conduction
Acetylcholine (ACh) during beta stimulation*	I_{Ca} decreased I_{Na} decreased I_f decreased	- Inotropic - Dromotropic - Chronotropic
ACh direct effect on K^+ currents§	I_{kACh} and I_{kATP} increased	Heart rate decreased
$Alpha_1$ -adrenergic stimulation	I_{to} decreased I_k decreased I_{kACh} decreased	+ Inotropic + Inotropic Atrial current, effects not clear

ATP=adenosine triphosphate; -=negative; +=positive; =increased.

*Data from Matsuda et al.[92]

Data from Matsuda et al.[216]

Data from Chang and Cohen[217]
§Data from Kurachi.[70]

Data from Fedida.[218]

Figure 14-19 Phospholipase C (PLC) signaling system in myocardium, linked to protein kinase C (PKC), through three receptors that couple to G protein $G_{q,}$ namely those for $alpha_1$ -adrenergic, angiotensin II (AII acting on the AT_1 receptor), AT_1 , and endothelin (ET). PLC splits phosphatidyl inositol bisphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG), the latter being membrane bound. IP_3 (and IP_4) release Ca^{2+} from the sarcoplasmic reticulum (SR) to activate protein kinase C (PKC) by translocating it from a cytosolic to a membrane-bound situation. Ca^{2+} released by IP_3 may also have a supportive inotropic role and be harmful in the reperfusion period.[37] PKC plays a role in growth regulation and as an effector of preconditioning (PC) that activates mitochondrial and sarcolemmal adenosine triphosphate (ATP)-sensitive potassium channels (see Fig. 14-36) (Figure Not Available) . (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven,

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receptors and ultimately activating the mitochondrial ATP-sensitive potassium channels.[104] Such multiple functions may be mediated by different isoforms of PKC, of which there are at least ten, the functions of which are still poorly understood. The isoforms are divided into three groups: (1) the conventional (which respond to calcium in vitro), (2) the novel (which respond to diacylglycerol but not to calcium), and (3) the atypical (which respond to neither calcium nor diacylglycerol but rather to phospholipids). The conventional beta isoforms, increased in the failing human heart,[105] may be linked to enhanced growth. [103] The novel isoforms epsilon and eta play a role in preconditioning, at least in the rabbit.[106] The epsilon isoforms may also be concerned with inotropy.[107] The function of the atypical group of isoforms is still unknown.

Inhibitory Signal Systems

There are successive brakes that can limit the potentially dangerous overactivity of the beta-adrenergic system, including the self-initiated receptor shutoff and activity of the cholinergic parasympathetic system, as already described. Other inhibitory signals include nitric oxide, adenosine, and the opioids.

Nitric Oxide as Messenger with Cyclic GMP as Target

Nitric oxide (NO), the focus of the Nobel Prize awards for 1998, may be generated by an enzyme either in the vascular endothelium (eNOS) or in certain circumstances in the cardiomyocytes by the inducible enzyme (iNOS). NO, a free radical gas, can permeate from the endothelial cells to have complex dose-dependent effects on the myocardium.[108] [109] NO synthesis in endothelial cells is increased by shear stress as during an increased blood flow, by increased cardiac loading,[110] by increased heart rate,[111] or by bradykinin. [108] The standard concept is that cyclic GMP is the second messenger of NO and that cyclic GMP can, by stimulation of the appropriate protein G-kinases (PKG), result in a decreased heart rate and in a negative inotropic effect. These actions are mediated by inhibition of the calcium channel[108] and/or by decreased sensitivity of the contractile proteins to cyclic GMP.[111]

NO-mediated formation of cyclic GMP, under the influence of guanylate cyclase, is thought to occur in response to (1) cholinergic stimulation, as already discussed, and (2) NO, derived from the endothelium or from NO donors such as the nitrates (Fig. 14-20) . NO enhances the negative inotropic effect of acetylcholine and decreases the positive inotropic effects of beta stimulation.[112] Therefore, the NO system, it is proposed, may have a negative modulatory role on the cardiac effects of autonomic stimulation in keeping with the proposed formation of cyclic GMP.[108] In addition, NO also decreases mitochondrial metabolism, thereby reducing myocardial oxygen demand. Angiotensin-converting enzyme inhibitors, decreasing the breakdown of bradykinin and thereby increasing formation of NO by the endothelium, may act likewise.[113]

Unexpected positive inotropic effects of low-dose NO have also been found.[109] The explanation may be (1) release of calcium from the SR by the messenger, cyclic ADP ribose (see Fig. 14-20) , and/or (2) inhibition of a cyclic GMP-sensitive myocardial

phosphodiesterase, thereby increasing cyclic AMP. Therefore, some workers regard NO as having dose-dependent bidirectional effects on the inotropic status. Likewise in heart failure, when both eNOS and iNOS are upregulated, effects may be either favorable or unfavorable.[111] Physiological concentrations of NO suppress apoptosis whereas higher levels stimulate it. Peroxynitrite ($ONOO^-$), formed from NO and superoxide, may help to explain the toxicity of the higher levels.

ADENOSINE SIGNALING.

Adenosine, like NO, is a physiological vasodilator. It is formed from the breakdown of ATP both physiologically (as during an increased heart

Figure 14-20 Nitric oxide messenger system. Proposed role in stimulating guanylate cyclase and cyclic guanosine monophosphate (cGMP) to cause vasodilation and possibly a negative inotropic effect. The physiological significance of the cyclic adenosine diphosphate (ADP) ribose path is still speculative, but it could explain the unexpected positive inotropic effect of cGMP in some experiments. RR=ryanodine receptor. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

load) and pathologically (as in ischemia). Adenosine can diffuse from myocardial cells to act on coronary arterial smooth muscle to cause vasodilation. The mechanism of the latter effect is reasonably well understood and involves the stimulation of vascular adenylate cyclase and cyclic AMP formation. A_2 receptors mediate such vasodilation. A_2 receptors have also been identified in cardiomyocytes, yet stimulation of such receptors does not have functional consequences.[114] Therefore, it is only the A_1 receptors that are coupled to adenylate cyclase by the inhibitory G protein ($alpha_i$ subunit) that are functional in the myocardium.

Other signal systems and other receptor subtypes are also involved in adenosine signaling.[115] First, A_1 receptors couple to the acetylcholine-sensitive potassium channel (current I_{kACh}) to stimulate channel opening and thereby to exert inhibitory effects on the sinus and atrioventricular nodes. The latter inhibition is the basis for the use of adenosine in the treatment of supraventricular nodal reentry arrhythmias. Second, A_1 receptors may couple to the PKC system, and thence to the ATP-sensitive potassium channel, thereby hypothetically explaining their role in preconditioning (see Intermittent Ischemia and Preconditioning). Third, A_3 receptors also precondition by means of PKC, without, however, the obvious hemodynamic effects of A_1 receptor stimulation.[116]

OPIOID RECEPTORS.

Opioids released in the central nervous system are known to participate in

cardiovascular regulation, by inhibiting sympathetic and promoting parasympathetic outflow. Such endogenous opiates, called the *endorphins,* may be involved in the benefits of cardiovascular training. In congestive heart failure, opioid activity may limit adrenergic activation. In animals, stimulation of opioid receptors may help to explain the phenomenon of hibernation.[117] In addition, opioid drugs such as morphine are often used in cardiovascular medicine and may have effects beyond pain relief. Opioid effects may be mediated, in part, through local cardiovascular opioid receptors that respond to stimulation of the opioid system, in response to conditions of physiological or psychosocial stress.

There are three opioid receptors, delta, kappa, and mu, of which the former two are found in the human heart whereas the mu receptors mediate signals that dampen the pain response. In the heart, the delta receptors inhibit the adrenergic system by coupling to G_{I} , thereby inhibiting the activation of adenyl cyclase by beta-adrenergic stimulation.[118] In addition, by stimulation of the PKC pathway (see later) they also mediate preconditioning.

Adaptive Signal Systems

These signals include (1) the phospholipase-protein kinase C system, important both in generating cell growth in response to hormonal stimuli and in protection from ischemia by preconditioning (see p. 459); (2) the stretch receptors, which can blend acute and chronic myocardial functional and growth responses to a chronically increased wall stress; (3) tumor necrosis factor-alpha and other cytokines, which mediate the normal inflammatory response and may be either adaptive, as in protection from ischemia-reperfusion, or maladaptive, as in severe heart failure; and (4) the beta-adrenergic adaption to heart failure, both adaptive and maladaptive.

STRETCH RECEPTORS.

Both myocardial and vascular cells can respond to stretch by activation of a group of poorly understood mechanoreceptors, also called stretch receptors. Activation of these receptors is linked to a series of intracellular phosphorylations including a crucial group of enzymes in the growth cascade, namely, MAP kinases.[119] Stretch receptors may respond to conformational changes by allowing increased entry of specific ions such as calcium, which may then initiate the intracellular signals. In addition, mechanically induced cytoskeletal distortion acting through integrins and other structural proteins can activate the MAP kinase cascade.[119] Of considerable interest is the concept that an early event in the sequence leading from muscle stretch to hypertrophy is release of angiotensin II from the stretched muscle.[120] Nonetheless, the dominant factor is stretch, not angiotensin II, as shown in a mouse knockout model of the angiotensin I receptor.[121]

CYTOKINES, INCLUDING TUMOR NECROSIS FACTORALPHA (TNF-alpha).

TNF-alpha is one of the family of peptide cytokines that form part of the injury response repertoire. Such cytokines mediate local events and are distinct from circulating

neurotransmitters or hormones. TNF-alpha mediates bifunctional effects.[122] Those considered as harmful include the promotion of apoptosis as may occur in heart failure. TNF-alpha may also have a beneficial effect in cardiac homeostasis, when its formation is stimulated as part of the growth response to mechanical stress or in response to myocardial ischemia-reperfusion injury.[123] Currently, it is not known why the intracellular signaling paths leading from the surface receptors for TNF-alpha sometimes lead to cell survival and other times to apoptosis. Two proposals are, first, that there are short-term adaptive and long-term maladaptive effects of TNF-alpha, and, second, that low concentrations are adaptive and high concentrations are maladaptive.[123] An important current question is whether the acute reduction of cardiac contractility induced by TNF-alpha and possibly mediated by NO is adaptive[124] and confers cardioprotection especially during ischemia-reperfusion, or maladaptive, leading to long-term malfunction.

Beta-Adrenergic Signaling in Heart Failure

In congestive heart failure (Fig. 14-21) there are increased levels of circulating catecholamines that result in prolonged excessive beta-adrenergic stimulation of the heart. As outlined already (see section on Physiological Switch-off, betaARK, and Arrestin), such excess stimulation causes desensitization, explained by both uncoupling and by receptor internalization. The latter change explains why the density of the $beta_1$ receptor may be decreased by as much as 50 to 70 percent,[125] a process called *downregulation.* Other changes to the $beta_1$ -adrenergic/cyclic AMP system include (1) decreased adenylate cyclase activity[126] ; (2) increased levels of inhibitory G_i proteins[75] [127] ; and (3) a decrease of the mRNA for the $beta_1$ receptor.[81] The downregulation of the $beta_1$ receptor in advanced heart failure results in relative upregulation of the cardiac $beta_2$ receptors so that the density of these receptors is increased relative to that of the $beta_1$ receptors. There is a newly recognized inhibitory link between $beta_2$ receptors and adenyl cyclase. These receptors unexpectedly also couple with the inhibitory G_i protein, thereby limiting experimental apoptosis. [127] Antiapoptosis is a new, albeit still hypothetical, therapeutic principle in heart failure. According to these concepts, $beta_1$ blockade in heart failure could leave intact this $beta_2$ G_i -mediated protective path. *Uncoupling* of both of the beta-receptor subtypes from the signaling system linked to G_s may be explained by the betaARK/arrestin mechanism, already described (see Fig. 14-17) . Thus there is decreased activity of both $beta_1$ receptor and $beta_2$ receptor G_s -linked signaling systems (see Fig. 14-21) . All these obstructions to the flow of signals from both $beta_1$ and $beta_2$ receptors result in less formation of cyclic AMP, which partially explains the poorly developed and low-amplitude calcium transients in human tissue from severe heart failure subjects.[128] Furthermore, calcium uptake into the SR is decreased by downregulation of the calcium uptake pump on the SR, SERCA 2a, in the failing human heart.[42] The response to $alpha_1$ stimulation in heart failure is also much diminished.[129] The net result is that despite the increased circulating catecholamine levels the inotropic response is diminished and contractility falls.

Figure 14-21 In advanced heart failure, there is depressed function of both the beta-adrenergic receptor signal system and the sarcoplasmic reticulum (SR). Both $beta_1$ - and $beta_2$ -adrenergic receptors are uncoupled from G_s , the stimulatory G protein. Activity of G_i , the inhibitory G protein, is increased ( ) by increased activity of its messenger RNA. The overall result is that activity of adenylate cyclase (AC) also falls. Consequently, there is less formation ( ) of cyclic adenosine monophosphate (cAMP) with less release of calcium ions from the SR. Uptake of calcium into the SR also drops, as a result of impaired activity of the calcium uptake pump SERCA 2a (see Fig. 14-11) . There is also decreased synthesis of this receptor ($beta_1$ AR mRNA) and of increased synthesis of beta-adrenergic receptor kinase (betaARK mRNA). betaARK phosphorylates the beta-adrenergic receptors so that they are uncoupled from G_s (negative sign between the adrenergic receptors and G_s). This uncoupling is further promoted by beta arrestin (see Fig. 14-17) . $Beta_2$ -adrenergic receptors may unexpectedly couple to G_i (see reference 89). M_2 =muscarinic receptor; ACh=acetylcholine. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

CONTRACTILE PERFORMANCE OF THE INTACT HEART

There are three main determinants of myocardial mechanical performance, namely, the Frank-Starling mechanism, the contractile state, and the heart rate. This section describes the cardiac cycle and then the determinants of left ventricular function.

The Cardiac Cycle

The cardiac cycle, fully assembled by Lewis [130] but first conceived by Wiggers,[131] yields important information on the temporal sequence of events in the cardiac cycle. The three basic events are (1) left ventricular contraction, (2) left ventricular relaxation, and (3) left ventricular filling (Table 14-3) . Although similar mechanical events occur in the right side of the heart, it is those on the left side that will be focused on.

LEFT VENTRICULAR CONTRACTION.

Left ventricular pressure starts to build up when the arrival of calcium ions at the contractile proteins starts to trigger actin-myosin interaction. On the electrocardiogram (ECG), the advance of the wave of depolarization is indicated by the peak of the R wave (Fig. 14-22) . Soon after, left ventricular pressure in the early contraction phase builds up and exceeds that in the left atrium (normally 10 to 15 mm Hg), followed about 20 milliseconds later by M_1 , the mitral component of the first heart sound. The exact relation of M_1 to mitral valve closure is open to dispute. Although mitral valve closure is often thought to coincide with the crossover point at which the left ventricular pressure starts to exceed the left atrial pressure,[132] in reality mitral valve closure is delayed because the valve is kept open by the inertia of the blood flow. Shortly thereafter, pressure changes in the right ventricle, similar in pattern but lesser in magnitude to

those in the left ventricle, cause the tricuspid valve to close, thereby creating T_1 , which is the second component of the first heart sound. During this phase of contraction between mitral valve and aortic valve opening, the left ventricular volume is fixed (*isovolumic contraction*), because both aortic and mitral valves are shut. As more and more myofibers enter the contracted state, pressure development in the left ventricle proceeds. The interaction of actin and myosin increases, and cross-bridge cycling augments. When the pressure in the left ventricle exceeds that in the aorta, the aortic valve opens, which is usually a clinically silent event. Opening of the aortic valve is followed by the phase of *rapid ejection*. The rate of ejection is determined not only by the pressure gradient across the aortic valve but also by the elastic properties of the aorta and the arterial tree, which undergoes systolic expansion. Left ventricular pressure rises to a peak and then starts to fall.

LEFT VENTRICULAR RELAXATION.

As the cytosolic calcium ion concentration starts to decline because of uptake of calcium into the SR under the influence of activated

TABLE 14-3 -- THE CARDIAC CYCLE

Left Ventricular Contraction
Isovolumic contraction (b)
Maximal ejection (c)
Left Ventricular Relaxation
Start of relaxation and reduced ejection (d)
Isovolumic relaxation (e)
LV filling: rapid phase (f)
Slow LV filling (diastasis) (g)
Atrial systole or booster (a)

The letters a-g refer to the phases of the cardiac cycle shown in Wiggers' diagram (Fig. 14-22) . These letters are arbitrarily allocated so that atrial systole (a) coincides with the a wave and (c) with the c wave of the jugular venous pressure.

Figure 14-22 The mechanical events in the cardiac cycle were first assembled by Lewis in 1920[130] but first conceived by Wiggers in 1915.[131] Note that mitral valve closure occurs *after* the crossover point of atrial and ventricular pressures at the start of systole. The visual phases of the ventricular cycle in the bottom panel are modified from Shepherd and Vanhoutte (Shepherd JT, Vanhoutte PM: The Human Cardiovascular System. New York, Raven Press, 1979, p 68.) For explanation of phases a to g, see Table 14-3 . ECG=electrocardiogram; JVP=jugular venous pressure; M_1 =mitral component of first sound at time of mitral valve closure; T_1 =tricuspid valve closure, second component of first heart sound;

AO=aortic valve opening, normally inaudible; A_2 =aortic valve closure, aortic component of second sound; P_2 =pulmonary component of second sound, pulmonary valve closure; MO=mitral valve opening, which may be audible in mitral stenosis as the opening snap. S_3 =third heart sound; S_4 =fourth heart sound; a=wave produced by right atrial contraction; c=carotid wave artifact during rapid LV ejection phase; v=venous return wave that causes pressure to rise while tricuspid valve is closed. Cycle length of 800 milliseconds for 75 beats/min. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

phospholamban, more and more myofibers enter the state of relaxation and the rate of ejection of blood from the left ventricle into the aorta falls during the *phase of reduced ejection*. During this phase, blood flow from the left ventricle to the aorta rapidly diminishes but flow through the arterial tree is maintained by aortic recoil--the Windkessel effect.[133] The pressure in the aorta exceeds the falling pressure in the left ventricle. The aortic valve closes, creating the first component of the second sound, A_2 (the second component, P_2 , results from closure of the pulmonary valve as the pulmonary artery pressure exceeds that in the right ventricle). Thereafter, the ventricle continues to relax. Because the mitral valve is closed during this phase, the left ventricular volume cannot change (*isovolumic relaxation*). When the left ventricular pressure falls to below that in the left atrium, the mitral valve opens (normally silent) and the filling phase of the cardiac cycle restarts (see Fig. 14-22) .

LEFT VENTRICULAR FILLING PHASES.

As left ventricular pressure drops below that in the left atrium, just after mitral valve opening, the *phase of rapid or early filling* occurs to account for most of ventricular filling. [134] Active diastolic relaxation of the ventricle may also contribute to early filling. Such rapid filling may cause the physiological third heart sound (S_3), particularly when there is a hyperkinetic circulation.[135] As pressures in the atrium and ventricle equalsize, left ventricular filling virtually stops (*diastasis*, separation). Renewed filling requires that the pressure gradient from the atrium to the ventricle should increase. This is achieved by *atrial systole* (or the *left atrial booster*), which is especially important when a high cardiac output is required, as during exercise, or when the left ventricle fails to relax normally, as in left ventricular hypertrophy.[134]

DEFINITIONS OF SYSTOLE AND DIASTOLE.

In Greek, *systole* means "contraction" and *diastole* means "to send apart." The start of systole can either be regarded as (1) the beginning of isovolumic contraction when left ventricular pressure exceeds the atrial pressure or (2) mitral valve closure (M_1). These correspond reasonably well, because mitral valve closure actually occurs only about 20 milliseconds after the crossover point of the pressures. Thus, in practice, the term *isovolumic contraction* often also includes this brief period of early systolic contraction even

before the mitral valve shuts, when the heart volume does not change substantially. *Physiological systole* lasts from the start of isovolumic contraction (where left ventricular pressure crosses over atrial pressure; see Fig. 14-22) to the peak of the ejection phase, so that physiological diastole commences as the left ventricular pressure starts to fall (Table 14-4) . This concept fits well with the standard pressure-volume curve. *Physiological diastole* commences as calcium ions are taken up into the sarcoplasmic reticulum, so that myocyte relaxation dominates over contraction, and the left ventricular pressure starts to fall as shown on the pressure-volume curve. In contrast, *cardiological systole* is demarcated by the interval between the first and second heart sounds, lasting from the first heart sound (M_1) to the closure of the aortic valve (A_2). The remainder of the cardiac cycle automatically becomes *cardiological diastole*. Thus, cardiological systole, demarcated by heart sounds rather than physiological events, starts fractionally later than physiological systole and ends significantly later. For the cardiologist, *protodiastole* is the early phase of rapid filling, the time when the third heart sound (S_3) can be heard. This sound probably reflects ventricular wall vibrations during rapid filling and becomes audible with an increase in left ventricular diastolic pressure or wall stiffness or rate of filling.

In contrast stands another physiological concept, promulgated by Brutsaert and colleagues,[136] who argue that diastole starts much later, only when the whole of the contraction-relaxation cycle is over. According to this minority view, diastole would occupy only a short portion of the cardiac cycle.[136] This definition of diastole, although seldom used in cardiological practice, does give a reminder that abnormalities of left ventricular contraction often underlie defective relaxation.

Contractility Versus Loading Conditions

CONTRACTILITY.

Contractility is the inherent capacity of the myocardium to contract independently of changes in the preload or afterload. Alternate names for contractility are the *inotropic state* (*ino*, "fiber"; *tropos*, "to move") or the contractile state. At a molecular level, an increased inotropic state can be explained by enhanced interaction between calcium ions and the contractile proteins. Increased contractility means a greater rate of contraction, to reach a greater peak force. Contractility is an important regulator of the myocardial oxygen uptake. Factors that increase contractility include exercise, adrenergic stimulation, digitalis, and other inotropic agents. Often an increased contractility is associated with enhanced rates of relaxation, called the *lusitropic effect*.

PRELOAD AND AFTERLOAD.

Any change in contractility should be independent of the loading conditions. The *preload*

is the load present before contraction has started, at

TABLE 14-4 -- PHYSIOLOGICAL VERSUS CARDIOLOGIC SYSTOLE AND DIASTOLE

Physiological Systole	**Cardiologic Systole**
Isovolumic contraction Maximal ejection	From M_1 to A_2 , including:
	Only part of isovolumic contraction*
	Maximal ejection
	Reduced ejection
Physiological Diastole	**Cardiologic Diastole**
Reduced ejection Isovolumic relaxation Filling phases	A_2 -M_1 interval (filling phases included)

*Note that M_1 occurs with a definite delay after the start of left ventricular contraction.

the end of diastole (the afterload is discussed later). The preload reflects the venous filling pressure that fills the left atrium, which in turn fills the left ventricle during diastole. When the preload increases, the left ventricle distends during diastole and the stroke volume rises according to Starling's law. The heart rate also increases by stimulation of the atrial mechanoreceptors that enhance the rate of discharge of the sinoatrial node. Thus, the cardiac output, the product of stroke volume and heart rate, rises.

Starling's Law of the Heart

VENOUS FILLING PRESSURE AND HEART VOLUME.

Starling, in 1918, related the venous pressure in the right atrium to the heart volume in the dog heart-lung preparation. He proposed that, within physiological limits, the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at each contraction. Starling did not, however, measure sarcomere length. He could only relate *left ventricular volume* to cardiac output. This holds in normal, compliant hearts. One modern version of Starling's law is that stroke volume is related to the end-diastolic volume. The left ventricular volume can now be directly measured by means of a number of imaging techniques (see Chap. 15) . Yet the value found depends on a number of simplifying assumptions and often neglects the confounding influence of the complex anatomy of the left ventricle. In practice, therefore, the left ventricular volume is not often measured but rather a variety of surrogate measures, such as left ventricular end-diastolic pressure or the pulmonary capillary wedge pressure, are used instead. Yet the relation between left ventricular end-diastolic volume and pressure is curvilinear depending on the left ventricular compliance.

FRANK AND ISOVOLUMIC CONTRACTION.

If a larger heart volume increases the initial length of the muscle fiber, to increase the stroke volume and hence the cardiac output, then diastolic stretch of the left ventricle actually increases contractility. Frank, in 1895, had already reported that the greater the initial left ventricular volume, the more rapid the rate of rise, the greater the peak pressure reached, and the faster the rate of relaxation.[137] Thus, he described both a positive *inotropic effect* and an increased lusitropic effect of increased cardiac volume at the onset of contraction. These complementary findings of Frank and Starling are often combined into the *Frank-Starling law*. Between them they could account for two of the mechanisms underlying the increased stroke volume of exercise, namely, both the increased inotropic state and the increased diastolic filling.

AFTERLOAD.

This is the systolic load on the left ventricle after it has started to contract. In the nonfailing heart, the left ventricle can overcome any physiological acute increase in load. With a chronically increased afterload, as occurs in sustained arterial hypertension or significant aortic stenosis, the left ventricle must hypertrophy. In clinical practice, the arterial blood pressure is often taken to be synonymous with the afterload, while ignoring the *aortic compliance*--the extent to which the aorta can "yield" during systole. A stiff aorta, as in isolated systolic hypertension of the elderly, increases the afterload.

PRELOAD AND AFTERLOAD ARE INTERLINKED.

In general, the preload is related to the degree to which the myocardial fibers are stretched at the end of diastole and the afterload is related to the wall stress generated by those fibers during systole. The distinctions just presented between preload and afterload do not allow for those situations when the two change concurrently. By the Frank-Starling law, an increased left ventricular volume leads to increased contractility, which in turn increases the systolic blood pressure and hence the afterload.

FORCE-LENGTH RELATIONSHIPS AND CALCIUM TRANSIENTS.

Proof that there is no increase in the calcium transient as the sarcomere length increases is provided by direct measurements (Fig. 14-23) . The favored explanation for the steep length-tension relation of cardiac muscles is *length-dependent activation,* whereby an increase in calcium sensitivity is the major factor explaining the steep increase of force development as the initial sarcomere length increases. This change may be explained by stretch of the titin molecule (see Fig. 14-3) . Is the degree of overlap of actin and myosin also involved? Whereas the overlap theory explains the force-length relationship in skeletal muscle, in cardiac muscle the situation is different

(Fig. 14-24). In cardiac muscle, even at 80 percent of the maximal length only 10 percent or less of the maximal force is developed. Thus, it can be predicted that cardiac sarcomeres must function near the upper limit of their maximal length (L_{max}). Rodriguez and colleagues[138] have tested this prediction by relating sarcomere length changes to volume changes of the intact heart. By implanting small radiopaque beads in only about 1 cm[3] of the left ventricular free wall and using biplane cineradiography, the motion of the markers could be tracked through various cardiac cycles, with allowances made for local myocardial deformation. Thus, the change in sarcomere length from approximately 85 percent of L_{max} to L_{max} itself is able to effect physiological left ventricular volume changes (Fig. 14-25). This estimate is remarkably close to the normal fiber shortening of 15 percent in the human heart in situ.[139]

ANREP EFFECT: ABRUPT INCREASE IN AFTERLOAD.

When the aortic pressure is elevated abruptly a positive inotropic effect follows within 1 or 2 minutes. This used to be called homeometric autoregulation (*homeo,* "the same"; *metric,* "length"), because it was apparently independent of muscle length and by definition a true inotropic effect. A reasonable speculation would be that increased left ventricular wall tension could act on myocardial stretch receptors to increase cytosolic sodium and then, by Na^+ /Ca^{2+} exchange, the cytosolic calcium. Thus, this effect would be different from that of an increase in preload (which acts by length activation).

Figure 14-23 Length-sensitization of the sarcomere. In the top panel, the sarcomere length (SL) is 1.65 mum, which gives very little force (f) development (see Fig. 14-7). In the bottom panel, at a near maximum sarcomere length (see Fig. 14-7), the same Ca^{2+} transient (c) with the same peak value and overall pattern causes a much greater force development. Therefore, there has been length-induced calcium sensitization. (Modified from Backx PH, ter Keurs HEDJ: Fluorescent properties of rat cardiac trabeculae microinjected with fura-2 salt. Am J Physiol 264:H1098-H1110, 1993.)

Figure 14-24 Schematic drawing illustrating general shape of ascending limb of *force-length relationship* in skeletal (A) and cardiac (B) muscle. Normalized force is plotted as a function of normalized length, that is, length relative to length at which maximum force is generated (L_{max}). Also shown is approximate disposition of thick and thin filaments at different points along the physiologically relevant portion of ascending limb. The maximum length (L_{max} 100%) corresponds to the situation at maximum sarcomere lengths (2.2 mum, see Fig. 14-25) or 2.15 mum (see Fig. 14-23) . (Modified from Fuchs F: Mechanical modulation of the Ca^{2+} regulatory protein complex in cardiac muscle. NIPS 10:6-12, 1995.)

Figure 14-25 Changes in sarcomere length during a typical cardiac contraction-relaxation cycle in the intact dog heart. During diastole the sarcomere length is 2.2 mum, reducing to 1.90 mum during systole. Starting at the top right, the *preload* is the maximum sarcomere length just before the onset of contraction. As ejection decreases the left ventricular volume, by somewhat more than half, sarcomere length falls from 2.20 to 1.90 mum. Then, during the rapid phase of filling (see Fig. 14-22) , the sarcomere length increases from 1.90 to 2.15 mum to be followed by the phase of constant sarcomere length (diastasis). (Modified from Rodriguez EK, Hunter WC, Royce MJ, et al: A method to reconstruct sarcomere lengths

and orientations to transmural sites in beating canine hearts. Am J Physiol 263:H293-H306, 1992. Copyright 1992, American Physiological Society.)

Wall Stress

Stress develops when tension is applied to a cross-sectional area, and the units are force per unit area. According to Laplace's law (Fig. 14-26) :

This equation, although an oversimplification, emphasizes two points. First, the larger the left ventricle and the greater its radius, the greater is the wall stress. Second, at any given radius (left ventricular size), the greater the pressure developed by the left ventricle, the greater the wall stress. An increase in wall stress achieved by either of these two mechanisms (left ventricular size or intraventricular pressure) will increase myocardial oxygen uptake. This is because a greater rate of ATP use is required, as the myofibrils develop greater tension. (For more details and formulae for circumferential and meridional wall stress, see Chapter 15.)

In cardiac hypertrophy, Laplace's law explains the effects of changes in wall thickness on wall stress (see Fig. 14-26) . The increased wall thickness due to hypertrophy balances the increased pressure, and the wall stress remains unchanged during the phase of compensatory hypertrophy. In congestive heart failure, the heart dilates so that the increased radius elevates wall stress. Furthermore, because ejection of blood is inadequate, the radius stays too large throughout the contractile cycle, and both end-diastolic and end-systolic tensions are higher.

WALL STRESS, PRELOAD, AND AFTERLOAD.

Preload can now be defined more exactly as the wall stress at the end of diastole and therefore at the maximal resting length of the sarcomere (see Fig. 14-25) . Measurement of wall stress in vivo is difficult because the radius of the left ventricle (see preceding sections) neglects the confounding influence of the complex anatomy of the left ventricle. Surrogate measurements of the indices of preload include left ventricular end-diastolic pressure or dimensions (the latter being

Figure 14-26 Wall stress increases as the afterload increases. The formula shown is derived from Laplace's law. The increased left ventricular pressure in aortic stenosis is compensated for by left ventricular wall hypertrophy, which decreases the denominator on the right side of the equation. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

the major and minor axes of the heart in a two-dimensional echocardiographic view).

The *afterload*, being the load on the contracting myocardium, is also the wall stress during left ventricular ejection. When afterload is elevated, an increased intraventricular pressure has to be generated first to open the aortic valve and then during the ejection phase. These increases translate into an increased myocardial wall stress, which can be measured either as an average value during systole or at end systole. *End-systolic wall stress* reflects the three major components of the afterload, namely, the peripheral resistance, the arterial compliance, and the peak intraventricular pressure. Decreased arterial compliance and increased afterload can be anticipated when there is aortic dilation, as in severe systemic hypertension or aortic stiffening in the elderly. Generally, in clinical practice, it is a sufficient approximation to take the systolic blood pressure as an indirect measure of the afterload (reflecting both peripheral resistance and peak intraventricular pressure), provided there is no significant aortic stenosis nor change in arterial compliance.

Aortic impedance (= arterial input impedance) gives another accurate measure of the afterload. The aortic impedance is the aortic pressure divided by the aortic flow at that instant, so that this index of the afterload varies at each stage of the contraction cycle. Factors reducing aortic flow, such as a high arterial blood pressure or aortic stenosis or loss of aortic compliance, will increase impedance and hence the afterload. During systole, when the aortic valve is open, an increased afterload is reflected by increasing ventricular wall stress. In left ventricular failure, aortic impedance is augmented not only by peripheral vasoconstriction but also by decreases in aortic compliance.[140] The problem with the clinical measurement of aortic impedance is that invasive instrumentation is required. An approximation can be found by using transesophageal echocardiography to determine aortic blood flow at, for example, the time of maximal increase of aortic flow just after aortic valve opening.

Heart Rate and Force-Frequency Relation

TREPPE OR BOWDITCH EFFECT.

An increased heart rate progressively enhances the force of ventricular contraction, even in an isolated papillary muscle preparation (Bowditch staircase phenomenon). Alternative names are the *treppe* (steps, German) phenomenon or positive inotropic effect of activation or force-frequency relationship (Figs. 14-27 and 14-28) (Figure Not Available) . Conversely, a decreased heart rate has a negative staircase effect. When stimulation becomes too rapid, force decreases.[141] The proposal is that during rapid stimulation, more sodium and calcium ions enter the myocardial cell than can be handled by the sodium pump and the mechanisms for calcium exit. Opposing the force-frequency effect is the negative contractile influence of the decreased duration of ventricular filling at high heart rates. The longer the filling interval, the better the ventricular filling and the stronger the subsequent contraction. This phenomenon can be shown in patients with atrial fibrillation with a variable filling interval.

Post-extrasystolic potentiation and the inotropic effect of paired pacing can be explained by the same model, again assuming an enhanced contractile state after the prolonged interval between beats. Nonetheless, the exact cellular mechanism remains to be

clarified.[142]

FORCE-FREQUENCY RELATIONSHIP IN HUMANS.

Muscle strips prepared from patients with mitral regurgitation behave very differently from normal muscle in response to an increased stimulation of frequency (see Fig. 14-28). (Figure Not Available) Normally, peak contractile force at a fixed muscle length (isometric contraction) is reached at 150 to 180 stimuli/min.[141] This is the human counterpart of the treppe phenomenon.

Figure 14-27 The Bowditch or *treppe* phenomenon, whereby a faster stimulation rate (bottom panel) increases the force of contraction (top panel). The stimulus rate is shown as the action potential duration on an analog analyzer in milliseconds (ms). The tension developed by papillary muscle contraction is shown in milliNewtons (mN) in the top panel. On cessation of rapid stimulation, the contraction force gradually declines. Hypothetically, the explanation for the increased contraction during the increased stimulation is repetitive Ca^{2+} entry with each depolarization and, hence, an accumulation of cytosolic calcium. (From Noble MIM: Excitation-contraction coupling. *In* Drake-Holland AJ, Noble MIM [eds]: Cardiac Metabolism. Chichester, John Wiley, 1983, pp 49-71.)

In severe mitral regurgitation there is hardly any response to an increased stimulation frequency. In muscle strips from normal hearts, optimal force development was reached at rates of about 120-150 beats/minute,[143] whereas in patients with cardiomyopathy, an increased heart rate produced a decreased twitch tension. In addition, in tissue from severely diseased hearts, the diastolic tension may rise markedly with the stimulation frequency,[144] suggesting that there is an excess of cytosolic calcium with deficient uptake into the sarcoplasmic reticulum.

OPTIMAL HEART RATE IN SITU.

In situ, the optimal heart rate is not only the rate that would give maximal mechanical performance of an isolated muscle strip but is also determined by the need for adequate time for diastolic filling. In normal humans, it is not possible to attach exact values to the heart rate required to decrease rather than to increase cardiac output or to keep it steady. Pacing rates of

Figure 14-28 (Figure Not Available) Force-frequency relationship in humans, comparing nonfailing controls with failing mitral regurgitation hearts. Plots of average steady-state isometric twitch tension versus stimulation frequency. Each point represents the mean ± SEM of eight control or mitral regurgitation preparations at 37°C. (Data from Mulieri LA, et al: Myocardial force-frequency defect in mitral regurgitation heart failure is reversed by forskolin. Circulation 88:2700-2704, 1993. Copyright 1993, American Heart Association.)

up to 150 beats/min can be tolerated, whereas higher rates cannot because of the

development of atrioventricular block. In contrast, during exercise, indices of left ventricular function still increase up to a maximum heart rate of about 170 beats/min, presumably because of enhanced contractility and peripheral vasodilation.[145] In patients with severe left ventricular hypertrophy, the critical heart rate is between 100 and 130 beats/min, with a fall-off in left ventricular function at higher rates.[144] [146]

Myocardial Oxygen Uptake (See also Chap. 34)

The myocardial oxygen demand can be increased by heart rate, preload, or afterload (Fig. 14-29) , factors that can all precipitate myocardial ischemia in the presence of coronary artery disease. The oxygen uptake can be augmented by increased contractility, as during beta-adrenergic stimulation. Because myocardial oxygen uptake ultimately reflects the rate of mitochondrial metabolism and of ATP production, any increase of ATP requirement will be reflected in an increased oxygen uptake. In general, factors increasing

Figure 14-29 Major determinants of the oxygen demand of the normal heart are heart rate, wall stress, and contractility. For use of pressure-volume area as index of oxygen uptake, see Figure 14-31. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

wall stress increase the oxygen uptake. An increased afterload causes an increased systolic wall stress which needs a greater oxygen uptake. An increased diastolic wall stress, resulting from an increased preload, will also require more oxygen because the greater stroke volume must be ejected against the afterload. In states of enhanced contractility, the rate of change of wall stress is increased. Thus, thinking in terms of wall stress provides a comprehensive approach to the problem of myocardial oxygen uptake. Because the systolic blood pressure is an important determinant of the afterload, a practical index of the oxygen uptake is systolic blood pressure times heart rate, the *double-product*. In addition, there may be a metabolic component to the oxygen uptake that is usually small but may be prominent in certain special conditions, such as the "oxygen wastage" found during abnormally high circulating free fatty acid values. The concept of wall stress in relation to oxygen uptake also explains why heart size is such an important determinant of the myocardial oxygen uptake (because the larger radius increases wall stress).

WORK OF THE HEART.

External work is done when a mass is lifted a certain distance. In terms of the heart, the cardiac output is the mass moved and the resistance against which it is moved is the blood pressure. Because volume work needs less oxygen than pressure work, it might be supposed that external work is not an important determinant of the myocardial

oxygen uptake. Yet, however, three determinants of the myocardial oxygen uptake are involved: preload (because this helps determine the stroke volume), afterload (in part determined by the blood pressure), and heart rate, as can be seen from the following formula:

where SBP=systolic blood pressure and SV=stroke volume. Thus, it is not surprising that heart work is related to oxygen uptake. The *pressure-work index* takes into account both the double-product (SBP×HR) and the HR×stroke volume, that is, cardiac output. The *pressure-volume area* is another index of myocardial oxygen uptake, requiring invasive monitoring for accurate measurements. External cardiac work can account for up to 40 percent of the total myocardial oxygen uptake.

In strict terms, the work performed needs to take into account not only pressure but also kinetic components. The latter is the component required to move the blood against the afterload. Normally, kinetic work is less than 1 percent of the total. In aortic stenosis, kinetic work increases sharply as the cross-sectional area of the aortic valve narrows, whereas pressure work increases as the gradient across the aortic valve rises. Currently, noninvasive measures of peak power production are being assessed as indices of cardiac contractility.

Efficiency of work is the relation between the work performed and the myocardial oxygen uptake. Exercise increases the efficiency of external work, an improvement that offsets any metabolic cost of the increased contractility.[147] Heart failure decreases the efficiency of work (Fig. 14-30) . Certain pharmacological agents, such as dobutamine, also improve efficiency in the failing heart.[148] The subcellular basis for changes in efficiency of work are not fully understood. Because as little as 12 to 14 percent of the oxygen uptake may be converted to external work,[147] it is probably the "internal work" that becomes less demanding. Internal ion fluxes (Na^+ /K^+ /Ca^{2+}) account for 20 to 30 percent of the ATP requirement of the heart, so that most ATP is spent on actin-myosin interaction, and much of that on generation of heat rather than on external work. An increased initial muscle length is known to sensitize the contractile apparatus to calcium, thereby theoretically increasing the efficiency of contraction by diminishing the amount of calcium flux required.

Figure 14-30 Marked increase in diastolic tension during pacing of muscle strip from advanced human heart failure. Note, in bottom panel, the increased myocardial oxygen uptake (MVO_2) with increased force (measured as the force-time integral). The combination of decreased cardiac force development and increased oxygen uptake indicates decreased efficiency of cardiac work. (Modified from Meyer M, Keweloh B, Guth K, et al: Frequency-dependence of myocardial energetics in failing human myocardium as quantified by a new method for the measurement of oxygen consumption in muscle strip preparations. J Mol Cell Cardiol 30:1459-1470, 1998.)

Can Contractility Be Measured?

FORCE-VELOCITY RELATIONSHIP AND MAXIMUM CONTRACTILITY IN MUSCLE MODELS.

If contractility is truly independent of the load and the heart rate, then unloaded heart muscle stimulated at a fixed rate should have a maximum value of contractility for any given magnitude of the cytosolic calcium transient. This value, the V_{max} of muscle contraction, is defined as the *maximal velocity of contraction* when there is no load on the isolated muscle or no afterload to prevent maximal rates of cardiac ejection. Beta-adrenergic stimulation increases V_{max} , and converse changes are found in the failing myocardium. The problem with this relatively simple concept is that V_{max} cannot be measured directly but is extrapolated from the peak rates of force development in unloaded muscle obtained from the intercept on the velocity axis.[149] In another extreme condition, there is no muscle shortening at all (zero shortening), and all the energy goes into development of pressure (P_o) or force (F_o). This situation is an example of *isometric shortening* (*iso,* "the same"; *metric,* "length"). Because the peak velocity is obtained at zero load when there is no external force development, the relationship is usually termed the *force-velocity relationship*.

The concept of V_{max} has been subject to much debate over many years chiefly because of the technical difficulties in obtaining truly unloaded conditions. Braunwald and associates[150] used cat papillary muscle to define a hyperbolic force-velocity curve, with V_{max} relatively independent of the initial muscle length but increased by the addition of norepinephrine. Another preparation used to examine force-velocity relations uses single cardiac myocytes isolated by enzymatic digestion of the rat myocardium and then permeabilized with a staphylococcal toxin. Again, the force-velocity relation is hyperbolic, suggesting the existence of

intracellular *passive elastic elements* that contribute to the load on the isolated myocyte.[151] In fact, the more hyperbolic and increased curvilinear nature of the force-velocity relationship in isolated myocytes than in the papillary muscle suggests that internal passive forces such as those generated by titin (see Fig. 14-4) are greater than expected in the isolated myocytes. In the intact heart, the noncontractile components contribute relatively little to overall mechanical behavior, at least in physiological circumstances.[152] Both data from papillary muscle and from isolated sarcomeres suggest that in unloaded conditions the intrinsic contractility as assessed by V_{max} does not change with initial fiber or sarcomere length.

MECHANISM OF BETA-ADRENERGIC EFFECTS ON FORCE-VELOCITY RELATIONSHIP.

The data on papillary muscles showing that norepinephrine can increase V_{max} could be explained either by an effect of beta-adrenergic stimulation on enhancing calcium ion entry or a direct effect on the contractile proteins, or both. Strang and coworkers[153]

showed that either isoproterenol (alpha-beta agonist) or protein kinase A (intracellular messenger) increased V_{max} by about 40 percent, concurrently with phosphorylation of troponin I and of C protein in an isolated ventricular myocyte preparation. The overall concept would be that beta-adrenergic stimulation mediates the major component of its inotropic effect through increasing the cytosolic calcium transient and the factors controlling it, such as the rate of entry of calcium ions through the sarcolemmal L-type channels, the rate of calcium uptake under the influence of phospholamban into the SR, and the rate of calcium release from the ryanodine receptor in response to calcium entry in association with depolarization. Of all these factors, phosphorylation of phospholamban may be the most important (see p. 453).

ISOMETRIC VERSUS ISOTONIC CONTRACTION.

Despite the similarities in the force-velocity patterns between the data obtained on papillary muscle and isolated myocytes, it should be considered that a number of different types of muscular contraction may be involved. For example, data for P_o are obtained under isometric conditions (length unchanged). When muscle is allowed to shorten against a steady load, the conditions are *isotonic* (*iso,* "same"; *tonic,* "contractile force"). Yet measurements of V_{max} have to be under totally unloaded conditions both in papillary muscles and in permeabilized myocytes.[149] Thus, the force-velocity curve may be generated by a combination of initial isometric conditions followed by isotonic contraction and then followed by abrupt and total unloading to measure V_{max} . Although an approximation of isometric conditions can be found in the whole heart during the phase of isovolumic contraction, isotonic conditions cannot prevail because the load is constantly changing during the ejection period, and complete unloading is impossible. Therefore, the application of force-velocity relations to the heart in vivo is limited.

PRESSURE-VOLUME LOOPS.

Measurements of pressure-volume loops are among the best of the current approaches to the assessment of the contractile behavior of the intact heart (see Fig. 15-2, p. 480). Major criticisms arise when it is assumed that E_s , the slope of the pressure-volume relationship (Fig. 14-31) , is necessarily linear (it may be curvilinear) or when E_s is used as an index of "absolute" contractility. Also in clinical practice, the need to change the loading conditions and the requirement for invasive monitoring lessen the usefulness of this index. Invasive measurements of the left ventricular pressure are required for the full loop, which is an indirect measure of the Starling relationship between the force (as measured by the pressure) and the muscle length (measured indirectly by the volume). During a positive inotropic intervention, the pressure-volume loop reflects a smaller end-systolic volume and a higher end-systolic pressure, so that the slope of the pressure-volume

Figure 14-31 Pressure-volume loop of left ventricle. Note the effects of beta-adrenergic catecholamines with both positive inotropic (increased slope of line E_s) and increased lusitropic (relaxant) effects. E_s =slope of pressure-volume relationship. The total pressure-volume area (for control area, see *abcd*) is

closely related to the myocardial oxygen uptake. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

relationship (E_s) has moved upward and to the left (see Fig. 14-31) . When the positive inotropic intervention is by beta-adrenergic stimulation, then enhanced relaxation (lusitropic effect) results in a lower pressure-volume curve during ventricular filling than in controls.

CONTRACTILITY: THEORY VERSUS PRACTICE.

Despite all the precautions that can be adopted to measure true contractility in isolated preparations, the practical application needs careful appraisal of the heart rate and the loading conditions, which should ideally be unchanged. Yet these can alter cytosolic calcium, as would a primary change in contractility. An increased heart rate, acting through the sodium pump lag mechanism, gives rise to an increased cytosolic calcium that is thought to explain the Treppe phenomenon. An increased preload involves increased fiber stretch, which in turn causes length-activation, explicable by sensitization of the contractile proteins to the prevailing cytosolic calcium concentration. An increased afterload may increase cytosolic calcium through stretch-sensitive channels. Thus, at the cellular level there is a clear overlap between contractility, which should be independent of load or heart rate, and the effects of load and heart rate. Hence, changes in the inotropic state as well as in the load and/or heart rate may all converge on the cytosolic calcium as the final messenger to the contractile proteins. A clinical example of this dilemma is in humans with atrial fibrillation and a constantly varying force-frequency relationship. Contractility, as measured in situ by pressure-volume loops, constantly changes from beat to beat, and the explanation could be either a "true" change in contractility or the operation of the Frank-Starling mechanism due to varying diastolic filling times.[154]

In clinical terms, it does nonetheless remain highly desirable to separate as far as possible the effects of a primary increase of load or heart rate from a primary increase in contractility. To apply the contractility concept to humans one needs to overcome the problem of obtaining a noninvasive index that is practical to measure and relatively free of the many assumptions that must be made about the loading conditions. The following chapter describes the techniques that can be used to estimate contractility in humans.

Ventricular Relaxation and Diastolic Dysfunction

Among the many complex cellular factors influencing relaxation, four are of chief interest (Fig. 14-32). First, the cytosolic calcium level must fall to cause the relaxation phase, a process requiring ATP and phosphorylation of phospholamban for uptake of calcium into the SR (Fig. 14-33). Second, the inherent viscoelastic properties of the myocardium are of importance. In the hypertrophied heart, because of changes in these properties, relaxation occurs more slowly. Third, increased phosphorylation of troponin I

enhances the rate of relaxation.[155] Fourth, the rate of relaxation varies directly with the systolic load. The history of contraction affects cross-bridge relaxation.[156] Within limits, the greater the systolic load, the faster the rate of relaxation. This complex relationship has been explored in detail by Brutsaert and coworkers,[136] but it could perhaps be simplified as follows. When the workload is high, peak cytosolic calcium is also thought to be high. A high end-systolic cytosolic calcium means that the rate of fall of calcium also can be greater, provided that the uptake mechanisms are functioning effectively. In this way the systolic pressure load and the rate of diastolic relaxation can be related. Furthermore, a greater muscle length (when the workload is high) at the end of systole should produce a more rapid rate of relaxation by the opposite of length-dependent sensitization, so that there is a more marked response to the rate of decline of calcium in early diastole. Yet, when the systolic load exceeds a certain limit, then the rate of relaxation is delayed,[156] perhaps because of too great a mechanical stress on the individual cross bridges. Thus, in congestive heart failure caused by an excess systolic load, relaxation becomes increasingly afterload dependent, so that therapeutic reduction of the systolic load should improve left ventricular relaxation.[157]

IMPAIRED RELAXATION AND CYTOSOLIC CALCIUM.

This chapter has used the *clinical* definition of diastole according to which diastole extends from aortic valve closure to the start of the first heart sound. The first phase of diastole is the isovolumic phase, which, by definition, does not contribute to ventricular filling. The second phase of rapid filling provides most of ventricular filling. The third phase of slow filling or diastasis accounts for only 5 percent of the total filling. The final atrial booster phase accounts for the remaining 15 percent.

Isovolumic relaxation is energy dependent, requiring ATP for the uptake of calcium ions by the SR (Fig. 14-32) , which is an active, not a passive, process. Impaired relaxation is an early event in the presence of myocardial ischemia. A proposed metabolic explanation is that there is impaired generation of energy, which diminishes the supply of ATP required for the early diastolic uptake of calcium by the SR. The result is that the cytosolic calcium level, which reaches a peak in systole, delays its return to normal in the early diastolic period. In other conditions, too, there is a relationship between the rate of diastolic decay of the calcium transient and diastolic relaxation, with a relation to impaired function of the SR.[158] When the rate of relaxation is prolonged by hypothyroidism, the rate of return of the systolic calcium elevation is likewise delayed, whereas opposite changes occur in hyperthyroidism. In congestive heart failure, diastolic relaxation also is delayed and irregular, as is the rate of decay of the cytosolic calcium elevation. Most patients with coronary artery disease have a variety of abnormalities of diastolic filling. Theoretically, such abnormalities of relaxation are potentially reversible because they depend on changes in patterns of calcium ion movement. Indices of the isovolumic phase and other indices of diastolic function are shown in Table 14-5 .

Figure 14-32 Factors governing the isovolumic relaxation phase of the cardiac cycle (see Fig. 14-22) . This period of the cycle extends from the aortic second sound (A_2) to the crossover point between the left

ventricular and left atrial pressures. The maximum negative rate of pressure development ($-dP/dt_{max}$), which gives the isovolumic relaxation rate, is measured either invasively or by a continuous wave Doppler velocity spectrum in aortic regurgitation. Isovolumic relaxation is increased (+ sign) when the rate of calcium uptake into the sarcoplasmic reticulum (SR) is enhanced, for example during beta-adrenergic stimulation (see Fig. 14-16). Isovolumic relaxation may also be enhanced when phosphorylation of troponin I (TnI), as in response to beta-adrenergic stimulation, may decrease the affinity of the contractile system for calcium. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation, Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

IS THERE LEFT VENTRICULAR SUCTION DURING EARLY FILLING?

A left ventricular suction effect can be found by carefully comparing left atrial and left ventricular pressures, and it occurs especially in the early diastolic phase of rapid filling. The sucking effect may be of most importance in mitral stenosis when the mitral valve does not open as it otherwise should in response to diastolic suction. During catecholamine stimulation, the rate of relaxation may increase to enhance the sucking effect and to prolong the period of filling. The proposed mechanism of sucking is as follows. When the end-systolic volume is less than the equilibrium volume, the shortened muscle fibers and collagen matrix may act as a compressed spring to generate recoil forces in diastole.

TABLE 14-5 -- SOME INDICES OF DIASTOLIC FUNCTION

Isovolumic Relaxation
$(-)dP/dt_{max}$ (Fig. 14-33)
Aortic closing-mitral opening interval
Peak rate of left ventricular wall thinning
Time constant of relaxation (tau)
Early Diastolic Filling
Relaxation kinetics on ERNA (rate of volume increase)
Early filling phase (E phase) on Doppler transmitral velocity trace
Diastasis
Pressure-volume relation indicates compliance
Atrial Contraction
Invasive measurement of atrial and ventricular pressures
Doppler transmitral pattern (E to A ratio)

ERNA=equilibrated radionuclide angiography; E=early filling phase, A=atrial contraction phase.

MEASUREMENT OF ISOVOLUMIC RELAXATION.

The rate of isovolumic relaxation can be measured by negative dP/dt_{max} at invasive catheterization. *Tau*, the time constant of relaxation, describes the rate of fall of left ventricular pressure during isovolumic relaxation and also requires invasive techniques for precise determination.[160] Tau is increased as the systolic left ventricular pressure rises.[156] Another index of relaxation can be obtained echocardiographically from the peak rate of wall thinning. The isovolumic relaxation time lies between aortic valve closure and mitral valve opening measured by signals of valve movements taken by Doppler echocardiography. In mitral regurgitation, the Doppler velocity profile can be used to calculate tau.[160] In each case, precise measurement is difficult and the range of normality is large.

ATRIAL FUNCTION.

The left atrium, besides its well-known function as a blood-receiving chamber, also acts as follows. First, by presystolic contraction and its function as a booster pump, it helps to complete left ventricular filling.[78] Second, it is the volume sensor of the heart, releasing atrial natriuretic peptide (ANP) in response to intermittent stretch and several other stimuli, including angiotensin II[161] and endothelin.[162] Third, the atrium contains receptors for the afferent arms of various reflexes, including mechanoreceptors that increase sinus discharge rate, thereby contributing to the tachycardia of exercise as the venous return increases *(Bainbridge reflex)*.

The atria have a number of differences in structure and function from the ventricles, having smaller myocytes with a shorter action potential duration as well as a more fetal type of myosin (both in heavy and light chains). Furthermore, the atria are more reliant on the phosphatidylinositol signal transduction pathway,[163] which may explain the relatively greater positive inotropic effect in the atria than in the ventricles in response to angiotensin II.[164] The more rapid atrial repolarization is thought to be due to increased outward potassium currents, such as I_{to} and I_{kACh} .[165] [166] In addition, some atrial cells have the capacity for spontaneous depolarization. In general, these histological and physiological changes can be related to the decreased need for the atria to generate high intrachamber pressures, rather being sensitive to volume changes, while retaining enough contractile action to help with left ventricular filling and to respond to inotropic stimuli.[78]

DIASTOLIC DYSFUNCTION AND MYOCARDIAL MECHANICAL PROPERTIES.

In hypertrophied hearts, as in chronic hypertension or severe aortic stenosis,[167] abnormalities of diastole are common and may precede systolic failure. Impaired relaxation is associated with an increase of the late (atrial) filling phase, and the E/A ratios on the mitral Doppler pattern decline (see Fig. 15-21 (Figure Not Available) , p. 496).[168]

The assessment of diastolic dysfunction is discussed in Chapter 15 .

EFFECTS OF ISCHEMIA AND REPERFUSION ON CONTRACTION AND RELAXATION

Contractile Impairment in Ischemia

HIGH-ENERGY PHOSPHATES.

Despite experimental differences, there is now widespread agreement that early contractile failure during ischemia (Fig. 14-33) can occur even when calcium transients are normal or near normal[169] [170] ; and, therefore, a metabolic cause must be sought. The latter could be either decreased sensitivity of the contractile proteins to calcium, as may be caused by acidosis, or inhibition of the cross-bridge cycle, as may be caused by the early rise in P_i . As creatine phosphate (CP) falls, the activity of the CP shuttle decreases so that "local" ATP, required for calcium movements in the contractile cycle, falls.[171] In addition, the free energy of hydrolysis of ATP decreases during ischemia.[172] The large increase in P_i , as a result of CP breakdown, decreases free energy of hydrolysis, as do the smaller decreases in ATP and increases in ADP. The fall in CP can also indirectly inhibit contractility through the accumulation of P_i , which decreases the contractile effects of any given concentration of cytosolic calcium. P_i may act by promotion of formation of weak rather than strong cross bridges.

Accumulation of neutral lactate during ischemia can promote mitochondrial damage, decrease the action potential duration, and inhibit glyceraldehyde-3-phosphate dehydrogenase. The mechanism of these lactate effects is not clear and may include extracellular acidosis with Na^+ /H^+ exchange, a subsequent gain in cell Na^+ , and then Na^+ /Ca^{2+} exchange with gain of harmful Ca^{2+} .

Segmental dyskinesia during ischemia may be explained by the

Figure 14-33 Can left ventricular (LV) mechanical failure during severe ischemia be explained by changes in the cytosolic calcium? These data show that when there is abrupt ischemic LV failure (LV pressure falls to zero in *C*), the calcium signal *(A)* increases before it falls. Ischemia is designated by the abrupt fall of coronary perfusion pressure to zero in this isolated rat heart preparation. During reperfusion there is also a dissociation between the cytosolic calcium oscillations, which are augmented (right hand panel of *A*) in contrast to LV contraction, which is decreased (right hand aspect of bottom panel), so that there is mechanical stunning. It is thought that excess calcium oscillations damage the contractile proteins (see Fig. 14-34) . (From Meisner A, Morgan JP: Contractile dysfunction and abnormal Ca^{2+} modulation during postischemic reperfusion in rat heart. Am J Physiol 268:H100-H111, 1995.)

effects of repetitive stretch on the poorly contractile ischemic segments, which then lose even more contractual activity.[173]

Potassium efflux. The mechanism of early potassium efflux in ischemia is not well understood, and there are three major theories. First, the ATP-inhibited potassium channel (K_{ATP}) may open as a result of cytosolic ATP deficiency. [174] Potassium channels such as those activated by sodium or by fatty acids may play a role. Second, inhibition of the sodium-potassium pump has long been suspected, but the onset of such inhibition is likely too late to explain early potassium egress, although probably contributing to the later phase of potassium loss. Third, co-ionic loss of potassium with negatively charged lactate and phosphate ions has often been proposed but the evidence for this is scanty.[175] The importance of potassium loss is that because the action potential duration is shortened, calcium influx may be diminished.[29]

Adenosine is formed during ischemia from the breakdown of ATP. It is potentially recyclable as a building block of ATP during resynthesis. Besides being the probable origin of the ischemic anginal pain,[176] adenosine has complex cardioprotective qualities. In response to stimulation of the A_1 receptor, [114] adenosine increases the inhibitory G protein (G_i), which, in turn, lessens the activity of adenylate cyclase and increases the opening probability of two types of potassium channels. The consequences include negative inotropic, chronotropic, and dromotropic effects, as well as coronary vasodilation. Adenosine may also play an important role in preconditioning.[177]

ISCHEMIC CONTRACTURE.

After 5 to 20 minutes of severe ischemia but depending on variable metabolic circumstances, including the cardiac glycogen reserve,[178] there is the gradual onset of ischemic contracture with a rise in diastolic pressure virtually without systolic activity. In general, even complete reperfusion never fully relieves ischemic contracture. The mechanisms for contracture include ATP depletion and a rise in cytosolic calcium (Fig. 14-33) . Of interest is the proposal that continued glycolysis and production of glycolytic ATP has a role in the maintenance of intracellular calcium homeostasis, probably acting indirectly by maintaining activity of the sodium pump.[179] As glycolysis is inhibited, diastolic tension increases.

New Ischemic Syndromes

The myocardium is now known to have a very diverse and flexible response to ischemia, varying from rapid contractile arrest to delayed stimulation of potentially protective synthetic pathways involving signals similar to those inducing growth. Three specific new entities recently identified constitute the *new ischemic syndromes,* namely, preconditioning, hibernation, and stunning.[180] All three have in common that they are differing responses to ischemia and reperfusion. Ischemic-reperfusion injury (Fig. 14-34)

is a well-recognized experimental entity, varying from reversible damage with mild transient ischemia to irreversible cell death with severe ischemia followed by reperfusion. Adverse effects associated with reperfusion include arrhythmias, mechanical dysfunction, degradation of contractile proteins such as troponin I, and apoptosis.[181] It has been proposed that these adverse effects are to some extent self-limited by *a repertoire of myocardial protective events resulting from activation of a variety of signaling and metabolic pathways.* At least some of these events appear to be triggered by reperfusion, whereas others result from the ischemic phase (Fig. 14-35) .

INTERMITTENT ISCHEMIA AND PRECONDITIONING.

Whereas many repetitive episodes of ischemia should produce cumulative damage, relatively few episodes or even one burst of short-lived severe ischemia followed by complete reperfusion causes preconditioning, the condition in which the myocardium is protected against a greater subsequent ischemic insult, with less threat of infarction. The overall pathways involved are complex, starting with an

Figure 14-34 The two major mechanisms causing ischemic reperfusion damage are oxygen-derived free radicals and calcium overload, probably with interactive effects. The end result shown here is a relative insensitivity of the contractile protein, troponin C (C) to calcium released from the sarcoplasmic-reticulum (SR). For role of proteolysis of troponin-I (Tn-I), see the article by Bolli and Marban.[200] (Reprinted with permission. Figure copyright © 2001 L. H. Opie.)

agonist acting on a heptahelical receptor and leading by means of PKC to activation of the MAP kinase complex (Fig. 14-36). (Figure Not Available) The latter may then lead to either (1) opening of the mitochondrial ATP-sensitive potassium channel (K_{ATP}) now thought to mediate short-term preconditioning[182] or to (2) nuclear synthesis of new growth factors and other protective proteins, including iNOS, which may explain delayed preconditioning ("second-window of protection").[183] [184] Although preconditioning can be triggered by a wide variety of events and even pharmacological stimuli, adenosine is the single agonist most consistently linked to this phenomenon. Adenosine formed during the ischemic period results in two crucial events: one is activation of PKC, which then (through unknown signals) is linked to the second major event, namely, opening of the mitochondrial K_{ATP} channel (see Fig. 14-36) (Figure Not Available) . [182] [185] The latter channel may also mediate delayed preconditioning in response to adenosine.[186]

An alternate mechanism for preconditioning is upregulation of G_i (see Fig. 14-36) (Figure Not Available) . Activation of the heptahelical receptors coupled to it, such as adenosine A_1 , muscarinic M_2 , and opioid receptors, leads to greater inhibition of adenylate cyclase and hence to an indirect antiadrenergic effect.[187] A third proposal is that ischemia activates the beta-adrenergic pathway, with receptor desensitization and attenuated accumulation of cyclic AMP during the repeat ischemia.[188] These proposals are not necessarily mutually exclusive, because of extensive postreceptor *cross talk* between the signaling pathways and because more than one pathway may be stimulated simultaneously. Preconditioning probably has clinical implications, because patients with preinfarction angina may suffer from a less severe infarct than those

thought to undergo sudden coronary occlusion without the opportunity for preconditioning.[189] [190]

Figure 14-35 Two possible additive components of postischemic dysfunction: (1) reperfusion-induced pathology, which can be restored through the use of a therapeutic intervention such as an antioxidant or calcium-limiting agent given transiently at the time of reperfusion; and (2) ischemic pathology from which the heart is slowly recovering. These may be additive to each other and to any additional reperfusion-induced component that is not amenable to the chosen intervention. (Modified from Hearse DJ: Stunning: A radical review. Cardiovasc Drugs Ther 5:853-876, 1991.)

Stunning (See also Chap. 34)

The first observation was that the recovery of mechanical function after transient coronary occlusion was not instant but delayed (see Fig. 14-35) . Thereafter, Braunwald and Kloner[199] defined "the stunned myocardium" as one characterized by prolonged postischemic myocardial dysfunction with eventual return of normal contractile activity. Stunning is now thought to occur in several clinical situations,[200] including delayed recovery from effort angina, unstable angina, early thrombolytic reperfusion, ischemic cardioplegia, cardiac transplantation, cardiac arrest, and coronary angioplasty. Interactive mechanisms thought to be responsible for stunning are an increased cytosolic calcium and the formation of oxygen-derived free radicals on reperfusion.[200] [201]

INCREASED CYTOSOLIC CALCIUM DURING EARLY REPERFUSION.

An excess cytosolic calcium is present in prolonged severe ischemia,[170] and restoration of energy with reperfusion will induce excess oscillations of calcium. Second, opening of the voltage-sensitive calcium channels during early reperfusion may also be important.[202] Third, release of Ca^{2+} from the SR is also likely, probably in response to free radicals.[200] [203] Fourth, calcium may enter the reperfused cells through the process of Na^+ /Ca^{2+} exchange, consequent on Na^+ /H^+ exchange.[202] [204] The latter exchanger may be directly activated by free radicals[205] or by endothelin released during reperfusion, acting on the ET_A receptors.[206] It may be predicted that all agents stimulating the phosphatidylinositol cycle and increasing IP_3 at the time of reperfusion should worsen stunning.[102] These include angiotensin II, endothelin,[207] and $alpha_1$ -adrenergic stimulation.[37] The myocardial angiotensin I receptor is upregulated after ischemia-reperfusion. When the receptor mRNA is inhibited by antisense nucleotides, then stunning is lessened.[208] Increased calcium transients may also explain reperfusion arrhythmias.[201] [209] Decreased systolic force generation may be linked to activation of proteases that partially digest troponin I and other contractile proteins.[200]

OXYGEN-DERIVED FREE RADICALS.

Substantial evidence shows that reperfusion produces free radicals that

Figure 14-36 (Figure Not Available) Proposed role of protein kinase C and mitochondrial adenosine triphosphate (ATP)-sensitive potassium channel in ischemic preconditioning (IPC). When ischemia is repeated, there is relative protection. Pharmacological PC by a variety of agents may act on G proteins, including the inhibitory G protein (G_i) and the G protein linked to phospholipase C (G_q, see Fig. 14-19) in mediating effects of preconditioning. The stimulatory G protein (G_s) may also be involved.[188] A_1 =subtype 1 of adenosine receptor; M_2 =subtype 2 of muscarinic receptor; BK=bradykinin; mito-$K_{(ATP)}$ =mitochondrial ATP-dependent potassium current. HSP=heat shock protein. NOS=nitric oxide synthase. (Modified from Opie LH: The Heart, Physiology, from Cell to Circulation. Philadelphia, Lippincott-Raven, 1998. Figure copyright L. H. Opie, © 2001.)

can depress cardiac contraction.[200] Hypothetically, free radicals may either directly depress contraction or do so by excessively increasing cytosolic calcium, for example by stimulating sodium-hydrogen transport with subsequent sodium-calcium exchange.[205] Thus, free radicals interact with calcium ions (see Fig. 14-34) . Other adverse effects of excess free radicals include promotion of apoptosis.[210] Support for the idea that free radicals contribute to stunning comes from the observation that antioxidants improve contractile function. Direct measurements of cytosolic calcium in stunned myocardium show that antioxidants decrease cytosolic calcium levels and increase the force of contraction.[211]

TNF-alpha AND OTHER CYTOKINES.

After ischemia, production of TNF-alpha both by interstitial cells and by human cardiomyocytes increases.[212] TNF-alpha theoretically may promote stunning by several mechanisms: desensitization of the contractile proteins to calcium[124] ; induction of other cardiodepressant agents such as nitric oxide or interleukin-1[212] ; or formation of free radicals.[212]

CHRONIC STUNNING.

Although experimental stunning typically lasts for hours, full mechanical recovery can sometimes take much longer, up to weeks after thrombolysis for acute myocardial infarction. To explain this finding, a current proposal is that there is a condition of late or chronic stunning.[199] [213] Hypothetically, this condition, part of the wide "stunning syndrome,"[200] would represent the end result of the short-term changes in cytosolic calcium and in free radical generation added to long-term changes in cytokines and growth factors. These events could then trigger complex changes in protein synthesis and degradation, to which would be added the physical forces acting on the ventricle that also shape the remodeling process. In patients with early stage myocardial

infarction, reperfused by percutaneous transluminal coronary angioplasty, a slow improvement in postinfarct left ventricular function occurs when an angiotensin-converting enzyme inhibitor is combined with a calcium antagonist.[214] Chronic stunning may be the explanation for some aspects of hibernation (see later). For example, repetitive ischemia precipitated by excitement in pigs with severe coronary stenosis can cause depressed mechanical function even in the absence of any measurable reduction of coronary blood flow at rest.[195]

ATRIAL STUNNING.

After cessation of atrial fibrillation, atrial contractility may be reduced or absent for up to several weeks despite normal electrical activity. Such stunning is clinically relevant, and potentially harmful, because it predisposes to formation of atrial thrombosis with risk of stroke. Calcium overload is the proposed mechanism, because atrial stunning is reduced by verapamil but increased by a calcium channel agonist.[215]

CONCURRENT EVENTS.

Because the human heart with advanced coronary artery disease is known to suffer from intermittent ischemia, ischemic-reperfusion injury and its consequences may all be occurring simultaneously. Thus the same heart may concurrently manifest one or more component of the new ischemic syndromes, namely stunning, hibernation, and preconditioning, as well as ischemic damage. When one episode of severe ischemia is followed by clinical reperfusion, as in thrombolysis, the extent of postischemic dysfunction could be determined by a combination of ischemic and reperfusion pathology, the former depending on the length of time that the myocardium has been ischemic and the latter potentially causing a spectrum of new ischemic syndromes.

Hibernation (See also Chap. 37)

The hibernating myocardium, like the hibernating animal, is temporarily asleep and can wake up to function normally when the blood supply is fully restored (Table 14-6) . Rahimtoola's proposal is that the fall of myocardial function to a lower level copes with the reduced myocardial oxygen supply and leads to self-preservation, so that the myocardium is "exquisitely regulated" and successfully adapted to the prevailing circumstances.[191] This sequence has been shown for acute experimental hibernation, lasting only a few hours, in which there is downgrading of contractile activity that matches the decreased coronary flow.[192] An alternative point of view, gaining ground, is that hibernation can occur even when the resting coronary flow is normal despite the presence of coronary disease. There is, however, firm evidence for an impaired coronary vascular reserve,[193] so that episodes of tachycardia would precipitate ischemia. Such recurrent episodes of ischemia would then leave behind a repetitively stunned myocardium. Thus, chronic hibernation, according to this proposal, is no more than cumulative stunning.[193] [194] [195]

Chronic hibernation in humans seems to be even more complex, without a good animal model. It is the combination of reversibly depressed regional wall motion and severe

coronary artery disease (see Chap. 37) . The exact limit of coronary flow that leads to hibernation is not so clearly defined but could be only 70 to 80 percent of normal coronary flow.[196] The hypocontractile segments that still have a sustained glucose extraction, as shown by positron emission tomography, have a high chance of recovery after coronary

TABLE 14-6 -- CHARACTERISTICS OF STUNNING, HIBERNATION, AND ISCHEMIA

PARAMETER	STUNNING	HIBERNATION	TRUE ISCHEMIA
Myocardial mechanical function	Reduced	Reduced	Reduced
Coronary blood flow	Post-ischemic: normal/high	Modestly reduced or low normal; intermittent ischemia-reperfusion	Most severely reduced
Myocardial energy metabolism	Normal or excessive	Reduced or low normal; in steady state with intermittent ischemia-reperfusion	Reduced; increasingly severe as ischemia proceeds
Duration	Hours to days; late stunning over weeks	Days to hours to months	Minutes to hours
Outcome	Full spontaneous recovery	Recovery if revascularized	Myocyte necrosis if severe ischemia persists
Proposed change in metabolic regulation of calcium	Cytosolic overload of calcium in early reperfusion with damage to contractile proteins	Possibly just enough glycolytic ATP to prevent contracture	Insufficient glycolytic ATP to prevent ischemic contracture and irreversibility

ATP=adenosine triphosphate.

Modified from Opie LH: The multifarious spectrum of ischemic left ventricular dysfunction: Relevance of new ischemic syndromes. J Mol Cell Cardiol 28:2403-2414, 1966.

artery bypass surgery. In contrast, those segments with a decreased glucose extraction almost uniformly fail to recover.[197] "Mismatch" refers to the increased glucose extraction of the viable myocardium that can be visibly contrasted to the poor coronary blood flow (ammonia signal on positron emission tomography). In one series, up to 27 percent of patients with ischemic cardiomyopathy could have enough viable segments to benefit by revascularization.[198] Postoperative recovery of contractile function may vary from rapid, within hours or even minutes, to long delays over weeks or even months.[193] Thus,

hibernation, like stunning, is a "syndrome."

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Chapter 15 - Assessment of Normal and Abnormal Cardiac Function

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THEORETICAL CONSIDERATIONS

Reasons to Focus on the Left Ventricle

The cardiovascular system supplies the tissues with oxygen and metabolic substrates and removes carbon dioxide and other waste products. This requires the integration of all its components (venous circulation, right side of the heart, lungs and pulmonary vascular system, left side of the heart, arterial circulation, and blood). Most circulatory dysfunction of cardiac origin in adults is due to abnormalities of the left ventricle. Thus, the clinical evaluation of cardiac function predominately concerns the performance of the left ventricle.

Levels of Integration: Myocardium, Pump, Cardiac Output

The performance of the left ventricle as a pump depends on the contraction of the sarcomeres in the myocardium as well as on the organization and configuration of the

left ventricular chamber, valvular function, and loading conditions. Ultimately, the interaction of the left ventricle, the other cardiac chambers, and the arterial, pulmonary, and venous circulations results in the cardiac output. Thus, cardiac function can be evaluated at several levels of integration: (1) myocardial function, (2) chamber (usually left ventricular) pump performance, and (3) integrated cardiac output. It is important to recognize at which level of integration cardiac function is being evaluated. For example, changes in cardiac output or the level of left ventricular pump function can result from many factors and do not merely reflect myocardial contractility. Thus, measurement of cardiac output alone provides a limited and insensitive assessment of ventricular function or of myocardial contractility. Furthermore, evaluation of left ventricular pump function alone cannot assess the adequacy of cardiac output or the level of myocardial contractility.

Factors Controlling Myocardial Function (See also Chap. 14)

Myocardial shortening is determined by four factors: (1) preload, (2) afterload, (3) the myocardial contractile state (contractility), and (4) heart rate and cardiac rhythm. Preload is the stretch of the myocardium before stimulation that determines the initial sarcomere length. Within the physiological range, the greater preload the stronger the contraction. Afterload is the load that the myocardium must bear to contract. The higher the afterload, the greater the pressure generated, but the less the amount of shortening. Myocardial contractility reflects the activation, formation, and cycling of the cross bridges between actin and myosin myofilaments. At constant preload and afterload, increased contractility results in a greater extent and velocity of shortening. The final determinants of cardiac function are the heart rate and rhythm. With increasing rate there is an enhancement of contractility under normal conditions (positive force-frequency relation). These factors (preload, afterload contractility, rate, and rhythm) represent a simplification of the fundamental processes because at the level of the sarcomere, load and contractility are interrelated.[1]

Left Ventricle in Pressure-Volume Plane: Transformation of Muscle to Pump Function

The transformation of myocardial function to left ventricular pump function can be understood by plotting the cardiac cycle in the pressure-volume plane.

LEFT VENTRICULAR PRESSURE-VOLUME LOOP.

The relationship between left ventricular pressure and volume in a normal ejecting beat is shown in Figure 15-1 . Contraction of the left ventricular myocardium begins at end diastole. The energy of the contraction is first used to increase ventricular pressure to the level of aortic diastolic pressure without a change in left ventricular volume as the aortic and mitral valves are closed. When left ventricular pressure exceeds aortic pressure, the aortic valve opens. Myocardial fibers shorten as blood is ejected through the open aortic valve, and ventricular volume decreases. After the contraction reaches its peak at end systole, the myocardial fibers begin to relax; and when left ventricular pressure falls below aortic pressure, the aortic valve closes and cardiac ejection stops. Ventricular pressure then declines rapidly as the ventricle relaxes. With opening of the mitral valve, left ventricular filling begins and the left ventricular pressure-volume loop is

completed.

When cardiac ejection is prevented in an experimental preparation, peak isovolumetric left ventricular pressure increases as ventricular volume increases, describing a straight line in the physiological range.[2] This is the end-systolic pressure-volume relation (ESPVR). Similarly, the upper left-hand corner of the pressure-volume loops of variably

Figure 15-1 A left ventricular (LV) pressure-volume loop describing one cardiac cycle. At end diastole the mitral valve closes. The left ventricle is a closed chamber because the pressure increases without a change in volume during isovolumetric contraction. When LV pressure exceeds aortic pressure, the aortic valve opens. During LV ejection, LV volume falls. Aortic valve closure occurs near the time of end systole. After aortic valve closure, LV pressure falls without a change in LV until LV pressure falls below left atrial pressure and mitral valve opening occurs. During diastole LV volume increases, completing the cardiac cycle. End systole falls on the LV end-systolic pressure-volume relation (ESPVR). (Redrawn from Little WC, Cheng CP: Left ventricular-arterial coupling in conscious dogs. Am J Physiol 261:H70, 1991.)

loaded beats, denoted as end systole in Figure 15-1 , fall close to isovolumetric ESPVR. The slope of this line, *termed* E_{ES} *,* has units of pressure per volume and denotes the maximum stiffness or elastance of the left ventricle. The slope and position of the ESPVR respond to changes in myocardial contractile state. An increase in contractility increases the slope of the ESPVR, shifting the line toward the left in the physiological range. Conversely, the ESPVR flattens and shifts to the right when there is depressed myocardial contractile function. Thus, the position and slope of the ESPVR can be used to measure the contractile state (see later).

The effects of altering preload, afterload, and contractility on left ventricular performance are readily described in the left ventricular pressure-volume plane. In the intact circulation, alteration of any of these three determinants of left ventricular performance elicits a prompt compensatory response that modifies the other two factors and heart rate. However, it is useful to analyze the effect of a change in each of these variables assuming for illustrative purposes that the other two factors remain constant.

An acute increase in afterload results in a greater proportion of the contraction energy being used to develop pressure so there is less myocardial shortening (Fig. 15-2) . As a result, ventricular emptying is impaired, resulting in a reduced stroke volume and decreased ejection fraction. Thus, increased afterload can decrease left ventricular systolic emptying in the absence of any depression of myocardial contractility (afterload mismatch). If an increase in preload (increased end-diastolic volume) occurs without a change in end-systolic pressure, a larger stroke volume is produced as the ventricle ejects to a similar end-systolic volume. A primary increase in myocardial contractility results in a steeper ESPVR. If preload and afterload remain constant, this results in an increase in stroke volume.

PRESSURE-VOLUME AREA AND MYOCARDIAL OXYGEN CONSUMPTION.

Left ventricular energetics can also be understood in the pressure-volume plane.[3] The area contained within the left ventricular pressure-volume loop is the stroke work (SW) (Fig. 15-3) . This is the external work performed by the ventricle. The remaining area under the ESPVR is the potential energy (PE) produced by the ventricular contraction but not resulting in external work. Myocardial oxygen consumption (MV_{O_2}) is linearly related to the sum of the SW and PE or total pressure-volume area (PVA)[3] [4] [5] [40A] (see Fig. 15-3) (see Chap. 34) . The inverse of the slope of the MV_{O_2} -PVA relation indicates the contractile efficiency. The intercept reflects the energy used for basal metabolism and excitation-contraction coupling.[6] Most positive inotropic interventions shift the MV_{O_2} -PVA relation upward, indicating an increase in these energy demands.

MEASUREMENT OF KEY VARIABLES

Pressures

The intracardiac, arterial, and venous pressures are important variables used in assessing cardiac function. These pressures have been traditionally measured using fluid-filled catheters, but, as described in Chapter 11 and as illustrated in Figure 15-4 , this technique can produce artifacts.[7] Arterial pressure can be obtained noninvasively by sphygmomanometry. Catheters tipped with a micromanometer provide a flat frequency response to above 100 Hz. Thus, a micromanometer can accurately measure cardiac pressures throughout the cardiac cycle. Micromanometers

Figure 15-2 The responses of the left ventricle to increased afterload, increased preload, and increased contractility are shown in the pressure-volume plane. ESPVR=end-systolic pressure-volume relation, E_{ES} =the slope of the end-systolic pressure-volume relation. See text for discussion.

Figure 15-3 *A,* Variably loaded pressure-volume loops generated by transient caval occlusion in a conscious animal. The upper left-hand corners of the loops define the left ventricular (LV) end-systolic pressure-volume relation (ESPVR). *B,* The stroke work (SW) is the area contained within the steady-state pressure-volume loop. The potential energy (PE) is the area under the remaining portion of the ESPVR. The total pressure-volume area (PVA) is the sum of SW and PE. *C,* The myocardial oxygen consumption (MV_{O_2}) is linearly related to the PVA. Inotropic stimulation with dobutamine shifts this relation upward, increasing the oxygen cost of PVA. See text for discussion. (Redrawn from Nozawa T, Cheng CP, Noda T, Little WC: Relation between left ventricular oxygen consumption and pressure-volume area in conscious dogs. Circulation 889:810, 1994. Copyright 1994, American Heart Association.)

are required to measure left ventricular dP/dt and determine the time constant of the isovolumetric decline in left ventricular pressure. Accurate pressure measurement with a micromanometer requires careful attention to calibration, drift, zeroing, and hydrostatic pressure gradients. Recently, Doppler echocardiographic techniques have allowed noninvasive estimation of intracardiac pressures.

NONINVASIVE PRESSURE MEASUREMENT.

Cuff sphygmomanometry (see Chap. 4) accurately measures arterial systolic and diastolic pressures. The combination of computer-controlled cuff inflation gated by the electrogram with Doppler measurements of brachial arterial flow or tonometry of the radial artery provides a quantitative measure of the entire arterial waveform.[7] [8]

Doppler echocardiography (see Chap. 7) can determine the velocity (v) of the systolic regurgitant jet across the tricuspid, mitral, or aortic valves. With the use of the modified Bernoulli equation for steady-state flow ($DeltaP=4v^2$) the pressure gradient (DeltaP) responsible for the regurgitant jet can be calculated. This can be used to estimate the time course of right and left ventricular systolic pressures.[9] [10] [11]

PULMONARY CAPILLARY WEDGE PRESSURE

(See Chap. 11) . Because the pulmonary venous pressure approximates left atrial pressure in most circumstances, the mean pulmonary capillary wedge pressure provides a clinically useful estimate of mean left atrial pressure and the left ventricular filling pressure.

Ventricular Volume

Angiographic techniques, described next, provide the most widely accepted means for measuring ventricular chamber volumes and segmental wall motion. They allow calculation of the extent and velocity of wall shortening and the assessment of regional wall motion. When they are combined with measurements of intraventricular pressure and wall thickness, wall tension and ventricular stiffness can be determined. Although noninvasive techniques are now widely used in the assessment of ventricular dimensions and volumes, their application to the assessment of cardiac function is based on the earlier work using ventricular angiography, which remains a benchmark for these measurements.

QUANTITATIVE ANGIOCARDIOGRAPHY.

The left ventricle is outlined most clearly by direct injection of contrast medium into the ventricular cavity.[12] In patients with severe aortic regurgitation the contrast material may be injected into the aorta, with the resultant reflux outlining the left ventricular cavity. Digital subtraction angiography util

Figure 15-4 Recording of left ventricular pressure from a fluid-filled catheter and a micromanometer catheter. The recording from the fluid-filled catheter is delayed slightly relative to the recording with the micromanometer. During portions of the cardiac cycle when left ventricular pressure is not rapidly changing (diastasis, end diastole, end systole) the pressures recorded through the two systems are nearly identical. When pressure is rapidly increasing or decreasing, the pressure recorded through the fluid-filled catheter initially lags behind the micromanometer pressure and then overshoots. (Recording courtesy of Dr. Che-Ping Cheng, Wake Forest University School of Medicine.)

izing injections into a peripheral vein, pulmonary artery, or left ventricle also may be used to define the left ventricle.

Unless the effects of premature contractions and of the resultant postextrasystolic potentiation are to be examined, ventricular irritability should be avoided during injection of the contrast material. Contact should be avoided between the tip of the catheter and the myocardium, and a multiholed catheter should be used to diminish the impact of the jet of contrast medium striking the endocardium. If premature contractions are induced, the premature contraction itself and the postpremature beats may exhibit changes in cardiac function. The premature ventricular contraction also may induce mitral and/or tricuspid regurgitation. However, because the contrast material usually is injected over 3 or 4 seconds and filming is carried out for 5 to 8 seconds, one or two cardiac cycles usually are available for analysis, even if a single premature contraction occurs at the beginning of the injection.

Injection of the contrast agent does not begin to produce hemodynamic changes (except for premature beats) until several beats after the injection. The hyperosmolarity produced by the contrast agent increases the blood volume, which begins to increase preload and heart rate within 30 seconds of the injection, an effect that may persist for as long as 2 hours. Conventional contrast agents (so-called ionic agents, such as meglumine diatrizoate) depress contractility directly; however, newer, nonionic agents minimize these adverse effects and may be safer for patients with marked elevations of left ventricular end-diastolic pressures (> 25 mm Hg) or depressed cardiac function.

In calculating ventricular volumes or dimensions from angiograms, it is essential to take into account and apply appropriate correction factors for magnification as well as for distortion resulting from nonparallel x-ray beams (pincushion distortion). To apply these correction factors, care must be exercised to determine with accuracy the tube-to-patient and tube-to-film distances.

THE CONDUCTANCE CATHETER.

The conductance technique provides a method to measure left ventricular volume on line in the cardiac catheterization laboratory avoiding the problems associated with multiple injections of contrast medium.[13] In this technique, a multielectrode catheter is passed across the aortic valve and the tip is advanced to the apex of the left ventricle.

An electrical field is generated (20 kHz, 0.03 mA RMS current) in the left ventricle between electrodes positioned at the top of the catheter in the apex and just above the aortic valve. Sensing electrodes that are evenly distributed along the catheter are used to measure the potential produced by the current. From these measurements, the resistance (and its inverse--conductance) between electrode pairs spanning the long axis of the left ventricle are calculated. The conductances from the electrode pairs are summed and converted to volume using a signal conditioner, assuming that all the current flows through blood in the left ventricular chamber.[13] Recently, the conductance catheter has been miniaturized for use in experimental studies of transgenic mice.[14]

NONINVASIVE METHODS.

Cardiac catheterization and quantitative selective angiography are the standard tools for evaluating the function of the heart, but these invasive procedures have some risk and are not suitable for repeated application in the same patient. Therefore, a continuing search has been made for reliable noninvasive methods of assessing cardiac volume. Such methods are needed particularly for detecting serial changes in cardiac function and in evaluating both acute and chronic effects of interventions such as drug therapy and cardiac operations. Discussed elsewhere in this book are the four principal noninvasive methods for assessing cardiac performance: echocardiography (see p. 162), radionuclide angiography (see Chap. 9) , ultrafast computed tomography (see Chap. 10) , and magnetic resonance imaging[14A] (see Chap. 10) . All of these are alternatives to contrast angiography for measurement of ventricular volumes and/or dimensions and, therefore, permit the noninvasive estimation of ejection phase indices (see later). All four noninvasive imaging methods allow estimation of ventricular systolic and diastolic volumes and both global and regional ejection fraction.

LEFT VENTRICULAR VOLUME.

The normal left ventricular end-diastolic volume averages 70 ± 20 (SD) ml/m^2 (Table 15-1) .[15] Left ventricular performance ordinarily is considered to be depressed when ventricular end-diastolic volume is clearly elevated (i.e., > 110 ml/m^2 , or > 2 SDs above the normal mean) and total stroke volume and/or cardiac index and work are either reduced or within normal limits, while heart rate and arterial pressure are normal.

Left ventricular stroke volume is the quantity of blood ejected with each beat and is the difference between end-diastolic volume and end-systolic volume. The normal stroke volume is 45 ± 13 ml/m^2 (see Table 15-1) . The cardiac output is equal to the stroke volume multiplied by the heart rate. In the absence of valvular regurgitation or intracardiac shunt, the angiographic stroke volume should correlate closely with an independent measurement of stroke volume (cardiac output/heart rate) using the Fick or thermodilution methods. In the presence of valvular regurgitation or a shunt lesion, the total stroke volume, determined by angiocardiography, is greater than the effective forward stroke volume, determined by the Fick or indicator dilution method. The difference between the two represents the regurgitant (or shunt) flow per cardiac cycle.

TABLE 15-1 -- LEFT VENTRICULAR VOLUME DATA IN PATIENTS

GROUP	NO. OF PATIENTS	END-DIASTOLIC VOLUME (ml/m^2)	STROKE VOLUME (ml/m^2)	MASS (gm/m^2)	EJECTION FRACTION
Normal*		70±20.0	45±13.0	92±16.0	0.67±0.08
AS	14	84±22.9	44±10.1	172±32.7	0.56±0.17
AR	22	193±55.4	92±30.9	223±73.0	0.56±0.13
AS and AR	13	138±36.5	75±19.1	231±56.9	0.53±0.10
MS	37	83±21.2	43±11.9	98±24.1	0.57±0.14
MR	29	160±53.1	87±21.3	166±49.9	0.47±0.10
MS and MR	29	106±34.4	58±14.7	119±27.8	0.57±0.12
A and M combined	45	130±55.8	69±25.5	156±55.9	0.55±0.12
Myocardial disease	15	199±75.7	44±14.5	145±27.6	0.25±0.09

AS=aortic valve stenosis with peak systolic pressure gradient >30 mm Hg; AR=aortic valve insufficiency with regurgitant flow >30 ml per beat; MS=mitral valve area <1.5 sq cm; MR=mitral valve regurgitant flow >20 ml per beat; A and M combined=combined aortic and mitral valve disease; myocardial disease=primary cardiomyopathy or myocardial disease secondary to coronary atherosclerosis.

From Dodge HT, Baxley WA: Left ventricular volume and mass and their significance in heart disease. Am J Cardiol 23:528, 1969.

*Normal values from Kennedy JW, et al: Quantitative angiocardiography: The normal left ventricle in man. Circulation 34:272, 1966.

Ejection Fraction.

The ejection fraction (EF) is the ratio between stroke volume (SV) and end-diastolic volume (EDV). In the presence of valvular regurgitation, the total stroke volume ejected by the ventricle (i.e., the sum of forward and regurgitant volumes) is used in this calculation. The regurgitant fraction (RF) is the ratio of regurgitant flow per beat to the total left ventricular stroke volume:

where SV total is determined by angiography and SV forward by the Fick or indicator

dilution method. When mitral and aortic regurgitation coexist, the regurgitant fraction reflects the sum of the two regurgitant volumes and does not distinguish between them. It is important to recognize that there are errors in measuring both total SV and forward SV. These errors summate in the calculation of the regurgitant volume and the regurgitant fraction. Thus, it is difficult to determine regurgitant volume.

LEFT VENTRICULAR MASS.

Left ventricular mass can be determined by M-mode or two-dimensional echocardiography using several techniques (see Chap. 7) .[16] In one of these methods, left ventricular mass is calculated as the difference between total ventricular volume (estimated from the product of the epicardial left ventricular length and the area of the left ventricle in the short axis) and the volume of the left ventricular cavity. Echocardiographically determined left ventricular mass is an important prognostic factor in patients with left ventricular hypertrophy. [17] [18] [19] Computed tomography and magnetic resonance imaging are also useful methods to accurately measure left ventricular mass (see Chap. 10) .[16] [16A]

Left ventricular wall thickness normally averages 10.9 ± 2.0 (SD) mm and left ventricular mass averages 92 ± 16 gm/m^2 (see Table 15-1) . Chronic cardiac dilatation secondary to volume overload or primary myocardial disease increases left ventricular mass, as does chronic pressure overload. Hypertrophy caused by pressure overload (such as aortic stenosis) is characterized by an increased muscle mass resulting from an augmentation of wall thickness with little change in ventricular chamber volume (concentric hypertrophy) (see Table 15-1) . In contrast, hypertrophy caused by volume overload or by primary myocardial disease is characterized by an increased muscle mass resulting from ventricular dilatation, with only a slight increase in wall thickness (eccentric hypertrophy) (see Table 15-1) .

LEFT VENTRICULAR FORCES.

The forces acting on the myocardial fibers within the ventricular wall can be calculated from the dimensions of the left ventricular cavity, wall thickness, and intraventricular pressure. Left ventricular tension (force/cm) is the force acting on a hypothetical slit in the ventricular wall that would pull its edges apart. According to Laplace's law, tension is the product of the intraventricular pressure and radius. Wall stress (sigma) is the force or tension per unit of cross-sectional area of the ventricular wall. Wall stress may be considered to act in three directions--circumferential, meridional, and radial (Fig. 15-5) . The calculation of stress requires assumptions concerning the shape and configuration of the ventricle.[20] [21] Circumferential wall stress, the strongest force generated within the ventricular wall, can be approximated as:

where CWS=circumferential wall stress in dynes per square centimeter×10^3 ; P=left ventricular pressure in dynes per square centimeter; a and b are major and minor

semiaxes (i.e., half the longest lengths), respectively, in cen

Figure 15-5 Circumferential ($sigma_c$), meridional ($sigma_m$), and radial ($sigma_r$) components of left ventricular wall stress from an ellipsoid model. The three components of wall stress are mutually perpendicular. (From Fifer MA, Grossman W: Measurement of ventricular volumes, ejection fraction, mass, and wall stress. *In* Grossman W [ed]: Cardiac Catheterization and Angiography. 5th ed. Philadelphia, Lea & Febiger, 1996, p 324.)

timeters; and h=left ventricular wall thickness in square centimeters.[22] Meridional wall stress (MWS) can be approximated as:

where r is the internal radius of the ventricle in centimeters.

Simultaneous recording of left ventricular dimensions and intraventricular pressure recorded with a high-fidelity micromanometer allows calculation of left ventricular tension and stress throughout the cardiac cycle. A simple method of analyzing the instantaneous left ventricular tension throughout the cardiac cycle consists of recording left ventricular pressure simultaneously with left ventricular diameter across the minor axis of the left ventricle determined by echocardiography. This combination of measurements provides the data necessary to calculate ventricular circumferential fiber shortening (at either the endocardium or the midwall) and midwall circumferential stress, using minor modifications of the equations presented earlier. However, the use of echocardiography, especially M mode, for these calculations is based on the assumption of uniform wall motion. This assumption is reasonable only in conditions that affect left ventricular function relatively uniformly, such as dilated cardiomyopathy or aortic or mitral regurgitation. These assumptions are not correct when there is regional left ventricular dysfunction.

During isovolumetric contraction, left ventricular wall tension and stress rise rapidly as the ventricle contracts without decreasing the chamber volume. During ejection, as the left ventricular cavity decreases in size and wall thickness increases, the stress and tension decline even though pressure is maintained.

REGIONAL VENTRICULAR WALL MOTION.

Ischemic heart disease typically produces regional abnormalities of contraction. Hyperkinesis of normal areas may compensate for impaired function of an abnormal region, leaving global left ventricular function normal or only minimally depressed. Thus, assessment of regional wall motion is more sensitive

Figure 15-6 Left ventricular angiograms in the 30-degree right anterior oblique (RAO) and 60-degree left anterior oblique (LAO) projections. End-diastolic (ED) and end-systolic (ES) frames are shown. Tracing of ED and ES images are superimposed on the far right. The images on top are from a patient with normal left ventricular contraction. The patient on the bottom has anterior-apical and septal akinesis (arrows).

in detecting ventricular dysfunction in such patients than analysis of global ventricular function.

Regional wall motion can be assessed with a variety of methods, including contrast angiography.[23] Marked focal abnormalities of contraction can be appreciated by visual inspection of ventriculograms; segments of abnormal ventricular contraction can be localized by superimposing end-diastolic and end-systolic outlines of the left ventricular cavity (Fig. 15-6). Akinesis is present when a portion of each of the two silhouettes shares a common line; dyskinesis is present when the end-systolic silhouette extends outside the end-diastolic silhouette. The abnormally contracting segments (both akinetic and dyskinetic) may be expressed simply as percentages of the total enddiastolic circumference. Hypokinesis (focal decreases in the extent of contraction) as well as asynchrony (abnormalities of timing of contraction) are less severe disturbances of contraction. Analysis of wall motion from multiple cine frames and automated border detection may be necessary for the detection of these more subtle abnormalities (Fig. 15-7) .[24]

RIGHT VENTRICULAR AND ATRIAL VOLUME.

The shape of the right ventricle is much more complex than the shape of the left ventricle. Thus, the prolate ellipsoid that is a useful model to calculate left ventricular volume is not appropriate for the right ventricle.[25] One method is to consider the right ventricle as a pyramid with a triangular base. An alternate approach is to calculate right ventricular volume using Simpson's rule.

The shape of each atria is less complex than that of the right ventricle. Thus, the atrial volumes can be calculated assuming an ellipsoidal geometry.[26]

Figure 15-7 Automated border recognition tracing of the left ventricular endocardial borders from two-dimensional echocardiograms obtained in the four-chamber *(A)* and short-axis *(B)* views. ROI=region of interest; MV=mitral valve; PM=papillary muscle. (From Hashimoto I, Ichida F, Miura M, et al: Automatic border detection identifies subclinical anthracycline cardiotoxicity in children with malignancy. Circulation

99:2369, 1999. Copyright 1999, American Heart Association.)

ASSESSMENT OF LEFT VENTRICULAR FUNCTION

The factors that determine myocardial function (preload, afterload, contractility, heart rate, and rhythm; see Chap. 14) can be estimated from left ventricular pressure and volume.

Preload (See also p. 464)

Left ventricular preload can be assessed from the left ventricular filling pressure, left ventricular end-diastolic volume, or left ventricular end-diastolic stress.[27] [28] The pressure distending the ventricle immediately before contraction is the end-diastolic pressure. In the absence of disease of the mitral valve this is equivalent to the pressure in the left atrium at this time (the post a wave or Z point pressure). When there is a vigorous atrial contraction, the end-diastolic pressure is substantially higher than the mean left atrial pressure. It is important to recognize that the amount of pulmonary congestion is related to the mean pulmonary capillary (or left atrial) pressure, whereas the end-diastolic volume is determined by the left ventricular end-diastolic pressure.[27] In the absence of pulmonary vascular disease, mean pulmonary capillary wedge pressure approximates the pulmonary artery diastolic pressure. In the presence of a tall v wave, the mean atrial pressure (and mean pulmonary capillary edge pressure) may exceed the ventricular end-diastolic pressure.[29]

The left ventricular preload depends on the end-diastolic volume produced by the distending pressure of the ventricle. Because interventions that alter end-diastolic pressure may also alter the relation between end-diastolic volume and pressure, changes in end-diastolic pressure do not always represent changes in end-diastolic volume or changes in end-diastolic fiber stretch.

Afterload

After aortic valve opening the ventricle ejects into the arterial circulation. Thus, the systolic pressure in the simplest sense represents the afterload opposing left ventricular ejection. However, arterial systolic pressure is not a pure measure of left ventricular afterload. The tension in the ventricular wall that the sarcomeres must overcome to shorten is related not only to the systolic pressure but also to the cavity size through the Laplace relation. Thus, at similar systolic pressures a larger ventricle will have greater wall tension than a smaller ventricle. Furthermore, the arterial systolic pressure depends not only on the characteristics of the arterial circulation but also on the pumping performance of the left ventricle. The more vigorous the left ventricular contraction, the larger the volume ejected and the higher the systolic pressure. Thus, left ventricular systolic function and left ventricular afterload are interrelated.

The steady-state arterial load opposing left ventricular ejection can be quantified as the peripheral vascular resistance.[3] ° This is calculated as the cardiac output divided by the mean arterial pressure minus the mean venous pressure (see Chap. 11) . Because

venous pressure is very low relative to mean arterial pressure, it is frequently neglected in this calculation. The peripheral vascular resistance provides only steady-state information concerning the relation between flow and pressure in the arterial system. However, the left ventricular ejection is pulsatile, and there are pulsatile elements to the arterial load that increase in importance with tachycardia, aging, and peripheral vascular disease.[31] [32]

The full relation between flow and arterial pressure can be evaluated in the frequency domain as the arterial input impedance.[33] [34] Calculation of the input impedance spectrum requires the high-fidelity measurement of aortic pressure and flow at the same point. The impedance spectrum consists of a magnitude and phase at each frequency. The magnitude of the impedance at a given frequency is the ratio of a sinusoidally varying pressure and related flow at that frequency. Because arterial pressure and flow do not vary sinusoidally, the Fourier transformation is used to mathematically describe the aortic pressure and flow as a combination of a fundamental sine wave (at the heart rate)

Figure 15-8 Recordings of ascending aortic pressure and flow *(A)* and the resulting aortic input impedance spectra *(B)* from a 56-year-old normotensive subject (
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) and a 61-year-old subject with isolated systolic hypertension (

), with an impedance spectrum from a young (28 years) normotensive subject (

), shown for comparison. Peripheral vascular resistance (R), impedance moduli of the first harmonic (Z_i) and characteristic impedance (Z_0) were all higher in the subject with isolated systolic hypertension. Also, the impedance moduli minimum was shifted to a higher frequency in the subject with isolated systolic hypertension. Yrs=years; Freq=frequency. (From Nichols WW, Nicolini FA, Pepine CJ: Determinants of isolated systolic hypertension in the elderly. J Hypertension 10[Suppl 6]:S73, 1992.)

Figure 15-9 Left ventricular arterial coupling assessed in the pressure-volume plane. The left ventricular end-systolic pressure-volume relation (ESPVR) is used to describe left ventricular systolic performance. *Top left,* Pressure-volume loops for variably loaded beats are shown with the upper left corner of each beat falling on the ESPVR (dotted line). *Top right,* The arterial circulation is described as a relation between stroke volume and end-systolic pressure (solid line). The slope of this relation represents the effective end-systolic arterial elastance (E_A). *Bottom left,* The left ventricular ESPVR and the aortic ESPVR (A_O P_{ES} -V_{ES}) are plotted on the same axis. End systole occurs at the intersection of the two relations. Thus, description of the arterial circulation in terms of the aortic P_{ES} -SV relation allows understanding of the coupling between the left ventricle and arterial circulation. (Redrawn from Little WC, Cheng CP: Left ventricular-arterial coupling in conscious dogs. Am J Physiol 261:H70, 1991. Reproduced by permission of the American Physiological Society.) *Bottom right,* Pressure-volume loops in the same format recorded in an elderly patient without cardiac disease. (Reproduced from Chen CH, Nakayama M, Nevo E, et al: Coupled systolic-ventricular and vascular stiffening with age: Implications for pressure

regulation and cardiac reserve in the elderly. J Am Coll Cardiol 32:1225, 1998.)

and a series of harmonic waves. The impedance spectrum is then calculated as the ratio of the pressure to flow at each frequency. Figure 15-8 provides an example of such an impedance spectrum. Although the impedance spectrum contains all the information concerning the linear relation between pulsatile flow and pressure in the arterial circulation, its clinical usefulness is limited by the difficulty in obtaining the appropriate measurement and the calculations.

Evaluation of the interaction of the left ventricle and the arterial system requires that they be described in similar terms. Description of the arterial system in the frequency domain does not easily allow this coupling to be assessed because the left ventricle is difficult to describe in these terms. Because the left ventricle can be evaluated in the pressure-volume plane, Sunagawa and colleagues[35] proposed that the arterial system be evaluated in an analogous manner. In this analysis, the arterial system is described by the relation between the stroke volume and end-systolic pressure (Fig. 15-9) . The higher the stroke volume, the greater the end-systolic pressure. The slope of this relation represents the effective arterial end-systolic elastance (E_A). If it is assumed that this relation passes through the origin, then E_A can be calculated as the ratio of end-systolic pressure to stroke volume. As shown in Figure 15-9 , this can be plotted on the left ventricular pressure-volume loop. End systole occurs at the intersection of the arterial and ventricular relations. The production of SW is maximum when the E_{ES} and E_A are approximately equal.[36]

Under usual conditions, E_A , the slope of the arterial end-systolic pressure stroke volume relation, can be approximated by the peripheral vascular resistance multiplied by the heart rate.[37] In older hypertensive patients, E_A may exceed the product of peripheral vascular resistance and heart rate. However, E_A can be accurately estimated over a wide range of conditions from arterial systolic (P_{SYS}) and diastolic pressures (P_{diast}) as: $(2\times P_{SYS} + P_{dias})/3$ divided by the stroke volume.[37]

Contractile State **(See also p. 464)**

In experimental cardiac muscle or isolated heart preparations, loading can be readily controlled and the effects of an intervention on the strength, extent, and velocity of muscle shortening indicate its effect on the contractile

Figure 15-10 *A,* Recording of left ventricular pressure (LVP), the rate of change of left ventricular pressure (dP/dt) and left ventricular volume (LVV). The maximum value of dP/dt, (dP/dt_{max}) increases in response to dobutamine; however, dP/dt_{max} also increases when left ventricular end-diastolic volume is

increased by infusing dextran. This demonstrates the sensitivity of dP/dt_{max} to both contractility and left ventricular end-diastolic volume (preload). (Data from Little WC: The left ventricular dP/dt_{max} -end-diastolic volume relation in closed chest dogs. Circ Res 56:808, 1985. Copyright 1985, American Heart Association.) *B,* Recordings in a normal subject demonstrating increase in dP/dt_{max} during increases in contractility produced by pacing tachycardia, isoproterenol, and exercise. (Modified from Inagaki M, Yokota M, Izawa H, et al: Impaired force-frequency relations in patients with hypertensive left ventricular hypertrophy. Circulation 99:1826, 1999. Copyright 1999, American Heart Association.)

TABLE 15-2 -- EVALUATION OF LEFT VENTRICULAR SYSTOLIC PERFORMANCE: NORMAL VALUES FOR SOME ISOVOLUMIC AND EJECTION PHASE INDICES

CONTRACTILITY INDICES	NORMAL VALUES (MEAN±SD)
Isovolumic Indices	
Maximum dP/dt	1650±300 mm Hg/sec
Maximum (dP/dt)/P	44±8.4 sec^{-1}
V_{PM} or peak [dP/dt 28P]	1.47±0.19 ML/sec
dP/dt/DP at DP=40 mm Hg	37.6±12.2 sec^{-1}
Ejection Phase Indices	
LVSW	81±23 gm-m
LVSWI	50±20 gm-m/M^2
EF: angio:	0.72±0.08
MNSER angio:	3.32±0.84 EDV/sec
MNSER echo:	2.29±0.30 EDV/sec
Mean V_{CF} angio:	1.83±0.56 ED circ/sec
echo:	1.09±0.12 ED circ/sec

dP/dt=rate of rise of left ventricular (LV) pressure; DP=developed LV pressure; ML=muscle lengths; LVSW=left ventricular stroke work; LVSWI=left ventricular stroke work index; MNSER=mean normalized systolic ejection rate; ED=end-diastolic; V=volume; circ=circumference; EF=ejection fraction.*From Grossman W: Evaluation of systolic and diastolic function of the myocardium. In Grossman W, Baim DS (eds): Cardiac Catheterization, Angiography, and Intervention, 5th ed. Philadelphia, Lea & Febiger, 1996, p 339.*

state. It is more difficult to make analogous measurements in patients in whom preload and afterload are interrelated and cannot be readily controlled. Many drugs that affect myocardial contractility also act on the arterial and/or venous beds, thereby altering

cardiac loading. Furthermore, in patients with valvular heart disease, it is necessary to evaluate the level of myocardial contractility despite the marked alterations in loading conditions. These considerations have led to the search for methods of evaluating cardiac function that go beyond analysis of the pumping function of the ventricle and provide an assessment of contractility. A number of indices of contractility have been proposed and investigated empirically. Unfortunately, there is no absolute measure of myocardial contractility; that is, there is no gold standard with which these indices can be compared. Furthermore, at the sarcomere level, contractility and load are interrelated and, thus, not independent variables.[1]

Many indices have been proposed as measures of left ventricular contractile function[38] (Table 15-2) . These can be divided into isovolumetric phase indices, ejection phase indices, and measures derived from left ventricular pressure-volume relations.

ISOVOLUMETRIC INDICES OF CONTRACTILITY. Ventricular dP/dt.

The maximum rate of rise of ventricular pressure (dP/dt_{max}) is highly sensitive to acute changes in contractility (Fig. 15-10) .[39] Under normal conditions dP/dt_{max} occurs before aortic valve opening; thus it is not affected by steady-state alterations in aortic pressure. However, dP/dt_{max} may be delayed until after aortic valve opening in patients with severe left ventricular depression or marked arterial vasodilation with very low aortic diastolic pressures. In the absence of these conditions, dP/dt_{max} can be considered to be relatively independent of afterload. However, dP/dt_{max} is very sensitive to changes in preload. This preload sensitivity is greater in ventricles with enhanced contractility but is reduced in depressed ventricles.[39] However, a change in dP/dt_{max} without a change in preload or with an opposite change in preload indicates an alteration in contractility.

Although dP/dt_{max} correlates with basal contractility, the wide variation between individuals and the marked preload dependence decreases its usefulness for assessing basal contractility. Instead, dP/dt_{max} is more useful in assessing directional changes in contractility during acute interventions when used in combination with a measure of left ventricular preload.

V_{max} .

This is the maximum velocity of shortening of the unloaded contractile elements (CE). It was originally proposed as a measure of myocardial contractility that is independent of preload or afterload. However, there are theoretical and practical limitations to the calculation of CE V_{max} in isolated muscle, and even more so in the intact heart. Because of the theoretical problems and practical difficulties in calculating V_{max} , it is no longer used as a clinical measure of contractility.

Relation Between dP/dt and Developed Pressure.

Some of the difficulties involving the calculation of V_{max} can be partially avoided by the selection of certain points on the curve relating dP/dt to DP, the developed left ventricular pressure (i.e., left ventricular pressure minus end-diastolic pressure). The dP/dt at a DP of 40 mm Hg, a level of pressure that almost always occurs before the opening of the aortic valve, is commonly used. dP/dt at a DP of 40 mm Hg and the maximum dP/dt/DP are useful for assessing directional changes in contractility, because it is unaffected by changes in afterload and less sensitive to changes in preload than dP/dt_{max} .

EJECTION PHASE INDICES.

The extent of left ventricular ejection can be measured as the stroke volume, ejection fraction, or fractional shortening, and the rate of ejection can be quantified as the mean and peak velocity of shortening (V_{CF}).[40A] All of these measurements are influenced by both contractility and load.[40] The marked preload dependence of the stroke volume is minimized by dividing by the end-diastolic volume producing the ejection fraction. However, the ejection fraction is sensitive to changes in afterload; so it is best to consider it a measure of systolic performance, because it is not a pure measure of contractility (see later).

The afterload dependence of the ejection fraction or measures of the left ventricular shortening can be minimized using concepts derived from the myocardial force-velocity relation of isolated cardiac muscle (Fig. 15-11) . For example, the relation between ejection fraction or frac

Figure 15-11 The relation between left ventricular ejection fraction (EF) and arterial load (E_a) in patients with aortic regurgitation. EF falls with increasing arterial load, both in patients with normal contractile function (solid circles) and those with impaired contractile performance (open circles). The fall in ejection performance (EF) with load is more marked in the patients with reduced contractile performance. (From Devlin WH, Petrusha J, Briesmiester K, et al: Impact of vascular adaptation to chronic aortic regurgitation on left ventricular performance. Circulation 99:1027, 1999. Copyright 1999, American Heart Association.)

tional

myocardial fiber shortening and left ventricular end-systolic stress, obtained in the basal state and during pharmacologically altered afterload, provides a useful framework for assessing the basal level of left ventricular contractility.[41] [42] [43] [44] Augmentation of V_{CF} at a constant wall stress signifies an improvement of contractility. These relations are particularly useful in patients who have a reduced ejection fraction, because it distinguishes between reduced myocardial shortening due to excessive afterload and that due to depressed myocardial contractility.[45] The V_{CF} -$sigma_{ES}$ relation during a

single beat is not defined by parallel straight lines; thus, it may not be accurately defined from measurements made from a single loading condition.[46]

PRESSURE-VOLUME RELATIONS.

As discussed earlier, consideration of the left ventricle in the pressure-volume plane provides a powerful method to understand left ventricular performance.[2] [47] [48] The generation of variably loaded beats allows determination of several relations that provide information concerning left ventricular contractility and systolic performance. The variably loaded beats can be produced by transient balloon occlusion of the inferior vena cava.[49] [50] An alternate approach is to generate a range of loading conditions using graded infusions of vasoactive agents, such as methoxamine and nitroprusside.[50] [51]

Left Ventricular ESPVR.

The upper left-hand corner of variably loaded pressure-volume loops defines the left ventricular ESPVR (Fig. 15-12) . In the physiological range, this relation can be approximated as a straight line. Thus, it can be described with a slope (E_{ES}) and volume axis intercept (V_0),[52] [53] that is,

The slope, which has dimensions of pressure/volume (units of mm Hg/ml), has been called the end-systolic elastance (E_{ES}). This represents the end-systolic stiffness of the left ventricle and indicates how sensitive ejection will be to increases in afterload (as reflected in the end-systolic pressure). With enhanced contractility, E_{ES} increases. The volume axis intercept (V_0) of the ESPVR has been referred to as the "dead volume" of the ventricle. This is the volume at which the left ventricle would generate no pressure. This volume intercept cannot be directly measured clinically. Instead, it must be determined by extrapolation and thus is subject to large errors.[52] [53] [54] In many clinical studies the extrapolated V_0 is negative, which is a physiological impossibility. This indicates the difficulties involved in accurately determining V_0 in clinical studies. [54]

The position of the ESPVR on the volume axis at the operating pressure (e.g., the end-systolic volume associated with an end-systolic pressure of 100 mm Hg) indicates the extent of ejection. Global increases in contractility, such as the infusion of dobutamine, both increase E_{ES} and shift the ESPVR to the left in the physiological range.[53] [54] Thus, at a constant afterload (i.e., constant left ventricular end-systolic pressure) the left ventricle with enhanced contractility ejects to a lower volume and is less sensitive to changes in systolic pressure. Global decreases in contractility produce the opposite effect. Thus, E_{ES} and the position of the ESPVR in the physiological range provide load-insensitive measures of the contractile state.[53] [54]

Regional left ventricular dysfunction resulting from coronary artery occlusion produces a parallel rightward shift of the left ventricular ESPVR in the physiological range with little

change in the E_{ES} .[55] [56] A similar parallel shift of the ESPVR occurs during dysynchronous activation of the left ventricle (Fig. 15-13) . [57] [58]

An echocardiographically determined left ventricular end-systolic dimension or cross-sectional area can be used as a surrogate for left ventricular volume in the left ventricular ESPVR provided there is not a segmental wall motion abnormality.[59] Automated echocardiographic border detection makes it possible to determine pressure-area relations on-line.[60]

There are practical and theoretical difficulties in using the ESPVR as a clinical measure of left ventricular contractility. First, to accurately define the ESPVR, a wide range of loading conditions must be obtained. Such alterations in

Figure 15-12 *A,* Variably loaded pressure-volume loops produced by caval occlusion in a conscious experimental animal. End systole occurs at the upper left corner of the pressure-volume loops. The end-systolic points of the variably loaded beats fall along a single relation, the left ventricular end-systolic pressure-volume relation (LV ESPVR). Within the physiological range, this relation is approximated by a straight line. The line can be described in terms of its slope (E_{ES}) and volume axis intercept (V_0). Note that the volume axis intercept results from extrapolation of the line outside the range of end-systolic pressures in which data can be acquired. An increase in contractile state, produced by infusing dobutamine, shifts the LV ESPVR toward the left while increasing the slope. (Data from Little WC, Cheng CP, Mumma M, et al: Comparison of measures of left ventricular contractile performance derived from pressure-volume loops in conscious dogs. Circulation 80:1378, 1989. Copyright 1989, American Heart Association.) *B* and *C,* Recordings of right atrial pressure (RAP), left ventricular volume (LVV) measured with the conductance catheter, and left ventricular pressure (LVP) in a patient during transient balloon occlusion of the inferior vena cava. These variably loaded beats are shown in the pressure-volume plane on the right. The upper left corner of these loops defines the LV ESPVR (dotted line). (From Kass DA: Clinical ventricular pathophysiology: A pressure-volume view. *In* Warltier DC [ed]: Ventricular Function. Baltimore, Williams & Wilkins, 1995.)

Figure 15-13 *Top,* Left ventricular (LV) pressure-volume loops in an experimental animal during transient caval occlusions. The upper left corners of the loops define the left ventricular end-systolic pressure-volume relation (ESPVR). During atrial pacing producing normal LV activation the ESPVR is shifted leftward in a parallel fashion, compared with ventricular pacing that produces dysynchronous LV activation and contraction. (From Park RC, Little WC, O'Rourke RA: Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. Circ Res 57:711, 1985.) *Bottom,* Steady-state left ventricular pressure-volume loop recorded using the conductance catheter in a patient with dilated cardiomyopathy and dysynchronous left ventricular activation due to left bundle branch block (LBBB). A decrease in dysynchronous contraction produced by left ventricular free wall pacing (LVFW) produced loops with greater width (stroke volume) as the end-systolic pressure-volume point shifted toward the left. (From Kass DA, Chen DH, Curry C, et al: Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 99:1570, 1999. Copyright 1999, American Heart Association.)

load may induce reflexly mediated changes in heart rate and left ventricular contractility. In addition, arterial vasoconstriction and vasodilation produce parallel shifts of the left ventricular ESPVR.[61] [62] Thus, the interventions required to accurately define the ESPVR may themselves alter the relation, thus confounding the ability to define the ESPVR with precision in clinical studies.[63]

A second difficulty in evaluating the ESPVR is the determination of the timing of end systole. End systole is defined as the upper-left-hand corner of the pressure-volume loop. This may not exactly correspond to aortic valve closure or the time of maximum ventricular elastance. This difference may be accentuated when there is reduced impedance to left ventricular ejection, as occurs in mitral regurgitation.[64]

A third difficulty is that the slope of the ESPVR depends on the size of the ventricle; thus it is not possible to define a normal range for E_{ES} . Attempts to correct for ventricular size have not been uniformly successful. However, this does not prevent E_{ES} from differentiating patients with normal from abnormal left ventricular contractile function.[65] One method of correcting for differences in left ventricular size is to evaluate the left ventricle in the stress-strain plane.[66] In this analysis the left ventricular end-systolic stress-strain relation is analogous to the ESPVR, except that which has been normalized for wall thickness and chamber size and configuration.

If V_0 is assumed to be small, then E_{ES} can be approximated by the ratio of left ventricular systolic pressure to end-systolic volume (P_{ES} /V_{ES}).[53] [67] This approach has the advantage of avoiding the need to evaluate multiply loaded beats. However, the P_{ES} /V_{ES} ratio is subject to large errors in estimating E_{ES} when V_0 is large and is not a sensitive measure of contractile performance. E_{ES} can also be estimated from a single cardiac cycle using the time varying elastance model to predict V_0 .[68]

Despite the theoretical and practical limitations to the clinical evaluation of contractility using the ESPVR, left ventricular pressure-volume analysis provides a powerful tool to help understand the interaction of contractile state and load to produce ventricular performance (Fig. 15-14) .

Other Pressure-Volume Relations.

Two other relations can be derived from variably loaded pressure-volume loops: the dP/dt_{max} -end-diastolic volume (V_{ED}) relation and SW-V_{ED} relation (Fig. 15-15) .

During caval occlusion, dP/dt_{max} and V_{ED} are linearly related.[39] The slope of the relation (dE/dt_{max}) represents the maximum rate of change of left ventricular elastance during contraction and is very sensitive to contractile state. Thus, this resting dP/dt_{max} -V_{ED} relation accounts for the preload-dependence of dP/dt_{max} , which increases when the contractile state is augmented. Although it is very sensitive to changes in contractile state, the dP/dt_{max} -V_{ED} relation has several limitations. First, dP/dt_{max} is more variable

than P_{ES} , and this relation is less stable than the ESPVR.[69] Second, the dP/dt_{max} -V_{ED} relation saturates at volumes only slightly above the operating point.[70] Thus, this relation can be defined only by preload reduction and not by pharmacologically produced increases in load.

SW is the external work performed by the left ventricle and is calculated as the area of the pressure-volume loop. It can be approximated as the product of the stroke volume and the mean arterial pressure. Thus, SW integrates the two determinants of tissue perfusion: flow and pressure. During caval occlusions, SW and V_{ED} are linearly related. SW is insensitive to arterial load in the physiological range; thus, the SW-V_{ED} relation is afterload independent under these conditions.[36] [71] [72] In response to increase in contractile state, the slope of this relation, termed *preload recruitable stroke work* (PRSW), increases. Thus, PRSW has been proposed as a load-independent measure of contractile state.[73] However, the SW-V_{ED} relation is not only determined by contractile state, but it also can be altered by changes in the diastolic left ventricular pressure-volume relation.[69] For example, the diastolic pressure-volume relation can be altered under some circumstances without a change in the ESPVR.[74] This alters the LV SW-V_{ED} relation and PRSW. Although importantly influenced by contractility, the SW-V_{ED} relation is best considered as a measure of integrated pump function (see later).

The SW-V_{ED} relation has several important advantages.[69] First, since SW integrates pressure and volume throughout the cardiac cycle it is free of noise and is remarkably stable. Second, during reductions in preload as produced by caval occlusion, both determinants of SW (stroke volume and end-systolic pressure) decline, producing a wide range of SW values. This wide range of data increases the statistical precision with which the SW-V_{ED} relation can be defined. Finally, the slope (PRSW) has dimensions of pressure; thus, it is independent of left ventricle cavity size.

Figure 15-14 Examples of variably loaded pressure-volume loops used to define the left ventricular end-systolic pressure-volume relations in four patients: normal ventricle, hypertrophic cardiomyopathy (HCM), left ventricular hypertrophy (LVH) due to hypertension (HTN), dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy (HCM). (From Pak PH, Maughan WL, Baughman KL, Kass DA: Marked discordance between dynamic and passive diastolic pressure-volume relations in idiopathic hypertrophic cardiomyopathy. Circulation 94:57, 1996. Copyright 1996, American Heart Association.)

MAXIMUM POWER.

The power generated by the left ventricle can be calculated as the product of aortic flow and pressure. The maximum power (PWR_{max}) responds to changes in contractile state, is insensitive to changes in the arterial circulation, and is linearly related to the square of

V_{ED} (V_{ED}^2) in the physiological range. [75] [76] Thus, PWR_{max}/V_{ED}^2 may provide a preload independent measure of contractility. PWR_{max}/V_{ED}^2 can be determined noninvasively using nuclear techniques or Doppler echocardiography to determine aortic flow and by measuring arterial pressure using indirect means.[77]

Clinical Evaluation of Determinants of Left Ventricular Function

Many of the complex measures just discussed are not appropriate for routine clinical use. Although left ventricular preload is most accurately determined by its end-diastolic volume, preload is usually assessed clinically by measurements of the pulmonary capillary wedge pressure (see earlier discussion). The level of left ventricular afterload can be estimated by the systolic arterial pressure (in the absence of aortic stenosis). When the systolic pressure is low, calculation of the vascular resistance can determine whether it is due to a low arterial tone (low vascular resistance) or inadequate cardiac output. Although, the left ventricular ejection fraction is a measure of left ventricular systolic performance (see later) in the absence of abnormal afterload or valvular disease, it reflects myocardial contractility. Similarly, left ventricular end-systolic volume (or dimension) when arterial systolic pressure is normal (100-140 mm Hg) indicates the operating position of the left ventricular ESPVR, reflecting systolic (and contractile) performance. Thus, echocardiographic measurements of left ventricular end-systolic dimension can be used to follow the contractile performance of patients with mitral or aortic regurgitation.[78] [79] [79A] [80]

Figure 15-15 Three relations describing left ventricular systolic performance derived from variably loaded pressure-volume loops: the left ventricular end-systolic pressure-volume relation, the relation between dP/dt_{max} and end-diastolic volume (V_{ED}), and the relation between stroke work and V_{ED}. All three relations can be approximated by a straight line within the range of data generated by transient caval occlusion. Each relation is shifted toward the left with an increase in slope in response to increase in contractile state produced by dobutamine. (From Little WC, Cheng CP, Mumma M, et al: Comparison of measures of left ventricular contractile performance derived from pressure-volume loops in conscious dogs. Circulation 80:1378, 1989. Copyright 1989, American Heart Association.)

LEFT VENTRICULAR PUMP FUNCTION (See also p. 462)

The contraction of individual sarcomeres is integrated into the myocardial shortening, which ultimately is expressed as the pumping function of the left ventricle. The left heart can be analyzed as a pump with an input (the pulmonary venous or mean left atrial pressure) and an output (which in simplest terms is the cardiac output=stroke volume×heart rate). The relationship between the input and output is the ventricular function curve or the Frank-Starling relationship (Fig. 15-16) . In this relationship, the output can be considered to be the stroke volume, cardiac output, or the SW.

A family of Frank-Starling curves reflects the response of the pump performance of the ventricle to a spectrum of contractile states, and the position of a given curve provides a description of ventricular contractility. Movement along a single curve represents the operation of the Frank-Starling principle, which indicates that stroke volume, cardiac output, or SW varies with preload. By contrast, upward or downward displacement of the curve represents a positive or negative inotropic effect, that is, an augmentation or depression of contractility, respectively (see Fig. 15-16) . However, it is important to recognize that this ventricular function curve represents a complex interaction of preload, afterload, and contractility.

The pump performance of the left ventricle depends on its ability to fill (diastolic performance) and to empty (systolic performance) (Fig. 15-17) . The forward stroke volume is equal to the end-diastolic volume multiplied by the effective ejection fraction (see later). Thus, the generation of stroke volume depends on the conversion of the filling pressure to end-diastolic volume (diastolic performance) and the generational stroke volume from the end-diastolic volume (systolic performance).[28]

Systolic Performance

Left ventricular systolic performance is reflected in the ability of the left ventricle to empty. Because myocardial contractility is an important determinant of the left ventricle's systolic performance, systolic performance and contractility are frequently considered to be interchangeable. However, they are not the same because the systolic performance of the left ventricle is also importantly influenced by load and ventricular configuration. Thus, it is possible to have abnormal systolic performance despite normal contractility when left ventricular afterload is excessive. Alternatively, left ventricular systolic performance may be nearly normal despite decreased myocardial contractility if left ventricular

Figure 15-16 Depiction of the Frank-Starling relationship. With increasing left ventricular filling pressure measured by the pulmonary capillary wedge pressure (reflecting the pulmonary venous pressure), there is an increase in cardiac output and stroke work. The positions of the curves are influenced by the contractile state of the left ventricle. An enhancement of contractile state shifts the curves upward, whereas a depression produces a downward shift.

Figure 15-17 Block diagram of left ventricular pump performance. The input is the pulmonary venous pressure, and the output is the cardiac output. These are related by the Frank-Starling relations (see Fig. 15-16) . The stroke volume depends on the end-diastolic volume (ED) and the effective left ventricular ejection fraction (EF). See text for discussion.

afterload is low, as occurs in some patients with mitral regurgitation.

Left ventricular systolic performance can be quantified as the left ventricular emptying fraction or ejection fraction. In the presence of a left-sided valvular regurgitant lesion (mitral regurgitation or aortic regurgitation) or a shunt (ventricular septal defect or patent ductus arteriosus), the left ventricular stroke volume may be high, whereas the forward stroke volume (stroke volume minus regurgitant volume or shunt volume), which contributes to useful cardiac output, is lower. Accordingly, the *effective* ejection fraction is the forward stroke volume divided by end-diastolic volume.[38] [81] The effective ejection fraction is a useful means to quantitate systolic function because it represents the functional emptying of the left ventricle that contributes to cardiac output and is relatively independent of left ventricular end-diastolic volume over the clinically relevant range. An operational definition of systolic dysfunction is an effective ejection fraction of less than 50 percent.[81] [82] When defined in this manner, systolic left ventricular dysfunction may result from impaired myocardial function, increased left ventricular afterload, and/or structural abnormalities of the left side of the heart.

If left ventricular contractile state and arterial properties remain constant as end-diastolic volume increases, the ejection fraction stays constant or increases slightly.[40] Thus, an increase in the end-diastolic volume will allow for a normal forward stroke volume despite a reduced effective ejection fraction.

Diastolic Performance

For the left ventricle to function as a pump, it must not only empty but also fill. The left atrial (and pulmonary venous) pressure is the source pressure for left ventricular filling. Thus, normal left ventricular diastolic function can be defined as filling of the left ventricle sufficient to produce a cardiac output commensurate with the body's needs with a normal pulmonary venous pressure (less than 12 mm Hg).[27] In some instances this definition of normal integrated diastolic performance can be met despite clear abnormalities of left ventricular diastolic properties. For example, a compensated patient with a dilated cardiomyopathy may have an adequate cardiac output at rest without an elevated pulmonary venous pressure despite impaired relaxation and a very abnormal left ventricular diastolic pressure-volume curve.

A patient with systolic dysfunction (reduced effective ejection fraction) requires a larger end-diastolic volume to produce an adequate stroke volume and cardiac output. If the larger left ventricular end-diastolic volume can be achieved without an abnormally high pulmonary venous pressure, this can compensate for impaired systolic performance. However, if the larger end-diastolic volume requires an elevation of pulmonary venous pressure, the systolic dysfunction (i.e., reduced effective ejection fraction) will result in diastolic dysfunction. Thus, when defined in this manner, systolic dysfunction in symptomatic patients is usually associated with diastolic dysfunction.

However, diastolic dysfunction frequently occurs in the absence of systolic dysfunction. As defined, diastolic dysfunction may be due to an obstruction to left ventricular filling or an external compression of the left ventricle, but it is usually considered to result from left ventricular abnormalities. Such left ventricular diastolic dysfunction may result from

increased myocardial stiffness or impaired relaxation. Relaxation can be slowed, decreasing early diastolic filling, or incomplete, which impairs filling throughout diastole and decreases end-diastolic distensibility. In the pressure-volume plane, reduced distensibility is represented by a leftward and upward shift of the end-diastolic pressure-volume relation (EDPVR) (Fig. 15-18) . When this occurs, significantly higher pressures are required to distend the left ventricle to achieve the same end-diastolic volume. If the shift in the EDPVR is severe enough, filling of the left ventricle to the level sufficient to produce a normal stroke volume can only be achieved with an elevated pulmonary venous pressure that will be associated with pulmonary congestion. Thus, an alteration in diastolic distensibility may produce pulmonary congestion and congestive heart failure in the absence of systolic dysfunction.[83] [84] [85]

Evaluation of Diastolic Performance

The indices of diastolic function can be organized into three groups: (1) measures of isovolumetric relaxation, (2) indices of passive left ventricular characteristics derived from the diastolic left ventricular pressure-volume relations, and (3) measurements of the pattern of left ventricular diastolic filling obtained from Doppler echocardiography or radionuclide angiography.[27] [86] [87]

ISOVOLUMETRIC RELAXATION.

Isovolumetric relaxation can be quantified by measuring its duration or by describing the time-course of the fall in left ventricular pressure. The duration of isovolumetric relaxation, or the time from aortic valve closure to mitral valve opening, can be measured by M-mode echocardiography. A similar interval, the time from aortic valve closure to the onset of mitral valve flow, can be measured by combining phonocardiography and Doppler echocardiography. The duration of isovolumetric relaxation depends not only on the rate of left ventricular relaxation but also on the difference in pressures between the aorta at the time of aortic valve closure and the left atrium at mitral valve opening.[88] Thus, the duration of isovolumetric relaxation can be increased by an elevation of aortic pressure or decreased by an increase in left atrial pressure. The time interval from minimal left ventricular volume to peak left ventricular filling rate can be measured using radionuclear angiography.[87] Because this time interval spans both isovolumetric relaxation and part of early filling, the interpretation is even more complicated than the duration of isovolumetric relaxation alone.

The time course of isovolumetric pressure decline has been quantitatively described by the peak rate of pressure fall (dP/dt_{min}) and the time constant of an exponential fit of the time course of isovolumetric pressure decline. Each of

Figure 15-18 *A,* Left ventricular end-diastolic pressure-volume relation (LV EDPVR) in a patient with

normal left ventricular function. The open triangles (delta) connected by the red line indicate the exponential end-diastole pressure-volume relation. The solid circles (
) show the viscoelastic effects during the filling of a single beat. (Modified from Pak PH, Maughan L, Baughman KL, Kass DA: Marked discordance between dynamic and passive diastolic pressure-volume relations in idiopathic hypertrophic cardiomyopathy. Circulation 94:57, 1996. Copyright 1996, American Heart Association.) *B,* The slope of the LV EDPVR indicates the passive chamber stiffness. Because the relation is exponential in shape, the slope increases as the end-diastolic pressure increases (curve A). A shift of the curve from A to B indicates that a higher LV pressure will be required to distend the LV to a similar volume; thus the ventricle is less distensible. (From Little WC, Downes TR: Clinical evaluation of left ventricular diastolic performance. Prog Cardiovasc Dis 32[4]:273, 1990.)

these requires the measurement of left ventricular pressure using a micromanometer. dP/dt_{min} is strongly influenced by the pressure at the time of aortic valve closure and is not a good measure of the rate of isovolumetric relaxation.

After aortic valve closure, left ventricular pressure declines in an exponential fashion during isovolumetric relaxation (Fig. 5-19) . The rate of pressure decline can be quantified by the time-constant of the exponential decline. The time-constant (tau) is increased by processes such as ischemia or other causes of myocardial depression that slow ventricular relaxation.[89] [90] It is shortened by an acceleration of the rate of active relaxation, as caused by an increase in heart rate or sympathetic stimulation. The time-constant of isovolumetric pressure decline can also be altered by changes in loading conditions. An increase in arterial pressure or end-diastolic volume can increase the time-constant, although changes in the preload at a constant arterial pressure may have less effect.[90]

Calculation of the time constant of left ventricular isovolumetric pressure decline has several technical limitations. Data are analyzed from the time of minimum dP/dt to a pressure 5 or 10 mm Hg above end-diastolic pressure. Even if pressure is measured every 2 milliseconds, there are only a limited number of data points. This contributes to a large beat-to-beat variability of tau.[91]

If mitral inflow is prevented, left ventricular pressure will decay to subatmospheric levels. Thus it has been suggested that the data should be fit to an exponential function with an asymptote (P_B):

This is usually done by differentiating both sides and then using the linear least squares technique to fit the equation:

The normal range of values of tau calculated using this method is 37 to 67 milliseconds.[92]

The use of an asymptote to calculate tau is particularly important when the external pressure of the left ventricle may be changing.[93] However, tau calculated from a nonfilling beat in an experimental animal in which the full time course of left ventricular

relaxation is available correlates most closely with tau calculated from a normal beat without the use of an asymptote.[94] To avoid the computational properties of nonlinear fitting in the calculation on tau without an asymptote, the relation is linearized using a natural

Figure 15-19 Left ventricular (LV) pressure measured at 2-millisecond intervals using a micromanometer. The LV pressure from the time of minimum dP/dt (dP/dt_{min}) to mitral valve opening is described by an exponential relation (solid line). After mitral valve opening, LV pressure deviates from the exponential line. $P_o + P_b$ =pressure (P) at dP/dt_{max} ; t=time; T=time constant of relaxation; P_B =baseline pressure. (From Little WC, Downes TR: Clinical evaluation of left ventricular diastolic performance. Prog Cardiovasc Dis 32[4]:273, 1990.)

logarithm transformation to result in:

The data are then fit to this equation using the linear least squares technique to determine tau. When calculated using this method the normal range of values for tau is 28 to 45 milliseconds.[92]

The time course of LV pressure during isovolumetric relaxation can also be characterized using noninvasive Doppler measurement of the velocity of a regurgitant jet across the mitral valve.[10] [11] In this method, the modified Bernoulli equation is used to approximate LV pressure during isovolumetric relaxation allowing calculation of the maximum rate of left ventricular pressure decline and the exponential time constant.

PASSIVE DIASTOLIC CHARACTERISTICS OF THE LEFT VENTRICLE.

The passive characteristics of the left ventricle can be described as the passive diastolic pressure-volume relation.[83] [90] Optimally, the passive left ventricular diastolic pressure-volume relation should be constructed from points that are obtained after relaxation is complete and at slow filling rates so that viscous effects are not present.[90] [95] Practically, this can be approximated using points obtained late in diastole, when relaxation is assumed to be complete, or from variously loaded beats at end diastole. However, it is important to correct for the effect of respiratory changes in intrathoracic pressure. The effective chamber stiffness can be calculated from the noninvasively measured time for early filling deceleration (see later).[96]

The slope of the EDPVR is the *chamber stiffness.* Because the pressure-volume relation is nonlinear, the chamber stiffness depends on the point on the curve in which it is measured; thus, stiffness increases with increasing volume (see Fig. 15-19) . Several

techniques have been proposed to correct for this effect by normalizing chamber stiffness. One approach is to approximate the pressurevolume relation by an exponential function. Another technique is to compare the chamber stiffness at a common pressure or volume. However, the analysis of chamber stiffness does not account for shifts in the pressure-volume relation that can occur from the alteration of load, diseases, or pharmacological agents.[90] The position of the diastolic pressure-volume relation indicates the distensibility of the left ventricle. For example, an upward shift indicates a less distensible ventricle.[97]

The *diastolic pressure-volume* relation represents the net passive characteristics of the left ventricular chamber. To derive information concerning the properties of the myocardium alone, the effects of wall thickness, ventricular configuration, size, and external pressure must be removed.[98] This can be accomplished by calculating the myocardial stress-strain relation from the chamber pressure-volume relation. In contrast to the slope of the pressure-volume relation, which assesses the amount of ventricular chamber distention under pressure, the stress-strain relation represents the resistance of the myocardium to stretch when subjected to stress. Thus, it should not be influenced by the configuration of the left ventricle. However, the calculation of stress requires the use of a geometric model of the left ventricle and the calculation of strain requires assumption of the unstressed left ventricular volume, which cannot be directly measured in the intact circulation. In addition to these potential theoretical limitations, these calculations require accurate measurements over a wide range of left ventricular pressures and volumes. Measurements made during rapid filling may be inappropriately influenced by active myocardial relaxation and viscoelastic effects. Observations during diastasis and atrial systole minimize this problem, but they may not supply a wide enough range of data points. The theoretical problems and the technical difficulties in determining myocardial stress-strain relations have limited their clinical application.

PATTERNS OF LEFT VENTRICULAR DIASTOLIC FILLING.

Analysis of the pattern of left ventricular filling can provide useful information about diastolic left ventricular performance. Such information can be obtained by determining the left ventricular volume or dimension throughout the cardiac cycle, using contrast or radionuclide angiography[87] or M-mode or two-dimensional echocardiography, or by measuring the left ventricular inflow velocity using a Doppler determination of mitral valve flow velocities. The most widely used method is Doppler measurement of mitral valve flow velocity.[99] [100] [101] [102] [103] The pattern of left ventricular filling can also be assessed using tissue Doppler measurements and color M-mode imaging.[100]

Mechanisms of Diastolic Filling.

To understand the significance of the patterns of left ventricular filling, it is important to consider the mechanisms of normal left ventricular filling.[99] [104] The events surrounding normal left ventricular filling are shown in Figure 15-20 (Figure Not Available) . From the time of aortic valve closure until mitral valve opening, the left ventricle is normally a closed chamber with a constant volume. Myocardial relaxation begins in the latter part of systole and causes a steep, exponential fall in intraventricular pressure as elastic elements of the left ventricle that were compressed and twisted during ejection are

allowed to recoil. Although no filling occurs during isovolumetric

Figure 15-20 (Figure Not Available) Recording of left ventricular (LV) pressure (P_{LV}), left atrial pressure (P_{LA}), left ventricular volume (LVV), and the rate of change of LV volume (dV/dt), which indicates the rate of LV filling. LV filling occurs early in diastole and during atrial systole in response to pressure gradient from the left atrium to the left ventricle. The early diastolic pressure gradient is generated as LV pressure falls below left atrial pressure and the late diastolic gradient is generated as atrial contraction increases left atrial pressure above LV pressure. (Data recorded in a conscious animal from Cheng CP, Freeman GL, Santamore WP, et al: Effect of loading conditions, contractile state and heart rate on early diastolic left ventricular filling in conscious dogs. Circ Res 66:814, 1990. Copyright 1990, American Heart Association.)

relaxation, the processes that determine the rate of decline of the isovolumetric pressure influence ventricular filling after opening of the mitral valve.[94] [105] For the first 30 to 40 milliseconds after mitral valve opening, relaxation of left ventricular wall tension is normally rapid enough to cause left ventricular pressure to fall, despite a substantial increase in left ventricular volume.[104] This fall in left ventricular pressure produces a pressure gradient that accelerates blood from the left atrium into the left ventricle, resulting in rapid early diastolic filling. The rate of early left ventricular filling is determined by the mitral valve pressure gradient (left atrial pressure-left ventricle pressure).[104] [106] Although peak filling occurs after the peak pressure gradient, the two are closely related. Two major factors (myocardial relaxation and left atrial pressure) determine the early diastolic mitral valve pressure gradient and the rate of left ventricular filling. Under normal circumstances more than two thirds of the stroke volume enters the left ventricle during early diastole.

After filling of the left ventricle begins, the mitral valve pressure gradient decreases and then transiently reverses. This occurs because left ventricular relaxation is nearing completion and the flow of blood from the left atrium fills the left ventricle, raising the left ventricular pressure while lowering the left atrial pressure. This reversed mitral valve pressure gradient decelerates and then stops the rapid flow of blood into the left ventricle early in diastole.[96] The pressures in the left atrial and left ventricle equilibrate as mitral flow nearly ceases; thus, little left ventricular filling occurs during the midportion of diastole, termed *diastasis.*

Atrial contraction increases atrial pressure late in diastole producing a left atrial-to-left ventricular pressure gradient that again propels blood into the left ventricle. After atrial systole, as the left atrium relaxes, its pressure decreases below left ventricular pressure, causing the mitral valve to begin closing.[107] The onset of ventricular systole produces a rapid increase in left ventricular pressure that seals the mitral valve and ends diastole.

Normal Pattern of Left Ventricular Filling.

The normal pattern of left ventricular filling is characterized by rapid filling early in

diastole with some additional filling during atrial contraction (see Figs. 7-34, p. 175, and

Figure 15-21 (Figure Not Available) Patterns of left ventricular (LV) filling as recorded by diastolic Doppler mitral flow velocities. In the normal pattern there is a large E wave and a small A wave. There are three abnormal patterns of mitral filling representing progressively worsening LV diastolic performance. With "impaired relaxation" the E wave is less than the A wave. The LV deceleration time (t_{dec}) is prolonged. In the "pseudonormalized" pattern the E wave is larger than A wave, however, t_{dec} is shortened. In the restricted filling pattern, E is much larger than A with a very short t_{dec}. (See also Table 15-4.) (Modified from Little WC, Warner JG Jr, Rankin KM, et al: Evaluation of left ventricular diastolic function from the pattern of left ventricular filling. Clin Cardiol 21:5, 1998.)

TABLE 15-3 -- NORMAL VALUES OF PARAMETERS OF LEFT VENTRICULAR DIASTOLIC FILLING MEASURED BY DOPPLER ECHOCARDIOGRAPHY

	ADULTS <41 YR	**ADULTS <55 YR**
Peak mitral flow velocity (E) (cm/sec)	76±13	63±11
Peak mitral filling rate (A) (cm/sec)	38±8	52±9
Mitral E/A	2.1±0.6	1.3±0.3
Mitral E deceleration time	184±24	
Mitral E deceleration rate (m/sec^2)	5.6±2.7	
Isovolumetric relaxation time (msec)	74±26	
Peak pulmonary venous AR wave (cm/sec)	18±3	25±5
Peak pulmonary venous S wave (cm/sec)	41±10	60±10
Peak pulmonary venous D wave (cm/sec)	53±10	38±10

Data from Little WC, Downes TR: Clinical evaluation of left ventricular diastolic performance. Prog Cardiovasc Dis 32:273, 1990; and Rakowski H., et al: Canadian consensus recommendations for the measurements and reporting of diastolic dysfunction by echocardiography. J Am Soc Echocardiogr 9:745 and 754, 1996.

15-21). This normal filling pattern can be quantified by measuring the peak early diastolic filling rate or mitral flow velocity (E), the integral of the early diastole filling or flow velocity, and the peak filling rate (A) or mitral flow velocity during atrial contraction.[99] [100] [101] [102] [103] The relative contribution of early and late (atrial) filling is commonly expressed as the E/A ratio. Normally, the E/A ratio is greater than 1.0. The time required for deceleration of the early diastolic flow (t_{dec}) and the rate of this deceleration (E/t_{dec}) are two other important parameters of the filling pattern. A variety of other measures have also been proposed. Table 15-3 lists the ranges of normal values for these measures. The wide range of normal values is caused by variations in the technique of performing the observations, which are both operator and equipment sensitive. Furthermore, the measures can be altered by many physiological factors.

Abnormal Patterns of Left Ventricular Filling.

The normal pattern of left ventricular filling is altered in many patients with cardiac disease.[99] [100] [101] [102] [103] [108] [109] Three abnormal patterns (in patients in sinus rhythm without mitral stenosis) have been identified indicating progressively greater impairment of diastolic function (see Figs. 7-34, p. 175, and15-21) (Figure Not Available) .

The first abnormal pattern of filling has been termed *delayed relaxation.* In this pattern there is reduced peak rate and amount of early left ventricular filling and the relative importance of atrial filling is enhanced. This results in a reversed E/A ratio of less than 1.0 (i.e., E<A). The decreased peak rate of early filling is due to a decreased early diastolic left atrial to left ventricle pressure gradient, resulting from a slowed rate of left ventricular relaxation[110] (Fig. 15-22) . The E deceleration time may be prolonged, owing to relative underfilling of the ventricle early in diastole. A "delayed relaxation" pattern can be seen in patients with left ventricular hypertrophy, arterial hypertension, and coronary artery disease and in normal elderly subjects. In many of these patients, mean left atrial pressure is within the normal range at rest and the patients are asymptomatic. In this situation, the vigorous atrial contraction compensates for the reduced early filling due to impaired left ventricular relaxation while maintaining a normal mean left atrial pressure.

Figure 15-22 Recordings of left ventricular (LVP) and left atrial pressures (LAP) and the rate of change of left ventricular volume (dV/dt) during control and serially during the development of pacing-induced heart failure in an experimental animal. During control there is a normal filling pattern with E larger than A. At 4 days a pattern of "impaired relaxation" has developed with a small E and large A. This occurs in response to a slowing of the rate of left ventricular relaxation and a smaller pressure gradient from the left atrium to the left ventricle early in diastole. As heart failure subsequently worsened, left atrial pressure increased. This ultimately resulted in a pattern of "pseudonormalization" at 2 to 3 weeks and a pattern of "restricted filling" at 4 weeks. The increased early filling (E) occurring during these patterns was associated with increases in the early diastolic left atrial to left ventricular pressure gradient produced by the marked increase in left atrial pressure. (From Ohno M, Cheng CP, Little WC: Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation 89:2241, 1994. Copyright 1994, American Heart Association.)

A second pattern of abnormal filling has been termed *pseudonormalized.* This pattern, in which the E/A ratio is greater than 1.0 (as occurs in normal persons) is seen in patients with a more severe impairment of diastolic performance than the pattern of delayed relaxation. The pseudonormalized pattern is due to a restoration of the normal early diastolic left ventricular pressure gradient due to an increase in left atrial pressure that compensates for the slowed rate of left ventricular relaxation[110] (see Fig. 15-22). The pseudonormalized pattern of filling is distinguished from normal by a more rapid rate of early diastolic flow deceleration, a faster deceleration time (typically<190 msec), and alterations in pulmonary venous flow velocity, mitral annular velocity, and flow

propagation (Table 15-4) . The deceleration time is proportional to the inverse of the square root of the left ventricular chamber stiffness.[96] [110] Thus, the faster deceleration time indicates an elevated left ventricular early diastolic chamber stiffness.[96]

A third abnormal pattern of left ventricular filling indicating a severe diastolic abnormality has been termed the *restrictive pattern.* In this pattern, the early filling is increased above the control level and greatly exceeds the filling that occurs during atrial contraction; thus, the E/A ratio is usually greater than 2.0. In fact, there may be little or no filling during atrial contraction. The deceleration time is less than 150 milliseconds, and the deceleration rate of early flow is rapid. This pattern is seen in patients with severe diastolic dysfunction and pulmonary congestion. The enhanced early filling in the "restrictive pattern" results from a markedly elevated left atrial pressure that more than offsets the slowing of left ventricular relaxation.[110] The "restrictive filling" pattern is seen in patients with severe pulmonary congestion,[111] constrictive pericarditis,[112] and restrictive cardiomyopathies such as cardiac amyloidosis[113] and is associated with a poor prognosis. This is particularly true if the restrictive pattern does not improve with therapy.[114]

The three abnormal patterns of left ventricular filling represent a continuum of increasing severity of diastolic abnormalities. The pattern of delayed relaxation may be observed in asymptomatic patients with only impaired diastolic reserve, whereas the pseudonormalized and restricted patterns occur in patients with progressively more severe diastolic dysfunction who almost always have pulmonary congestion.

Calculation of Early Diastolic Chamber Stiffness.

In the absence of mitral stenosis, the E deceleration time is determined by the net stiffness of the left ventricle and left atrium.[110] However, during the time of E deceleration, left atrial pressure is kept relatively constant by pulmonary venous inflow; thus, E deceleration time is predominantly influenced by left ventricular stiffness.[96] Accordingly, effective early diastolic left ventricular chamber stiffness (K_{LV}) can be estimated from the E deceleration time (t_{dec}) as:

TABLE 15-4 -- STAGES OF DIASTOLIC DYSFUNCTION

PARAMETER	NORMAL (YOUNG)	NORMAL (ADULT)	DELAYED RELAXATION	PSEUDO-NORMAL FILLING	RESTRICTIVE FILLING
E/A (cm/sec)	>1	>1	<1	1-2	>2
DT (msec)	<220	<220	>220	150-200	<150
IVRT (msec)	<100	<100	>100	60-100	<60

S/D	<1	1	1	<1	<1
AR (cm/sec)	<35	<35	<35	35*	25*
V_p (cm/sec)	>55	>45	<45	<45	<45
E_a (cm/sec)	>10	>8	<8	<8	<8

AR=pulmonary venous peak atrial contraction reversed velocity; DT=early left ventricular filling deceleration time; E/A=early-to-atrial left ventricular filling ratio; E_a =peak early diastolic annular myocardial velocity; IVRT=isovolumic relaxation time; S/D=systolic-to-diastolic pulmonary venous flow ratio; V_p =color M-mode flow propagation velocity.

From Garcia MJ, et al: New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 32:872, 1998.

*Unless atrial mechanical failure is present.

Pulmonary Venous Flow Patterns.

The pattern of blood flow in the pulmonary veins provides additional information on diastolic filling.[86] [100] [115] The velocity of pulmonary venous flow can be measured by transthoracic Doppler evaluation in most patients.[116] The pulmonary venous flow velocity has three waves (see Figs. 7-34, p. 175, and 15-23) : (1) the S wave, indicating antegrade flow into the left atrium during ventricular systole; (2) the D wave, indicating antegrade flow early in diastole just following the peak of the E wave mitral valve flow; and (3) the AR wave of retrograde flow out of the left atrium during atrial systole. The S and D waves correspond to the x and y descents in the left atrial pressure, whereas the pulmonary venous AR wave corresponds to the left atrial a wave. When left ventricular end-diastolic stiffness is increased, the AR wave is augmented unless atrial systolic failure or atrial fibrillation is present. Thus, pseudonormalized and restricted mitral flow patterns are associated with large, prolonged AR waves that have a peak flow velocity greater than 35 cm/sec and are prolonged beyond the termination of the "a" wave of the mitral inflow velocity.[99] [100] [115] [117] However, some patients with restricted filling may have atrial systolic failure producing small or absent AR waves.[100]

Tissue Doppler and Color M-Mode Imaging.

Tissue Doppler can measure the velocity of mitral annular motion as the left ventricle fills (Fig. 15-24) . The motion occurs early in diastole (E_m) and during late diastole (A_m) reflecting the LV filling pattern.[100] [118] Thus, the E_m /A_m ratio is similar to the mitral E/A

but may be less load dependent. Color M-mode imaging (see Fig. 15-24) measures the rate of flow propagation into the left ventricle in early diastole.[100] [119] This is reduced in conditions associated with impaired relaxation.

Figure 15-23 Pulmonary venous flow velocity recording obtained with pulsed wave Doppler demonstrating normal forward flow in systole (S) and diastole (D) and regurgitant flow during atrial contraction (AR). (Modified from Jensen JL, Williams FE, Beilby BJ, et al: Feasibility of obtaining pulmonary venous flow velocity in cardiac patients using transthoracic pulsed wave Doppler technique. J Am Soc Echocardiogr 10:64, 1997. Reproduced by permission of the American Society of Echocardiography.)

Figure 15-24 Noninvasive evaluation of left ventricular filling in a patient with diastolic dysfunction due to hypertrophic cardiomyopathy. The mitral inflow velocity shows an "impaired relaxation" pattern with E/A less than 1.0. The pulmonary venous flow pattern shows a large, prolonged atrial regurgitant (Ar) flow; the tissue Doppler measurement of mitral annular motion shows an early diastolic motion (E_a) less than the atrial expansion (A_a), corresponding to the mitral inflow pattern. The early diastolic flow propaga tion velocity measured by color M-mode imaging is reduced. (Reproduced from Nagueh SF, Lakkis NM, Middleton KJ, et al: Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. Circulation 99:258, 1999. Copyright 1999, American Heart Association.)

The mitral annular velocity profile and flow propagation velocity can be integrated with mitral inflow and pulmonary venous velocity to help distinguish pseudonormal and restricted filling (see Table 15-4).

Clinical Evaluation of Left Ventricular Systolic and Diastolic Performance

Left ventricular systolic performance is most simply evaluated by the ejection fraction. Unless afterload is abnormally reduced, or there is valvular regurgitation or a left-to-right shunt, an ejection fraction (greater than 0.50) indicates normal systolic left ventricular performance. A reduced ejection fraction can be due to depressed myocardial contractility or elevated afterload. The ejection fraction is not importantly influenced by most physiological changes in preload.

Left ventricular diastolic performance is more difficult to simply evaluate. A patient can be suspected of having diastolic dysfunction if there is clinical evidence of elevated left-sided filling pressures (i.e., pulmonary congestion). Left ventricular diastolic dysfunction can be associated with systolic dysfunction or may be a primary abnormality if the ejection fraction is preserved. In the presence of sinus rhythm, further clinical assessment of diastolic function can be performed by Doppler echocardiographic measurement of the pattern of mitral inflow velocity. In the absence of mitral stenosis, if the E/A is greater than 1.0 and the E deceleration time is greater than 190 milliseconds, diastolic function is probably normal. This can be confirmed by an isovolumic relaxation time of less than 100 milliseconds and a pulmonary venous AR wave less than 35 cm/sec that ends before the mitral A wave. An E/A less than 1.0 (impaired relaxation pattern) associated with a pulmonary venous AR wave that is elevated (> 35 cm/sec)

and prolonged beyond the mitral A wave indicates mild-to-moderate diastolic dysfunction. An E/A greater than 1.0 associated with an E deceleration time less than 190 milliseconds and/or an enlarged delayed AR wave (pseudonormalized or restricted patterns) indicates more severe diastolic dysfunction. An E deceleration time less than 150 milliseconds indicates a stiff left ventricle and a poor prognosis, especially if it does not lengthen after diuresis.

Assessment of Right Ventricular Performance

Although most attention in adult cardiology is appropriately focused on the performance of the left ventricle, the right ventricle may be an important contributor to cardiac dysfunction.[120] The concepts of preload, afterload, and contractility and most of the methods of evaluating left ventricular performance are also applicable to the right ventricle. The ejection of the thin-walled right ventricle is more sensitive to increases in afterload than the left ventricle. Right ventricular dilatation in response to increased afterload is limited by the tethering of the right ventricle to the much thicker left ventricle and the limitations imposed by the pericardium. With increased afterload, the thin-walled right ventricle dilates, causing functional tricuspid regurgitation. Right ventricular performance can be importantly influenced by the presence and severity of such regurgitation.

Right ventricular volume and ejection fraction can be measured using echocardiography, radionuclear techniques, and angiography. In addition, right ventricular stroke volume

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and ejection fraction can be monitored on-line using the thermodilution technique.[121] This is performed by injecting a bolus of cold dextran solution into the right atrium while the temperature in the pulmonary artery is recorded using a rapidly responding thermistor mounted on a catheter. This technique, which allows serial measurements, is convenient, reproducible, and reasonably accurate.

The right ventricular ESPVR can be determined with a manometer-tipped catheter in the right ventricle and either an impedance catheter or a radionuclide ventriculogram to provide simultaneous measurements of right ventricular volume while varying right ventricular load.[122] [123] The right ventricular ESPVR behaves in a similar manner as the left ventricular ESPVR discussed earlier. The right ventricular ESPVR is linear in the physiological range and is shifted upward and leftward by the positive inotropic agent dobutamine.

INTEGRATED CARDIOVASCULAR PERFORMANCE

Cardiac Output (See Chap. 11)

The integrated pumping function of the cardiovascular system results in the cardiac output. The cardiac output can be measured using indicator dilution techniques discussed in Chapter 11 or by the Fick principle (see below).[1,2,4]

The cardiac output is usually corrected for body size and expressed as the cardiac index. The normal range for the cardiac index at a basal (resting) state in the supine position is wide, between 2.5 and 4.2 liters/min/m^2 . The wide normal range makes it possible for cardiac output to decline by almost 40 percent and still remain within the normal limits. Thus, a low cardiac index of less than 2.5 liters/min/m^2 usually represents a marked disturbance of cardiovascular performance and is almost always clinically apparent. Although the resting cardiac output (or index) is insensitive in detecting mild to moderate cardiac impairment, it provides a valuable measure of the integrated function

Figure 15-25 Relation between arteriovenous oxygen (AV_{O_2}) difference (broken line) and cardiac index (solid curve) in normal subjects at rest *(center)* and during exercise *(right)*, and in the patient with progressively worsening myocardial failure *(left)*. (From Grossman W: Blood flow measurement: The cardiac output. *In* Grossman W, Baim DS: Cardiac Catheterization, Angiography and Intervention. 5th ed. Philadelphia, Lea & Febiger, 1996, p 110.)

TABLE 15-5 -- CLINICAL MEASURES OF LEFT VENTRICULAR PERFORMANCE

Preload
Pulmonary capillary wedge pressure
Left ventricular end-diastolic volume
Afterload
Arterial systolic pressure
Vascular resistance
Contractility
Left ventricular ejection fraction (normal afterload)
Left ventricular dP/dt_{max} (at constant LVEDV)
Left ventricular end-systolic volume or dimension
Systolic function
Left ventricular ejection fraction
Stroke work
Diastolic function
Pulmonary capillary wedge pressure
Mitral valve flow velocity
Pulmonary venous flow velocity
Other echo-Doppler parameters (e.g., isovolumic relaxation time, peak early diastolic annular myocardial velocity, propagation velocity)
Integrated cardiopulmonary function
Mixed venous oxygen saturation
Exercise performance

of the cardiovascular system, especially in critically ill patients.

Arterial-Venous Oxygen Difference

The most critical function of the cardiovascular system is to supply the tissues with oxygen. This requires the integrated action of the heart, circulation, lungs, and the peripheral metabolism.[125] As defined by the Fick principle, the oxygen delivered to the body is the product of the cardiac output and the difference in oxygen content of the arterial blood and the mixed venous blood (A-V_{O_2} difference).[124] Under normal circumstances at rest, adequate oxygen supply to the tissues is produced with an A-V_{O_2} difference of 40 ± 10 ml O_2 /liter. With nearly fully oxygenated arterial blood (> 98 percent saturation) and normal hemoglobin concentration and oxygen-carrying capacity, the normal A-V_{O_2} difference is achieved with a mixed venous oxygen saturation of more than 70 percent. If the cardiac output is inadequate, the tissues extract more oxygen and the A-V_{O_2} difference increases. In this situation mixed venous oxygen saturation falls (Fig. 15-25). Thus, a normal mixed venous oxygen saturation (> 70 percent) indicates that the cardiac output (and other components of the circulation) are adequate to meet the body's demands.[126] [127]

A wide A-V_{O_2} difference and reduced mixed venous oxygen saturation may result from an abnormality of cardiovascular function that is limiting the cardiac output, a defect in the oxygen-carrying capacity of the blood, or pulmonary disease. When the ability to increase oxygen extraction is exhausted, anaerobic metabolism produces lactate and venous lactate levels rise precipitously.[128]

The myocardium extracts oxygen nearly maximally from blood at rest. Thus, the coronary sinus oxygen saturation is low (<40 percent) and the myocardium cannot use an increase in oxygen extraction as a compensatory mechanism for inadequate coronary flow.

During exercise the body's oxygen consumption increases.[123A] [123B] This increased need is met by a combination of an increase in cardiac output and a widening of the A-V_{O_2} difference. [124] For example, during very strenuous exercise, the oxygen consumption increases up to 18-fold. This is accomplished by a 6-fold increase in cardiac output (from 3 to 18 liters/min/m^2) and a 3-fold increase in the A-V_{O_2} difference (from 40 to 120 ml/liter), with the mixed venous oxygen saturation decreasing from 75 to 25 percent.

Cardiopulmonary Exercise Testing

The integrated performance of the cardiovascular and pulmonary systems can be evaluated by cardiopulmonary exercise testing, which is discussed on pp. 129-131.

CLINICAL EVALUATION OF CARDIAC PERFORMANCE

Many of the measures of cardiac performance just described are important for their conceptual value and role in special situations and clinical investigations. The measures of various aspects of cardiac performance most commonly used in clinical practice are summarized in Table 15-5 .

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ASSESSMENT OF LEFT VENTRICULAR FUNCTION

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Chapter 16 - Pathophysiology of Heart Failure

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Heart (or cardiac) failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only from an elevated filling pressure. It is usually, but not always, caused by a defect in myocardial contraction, that is, by *myocardial failure.* However, in some patients with heart failure a similar clinical syndrome is present but there is no detectable abnormality of *myocardial* function. In many such cases, heart failure is caused by conditions in which the normal heart is suddenly presented with a load that exceeds its capacity or in which ventricular filling is impaired.[1] *Heart failure* should be distinguished from *circulatory failure,* in which an abnormality of some component of the circulation--the heart, the blood volume, the concentration of oxygenated hemoglobin in the arterial blood, or the vascular bed--is responsible for the inadequate cardiac output.

Thus, the terms myocardial failure, heart failure, and circulatory failure are not synonymous but refer to progressively more inclusive entities. Myocardial failure, when sufficiently severe, always causes heart failure, but the converse is not necessarily the case, because a number of conditions in which the heart is suddenly overloaded (e.g., acute aortic regurgitation secondary to acute infective endocarditis) can cause heart

failure in the presence of normal myocardial function, at least early in the course of the illness. Myocardial failure may be associated with systolic dysfunction, diastolic dysfunction, or both. Also, conditions such as tricuspid or mitral stenosis and constrictive pericarditis, which interfere with cardiac filling, can cause heart failure without myocardial failure. Heart failure, in turn, always causes circulatory failure, but again the converse is not necessarily the case, because a variety of noncardiac conditions (e.g., hypovolemic shock) can produce circulatory failure at a time when cardiac function is normal or only modestly impaired.

The hemodynamic, contractile, and wall motion disorders in heart failure are discussed in the chapters on echocardiography (see Chap. 7) , cardiac catheterization (see Chap. 11) , radionuclide imaging (see Chap. 9) , and assessment of cardiac function (see Chap. 15) . In this chapter, the focus is on the physiological, neurohumoral, biochemical, molecular, and cellular changes characteristic of heart failure.

SHORT-TERM ADAPTIVE MECHANISMS

In the presence of a primary disturbance in myocardial contractility or an excessive hemodynamic burden placed on the ventricle, or both, the heart depends on a number of adaptive mechanisms for maintenance of its pumping function[2] (Table 16-1) . Most important among these are (1) the Frank-Starling mechanism, in which an increased preload helps to sustain cardiac performance; (2) activation of neurohumoral systems, especially the release of the neurotransmitter norepinephrine (NE) by adrenergic cardiac nerves (see p. 520), which augments myocardial contractility, and the activation of the renin-angiotensin-aldosterone system (see p. 524) and other neurohumoral adjustments that act to maintain arterial pressure and perfusion of vital organs; and (3) myocardial remodeling with or without cardiac chamber dilatation, in which the mass of contractile tissue is augmented (see p. 507). The first two of these adaptations occur rapidly, over minutes to hours of the onset of severe myocardial dysfunction, and may be adequate to maintain the overall pumping performance of the heart at relatively normal levels. Myocardial hypertrophy and remodeling develop more slowly, over weeks to months, and play an important role in long-term adaptation to hemodynamic overload. However, the capacity of each of these mechanisms to sustain cardiac performance in the face of hemodynamic overload is finite and, when chronically maintained, becomes maladaptive.

HEMODYNAMIC AND CIRCULATORY CONSEQUENCES OF HEART FAILURE (SeeChap. 15) .

Cardiac output is often depressed, and the arterial/mixed venous oxygen difference is widened in the basal state in patients with the common forms of heart failure secondary to ischemic heart disease, hypertension, primary myocardial disease, valvular disease, and pericardial disease (so-called low-output, systolic heart failure). In cases of mild heart failure, the cardiac output may be normal at rest but fails to rise normally during exercise. When the volume of blood delivered into the systemic arterial bed is chronically reduced, and/or when one or both ventricles has an elevated filling pressure, a complex sequence of adjustments occurs that ultimately results in the *retention of sodium and water* in the intravascular and interstitial compartments. Many of the clinical

manifestations of heart failure such as dyspnea and edema

TABLE 16-1 -- SHORT-TERM AND LONG-TERM RESPONSES TO IMPAIRED CARDIAC PERFORMANCE

RESPONSE	SHORT-TERM EFFECTS*	LONG-TERM EFFECTS
Salt and water retention	Augments preload	Causes pulmonary congestion, anasarca
Vasoconstriction	Maintains blood pressure for perfusion of vital organs (brain, heart)	Exacerbates pump dysfunction (afterload mismatch); increases cardiac energy expenditure
Sympathetic stimulation	Increases heart rate and ejection	Increases energy expenditure
Sympathetic desensitization		Spares energy
Hypertrophy	Unloads individual muscle fibers	Leads to deterioration and death of cardiac cells; cardiomyopathy of overload
Capillary deficit		Leads to energy starvation
Mitochondrial density	Increase in density helps meet energy demands	Decrease in density leads to energy starvation
Appearance of slow myosin		Increases force, decreases shortening velocity and contractility; is energy sparing
Prolonged action potential		Increases contractility and energy expenditure
Decreased density of sarcoplasmic reticulum calcium-pump sites		Slows relaxation; may be energy sparing
Increased collagen	May reduce dilatation	Impairs relaxation

From Katz AM: Cardiomyopathy of overload: A major determinant of prognosis in congestive heart failure. N Engl J Med 322:100, 1990. Copyright 1990, Massachusetts Medical Society.

*Short-term effects are mainly adaptive and occur after hemorrhage and in acute heart failure.

Long-term effects are mainly deleterious and occur in chronic heart failure.

are secondary to this excessive retention of fluid (see Chap. 17).

Interaction Between the Frank-Starling Mechanism and the Adrenergic Nervous System

It is useful to consider the function of the normal and failing heart within the framework of the Frank-Starling mechanism, in which an increase in preload, reflected in an elevation of end-diastolic volume, augments ventricular performance. The normal relationship between ventricular end-diastolic volume and performance is shown in Figure 16-1 , curve 1. During exercise and other stresses, the increases in adrenergic nerve impulses to the myocardium, the concentration of circulating catecholamines (see p. 520), and tachycardia all augment myocardial contractility with a shift from curve 1 to curve 2. Ventricular performance, as reflected in stroke work or cardiac output, increases with little change in end-diastolic pressure and volume. This is represented by a shift from point A to point B in Figure 16-1. Vasodilation occurs in the exercising muscles, reducing peripheral vascular resistance and aortic impedance. This ultimately allows achievement of a greatly elevated cardiac output during exercise, at an arterial pressure only slightly greater than in the resting state. During intense exercise, cardiac output can rise to a maximal level if use is made of the Frank-Starling mechanism, as reflected in modest increases in the left ventricular end-diastolic volume and pressure (point B to point C).

In moderately severe systolic heart failure, as represented by curve 3, cardiac output and external ventricular performance at rest are within normal limits but are maintained at these levels only because the end-diastolic fiber length and the ventricular end-diastolic volume (ventricular preload) are elevated (i.e., through the operation of the Frank-Starling mechanism). The elevations of left ventricular diastolic pressure are associated with abnormally high levels of pulmonary capillary pressure, contributing to the dyspnea experienced by patients with heart failure, sometimes even at rest (point D).

Heart failure is characterized by generalized adrenergic activation and parasympathetic withdrawal[3] (Fig. 16-2) . This leads to stimulation of myocardial contractility, tachycardia, sodium retention, renin release, and generalized systemic vasoconstriction. Heart failure is frequently accompanied by reductions in NE stores and myocardial beta-adrenoceptor density (see p. 523) and therefore in the inotropic response to impulses in the cardiac adrenergic nerves. As a consequence, ventricular function (performance) curves cannot be elevated to normal levels by the adrenergic nervous system and the normal improvement of contractility that takes place during exercise is attenuated (Fig. 16-1 , curves 3 to 3
). The factors that tend to augment

Figure 16-1 Diagram showing the interrelationship of influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required during rest, walking, and maximal activity are designated on the ordinate. The dotted lines are the descending limbs of the ventricular performance

curves, which are rarely seen during life but that show what the level of ventricular performance would be if end-diastolic volume could be elevated to very high levels. (Modified from Braunwald E, Ross J Jr, Sonnenblick EH: Mechanisms of Contraction of the Normal and Failing Heart. Boston, Little, Brown, 1979.)

Figure 16-2 Mechanisms for generalized sympathetic activation and parasympathetic withdrawal in heart failure. *A,* Under normal conditions, inhibitory (-) inputs from arterial and cardiopulmonary baroreceptor afferent nerves are the principal influence on sympathetic outflow. Parasympathetic control of heart rate is also under potent arterial baroreflex control. Efferent sympathetic traffic and arterial catecholamines are low, and heart rate variability is high. *B,* As heart failure progresses, inhibitory input from arterial and cardiopulmonary receptors decreases and excitatory (+) input increases. The net response to this altered balance includes a generalized increase in sympathetic nerve traffic, blunted parasympathetic and sympathetic control of heart rate, and impairment of the reflex sympathetic regulation of vascular resistance. Anterior wall ischemia has additional excitatory effects on efferent sympathetic nerve traffic. See text for details. Ach=acetylcholine; CNS=central nervous system; E=epinephrine; Na^+ =sodium; NE=norepinephrine. (From Floras JS: Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. J Am Coll Cardiol 22:72A, 1993.)

ventricular filling during exercise push the failing ventricle even farther along its flattened, depressed function curve. There is an inordinate elevation of ventricular end-diastolic volume and pressure and therefore of pulmonary capillary pressure.[4] The elevation of the latter intensifies dyspnea and plays an important role in limiting the intensity of exercise that the patient can perform. According to this formulation, left ventricular failure becomes fatal when the left ventricular function curve becomes depressed (curve 4) to the point at which either cardiac output is insufficient to satisfy the requirements of the peripheral tissue at rest or the left ventricular end-diastolic and pulmonary capillary pressures are elevated to levels that result in pulmonary edema or both (point E).

Vascular Redistribution of Left Ventricular Output

Maintenance of arterial pressure in the presence of a reduced cardiac output is a primitive but effective compensatory mechanism. In hypovolemia and heart failure, this important mechanism is brought into play to allow the limited cardiac output to be most useful for survival. Thus, vasoconstriction occurs earliest and is most intense in areas that are not vital for immediate survival.

INCREASED VASOCONSTRICTOR ACTIVITY.

The major mechanism of increased vascular tone is an increase in the activity of vasoconstrictor systems, in particular, the sympathetic nervous system, the renin-angiotensin system, and the endothelin system. In patients with moderately severe heart failure, in whom the cardiac output at rest is normal, abnormal vasoconstriction occurs when an additional burden (e.g., exercise, fever, or anemia) is

imposed on the circulation and the cardiac output does not rise normally to meet the peripheral demands. As cardiac performance declines, left ventricular output is ultimately redistributed, even at rest. This redistribution maintains the delivery of oxygen to vital organs such as the brain and heart, whereas blood flow to less critical areas, such as the skin, skeletal muscle, gut, and kidney, is reduced.[5] [6] [7]

This underperfusion of skeletal muscle leads to anaerobic metabolism,[8] lactic acidosis, an excess oxygen debt, weakness, and fatigue. Occasionally, serious complications can result from the redistribution

of cardiac output and the resulting regional reductions of blood flow. These include marked sodium and nitrogen retention as a consequence of diminished renal perfusion, hepatic dysfunction, and, very rarely, gangrene of the tips of the phalanges and mesenteric infarction.

With heart failure there is a generalized increase in sympathetic activity. Neurograms obtained from adrenergic nerves to the limbs display an increased traffic in patients with heart failure.[9] Substantial changes also occur in the function of the adrenergic nerves that innervate splanchnic and renal vessels.[10] Although direct neurograms of these beds are not feasible in patients, it has been shown that exercise induces a much more marked reduction in mesenteric blood flow and elevation of mesenteric vascular resistance in dogs with experimental heart failure than in normal dogs.[11] Similar changes during exercise were observed in other major visceral vascular beds, such as the renal bed. Evidence that this intense vasoconstriction during exercise is mediated by the adrenergic nervous system is provided by observations on dogs with experimentally produced heart failure in which one kidney was denervated. Blood flow through the normal kidney declined precipitously during exercise, and calculated renal vascular resistance increased markedly. In contrast, little change in renal blood flow and calculated renal vascular resistance occurred in the denervated kidney.[11] This intensive visceral vasoconstriction during exercise helps to divert the limited cardiac output to exercising muscle but, conversely, may contribute to hypoperfusion of the gut and kidneys.

The renin-angiotensin and endothelin systems also contribute to the increased systemic vascular tone in heart failure. These potent vasoconstrictor systems are activated in patients with heart failure (see p. 526), where their contribution to systemic vasoconstriction has been demonstrated by the ability of specific inhibitors for angiotensin[12] and endothelin[13] receptors to cause vasodilation in patients with heart failure.

ENDOTHELIAL DYSFUNCTION.

Both ischemia-induced and exercise-induced vasodilation in the extremities are attenuated in patients with heart failure.[14] This attenuation is related in part to

endothelial dysfunction (see Chap. 34) . The response of blood flow to infused acetylcholine and methacholine, which are endothelium-dependent vasodilators, is reduced in heart failure (Fig. 16-3) . The vasodilator response can be restored by the administration of L-arginine,

Figure 16-3 Responses of forearm blood flow (FBF) to acetylcholine in patients with heart failure (HF) ( ) and in control subjects ( ). The FBF at rest and during infusion of acetylcholine (Ach) was less in patients with heart failure than in control subjects. The magnitudes of the increases in FBF in response to ACh were less in patients with heart failure than in control subjects. In contrast, the responses to sodium nitroprusside were comparable. (From Hirooka Y, Imaizumi T, Tagawa T, et al: Effects of L-arginine on impaired acetylcholine-induced and ischemic vasodilation of the forearm in patients with heart failure. Circulation 90:658, 1994. Copyright, 1994 American Heart Association.)

a precursor of endothelium-derived nitric oxide (NO). These findings suggest that defective endothelial function contributes to the impaired vasodilator capacity in heart failure. The mechanisms potentially responsible include impaired endothelial cell receptor function, deficiency of L-arginine substrate, abnormal expression of nitric oxide synthase (NOS), and the impaired release or rapid degradation of the endothelium-derived relaxing factor NO.[15] Impaired endothelial function is improved in patients by regular exercise.[16]

CHANGES IN THE VASCULAR WALL.

The sodium content of the vascular wall is increased in heart failure, and this contributes to the stiffening, thickening, and compression of blood vessel walls, which raises vascular resistance and also prevents normal vasodilation during exercise.[5] The veins in the extremities of patients with heart failure are also constricted by the activity of the adrenergic nervous system as well as by circulating venoconstrictors (NE, angiotensin, and endothelin). This venoconstriction results in displacement of blood to the heart and lungs.

2,3-DIPHOSPHOGLYCERATE.

A progressive decline in the affinity of hemoglobin for oxygen due to an increase in 2,3-diphosphoglycerate (DPG) also occurs in heart failure.[17] The rightward shift in the oxygen-hemoglobin dissociation curve represents a compensatory mechanism that facilitates oxygen transport; the increased DPG, tissue acidosis, and the slowed circulation characteristic of heart failure act synergistically to maintain the delivery of oxygen to the metabolizing tissues in the face of a reduced cardiac output.

CHRONIC MYOCARDIAL REMODELING

PATTERNS OF VENTRICULAR REMODELING.

The development of ventricular hypertrophy constitutes one of the principal mechanisms

by which the heart compensates for an increased load.[18] Grossman and associates examined systolic and diastolic wall stresses in normal subjects and in patients with chronic pressure- and volume-overloaded left ventricles who were compensated and not in heart failure.[19] Left ventricular mass was increased approximately equally in both the pressure- and volume-overloaded groups. There was a substantial increase in wall thickness in the pressure-overloaded ventricles but only a mild increase in wall thickness in the volume-overloaded ventricles (Fig. 16-4) . The latter was just sufficient to counterbalance the increased radius, so that the ratio of wall thickness to radius remained normal for the patients with volume-overload hypertrophy. This ratio was substantially increased in patients with pressure-overload hypertrophy, in whom there was disproportionate thickening of the ventricular wall. These observations are consistent with those of other investigators, who have indicated that myocardial hypertrophy develops in a manner that maintains systolic stress within normal limits.[20] [21] Thus, when the primary stimulus to hypertrophy is pressure overload, the resultant acute increase in systolic wall stress leads to parallel replication of myofibrils, thickening of individual myocytes,[22] and concentric hypertrophy. The wall thickening is usually sufficient to maintain a normal level of systolic stress (Fig. 16-5) .

When the primary stimulus is ventricular volume overload, increased diastolic wall stress leads to replication of sarcomeres in series, elongation of myocytes, and ventricular dilatation. This, in turn, results in a modest increase in systolic stress[23] (by the Laplace relationship), which causes proportional wall thickening that returns systolic stress toward normal.[23A] Thus, in compensated subjects, both volume and pressure overload alter ventricular geometry and wall thickness, so that systolic stress does not change greatly. Pressure and volume overload also result in distinct cellular phenotypes at the molecular level with different patterns of activation of genes for several peptide growth factors.[6] This heterogeneity at the molecular level presumably reflects differences in the way the two types of hemodynamic overload activate signaling pathways and, in turn, the resultant cellular changes that manifest at the tissue and organ levels.

Figure 16-4 The morphologic response to a hemodynamic overload depends on the nature of the stimulus. When the overload is predominately due to an increase in pressure (e.g., with systemic hypertension or aortic stenosis) the increase in systolic wall stress leads to the parallel addition of sarcomeres and widening of the cardiac myocytes, resulting in concentric hypertrophy of the ventricle. When the overload is predominately due to an increase in ventricular volume, the increase in diastolic wall stress leads to the series addition of sarcomeres, lengthening of cardiac myocytes, and eccentric chamber hypertrophy. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.2.)

Left ventricular wall thickness is a critical determinant of ventricular performance in patients with pressure-overload hypertrophy due to aortic stenosis or hypertension. Impaired performance in such patients may be secondary to inadequate hypertrophy,

leading to increased wall stress (afterload), which in turn may be responsible for inadequate muscle shortening.[23A] This condition has been termed "afterload-mismatch" by Ross.[24] His group found that when the aorta in conscious dogs was suddenly constricted, left ventricular systolic pressure rose, the left ventricle dilated, and the left ventricular wall thinned; this was associated with a large increase in wall stress and a reciprocal reduction in the extent and velocity of shortening.[25] During the next few weeks, the left ventricle became hypertrophied and left ventricular wall stress and shortening both returned toward normal. When the constriction was suddenly released, wall stress declined and shortening became supernormal.

Prolonged athletic training causes a moderate increase in myocardial mass (see also Chap. 59) . Isotonic exercise, such as long-distance running or swimming, resembles volume overload and causes an increase in left ventricular diastolic volume, with only mild thickening of the wall. Isometric exercise, such as weightlifting or wrestling, resembles pressure overload and causes an increase in wall thickness. Neither form of hypertrophy appears to be deleterious in the absence of heart disease and rapidly disappears when training is discontinued.

CELLULAR CHANGES IN MYOCARDIAL REMODELING.

One of the early cellular changes that occurs after a stimulus for hypertrophy is applied is the synthesis of mitochondria; presumably, the expanded mitochondrial mass provides the high-energy phosphates required to meet the increased energy demands of the hypertrophied cell. This is accompanied by an expansion of the myofibrillar mass. After the neonatal period, the increase in myocardial mass is associated with a proportional increase in the size of individual cells (i.e., hypertrophy), without any increase (or a minimal increase) in the number of cells (i.e., without hyperplasia).[2] Myocytes isolated from animals with pressure overload hypertrophy due to aortic constriction are thickened,[26] whereas myocytes from animals with volume overload due to an aortocaval fistula are elongated.[27] Myocytes from patients with heart failure due to chronic ischemic cardiomyopathy are longer and, to a lesser extent, wider[28] than normal cells (Fig. 16-6) .

These changes within the myocyte are accompanied by changes in both the quantity and quality of collagen within the extracellular matrix.[29] Taken together, these changes in myocyte geometry and the extracellular matrix result in remodeling of the myocardium. Hemodynamic overload reactivates growth factors present in the embryonic heart but dormant in the normal adult heart. These reactivated growth factors stimulate the hypertrophy of cardiac myocytes and regulate the synthesis and degradation of the extracellular matrix. Current understanding of the fundamental mechanisms responsible for myocardial remodeling is described on p. 510 .

Figure 16-5 The normal (N) relationship between left ventricular wall thickness (h) and chamber radius (r) is shown *(first panel)*. An acute increase in systolic pressure (acute load) causes an increase in systolic wall stress, which can be approximated by the equation P×r/h, where P is left ventricular systolic pressure. Diastolic wall stress is also increased when there is chamber dilatation or when diastolic pressure is elevated *(second panel)*. If sufficient compensatory hypertrophy occurs, the increase in

ventricular wall thickness may normalize the systolic and diastolic wall stresses *(third panel)*. However, if additional chamber dilatation occurs or the increase in wall thickness is insufficient, systolic and diastolic wall stresses remain abnormally elevated. In this situation, further chamber dilatation may occur in association with hemodynamic failure *(fourth panel)*. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction. Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.2.)

Figure 16-6 Isolated cardiac myocytes obtained from human left ventricular myocardium. *A,* Myocyte from a normal heart (bar=100 m). *B,* A hypertrophied myocyte from the left ventricle of a patient with ischemic cardiomyopathy, viewed at the same magnification as in *A.* This myocyte is longer than the normal myocyte. The myocytes have been stained with rhodamine-phalloidin for visualization of the sarcomere structure. In the myocyte from the failing heart there has been addition of sarcomeres. These are otherwise organized in a normal pattern. (Modified from Gerdes AM, et al: Structural remodeling of cardiac myocytes in patients with ischemic cardiomyopathy. Circulation 86:426, 1992. Copyright 1992, American Heart Association.)

ULTRASTRUCTURAL CHANGES.

There are a number of structural features of hypertrophied human myocytes (Fig. 16-7 (Figure Not Available)). These include abnormal Z-band patterns, multiple intercalated discs, and prominent collagen fibrils connecting adjacent myocardial cells. Nuclei are enlarged and lobulated and contain well-developed nucleoli; there is an abundance of ribosomes, presumably reflecting enhanced protein synthesis. However, electron microscopic studies of myocardium removed from overloaded, dilated hearts fixed at the elevated filling pressures that existed during life have revealed sarcomere lengths averaging 2.2 mum--no longer than those at the apex of the length/active tension curve of normal cardiac muscle.[30] This finding indicates that the depressed contractility of failing heart muscle is *not* due to the disengagement of actin and myosin filaments.

Mechanical Performance of Remodeled Myocardium

When an excessive pressure or volume load is imposed on the ventricle, myocardial remodeling occurs, providing one of the aforementioned key compensatory mechanisms that permits the ventricle to sustain an increased load.[18] However, as described later, a ventricle subjected to an abnormally elevated load for a prolonged period may fail to maintain compensation despite the presence of ventricular hypertrophy and pump failure may ultimately occur.[31]

ISOLATED MUSCLE.

Cardiac muscle isolated from animals in which the heart had been subjected to a controlled stress has been studied by many investigators. One convenient experimental model of ventricular pressure overload is the cat (or ferret) with pulmonary artery constriction. Papillary muscles are then removed from the right ventricles in which either

hypertrophy or overt failure has developed, and the excised muscles are studied in vitro.[32] [33] Both right ventricular hypertrophy and failure reduce the maximum velocity of (unloaded) shortening (Vmax) of excised muscle below the values observed in muscles obtained from normal cats. These changes are more marked in animals in which heart failure has been present than in those with hypertrophy alone (Fig. 16-8) . Because the depression of myocardial contractility is evident in vitro, when the muscle's physical and chemical milieu is controlled, it is considered to be *intrinsic* and not the result of

Figure 16-7 (Figure Not Available) The early stage of cardiac hypertrophy *(A)* is characterized morphologically by increases in the number of myofibrils and mitochondria as well as enlargement of mitochondria and nuclei. Muscle cells are larger than normal, but cellular organization is largely preserved. At a more advanced stage of hypertrophy *(B),* preferential increases in the size or number of specific organelles, such as mitochondria, as well as irregular addition of new contractile elements in localized areas of the cell, result in subtle abnormalities of cellular organization and contour. Adjacent cells may vary in their degree of enlargement. Cells subjected to long-standing hypertrophy *(C)* show more obvious disruptions in cellular organization, such as markedly enlarged nuclei with highly lobulated membranes, which displace adjacent myofibrils and cause breakdown of normal Z-band registration. The early preferential increase in mitochondria is supplanted by a predominance by volume of myofibrils. The late stage of hypertrophy *(D)* is characterized by loss of contractile elements with marked disruption of Z bands, severe disruption of the normal parallel arrangement of the sarcomeres, deposition of fibrous tissue, and dilation and increased tortuosity of T tubules. (From Ferrans VJ: Morphology of the heart in hypertrophy. Hosp Pract 18:69, 1983. Copyright 1983, McGraw-Hill Companies, Inc.)

Figure 16-8 *A,* Relation between muscle length and tension of papillary muscles from normal (circles), hypertrophied (RVH, squares), and failing (CHF, triangles) right ventricles. Open symbols=resting tension; filled symbols=actively developed tension. Tension is corrected for cross-sectional area (g/mm^2). Numbers in parentheses=number of animals. *B,* Force-velocity relations of the three groups of cat papillary muscles. Average values ± SEM are given for each point. Velocity has been corrected to muscle lengths per second (L_0 /sec). (From Spann JF Jr, Buccino RA, Sonnenblick EH, Braunwald E: Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. Circ Res 21:341, 1967. Copyright 1967, American Heart Association.)

any humoral or neural stimuli or abnormal loading conditions that are present in vivo. The depression of contractility in hypertrophied myocardium is less marked or even absent when the stress is imposed slowly and when the measurements are made during a stable phase of the ventricular response to overload.

The findings just summarized are, in general, consonant with those of a number of other investigations on cardiac muscle isolated from animals with experimentally produced pressure overload. For example, the trabeculae carnae or papillary muscles removed from the left ventricles of rats with left ventricular hypertrophy secondary to aortic constriction or renovascular hypertension also exhibit depression of the velocity of isotonic shortening and prolongation of duration of the action potential, of isometric contraction, and of the time-to-peak tension, even when the development of isometric tension is normal.[34] The force and rate of force development are also depressed in isometrically contracting myocardium obtained from hearts with totally different forms of

heart failure (e.g., Syrian hamsters with hereditary cardiomyopathy), as well as papillary muscles removed from the left ventricles of patients with heart failure due to chronic valvular disease.[35] In nonfailing myocardium, the force of contraction and rate of tension development rise with increased stimulation frequency, the so-called *positive force-frequency relationship* (see Chap. 14) . However, there is evidence of an abnormal (negative) force-frequency relationship in failing human myocardium.[36] The mechanism responsible for the negative force-frequency response appears to be impaired reuptake of calcium into the sarcoplasmic reticulum (SR) due to a decrease in Ca^{2+} adenosine triphosphatase (ATPase) (SERCA2) activity in failing myocardium [37] , [38] (see p. 512).

INTACT HEARTS.

Changes in performance of the intact heart subjected to abnormal hemodynamic loads are, in general, similar to those in isolated cardiac tissue. Thus, the right ventricles of cats with pulmonary artery constriction exhibit a marked depression paralleling that observed in the isolated papillary muscles removed from these ventricles.[39] When compared with normal values, the active tension developed by the right ventricle at equivalent end-diastolic fiber lengths is markedly reduced in cats with heart failure produced by pressure overload.

Immediately after the imposition of a volume overload (e.g., the opening of a large arteriovenous fistula), the contractility of the ventricle, as reflected in the end-systolic stress-circumference relationship, may actually increase, perhaps as a consequence of adrenergic stimulation. However, it then declines, while overall hemodynamic performance (i.e., cardiac work) is sustained.[40] Later in the course of a large volume overload, overt clinical heart failure develops, accompanied by increases in left ventricular end-diastolic volume and in the ratio of left ventricular weight to body weight and by depressed indices of left ventricular contractility [41] (see Chap. 15) . As the ventricle fails, it moves to the right along a depressed performance (function) curve, so that it requires an abnormally elevated end-diastolic volume (and often an elevation of end-diastolic pressure as well) to generate a level of tension equal to that achieved by the normal heart at a normal end-diastolic volume.

Transition to Heart Failure

When the ventricle is stressed, by either a pressure or a volume overload, the initial response is an increase in sarcomere length, so that the overlap between myofilaments becomes optimal (i.e., approximately 2.2 mum). This is followed by an increase in the total muscle mass, although, as already noted (see p. 507), the pattern and extent of remodeling differ depending on whether the stress is a pressure load or a volume load.

When the hemodynamic overload is severe, myocardial contractility becomes depressed. In an animal model of pressure overload hypertrophy produced by gradually tightening a hydraulic constrictor around the ascending aorta, there was depression of myocardial contractility, as assessed by *load-independent* contractility indices, suggesting that the cardiac dysfunction in this model was not due to insufficient hypertrophy causing afterload mismatch but to a depression of the myocardium's

intrinsic contractility.[42] Impaired myocardial contractility has also been observed in patients with hypertension and fully compensatory ventricular hypertrophy, normal myocardial stress, and apparently normal pump function. Such patients have displayed reduction of intramural myocardial shortening, as determined by spatial modulation of magnetization, using magnetic resonance imaging techniques[43] ; this reduction indicates a depression of myocardial contractility in the presence of apparently normal loading conditions.

In its mildest form, this depression is manifested by a reduction in the velocity of shortening of unloaded myocardium (Vmax) (see Fig. 16-8) or by a reduction in the rate of force development during isometric contraction[32] but by little if any reduction in the development of maximal isometric force or in the extent of shortening of afterloaded isotonic contractions. As myocardial contractility becomes further depressed, a more extensive reduction in Vmax occurs, now accompanied by a decline in isometric force development and shortening. At this point, circulatory compensation may still be provided by cardiac dilation and an increase in muscle mass, which tend to maintain wall stress at normal levels. Although cardiac output and stroke volume remain normal in the resting state, the ejection fraction at rest as well as the maximal cardiac output that can be attained during stress decline.[43A] As contractility falls farther, overt congestive heart failure, reflected in a depression of cardiac output and work and/or an elevation of ventricular end-diastolic volume and pressure at rest, supervenes.

MOLECULAR MECHANISMS OF MYOCARDIAL REMODELING AND FAILURE

As described by Meerson[44] (Table 16-2) , immediately on imposition of a large pressure load the increase in work performed by the ventricle exceeds the augmentation of cardiac mass and the heart dilates. As discussed earlier, a compensatory phase sets in as the ventricle remodels and the contractile function returns to approximately normal levels. If the compensatory response is adequate to "match" the work demands, a period of relative stability ensues. However, if the extent or form of myocardial remodeling is insufficient or if the magnitude of the overload increases further, regardless of the initial cause, there is further deterioration in myocardial function as a consequence of "afterload mismatch," that is, inadequate hypertrophy to normalize mechanical stress on the myocyte; and a vicious circle is created. Later, in what Meerson has termed the "exhaustion" phase, several macroscopic events take place: there may be myofibrillar lysis, an increase in the number of lysosomes (presumably to digest worn-out cell constituents), distortion of the SR,[45] a reduction in the surface density of the key tubular system, and fibrous replacement of cardiac cells.[46]

It is now recognized that myocardial remodeling and the transition from compensated hypertrophy to failure of the myocardium involves a complex of events at the molecular and cellular level.[31] [47] These events include (1) myocyte growth or hypertrophy, (2) changes in myocyte phenotype with reexpression of fetal gene programs and decreased expression of adult gene programs, (3) alterations in the expression and/or function of proteins involved in excitation-contraction coupling and contraction, (3) myocyte death

due to necrosis and apoptosis, (4) changes in the extracellular matrix, and (5) abnormalities in energetics (Fig. 16-9) .

TABLE 16-2 -- THREE STAGES IN THE RESPONSE TO A SUDDEN HEMODYNAMIC OVERLOAD

Stage 1: (Days) Transient Breakdown
Circulatory: Acute heart failure; pulmonary congestion, low output Cardiac: Acute left ventricular dilatation; early hypertrophy Myocardial: Increased content of mitochondria relative to myofibrils
Stage 2: (Weeks) Stable Hyperfunction
Circulatory: Improved pulmonary congestion and cardiac output Cardiac: Established hypertrophy Myocardial: Increased content of myofibrils relative to mitochondria
Stage 3: (Months) Exhaustion and Progressive Cardiosclerosis
Circulatory: Progressive left ventricular failure Cardiac: Further hypertrophy with progressive fibrosis Myocardial: Cell death

From Katz AM: Energy requirements of contraction and relaxation: Implications of inotropic stimulation of the failing heart. In Just H, Holubarsch C, Scholz H (eds): Inotropic Stimulation and Myocardial Energetics. New York, Springer-Verlag, 1989, p 49.

Together, these events result in changes in myocardial structure (e.g., increase in myocardial mass, chamber dilation) and function (e.g., impaired systolic and/or diastolic function) that often lead to further pump dysfunction and hemodynamic overload. Several stimuli for these changes include mechanical strain on the myocyte, neurohormones (e.g., NE, angiotensin), inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-alpha]), other peptides and growth factors (e.g., endothelin) and reactive oxygen species (e.g., superoxide, NO).[31] [47] [48] [49] These stimuli are increased both systemically and in the myocardium in response to circulatory failure and hemodynamic overload and, therefore, are an important link in the pathogenesis of progressive myocardial failure.[23A]

Myocyte Loss

Impaired myocardial contractile function may reflect a decrease in the number of viable, fully functional myocytes, a decrement in the function of viable myocytes, or a combination of these mechanisms. Myocyte loss may occur by one of two major mechanisms--necrosis or apoptosis.

NECROSIS.

Necrosis occurs when the myocyte is deprived of oxygen or energy, leading to the loss of cellular membrane integrity, the influx of extracellular fluid, cellular swelling, and the release of proteolytic enzymes that

Figure 16-9 Overview of the pathophysiology of myocardial remodeling. Remodeling stimuli such as increased mechanical wall stress and neuroendocrine activation lead to a complex of molecular and cellular events, including hypertrophy of cardiac myocytes, changes in gene expression with a reexpression of fetal programs and decreased expression of adult programs, changes in the quantity and nature of the interstitial matrix, and cell death. These events lead to changes in the structure and function of the ventricle, which may result in further pump dysfunction and increased wall stresses, thereby promoting further pathological remodeling. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.2.)

cause cellular disruption. Myocyte necrosis may be localized, as in myocardial infarction, or diffuse, as from idiopathic dilated cardiomyopathy, myocardial damage by toxic agents such as daunorubicin (see Chap. 69) , or myocarditis. In addition, capillary density and coronary reserve are reduced in remodeled myocardium[50] and may result in diffuse ischemia, which is most severe in the subendocardium. Thus, Vatner and associates have demonstrated a diminished response of endocardial blood flow to adenosine and exercise-induced vasodilation in dogs with pressure overload hypertrophy.[51] This is caused in part by hypertrophy and in part by an exercise-induced increase in left ventricular subendocardial wall stress. The reduced subendocardial perfusion in turn may cause subendocardial ischemic cell necrosis and replacement fibrosis, which impair both systolic and diastolic function, accelerating the development of heart failure (see Chap. 34)

APOPTOSIS.

In contrast to necrosis, apoptosis (programmed cell death) is an energy-dependent process by which a specific genetic program leads to the activation of a molecular cascade that causes the degradation of nuclear DNA. Also in contrast to necrosis, apoptosis is marked by the involution of the myocyte, eventuating in phagocytosis by neighboring cells[52] [53] (Fig. 16-10) . Apoptosis is a common cellular mechanism during organogenesis and in adult cells that have a rapid turnover rate, such as blood cells and gut epithelium. Because cardiac myocytes are terminally differentiated, it was not generally believed that they would undergo apoptosis. However, there have now been several reports demonstrating the presence of apoptotic myocytes in failing human myocardium[54] (Fig. 16-11) , as well as in models of myocardial failure[55] and hemodynamic overload.[56] [57] Several factors known to be present or increased in the failing myocardium have been shown to cause apoptosis of cardiac myocytes in vitro, including catecholamines acting through beta-adrenergic receptors,[58] [59] angiotensin II, reactive oxygen species, [60] NO,[61] inflammatory cytokines,[61] and mechanical strain. [62]

[63] Although the role of apoptosis in the transition to failure is not known, it appears likely that it represents an important cause of cell death in the failing heart.[2] The therapeutic success of drugs that antagonize angiotensin II (i.e., angiotensin-converting enzyme [ACE] inhibitors) and catecholamines (i.e., beta-adrenergic

Figure 16-10 Comparison of apoptotic and necrotic cell death. Apoptosis is an energy-dependent process triggered by specific cell signals (e.g., the binding of Fas to its receptor [the FAS receptor] on the cell membrane), which leads to the activation of a biochemical cascade (caspases) that causes the fragmentation of nuclear DNA. In contrast, necrosis may result from ischemia, leading to a depletion of adenosine triphosphate that results in the loss of normal cellular membrane function, disruption of transmembrane ionic gradients, and membrane rupture. (From Haunstetter A, Izumo S: Apoptosis: Basic mechanisms and implications for cardiovascular disease. Circulation 82:1111, 1998. Copyright 1998, American Heart Association.)

Figure 16-11 Evidence of increased apoptotic death of cardiac myocytes in failing human myocardium. *A,* Two myocyte nuclei stained with propidium iodide (arrows). *B,* The same field stained with deoxyuridine triphosphate by the so-called TUNEL reaction to label fragmented DNA, a hallmark of apoptosis (arrow). Normal nucleus (arrowhead) is not stained. *C,* The frequency of apoptotic myocytes observed in myocardium obtained from patients undergoing cardiac transplantation as compared with a nonfailing heart. The frequency of apoptotic myocytes increased from about 10 per million in nonfailing hearts to about 2300 per million in failing hearts. (From Olivetti G, Abbi R, Quaini F, et al: Apoptosis in the failing human heart. N Engl J Med 336:1131-1141, 1997.)

antagonists), both of which promote apoptosis, suggests that this may be an important mechanism for myocardial failure.

Dropout of individual myocytes has also been observed in the senescent rat[64] and human heart (see Chap. 57) . Olivetti and colleagues reported a loss of an average of 38 million nuclei per year in aging persons without cardiovascular disease.[54] This loss in myocyte number was accompanied by a reciprocal increase in myocyte cell volume per nucleus, thereby preserving ventricular wall thickness.[65]

This process, which appears to reflect myocyte death by both necrosis and apoptosis,[50] may contribute to cardiac dysfunction and, when there is an additional stress such as hypertension, to the development of heart failure in the elderly (see Chap. 57) .

Alterations in Excitation-Contraction Coupling (See p. 451)

In addition to reducing the absolute number of myocytes, as described earlier, hemodynamic overload may cause a decrease in the *intrinsic* contractility of individual myocytes. Several functional abnormalities involving excitation-contraction coupling, contractile proteins, and energetics have been identified in hypertrophied and failing

myocardium. At the molecular level, alterations have been observed in the expression of numerous proteins that are central to normal myocardial structure and function. There is strong evidence from both in vitro and animal studies to suggest that these molecular events are secondary to both mechanical forces and a variety of neuronal, endocrine, and autocrine/paracrine mediators that act on the myocardium. It is not clear whether these alterations are responsible for the impaired myocardial function of heart failure, are in some way adaptive, or simply accompany the heart failure state as "epiphenomena."

ROLE OF CALCIUM IN EXCITATION-CONTRACTION COUPLING.

Ca^{2+} plays a central role in the regulation of myocardial contraction and relaxation.[66] Hypocalcemia, secondary to hypoparathyroidism and a variety of other conditions, can cause heart failure that is responsive to the infusion of calcium.[67] Elevation of serum ionized Ca^{2+} has been shown to augment contractility in patients with renal failure undergoing dialysis[68] and in patients with severe heart failure secondary to cardiomyopathy who have downregulation of beta-adrenergic receptors.[69]

Myocardium obtained at the time of cardiac transplantation from patients with end-stage heart failure exhibits abnormal prolongation of the action potential and developed force and impaired relaxation.[70] Observations using the Ca^{2+} indicator aequorin in whole myocardium have shown that these alterations in electrical and contractile properties are associated with a prolonged elevation of the intracellular Ca^{2+} transient during relaxation. [70] Likewise, in myocytes obtained from patients with end-stage heart failure, the action potential is prolonged. The intracellular Ca^{2+} transient, as assessed by the fluorescent indicator fura-2, demonstrates a blunted rise with depolarization reflecting a slower delivery of Ca^{2+} to the contractile apparatus (causing slower activation) and a slowed rate of fall during repolarization (causing slowed relaxation) (Fig. 16-12) .[71] These two abnormalities could, in theory, explain both systolic and diastolic dysfunction.

Additional evidence of abnormal myocardial Ca^{2+} handling is provided by the observation that there is a reduction in the amount of tension-independent heat produced in myocardium from patients with heart failure.[72] Tension-independent heat, which is believed to reflect the energy expended for Ca^{2+} transport, can be used to estimate the amount of Ca^{2+} cycled per heartbeat. With this approach, it was shown that Ca^{2+} cycling is reduced by approximately 50 percent in failing human myocardium.[72]

FORCE-FREQUENCY RELATIONSHIP.

Excitation-contraction coupling can also be assessed by examination of the force-frequency response. As pointed out on page 466 , in normal myocardium, contractile force increases with increasing rates of stimulation, whereas in myocardium obtained from patients with end-stage heart failure the force-frequency response is markedly attenuated.[73] A similar phenomenon is observed in patients with heart failure studied at the time of catheterization.[74] In patients with normal ventricular function, left ventricular contractility (as measured by +dP/dt or the end-systolic pressure-volume

ratio)

Figure 16-12 Abnormal action potential and intracellular calcium transient in failing cardiac myocytes. *Top,* The action potential recorded in a myocyte isolated from the heart of a patient with dilated cardiomyopathy is markedly prolonged, as compared with that in a myocyte from a normal heart (control). Such abnormalities could contribute to both the generation of arrhythmias and the abnormal diastolic relaxation. *Bottom,* The intracellular calcium transient measured with the fluorescent calcium indicator fura-2 is also markedly abnormal in myocytes isolated from the myocardium of patients with dilated cardiomyopathy. As compared with a normal myocyte (control), the myocyte from a patient with dilated cardiomyopathy shows an attenuated rise with depolarization (arrow) and a markedly delayed return to baseline. These abnormalities reflect the altered expression or function of key calcium handling proteins (e.g., Ca^{2+} -ATPase) and likely contribute to the abnormal action potential in the top illustration. (Modified from Beuckelmann DJ, Nabauer M, Erdmann E: Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation 85:1046, 1992. Copyright 1992, American Heart Association.)

increases progressively as heart rate is increased by atrial pacing. By comparison, in patients with severe heart failure there is little or no increase in either contractile index. The normal force-frequency relationship depends on the cycling of Ca^{2+} between the SR and cytoplasm with each beat, an event that is accomplished by several enzymes and channels located in the sarcolemma, SR, and mitochondria[66] (see Chap. 14) . The expression and/or function of a number of these proteins may be altered in hypertrophied and failing myocardium[75] (Table 16-3) , thereby leading to intrinsic dysfunction of otherwise viable myocytes.

SARCOPLASMIC RETICULUM Ca^{2+} -ATPase AND PHOSPHOLAMBAN (see also p. 452).

A number of alterations in the SR in the failing heart have been described (Table 16-4) . Ca^{2+} reuptake by the SR is mediated primarily by the ATP-dependent enzyme Ca^{2+} -ATPase (SERCA2).[75] The activity of SERCA2 is inhibited by the associated protein phospholamban,[75] [76] [77] and this inhibition is relieved by cyclic adenosine monophosphate (AMP)-mediated (e.g., by beta-adrenergic receptor stimulation) phosphorylation of phospholamban, thereby resulting in increased Ca^{2+} reuptake into the SR and the acceleration of diastolic relaxation. The reuptake of Ca^{2+} by the SR is also important for normal

TABLE 16-3 -- CALCIUM HOMEOSTASIS IN FAILING HUMAN MYOCARDIUM

Intracellular Calcium Levels

Basal (diastolic)

Peak (systolic)

Rate of fall with diastole

Calcium-Handling Proteins and/or mRNA Levels

SR CA^{2+} -ATPase

Phospholamban

Ca^{2+} release channel

Voltage-dependent Ca^{2+} channels

Na^{+} /Ca^{2+} exchanger

Calsequestrin

---

systolic function, which requires that ample SR Ca^{2+} be available for release during systole to mediate contraction.[75]

Several reports indicate that the levels of SERCA2 messenger RNA (mRNA) and protein are reduced in myocardium obtained from patients with end-stage heart failure[78] [79] and animal models of heart failure.[80] The decrease in SERCA2, which is part of an "adult" gene program in cardiac muscle, correlates inversely with the reexpression of fetal genes such as atrial natriuretic peptide (Fig. 16-13) . Similarly, there is a shift from the gene encoding the adult isoform of myosin heavy chain (alpha-myosin heavy chain) to that encoding the fetal isoform (beta-myosin heavy chain) (see p. 514). This shift in SERCA2 expression is associated with a corresponding reduction in SR Ca^{2+} reuptake or in Ca^{2+} -ATPase activity in some[81] [82] but not all[83] studies in explanted human myocardium from patients with severe failure. Furthermore, the decrease in SERCA protein and Ca^{2+} -ATPase activity has been shown to correlate inversely with the force-frequency relationship,[20] [82] suggesting that reduced expression of SERCA2 contributes to intrinsic myocyte dysfunction. In vitro, mechanical strain[5] and several agonists such as NE and angiotensin downregulate the expression of SERCA2 in cardiac myocytes.

Because phospholamban activity inhibits SERCA2, the net activity of SERCA2 depends on the ratio of SERCA2 to phospholamban.[84] [85] The expression of phospholamban is also decreased in failing human myocardium[37] [81] and may thereby provide a partial compensation for the downregulation of SERCA2. Viral expression vectors have been used to express SERCA2 and phospholamban in cultured cardiac myocytes.[85] [86] [87] SERCA2 has also been expressed in transgenic mice[88] and in rat heart after direct injection of an

TABLE 16-4 -- SARCOPLASMIC RETICULUM ALTERATIONS IN THE FAILING HEART

PROTEIN	CHANGE IN HUMAN HEART FAILURE
Sarcoplasmic Reticulum	
Calcium pump ATPase (SERCA)	Normal or decreased
Phospholamban	Normal or decreased
Calcium release channel (ryanodine receptor)	Normal or decreased
Calsequestrin	Normal
Calreticulin	Normal
Plasma Membrane	
L-type calcium channels	?Increased channel opening
Sodium/calcium exchanger	Increased
Sodium pump	Reexpression of fetal isoforms

From Katz AM: Heart Failure. Philadelphia, Lippincott Williams & Wilkins, 2000.

adenovirus carrying the gene.[52] These or similar approaches might allow the use of SERCA2 or inhibitors of phospholamban to augment myocyte function in patients.

Na^+ /Ca^{2+} EXCHANGER (see also p. 454).

The Na^+ /Ca^{2+} exchanger is the major route by which Ca^{2+} is removed from the cardiac myocyte and can account for approximately 20 percent of the removal of Ca^{2+} from the cytoplasm during diastole. [89] The mRNA and protein levels of the Na^+ /Ca^{2+} exchanger were found to be increased in myocardium obtained from patients with heart failure due to both ischemic and idiopathic dilated cardiomyopathy and correlated inversely with the decrease in SERCA2 mRNA levels.[89] This augmentation in Na^+ /Ca^{2+} exchange activity might be a compensatory response to the reduction in Ca^{2+} reuptake caused by a decrease in SERCA2. In animals with experimental heart failure, impaired cytosolic Ca^{2+} removal due to reduced SERCA2 was partially compensated for by an increase in the Na^+ /Ca^{2+} exchanger.[80] Although this would facilitate diastolic Ca^{2+} removal, it might do so at the expense of increased arrhythmogenicity, because this Ca^{2+} efflux is associated with an influx of Na^+ that can prolong depolarization and cause afterdepolarizations.

THE Ca^{2+} RELEASE CHANNEL.

The Ca^{2+} release channel (CRC), located on the SR, mediates the release of Ca^{2+} from the SR into the myoplasm during systole.[66] Some,[78] [90] but not all,[91] studies in failing human myocardium have shown decreases in the mRNA level for the CRC.

VOLTAGE-DEPENDENT Ca^{2+} CHANNEL.

The mRNA and protein levels of the voltage-dependent Ca^{2+} channel also have been shown to be decreased in failing human myocardium obtained from patients with both ischemic heart disease and dilated cardiomyopathy.[92]

CALSEQUESTRIN.

This is the major protein in the SR that binds Ca^{2+} and thereby serves a storage function. Several studies have found calsequestrin mRNA levels to be unchanged in failing human myocardium.[93]

Alterations in the Contractile Apparatus

The fraction of cell volume composed of myofibrils is initially increased in animal models of pressure-induced hypertrophy.[94] Patients with aortic stenosis without heart failure exhibit a normal fraction of myofibrils per cell, whereas those with left ventricular failure show a significant reduction in cell volume occupied by myofibrils, suggesting that this reduction in the quantity of the contractile machinery

Figure 16-13 Inverse relationship between the mRNA levels for the fetal gene atrial natriuretic factor (ANF) and the adult muscle-specific gene encoding Ca^{2+} -ATPase in ventricular myocardium obtained from patients with various degrees of myocardial failure. The reexpression of a fetal gene program is typical of hypertrophied and failing myocardium. (Modified from Arai M, Matsui H, Periasamy M: Sarcoplasmic reticulum gene expression in cardiac hypertrophy and heart failure. Circ Res 74:555, 1994. Copyright 1994, American Heart Association.)

TABLE 16-5 -- CONTRACTILE PROTEIN ALTERATIONS IN THE FAILING HEART

PROTEIN	EXPERIMENTAL HEART FAILURE	HUMAN HEART FAILURE
Myosin heavy chain	Reversion to fetal phenotype	Reversion to fetal phenotype
Myosin light chains	Reversion to fetal phenotype	Reversion to fetal phenotype
Actin	Reversion to fetal phenotype	No change
Troponin I	Reversion to fetal phenotype	Reversion to fetal phenotype
Troponin T	Reversion to fetal phenotype	?Reversion to fetal phenotype

Troponin C	No change	No change
Tropomyosin	No change	No change

From Katz AM: Heart Failure. Philadelphia, Lippincott Williams & Wilkins, 2000.

may play a role in the development of cardiac decompensation.[95] In end-stage heart failure in the human, electron microscopic observations likewise show a reduction of ventricular myofibrillar protein (Table 16-5) .[96]

REDUCTION OF MYOSIN ATPASE ACTIVITY.

Considerable data suggest that qualitative, as well as quantitative, alterations of contractile proteins occur in heart failure. First, the finding that the reduced velocity of contraction of failing myocardium occurs in chemically skinned ventricular fibers suggests that this change reflects intrinsic alterations in the contractile apparatus. Early studies showed that the activity of myofibrillar ATPase is reduced in the hearts of patients who died of heart failure.[97] Furthermore, reductions in the activities of myofibrillar ATPase, actomyosin ATPase, or myosin ATPase have been demonstrated in heart failure induced in cats by pulmonary artery constriction,[98] in guinea pigs with constriction of the ascending aorta,[99] in dogs with constriction of the pulmonary artery or aorta,[100] and in rats with renovascular hypertension.[101] These depressions of enzymatic activity could occur if an altered subunit of the myosin molecule (i.e., the portion of the molecule responsible for the ATPase activity) were produced in the overloaded heart and reduced contractility by lowering the rate of interaction between actin and myosin filaments. A reduction in the Mg^{2+} -ATPase activity (which expresses the response of myofibrils to Ca^{2+}) has been demonstrated in myofibrils obtained from patients with end-stage heart failure at the time of transplantation and in less sick patients undergoing valve replacement.[102]

MYOSIN ISOFORM CHANGES.

Animal studies have indicated that when the adult heart hypertrophies, fetal and neonatal forms of contractile proteins (termed isoforms) and other proteins (such as atrial natriuretic peptide) reappear, signifying reexpression of the genes for these fetal and neonatal isoforms. Thus, hemodynamic overload leads to enhanced overall protein synthesis[2] and alters the proteins qualitatively as well (i.e., it leads to the synthesis of protein isoforms that were present during fetal and neonatal life when protein synthesis in the heart was also rapid).

Altered isoforms of cardiac proteins may arise from the expression of different members of a multigene family or from the assembly of the same gene in a different pattern.[103] In rodents the predominant myosin heavy chain (MHC) is the "fast" V_1 isoform (high ATPase activity, encoded by the alpha-MHC gene). With pressure-induced hypertrophy or myocardial failure after myocardial infarction in the rat, there is the reexpression of the "slow" V_3 isoform (low ATPase activity, encoded by the beta-MHC gene), and deinduction of the V_1 isoform.[103] Although a shift in MHC isoforms would provide an attractive explanation for the reduction in myofibrillar ATPase activity observed in failing

human myocardium, the predominant MHC isoform in humans is the slower V_3 isoform (encoded by the beta-MHC gene) and alpha-MHC mRNA has been difficult to detect, thus making it appear unlikely that a shift in myosin isoforms is responsible for the observed decrease in myosin ATPase activity in failing human myocardium. However, the use of more refined methodology has demonstrated that alpha-MHC accounts for about 33 percent of MHC mRNA in normal human myocardium and is markedly reduced to about 2 percent in failing myocardium[104] [105] (Fig. 16-14) . It remains to be determined whether the decrease in alpha-MHC mRNA translates into a comparable decrease in the ratio of the beta- to alpha-MC protein isoforms, and, thus, a decrease in ATPase activity.

ALTERED REGULATORY PROTEINS.

Another possible cause of a decrease in contractile protein function is an

Figure 16-14 Change in the expression of myosin heavy chain (MHC) mRNAs in failing myocardium. The alpha- and beta-MHC mRNAs encode for "fast" and "slow" isoforms with high and low ATPase activity, respectively. The ratio of alpha-MHC to beta-MHC is low in fetal myocardium and increases during normal development to adulthood. Shown is a Northern blot of mRNA obtained from the myocardium of patients with left ventricular failure (F-LV) or with normal ventricular function (Control). The ratio of alpha-MHC to beta-MHC is markedly reduced in the failing myocardium. Theoretically, such a shift in MHC isoforms could result in a decrease in the intrinsic contractile function of the myocyte. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.9.)

Figure 16-15 The regulation of extracellular matrix degradation is determined by the balance between the activity of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). Both an increase in MMP activity and a decrease in TIMP activity have been observed in failing myocardium from patients. Theoretically, such an increase in the MMP/TIMP ratio could contribute to depletion of the fibrillar collagen struts that tether myocytes together and might thus contribute to chamber dilation. Conversely, an increase in extracellular matrix accumulation, which might occur as the result of a decrease in the MMP/TIMP ratio or an increase in matrix synthesis, could contribute to chamber stiffness and abnormal relaxation. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.13.)

alteration in the expression and/or activity of regulatory proteins. In animals with experimental heart failure, there are changes in the myosin light chain and the troponin-tropomyosin complex.[106] Changes in myosin light-chain isoforms have been observed in the atria and ventricles of patients subjected to increased mechanical stress[107] ; and the expression of troponin-T, a component of the troponin complex that regulates the interaction of myosin and actin, was found to be altered in failing human

myocardium.[108] In normal myocardium, troponin-T is expressed as a single isoform (T_1), which accounts for approximately 98 percent of the troponin-T. In myocardium from patients with end-stage heart failure, a second isoform (T_2) was expressed at increased levels, and its level of expression was related to the severity of heart failure.[108]

Mice with deletion of the troponin-I gene are born normally but express a fetal isoform of troponin that takes the place of the absent adult isoform. Over time the expression of the fetal isoform decreases, and the mice develop lethal heart failure.[109] The functional significance of changes in the expression of troponin and other regulatory proteins is not known. However, these observations suggest that changes in myosin activity could be due to changes in regulatory proteins and need not reflect alterations in the contractile proteins themselves.

Alterations in the Matrix

The structural properties of the ventricle are determined not only by its myocytes but also by the interstitial connective tissue, which is rich in types I and III fibrillar collagen.[110] [111] The latter provide struts along which the myocytes are aligned. Branches of collagen fibers course at right angles to connect and align muscle bundles. Thus, a depletion of these struts may lead to chamber dilation. As Weber has pointed out, the amount and type of extracellular matrix can also have profound effects on the diastolic properties of the myocardium by affecting its elasticity and physical disposition.[110]

REGULATION OF INTERSTITIAL COLLAGEN.

The quantity and nature of the collagen in the extracellular matrix is determined by the balance between synthesis and degradation. The latter is regulated by the opposing actions of matrix metalloproteinases (MMPs), a family of enzymes that degrade matrix proteins, and tissue inhibitors of metalloproteinases (TIMPs), a family of enzymes that inhibit the activity of MMPs[112] (Fig. 16-15) .

COLLAGEN STRUT DEPLETION.

In myocardium from humans

Figure 16-16 Representative photomicrographs of left ventricular myocardium from pigs with rapid pacing-induced myocardial failure showing the effects of pacing and inhibitor of matrix metalloproteinase (MMP) activity on the fibrillar collagen weave surrounding cardiac myocytes. With rapid pacing there is a disruption and depletion of fibrillar collagen. Treatment with an inhibitor of MMP activity attenuated these effects on fibrillar collagen and reduced the extent of left ventricular dilation. (Modified from Spinale FG, Coker ML, Krombach SR, et al: Matrix metalloproteinase inhibition during the development of congestive heart failure: Effects on left ventricular dimensions and function. Circ Res 85:364, 1999. Copyright 1994, American Heart Association.)

and animal models of systolic failure, ultrastructural observations have shown a depletion of the fibrillar collagen struts that help to maintain the alignment of myocytes[113] (Fig. 16-16) . It has been proposed that *depletion* of the collagen struts may contribute to chamber dilation by allowing "slippage" of myocytes.[114] [115] This observation is consistent with the observation that the activity of MMPs is increased in myocardium obtained from patients with end-stage heart failure[116] and in animal models of heart failure. [117] Likewise, the activity of TIMPs is decreased in myocardium from patients with end-stage heart failure.[118] A role for MMPs is supported by the demonstration that an MMP inhibitor partially protected against the loss of collagen struts in an animal model of heart failure.[119]

INTERSTITIAL MATRIX ACCUMULATION.

On the other hand, in experimentally induced chronic pressure overload hypertrophy,[120] as well as in patients with hypertension, there is an *increase* in the quantity of interstitial collagen, which may contribute to the characteristic abnormalities of diastolic function. The spontaneously hypertensive rat develops progressive myocardial hypertrophy and failure with age.[121] Papillary muscles from these animals have increased passive stiffness that is associated with increased left ventricular collagen concentration, interstitial fibrosis,[122] and expression of mRNAs for collagen and transforming growth factor-alpha (TGF-alpha).[123] Treatment with the ACE inhibitor captopril prevented the increases in muscle stiffness, interstitial fibrosis, and the induction of collagen and TGF-alpha mRNAs.[124] [125] Thus, it seems likely that pathways leading to increased collagen accumulation are involved in the pathogenesis of diastolic dysfunction.

Myocardial Energetics in Heart Failure (See also p. 467)

Heart failure frequently occurs in the presence of adequate myocardial perfusion, oxygen, and substrate. When contractility is acutely depressed, myocardial oxygen consumption of the intact ventricle also declines.[126] Similarly, patients with chronic impairment of left ventricular performance and reduction of the velocity of myocardial fiber shortening exhibit reduction of coronary blood flow and myocardial oxygen consumption per gram of muscle.[127] Marked reductions in myocardial oxygen consumption have been described in the Syrian hamster with hereditary cardiomyopathy.[128] Papillary muscles removed from cats with pressure overload-induced right ventricular hypertrophy exhibit a depression of both contractility and oxygen consumption per unit of tension development.[33] The pathophysiological importance of these observations is not known. Potentially, the lowered energy needs of the failing heart may reflect an appropriate matching of energy demands, a disproportionate decrease beyond the needs of the tissue, or a protective mechanism.

MYOCARDIAL ENERGY PRODUCTION.

Considerable dispute has centered on the question of whether mitochondrial oxidative

phosphorylation (i.e., energy production) is abnormal in heart failure. Early studies indicated that electron transport and the tightness of respiratory control are normal in mitochondria obtained from failing human hearts[129] and cat hearts with experimental heart failure produced by pressure overload.[130] On the other hand, in one study in which mitochondria from the hearts of patients with end-stage dilated cardiomyopathy were studied, a reduction in cytochrome-a content and in cytochrome-dependent enzyme activity was reported.[131] The cytochromes are located in the inner mitochondrial membrane and are constituents of the respiratory chain that couples oxidation to the synthesis of chemical energy. Mitochondria obtained from failing human cardiac muscle have also shown reduced oxygen consumption during active phosphorylation and reduced rates of NADH-linked respiratory activity.[131] These and other observations have led to the thesis that myocardial failure in the setting of hemodynamic overload may be related to an inability of the energy-producing system, (i.e., the mitochondria) to keep pace with the needs of the contractile apparatus. Katz has proposed that the mitochondrial abnormalities in the failing heart may be the result of damage to these structures and that this damage reduces the high-energy phosphates available for the contraction of the failing heart.[2]

The nucleotide-transporting protein located on the inner mitochondrial membrane, the so-called ADP-ATP carrier, has been identified as an autoantigen in viral myocarditis and dilated cardiomyopathy. In guinea pigs immunized to this carrier protein, both myocardial oxygen consumption and cardiac work fell.[132] These findings are compatible with the hypothesis that the impaired cardiac performance in some cases of myocarditis (and dilated cardiomyopathy) may be secondary to an imbalance between energy delivery and demand.

MYOCARDIAL ENERGY RESERVES.

In compensated hypertrophy, observations on myocardial ATP concentration have shown no consistent change.[133] However, in myocardium from dogs with myocardial failure due to rapid pacing or chronic ischemia, and from humans with end-stage cardiomyopathy, total creatine kinase activity and the concentrations of phosphocreatine and creatine are decreased.[133] [134] [135] These observations have led to the hypothesis that myocardial failure may be the consequence of a decreased energy reserve[133] or at least that such decreased reserve contributes to the development of heart failure (Fig. 16-17) . The measurement of creatine kinase flux provides a sensitive measure of myocardial energy reserves and may detect abnormalities in the absence of changes in ATP and phosphocreatine concentrations. By studying high-energy flux in vivo using nuclear magnetic resonance technology, it was demonstrated that creatine kinase activity is markedly reduced in the myopathic Syrian hamster.[136] This abnormality was almost completely corrected by treatment with the converting enzyme inhibitor enalapril. Likewise, in turkeys with furazolidone-induced heart failure, contractile failure was associated with a decrease in ATP, phosphocreatine activity, and creatine kinase activity.[137] The mechanism responsible for a decrease in creatine kinase activity

Figure 16-17 Some of the vicious cycles that operate in the overloaded heart. Overload both increases

energy utilization and stimulates growth. The former contributes directly to a state of energy starvation, which is made worse by several consequences of maladaptive hypertrophy that decrease energy supply. The latter include myocyte elongation, which causes remodeling, a progressive dilatation that increases wall tension so as to increase the overload. Growth stimuli also promote apoptosis, which by decreasing the number of viable cardiac myocytes increases the load on those that survive. Hypertrophy also causes architectural changes that reduce the energy supply to working cardiac myocytes. (From Katz AM: Heart Failure. Philadelphia, Lippincott Williams & Wilkins, 2000.)

is not understood but is associated with alterations in the isoforms of creatine kinase. In failing myocardium, there is a decrease in the adult (MM) isoform and an increase or no change in the fetal isoform (MB).[133] The effect of decreased creatine kinase activity on myocardial function and energetics was tested in mice with genetic deficiencies of the creatine kinase M-isoform, mitochondrial-isoform, or both.[138] Surprisingly, mice with these deficiencies had normal baseline function and responses to calcium. However, the mice lacking both isoforms had a greater increase in adenosine diphosphate (ADP) and a more pronounced decrease in the free energy released from ATP, suggesting that work was more energetically costly.

Nuclear magnetic resonance (NMR) spectroscopy with phosphorus-31, a noninvasive technique (see Chap. 9) has been employed to study the phosphocreatine to ATP ratio (PCr/ATP) in normal subjects and in patients. Reductions have been described in patients with severe aortic valve disease, cardiomyopathy, and myocardial ischemia.[139] [140] [141] In patients with chronic mitral regurgitation the reductions in PCr/ATP have been found to be related to the severity of the hemodynamic impairment as reflected in the left ventricular end-systolic diameter (Fig. 16-18) . The extent of reduction of the ratio has been shown to correlate with the clinical severity of the heart failure and with the prognosis (Fig. 16-19). [142] These changes in the PCr/ATP may be caused by the previously mentioned reduction of creatine phosphorylation and of creatine kinase activity.[133] [134] [135] [137]

One unusual form of heart failure that is primarily related to a reduction of myocardial energy stores is that due to phosphate deficiency. Chronic hypophosphatemia induced by dietary means is associated with reversible depression of myocardial performance in isolated muscle as well as in the intact heart of animals and humans, presumably as a consequence of reduced ATP stores.[143] [144]

In the final analysis the reductions of high-energy phosphates in the failing heart results in a decrease in the quantity of energy made available by the hydrolysis of ATP. The reduction of the ATP/ADP ratio reduces the energy available to the SR for calcium uptake, thereby impairing relaxation (diastolic failure) and to the contractile apparatus, impairing cross-bridge cycling (systolic failure).[2]

Figure 16-18 Echocardiographic parameters versus PCr/ATP (LVM/BSA) is given in g/cm^2 . ESD=left ventricular end-systolic diameter. (From Conway MA, et al: Mitral regurgitation: Impaired systolic function,

eccentric hypertrophy, and increased severity are linked to lower phosphocreatine/ATP ratios in humans. Circulation 97:1716, 1998. Copyright 1998, American Heart Association.)

Figure 16-19 Cardiac[31] P-MR spectra. *From top to bottom:* spectra from volunteer patients with dilated cardiomyopathy (DCM) with normal phosphocreatine/ATP ratio and severely reduced phosphocreatine/ATP ratio: the latter patient died 7 days after the magnetic resonance examination. (*From Neubauer S, Horn M, Cramer M, et al: Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation 96:2190, 1997. Copyright 1997, American Heart Association.*)

EFFECTS OF NITRIC OXIDE ON MYOCARDIAL ENERGETICS.

There is evidence that NO may be an important regulator of myocardial energetics. NO has been shown to inhibit myocardial oxygen consumption by means of an effect on mitochondrial respiration.[145] [146] This action of NO was demonstrated in human myocardium and found to be preserved in myocardium from patients with heart failure.[147] It has been proposed that a bradykinin-mediated increase in NO by the vascular endothelium may contribute to the beneficial effects of ACE inhibitors by inhibiting myocardial oxygen demands.[148] NO has also been shown to inhibit creatine kinase and reduce the availability of ATP. In isolated rat hearts, perfusion with the NO donor S-nitroacetylcysteine (SNAC) inhibited the ability of calcium to increase the rate-pressure product. This effect was associated with inhibition of creatine kinase activity and a decrease in ATP.[38] The level of NO in the failing heart is controversial. On the one hand, increased expression of inducible NO synthase has been observed in failing myocardium.[149] On the other hand, direct measurement of NO in dogs with pacing-induced heart failure demonstrated a decrease in tissue NO associated with an increase in respiratory quotient and a shift in substrate utilization from free fatty acids to glucose.[150]

PATHOPHYSIOLOGY OF DIASTOLIC HEART FAILURE (See also Chaps. 14 and 15)

Alterations in Diastolic Properties

Approximately one third of patients with congestive heart failure have predominantly diastolic heart failure (see Chap. 17) , which may be defined as pulmonary (or systemic)

venous congestion, and the symptoms consequent thereto, in the presence of normal or almost normal systolic function.[151] [151A] [151B] Another third have impairment of both systolic and diastolic function, and the remainder primarily have disordered systolic function. Among subjects with the clinical diagnosis of congestive heart failure in the Framingham Heart Study population, 51 percent had a left ventricular ejection fraction (LVEF) greater than or equal to 0.50.[152] Sixty-five percent of the subjects with an LVEF

greater than or equal to 0.50 were women, whereas men constituted 75 percent of the subjects with an LVEF less than 0.50. The annual mortality rate in patients with an LVEF greater than or equal to 0.50 (8.7 percent) was lower than in patients with an LVEF less than 0.50 (18.9 percent) but still approximately fourfold greater than in age-matched control subjects.

ALTERED VENTRICULAR RELAXATION (See also p. 470).

Although two aspects of the heart's diastolic characteristics (i.e., relaxation and wall stiffness) are often considered together, they actually describe two different properties.[151C] Relaxation (inactivation of contraction) is a dynamic process that begins at the termination of contraction and occurs during isovolumetric relaxation and early ventricular filling (Fig. 16-20 ; see also Fig. 14-32) . The rate of ventricular relaxation is controlled primarily by the uptake of Ca^{2+} by the SR but also by the efflux of Ca^{2+} from the myocyte. These processes are regulated by SERCA2, as well as by sarcolemmal calcium pumps (see p. 513, Table 16-3) . Because these Ca^{2+} movements are against concentration gradients, they are energy consuming. Therefore, ischemia-induced ATP depletion interferes with these processes and slows myocardial relaxation (see Fig. 16-20 *A*). On the other hand, beta-adrenergic receptor stimulation, by increasing cyclic AMP and cyclic AMP-dependent protein kinase activity, causes the phosphorylation of phospholamban (see Chap. 14) , which accelerates Ca^{2+} uptake by the SR and thereby enhances relaxation.

An acute increase in ventricular afterload has also been shown to slow myocardial relaxation.[153] Thus, when pressure overload is applied (before compensatory hypertrophy has normalized afterload), ventricular relaxation is slowed. Myocardium isolated from patients with hypertrophic cardiomyopathy[154] and from ferrets with pressure-overload hypertrophy[155]

Figure 16-20 Mechanisms that cause diastolic dysfunction. Only the bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; dashed lines represent patients with diastolic dysfunction. (From Zile MR: Diastolic dysfunction: Detection, consequences, and treatment: II. Diagnosis and treatment of diastolic function. Mod Concepts Cardiovasc Dis 59:1, 1990. Copyright 1990, American Heart Association.)

exhibits a prolonged calcium transient (i.e., a prolonged elevation of myoplasmic Ca^{2+}) associated with a prolonged tension decay, findings consistent with delayed uptake of Ca^{2+} by the SR.

ALTERED VENTRICULAR FILLING.

During early ventricular filling the myocardium normally lengthens rapidly and homogeneously. Regional variation in the onset, rate, and extent of myocardial lengthening is referred to as *ventricular heterogeneity,* or *diastolic asynergy;* temporal dispersion of relaxation, with some fibers commencing to lengthen later than others, is referred to as *diastolic asynchrony.* [156] Both diastolic asynergy and asynchrony interfere

with early diastolic filling. In contrast to these early diastolic events, myocardial *elasticity* (i.e., the change in muscle length for a change in force), ventricular *compliance* (i.e., the change in ventricular volume for a given change in pressure), and ventricular *stiffness* (i.e., the inverse of compliance) are generally measured in the relaxed ventricle at end-diastole.

These diastolic properties of the ventricle are described by its curvilinear pressure-volume relation (see Fig. 16-20 *B-D*). The slope of a tangent to this curvilinear relation (dP/dv) defines the chamber compliance at any level of filling pressure. An increase in chamber stiffness may occur secondary to any one or a combination of these three mechanisms:

1. *A rise in filling pressure* (i.e., movement of the ventricle up along its pressure-volume [stress-strain] curve to a steeper portion) (see Fig. 16-20 *D*).[157] This may occur in conditions such as volume overload secondary to acute valvular regurgitation and in acute left ventricular failure due to myocarditis.
2. *A shift to a steeper ventricular pressure-volume* (see Fig. 16-20 *C*) *or stress-strain curve.* This results most commonly from an increase in ventricular mass and wall thickness. Thus, although hypertrophy constitutes a principal compensatory mechanism to sustain systolic emptying of the overloaded ventricle, it may simultaneously interfere with the ventricle's diastolic properties and impair ventricular filling. This shift to a steeper pressure-volume curve can also be caused by an increase in *intrinsic* myocardial stiffness (the stiffness of a unit of the cardiac wall regardless of the total mass or thickness of the myocardium), as occurs with disorders in which there is myocardial infiltration (e.g., amyloidosis), endomyocardial fibrosis, or myocardial ischemia.
3. *A parallel upward displacement of the diastolic pressure-volume curve.* This is generally referred to as a *decrease in ventricular distensibility* and is usually caused by extrinsic compression of the ventricles, as occurs in cardiac tamponade or constrictive pericarditis (see Chap. 50) (see Fig. 16-20*B*).

Chronic Changes in Ventricular Diastolic Pressure-Volume Relationships

The compliance of the left ventricle, reflected in the end-diastolic pressure-volume relationship, is altered in a variety of cardiac disorders, reflecting one or more basic mechanisms (Fig. 16-20) (see Chap. 17). Substantial shifts in the diastolic pressure-volume curve of the left ventricle can be demonstrated during sustained volume overload.[158] For example, dogs with large chronic arteriovenous fistulas exhibit a rightward displacement of the entire diastolic pressure-volume curve, whereby ventricular volume is greater at any end-diastolic pressure but the slope of this curve is steeper, indicating increased chamber stiffness.[159] Patients with severe volume overloading due to chronic aortic and/or mitral regurgitation demonstrate similar shifts of the diastolic left ventricular pressure-volume relationship. Similar changes frequently occur in patients with dilated or ischemic cardiomyopathy or after large transmural myocardial infarction (see later).

In contrast, concentric left ventricular hypertrophy, as occurs in aortic stenosis, hypertension, and hypertrophic cardiomyopathy, shifts the pressure-volume relation of the ventricle to the left along its volume axis so that at any diastolic volume ventricular diastolic pressure is abnormally elevated[160] [161] [162] [162A] (see Fig. 16-20 *C*). In contrast to the changes in the diastolic properties of the ventricular *chamber,* the stiffness of *each unit of myocardium* may or may not be altered in the presence of myocardial hypertrophy secondary to pressure overload.[4] In the presence of concentric left ventricular hypertrophy, there is an inverse relationship between the thickness of the posterior wall of the ventricle and its peak thinning rate during early diastole[163] ; a higher-than-normal diastolic ventricular pressure is required to fill the hypertrophied ventricle. Patients with hypertension have demonstrated slowing of ventricular filling, even when systolic function is normal.[164]

ISCHEMIC HEART DISEASE.

Marked changes in the diastolic properties of the left ventricle can occur in the presence of ischemic heart disease. First, as already pointed out, acute myocardial ischemia slows ventricular relaxation (see Fig. 16-20 *A*) and increases myocardial wall stiffness.[165] Myocardial infarction causes more complex changes in ventricular pressure-volume relationships, depending on the size of the infarct and the time after infarction at which the measurements are made. Infarcted muscle tested very early exhibits reduced stiffness.[166] Subsequently, the development of myocardial contracture, interstitial edema, fibrocellular infiltration, and scar contribute to stiffening of the necrotic tissue and thereby to increased chamber stiffness, with a steeper ventricular pressure-volume curve (a greater increase in pressure for any increase in volume).[167] Later still, in the case of large infarcts, left ventricular remodeling and dilatation cause a rightward displacement of the pressure-volume curve,[168] resembling that observed in volume overload. The subendocardial ischemia that is characteristic of severe concentric hypertrophy (even in the presence of a normal coronary circulation) intensifies the failure of relaxation[51] ; and when coronary artery obstruction accompanies severe hypertrophy, this abnormality may be particularly severe. Tachycardia, by reducing the duration of diastole and thereby intensifying ischemia, exaggerates this diastolic abnormality and may raise ventricular diastolic pressure even while reducing diastolic ventricular volume, whereas bradycardia has the opposite effect. Successful treatment of ischemia improves diastolic relaxation and lowers ventricular diastolic and pulmonary venous pressures, thereby reducing dyspnea.

CARDIOMYOPATHY AND PERICARDIAL DISEASE.

The restrictive cardiomyopathies, especially those such as amyloid heart disease with intracardiac infiltration, the transplanted heart during rejection, and endomyocardial fibrosis (see Chap. 48), all are characterized by upward and leftward displacement of the diastolic pressure-volume relation, with a higher pressure at any volume and a greater increase in diastolic pressure for any increase in volume. Pericardial tamponade and constrictive pericarditis also change the apparent diastolic properties of the heart

(see Chap. 50). Early filling is unimpaired because the myocardium is normal. However, filling is abruptly halted in mid diastole by the constricted or tamponading pericardium, which imposes its mechanical properties on those of the ventricle in the latter half of diastole (see Fig. 16-20*B*).

NEUROHORMONAL, AUTOCRINE, AND PARACRINE ADJUSTMENTS (See also Chap. 21)

A complex series of neurohormonal changes takes place consequent to the two principal hemodynamic alterations in heart failure: reduction of cardiac output and atrial hypertension.

Figure 16-21 Factors responsible for diastolic dysfunction and increased left ventricular diastolic pressure. (From Gaasch WH, Izzi G: Clinical diagnosis and management of left ventricular diastolic dysfunction. *In* Hori M, Suga H, Baan J, Yellin EL [eds]: Cardiac Mechanics and Function in the Normal and Diseased Heart. New York, Springer-Verlag, 1989, p 296.)

Many of these neurohormonal changes occur in response to the inadequate arterial volume characteristic of systolic heart failure.[169] In the early stages of severe, acute systolic failure, these changes--heightened adrenergic drive, activation of the renin-angiotensin-aldosterone axis, and the augmented release of vasopressin and endothelin--are truly compensatory and act to maintain perfusion to vital organs and to expand the inadequate arterial blood volume and renal retention of sodium and water (Figs. 16-21 and 16-22) . However, each of these mechanisms may be thought of as a "double-edged sword." As heart failure becomes chronic, several of these compensatory mechanisms can cause undesirable effects, such as excessive vasoconstriction, increased afterload, excessive retention of salt and

Figure 16-22 Mechanisms by which high-output or low-output heart failure leads to the activation of neurohumoral vasoconstrictor systems and renal sodium and water retention. (From Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. N Engl J Med 341:577, 1999; adapted from Schrier RW: Pathogenesis of sodium and water retention in high-output and low output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. N Engl J Med 319:1065, 1988.)

Figure 16-23 Unloading of high-pressure baroceptors (circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system. The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II

constricts blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The lines designate circulating hormones. (*Modified from Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. N Engl J Med 341:577, 1999.*)

water, electrolyte abnormalities, and arrhythmias (see Table 16-1) . In contrast, other responses, such as the release of atrial natriuretic peptide (ANP) in response to atrial distention, may oppose these adverse effects by causing vasodilation, increased excretion of salt and water, and inhibition of sympathetic activity.[170]

A variety of mediators are involved in control of the cardiovascular system in heart failure. Some are circulating hormones (endocrine effect). Some act on neighboring cells of another type (paracrine effect) or on the cell of origin (autocrine effect).[171] These include peptides that act primarily locally in the vicinity of their production, such as endothelin, peptide growth factors (e.g., TGF-alpha), and inflammatory cytokines (e.g., interleukin-1-beta [IL-1beta] and TNF-alpha). These and other local mediators act in concert with the autonomic nervous system and circulating hormones to modulate cardiovascular organ function. In addition, as discussed on p. 527 , many if not all of these mediators have effects on the growth, death, and phenotype of cardiovascular tissues and may thereby play an important role in the "remodeling" of myocardium and its progression to failure (see Fig. 16-8) . [31]

Autonomic Nervous System

INCREASED SYMPATHETIC ACTIVITY (see Figs. 16-22 and 16-23).

Measurements of the concentration of the adrenergic NE in arterial blood provide an index of the activity of this system, which is crucial to the normal regulation of cardiac performance. At rest, in patients with advanced heart failure, the circulating NE concentration is much higher, generally two to three times the level found in normal subjects,[172] and is accompanied by elevation of circulating dopamine and sometimes by epinephrine as well; the latter reflects increased adrenomedullary activity. Measurement of 24-hour urinary NE excretion also reveals marked elevations in patients with heart failure.[173] In the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD) trial (see Chap. 18), plasma NE was significantly elevated, even in asymptomatic patients, and was further elevated in patients with symptomatic heart failure (Fig. 16-24) .[174] During comparable levels of exercise, much greater elevations in circulating NE occur in patients with heart failure than in normal subjects, presumably reflecting greater activation of the adrenergic nervous system during exercise in these patients.[175]

The elevation of circulating NE may result from a combination of increased release of NE from adrenergic nerve endings and its consequent "spillover" into plasma, as well as reduced uptake of NE by adrenergic nerve endings.[176] Patients with heart failure demonstrate increased adrenergic nerve outflow, as measured by microneurography of the peroneal nerve; and the level of nerve activity correlates with the concentration of plasma NE (Fig. 16-25) . [177] The level of adrenergic nerve activity also correlates directly with the levels of left and right ventricular filling pressures.[177] Whereas the

normal heart usually extracts NE, in patients with heart failure the coronary sinus NE level exceeds the arterial level, indicating increased adrenergic activation of the heart.[178] Drugs such as the alpha$_2$ -agonist guanabenz (which reduces adrenergic nerve impulse traffic) and bromocriptine[179] (a presynaptic dopamine-2 agonist) reduce plasma NE, indicating that presynaptic control of adrenergic nervous activity is intact in patients with heart failure. It has been suggested that treatment with such agents might be useful in the treatment of heart failure.[179]

The extent of elevation of plasma NE concentration that occurs in patients with heart failure correlates directly with the severity of the left ventricular dysfunction, as reflected in the height of the pulmonary capillary wedge pressure and depression of the cardiac index,[172] [180] and with cardiac mortality.[181] The augmented adrenergic outflow from the central nervous system in patients with heart failure may trigger ventricular tachycardia or even sudden cardiac death, particularly in the presence of myocardial ischemia. However, it is

Figure 16-24 Activation of neurohormonal systems in patients with heart failure. In patients studied in the SOLVD trials, plasma norepinephrine, renin activity, atrial natriuretic factor (ANF), and arginine vasopressin (AVP) were elevated in patients with symptomatic heart failure enrolled in the treatment trial, and also, albeit to a lesser degree, in asymptomatic patients enrolled in the prevention trial. (Modified from Francis GS, Benedict C, Johnstone DE, et al: Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: A substudy of the studies of left ventricular dysfunction (SOLVD). Circulation 82:1724, 1990. Copyright 1990, American Heart Association.)

not clear whether the elevated levels of circulating NE in patients who subsequently die of heart failure are causally related to death as a consequence of their vasoconstrictor, arrhythmogenic, or other actions or whether they merely reflect the severity of the underlying heart failure.

In addition to activation of beta-adrenergic receptors in the heart, the heightened activity of the adrenergic nervous system leads to stimulation of myocardial alpha$_1$ -adrenergic receptors, which elicits a modest positive inotropic effect.[182] Stimulation of myocardial alpha$_1$ -adrenergic receptors may also cause myocyte hypertrophy, changes in phenotype characterized by the reexpression of a fetal gene program,[183] and the induction of peptide growth factors.[184] Alpha$_1$ -adrenergic receptors are of low density in the human heart; however, in contrast to beta$_1$ -adrenergic receptors, which are downregulated, alpha$_1$ -adrenergic receptors appear to be unchanged in number in failing human myocardium.[185]

CARDIAC NOREPINEPHRINE DEPLETION.

The concentration of NE in atrial[173] and ventricular tissue[35] removed at operation from patients with heart failure is extremely low. In patients, it has been reported that cardiac NE content determined from endomyocardial biopsies correlates directly with the ejection fraction and inversely with plasma epinephrine concentration.[186] NE concentrations are also markedly depressed in the ventricles of dogs with right ventricular failure produced by the creation of pulmonary stenosis and tricuspid regurgitation.[187] Local cardiac NE stores do not appear to play any role in the *intrinsic* contractile state of cardiac muscle. Thus, no differences were found in the length-tension or force-velocity relationships displayed by papillary muscles removed from normal cats and from cats with NE depletion produced by chronic cardiac denervation or reserpine pretreatment.[187] However, the reduction in cardiac NE stores represents a depletion of the adrenergic neurotransmitter in adrenergic nerve endings, and, as a consequence, the response to activation of the sympathetic nervous system is blunted[188] (see Fig. 16-1) .

The mechanism responsible for cardiac NE depletion in severe heart failure is not clear; it may be an "exhaustion" phenomenon from the prolonged adrenergic activation of the cardiac adrenergic nerves in heart failure. Reductions in the activity of tyrosine hydroxylase,[189] which catalyzes the rate-limiting step in the biosynthesis of NE, and in the rate at which noradrenergic vesicles can take up dopamine have also been incriminated. In patients with cardiomyopathy, iodine-131-labeled metaiodobenzylguanidine (MIBG), a radiopharmaceutical that is taken up by adrenergic nerve endings, is not taken up normally, [190] , [191] suggesting that NE reuptake is impaired in heart failure. Treatment with the beta-adrenergic antagonist metoprolol was associated with correction of MIBG uptake.[192]

ABNORMAL BAROREFLEX CONTROL IN HEART FAILURE

Increased adrenergic activity in heart failure is due, in part, to abnormal baroreflex control of adrenergic outflow from the central nervous system (see Figs. 16-22 and 16-23) . In dogs with experimental heart failure, carotid occlusion elicits a blunted reflex response of heart rate, arterial pressure, and vascular resistance.[193] The possibility of defective adrenergic control of heart rate in patients with heart failure has been studied by observing the reflex hemodynamic responses to stimuli such as upright tilt and vasodilator-induced hypotension.[194]

An inappropriately depressed increase in heart rate in humans with heart failure was observed when arterial pressure was reduced through administration of vasodilators.[195] Whereas the changes in

Figure 16-25 Activation of the sympathetic nervous system in heart failure. There is an increased rate of

sympathetic nerve activity (SNA), as measured by the rate of nerve firing in the peroneal nerve, in patients with heart failure *(A).* Studies of the clearance of plasma norepinephrine in normal (NL) subjects and patients with heart failure (CHF) indicate that both increased spillover *(B)* and decreased clearance *(C)* contribute to the higher norepinephrine levels observed in patients with heart failure. (*A,* modified from Leimbach WN Jr, Wallin G, Victor RG, et al: Direct evidence from intrarenal recordings for increased central sympathetic outflow in patients with heart failure. Circulation 73:913, 1986. Copyright 1986, American Heart Association. *B* and *C,* modified from Davis D, et al: Abnormalities in systemic norepinephrine kinetics in human congestive heart failure. Am J Physiol 254:E760, 1988.)

mean arterial pressure observed in response to the vasodilators were similar in patients with heart failure and in control subjects, the changes in heart rate after vasodilators correlated significantly with the changes in concentration of circulating NE and with the sum of circulating NE and epinephrine. In normal individuals, both heart rate and catecholamine concentrations rose, whereas in patients with heart failure, in whom resting catecholamine levels were already increased, cardiac acceleration was blunted and catecholamine concentration failed to rise normally. Similarly, during upright tilt there is a blunting of the normal increases in plasma NE, forearm vascular resistance, and hepatic vascular resistance in patients with heart failure.[196] Some patients with heart failure exhibit a major reduction in arterial pressure during tilting, analogous to what is observed in idiopathic orthostatic hypotension.[197] Further evidence for impairment of baroreflex control of the systemic circulation comes from investigations in which lower body negative pressure fails to cause normal reflex augmentation of forearm vascular resistance.[198]

ATRIAL STRETCH RECEPTORS.

Abnormal baroreflex control also contributes to the reduced ability of patients with heart failure to excrete salt and water. Under normal circumstances, elevated left atrial pressure stimulates atrial stretch receptors. The increased activity of both myelinated and nonmyelinated (C-fiber) afferents[199] inhibits the release of antidiuretic hormone, thereby increasing water excretion, which in turn reduces plasma volume and would act to restore left atrial pressure to normal. In addition, enhanced left atrial stretch receptor activation depresses renal efferent sympathetic nerve activity and increases renal blood flow and glomerular filtration rate, thereby enhancing the ability of the kidney to reduce plasma volume.

With continued stimulation as occurs in heart failure, there is desensitization of atrial (and arterial) baroreceptors. Zucker and coworkers observed that the decreased sensitivity of left atrial stretch receptors in dogs with heart failure is the result of cardiac dilatation and alterations in atrial compliance and is reversible after reversal of heart failure.[200] This resetting of atrial receptors may be responsible for the inappropriately high plasma antidiuretic hormone levels in heart failure and may contribute to the renal vasoconstriction, peripheral edema, ascites, and hyponatremia characteristic of chronic severe heart failure. With chronic heart failure and its attendant cardiac distention and decreased sensitivity of cardiac receptors, the reflex inhibition of adrenergic activity disappears. The adrenergic drive to the peripheral vascular bed and the adrenal medulla is enhanced, contributing to the sodium retention, the tachycardia, and the vasoconstricted state characteristic of heart failure.

There is evidence that abnormal baroreflex control is associated with increased activity of Na^+ ,K^+ -ATPase in the baroreceptors.[201] Digitalis glycosides can partially correct the blunted baroreceptor responsiveness in patients with heart failure.[198] This ability of digitalis to correct baroreflex function and thereby suppress adrenergic nerve activity may play a significant role in its clinical efficacy (see Chap. 18) . It has been shown that NO increases baroreflex sensitivity, whereas angiotensin II decreases it and that exogenous NO and blockade of angiotensin receptors can correct the reduced baroreceptor sensitivity in experimental heart failure.[53] [202] [203] The abnormal baroreflex response in patients with heart failure is usually corrected by cardiac transplantation[204] and is not associated with structural changes in the carotid sinus nerve fiber,[205] indicating that it is a secondary manifestation (not a cause) of heart failure.

Beta-Adrenergic Receptor-G Protein-Adenylyl Cyclase Pathway

BETA-ADRENERGIC RECEPTORS (See also p. 461).

Ventricles obtained from patients with heart failure demonstrate a marked reduction in beta-adrenergic receptor density, isoproterenol-mediated adenylyl cyclase stimulation, and the contractile response to beta-adrenergic agonists.[206] [206A] It is generally believed that the downregulation of beta-adrenergic receptors is mediated by increased levels of NE in the vicinity of the receptor. In patients with right ventricular failure secondary to primary pulmonary hypertension, $beta_1$ -adrenergic receptors are downregulated in the right ventricle but not in the normally functioning left ventricle,[207] suggesting that beta-adrenergic receptor downregulation is due to a local chamber-specific mechanism, presumably an increase in local NE concentrations. In patients with dilated cardiomyopathy, this reduction in receptor

Figure 16-26 Downregulation of beta-adrenergic receptors in myocardium from patients with heart failure. Although human ventricular myocardium expresses both $beta_1$ - and $beta_2$ -adrenergic receptor subtypes, only the $beta_1$ subtype is significantly downregulated in failing myocardium *(A).* Downregulation of $beta_1$ receptors is associated with upregulation of beta-adrenergic receptor kinase (betaARK), an enzyme that phosphorylates beta-adrenergic receptors and thereby contributes to their uncoupling from second messenger pathways *(B).* In addition, the mRNA level for $beta_1$ -, but not $beta_2$ -, adrenergic receptors is decreased in failing human myocardium *(C* and *D).* NF=nonfailure; F=congestive heart failure; DCM=dilated cardiomyopathy; ICM=ischemic cardiomyopathy. (Data from Bristow MR: Changes in myocardial and vascular receptors in heart failure. J Am Coll Cardiol 22:61A, 1993; and Ungerer M, Bohm M, Elce JS, et al: Altered expression of beta-adrenergic receptor kinase and $beta_1$ -adrenergic receptors in the failing human heart. Circulation 87:454, 1993. Copyright 1993, American Heart Association.)

density is proportional to the severity of heart failure and involves primarily $beta_1$, but

not $beta_2$, receptors, thus reducing the ratio of $beta_1$ to $beta_2$ receptors (Fig. 16-26 *A*).[208] The $beta_2$ receptor, although not downregulated, becomes partially "uncoupled" from its effector enzyme (adenylyl cyclase),[209] producing a similar effect.

The relative roles of beta-adrenergic receptor downregulation versus receptor uncoupling may depend on the cause of heart failure.[209A] In myocardium obtained from patients with heart failure secondary to ischemic heart disease, there is a relatively greater degree of receptor desensitization than in myocardium from patients with ischemic cardiomyopathy.[210] This observation, together with apparent differences in the regulation of G-protein function (discussed later), has led to the suggestion that there are differences in the behavior of the beta-adrenergic receptor-G-protein complex in these forms of heart failure. In myocardium from patients with heart failure the level of $beta_1$ -adrenergic receptor mRNA is decreased, indicating that downregulation of $beta_1$ -adrenergic receptors is mediated, at least in part, by a decrease in receptor synthesis, whereas the level of $beta_2$ -adrenergic receptor mRNA is unchanged (see Fig. 16-26 *C* and *D*). In addition, there are increases in the expression of beta-adrenergic receptor kinase (betaARK) and its mRNA level in failing human myocardium (see Fig. 16-26 *B*).[211] betaARK is an enzyme that phosphorylates both $beta_1$ - and $beta_2$ -adrenergic receptors and thereby plays a central role in uncoupling of the receptor from its G protein.[211] Increased betaARK activity may therefore contribute to the uncoupling of both $beta_1$ - and $beta_2$ -adrenergic receptors in patients with heart failure.

Downregulation of $beta_1$ receptors in patients with heart failure may be reversed by the administration of metoprolol, a relatively specific $beta_1$ antagonist. The long-term clinical benefit of beta blockade in heart failure (see Chap. 18) has been reported to be associated with both a restoration of myocardial beta receptor density and the contractile response to administered catecholamines.[212] Although these effects may contribute to improved adrenergic responsiveness, they are not seen with all beta blockers[213] and therefore do not appear to be critical to the beneficial effects of these drugs on ventricular remodeling or clinical outcomes.

G PROTEINS AND ADENYLYL CYCLASE (See also p. 455).

G proteins play a crucial role in coupling receptors, including beta-adrenergic receptors, to effector enzymes such as adenylyl cyclase (see Chap. 14) . Cardiac cells contain at least two types of G proteins: (1) G_s , which mediates the stimulation of adenylyl cyclase (and thereby causes a rise in intracellular cyclic AMP, which in turn stimulates Ca^{2+} influx into the myocyte through Ca^{2+} channels in the sarcolemmal membrane and accelerates the uptake of Ca^{2+} by the SR); and (2) G_i , which mediates the inhibition of adenylyl cyclase and has the opposite effect on the movements of Ca^{2+} .

Heart failure caused by dilated cardiomyopathy is associated with an increase in G_i activity and protein level in heart muscle,[214] which may be accompanied by a reduction

in the activity of adenylyl cyclase.[215] The mechanism responsible for the increase in G_i activity is not known. The mRNA levels of G_i are not increased in the myocardium of patients with heart failure,[216] suggesting that the increase in G_i activity reflects events at the posttranscriptional level. G_s appears normal in failing human myocardium.[216] Overall, heart failure is characterized by an increase in the ratio of G_i to G_s .[216] The functional consequences of an increase in G_i activity remain to be established.

REDUCED ADRENERGIC SUPPORT OF THE FAILING HEART.

The importance of the adrenergic nervous system in maintaining ventricular contractility when myocardial function is depressed in heart failure is demonstrated by the effects of adrenergic blockade. *Acute* pharmacological blockade of the adrenergic nervous system may cause intensification of heart failure as well as sodium and water retention.[217] [218] [219] The *acute* administration of beta blockers to patients with heart failure results in reductions in both systolic and diastolic myocardial function.[220] Despite the long-term salutary effects of beta-blocker therapy in patients with heart failure[220A] (see Chaps. 18 and 21) , caution should be exercised in using these agents, particularly at the initiation of therapy and in patients in whom heart failure is severe or of recent onset.

Because of the depletion of cardiac NE stores and desensitization of the postsynaptic beta-adrenoceptor pathway, the capacity of the myocardium to produce cyclic AMP is diminished, sometimes profoundly, in patients with heart failure.[221] As a consequence, the failing heart loses an important compensatory mechanism. In patients with heart failure, downregulation of postsynaptic beta-adrenoceptors in the sinoatrial node contributes to the attenuated chronotropic response to exercise.[175] Likewise, the positive inotropic response to an intracoronary infusion of the beta-adrenergic agonist dobutamine is markedly reduced in patients with heart failure.[222] The degree of attenuation of both the chronotropic and positive inotropic responses to adrenergic stimulation are correlated with the level of baseline adrenergic activation as reflected by the concentration of plasma NE.[175] [222] An important therapeutic consequence of the alterations of the beta-adrenergic pathway described earlier is that the positive inotropic response to beta-adrenoceptor agonists, and to a lesser extent to phosphodiesterase inhibitors, is markedly reduced in myocardium obtained from patients with end-stage heart failure.

ADVERSE EFFECTS OF ADRENERGIC STIMULATION

Although increased adrenergic activity may play a compensatory role over the short term, *chronic* adrenergic activation may be deleterious by increasing afterload and precipitating cardiac arrhythmias. Thus, it has been postulated that in heart failure there may be a positive feedback loop causing a vicious circle. According to this concept, heart failure activates the adrenergic nervous system (as well as activating the

renin-angiotensin system and stimulating the release of vasopressin and endothelin); this causes increases in preload and afterload that further depress ventricular function and increase the heart's demands for energy.

Increased adrenergic nerve activity may also influence the chronic remodeling of the myocardium by affecting the progression of myocardial failure through direct harmful effects of NE on adrenergic receptors located on several cell types in the myocardium, including cardiac myocytes and fibroblasts. The tonic stimulation of beta-adrenergic receptors, or the downstream cyclic AMP pathway to which they are coupled, results in death of cardiac myocytes by apoptosis. In vitro, tonic exposure to NE causes apoptosis of adult rat cardiac myocytes that is mediated through the beta-adrenergic receptor adenylyl cyclase and cyclic AMP[58] (Fig. 16-27) . A similar effect is seen in neonatal rat cardiomyocytes.[59] Likewise, the chronic infusion of isoproterenol to rats causes myocardial failure associated with apoptosis,[223] and transgenic mice that overexpress either the $beta_1$ -adrenergic receptor or G_s [224] [225] [225A] develop myocardial failure associated with myocyte apoptosis. When viewed from this perspective, the desensitization of the beta-adrenergic pathway, although impairing short-term myocardial function, may protect the myocardium from increased adrenergic activation.

Stimulation of $alpha_1$ -adrenergic receptors can induce hypertrophy in cardiac myocytes associated with the reappearance of fetal genes and fetal isoforms of proteins involved in the development of

Figure 16-27 Effect of norepinephrine (NE) on myocyte apoptosis. Adult rat cardiac myocytes in tissue culture were exposed to control media *(A)* or NE *(B)* for 24 hours and apoptosis was measured by the TUNEL staining for fragmented DNA shown in two nuclei in this panel. NE caused an approximately fourfold increase in TUNEL-positive myocytes *(C).* This effect of NE was abolished by a beta-adrenergic antagonist and mimicked by beta-adrenergic agonists but not affected by an alpha-adrenergic antagonist. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.12.)

contractile force, the regulation of myocardial energetics, and excitation-contraction coupling.[183] [226] In addition, NE, acting on both $alpha_1$ -adrenergic and beta-adrenergic receptors located on cardiac myocytes and fibroblasts,[184] [227] can induce the expression of a variety of peptide growth factors that have been shown to have important effects on the growth and phenotype of myocytes and fibroblasts.[228]

PARASYMPATHETIC FUNCTION IN HEART FAILURE

Cardiac enlargement, with or without heart failure, is associated with marked disturbances of parasympathetic as well as sympathetic function.[229] The parasympathetic restraint on sinoatrial node automaticity is markedly reduced in patients with heart failure (see Fig. 16-2) , who exhibit less heart rate slowing for any given elevation of systemic arterial pressure than do normal subjects. The sensitivity of the baroreceptor reflex to an increase in pressure has also been shown to be

significantly reduced in dogs with heart failure.[193] Measurements of heart rate variability, which indirectly reflect autonomic nervous system function, indicate that parasympathetic activity in patients with heart failure is abnormal both at rest and in response to exercise.[230]

Abnormal parasympathetic function may also be altered at the level of the peripheral nerve and the postsynaptic receptor. Cardiomyopathic hamster hearts display a reduction in the activity of choline acetyltransferase, an enzyme that provides an estimate of the density of parasympathetic innervation,[231] and there is evidence that the density of high-affinity muscarinic receptors is reduced in the hearts of dogs with experimental heart failure.[232]

Renin-Angiotensin System

In low cardiac output states, there is activation of the renin-angiotensin system (RAS), which operates in concert with the activated adrenergic nervous-adrenal medullary system to maintain arterial pressure and to retain sodium and water

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Figure 16-28 The systemic and tissue components of the renin-angiotensin system. Several tissues, including myocardium, vasculature, kidney, and brain, have the capacity to generate angiotensin II independent of the circulating renin-angiotensin system. Angiotensin II produced at the tissue level may play an important role in the pathophysiology of heart failure. (Modified from Timmermans PB, Wong PC, Chiu AT, et al: Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 45:205, 1993.)

(see Figs. 16-22 and 16-24 *B*). These two compensatory systems are clearly coupled; stimulation of $beta_1$ -adrenoceptors in the juxtaglomerular apparatus of the kidneys as a consequence of heightened adrenergic drive is a principal mechanism responsible for the release of renin in acute heart failure. Activation of the baroreceptors in the renal vascular bed by a reduction of renal blood flow is also responsible for the release of renin; and, in patients with severe chronic heart failure after salt restriction and diuretic treatment, reduction of the sodium presented to the macula densa contributes to the release of renin. Elevated plasma renin activity is a common, although not universal, finding in heart failure.[172] [174] [233] In the SOLVD study, plasma angiotensin II was significantly elevated even in asymptomatic patients and was further elevated in patients with symptomatic heart failure (see Fig. 16-24) .[174]

ADVERSE EFFECTS OF RAS ACTIVATION.

Angiotensin II is a potent peripheral vasoconstrictor and contributes, along with increased adrenergic activity, to the excessive elevation of systemic vascular resistance and the vicious circle already referred to (see p. 520) in patients with heart failure.

Angiotensin II also enhances the adrenergic nervous system's release of NE. Aldosterone has potent sodium-retaining properties and contributes to the development of edema (see Fig. 16-22) . Therefore, it is not surprising that interruption of the renin-angiotensin-aldosterone axis by means of an ACE inhibitor reduces system vascular resistance, diminishes afterload, and thereby elevates cardiac output in heart failure. In some patients these compounds also exert a mild diuretic action, presumably by lowering the angiotensin II-stimulated production of aldosterone.[233A] [233B] [233C]

Angiotensin II may also play a direct role in modifying the structure and function of the myocardium.[233D] In cardiac myocytes in culture, angiotensin caused cellular hypertrophy, the induction of fetal gene programs,[234] and apoptosis.[235] Angiotensin also appears to play a role in mediating the apoptotic effect of mechanical strain and is a potent stimulator of several signaling pathways,[236] including those involved in the regulation of the extracellular matrix.[124] [236A]

TISSUE RENIN-ANGIOTENSIN SYSTEM (RAS).

The major portion (90 to 99 percent) of ACE in the body is found in tissues, and only 1 to 10 percent is found in the circulation.[237] All of the necessary components of the RAS (Fig. 16-28) are likewise present in several organs and tissues, including the vasculature, heart, and kidneys. In myocardium from animals with experimental myocardial hypertrophy or failure, there is increased expression of ACE[238] and angiotensinogen,[239] the substrate for angiotensin I production by renin. It has been suggested that the tissue RAS may be activated during compensated heart failure at a time when activity of the circulating system can be relatively normal (Fig. 16-29) . The tissue production of angiotensin II may also occur by a pathway not dependent on ACE (the chymase pathway). This pathway may be of major importance in the myocardium,[240] particularly when the levels of renin and angiotensin I are increased by the use of ACE inhibitors. The density of ACE binding sites is increased in myocardium from patients with end-stage heart failure due to idiopathic cardiomyopathy.[241]

ANGIOTENSIN RECEPTORS.

The predominant angiotensin receptor in the vasculature is the angiotensin$_1$ subtype. In human myocardium it appears that both angiotensin$_1$ (AT_1) and angiotensin$_2$ (AT_2) receptor subtypes are present, and the AT_2 receptor predominates in a ratio of 2:1.[242] The number of AT_1 and AT_2 receptors is normal in patients with moderate heart failure but downregulated in patients with end-stage heart failure.[243] [243A] Downregulation of the AT_1 subtype has been observed in myocardium from patients

Figure 16-29 Relative roles of the circulating and tissue renin-angiotensin systems postulated in patients with heart failure. The tissue system may have alternative pathways for the production of angiotensin II that do not depend on converting enzyme (e.g., chymase) and that therefore are not suppressed by converting enzyme inhibitors. It has been proposed that activation of the tissue renin-angiotensin system may follow a different time course than that of the circulating system, particularly during the compensated

phase of heart failure when the circulating renin-angiotensin system may be relatively quiescent and during treatment with converting enzyme inhibitors that may increase the activity of the tissue system by elevating circulating renin levels. (Modified from Dzau VJ: Tissue renin-angiotensin system in myocardial hypertrophy and failure. Arch Intern Med 153:937, 1993. Copyright 1993, American Medical Association.)

with both ischemic and idiopathic dilated cardiomyopathy and associated with a decrease in the mRNA level for the receptor.[2]

ARGININE VASOPRESSIN

Arginine vasopressin (AVP) is a pituitary hormone that plays a central role in the regulation of free water clearance and plasma osmolality (see Fig. 16-23) . Circulating AVP is elevated in many patients with heart failure,[244] even after correction for plasma osmolality. Patients with acute heart failure secondary to massive myocardial infarction may have particularly elevated levels,[245] which are usually associated with elevated concentrations of catecholamines and renin. The plasma AVP concentration was significantly elevated in asymptomatic patients in the prevention arm of the SOLVD study and was elevated further in patients with symptomatic heart failure (see Fig. 16-24) . [174] Control of circulating AVP concentration is abnormal in patients with heart failure who fail to show the normal reduction of AVP with a reduction of osmolality. This may contribute to their inadequate ability to excrete free water and hence to the plasma hypoosmolarity in some patients with heart failure. Decreased sensitivity of atrial stretch receptors, which normally inhibit AVP release with atrial distention, may contribute to the elevation of circulating AVP. In addition, patients with heart failure exhibit failure of the normal suppression of AVP after administration of ethanol.[246]

Two types of AVP receptors (V_1 and V_2) have been identified in a variety of tissues. In dogs with pacing-induced heart failure, the selective inhibition of V_1 receptors increased cardiac output without affecting electrolytes or hormone levels.[247] In contrast, inhibition of V_2 receptors increased serum sodium concentration, plasma renin activity, and plasma AVP levels but did not affect hemodynamics. When the two inhibitors were combined, the hemodynamic effects were potentiated. These results suggest that, in addition to regulating free water clearance through the V_2 receptor, in heart failure AVP may contribute to systemic vasoconstriction through the V_1 receptor.

Natriuretic Peptides

Three natriuretic peptides--atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-natriuretic peptide (CNP)--have been identified in humans.[248] ANP is stored mainly in the right atrium and released in response to an increase in atrial distending pressure. This peptide causes vasodilation and natriuresis and counteracts the water-retaining effects of the adrenergic, renin-angiotensin, and AVP systems. BNP is stored mainly in cardiac ventricular myocardium and may be responsive--albeit less

so than ANP--to changes in ventricular filling pressures.[249] BNP has a high level of homology with ANP at the structural level and, like ANP, causes natriuresis and vasodilation. CNP is located primarily in the vasculature. Although the physiological role of CNP is not yet clarified, it appears that it may play an important regulatory role in juxtaposition to the RAS system. At least three receptors for natriuretic peptides (A, B, and C) have been identified.[248] The A and B receptors mediate the vasodilatory and natriuretic effects of the peptides. The C type receptor appears to act primarily as a clearance receptor, which, along with neutral endopeptidase, regulates available levels of the peptides.

Circulating levels of both ANP and BNP are elevated in the plasma of patients with heart failure.[250] In normal human hearts, ANP predominates in the atria, where there is also a low level of expression of BNP and CNP. In patients with heart failure, the atrial content of ANP is unchanged and the contents of BNP and CNP increase 10-fold and 2- to 3-fold, respectively. [250] [250A] In the SOLVD study, the level of plasma ANP was elevated even in asymptomatic patients and was further elevated in patients with symptoms (see Fig. 16-24) .[174] Although the atrial peptides are present only in very low levels in normal ventricular myocardium, in patients with heart failure all three peptides are markedly elevated,[250] and ventricular production contributes significantly to the circulating levels.[251] The secretion of ANP and BNP appears to be regulated mainly by wall tension. The N-terminal of the ANP free-hormone (N-terminal pro-ANP) has a longer half-life and greater stability than ANP and has been shown to be a powerful and independent predictor of cardiovascular mortality and the development of heart failure.[252] ANP levels normalize after cardiac transplantation.[253]

The hemodynamic and natriuretic responses to an infusion of ANP are attenuated in patients and experimental animals with heart failure.[254] However, studies using an ANP receptor antagonist in dogs with pacing-induced heart failure showed that, despite attenuated hemodynamic and renal effects, the peptide continues to exert an important suppressive effect on the activity of the RAS and NE levels.[255] One approach that attempts to capitalize on the beneficial effects of the natriuretic peptides is to inhibit their degradation through the use of neutral endopeptidase inhibitors. The infusion of the endopeptidase inhibitor candoxatrilat into patients with heart failure mimics the action of infused ANP; it causes a reduction in left- and right-sided heart filling pressures associated with suppression of plasma NE levels and a transient reduction in plasma vasopressin, aldosterone, and renin activity.[256] In addition to the beneficial effect of natriuretic peptides on neurohormones, renal function, and hemodynamics, there is evidence that the natriuretic peptides may directly inhibit myocyte and vascular smooth muscle hypertrophy and interstitial fibrosis.[257] [258]

Endothelin and Other Peptides

Endothelin is a potent peptide vasoconstrictor released by endothelial cells throughout the circulation. [259] , [260] Three endothelin peptides (endothelin-1, endothelin-2, and endothelin-3) have been identified, all of which are potent constrictors. At least two subtypes of endothelin receptors (types A and B) have been recognized. The release of endothelin from endothelial cells in vitro can be enhanced by several vasoactive agents (e.g., NE, angiotensin II, thrombin) and cytokines (e.g., TGF-beta and IL-1beta). Several

reports have documented an increase in circulating levels of endothelin-1 in patients with heart failure.[261] [262] [262A] Plasma endothelin correlates directly with pulmonary artery pressures and, in particular, the pulmonary vascular resistance and the resistance ratio of pulmonary vascular resistance to systemic resistance. This has led to the suggestion that endothelin plays a pathophysiological role in mediating pulmonary hypertension in patients with heart failure. In normal subjects, plasma endothelin levels increase with orthostatic stress. However, in heart failure patients, endothelin levels are already elevated and show no further increase with orthostatic stress, similar to the pattern of response seen with a variety of other vasoconstrictor substances, including angiotensin and NE.[262] Plasma endothelin levels have been shown to be increased in patients with acute myocardial infarction and to correlate with the Killip class in these patients.[263]

Antagonists of endothelin receptors are available and have been used to demonstrate the physiological effects of endothelin. When administered to rats with heart failure after myocardial infarction, the endothelin antagonist bosentan, which blocks both $endothelin_A$ and $endothelin_B$ receptors, decreased arterial pressure and had an additive effect to that of an ACE inhibitor.[264] In cultured cardiac myocytes, endothelin induces cellular hypertrophy associated with the induction of fetal genes.[265] In rats with pressure overload-induced hypertrophy caused by aortic banding, administration of the $endothelin_A$ receptor antagonist BQ123 transiently inhibited myocyte hypertrophy and prevented fetal gene induction.[266] In rats with myocardial infarction, chronic administration of endothelin antagonists resulted in a reduction in left ventricular chamber remodeling enlargement, improved hemodynamic function, and improved survival (Fig. 16-30) . [267] [268] [269] These observations suggest that endothelin receptor antagonists may be of value in both the acute and chronic treatment of patients with heart failure.[270] Administration of endothelin antagonists to patients has been shown to improve hemodynamic function,[271] [272] [273] but the long-term effects on disease progression and survival are not known.

Figure 16-30 Effect of the endothelin receptor antagonist bosentan on left ventricular remodeling 8 weeks after a myocardial infarction in the rat. The left ventricular diastolic pressure-volume relationship was shifted rightward after infarction indicative of chamber dilation. In rats with a large infarction, bosentan reduced the extent of rightward shift. (Modified from Fraccarollo D, Hu K, Galuppo P, et al: Chronic endothelin receptor blockade attenuates progressive ventricular dilation and improves cardiac function in rats with myocardial infarction: Possible involvement of myocardial endothelin system in ventricular remodeling. Circulation 96:3963-3973, 1998. Copyright 1998, American Heart Association.)

Several other peptides, including acidic fibroblast growth factor, basic fibroblast growth factor, TGF-beta1, and platelet-derived growth factor have been shown to affect the growth and phenotype of cardiac myocytes or fibroblasts in vitro.[274] The expression of these and other peptides is increased in myocardium after myocardial infarction[275] [276] [277] or with hemodynamic overload,[278] suggesting that they may play a role in the

orchestration of myocardial remodeling.

Inflammatory Cytokines, Including TNF-alpha (See also p. 461)

Inflammatory cytokines, including TNF-alpha and IL-1beta, may play an important role in the pathogenesis of myocardial failure.[278A] In vitro, these and other inflammatory cytokines can regulate growth and gene expression in cardiac myocytes and other cells present in the myocardium. The circulating levels of TNF-alpha and interleukin-6 (IL-6) are increased in patients with heart failure.[279] [280] The failing myocardium, itself, may be a source of inflammatory cytokines, which might thus be present in high local concentrations.[281]

Inflammatory cytokines have protean effects on the myocardium. TNF-alpha can induce immediate myocardial dysfunction and has been shown to attenuate intracellular calcium transients in vitro.[282] [283] [284] [284A] In cultured cardiac myocytes, TNF-alpha and IL-1beta can stimulate hypertrophy and re-expression of a fetal gene program,[285] [286] [287] and both can cause apoptosis,[61] [288] which may be mediated, in part, by NO.[61] [289] The chronic systemic infusion of TNF-alpha in rats resulted in left ventricular failure[290] (Fig. 16-31) , and mice that overexpress TNF-alpha in the myocardium developed a dilated cardiomyopathy that was associated with increased myocyte apoptosis.[291] [292] Pilot clinical trials with soluble TNF-alpha receptors that reduce the level of TNF-alpha available to the tissues have suggested that this may a feasible form of therapy for patients.[293]

Nitric Oxide

Two isoforms of nitric oxide synthase (NOS), termed NOS2 and NOS3, are expressed in human myocardium. NOS2 is an inducible isoform that is not normally expressed in the myocardium but is synthesized de novo in response to inflammatory cytokines, thereby causing high levels of NO production. The expression and activity of NOS2 are increased in myocardium obtained from patients with severe heart failure,[149] [294] possibly as a result of stimulation by inflammatory cytokines.

There are several ways that NO might affect the myocardium.[295] It has been shown that NO mediates the inhibitory effect of inflammatory cytokines on the contractile response to beta-adrenergic stimulation in cardiac myocytes and myocardium by the induction of NOS2.[296] [297] In normal subjects, the intracoronary infusion of nitroprusside, an NO donor, improved left ventricular distensibility,[298] whereas inhibition of NO synthesis by the intracoronary infusion of an NOS inhibitor potentiated the positive inotropic response to dobutamine in patients with left ventricular dysfunction.[299] As discussed earlier, NO may also act directly on myocytes to cause apoptosis[61] [289] or regulate phenotype.[300]

Oxidative Stress

There is evidence that oxidative stress is increased both systemically and in the myocardium of patients with heart failure.[23] [48] [301] [302] Increased oxidative stress may be due to reduced antioxidant capacity[23] or the increased production of reactive oxygen

species, which may be a consequence of mechanical strain on the myocardium[62] or stimulation by inflammatory cytokines. Reactive oxygen species can stimulate myocyte hypertrophy, reexpression of fetal gene programs, and apoptosis in cardiac myocytes in culture.[60] Mice with knockout of the antioxidant enzyme manganese superoxide dismutase (MnSOD) develop dilated cardiomyopathy and die at a young age.[303] Conversely, in animal models of hemodynamic overload-induced remodeling and failure, treatment with antioxidants prevented the progression to myocardial failure,[304] leading to the suggestion that antioxidants might be of therapeutic value in patients.

Figure 16-31 Transgenic mice that overexpress tumor necrosis factor-alpha in the heart developed a dilated cardiomyopathy that was associated with reduced survival. Survival was worst in a line of mice with the highest level of TNF-alpha expression, intermediate in mice with a lower level of TNF-alpha expression, and best in nontransgenic controls. (From Sawyer DB, Colucci WS: Molecular and cellular events in myocardial hypertrophy and failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction, Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, p 4.17.)

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Chapter 17 - Clinical Aspects of Heart Failure: High-Output Failure; Pulmonary Edema

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Definition

Heart failure is a principal complication of virtually all forms of heart disease. A panel of the National Heart, Lung and Blood Institute described this condition as follows:
Heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at a rate required by the metabolizing tissues or when the heart can do so only with an elevated filling pressure. The heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues may be due to insufficient or defective cardiac filling and/or impaired contraction and emptying. Compensatory mechanisms increase blood volume and raise cardiac filling pressures, heart rate, and cardiac muscle mass to maintain the heart's pumping function and cause redistribution of blood flow. Eventually, however, despite these compensatory mechanisms, the ability of the heart to contract and relax declines progressively, and the heart failure worsens.[1]

An alternative definition, which focuses more on the clinical consequences of heart

failure, has been offered by Packer: "Congestive heart failure (CHF) represents a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention, and reduced longevity."[2] Included in these two definitions is a wide spectrum of clinical and pathophysiological states, ranging from the rapid impairment of pumping function (occurring when, for example, a massive myocardial infarction suddenly develops) to the gradual but progressive impairment of myocardial function, observed at first only during stress in a patient whose heart sustains a pressure or volume overload for a prolonged period. *Myocardial failure,* a term used to denote abnormal systolic or diastolic function, may be asymptomatic or progress to heart failure. Circulatory failure is not synonymous with heart failure, because a variety of noncardiac conditions (e.g., hemorrhagic shock) can lead to circulatory collapse while cardiac function is preserved.

The clinical manifestations of heart failure vary enormously and depend on a variety of factors, including the age of the patient, the extent and rate at which cardiac performance becomes impaired, and the ventricle initially involved in the disease process. A broad spectrum of severity of impairment of cardiac function is ordinarily included within the definition of heart failure, ranging from the mildest, which is manifest clinically only during stress, to the most advanced form, in which cardiac pump function is unable to sustain life without external support.

Useful criteria for the diagnosis of heart failure emerged from the Framingham Study[3] (Table 17-1) .

TABLE 17-1 -- FRAMINGHAM CRITERIA FOR CONGESTIVE HEART FAILURE

Major Criteria
Paroxysmal nocturnal dyspnea
Neck vein distention
Rales
Radiographic cardiomegaly
Acute pulmonary edema
S_3 gallop
Central venous pressure>16 cm H_2 O
Circulation time 25 sec
Hepatojugular reflux
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy
Weight loss 4.5 kg in 5 days in response to treatment of congestive heart failure
Minor Criteria

Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Decrease in vital capacity by one third from maximal value recorded
Tachycardia (rate
120 beats/min)

The diagnosis of congestive heart failure in this study required that two major or one major and two minor criteria be present concurrently. Minor criteria were acceptable only if they could not be attributed to another medical condition.

From Ho KL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 22(Suppl A):6A, 1993.

Incidence and Prevalence

Heart failure is a relatively common disorder. It is estimated that 4.6 million persons in the United States are being treated for heart failure, with 550,000 new cases diagnosed each year.[4] [5] The prevalence of heart failure increases dramatically with age, occurring in 1 to 2 percent of persons aged 50 to 59 and up to 10 percent of individuals older than the age of 75 (Fig. 17-1) .[3] [5] Approximately 80 percent of all heart failure admissions occur in patients older than 65; as a result, heart failure is the leading discharge diagnosis in persons aged 65 years or older in the United States.[6] Despite a steady decline in the incidence of coronary artery disease and stroke, both the incidence and prevalence of heart failure continue to rise. Between 1985 and 1995 the number of heart failure hospitalizations increased by 51 percent,[7] and 870,000 hospital discharges for heart failure occurred in 1996.[4] In the United States, approximately 45,000 deaths each year are primarily caused by heart failure and heart failure is listed as a contributing cause in 260,000 deaths.[8] [9] This trend may be due in part to the aging of the population and in part to the improved survival of patients with cardiovascular disease. Heart failure has an enormous economic impact on the U.S. health care system, owing to direct medical costs, disability, and loss of employment. Estimated treatment costs in 1994 were $38 billion, of which $23 billion were spent on hospitalizations.[10] The cost of hospitalizations for heart failure is twice that for all forms of cancer and myocardial infarctions combined.[10]

Forms and Causes of Heart Failure

Forward Versus Backward Heart Failure

The clinical manifestations of heart failure arise as a consequence of inadequate cardiac output and/or damming up of blood behind one or both ventricles. These two

principal mechanisms are the basis of the so-called forward and backward pressure theories of heart failure. The *backward failure hypothesis,* first proposed in 1832 by James Hope, contends that when the ventricle fails to discharge its contents, blood accumulates and pressure rises in the atrium and the venous system emptying into it.[11] There is substantial physiological evidence in favor of this theory. As discussed in Chapters 14 and 15 , the inability of cardiac muscle to shorten against a load alters the relationship between ventricular end-systolic pressure and volume so that end-systolic volume rises. The following sequence then occurs, which at first maintains cardiac output at a normal level: (1) ventricular end-diastolic volume and pressure increase; (2) the volume and pressure rise in the atrium behind the failing ventricle; (3) the atrium contracts more vigorously (a manifestation of Starling's law, operating on the atrium)[12] ; (4) the pressure in the venous and capillary beds behind (upstream to) the failing ventricle rises; and (5) transudation of fluid from the capillary bed into the interstitial space (pulmonary or systemic) increases. Many of the symptoms characteristic of heart failure can be traced to this sequence of events and the resultant increase in fluid in the interstitial spaces of the lungs, liver, subcutaneous tissues, and serous cavities.

In many patients, the entire sequence of events just outlined may transpire while cardiac output *at rest* is still within normal limits. Indeed, the backward failure hypothesis invokes one of the principal compensatory mechanisms in heart failure, that is, Starling's law of the heart, in which distention of the ventricle helps to maintain cardiac output. The failing ventricle operates on an ascending, albeit depressed and flattened, function curve,[13] and the augmented ventricular

Figure 17-1 Prevalence rates of congestive heart failure (CHF) among Framingham Heart Study subjects, by gender and age. Among men (open bars), the prevalence increased from 8 cases/1000 in those aged 50-59 years to 66 cases/1000 in those aged 80-89 years. Among women (solid bars), the prevalence increased from 8 cases/1000 in those aged 50-59 years to 79 cases/1000 in those aged 80-89 years. (From Ho KK, et al: The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 22:6A, 1993.)

end-diastolic volume and pressure characteristic of heart failure may aid in the maintenance of cardiac output.

An important extension of the backward failure theory is the development of right ventricular failure as a consequence of left ventricular failure. According to this concept, the elevation of left ventricular diastolic, left atrial, and pulmonary venous pressures results in backward transmission of pressure into the pulmonary arterial circulation and leads to pulmonary hypertension, which ultimately causes right ventricular failure. Often, pulmonary vasoconstriction plays a part in this form of pulmonary hypertension as well.

Eighty years after publication of Hope's work, Mackenzie proposed the *forward failure hypothesis,* which relates clinical manifestations of heart failure to inadequate delivery of blood into the arterial system.[14] According to this hypothesis, the principal clinical manifestations of heart failure are due to reduced cardiac output, which results in diminished perfusion of vital organs, including the brain, leading to mental confusion; skeletal muscles, leading to weakness; and kidneys, leading to sodium and water

retention through a series of complex neurohormonal mechanisms.[15] This retention of sodium and water, in turn, augments extracellular fluid volume and ultimately leads to symptoms of heart failure due to congestion of organs and tissues.

Although these two seemingly opposing views concerning the pathogenesis of heart failure led to lively controversy during the first half of the 20th century, it no longer seems fruitful to make a rigid distinction between backward and forward heart failure, because *both* mechanisms appear to operate in the majority of patients with chronic heart failure. Exceptions may occur, however, and some patients, particularly those with *acute* decompensation, develop relatively pure forms of forward or backward failure. For instance, a massive myocardial infarction may result in either (1) forward failure with a marked reduction of left ventricular output and cardiogenic shock and clinical manifestations secondary to impaired perfusion (e.g., hypotension,

mental confusion, oliguria) or (2) backward failure with a small transient inequality of output between the two ventricles, resulting in acute pulmonary edema. More commonly, patients with large myocardial infarctions develop a combination of forward and backward failure, with symptoms resulting from both inadequate cardiac output and pulmonary congestion.

RIGHT-SIDED VERSUS LEFT-SIDED HEART FAILURE

Implicit in the backward failure theory is the idea that fluid localizes behind the specific cardiac chamber that is *initially* affected. Thus, symptoms secondary to pulmonary congestion initially predominate in patients with left ventricular infarction, hypertension, or aortic or mitral valve disease; that is, they manifest *left-sided heart failure.* With time, however, fluid accumulation becomes generalized, and ankle edema, congestive hepatomegaly, ascites, and pleural effusion occur; thus, the patients subsequently exhibit *right-sided heart failure* as well.

FLUID RETENTION IN HEART FAILURE.

Fluid retention in heart failure is caused in part by reduction in glomerular filtration rate and in part by activation of the renin-angiotensin-aldosterone system. Reduced cardiac output is associated with a lowered glomerular filtration rate and an increased elaboration of renin, which, through the activation of angiotensin, results in the release of aldosterone (see Chap. 16). The combination of impaired hepatic function, owing to hepatic venous congestion, and reduced hepatic blood flow, interferes with the metabolism of aldosterone, further raising its plasma concentration and augmenting the retention of sodium and water.

Cardiac output (and glomerular filtration rate) may be normal in many patients with heart failure, particularly when they are at rest. However, during stress, such as physical exercise or fever, the cardiac output fails to rise normally, the glomerular filtration rate

declines, and the renal mechanisms for salt and water retention described earlier come into play. In addition, ventricular filling pressure and therefore pressures in the atrium and systemic veins behind (upstream to) the ventricle may be normal at rest, only to rise abnormally during stress. This, in turn, may cause transudation and symptoms of tissue congestion (pulmonary in the case of the left ventricle and systemic in the case of the right) during exercise. For this reason, simple rest may induce diuresis and relieve symptoms in many patients with mild-to-moderate heart failure.

ACUTE VERSUS CHRONIC HEART FAILURE

The clinical manifestations of heart failure depend importantly on the *rate* at which the syndrome develops and specifically on whether sufficient time has elapsed for compensatory mechanisms to become operative and for fluid to accumulate in the interstitial space (Table 17-2) . For example, when a previously normal individual suddenly develops a serious anatomical or functional abnormality of the heart, such as massive myocardial infarction, tachyarrhythmia with a very rapid rate, or rupture of a valve secondary to infective endocarditis, a marked reduction in cardiac output will occur, associated with symptoms due to inadequate organ perfusion and/or acute congestion of the venous bed behind the affected ventricle. If the same anatomical abnormality develops gradually, or if the patient survives the acute insult, a number of adaptive mechanisms become operational, especially cardiac remodeling and neurohormonal activation, and these allow the patient to adjust to and tolerate not only the anatomical abnormality but also a reduction in cardiac output with less difficulty.

LOW-OUTPUT VERSUS HIGH-OUTPUT HEART FAILURE

Low cardiac output at rest, or in milder cases during exertion and other stresses, characterizes heart failure occurring in most forms of cardiovascular disease (i.e., congenital, valvular, rheumatic, hypertensive, coronary, and cardiomyopathic). A variety of high cardiac output states, including thyrotoxicosis, arteriovenous fistulas, beriberi, Paget's disease of bone, and anemia (discussed later in this chapter), may lead to heart failure as well. Low-output heart failure is characterized by clinical evidence of systemic vasoconstriction with cold, pale, and sometimes cyanotic extremities. In advanced forms of low-output failure, marked reduction in the stroke volume is reflected by a narrowing of the pulse pressure.[16] In contrast, in high-output heart failure, the extremities are usually warm and flushed and the pulse pressure is widened or at least normal.

The ability of the heart to deliver the oxygen required by the metabolizing tissues is reflected in the arterial-mixed venous oxygen difference, which is abnormally widened (i.e., >50 ml/liter in the resting state) in patients with low-output heart failure. This difference may be normal or even reduced in high-output states, owing to elevation of the mixed venous oxygen saturation by the admixture of blood that has been shunted away from metabolizing tissues.

Systolic Versus Diastolic Heart Failure

Implicit in the physiological definition of heart failure (inability to pump an adequate

volume of blood and/or to do so only from an abnormally elevated filling pressure) is that heart failure can be caused by an abnormality in systolic function leading to a defect in the expulsion of blood (i.e., *systolic heart failure*) or by an abnormality in diastolic function leading to a defect in ventricular filling (i.e., *diastolic heart failure*) (Fig. 17-2) . The former is the more familiar, classic heart failure associated with an impaired inotropic state. Less familiar, but perhaps just as important, is diastolic heart failure, in which the ability of the ventricle(s) to accept blood is impaired.[17] [18] [18A] (See also pp. 456, 493, and 517.) This may be due to slowed or incomplete ventricular relaxation, which may be transient, as occurs in acute ischemia, or sustained, as in concentric myocardial hypertrophy or restrictive cardiomyopathy secondary to infiltrative conditions such as amyloidosis. The principal clinical manifestations of systolic failure result from an inadequate cardiac output and secondary salt and water retention (forward heart failure), whereas the major consequences of diastolic failure relate to elevation of the ventricular filling pressure, and the high venous pressure upstream to the ventricle, causing pulmonary and/or systemic congestion (backward heart failure).

TABLE 17-2 -- ACUTE VS. CHRONIC HEART FAILURE

FEATURE	ACUTE HEART FAILURE	DECOMPENSATED CHRONIC HEART FAILURE	CHRONIC HEART FAILURE
Symptom severity	Marked	Marked	Mild to moderate
Pulmonary edema	Frequent	Frequent	Rare
Peripheral edema	Rare	Frequent	Frequent
Weight gain	None to mild	Frequent	Frequent
Whole-body fluid volume load	No change or mild increase	Moderate to marked increase	Mild to marked increase
Cardiomegaly	Uncommon	Usual*	Common*
Ventricular systolic function	Reduced, normal, or hypercontractile	Reduced*	Reduced*
Wall stress	Elevated	Markedly elevated	Elevated
Activation of sympathetic nervous system	Marked	Marked	Mild to marked
Activation of renin-angiotensin-aldosterone system	Often increased	Marked	Mild to marked
Reparable, reversible causative lesion(s)	Common	Occasional	Occasional

Clinical and pathophysiological characteristics of the two major categories of unstable heart failure (acute heart failure and decompensated chronic heart failure) are compared with those of chronic heart failure.

Adapted from Leier CV: Unstable heart failure. In Colucci WS (ed): Heart Failure: Cardiac Function and Dysfunction. 2nd ed. In Braunwald E (series ed): Atlas of Heart Diseases, vol 4. Philadelphia, Current Medicine, 1999, pp 9.1-9.17.

*Patients with diastolic heart failure may have little to no cardiomegaly and normal systolic function.

Figure 17-2 *A,* Schematic of a pressure-volume loop from a normal subject (dotted line) and a patient with diastolic dysfunction (solid line). Dashed lines represent the diastolic pressure-volume relation. Isolated diastolic dysfunction is characterized by a shift in the pressure-volume loop to the left. Contractile performance is normal (normal or increased ejection fraction, normal or slightly decreased stroke volume). However, left ventricular (LV) pressures throughout diastole are increased: at a common diastolic volume=70 ml/m[2] , LV diastolic pressure is 25 mm Hg in the patient with diastolic failure compared with a diastolic pressure of 5 mm Hg in the normal subject. *B,* Schematic of pressure-volume loop from a normal subject (dotted line) and a patient with systolic dysfunction (solid line). Dashed line represents the diastolic pressure-volume relation. Systolic dysfunction is characterized by displacement of the pressure-volume loop to the right. Despite compensatory dilation, stroke volume or ejection fraction remains low. LV diastolic pressures are increased as a result of large LV volume. (From Zile MR: Diastolic dysfunction: Detection, consequences, and treatment: II. Diagnosis and treatment of diastolic dysfunction. Mod Concepts Cardiovasc Dis 59:1, 1990.)

There are many examples of pure systolic or diastolic heart failure. Examples of the former are patients with acute massive myocardial infarction or pulmonary embolism, whereas examples of the latter are patients with hypertrophic or restrictive cardiomyopathy. Community-based, epidemiological studies have demonstrated that diastolic heart failure is more common than was previously thought and is particularly prevalent in elderly women with hypertension.[19] [20] However, in many patients, systolic and diastolic heart failure coexist. The most common form of heart failure, that caused by chronic coronary artery disease, is an example of combined systolic and diastolic failure. In this condition, systolic failure is caused by both the chronic loss of contracting myocardium secondary to prior myocardial infarction and the acute loss of myocardial contractility induced by transient ischemia. Diastolic failure is due to the ventricle's reduced compliance caused by replacement of normal, distensible myocardium with nondistensible fibrous scar tissue and by the acute reduction of diastolic distensibility during ischemia. A number of clinical features and laboratory findings characterize these two forms of heart failure (Table 17-3) . However, it is important to recognize that the clinical features of heart failure may be similar whether left ventricular systolic function is normal or depressed,[20] [21] underscoring the need for evaluation of ventricular function in all patients with heart failure.

CAUSES OF HEART FAILURE

From a clinical viewpoint, it is useful to classify the causes of heart failure into three broad categories: (1) *underlying causes,* comprising the structural abnormalities--congenital or acquired--that affect the peripheral and coronary vessels, pericardium, myocardium, or cardiac valves and lead to the increased hemodynamic burden or myocardial or coronary insufficiency responsible for heart failure; (2) *fundamental causes,* comprising the biochemical and physiological mechanisms through which either an increased hemodynamic burden or a reduction in oxygen delivery to the myocardium results in impairment of myocardial contraction (see Chap. 16 ;) and (3) *precipitating causes,* including the specific causes or incidents that precipitate heart failure in 50 to 90 percent of episodes of clinical heart failure.[22]

It is helpful for the clinician to identify both the underlying and the precipitating causes of heart failure. Appropriate management of the underlying heart disease (e.g., surgical correction of a congenital defect or an acquired valvular abnormality or pharmacological management of hypertension) may prevent the development or recurrence of heart failure. Similarly, treatment of a precipitating cause such as an infection will often terminate an episode of heart failure and may be lifesaving. More important, *avoidance* of a precipitating cause can *prevent* heart failure.

TABLE 17-3 -- SYSTOLIC VS. DIASTOLIC HEART FAILURE

PARAMETERS	SYSTOLIC	DIASTOLIC
History		
Coronary artery disease	+++	++
Hypertension	++	++++
Diabetes	++	++
Valvular heart disease	++++	-
Paroxysmal dyspnea	++	+++
Physical Examination		
Cardiomegaly	+++	+
Soft heart sounds	++++	+
S_3 gallop	+++	+
S_4 gallop	+	+++
Hypertension	++	++++

Mitral regurgitation	+++	+
Rales	++	++
Edema	+++	+
Jugular venous distention	+++	+
Chest Roentgenogram		
Cardiomegaly	+++	+
Pulmonary congestion	+++	+++
Electrocardiogram		
Left ventricular hypertrophy	++	++++
Q waves	++	+
Low voltage	+++	-
Echocardiogram		
Left ventricular hypertrophy	++	++++
Left ventricular dilation	++	-
Left atrial enlargement	++	++
Reduced ejection fraction	++++	-

Certain aspects of the history and physical examination, along with clinical measurements, may help to distinguish diastolic dysfunction from systolic heart failure. For example, patients with hypertensive heart disease, and particularly severe left ventricular hypertrophy, often experience heart failure because of diastolic dysfunction.

Plus signs indicate "suggestive" (the number reflects relative weight). *Minus signs* indicate "not very suggestive."*Adapted from Young JB: Assessment of heart failure. In Colucci WS (ed): Heart Failure: Cardiac Function and Dysfunction. 2nd ed. In Braunwald E (series ed): Atlas of Heart Diseases, vol 4. Philadelphia, Current Medicine, 1999, pp 7.1-7.19.*

Overt heart failure may also be precipitated by the progression of the underlying heart disease. A previously stable, compensated patient may develop heart failure that is apparent clinically for the first time when the intrinsic process has advanced to a critical point, such as with further narrowing of a stenotic aortic valve or progressive obliteration of the pulmonary vascular bed in a patient with cor pulmonale. Alternatively, decompensation may occur as a result of failure or exhaustion of the compensatory mechanisms, but without any change in the load on the heart, in patients with chronic severe pressure or volume overload.

Precipitating Causes of Heart Failure

In one study of 101 patients admitted to an inner city municipal hospital with the

diagnosis of heart failure, precipitating factors could be identified in 93 percent.[23]

INAPPROPRIATE REDUCTION OF THERAPY.

Perhaps the most common cause of decompensation in a previously compensated patient with heart failure is inappropriate reduction in the intensity of treatment, be it dietary sodium and fluid restriction, pharmacological therapy, or both. Many patients with serious underlying heart disease, regardless of whether they have previously experienced heart failure, may be relatively asymptomatic for as long as they carefully adhere to their treatment regimen. Dietary excesses of sodium, incurred frequently on vacations or holidays or during an illness of the spouse responsible for preparing the patient's meals, are frequent causes of rapid cardiac decompensation. Education of the patient and family is a simple and effective measure to prevent this common clinical problem. Self-discontinuation or physician withdrawal of effective pharmacotherapy such as angiotensin-converting enzyme (ACE) inhibitors or digoxin can precipitate heart failure.[24]

ARRHYTHMIAS.

Cardiac arrhythmias are common in patients with underlying structural heart disease and commonly precipitate or intensify heart failure. The development of arrhythmias may precipitate heart failure through several mechanisms:

1. *Tachyarrhythmias,* most commonly atrial fibrillation, reduce the time available for ventricular filling. When there is already an impairment of ventricular filling, as in mitral stenosis, or reduced ventricular compliance, as in left ventricular hypertrophy, tachycardia will raise atrial pressure and reduce cardiac output further. In addition, tachyarrhythmias increase myocardial oxygen demands and, in a patient with obstructive coronary artery disease, may induce or intensify myocardial ischemia. This, in turn, impairs both diastolic and systolic function, thereby raising left atrial and pulmonary capillary pressure further and causing pulmonary congestion. Tachycardia may also directly impair contractility in failing human myocardium, owing in part to a negative force-frequency relationship[25] (see Chap. 14), and, if persistent, may cause a reversible dilated cardiomyopathy.[26]
2. *Marked bradycardia* in a patient with underlying heart disease usually depresses cardiac output, because stroke volume may already be maximal and cannot rise farther to maintain cardiac output.
3. *Dissociation between atrial and ventricular contraction,* which occurs in many arrhythmias, results in loss of the atrial booster pump mechanism, which impairs ventricular filling, lowers cardiac output, and raises atrial pressure.[12] This loss is particularly deleterious in patients with impaired ventricular filling due to concentric cardiac hypertrophy (e.g., in systemic hypertension, aortic stenosis, and hypertrophic cardiomyopathy).
4. *Abnormal intraventricular conduction,* which occurs in many arrhythmias such as ventricular tachycardia, impairs myocardial performance because of loss of the normal synchronicity of ventricular contraction. In addition to precipitating heart

failure, arrhythmias (sometimes fatal) may be *caused* by heart failure.[27]

MYOCARDIAL ISCHEMIA OR INFARCTION.

In patients with obstructive coronary artery disease, acute myocardial infarction (see Chap. 35), unstable angina (see Chap. 36), or silent ischemia (see Chap. 37) can precipitate heart failure. Reduced myocardial oxygen delivery may be exacerbated by the increase in myocardial oxygen demand resulting from tachycardia and hypertension. Mitral regurgitation due to ischemic papillary muscle dysfunction may contribute to heart failure and lead to acute pulmonary edema.

SYSTEMIC INFECTION.

Any serious infection may precipitate cardiac failure. The mechanisms include increased total body metabolism as a consequence of fever, discomfort, and cough, which increase the hemodynamic burden on the heart; the accompanying sinus tachycardia plays an additional adverse role. Patients with congestive heart failure are particularly susceptible to pulmonary infections, presumably because of the diminished ability of congested lungs to expel respiratory secretions. Furthermore, it is postulated that increased circulating levels of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-1beta, which impair myocardial function in sepsis,[28] may precipitate heart failure in the setting of non-life-threatening bacterial or viral infections.[29] [29A]

PULMONARY EMBOLISM (see also Chap. 52).

Patients with heart failure, particularly when obese or confined to bed, are at high risk of developing pulmonary emboli. Such emboli may increase the hemodynamic burden on the right ventricle by elevating pulmonary artery pressure and pulmonary vascular resistance further and may cause fever, tachypnea, hypoxemia, and tachycardia, the deleterious effects of which have already been discussed. Congestive heart failure, when present in patients with acute pulmonary embolism, is a strong independent predictor of both short-term[30] and long-term[31] mortality.

PHYSICAL, EMOTIONAL, AND ENVIRONMENTAL STRESS.

Intense, prolonged exertion or severe fatigue, such as may result from prolonged travel or emotional crises, and a severe climatic change (e.g., to a hot, humid environment) are relatively common precipitants of cardiac decompensation.

CARDIAC INFECTION AND INFLAMMATION.

Myocarditis as a consequence of a variety of inflammatory, allergic, or infectious processes, including viral myocarditis (see Chap. 48), or of infective endocarditis (see Chap. 47) may impair myocardial function directly and exacerbate existing heart disease. The anemia, fever, and tachycardia that frequently accompany these

processes are also deleterious. In patients with infective endocarditis, additional valvular damage resulting, for example, in marked aortic or mitral regurgitation may also precipitate cardiac decompensation.

DEVELOPMENT OF AN UNRELATED ILLNESS.

Heart failure may be precipitated in patients with compensated cardiovascular disease when an unrelated illness develops. For example, the development of acute or acute-on-chronic renal failure[31A] may further impair the ability of patients with heart failure to excrete sodium and thus may exacerbate fluid retention (see Chap. 72). Similarly, blood transfusion or the administration of sodium-containing fluid during and after a noncardiac operation may result in sudden heart failure in patients with underlying heart disease.

ADMINISTRATION OF CARDIAC DEPRESSANTS OR SALT-RETAINING DRUGS.

A number of drugs depress myocardial function; among these are beta-adrenergic antagonists, nondihydropyridine calcium antagonists (verapamil and diltiazem), many antiarrhythmic agents, inhalation and intravenous anesthetics (see Chap. 61), and antineoplastic drugs such as doxorubicin and cyclophosphamide (see Chap. 69). Others, such as estrogens, corticosteroids, and nonsteroidal antiinflammatory agents,[31B] may cause salt and water retention. Any of these drugs, when administered to a patient with already impaired cardiac function, can precipitate or aggravate heart failure.

CARDIAC TOXINS.

Alcohol is a potent myocardial depressant and may be responsible for the development of cardiomyopathy (see Chap. 48), arrhythmias, and sudden death.[32] In patients with asymptomatic or mildly symptomatic left ventricular dysfunction, excessive alcohol consumption may precipitate heart failure, either directly by an acute depression of myocardial contractility[33] or indirectly through the development of tachyarrhythmias, most commonly atrial fibrillation,[34] or thiamine deficiency. Illicit use of cocaine may precipitate acute heart failure by a number of mechanisms, including myocardial ischemia or infarction,[35] severe hypertension, arrhythmias, myocarditis, or, in the case of injection drug users, acute infective endocarditis (see Chap. 47).

HIGH-OUTPUT STATES.

Acute heart failure may be precipitated in patients with underlying heart disease, such as valvular heart disease, by the development of one of the hyperkinetic circulatory states, such as pregnancy or anemia (see later in this chapter).

DEVELOPMENT OF A SECOND FORM OF HEART DISEASE.

Patients with one form of heart disease often remain compensated until they develop a second form. For example, a patient with chronic hypertension and left ventricular hypertrophy but without left ventricular failure may be asymptomatic until a myocardial infarction (which may be silent) develops and precipitates heart failure. Alternatively, a patient with chronic, well-compensated mitral regurgitation may develop heart failure secondary to uncontrolled hypertension or superimposed infective endocarditis.

It is essential to search for these precipitating causes systematically in all patients with congestive heart failure, because lack of recognition or treatment or both may be responsible for refractory or recurrent heart failure. In most instances, the precipitant can be treated effectively, after which appropriate measures should be instituted to avoid recurrence. When a precipitating cause of heart failure can be identified, it generally signifies a better prognosis than when a similar degree of heart failure is due simply to progression of the underlying cardiac disease.

SYMPTOMS OF HEART FAILURE

Respiratory Distress

Breathlessness, a cardinal manifestation of left ventricular failure, may present with progressively increasing severity as (1) exertional dyspnea, (2) orthopnea, (3) paroxysmal nocturnal dyspnea, (4) dyspnea at rest, and (5) acute pulmonary edema.

EXERTIONAL DYSPNEA (see Chap. 3).

The principal difference between exertional dyspnea in normal subjects and in patients with heart failure is the degree of activity necessary to induce the symptom.[36] Indeed, as heart failure first develops, exertional dyspnea may simply appear to be an aggravation of the breathlessness that occurs in normal subjects during activity. An effort should be made to ascertain whether a *change* in the extent of exertion that causes dyspnea has actually occurred. As left ventricular failure advances, the intensity of exercise resulting in breathlessness declines progressively. However, there is no close correlation between subjective exercise capacity and objective measures of left ventricular performance at rest in patients with heart failure.[37] [38] Also, exertional dyspnea may be absent in patients with heart failure who are sedentary for a variety of reasons, such as habit, severe angina, intermittent claudication, or a noncardiovascular condition (e.g., osteoarthritis).

ORTHOPNEA.

This symptom may be defined as dyspnea that develops in the recumbent position and is relieved by elevation of the head with pillows. As in the case of exertional dyspnea, it is a *change* in the number of pillows required that is important. In the recumbent position

there is reduced pooling of fluid in the lower extremities and abdomen; blood is displaced from the extrathoracic to the thoracic compartment. The failing left ventricle cannot accept and pump out the extra blood volume delivered to it by the competent right ventricle without dilating. Pulmonary venous and capillary pressures rise further, causing interstitial pulmonary edema, reduced pulmonary compliance, increased airway resistance, and dyspnea. In contrast to paroxysmal nocturnal dyspnea (see later), orthopnea occurs rapidly, often within a minute or two of assuming recumbency and develops when the patient is awake. It is a nonspecific symptom and may occur in *any* condition in which vital capacity is low. Marked ascites, for example, whatever its cause, may cause orthopnea. Likewise, a large pleural effusion of any etiology may cause a sensation of breathlessness on lying down. Patients with severe chronic obstructive lung disease sometimes complain of orthopnea. *Trepopnea* is a rare form of orthopnea limited to one lateral decubitus position. It has been attributed to distortions of the great vessels in one position but not in the other.

The patient with orthopnea generally elevates his or her head and chest on several pillows to prevent nocturnal breathlessness and subsequently the development of paroxysmal nocturnal dyspnea. In advanced left ventricular failure, orthopnea may be so severe that the patient cannot lie down and must spend the night in the sitting position. Often such patients are observed sitting at the side of the bed, slumped over a bedside table, or sleeping upright in a chair.

COUGH.

This may be caused by pulmonary congestion, occurs under the same circumstances as dyspnea (i.e., during exertion or recumbency), and is relieved by treatment of heart failure. Thus a nonproductive cough in patients with heart failure is often a "dyspnea equivalent," whereas a cough on recumbency may be considered an "orthopnea equivalent." If cough does not improve with diuresis, other common causes to consider in patients with heart failure include cough due to concomitant pulmonary disease (see later) and cough related to angiotensin-converting enzyme inhibitors.[39]

PAROXYSMAL NOCTURNAL DYSPNEA.

Attacks of paroxysmal dyspnea usually occur at night. The patient awakens, often quite suddenly, and with a feeling of severe anxiety and suffocation, sits bolt upright and gasps for breath. Bronchospasm, which may be caused by congestion of the bronchial mucosa and by interstitial pulmonary edema compressing the small airways, increases ventilatory difficulty and the work of breathing and is a common complicating factor. The associated wheezing is responsible for the alternate name of this condition, *cardiac asthma.* In contrast to orthopnea, which may be relieved immediately by sitting upright at the side of the bed with the legs dependent, attacks of paroxysmal nocturnal dyspnea may require 30 minutes or longer in this position for relief. Episodes of paroxysmal nocturnal dyspnea may be so frightening that the patient may be afraid to go back to sleep, even after the symptoms have abated.

The reason for the common occurrence of these episodes at night is not clear, but it seems likely that the combination of (1) the slow resorption of interstitial fluid from the

dependent portion of the body and the resultant expansion of thoracic blood volume, (2) elevation of thoracic blood volume and of the diaphragm that occurs immediately on assuming recumbency (as described earlier for orthopnea), (3) reduced adrenergic support of left ventricular function during sleep, and (4) normal nocturnal depression of the respiratory center all play major roles. Paroxysmal nocturnal dyspnea is a common clinical feature associated with Cheyne-Stokes respiration in patients with heart failure (see later).[40]

TABLE 17-4 -- MECHANISMS OF DYSPNEA IN HEART FAILURE

Decreased Pulmonary Function
Decreased compliance Increased airway resistance
Increased Ventilatory Drive
Hypoxemia: PCW
dot(V)/dot(Q) mismatch: PCW, CO Increased CO_2 production:
CO, lactic acidosis
Respiratory Muscle Dysfunction
Decreased strength Decreased endurance Ischemia

PCW=mean pulmonary capillary wedge pressure;dot(V)/dot(Q) Q=ventilation/perfusion; CO=cardiac output; CO_2 =carbon dioxide.

Adapted from Mancini DM: Pulmonary factors limiting exercise capacity in patients with heart failure. Prog Cardiovasc Dis 37:347, 1995.

MECHANISMS OF DYSPNEA (Table 17-4)

Increased awareness of respiration or difficulty in breathing is commonly associated with pulmonary capillary hypertension caused by an elevation of left atrial or left ventricular filling pressure.[36] Patients with left ventricular failure typically exhibit a restrictive ventilatory defect, characterized by a reduction of vital capacity as a consequence of the replacement of the air in the lungs with blood or interstitial fluid or both. Consequently, the lungs become stiffer, air trapping occurs because of earlier than normal closure of dependent airways, and the work of breathing is increased because

higher intrapleural pressures are needed to distend the stiff lungs.[41] Tidal volume is reduced, and respiratory frequency rises in a compensatory fashion. Engorgement of blood vessels may reduce the caliber of the peripheral airways, increasing airway resistance. In addition, there are alterations in the distribution of ventilation and perfusion, resulting in widened alveolar-arterial differences for oxygen, hypoxemia, and an increased ratio of dead space to tidal volume. Thus, dyspnea and orthopnea in heart failure are clinical expressions of pulmonary venous and capillary congestion. Paroxysmal nocturnal dyspnea reflects the presence primarily of *interstitial* edema, whereas pulmonary edema, in which there is transudation and expectoration of blood-tinged fluid (see p. 553), is often a manifestation of *alveolar* edema.

Whatever abnormalities in mechanics and gas exchange function of the lung exist at rest, they are aggravated during exercise (and sometimes during recumbency) when pulmonary venous and capillary pressures rise further. Transudation of fluid from the intravascular to the extravascular space results in greater stiffening of the lungs, an augmentation in the work of breathing, and increased resistance to air flow.[41] There is an increased ventilatory drive, as a consequence of the stimulation of stretch receptors in the pulmonary vessels and interstitium, as well as of hypoxemia and metabolic acidosis. The increased work of breathing, combined with a low cardiac output and resulting impaired perfusion of the respiratory muscles, causes fatigue and ultimately the sensation of dyspnea.[42] [43]

Dyspnea occurs whenever the work of respiration is excessive. Increased force generation is required for the respiratory muscles to move a given volume of air if the compliance of the lungs is reduced or the resistance to air flow is increased[44] [45] ; both of these changes occur in left-sided heart failure. Dyspnea at rest also may occur in the late stages of heart failure when very low cardiac output, hypoxemia, and acidosis combine to reduce the delivery of oxygen to the respiratory muscle.[42] [45] Dyspnea may occur *without* pulmonary congestion in patients with right ventricular failure, a fixed low cardiac output, and/or a right-to-left shunt.

Differentiation Between Cardiac and Pulmonary Dyspnea

In most patients with dyspnea there is obvious clinical evidence of disease of either the heart *or* the lungs, but in some the differentiation between cardiac and pulmonary dyspnea may be difficult.[36] Like patients with heart failure, those with chronic obstructive pulmonary disease also may awaken at night with dyspnea, but this is usually associated with sputum production; the dyspnea is relieved after patients rid themselves of secretions by coughing rather than specifically by sitting up. When the dyspnea arises after a history of intensified cough and expectoration, it is usually primarily pulmonary in origin. *Acute cardiac asthma* (paroxysmal nocturnal dyspnea with prominent wheezing) usually occurs in patients who have obvious clinical evidence of heart disease and may be further differentiated from acute bronchial asthma by diaphoresis and bubblier airway sounds and the more common occurrence of cyanosis.

The difficulty in distinguishing between cardiac and pulmonary dyspnea may be compounded by the coexistence of diseases involving both organ systems. Thus, patients with a history of chronic bronchitis or asthma who develop left ventricular failure

tend to develop particularly severe bronchoconstriction and wheezing in association with bouts of paroxysmal nocturnal dyspnea and pulmonary edema. Airway obstruction and dyspnea that respond to bronchodilators or smoking cessation favor a pulmonary origin of the dyspnea, whereas symptomatic improvement with diuretics and/or nitrates supports heart failure as the cause of dyspnea. Dyspnea that persists despite appropriate cardiovascular or respiratory pharmacotherapy may be related to psychosocial factors (e.g., anxiety, emotional stress).[46]

PULMONARY FUNCTION TESTING.

This should be carried out in patients in whom the etiology of dyspnea is unclear despite detailed clinical evaluation. The major alterations in pulmonary function tests in heart failure are reductions of vital capacity, total lung capacity, pulmonary diffusion capacity, and pulmonary compliance; resistance to air flow is moderately increased; residual volume and functional residual volume are normal. Often there is hyperventilation at rest and during exercise, an increase in dead space, and some abnormalities of ventilation-perfusion relations with slight reductions in arterial Pco_2 and Po_2 . With pulmonary capillary hypertension, pulmonary compliance decreases and there is air trapping because of earlier than normal closure of dependent airways. The airway resistance rises,[47] as does the work of breathing.

Rarely, it may be difficult, on clinical examination, to differentiate among cardiac dyspnea, dyspnea based on *malingering,* and dyspnea caused by *anxiety.*[46] Careful observation for the appearance of effortless or irregular respiration during exercise testing often helps to identify the patient in whom dyspnea is related to the latter two noncardiac causes. Patients whose anxiety focuses on the heart may exhibit sighing respiration and difficulty in taking a deep breath as well as dyspnea at rest. Their breathing patterns are not rapid and shallow, as in cardiac dyspnea. Rarely a "therapeutic test" is helpful, and amelioration of dyspnea, accompanied by a weight loss exceeding 2 kg induced by administration of a diuretic, supports a cardiac origin for the dyspnea. Conversely, failure of these measures to achieve such weight reduction and to diminish dyspnea weighs heavily against a cardiac origin.

Reduced Exercise Capacity

MECHANISMS OF EXERCISE INTOLERANCE.

A nearly universal manifestation of heart failure is a reduction in exercise capacity.[48] Although exercise capacity may be limited for a variety of reasons in patients with heart failure, the most common causes are the development of dyspnea due to pulmonary vascular congestion and the failure of the cardiovascular system to provide sufficient blood flow to exercising muscles. The latter reflects primarily an inadequate cardiac output response to exercise due to reductions in stroke volume and heart rate.[49] [50] [51] In addition to the impaired central hemodynamic response to exercise, a number of other factors may contribute to reduced exercise capacity in patients with heart failure, including an attenuated peripheral vascular response,[52] [53] [54] abnormal skeletal muscle metabolism,[55] deconditioning of skeletal and respiratory muscles,[41] [55] [56] and patient

anxiety related to the development of exertional symptoms. A recent study demonstrated a rapid improvement in the peripheral vascular response to exercise after intensive, hemodynamically guided therapy.[54] There is evidence that the judicious use

of cardiac rehabilitation can improve functional capacity, quality of life, and outcomes in patients with heart failure,[57] [58] possibly by improving autonomic control of the circulation and peripheral muscle blood flow,[58A] reversing abnormalities of skeletal muscle metabolism, and improving patients' perceptions of their quality of life and symptom severity[59] (see also Chap. 39).

Exercise Testing (See also Chap. 6.)

MAXIMAL EXERCISE CAPACITY.

Exercise stress testing may be an exceedingly useful adjunct in the *clinical assessment* of patients with suspected or known heart failure.[48] [60] With use of a bicycle ergometer or treadmill and a progressively increasing load, the maximum level of exercise that can be achieved can be determined; the latter correlates closely with the total oxygen uptake (dot(V)o_2). Close observation of the patient during an exercise test may disclose obvious difficulty in breathing at a low level of exercise (or the opposite). Thus, this simple test may be considered to be an extension of the clinical examination.

A more formal assessment, in which dot(V)o_2 is measured at each stage of exercise, or preferably in which dot(V)o_2 and dot(V)co_2 are measured continuously, allows determination of maximum dot(V)o_2 . It also permits measurement of the anaerobic threshold (i.e., the point during the exercise test at which the respiratory quotient rises as a consequence of the production of excess lactate). A progressive exercise test is carried out until (1) dot(V)o_2 fails to rise with further increases in activity or (2) the patient is limited by severe dyspnea and/or fatigue. When the dot(V)$_{O_2}$ is less than 25 ml/kg/min and the reduction is caused by a cardiac abnormality (rather than by pulmonary disease, anemia, peripheral vascular disease, an orthopedic disability, marked obesity, severe deconditioning, or malingering), it may be used to classify the severity of heart failure. It may also be used to follow the progress of the patient, assess the efficacy of therapeutic maneuvers, and assess prognosis.[60] [61] [62]

SUBMAXIMAL EXERCISE CAPACITY.

Because usual daily activities generally require much less than maximal exercise capacity, the measurement of submaximal exercise capacity may provide information that is complementary to that provided by maximal exercise testing.[63] [64] In contrast to maximal exercise capacity, which reflects the adequacy of the central hemodynamic response, the ability to sustain a submaximal exercise effort may reflect regulation of

blood flow to the skeletal musculature. Submaximal exercise capacity can be assessed by measuring the duration of exercise at a constant workload that is generally chosen to be at or below the patient's anaerobic threshold.[65] A rough approximation of the submaximal exercise capacity can be obtained by measuring the distance walked in a fixed period of time.[66] The "6-minute walk test," most common of the fixed-time tests, measures the distance walked on level ground in 6 minutes.[67] [68] In this test, the patient is asked to walk along a level corridor as far as he or she can in 6 minutes. The patient can slow down or even stop, may be given a carefully controlled level of encouragement, and is told when 3 and 5 minutes have elapsed. The 6-minute walk test and other similar submaximal tests[69] are being evaluated in clinical trials to determine if they are capable of detecting a therapeutic response. They are moderately predictive of maximal oxygen consumption (Fig. 17-3) , and as noted later, the 6-minute walk test independently predicts morbidity and mortality.[68] [70] Another form of submaximal exercise test measures the distance walked on a self-powered treadmill.[71]

OTHER SYMPTOMS

FATIGUE AND WEAKNESS.

These symptoms, often accompanied by a feeling of heaviness in the limbs, are generally related to poor perfusion of the skeletal muscles in patients with a lowered cardiac output. They may be associated with impaired vasodilation and altered metabolism in skeletal muscle.[52] [55] However, fatigue and weakness

Figure 17-3 Relationship between the distance walked in 6 minutes and the peak oxygen consumption in 45 patients with advanced heart failure (age 49 ± 8 years; New York Heart Association Class 3.3 ± 0.6; left ventricular ejection fraction 0.20 ± 0.06) (r=0.64, p=0.0001). In this study, distance walked less than 300 meters predicted an increased likelihood of death or hospital admission for inotropic or mechanical support. Because the 6-minute walk test involves only a submaximal exercise effort, it may be sensitive to changes in exercise function in the work range that is relevant to normal daily activities. (From Cahalin LP, et al: The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 110:325, 1996.)

are nonspecific symptoms and may be caused by a variety of noncardiopulmonary diseases, as well as by neurasthenia and depression. In heart failure, fatigue and weakness may also be caused by sodium depletion, hypovolemia, or both, usually resulting from excessive treatment with diuretics and restriction of dietary sodium and oral fluid intake. Beta-adrenergic antagonists also may cause fatigue.

URINARY SYMPTOMS.

Nocturia may occur relatively early in the course of heart failure. Urine formation is suppressed during the day when the patient is upright and active; this is due, at least in part, to a redistribution of blood flow away from the kidneys during activity. When the patient rests in the recumbent position at night, the deficit in cardiac output in relation to oxygen demand is reduced, renal vasoconstriction diminishes, and urine formation increases. Nocturia may be troublesome in that it prevents the patient with heart failure

from obtaining much-needed rest. The diurnal pattern of urine flow characteristic of heart failure contrasts sharply to that existing in renal failure, in which urine formation occurs at a reasonably constant rate, both day and night. *Oliguria* is a sign of late cardiac failure and is related to the suppression of urine formation as a consequence of severely reduced cardiac output.

CEREBRAL SYMPTOMS.

Confusion, impairment of memory, anxiety, headache, insomnia, bad dreams or nightmares, and, rarely, psychosis with disorientation, delirium, and even hallucinations may occur in elderly patients with advanced heart failure,[72] particularly in those with accompanying cerebral arteriosclerosis.

SYMPTOMS OF PREDOMINANT RIGHT-SIDED HEART FAILURE.

Breathlessness is not as prominent in isolated right ventricular failure as it is in left-sided heart failure because pulmonary congestion is usually absent. Indeed, when a patient with mitral stenosis or left ventricular failure develops right ventricular failure, the more severe forms of dyspnea (i.e., paroxysmal nocturnal dyspnea and episodic pulmonary edema) tend to diminish in frequency and intensity.

Congestive hepatomegaly may produce discomfort, generally described as a dull ache or heaviness, in the right upper quadrant or epigastrium. This discomfort, which is caused by stretching of the hepatic capsule, may be severe when the liver enlarges rapidly, as in acute right-sided heart failure. In contrast, chronic, slowly developing hepatic enlargement is generally painless. Other gastrointestinal symptoms, including anorexia, nausea, bloating, a sense of fullness after meals, and constipation, are due to congestion of the liver and gastrointestinal tract. In severe, preterminal heart failure, inadequate bowel perfusion can cause abdominal pain, distention, and bloody stools.

Functional Classification

A classification of patients with heart disease based on the relation between symptoms and the amount of effort required

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to provoke them was developed by the New York Heart Association (NYHA).[73] Although there are obvious limitations to assigning numerical values to subjective findings, this classification is nonetheless useful in comparing groups of patients as well as the same patient at different times. In addition, NYHA Class has proven to be a strong, independent predictor of survival in patients with chronic heart failure.[74]

Class I--*No limitation:* Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.

Class II--*Slight limitation of physical activity:* Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.

Class III--*Marked limitation of physical activity:* Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

Class IV--*Inability to carry on any physical activity without discomfort:* Symptoms of congestive failure are present even at rest. With any physical activity, increased discomfort is experienced.
As discussed in Chapter 3 , the accuracy and reproducibility of this classification are limited. To overcome these limitations, Goldman and associates[75] have developed a useful classification based on the estimated metabolic cost of various activities (see Table 3-11).

QUALITY OF LIFE.

The three main goals of treatment for heart failure are to reduce symptoms, prolong survival, and improve quality of life. A good "quality of life" implies the ability to live as one wants, free of physical, social, emotional, and economic limitations. Heart failure can have an enormous deleterious impact on the quality of life. Although a number of generic instruments are available to assess health-related quality of life,[76] the Minnesota Living with Heart Failure (MLHF) questionnaire was designed specifically for use in these patients.[77] It consists of 21 brief questions, each of which is answered on a scale of 0 to 5. Eight questions have a strong relationship to the symptoms of dyspnea and fatigue and are referred to as *physical dimension measures.* Five other questions that are strongly related to emotional issues are referred to as *emotional dimension measures.* The test is self-administered and takes only 5 to 10 minutes to complete. For each question, the patient selects a number from 0 to 5. Zero indicates that heart failure had no effect, and 5 indicates a very large effect. Although such questionnaires have little role in routine clinical management of patients, they have provided valuable information in clinical research settings by allowing the response to various pharmacological therapies to be quantified.[77] [78] [78A] Quality of life instruments have also been used to assess response to cardiac rehabilitation (Fig. 17-4) [58] and multidisciplinary, disease management programs.[79]

Physical Findings (See also Chap. 4)

GENERAL APPEARANCE.

Patients with mild or moderate heart failure appear to be in no distress after a few minutes of rest. However, they may be obviously dyspneic during and immediately after moderate activity. Patients with left ventricular failure may become uncomfortable if they lie flat without elevation of the head for more than a few minutes. Those with severe heart failure appear anxious and may exhibit signs of air hunger in this position. Patients with heart failure of recent onset appear acutely ill but are usually well nourished, whereas those with chronic heart failure often appear malnourished and sometimes

even cachectic. Chronic, marked elevation of systemic venous pressure may produce exophthalmos and severe tricuspid regurgitation and may lead to visible systolic pulsation of the eyes[80] and of the neck veins. Cyanosis, icterus,

Figure 17-4 Changes in the Minnesota Living with Heart Failure (MHL) questionnaire scores for stable heart failure patients enrolled in a 12-month exercise training program (open circles) compared with untrained controls (closed circles) at baseline (test 1) and after 2, 14, and 24 months (tests 2, 3, and 4). MHL scores improved significantly in trained patients after 2 months and remained stable after the subsequent 12-month exercise training program and during follow-up (*p<0.001 for all comparisons). Exercise training was associated with an increase in peak dot(V)$_{O_2}$ and reductions in both mortality and hospital readmission for heart failure. (From Belardinelli R, et al: Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. Circulation 99:1173, 1999. Copyright 1999, American Heart Association.)

and a malar flush may be evident in patients with severe heart failure.

In mild or moderate heart failure, stroke volume is normal at rest; in severe heart failure, it is reduced, and this is reflected in a diminished pulse pressure and dusky discoloration of the skin. With very severe heart failure, particularly if the cardiac output has declined acutely, systolic arterial pressure may be reduced. The pulse may be rapid, weak, and thready. The proportional pulse pressure (pulse pressure/systolic pressure) shows some correlation with the cardiac output. In one study,[16] when it was less than 25 percent, it usually reflected a cardiac index of less than 2.2 liters/min/m^2 .

INCREASED ADRENERGIC ACTIVITY.

This is responsible for a number of physical signs, including peripheral vasoconstriction, manifested as pallor and coldness of the extremities and cyanosis of the digits. There may be diaphoresis with sinus tachycardia, loss of normal sinus rhythm, and obvious distention of the peripheral veins secondary to venoconstriction. Diastolic arterial pressure may be slightly elevated.

PULMONARY RALES.

Moist rales result from the transudation of fluid into the alveoli and then into the airways. Rales heard over the lung bases are characteristic of congestive heart failure of at least moderate severity. In acute pulmonary edema, coarse, bubbling rales and wheezes are heard over both lung fields and are accompanied by the expectoration of frothy, blood-tinged sputum (see p. 555). However, the absence of rales does not exclude considerable elevation of pulmonary capillary pressure.[16] With congestion of the bronchial mucosa, excessive bronchial secretions or bronchospasm or both may give rise to rhonchi and wheezes. Rales are usually heard at both lung bases, but if unilateral they occur more commonly on the right side.

SYSTEMIC VENOUS HYPERTENSION.

This can be detected more readily by inspection of the jugular veins, which provides a useful index of right atrial pressure.[81] The upper limit of normal of the jugular venous pressure is approximately 4 cm above the sternal angle when the patient

is examined at a 45-degree angle, corresponding to a right atrial pressure of less than 10 cm of water. When tricuspid regurgitation is present, the *v* wave and *y* descent are most prominent. The jugular venous pressure normally declines on inspiration, but in patients with heart failure (and in those with constrictive pericarditis; see Chap. 50) it rises, a finding known as *Kussmaul's sign.*[81] Rarely, venous pressure may be so high that the peripheral veins on the dorsum of the hands or in the temporal region are dilated.

HEPATOJUGULAR REFLUX.

In patients with mild right-sided heart failure, the jugular venous pressure may be normal at rest but rises to abnormal levels with compression of the right upper quadrant, a sign known as the *hepatojugular reflux.* To elicit this sign, the right upper quadrant should be compressed firmly, gradually, and continuously for up to 1 minute while the veins of the neck are observed. The patient should be advised to avoid straining, holding the breath, or carrying out a Valsalva maneuver. A positive test (i.e., expansion of the jugular veins during and immediately after compression) usually reflects the combination of a congested abdomen and inability of the right side of the heart to accept or eject the transiently increased venous return.

CONGESTIVE HEPATOMEGALY.

The liver often enlarges *before* overt edema develops, and it may remain so even after other symptoms of right-sided heart failure have disappeared. If hepatomegaly has occurred rapidly and relatively recently, the liver is usually tender, owing to rapid stretching of its capsule. In long-standing heart failure this tenderness disappears, even though the liver remains enlarged. *Splenomegaly* may also occur in the presence of severe congestive hepatomegaly in patients with tricuspid valve disease or constrictive pericarditis.

EDEMA.

Although a cardinal manifestation of heart failure, edema does not correlate well with the level of systemic venous pressure. In patients with chronic left ventricular failure and a low cardiac output, extracellular fluid volume may be sufficiently expanded to cause edema in the presence of only slight elevations of systemic venous pressure. A substantial gain of extracellular fluid volume, a minimum of 4 liters in adults, must

usually take place before peripheral edema is manifested.

Edema in heart failure is usually symmetrical, is pitting, and generally occurs first in the dependent portions of the body, where the systemic venous pressure rises to its highest levels. Accordingly, cardiac edema in ambulatory patients is usually first noted in the feet or ankles at the end of the day and generally resolves overnight. In bedridden patients it is most commonly found over the sacrum. Late in the course of heart failure, edema may become massive and generalized (anasarca). Long-standing edema results in pigmentation, reddening, and induration of the skin of the lower extremities, usually the dorsum of the feet and the pretibial areas. In patients with advanced heart failure and cachexia, associated hypoalbuminemia may exacerbate the accumulation of extravascular fluid.

HYDROTHORAX (PLEURAL EFFUSION).

Because the pleural veins drain into both the systemic and the pulmonary venous beds, hydrothorax is observed most commonly in patients with hypertension involving both venous systems; it also may occur when there is marked elevation of pressure in either venous bed. An increase in capillary permeability probably also plays a role in the pathogenesis of cardiac hydrothorax, since the protein content of the pleural fluid may be significantly greater (2 to 3 gm/dl) than that found in edema fluid (0.5 gm/dl). Hydrothorax is usually bilateral, but when unilateral it is usually confined to the right side of the chest. When hydrothorax develops, dyspnea usually intensifies, owing to a further reduction in vital capacity. Although the excess fluid in hydrothorax usually resorbs as heart failure improves, loculated, interlobar effusions may persist.

ASCITES.

This finding occurs in patients with increased pressure in the hepatic veins and in the veins draining the peritoneum. Ascites usually reflects long-standing systemic venous hypertension. In patients with organic tricuspid valve disease and chronic constrictive pericarditis, ascites may be more prominent than subcutaneous edema. As in the case of hydrothorax, there is increased capillary permeability because the protein content is similar to that of hepatic lymph (i.e., four to six times that of edema fluid). Protein-losing enteropathy may rarely occur in patients with visceral congestion,[82] [83] and the resultant reduced plasma oncotic pressure may lower the threshold for the development of ascites.

Cardiac Findings

The presence of cardiac disease is usually readily evident on clinical examination of patients with congestive heart failure.

CARDIOMEGALY.

This finding is nonspecific and occurs in the majority of patients with chronic systolic heart failure. Notable exceptions include diastolic heart failure due to chronic

hypertension, heart failure associated with chronic constrictive pericarditis or restrictive cardiomyopathy, and acute forms of heart failure.

GALLOP SOUNDS.

Protodiastolic sounds, generally emanating from the left ventricle (but occasionally from the right) and occurring 0.13 to 0.16 second after the second heart sound, are common findings in healthy children and young adults. Such physiological sounds are seldom audible in healthy persons after age 40 but occur in patients of all ages with heart failure and are referred to as *protodiastolic,* or S_3 *, gallops.*[84] In older adults they generally signify the presence of heart failure.

PULSUS ALTERNANS.

This sign is characterized by a regular rhythm with alternating strong and weak ventricular contractions (Fig. 17-5) .

Figure 17-5 Pulsus alternans in a 51-year-old woman with long-standing hypertension and severe biventricular heart failure. The aortic pressure tracing reveals prominent alternations in the systolic blood pressure. The regularity of the pulsus alternans is interrupted by a ventricular premature beat (arrow). (From McLaughlin DP: Pulsus alternans. N Engl J Med 341:955, 1999.)

It should be distinguished from the alternation of strong and weak beats that occurs in pulsus bigeminus, in which the weak beat follows the strong beat by a shorter time interval than the strong beat follows the weak. In pulsus alternans, the beats are equally spaced or the weak beat is slightly closer to the succeeding than to the preceding beat. Severe pulsus alternans may be detected either by palpation of the peripheral pulses (the femoral more readily than the brachial, radial, or carotid) or by sphygmomanometry. As the cuff is slowly deflated, only alternate beats are audible for a variable number of millimeters of mercury below the systolic level, depending on the severity of the alternans, and then all beats are heard. Rarely, the weak beat is so small that the aortic valve is not opened, and this results in an apparent halving of the pulse rate, a condition referred to as *total alternans.* Pulsus alternans may be accompanied by alternation in the intensity of the heart sounds and of existing heart murmurs.

Pulsus alternans occurs most commonly in systolic heart failure. It is usually associated with a ventricular protodiastolic gallop sound (S_3). It signifies advanced myocardial disease and often disappears with treatment of heart failure. Pulsus alternans often can be elicited by assumption of the erect posture and tends to be present during tachycardia. It is often initiated by a premature beat.

Pulsus alternans is attributed to an alternation in the stroke volume ejected by the left ventricle[85] and, ultimately, to a deletion in the number of contracting cells in every other cycle, presumably owing to incomplete myocardial recovery.[86] Rarely, pulsus alternans is accompanied by *electrical alternans;* however, the latter condition is usually not due to mechanical alternans but to alternating positions of the heart within the fluid-filled pericardial sac. Demonstration of *sympathetic alternans* (i.e., alternation in the amplitude of muscle sympathetic nerve activity) in association with pulsus alternans has provided direct evidence for arterial baroreflex control of muscle sympathetic nerve activity in congestive heart failure.[87]

ACCENTUATION OF P_2 AND SYSTOLIC MURMURS.

With the development of left ventricular failure, pulmonary artery pressure rises and P_2 becomes accentuated--often louder than A_2 -- and more widely transmitted. *Systolic murmurs* are common in heart failure, owing to the functional mitral or tricuspid regurgitation that may occur secondary to ventricular dilatation. Often these murmurs diminish or disappear when compensation is restored.[88]

ABNORMAL RESPONSE TO THE VALSALVA MANEUVER (Fig. 17-6) .

Performance of this maneuver--forced expiration against a closed glottis--is helpful in the diagnosis of heart failure. The test has been standardized as follows: The patient is asked to blow against an aneroid manometer and to maintain a pressure of 40 mm Hg for 30 seconds. Intrathoracic pressure rises, venous return to the heart diminishes, stroke volume falls, and venous pressure rises. Arterial pressure tracings normally show four distinct phases (Fig. 17-6 *A*): (1) an initial rise in arterial pressure, which represents transmission to the periphery of the increased intrathoracic pressure; (2) with continuation of the strain and the accompanying reduction of venous return, reductions in systolic, diastolic, and pulse pressures accompanied by a reflex increase in heart rate; (3) on release of the strain, a sudden drop of arterial pressure equivalent to the fall in intrathoracic pressure; and (4) an overshoot of arterial pressure to above control levels, with a wide pulse pressure and bradycardia, due to a transient rise in cardiac output as blood pooled in the venous system returns to the heart with the release of the strain.

In heart failure (see Fig. 17-6 *C*), phases 1 and 3 are normal; that is, there is normal transmission of the elevated intrathoracic pressure into the arterial tree during phase 1 and sudden loss of this with the release of the strain during phase 3. However, because the heart operates on the flat portion of its Starling curve, the impedance of venous return during phase 2 does not affect stroke volume. Therefore, the baroreceptor reflex is not activated, and there is no overshoot on release of the strain. This results in a "square-wave" appearance of the tracing. The abnormal blood pressure response is associated with "pseudonormalization" of the transmitral filling velocity pattern observed by Doppler echocardiography. An intermediate response (the so-called absent-overshoot response) to the Valsalva maneuver has been demonstrated in

patients with moderate depression of left ventricular systolic function (see Fig. 17-6 *B*).

Although the Valsalva maneuver can be recorded most accurately through an indwelling needle, careful palpation of the pulse in normal individuals allows detection of phases 2 and 4 and their absence and slowing of the pulse in phase 4.[89] Alternatively, bedside sphygmomanometric determination of arterial blood pressure may be used with the Valsalva maneuver.[90] [90A]

FEVER.

A low-grade fever (38°C), which results from cutaneous vasoconstriction and therefore impairment of heat loss, may occur in severe heart failure. Fever usually subsides when compensation is restored. Greater elevations of temperature usually signify the presence of infection, pulmonary infarction, or infective endocarditis.

CARDIAC CACHEXIA.

Long-standing, severe congestive heart failure, particularly right ventricular failure, may lead to anorexia as a consequence of hepatic and intestinal congestion, and mesenteric hypoperfusion. Occasionally, there is impaired intestinal absorption of fat[91] and, rarely, protein-losing enteropathy.[82] [83] Patients with heart failure also may exhibit increased total metabolism secondary to (1) an augmentation of myocardial oxygen consumption, as occurs in patients

Figure 17-6 Arterial pressure responses during the bedside Valsalva maneuver. *A,* "Sinusoidal" arterial pressure response in a patient with normal left ventricular function. (The four distinct phases are discussed in detail in the text.) *B,* "Absent overshoot" arterial pressure response in a patient with moderate depression of left ventricular systolic function. *C,* "Square-wave" arterial pressure response in a patient with chronic heart failure due to severe depression of left ventricular systolic function. Because the heart operates on the flat portion of the ventricular function curve, the impedance of venous return during phase 2 does not affect stroke volume. Therefore, the baroreceptor reflex is not activated, and there is no overshoot on release of the strain (see text). (From Zema MJ, et al: Left ventricular dysfunction: Bedside Valsalva manoeuvre. Br Heart J 44:560, 1980.)

with aortic stenosis and hypertension, (2) excessive work of breathing, (3) low-grade fever, (4) increased activity of the sympathetic nervous system, and (5) elevated levels of circulating tumor necrosis factor-alpha.[92] This proinflammatory cytokine is produced by monocytes and contributes to cachexia and anorexia. There is also evidence that inflammatory cytokines, including tumor necrosis factor-alpha, may depress myocardial contractility,[93] [94] and contribute to ventricular remodeling by stimulating myocyte apoptosis[95] and turnover of the extracellular matrix.[29A] [96]

Other metabolic pathways that cause catabolic/anabolic imbalance and that have been implicated in wasting associated with heart failure include the growth hormone-insulin-like growth factor-1 system and the pituitary-thyroid hormone axis.[97] [98] The combination of reduced caloric intake and increased caloric expenditure may lead

to a reduction of tissue mass and, in severe cases, to cardiac cachexia. In some patients the cachexia may be severe enough to suggest the presence of disseminated malignant disease. In others, the loss of lean body mass may be masked by the accumulation of edema. Cardiac cachexia is a marker of increased mortality in heart failure.[98]

CHEYNE-STOKES RESPIRATION.

Also known as *periodic* or *cyclic respiration,* Cheyne-Stokes respiration is characterized by the combination of depression in the sensitivity of the respiratory center to carbon dioxide and left ventricular failure.[40] [99] During the apneic phase, arterial P_{O_2} falls and P_{CO_2} rises; this combination excites the depressed respiratory center, resulting in hyperventilation and, subsequently, hypocapnia, followed by another period of apnea. The principal causes of depression of the respiratory center in patients with Cheyne-Stokes respiration are cerebral lesions such as cerebral arteriosclerosis, stroke, or head injury. These causes are often exaggerated by sleep, barbiturates, and narcotics, all of which further depress the sensitivity of the respiratory center. Left ventricular failure, which prolongs the circulation time from the lung to the brain, results in a sluggish response of the system and is responsible for the oscillations

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between apnea and hyperpnea that prevent return to a steady state of ventilation and blood gases.

Cheyne-Stokes respiration is seen in up to 40 percent of heart failure patients. Usually patients are not aware of Cheyne-Stokes respiration. However, it can be readily observed in a sleeping patient or a history can be elicited from the patient's bed partner. Cheyne-Stokes respiration may contribute to daytime sleepiness,[100] insomnia, and snoring.

PATHOLOGICAL FINDINGS

LUNGS.

In patients who have died of left ventricular failure, the lungs are enlarged, firm, and dark and may be filled with bloody fluid. With long-standing pulmonary congestion, they are brown with deposition of hemosiderin and usually do not seep edema fluid. On microscopic examination, the capillaries are engorged, and there is thickening of the alveolar septa as well as extravasation of large mononuclear cells containing red blood cells or hemosiderin granules or both.[101] Often the pulmonary vessels show medial hypertrophy and intimal hyperplasia.

LIVER.

In acute right-sided heart failure, the liver is enlarged, firm, and filled with fluid. On microscopic examination, the central hepatic veins and sinusoids are dilated. With chronic right-sided heart failure, the liver returns to normal size, subsequently atrophies, and becomes "nutmeg" in appearance as a consequence of the dark red areas of central venous congestion and the lighter, fatty area in the periphery of the lobule. Cardiac cirrhosis is characterized by central lobular necrosis and atrophy, as well as extensive or patchy fibrous retraction. In addition, there may be fibrosis and thrombosis of the hepatic veins.[102] Because cardiac cirrhosis is a function of the level of hepatic venous pressure and the duration of its elevation, it is not surprising that it occurs most commonly in patients with chronic constrictive pericarditis and organic tricuspid valve disease. In patients with left ventricular failure, central hepatic necrosis without evidence of passive congestion may be present.[103]

Liver biopsy specimens in patients with acute heart failure exhibiting fulminant hepatic failure show bridging centrolobular necrosis. Presumably, the hypoxia caused by hypoperfusion produces hepatocyte necrosis[104] ; erythrocytes may then enter the space of Disse between damaged endothelial cells. The changes resulting from acute heart failure may be transient if there is hemodynamic recovery.[105]

OTHER VISCERA.

Patients with chronic hepatic venous hypertension develop portal hypertension that results in congestive splenomegaly. On microscopic examination, the spleen shows dilatation of the sinusoids and fibrosis with thickening of the splenic capsule; and there is chronic passive congestion of the pancreas and of the veins and capillaries of the gastrointestinal tract. Rarely, intense mesenteric vasoconstriction without thrombotic or embolic occlusion of a mesenteric artery may lead to a hemorrhagic, nonbacterial enterocolitis, with hemorrhagic necrosis.

Laboratory Findings

Proteinuria and a high urine specific gravity are common findings in heart failure. Blood urea nitrogen and creatinine levels are often moderately elevated secondary to reductions in renal blood flow and glomerular filtration rate[15] (prerenal azotemia).

SERUM ELECTROLYTES.

Serum electrolyte values are generally normal in patients with mild or moderate heart failure before treatment. However, in severe heart failure, prolonged sodium restriction, coupled with intensive diuretic therapy and the inability to excrete free water, may lead to dilutional hyponatremia. Hypervolemic hyponatremia occurs because of substantial expansion of extracellular fluid volume and a normal or only slightly increased level of total body sodium. It may be accompanied by, and presumably is caused in part by, elevated circulating levels of arginine vasopressin.[106] Serum potassium levels are usually normal, although the prolonged administration of kaliuretic diuretics, such as the thiazides or loop diuretics, may result in hypokalemia. Secondary hyperaldosteronism

may also contribute to hypokalemia. Hyperkalemia may occur in patients with severe heart failure[107] who show marked reductions in glomerular filtration rate and inadequate delivery of sodium to the distal tubular sodium-potassium exchange sites, particularly if such patients are also receiving potassium-retaining diuretics and/or angiotensin-converting enzyme inhibitors. Other common electrolyte abnormalities observed in heart failure include hypophosphatemia and hypomagnesemia[108] (commonly associated with alcohol use) and hyperuricemia, which may precipitate gout.

LIVER FUNCTION TESTS.

Congestive hepatomegaly and cardiac cirrhosis are often associated with impaired hepatic function, characterized by abnormal values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), and other liver enzymes.[109] Hyperbilirubinemia, both direct and indirect, is common; and in severe cases of acute (right or left) ventricular failure, frank jaundice may occur. *Acute* hepatic venous congestion can result in severe jaundice with a bilirubin level as high as 15 to 20 mg/dl, elevation of AST to more than 10 times the upper limit of normal, and elevation of the serum alkaline phosphatase level, as well as prolongation of the prothrombin time. Both the clinical and the laboratory pictures may resemble viral hepatitis, but the impairment of hepatic function is rapidly ameliorated by successful treatment of heart failure.[105] In patients with long-standing cardiac cirrhosis, albumin synthesis may be impaired, with resultant hypoalbuminemia, intensifying the accumulation of fluid. Fulminant hepatic failure and coma are uncommon, late, and sometimes terminal complications of cardiac cirrhosis. In general, disturbances of hepatic function are frequent when right atrial pressure rises above 10 mm Hg and cardiac index declines below 1.5 l/min/m^2 .

The Chest Roentgenogram (See also Chap. 8)

Two principal features of the chest roentgenogram are useful in the evaluation of patients with heart failure.

The *size and shape of the cardiac silhouette* provide important information concerning the precise nature of the underlying heart disease. Both the cardiothoracic ratio and the heart volume determined on the plain film are relatively specific but insensitive indicators of increased left ventricular end-diastolic volume. Although there is a weak, inverse correlation between the cardiothoracic ratio and left ventricular ejection fraction in patients with heart failure, the relationship is not clinically useful in the individual patient.[110]

In the presence of normal pulmonary capillary and venous pressure, the lung bases are better perfused than the apices in the erect position, and the vessels supplying the lower lobes are significantly larger than are those supplying the upper lobes. With elevation of left atrial and pulmonary capillary pressures, interstitial and perivascular edema develops and is most prominent at the lung bases because hydrostatic pressure is greater there. When pulmonary capillary pressure is slightly elevated (i.e., 13 to 17 mm Hg), the resultant compression of pulmonary vessels in the lower lobes causes equalization in size of the vessels at the apices and bases. With greater pressure

elevation (18 to 23 mm Hg), actual pulmonary vascular redistribution occurs[111] (i.e., further constriction of vessels leading to the lower lobes and dilatation of vessels leading to the upper lobes) (see Fig. 8-18*A* (p. 255). When pulmonary capillary pressures exceed 20 to 25 mm Hg, interstitial pulmonary edema occurs (see Fig. 8-18*B*). This may be of several varieties: (1) *septal,* producing Kerley's lines (i.e., sharp, linear densities of interlobular interstitial edema); (2) *perivascular,* producing loss of sharpness of the central and peripheral vessels; and (3) *subpleural,* producing spindle-shaped accumulations of fluid between the lung and adjacent pleural surface. When pulmonary capillary pressure exceeds 25 mm Hg, alveolar edema, with a cloudlike appearance and concentration of the fluid around the hili in a "butterfly" pattern, and large pleural effusions may occur (see Fig. 8-18*C*). With elevation of systemic venous pressure, the azygos vein and superior vena cava may enlarge.

In patients with chronic left ventricular failure, higher pulmonary capillary pressures can be accommodated with

fewer clinical and radiological signs,[16] , [81a] , [112] presumably due to enhanced lymphatic drainage. In one study of 22 patients with advanced heart failure referred for cardiac transplant evaluation, all of whom had pulmonary capillary wedge pressures greater than or equal to 25 mm Hg, 68 percent had "no" or "minimal" pulmonary congestion on chest roentgenogram.[112]

PROGNOSIS

Survival is reduced in patients with heart failure, which accounts for a substantial portion of all deaths from cardiovascular diseases. The overall 5-year mortality for all patients with heart failure is approximately 50 percent, and the 1-year mortality in patients with severe heart failure may be as high as 35 to 40 percent. In the United States alone, approximately 250,000 patients die of heart failure each year.[8] The Framingham Heart Study found that between the years 1948 and 1988, patients with a diagnosis of heart failure had a median survival of 1.7 years for men and 3.2 years for women, despite the fact that the patients with the poorest prognosis, that is, those dying within 90 days of the diagnosis, were excluded from the analysis.[113] More recent data from the Framingham Study demonstrates improved survival in patients with heart failure and preserved systolic function,[19] although data from Olmstead County, Minnesota, suggests equally poor survival in patients with systolic or diastolic heart failure.[20] Over 90 percent of deaths in patients with congestive heart failure are due to cardiovascular causes, most commonly progressive heart failure and sudden cardiac death.

A large number of factors have been found to correlate with mortality in patients with heart failure (Table 17-5) .[74] These fall into four major categories:

CLINICAL.

In general, male gender,[113] [114] the presence of coronary artery disease as the etiology of heart failure,[115] the presence of an audible S_3 , low pulse and systolic arterial pressures, a high NYHA Class (Fig. 17-7) , and reduced exercise capacity (Fig. 17-8) [51] , [62] ,[62a] have each been shown to be associated with increased mortality. When the NYHA Class is integrated with the maximal O_2 consumption (dot(V)$_{O_2}$ max) determined during exercise, the mortality is 20 percent per year in patients in Class III with a dot(V)$_{O_2}$ max of

TABLE 17-5 -- FACTORS AFFECTING SURVIVAL IN PATIENTS WITH HEART FAILURE

Clinical
Male gender
Coronary artery disese etiology
New York Heart Association class
Exercise capacity
Heart rate at rest
Systolic arterial pressure
Pulse pressure
S_3 gallop
Cheyne-Stokes respiration
Cardiac cachexia
Hemodynamic
Left ventricular ejection fraction
Right ventricular ejection fraction
Left ventricular stroke work index
Left ventricular filling pressure
Right atrial pressure
Left ventricular systolic pressure
Mean arterial pressure
Cardiac index
Exercise cardiac output or stroke work index
Systemic vascular resistance
Biochemical
Plasma norepinephrine
Plasma renin
Plasma arginine vasopressin
Plasma atrial and brain natriuretic peptides
Plasma endothelin-1
Plasma interleukin-6
Serum sodium
Serum potassium and total potassium stores
Serum magnesium
Electrophysiological

Frequent ventricular extrasystoles
Nonsustained ventricular tachycardia
Ventricular tachycardia
Atrial fibrillation

10 to 15 ml/kg/min and rises to 60 percent in patients in Class IV with a dot(V)O_2 max of less than 10 ml/kg/min.[116] The distance walked in 6 minutes predicted both morbidity and mortality in the Studies of Left Ventricular Dysfunction

Figure 17-7 Clinical correlates of survival in heart failure. Based on data from several contemporary, placebo-controlled clinical trials, it can be estimated that the 1-year mortality is on the order of 50 to 60 percent in patients with New York Heart Association (NYHA) functional Class IV symptoms, 15 to 30 percent in patients with Class II-III symptoms, and 5 to 10 percent in asymptomatic patients with left ventricular dysfunction. Patients in CONSENSUS I were in NYHA Class IV and were treated with digitalis and diuretics; patients in SOLVD (prevention) and SAVE had reduced LV ejection fractions (35 and 40 percent, respectively) but no or mild limitation (NYHA Classes I or II). Patients in PROMISE, SOLVD (treatment) and VHeFT-I were in moderate failure (NYHA Classes II or III). (From Young JB: Assessment of heart failure. *In* Colucci WS [ed]: Heart Failure: Cardiac Function and Dysfunction. 2nd ed. *In* Braunwald E [series ed]: Atlas of Heart Diseases. Vol 4. Philadelphia, Current Medicine, 1999, pp 7.1-7.19.)

Figure 17-8 Kaplan-Meier survival analysis in patients with severe left ventricular dysfunction stratified by peak oxygen consumption (dot(V)O_2) as measured by cardiopulmonary exercise testing during evaluation for cardiac transplantation. Patients with a peak dot(V)O_2 of 10 ml/kg/min or less had significantly reduced survival rates compared with patients with peak dot(V)O_2 > 14 ml/kg/min. (From Mancini DM, et al: Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 83:778, 1991. Copyright 1991, American Heart Association.)

(SOLVD) trial [70] (Fig. 17-9) . Other clinical predictors of mortality in chronic heart failure include Cheyne-Stokes respiration,[117] cardiac cachexia,[98] and exercise capacity (see Fig. 17-12 *B*).

HEMODYNAMIC.

Variables such as cardiac index, stroke work index, left ventricular cavity size, and both left and right ventricular ejection fraction[118] [119] (Fig. 17-10) have been shown to correlate directly with survival in patients with heart failure, whereas systemic vascular resistance and heart rate correlate inversely. Combinations of hemodynamic abnormalities, such as depression of stroke work associated with elevation of filling pressure and systemic vascular resistance, are associated with a poor prognosis. More recent studies have examined the impact of exercise hemodynamics on survival and

found that the stroke work index[120] and cardiac output[51] responses to exercise provide valuable independent prognostic information (Fig. 17-11) . In one study, patients with reduced cardiac output response to exercise and dot(V)O_2 max less than or equal to 10 ml/

Figure 17-9 Mortality (%) as a function of performance level (based on distance walked). Mortality decreased as performance on the 6-minute walk test improved. (From Bittner V, et al: Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA 270:1702, 1993. Copyright 1993, American Medical Association.)

Figure 17-10 In a multivariate analysis of survival in the VHeFT studies, the left ventricular ejection fraction (LVEF) and the peak oxygen consumption (peak dot(V)O_2) were found to have independent prognostic value. An LVEF
0.28 and a peak dot(V)O_2
14.5 ml/kg/min each predicted a poor survival, and the finding of both predicted a worse survival than if only one or the other were present. (From Cohn JN, et al: Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 87:VI-5, 1993. Copyright 1993, American Heart Association.)

kg/min had an extremely poor prognosis (i.e., 1-year survival rate of 38 percent).[51] Others have shown that dot(V)O_2 max is superior to hemodynamic measurements in predicting outcome in severe heart failure.[121]

BIOCHEMICAL.

The observation that there is activation of the neurohormonal axis in heart failure has prompted examination of the relations between a variety of biochemical measurements and clinical outcome (Figs. 17-12 , Fig. 17-13, , Fig. 17-14). Strong inverse correlations have been reported between survival and plasma levels of norepinephrine (see Fig. 17-12 *A*), [74] [122] [123] [124] renin,[74] [124] [125] arginine vasopressin,[125]

Figure 17-11 Hemodynamic responses to exercise were measured in ambulatory patients with chronic heart failure referred for cardiac transplant evaluation. Patients with normal cardiac output (CO) response to exercise (83 patients) had a better 1-year survival rate (95%) than did those with reduced CO responses (102 patients; 1-year survival, 72%). (From Chomsky DB, et al: Hemodynamic exercise testing: A valuable tool in the selection of cardiac transplantation candidates. Circulation 94:3176, 1996. Copyright 1996, American Heart Association.)

Figure 17-12 Markers of survival in heart failure. *A,* Life-table analysis of survival, according to tercile, based on level of plasma norepinephrine (PNE). Group 1 (<400 pg/ml) contained 27 patients, group 2 (400 to 800 pg/ml) had 49 patients, and group 3 (> 800 pg/ml) had 30 patients. The probability of survival in each group was significantly different from the probabilities in the other two groups. (From Cohn JN, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311:822, 1984.) *B,* Kaplan-Meier survival curve for patients with coronary artery disease with a short (3-min) or long (12-min) exercise time in the modified Bruce protocol. (From Cleland JGE, Darque HJ, Ford I: Mortality in heart failure: Clinical variables of prognostic value. Br Heart J 58:572, 1987.

atrial and brain natriuretic peptide (see Figs. 17-13 *A* and Figs. 17-13*B*), [126] [127] endothelin-1 (see Fig. 17-14*A*) [128] and interleukin-6 (see Fig. 17-14*B*).[129] The concentrations of these substances reflect the severity of the underlying impairment of circulatory function. In addition, some may exert adverse hemodynamic effects; norepinephrine, angiotensin II, and arginine vasopressin are potent vasoconstrictors, augmenting ventricular afterload and thereby reducing the shortening of myocardial fibers. Furthermore, they may be directly responsible for adverse biochemical effects on the myocardium. For example, the elevated norepinephrine concentration may be responsible for ventricular tachyarrhythmias, as may hypokalemia and reduction of total-body potassium stores resulting from the activation of the renin-angiotensin-aldosterone system (and the administration of potassium-losing diuretics).[130] Norepinephrine also exerts direct toxic effects on the myocardium, including stimulation of cellular hypertrophy, apoptosis, and changes in extracellular matrix regulation, and thus contributes directly to ventricular remodeling and disease progression[131] (see Chap. 16). Like norepinephrine, endothelin-1 is a potent vasoconstrictor peptide that exerts growth-promoting effects on the myocardium.[29] Hyponatremia also correlates well with increased mortality,[125] but it is likely that this variable reflects activation of the renin-angiotensin-aldosterone axis.

In many studies, the aforementioned variables have been assessed in a univariate manner (i.e., independently of one another) and there is disagreement regarding which provides *independent* prognostic information. However, Cohn and Rector have shown that while ventricular function, as expressed in ejection fraction, appears to have the most profound effect on survival in patients with advanced heart failure, exercise tolerance (as reflected in peak O_2 consumption during a progressive exercise test) and activation of the sympathetic nervous system (as reflected in the plasma norepinephrine concentration) *each* provide important independent information.[74]

Figure 17-13 *A,* Kaplan-Meier analysis of cumulative rates of survival in patients with heart failure stratified into two groups on the basis of median plasma concentration of atrial natriuretic peptide (ANP) (125 pg/ml). (From Gottlieb SS, et al: Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. J Am Coll Cardiol 13:1534, 1989.) *B,* Kaplan-Meier survival analysis in patients with chronic heart failure stratified into two groups on the basis of median plasma concentration of brain natriuretic peptide (BNP) (73 pg/ml). (From Tsutamoto T, et al: Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 96:509, 1997. Copyright 1997, American Heart Association.)

Figure 17-14 *A,* Kaplan-Meier analysis showing cumulative rates of event-free survival in patients with chronic heart failure stratified into two groups based on big endothelin-1 (big-ET) plasma concentration. (From Hulsmann M, et al: Value of cardiopulmonary exercise testing and big endothelin plasma levels to predict short-term prognosis in patients with chronic heart failure. J Am Coll Cardiol 32:1695, 1998.) *B,* Kaplan-Meier survival analysis in patients with chronic heart failure stratified into two groups based on median plasma concentration of interleukin-6 (IL-6) (4.6 pg/ml). (From Tsutamoto T, et al: Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol 31:391, 1998.)

ELECTROPHYSIOLOGICAL.

Death in patients with severe congestive heart failure occurs either by progressive pump failure or, in as many as one half of all patients, suddenly and unexpectedly, presumably from an arrhythmia. When present, a variety of arrhythmias, especially frequent ventricular extrasystoles,[132] ventricular tachycardia, [133] left bundle branch block, and atrial fibrillation,[134] [135] have been shown to be predictors of mortality. What is not yet clear is whether these arrhythmias are simply indicators of the severity of left ventricular dysfunction or whether they are responsible for and trigger fatal arrhythmias. Although there is some evidence that ventricular arrhythmias confer independent adverse prognostic effects,[133] this may not hold true after adjusting for other variables, especially ejection fraction.[136] ,[136a] Furthermore, the routine treatment of patients with heart failure-associated arrhythmias with antiarrhythmic drugs has not been shown to exert a protective effect and reduce mortality. The role of amiodarone and the implantable cardioverter-defibrillator in the primary prevention of sudden cardiac death in patients with left ventricular dysfunction is currently being tested in two large, randomized controlled trials.[137]

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High-Output Heart Failure (Table 17-6)

High-cardiac output states by themselves are seldom responsible for heart failure, but their development in the presence of underlying heart disease often precipitates heart failure.[138] In these conditions, which are often characterized by arteriovenous shunting, the requirements of the peripheral tissues for oxygen can be satisfied only by an increase in cardiac output. Although the normal heart is capable of augmenting its output on a long-term basis, this may not be true of the diseased heart.

Anemia (See also Chap. 69)

Chronic anemia is associated with high cardiac output when hemoglobin is less than or approximately 8 gm/dl. Reduced systemic vascular resistance, which results from decreased arteriolar tone and decreased blood viscosity, plays an important role in the pathophysiology of this high-output state (Fig. 17-15) (Figure Not Available) . Enhanced basal production of endothelium-derived nitric oxide may be responsible, in part, for the low systemic vascular resistance in anemia patients.[139]

HISTORY.

Chronic anemia in the absence of underlying heart disease produces surprisingly few symptoms, which may consist of easy fatigability, mild exertional dyspnea, and occasionally palpitations and cardiac awareness. Anemia, even when severe, rarely causes heart failure or angina pectoris in patients with normal hearts; when these problems occur, it is likely that the high cardiac output is superimposed on some specific cardiac abnormality, such as valvular or ischemic heart disease.

PHYSICAL EXAMINATION.

The anemic patient often has a pale, "pasty" appearance; in African Americans, the finding of paleness of the conjunctivae, mucous membranes, and palmar creases is helpful. Arterial pulses are bounding; "pistol shot" sounds can be heard over the femoral arteries (Traube's sign), and subungual capillary pulsations (Quincke's pulse) are present, as in patients with aortic regurgitation. A medium-pitched, midsystolic murmur along the left sternal border, generally grade 1/6 to 3/6 in intensity (seldom accompanied by a thrill), is common. Heart sounds are accentuated, and the pulmonic component of the second heart sound may be particularly prominent in patients with sickle cell anemia and pulmonary hypertension; in such patients, a right ventricular lift can usually be palpated. A mid-diastolic flow murmur secondary to augmented blood flow across the mitral orifice, holosystolic murmurs resulting from tricuspid and mitral regurgitation

TABLE 17-6 -- HIGH CARDIAC OUTPUT STATES

Anemia
Acquired arteriovenous fistulas
Post-traumatic
Iatrogenic
Infectious
Surgical (hemodialysis)
Congenital arteriovenous fistulas
Hemangiomas
Hereditary hemorrhagic telangiectasia
Thyrotoxicosis
Beriberi heart disease
Paget's disease of bone
Fibrous dysplasia
Multiple myeloma
Polycythemia vera
Carcinoid syndrome
Pregnancy

secondary to ventricular dilatation, and, rarely, diastolic murmurs resulting from aortic and pulmonic valve incompetence secondary to dilatation of these vessels may be heard. A protodiastolic gallop sound (S_3) frequently is audible at the cardiac apex.

Jugular venous distention is uncommon; and although peripheral edema and hepatomegaly are occasionally present, they may be due not only to heart failure but also to accompanying abnormalities such as hypoalbuminemia and nutritional deficiency.

DIAGNOSTIC TESTING.

In patients with severe chronic anemia without underlying heart disease, the chest roentgenogram usually demonstrates mild to moderate cardiomegaly. The electrocardiogram often does not show any specific changes but may reveal tachycardia and T wave inversions in the lateral precordial leads. The echocardiogram generally shows a modest and symmetrical increase in the size of all chambers, with large systolic excursions of the septal and posterior left ventricular walls. In addition, an attenuated increase in the fractional shortening in response to exercise and abnormal ventricular filling may be seen.[140] These findings are superimposed on those resulting from the underlying heart disease. Hematological and blood chemistry findings reflect the specific type of anemia present.

MANAGEMENT.

Treatment of heart failure associated with severe anemia should be specific for the anemia (e.g., iron, folate, vitamin B_{12}). When heart failure is present, diuretics and cardiac glycosides are advisable, although some believe that the latter drugs are not helpful in this condition.

When both heart failure and anemia are severe, treatment must be carried out on an urgent basis and presents a difficult challenge. On the one hand, correction of the anemia is desirable to increase oxygen delivery to metabolizing tissues and thereby decrease the need for a sustained high cardiac output. On the other hand, rapid expansion of the blood volume may intensify the manifestations of heart failure.

The diagnostic steps for determining the etiology of the anemia should be taken immediately (e.g., blood drawn for serum iron, folate, and vitamin B_{12} and reticulocyte count, review of peripheral smear, and stool guaiac). The patient should be placed at bed rest and given supplementary oxygen. *Packed red blood cells* should then be transfused slowly (250 to 500 ml/24 hr), preceded and/or accompanied by vigorous diuretic therapy (e.g., furosemide, 40 mg intravenously every 8 to 12 hours), and the patient should be observed closely for the development or exacerbation of dyspnea and pulmonary rales. If worsening heart failure occurs, the transfusion should be discontinued or slowed to avoid precipitating pulmonary edema. Vasodilator therapy is seldom helpful, because impedance to left ventricular emptying is already markedly reduced in most cases.

Systemic Arteriovenous Fistulas

Systemic arteriovenous fistulas may be congenital or acquired; the latter are usually posttraumatic or iatrogenic. Increased cardiac output associated with such fistulas depends on the size of the communication and the magnitude of the resultant reduction in systemic vascular resistance.

The *physical findings* depend on the underlying disease and the location and size of the shunt. In general, a widened pulse pressure, brisk carotid and peripheral arterial pulsations, and mild tachycardia are present. The extremities are often warm and flushed. *Branham's sign* (also called *Nicaladoni-Branham's sign*), which consists of slowing of the heart after manual compression of the fistula,[141] is present in the majority of cases; this maneuver also raises arterial and lowers venous pressure. It appears to result from the operation of a cardioaccelerator reflex with both afferent and efferent pathways in the vagus nerves.[142] The decrease in heart rate after fistula occlusion correlates with the flow in the fistula.[141]

The skin overlying the fistula is warmer than normal, and a continuous "machinery" murmur and thrill are usually present over the lesion. Third and fourth heart sounds are commonly heard, as well as a precordial midsystolic murmur secondary to increased cardiac output. The electrocardiographic changes of left ventricular hypertrophy are often seen. Rarely, the fistula may become infected, leading to bacterial endarteritis.

ACQUIRED ARTERIOVENOUS FISTULAS.

These occur most frequently after such injuries as gunshot wounds and stab wounds and may involve any part of the body, most frequently the thigh. Blood flow in the affected limb distal to the fistula diminishes after the creation of the fistula but then returns to normal and often increases with the passage of time. As a consequence, the affected limb is usually larger than its opposite member and the overlying skin is warmer; cellulitis, venostasis, edema, and dermatitis with pigmentation frequently occur, in part as a consequence of chronically elevated venous pressure. Surgical repair or excision is generally advisable in fistulas that develop after gunshot wounds or trauma.

Femoral arteriovenous fistulas following diagnostic or interventional cardiac catheterization are uncommon but may result in high-output cardiac failure.[143] When a continuous bruit is heard over the femoral artery site, a duplex vascular

Figure 17-15 (Figure Not Available) Diagram showing the pathophysiological mechanisms underlying the high cardiac output state associated with anemia. Decreased blood viscosity and a reduction in arteriolar tone resulting from tissue hypoxia and lactic acidosis contribute to reduced systemic vascular resistance, which in turn increases cardiac output. (From Hassapoyannes CA, et al: Other causes and contributing factors to congestive heart failure. *In* Hosenpud JD, Greenberg BH [eds]: Congestive Heart Failure, New York, Springer-Verlag, 1994, pp 281-300.)

ultrasound should be obtained to rule out an arteriovenous fistula; rarely, angiography is required to make the diagnosis. Although the traditional approach to management of catheterization-related femoral artery injuries has been surgical repair, newer techniques include ultrasound-guided compression and percutaneous stent placement.[143]

A rare form of acquired arteriovenous fistula results from spontaneous rupture of an aortic aneurysm into the inferior vena cava.[144] This usually produces an enormous arteriovenous shunt and rapidly progressive left ventricular failure. On physical examination, a pulsating mass can be readily palpated superficially in the abdomen and a continuous bruit is audible. Survival depends on prompt diagnosis and surgical closure. Massive fistulas may also be associated with Wilms' tumors of the kidney, and these have been reported to cause high-output cardiac failure in children.[145]

High-output heart failure resulting from the arteriovenous shunts surgically constructed for vascular access in patients undergoing long-term hemodialysis is common.[146] Cardiac outputs as high as 10 liters/min, which decrease substantially during temporary occlusion of the shunt, have been found in such patients. These values also reflect the chronic anemia present in many of these patients, but it is clear that it is the added hemodynamic burden imposed by the shunt that precipitates heart failure in patients who had previously tolerated chronic anemia without apparent impairment of cardiac function. It is usually possible to revise or band the fistula to reduce it to the appropriate size for dialysis without compromising cardiac function. If this is ineffective, the shunt should be surgically closed and a new arteriovenous fistula created.

CONGENITAL ARTERIOVENOUS FISTULAS

Congenital arteriovenous fistulas result from arrest of the normal embryonic development of the vascular system and are structurally similar to embryonic capillary networks. They range from barely noticeable strawberry birthmarks to enormous clusters of engorged vascular channels that may deform an entire extremity.[147] Most frequently, the vessels of the lower extremities are involved. When fistulas are large, patients generally complain of disfigurement as well as swelling and pain in the limb. On physical examination, erythema and cyanosis are often present, as are venous varices, a continuous murmur, and thrill. Examination also shows hemangiomatous changes associated with venous distention, deformity, and increased limb length. The fistulous connection may involve any vascular bed, including an internal mammary artery-pulmonary artery connection. *Left-sided heart failure* occurs, particularly in patients with larger lesions that involve the pelvis as well as the extremities.[148] Angiography is useful in confirming the diagnosis and in determining the physical extent of the anomaly.

Surgical excision is the ideal treatment,[149] but in many instances the lesions are not sufficiently localized to permit this. The results of ligation and excision have been unsatisfactory in the majority of cases, because the congenital arteriovenous communications are usually not confined to a single anatomical segment or to a circumscribed anatomical region. Complete cure of these lesions is possible in only a few instances. Embolization of Gelfoam pellets delivered through a catheter has been reported to obliterate multiple systemic arteriovenous fistulas and thereby diminish high-output heart failure.

HEREDITARY HEMORRHAGIC TELANGIECTASIA.

Also known as *Osler-Weber-Rendu disease,* this condition may be associated with arteriovenous fistulas, particularly in the lungs[150] and liver. Involvement of the liver, in particular, can produce a hyperkinetic circulation,[151] with heart failure as well as hepatomegaly, abdominal bruits, abdominal angina, or severe portal hypertension. Because of the presence of oxygenated blood in the inferior vena cava and right atrium, this condition may be misdiagnosed as atrial septal defect. Staged embolization of hepatic arteries may result in clinical improvement.[151] [152]

The congenital arteriovenous communications resulting from *infantile hemangioendothelioma of the liver* are commonly associated with marked increases in cardiac output, sometimes as high as 10 liters/min, and congestive heart failure.[153] These lesions may be quite large, increase in size with time, and lead to heart failure, even in infancy. They are often associated with sizable cutaneous hemangiomas, which should alert the clinician to the possibility of their presence. Ultrasonography and computed tomography are the most useful noninvasive diagnostic tools. Treatment strategies include medical management with corticosteroids or interferon alfa or, in cases of failed medical therapy, use of percutaneous or surgical intervention, including hepatic artery ligation or embolization, resectional surgery, or orthotopic liver transplant.

Hyperthyroidism (See also Chap. 64.)

The principal findings on the physical examination of the cardiovascular system are tachycardia, a widened pulse pressure, brisk carotid and peripheral arterial pulsations, a hyperkinetic cardiac apex, and loud first heart sound. A midsystolic murmur along the left sternal border, secondary to increased flow, is common; occasionally, this murmur has an unusual scratchy component (the so-called Means-Lerman scratch), thought to be due to the rubbing together of normal pleural and pericardial surfaces by the hyperdynamic heart. Rarely, systolic murmurs of mitral and tricuspid regurgitation, presumably secondary to papillary muscle dysfunction, may occur.

THYROTOXIC HEART DISEASE

As in many other high-output states, the hyperkinetic state of hyperthyroidism does not usually lead to heart failure in the absence of underlying cardiovascular disease. The normal heart appears capable of tolerating the burden imposed by hyperthyroidism simply by means of dilatation and hypertrophy.[154] , [155] ,[155a] However, heart failure may be precipitated when the elevated flow load of hyperthyroidism is superimposed on a reduced cardiovascular reserve (i.e., a patient with heart disease who is compensated). Similarly, in patients with obstructive coronary artery disease who are asymptomatic or who have only mild evidence of ischemia in the euthyroid state, the demand for increased coronary blood flow with hyperthyroidism frequently leads to an exacerbation of angina. Rarely, hyperthyroidism may cause a reversible dilated cardiomyopathy with low cardiac output heart failure. The high output cardiac failure of hyperthyroidism is frequently accompanied by and exacerbated by atrial fibrillation and a rapid ventricular

rate.

MANAGEMENT.

Beta-adrenergic antagonists may be both helpful and harmful in patients with thyrotoxic heart disease and heart failure. Although they may be beneficial by lowering the ventricular rate, particularly by prolonging the refractory period of the atrioventricular conduction system in patients with atrial fibrillation, these agents also may diminish myocardial contractility by blocking the adrenergic support of the heart. Therefore, beta-adrenergic blockade must be administered cautiously to the patient with thyrotoxic heart disease and heart failure and only after treatment with a digitalis glycoside, with the patient at rest and under careful observation. The initial dose should be small (e.g., propranolol, 0.5 mg intravenously or 10 mg orally two to three times daily), and the patient should be observed after the administration to be sure that heart failure is not intensified. In addition to beta-adrenergic blockade, appropriate antithyroid medication (e.g., methimazole, propylthiouracil) should be prescribed.

It is particularly important to recognize *apathetic hyperthyroidism,* [156] a condition in the elderly in which the usual clinical manifestations of thyrotoxicosis, such as palpitations, tachycardia, and moist skin, are not present. In such patients, the first clinical signs of hyperthyroidism may be unexplained heart failure, an exacerbation of angina pectoris, or unexplained atrial fibrillation,[157] usually but not always with a rapid ventricular rate.

Beriberi Heart Disease (Table 17-7)

PATHOGENESIS AND CLINICAL CONSIDERATIONS.

Thiamine pyrophosphate (TPP), the most abundant thiamine ester found in tissues, is essential for carbohydrate metabolism. Beriberi heart disease is due to severe thiamine deficiency persisting for at least 3 months. Clinical beriberi is found most frequently in the Far East,[158] although even in that part of the world it is far less prevalent now than in the past. It occurs predominantly in those individuals whose staple diet consists of polished rice, which is deficient in thiamine but high in carbohydrates, or foods containing thiaminases. The presence of thiamine in the enriched flour used in white bread has virtually eradicated this disease in the United States and western Europe, where beriberi is found most commonly in diet faddists[159] and alcoholics. Like polished rice, alcohol is low in vitamin B_1 but has a high carbohydrate content. In the West, alcoholics become thiamine deficient not only because of a low intake and impaired absorption and storage of the vitamin but also because they eat "junk" foods[159] or drink large quantities of beer. The high carbohydrate content of these foods leads to a greater requirement for thiamine.

Patients in Asia present with edema, ranging from peripheral edema to anasarca, as well as general malaise, and fatigue. The elevation of cardiac output[160] is presumably secondary to the reduced systemic vascular resistance and augmented venous return (Fig. 17-16) .

PHYSICAL FINDINGS.

In most cases in Western countries, physical findings of the high-output state and usually of severe generalized malnutrition and vitamin deficiency are present. Evidence of peripheral polyneuropathy with sensory and motor deficits is common ("dry beriberi"), as is the presence of nutritional "cirrhosis" characterized by paresthesias of the extremities, absent or decreased knee and

TABLE 17-7 -- DIAGNOSTIC CRITERIA FOR BERIBERI HEART

Clinical Features
Dependent edema
Low peripheral vascular resistance: decreased minimum blood pressure and increased pulse pressure
Hyperkinetic circulatory state: midsystolic murmur and third heart sound
Cardiomegaly
T-wave changes (inverted, diphasic, depressed) on electrocardiogram
Peripheral neuritis
Dietary deficiency for at least 3 months or chronic alcoholism
Presence of Thiamine Deficiency
Decrease in blood thiamine concentration
Decrease in erythrocyte transketolase activity
Increase in TTP effect
Improvement After Adequate Thiamine Replacement

From Kawai C, Nakamura Y: The heart in nutritional deficiencies. In Abelmann WH (ed): Cardiomyopathies, Myocarditis, and Pericardial Disease. In Braunwald E (series ed): Atlas of Heart Diseases, vol 2. Philadelphia, Current Medicine, 1995, pp 7.1-7.18.

ankle jerks, painful glossitis, the anemia of combined iron and folate deficiency, and hyperkeratinized skin lesions.

Beriberi heart disease[158] [160] [161] is characterized by biventricular failure, sinus rhythm, and marked edema ("wet beriberi"). There is arteriolar vasodilatation; and the cutaneous vessels may be dilated, or in later cases with heart failure they may be constricted. Therefore, the absence of warm hands does not exclude the diagnosis of beriberi. A third heart sound and an apical systolic murmur are heard almost invariably, and there is a wide pulse pressure characteristic of the hyperkinetic state.

Heart failure may develop explosively in beriberi, and some patients succumb to the illness within 48 hours of the onset of symptoms. *Shoshin* (Japanese for "acute damage

to the heart") *beriberi,* found most frequently in Asia and Africa, is a fulminant form of thiamine deficiency[162] [163] characterized by hypotension, tachycardia, and lactic acidosis. If left untreated, patients with this disorder die within hours of cardiogenic shock and pulmonary edema. Thus, because the course of the disease may advance rapidly, treatment must be begun immediately once the diagnosis has been established. In the Western world, this fulminant form of the disease is uncommon.

LABORATORY FINDINGS.

The electrocardiogram characteristically exhibits low voltage of the QRS complex, prolongation of the QT interval, and low voltage or inversion of T waves, most commonly in the right precordial leads. The chest roentgenogram usually shows biventricular enlargement, pulmonary congestion, and pleural effusions. In alcoholics with beriberi heart disease, the left ventricular ejection fraction and peak rate of rise of left ventricular pressure are usually reduced.[161] The role played by alcoholic cardiomyopathy (see Chap. 48) in this hemodynamic picture is not clear. The cardiac output falls, and the peripheral resistance rises acutely when thiamine is administered in the catheterization laboratory (see Fig. 17-16). [160] [161]

Laboratory diagnosis of thiamine deficiency can be made by demonstration of increased serum pyruvate and lactate levels in the presence of a low red blood cell transketolase level.[160] [164] Enhancement in transketolase activity resulting from added thiamine pyrophosphate (TPP) is referred to as the TPP effect. A TPP effect greater than 15 percent suggests thiamine deficiency. The thiamine concentration may be determined in biological fluids to confirm the diagnosis. Finally, an objective clinical and hemodynamic response to thiamine administration (see later) is considered diagnostic.

At *postmortem examination,* the heart usually shows simple dilation without other changes. On microscopic examination, there is sometimes edema and hydropic degeneration of the muscle fibers. Nonspecific but abnormal histological and electron microscopic changes have been found in cardiac biopsy specimens.

TREATMENT.

Akbarian and coworkers have reported careful hemodynamic studies that suggest that vasomotor depression or paralysis may be responsible for the depressed vascular resistance.[165] They studied four patients in whom ethanol excess was responsible for the thiamine deficiency. All had increased heart rate and cardiac index (averaging 6 liters/min/m[2]) and reduced arterial-mixed venous oxygen difference and systemic vascular resistance. Right and left ventricular filling pressures and blood volume were also elevated.

Patients with beriberi heart disease fail to respond adequately to digitalis and diuretics alone. However, improvement after the administration of thiamine (up to 100 mg intravenously followed by 25 mg/day orally for 1 to 2 weeks) may be dramatic. Marked diuresis, decrease in heart rate and size, and clearing of pulmonary congestion may occur within 12 to 48 hours.[158] [165] However, the acute reversal of the vasodilation

induced by correction of the deficiency may cause

Figure 17-16 Hemodynamic changes in beriberi heart disease before and after treatment with intravenous thiamine in patients younger than or older than or equal to 20 years of age. Wet beriberi is characterized by increases in cardiac index *(A),* stroke index *(B),* heart rate *(C),* blood turnover rate *(D)* and circulating blood volume *(E),* and a decrease in peripheral vascular resistance *(F),* particularly in younger patients. Thiamine replacement results in a rapid reversal of the high output state. (From Kawai C, Nakamura Y: The heart in nutritional deficiencies. *In* Abelmann WH [ed]: Cardiomyopathies, Myocarditis, and Pericardial Disease. *In* Braunwald E [series ed]: Atlas of Heart Diseases. Vol 2. Philadelphia, Current Medicine, 1995, pp 7.1-7.18.)

the unprepared left ventricle to go into low-output failure. Therefore, patients should receive a glycoside and diuretic therapy along with thiamine. Thiamine replacement also results in improvement in the polyneuropathy caused by thiamine deficiency.[166]

In endemic areas, effective management of beriberi heart disease also involves disease prevention. Recommendations include (1) ingestion of germ-retaining polished rice, undermilled rice, or rice enriched with thiamine, (2) avoidance of excessive intake of carbonated beverages and strenuous exercise during hot summer months, (3) avoidance of chronic diuretic therapy, and (4) baking or boiling foods that contain thiaminase, such as clams or raw fish.

Latent thiamine deficiency may occur in conditions such as alcoholic cardiomyopathy and in other forms of refractory heart failure, possibly related to chronic furosemide therapy.[167] Postulated mechanisms for the thiamine-wasting effects of furosemide include increased urinary excretion[168] and decreased myocardial uptake.[169] Other clinical situations in which latent thiamine deficiency may develop include chronic ambulatory peritoneal dialysis or hemodialysis and refeeding after starvation. The possibility of thiamine deficiency should be considered in patients with heart failure of obscure origin.

Paget's Disease

PATHOGENESIS.

Paget's disease of bone (osteitis deformans) is an asymmetrical process characterized by excessive resorption of bone followed by replacement of normal marrow with vascular, fibrous connective tissue and of resorbed bone with coarse, trabecular bone. Paget's disease is most commonly asymptomatic and is diagnosed on a plain film or because of a high serum alkaline phosphatase level obtained for other reasons. Because of the increased vascularity of bone affected by Paget's disease, it has been assumed that this high flow occurred through the involved bone. However, it appears that the additional blood flow through an affected, resting limb passes through the

cutaneous tissue overlying the involved bone, possibly secondary to local heat production resulting from the increased metabolic activity of affected bone.[170] Increased production of interleukin-6 by pagetic bone and marrow cells of Paget's disease,[171] and secondary hyperparathyroidism contribute to the progression of disease.

CLINICAL FINDINGS.

These are a function of the extent of the disease and the specific bones involved. Involvement of at least 15 percent of the skeleton by Paget's disease in an active stage, accompanied by a high alkaline phosphatase level, is necessary before a clinically significant augmentation of cardiac output is observed. Such a high-output state may be well tolerated for years with the patient remaining asymptomatic.[171] However, if a specific cardiac disorder (e.g., valvular disease, coronary stenosis) is present, the combination may cause rapid clinical deterioration.

The cardiovascular findings are not distinguishable from those in other conditions with high-output states. However, metastatic calcifications are characteristic, and, if they involve the heart, may lead to sclerosis and calcification of the valve rings, with extension into the interventricular septum. The electrocardiogram may show atrioventricular conduction disturbance or bundle branch block. Echocardiograms often demonstrate aortic sclerosis or stenosis, as well as left ventricular dilation, hypertrophy, and mild systolic dysfunction.[172]

Other Causes of High-Output Cardiac Failure

FIBROUS DYSPLASIA.

This condition, in which there is proliferation of fibrous tissue in bone, also may be associated with an elevated cardiac output, especially when multiple bones are involved.[173] *McCune-Albright syndrome*, a congenital disorder characterized by polyostotic fibrous dysplasia, cafe au lait spots, and sexual precocity, is more common in females (10:1) and has been linked to post-zygotic mutations in genes encoding G_{alphas} proteins.[174] Calcitonin may be an effective treatment in widespread disease.

MULTIPLE MYELOMA.

Increased cardiac output and less commonly high-output heart failure have been described in this condition.[175] The mechanism is not clear; it may be due to the associated anemia and/or hyperperfusion of the neoplastic tissue, especially in patients with extensive bone disease.[176] Arteriovenous shunting has been demonstrated in involved bones using intraarterial injection of radiolabeled albumin and correlates with cardiac index.[177]

OTHER CONDITIONS.

High-output heart failure also occurs in pregnancy (see Chap. 65), renal disease,

especially glomerulonephritis (see Chap. 72), cor pulmonale (see Chap. 54), polycythemia vera (see Chap. 69), the carcinoid syndrome (see Chap. 48), and marked obesity.[177A]

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Pulmonary Edema

MECHANISM OF PULMONARY EDEMA

ALVEOLAR-CAPILLARY MEMBRANE.

Pulmonary edema develops when the movement of liquid from the blood to the interstitial space, and in some instances to the alveoli, exceeds the return of liquid to the blood and its drainage through the lymphatics.[178] The barrier between pulmonary capillaries and alveolar gas, the alveolar-capillary membrane, consists of three anatomical layers with distinct structural characteristics: (1) cytoplasmic projections of the capillary endothelial cells that join to form a continuous cytoplasmic tube; (2) the interstitial space, which varies in thickness and may contain connective tissue fibrils, fibroblasts, and macrophages between the capillary endothelium and the alveolar epithelium, terminal bronchioles, small arteries and veins, and lymphatic channels; and (3) the lining of the alveolar wall, which is continuous with the bronchial epithelium and is composed predominantly of large squamous cells (type I) with thin cytoplasmic projections.

There is normally a continuous exchange of liquid, colloid, and solutes between the vascular bed and interstitium.[179] A pathological state exists only when there is an increase in the net flux of liquid, colloid, and solutes from the vasculature into the interstitial space. Experimental studies have confirmed that the basic principles outlined in the classic Starling equation apply to the lung as well as to the systemic circulation.$Q_{(iv\text{-}int)} = K_f [(P_{iv} - P_{int}) - sigma_f (II_{iv} - II_{int})]$where Q=net rate of transudation (flow of liquid from blood vessels to interstitial space), P_{int} =interstitial hydrostatic pressures, P_{iv} =intravascular hydrostatic pressures, II_{int} =interstitial colloid osmotic pressure, II_{iv}

=intravascular colloid osmotic pressure, $sigma_f$ =reflection coefficient for proteins, and K_f =hydraulic conductance.

LYMPHATICS.

These vessels serve to remove solutes, colloid, and liquid derived from the blood vessels. Because of a more negative pressure in the peribronchial and perivascular interstitial space and the increased compliance of this nonalveolar interstitium, liquid is more likely to increase here once the pumping capacity of the lymphatic channels is exceeded. As a consequence of the development of interstitial edema, small airways and blood vessels may become compressed.

The lymphatics play a key role in removing liquid from the interstitial space, and if the pumping capacity of the lymphatic channels is exceeded, pulmonary edema will occur. It has been estimated that an average 70-kg person at rest has a Q_{lymph} of approximately 20 ml/hr,[180] and experimentally, lymph flow rates of up to 10 times control values have been reported. Thus it is possible that lymphatic pumping capacity can be as great as 200 ml/hr in an average-sized adult. With chronic elevations of left atrial pressure, the pulmonary lymphatic system hypertrophies and is able to transport greater quantities of capillary filtrate, thereby protecting the lungs from edema. By contrast, a sudden marked increase in pulmonary capillary pressure can be rapidly fatal in a patient not preconditioned by growth of the lymphatic drainage system.

SEQUENCE OF FLUID ACCUMULATION DURING PULMONARY EDEMA.

Whether initiated by an imbalance of Starling forces or by primary damage to the various components of the alveolar-capillary membranes, the sequence of liquid exchange and accumulation in the lungs is the same and can be represented in three stages. In *stage 1,* there is an increase in mass transfer of liquid and colloid from blood capillaries through the interstitium. Despite the increased filtration, there is no measurable increase in interstitial volume because there is an equal increase in lymphatic outflow. *Stage 2* occurs when the filtered load from the pulmonary capillaries is sufficiently large that the pumping capacity of the lymphatics is approached or exceeded, and liquid and colloid begin to accumulate in the more compliant interstitial compartment surrounding bronchioles, arterioles, and venules. In *stage 3,* further increments in filtered load exceed the volume limits of the loose interstitial spaces, causing distention of the less compliant interstitial space of the alveolar-capillary septum and resulting in alveolar flooding.

GRAVITY DEPENDENCE OF PULMONARY EDEMA.

Because blood is more dense than gas-containing lung, the effects of gravity are much greater on the distribution of blood flow than on the distribution of tissue forces in the lung. From apex to base, the effective perfusion pressure of the pulmonary circulation (P_{pa}) increases by approximately

Figure 17-17 Schematic representation of the gravity-dependent, apex-to-base distribution of pulmonary blood flow in an upright lung. Pulmonary artery pressure (P_a) and pulmonary venous pressure (P_v) increase on a hydrostatic basis as the base is approached. Alveolar pressure (P_A) is constant with vertical distance. (The three zones are described in detail in the text.)

1 cm H_2O/cm vertical distance, whereas pleural pressures (P_{p1}) increase by only 0.25 cm H_2O/cm vertical distance.[181] Pulmonary capillaries (or alveolar vessels) are exposed to alveolar pressure (P_{alv}), which does not vary from apex to base. In contrast, pulmonary arteries, arterioles, veins, and venules (extraalveolar vessels) are exposed to pleural pressure, which does vary from apex to base. The consequences of these differences in forces on ventilation-perfusion relationships are described in three zones (Fig. 17-17) . In *zone 1* (apex), pulmonary arterial pressure is less than alveolar pressure, and thus blood flow is strikingly diminished. In *zone 2* (midlung), arterial pressure exceeds alveolar pressure, which in turn exceeds venous pressure. In *zone 3* (base), venous pressure exceeds alveolar pressure, resulting in distention of collapsible capillaries. Mean intravascular pressures are greatest in this zone; hence, with elevations of venous pressure or with disruption of alveolar-capillary membranes, edema formation is both more rapid and greatest at the lung bases.

In normal, erect humans, perfusion is greater in the basilar lung regions than in the apical ones. Deviation from this gravity-dependent pattern has been called *vascular redistribution,* a relative reduction in perfusion of the bases with a relative increase in apical perfusion. This phenomenon is most likely due to compression of the lumina of basilar vessels secondary to the greater and more rapid formation of edema at the lung bases and the tendency for extravascular liquid formed elsewhere to gravitate toward the bases. The situation that occurs with chronic elevations of left atrial pressure, as in mitral stenosis or chronic heart failure, should be contrasted to that of acute pulmonary edema. Clinical experience with such chronic conditions suggests that redistribution of blood flow does occur, but with minimal or no evidence of interstitial edema and often in the absence of alveolar edema.

Classification of Pulmonary Edema

The two most common forms of pulmonary edema are that initiated by an imbalance of Starling forces and that initiated by disruption of one or more components of the alveolar-capillary membrane (Table 17-8) .[182] [183] Less often, lymphatic insufficiency can be involved as a predisposing, if not initiating, factor in the genesis of edema. Although the initiating or primary mechanism may be clearly identifiable, multiple factors come into play during the development of edema; and irrespective of the initiating event, the stage of alveolar flooding is characterized to some degree by disruption of the alveolar-capillary membrane.[184]

Imbalance of Starling Forces

INCREASED PULMONARY CAPILLARY PRESSURE.

Pulmonary edema will occur only when the pulmonary capillary pressure rises to values exceeding the plasma colloid osmotic pressure, which is approximately 28 mm Hg in the human. Because the normal pulmonary capillary pressure is 8 to 12 mm Hg, there is a substantial margin of safety in the development of pulmonary edema. Although pulmonary capillary pressures must be abnormally high to increase the flow of interstitial fluid, at a time when edema is clearly present these pressures may not correlate with the severity of pulmonary edema.[185] In fact, pulmonary capillary wedge pressures may have returned to normal at a time when there is still considerable pulmonary edema, because time is required for removal of both interstitial and alveolar edema. Other factors obscure the relationship between the severity of edema and measured pulmonary capillary pressures in addition to slower rates of removal after edema has collected. The rate of increase in lung liquid at any given elevation of capillary pressure is

TABLE 17-8 -- CLASSIFICATION OF PULMONARY EDEMA BASED ON INITIATING MECHANISM

I. Imbalance of Starling forces
A. Increased pulmonary capillary pressure
1. Increased pulmonary venous pressure without left ventricular failure (e.g., mitral stenosis)
2. Increased pulmonary venous pressure secondary to left ventricular failure
3. Increased pulmonary capillary pressure secondary to increased pulmonary arterial pressure (so-called overperfusion pulmonary edema)*
B. Decreased plasma oncotic pressure: hypoalbuminemia secondary to renal, hepatic, protein-losing enteropathic, or dermatological disease or nutritional causes
C. Increased negativity of interstitial pressure
1. Rapid removal of pneumothorax with large applied negative pressures (unilateral)
2. Large negative pressures due to acute airway obstruction along with increased end-expiratory volumes (asthma)*
D. Increased interstitial oncotic pressure: no known clinical or experimental example
II. Altered alveolar-capillary membrane permeability (acute respiratory distress syndrome)
A. Infectious pneumonia--bacterial, viral, parasitic
B. Inhaled toxins (e.g., phosgene, ozone, chlorine, Teflon fumes, nitrogen dioxide, smoke)

C. Circulating foreign substances (e.g., snake venom, bacterial endotoxins, alloxan , alpha-naphthyl thiourea)

D. Aspiration of acidic gastric contents

E. Acute radiation pneumonitis

F. Endogenous vasoactive substances (e.g., histamine, kinins*)

G. Disseminated intravascular coagulation

H. Immunological--hypersensitivity pneumonitis, drugs (nitrofurantoin), leukoagglutinins

I. Shock lung in association with nonthoracic trauma

J. Acute hemorrhagic pancreatitis

III. Lymphatic insufficiency

A. Post lung transplant

B. Lymphangitic carcinomatosis

C. Fibrosing lymphangitis (e.g., silicosis)

IV. Unknown or incompletely understood

A. High-altitude pulmonary edema

B. Neurogenic pulmonary edema

C. Heroin overdose

D. Pulmonary embolism

E. Preeclampsia-eclampsia

F. Post cardioversion

G. Post anesthesia

H. Post cardiopulmonary bypass

*Not certain to exist as a clinical entity.

Not certain that this, as a single factor, leads to clinical pulmonary edema.

Predominantly an experimental technique.

related to the functional capacity of lymphatics, which may vary from patient to patient, and to variations in interstitial oncotic and hydrostatic pressures.

HYPOALBUMINEMIA.

Pulmonary edema does not develop with hypoalbuminemia alone. However, hypoalbuminemia may alter the fluid conductivity of the interstitial space so that liquid moves more easily between capillaries and lymphatics.[186] Therefore, in addition to hypoalbuminemia, there must be some elevations of pulmonary capillary pressure, but only small increases are necessary before pulmonary edema ensues in the presence of hypoalbuminemia. Indeed, in such patients, only moderate fluid overload can precipitate overt pulmonary edema in the absence of left ventricular failure.

INCREASED NEGATIVE INTERSTITIAL PRESSURE.

Pulmonary edema may be associated with rapid removal of pleural air to relieve a pneumothorax--so-called reexpansion pulmonary edema.[187] Usually, the pneumothorax has been present for several hours to days, allowing time for alterations in surfactant so that large negative pressures are necessary to open collapsed alveoli. In these instances, the edema is unilateral and is most often only a radiographic finding with few clinical findings. In rare cases, reexpansion pulmonary edema may be severe and require rapid and extensive clinical treatment.[187] Studies using radiolabeled transferrin suggest that an abnormality in microvascular permeability contributes to the development of localized pulmonary edema.[188]

PRIMARY ALVEOLAR-CAPILLARY MEMBRANE DAMAGE

Many diverse medical and surgical conditions are associated with pulmonary edema that is due to damage of the alveolar-capillary membrane, rather than to a primary alteration in Starling forces. These conditions include acute pulmonary infections and pulmonary effects of gram-negative sepsis and nonthoracic trauma, as well as any condition associated with disseminated intravascular coagulation.[182] [189] Despite the diversity of underlying causes, once diffuse alveolar-capillary injury has occurred, the pathophysiological and clinical sequence of events is quite similar in most patients. Because of the resemblance of the clinical picture to that seen with respiratory distress of the neonate, these conditions have been referred to as the *acute respiratory distress syndrome* (ARDS).[190] [191]

Direct evidence for increased capillary permeability has come mainly from experimental studies in which pulmonary edema has been produced by endotoxin infusion; hemorrhagic shock[192] ; infusion of oleic acid,[193] alloxan, thiourea,[194] phorbol myristate acetate, or complement fragments[195] ; freebase cocaine smoking [196] ; and inhalation of high concentrations of oxygen[197] or toxic gases, such as phosgene, ozone,[198] and nitrogen dioxide.[199] It is probable, though not yet proved, that increased permeability of the alveolar-capillary membrane is an initiating event in most of the cases designated as ARDS.

Cardiogenic Pulmonary Edema

CLINICAL MANIFESTATIONS.

During *stage 1*, the distention and recruitment of small pulmonary vessels secondary to elevation of left atrial pressure may actually improve gas exchange in the lung and augment slightly the diffusing capacity for carbon monoxide. It is doubtful that any symptoms, except for exertional dyspnea, accompany these abnormalities, and physical findings in the lungs would be scarce except for mild inspiratory rales due to opening of closed airways. With progression to *stage 2*, *interstitial edema* attributable to increased liquid in the loose interstitial space contiguous with the perivascular tissue of larger vessels may cause a loss of the normally sharp radiographic definition of pulmonary vascular markings, haziness and loss of demarcation of hilar shadows, and thickening of interlobular septa (Kerley B lines)[200] (see Fig. 8-18*B*). Competition for space between vessels, airways, and increased liquid within the loose interstitial space may compromise small airway lumina, particularly in the dependent portions of the lungs, and there may be reflex bronchoconstriction. A mismatch exists between ventilation and perfusion that results in hypoxemia and more wasted ventilation. Indeed, in the setting of acute myocardial infarction, the degree of hypoxemia correlates with the degree of elevation of the pulmonary capillary wedge pressure. Tachypnea is a frequent finding with interstitial edema and has been attributed to stimulation by the edema of interstitial J-type receptors or to stretch receptors in the interstitium rather than to hypoxemia, which is rarely of sufficient magnitude to stimulate breathing. There are few changes in the standard spirometric indices.

With the development of alveolar flooding, or *stage 3* edema, gas exchange is quite abnormal, with severe hypoxemia and often hypocapnia. Alveolar flooding can proceed to such a degree that many large airways are filled with blood-tinged foam that can be expectorated. Vital capacity and other lung volumes are markedly reduced. A right-to-left intrapulmonary shunt develops as a consequence of perfusion of the flooded alveoli. Although hypocapnia is the rule, hypercapnia with acute respiratory acidemia can occur in more severe cases or in patients with concomitant chronic obstructive pulmonary disease. It is in such instances that morphine, with its well-known respiratory depressant effects, should be used with caution.

DIAGNOSIS.

Acute cardiogenic pulmonary edema is the most dramatic symptom of left-sided heart failure.[201] Impaired left ventricular systolic and/or diastolic function, mitral stenosis, or whatever causes elevated left atrial and pulmonary capillary pressures leads to cardiogenic pulmonary edema, which, in turn, interferes with oxygen transfer in the lungs and depresses arterial oxygen tension. Simultaneously, the sensation of suffocation and oppression in the chest intensifies the patient's fright, elevates heart rate and blood pressure, and further restricts ventricular filling. The increased discomfort and work of breathing place an additional load on the heart, and cardiac function becomes depressed further by the hypoxia. If this vicious circle is not interrupted, it may lead rapidly to death.

Acute cardiogenic pulmonary edema differs from orthopnea and paroxysmal nocturnal

dyspnea in the more rapid and extreme development of pulmonary capillary hypertension. Acute pulmonary edema is a terrifying experience for the patient and often the bystander as well. Usually extreme breathlessness develops suddenly, and the patient becomes extremely anxious, coughs, and expectorates pink, frothy liquid, causing him or her to feel as if he or she is literally drowning. The patient sits bolt upright, or may stand, exhibits air hunger, and may thrash about. The respiratory rate is elevated, the alae nasi are dilated, and there is inspiratory retraction of the intercostal spaces and supraclavicular fossae that reflects the large negative intrapleural pressures required for inspiration. The patient often grasps the sides of the bed to allow use of the accessory muscles of respiration. Respiration is noisy, with loud inspiratory and expiratory gurgling sounds that are often easily audible across the room. Sweating is profuse, and the skin is usually cold, ashen, and cyanotic, reflecting low cardiac output and increased sympathetic drive.

On auscultation, there are many adventitious lung sounds, with rhonchi, wheezes, and moist and fine crepitant rales that appear at first over the lung bases but then extend upward to the apices as the condition worsens. Cardiac auscultation may be difficult because of the respiratory sounds, but a third heart sound and an accentuated pulmonic component of the second heart sound are frequently present.

The patient may suffer from intense precordial pain if the pulmonary edema is secondary to acute myocardial infarction (see Chap. 35). Unless cardiogenic shock is present, arterial pressure is usually elevated above the patient's normal level as a result of excitement and discomfort, which cause adrenergically mediated vasoconstriction. Because of the presence of systemic hypertension, it may be suspected (inappropriately) that the pulmonary edema is due to hypertensive heart disease. However, it should be noted that the latter condition is now quite uncommon, and if arterial pressure is elevated, examination of the fundi will usually indicate whether or not hypertensive heart disease is actually present.

DIFFERENTIATION FROM BRONCHIAL ASTHMA.

It may be difficult to differentiate severe bronchial asthma from acute pulmonary edema, since both conditions may be associated with extreme dyspnea, pulsus paradoxus, demands

for an upright posture, and diffuse wheezes that interfere with cardiac auscultation. In bronchial asthma, there is usually a history of previous similar episodes and the patient is frequently aware of the diagnosis. During the acute attack, the asthmatic patient does not usually sweat profusely, and arterial hypoxemia, although present, is not usually of sufficient magnitude to cause cyanosis. In addition, the chest is hyperexpanded and hyperresonant and use of accessory muscles is most prominent during respiration. The wheezes are more high pitched and musical than in pulmonary edema, and other adventitious sounds such as rhonchi and rales are less prominent.

The patient with acute cardiogenic pulmonary edema usually perspires profusely and is frequently cyanotic, owing to desaturation of arterial blood and decreased cutaneous blood flow. The chest is often dull to percussion, there is no hyperexpansion, accessory muscle use is less prominent than in asthma, and moist, bubbly rales and rhonchi are heard in addition to wheezes. As the patient recovers, the radiological appearance of pulmonary edema usually resolves more slowly than the elevated pulmonary capillary wedge pressure.

PULMONARY CAPILLARY WEDGE PRESSURE MEASUREMENTS.

Measurement of pulmonary capillary wedge pressure by means of a flow-directed catheter (see Chap. 11) may be critical in the differentiation between pulmonary edema secondary to an imbalance of Starling forces (i.e., cardiogenic pulmonary edema) and that secondary to alterations of the alveolar-capillary membrane. Specifically, a pulmonary capillary wedge or pulmonary artery diastolic pressure exceeding 25 mm Hg in a patient without previous pulmonary capillary pressure elevation (or exceeding 30 mm Hg in a patient with chronic pulmonary capillary hypertension) and with the clinical features of pulmonary edema strongly suggests that the edema is cardiogenic.

After effective treatment of the pulmonary edema, patients are often restored rapidly to the condition that existed before the attack, although they usually feel exhausted. Between attacks of pulmonary edema, there may be few symptoms or signs of heart failure.

Pulmonary Edema of Unknown Pathogenesis

HIGH-ALTITUDE PULMONARY EDEMA (HAPE).

HAPE is a noncardiogenic pulmonary edema that occurs most commonly in healthy young adults who ascend rapidly to altitudes in excess of 2500 m and who then engage in strenuous exercise at that altitude before they have become acclimated.[202] [203] [204] [205] [206] Estimates place the incidence at 6.4 clinically apparent cases per 100 exposures to high altitude in persons younger than 21 years of age and 0.4 cases per 100 exposures in those older than 21 years. In addition to age, the major factors that determine the occurrence of HAPE are the altitude, the speed of ascent, and individual susceptibility. Usually within 1 day of ascent, affected individuals complain of cough, dyspnea, and reduced exertional tolerance. These symptoms may progress rapidly as pulmonary edema worsens and may be associated with chest pain, orthopnea, and pink frothy sputum. Clinical evaluation reveals tachycardia, bilateral rales, and cyanosis, accompanied by marked arterial hypoxemia and radiographic evidence of discrete, patchy pulmonary infiltrates. As HAPE progresses and then resolves, pulmonary infiltrates often become diffuse and homogeneous.

A central abnormality in the pathophysiology of HAPE is an abnormal rise in pulmonary artery pressures and pulmonary vascular resistance in response to hypoxia (Fig. 17-18) . [202] [204] Possible mechanisms underlying the exaggerated hypoxic pulmonary vascular

response in susceptible individuals include a decreased hypoxic ventilatory response, increased sympathetic activity, and augmented release and/or decreased clearance of endothelin-1.[205] The association of HAPE with the major histocompatibility antigens HLA-DR6 and HLA-DQ4 also suggests an immunogenetic susceptibility.[206] [206A] Inhomogeneous vasoconstriction during exercise resulting in overperfused areas and "stress failure" of the pulmonary capillaries[203] is believed to contribute to the development of pulmonary edema.

Reversal of this syndrome is both rapid (less than 48 hours) and certain, either by returning the patient to a lower altitude and/or by administering a high inspiratory concentration of oxygen. Sleeping below 2500 m, slow ascent with gradual acclimatization, and avoidance of heavy exertion for the first 2 or 3 days at high altitude are thought to be preventive. Nifedipine has been used successively both in the treatment of clinical HAPE and as prophylaxis.[207] Inhaled nitric oxide, either alone or in combination with supplemental oxygen, may also be effective in lowering pulmonary vascular resistance and improving gas exchange.[208]

NEUROGENIC PULMONARY EDEMA.

A variety of central nervous system disorders including head trauma, seizures, and subarachnoid hemorrhage can be associated with acute pulmonary edema (without detectable left ventricular dysfunction).[209] [210] It is believed that sympathetic overactivity shifts blood from the systemic to the pulmonary circulation, with secondary elevations of left atrial and pulmonary capillary pressures. Thus, an imbalance of Starling forces (i.e., a hydrostatic

Figure 17-18 Diagram to show the sequence of events in the pathogenesis of high altitude pulmonary edema (HAPE). (From West JB, Mathieu-Costello O: High-altitude pulmonary edema is caused by stress failure of pulmonary capillaries. Int J Sports Med 13:S54, 1992.)

mechanism[211]) may be the basis for this form of pulmonary edema. Pulmonary capillary leak due to pressure-induced mechanical injury and/or direct nervous system control over capillary permeability may also play a contributory role.[212] [213] Treatment consists of ventilatory support and maneuvers to reduce intracranial pressure. A reversible impairment in left ventricular systolic function resulting in hypotension may accompany noncardiogenic pulmonary edema.[214]

NARCOTIC OVERDOSE PULMONARY EDEMA.

First described by Osler in 1880, acute pulmonary edema is a well-recognized sequela of heroin overdose.[215] [216] [217] Because of the illicit traffic in this drug, which is given by the intravenous route, the syndrome was initially thought to be due to injected impurities

rather than to the heroin itself. However, because oral methadone and dextropropoxyphene also can be associated with pulmonary edema,[218] [219] the syndrome cannot be attributed entirely to injected impurities. The fact that edema fluid contains protein concentrations nearly identical to those found in plasma[220] and that pulmonary capillary wedge pressures, when measured, are normal[221] argues for an alveolar-capillary membrane leak as the initiating cause.

PULMONARY EMBOLISM (see Chap. 52).

Acute pulmonary edema in association with either a massive embolus or multiple smaller emboli has been well described and most often attributed to concomitant left ventricular dysfunction due to a combination of hypoxemia and encroachment of the interventricular septum on the left ventricular cavity.[222] It has been suggested that in the pulmonary edema due to pulmonary microthrombi an increase in permeability of the alveolar-capillary membrane occurs.[189] [223]

ECLAMPSIA (see Chap. 65).

Acute pulmonary edema is a well-recognized complication of preeclampsia-eclampsia, occurring with an overall frequency of 3 percent.[224] [225] The incidence is higher in women who are older, who are multiparous, and who have preexisting chronic hypertension. The majority of cases, approximately 70 percent, occur post partum. Multiple factors including cerebral dysfunction with massive sympathetic discharge, left ventricular dysfunction secondary to acute systemic hypertension, hypervolemia due to excessive colloid and crystalloid infusions, hypoalbuminemia secondary to renal losses, and disseminated intravascular coagulation may play a role in the pathogenesis. Invasive studies commonly reveal increased pulmonary capillary pressures, elevated cardiac index, and normal systemic vascular resistance, although hemodynamics consistent with pulmonary capillary leak have also been reported.[226] [227] Echocardiography may show normal, hyperdynamic, or depressed left ventricular systolic function with or without diastolic dysfunction.[228] The occurrence of pulmonary edema in obstetrical patients is associated with high maternal and perinatal morbidity and mortality.[225]

POST CARDIOVERSION.

Although pulmonary edema has been documented to occur after cardioversion,[229] the mechanism is poorly understood. Ineffective left atrial function immediately after cardioversion has been suggested as a contributing factor, yet left ventricular dysfunction[229A] and neurogenic mechanisms are also possible. Additional contributory factors may include underlying cardiac disease, cardiodepressant anesthetic agents, and pulmonary and/or cardiac emboli. One half of cases occur within 3 hours after cardioversion, and mortality has been reported to be as high as 18 percent.[229]

POST ANESTHESIA.

In previously healthy subjects, pulmonary edema has been found in the early

postanesthesia period without a clear relationship to fluid overload or any subsequent evidence of left ventricular dysfunction.[230] The basis for this disorder is unknown, but proposed mechanisms include postanesthesia laryngospasm with marked negative intrathoracic pressure,[230A] hypoxia, and/or a hyperadrenergic state.

POST CARDIOPULMONARY BYPASS.

Although all patients who undergo cardiopulmonary bypass obviously have significant heart disease, the development of edema has been associated with normal left atrial pressures.[231] Alterations of surfactant due to prolonged collapse of the lung during the procedure, with subsequent need to apply high negative intrapleural pressures for reexpansion, and release of toxic substances including thromboxane have been suggested as mechanisms. Some data suggest that allergic reactions to fresh frozen plasma or protamine may account for some episodes.[231] The matter is far from settled, but the syndrome is fortunately rare.

HANTAVIRUS PULMONARY SYNDROME.

In Asia, hantaviruses are associated with hemorrhagic fever and renal disease. In 1993, an outbreak of severe respiratory illness occurred in the southwestern United States and was attributed to a newly described hantavirus.[232] The majority of patients affected were Native American. Prodromal symptoms included fever, myalgia, cough, dyspnea, and gastrointestinal symptoms. Most infected patients developed rapidly progressive noncardiogenic pulmonary edema associated with profound hypotension, with a case-fatality rate of 76 percent. Local T cells acting on the infected pulmonary vascular endothelium result in the production of cytokines, including interferon gamma and tumor necrosis factor-alpha, which may play an important role in the reversible increase in vascular permeability.[233]

Differential Diagnosis of Pulmonary Edema

The differentiation between the two principal forms of pulmonary edema, that is, cardiogenic (hemodynamic) and noncardiogenic (caused by alterations in the alveolar-capillary membrane), usually can be made through assessment of the clinical context in which it occurs and through examination and consideration of the clinical data as shown in Table 17-9 . Although this approach suggests an either/or situation, this may not be the case in reality. For example, sudden and large increases in intravascular pressure may disrupt the capillary and alveolar membranes leading to interstitial edema and alveolar loading with macromolecules that produce an edema liquid more compatible with noncardiogenic causes.[234] Thus, a primary hemodynamic event can cause an alveolar-capillary membrane leak. Furthermore, only mild elevations in capillary hydrostatic pressures in the presence of alveolar capillary damage can cause an increase in the rate and extent of edema formation. Therefore, hemodynamic factors can and do play a role in increasing and perpetuating increased permeability.

TABLE 17-9 -- INITIAL DIFFERENTIATION OF CARDIOGENIC FROM NONCARDIOGENIC PULMONARY EDEMA

	CARDIOGENIC PULMONARY EDEMA	NONCARDIOGENIC PULMONARY EDEMA
History		
Acute cardiac event	Usually	Uncommon (but possible)
Physical Examination		
Cardiac output state	Low-flow state (cool periphery)	High-flow state (warm periphery, bounding pulses)
S_3 gallop	Present	Absent
Jugular venous distention	Present	Absent
Crackles	Wet	Dry
Underlying noncardiac disease (e.g., peritonitis)	Usually absent	Present
Laboratory Tests		
Electrocardiogram	Ischemia/infarction	Usually normal
Chest x-ray	Perihilar distribution	Peripheral distribution
Cardiac enzymes	May be elevated	Usually normal
Pulmonary capillary pressure	>18 mm Hg	<18 mm Hg
Intrapulmonary shunting	Small	Large
Edema fluid/serum protein	<0.5	>0.7

From Sibbald WJ, Cunningham DR, Chin DN: Noncardiac or cardiac pulmonary edema? A practical approach to clinical differentiation in critically ill patients. Chest 84:460, 1983.

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Chapter 18 - Treatment of Heart Failure: Pharmacological Methods

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Pharmacological therapy for heart failure (HF) is divided into two distinct settings and approaches: treatment of *decompensated HF* and treatment of *chronic stable HF* (Table 18-1) . The goals of these two types of treatment are different, and part of the challenge of treating individual HF patients is the art of converting patients in the former category to the latter. In the treatment of patients with decompensated HF, the goals are to stabilize the patient clinically, restore organ perfusion, return filling pressure to optimal levels, and begin the conversion to chronic therapy. In contrast, the goals of treatment of patients with chronic stable HF are to enhance survival and minimize symptoms. As discussed below, diuretics, vasodilators, and positive inotropic agents are used for both purposes, while neurohormonal/cytokine inhibitors are primarily used to enhance survival.

TABLE 18-1 -- CLASSES OF DRUGS USED TO TREAT HEART FAILURE

DRUG CLASS	USE

Diuretics	
Carbonic anhydrase inhibitors (acetazolamide) Na+, K+, 2Cl-- cotransporter inhibitors ("loop" diuretics) Na+/Cl-- cotransporter inhibitors (thiazides) Epithelial Na+ channel inhibitors (triamterene, amiloride) Type I (mineralocorticoid/glucocorticoid) receptor antagonists (spironolactone) Vasopressin V_2 receptor antagonists Natriuretic peptides	DHF (IV), CSHF (p.o.) stage B-D (NYHA Class II-IV)
Vasodilators	
Nitrovasodilators "Directly acting" or unknown mechanism vasodilators Calcium channel blockers ATP-regulated K+ channel activators Vasodilator prostaglandins Natriuretic peptides Neurohormonal inhibitors	DHF (IV), CSHF (p.o.) stage B-D (NYHA Class II-IV)
Positive Inotropic Agents	
Digitalis derivatives Beta-adrenergic receptor agonists Phosphodiesterase inhibitors Phosphodiesterase inhibitors with calcium sensitizer action Pure calcium sensitizers	DHF (IV), CSHF (p.o.) stage B-D (NYHA Class II-IV)
Neurohormonal or Cytokine Inhibitors	
Renin-angiotensin-aldosterone inhibitors Antiadrenergic compounds Endothelin antagonists Neutral endopeptidase inhibitors Tumor necrosis factor-alpha inhibitors	CSHF (p.o. or other) stage A-D (NYHA Class I-IV)
Future/Novel Directions	
Gene therapy Pharmacogenomic-based therapy Novel molecular targets	No current indications

ATP=adenosine triphosphate; CSHF=chronic stable heart failure; DHF=decompensated heart failure; NYHA=New York Heart Association.

Diuretics

The importance of diuretics in the treatment of HF relates to the central role of the kidney as the target organ of many of the neurohumoral and hemodynamic changes that occur in response to a failing heart.[1] [2] [3] [4] The net effect of these physiological responses is an increase in salt and water retention, which results in expansion of the extracellular fluid volume. This effect is highlighted in Figure 18-1 , where the adrenergic and the renin-angiotensin (RAS) systems, two very important compensatory neurohormonal mechanisms that are activated in concert early in the course of HF, produce volume expansion. In the case of adrenergic mechanisms, volume expansion occurs via beta-adrenergic receptor-mediated nonosmotic release of vasopressin from the pituitary gland, and in the case of RAS mechanisms, volume expansion occurs through angiotensin II-mediated increases in aldosterone and vasopressin secretion and stimulation of thirst.[2] , [4] In the short-term, volume expansion serves to sustain cardiac output and tissue perfusion by allowing the heart to operate higher on the ventricular function (Frank-Starling) curve. However, these physiological adaptations also result in higher end-diastolic filling pressure and increased wall stress in diastole and systole, which contributes to hypertrophy and remodeling (see Chap. 16) and may cause dyspnea or even pulmonary edema.

With the exception of the aldosterone antagonist spironolactone (see p. 566), diuretics do not influence the natural history of chronic HF. However, diuretics improve congestive symptoms and may also slow the progression of ventricular remodeling by reducing ventricular filling pressure and wall stress. The acute effect of diuretics in patients with HF-related volume overload is to decrease left ventricular filling pressure without much change in cardiac output, because of the depressed and flat Frank-Starling curve in these subjects as depicted in Figure 18-2 .

Figure 18-1 Hemodynamic and biological consequences of coordinated activation of the adrenergic and renin-angiotensin systems in heart failure.

Figure 18-2 Frank-Starling relationship for ventricular function in heart failure. In patients with heart failure, the normal relationship between cardiac output (y-axis) and filling pressure (x-axis) is shifted lower and to the right such that a low-output state and congestive symptoms may be coincident. At one extreme, the addition of a pure inotropic agent, such as digoxin, primarily increases stroke volume with minimal impact on filling pressure. Conversely, the addition of a diuretic primarily decreases filling pressure without having an impact on cardiac output. Clinically, it is common to use multiple classes of agents, or agents with combined effects, to produce both increased cardiac output and decreased filling pressure. (Adapted from Cohn JN, Franciosa JA: Vasodilator therapy of cardiac failure [first of two parts]. N Engl J Med 297:27-31, 1977.)

RENAL ADAPTATION TO HEART FAILURE (see also Chap. 72)

Increased salt and water retention by the kidney is due primarily to characteristic

alterations in intrarenal hemodynamics that occur in response to decreased cardiac output. In addition, salt and water retention activates the adrenergic nervous system and several hormonal and cytokine systems (see Chap. 16) . A decrease in cardiac output results in increased peripheral and intrarenal vascular resistance, activation of intrarenal and other tissue vasoconstrictor systems such as endothelin, and release of arginine vasopressin (AVP, antidiuretic hormone) from the posterior pituitary gland. Increased adrenal cortical activity promotes aldosterone synthesis and release, while increased intraatrial and intraventricular pressure promotes the production and secretion of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in cardiac muscle.

INTRARENAL HEMODYNAMICS IN HEART FAILURE.

The changes in intrarenal hemodynamics that occur early in the course of HF result in preservation of the glomerular filtration rate (GFR) despite a decline in cardiac output and renal blood flow.[1] [2] [3] [4] Although increases in adrenergic activity and local release of angiotensin II act to increase resistance in both the afferent and efferent glomerular arterioles, preservation of the GFR is due in large part to a greater increase in efferent than in afferent arteriolar tone. Pressure differences across the glomerulus (P_{Gc}), and across the glomerular capillary membrane and Bowman's space (P_t) are two major determinants of single-nephron GFR. The other main determinants of single-nephron GFR are the glomerular membrane ultrafiltration coefficient (K_f), which tends to decline in HF, and differences between glomerular capillary and proximal tubular colloid osmotic pressure, which are usually unchanged in HF.

Maintenance of single-nephron GFR, despite a fall in renal blood flow and glomerular plasma flow, results in an increase in the fraction of renal plasma flow that is filtered by the kidney (i.e., the "filtration fraction"). This increase in the fraction of glomerular plasma flow, which alters the proximal tubule, leads to an increase in protein concentration and therefore in colloid osmotic pressure in the postglomerular,

peritubular capillaries since most proteins that contribute to oncotic pressure are not filtered by normal glomerular membranes. The increased filtration fraction also leads to an increase in hydrostatic pressure in the proximal tubule relative to the peritubular capillaries, which in addition to the increase in colloid osmotic pressure in this portion of the nephron, favors the reuptake of solute and water by the proximal tubule.

Besides their importance in mediating increased renal salt and water resorption in HF, these characteristic alterations in glomerular hemodynamics are often significantly affected by several classes of drugs used in the treatment of HF. The kidney's ability to autoregulate and sustain the GFR, despite a falling cardiac output in worsening HF, will be compromised by any drug that lowers mean arterial pressure. Therefore, the GFR may fall despite an increase in cardiac output after the administration of a vasodilator. The importance of efferent arteriolar tone to maintenance of the GFR in HF also means that administration of RAS antagonists may result in a decline in GFR in some patients

despite clinically significant increases in cardiac output.

NEUROHORMONAL/CYTOKINE ACTIVATION.

In addition to these hemodynamic changes in the proximal nephron, increased renal sympathetic nerve activity activates the intrarenal RAS and has direct tubular effects that result in augmented salt retention along the nephron.[2] , [5] Activation of a local endothelin-1-generating system also occurs.[6] As a result of these renal vasoconstrictor influences, renal blood flow is directed away from superficial cortical nephrons to the more efficient solute-resorbing juxtamedullary nephrons. These nephrons rely on the high capacity of the ion transport carriers in the loop of Henle and the countercurrent mechanism of the medulla to allow the formation of concentrated urine. Elevated AVP levels cause further reductions in free water clearance by the kidney. This reduced clearance of free water, coupled with the increased thirst of many patients with advanced HF (perhaps caused by higher intracerebral angiotensin II levels), often leads to a hypotonic edematous state. As with other complex biological systems, countervailing intrarenal and humoral responses also occur, including increased prostaglandin E_2 and prostacyclin levels within the kidney and the release of humoral natriuretic factors, including ANP and BNP.[1] [4] [5]

MECHANISMS OF ACTION OF DIURETICS

By definition, a diuretic is any drug that increases urine flow. However, the term "diuretic" is commonly used to refer to agents that enhance the delivery of sodium chloride, other small ions, and water into urine. In this context, agents such as cardiac glycosides and dopamine may indirectly increase urine production by enhancing renal blood flow and the GFR, which promotes a fall in the glomerular filtration fraction and thereby diminishes water and solute resorption by the proximal tubule. Furthermore, endogenous substances such as ANP or BNP, when administered as drugs, may have salutary effects on cardiovascular function, as well as on intrarenal hemodynamics and tubular sodium resorption.

Most diuretics, however, act directly on the kidney to inhibit solute and water reabsorption. A number of classification schemes for diuretics have been proposed on the basis of their mechanism of action, their anatomical locus of action in the nephron, and the form of diuresis that they elicit. Diuretics can be classified according to whether they induce a "solute" or "water" diuresis. Of the latter ("aquaretics"), only three agents are of clinical relevance: demeclocycline, lithium, and vasopressin V_2 receptor antagonists, each of which, by different mechanisms, inhibits the action of AVP on the collecting duct, thereby increasing free water clearance. Drugs that cause solute diuresis are subdivided into two types: osmotic diuretics, which are nonresorbable solutes that osmotically retain water and other solutes in the tubular lumen, and drugs that selectively inhibit ion transport pathways across tubular epithelia, which constitute the majority of potent, clinically useful diuretics.

Since many of the specific ion transport proteins that are the molecular targets for diuretics have recently been cloned and their intrarenal distribution characterized, a new

classification of these drugs based on their molecular pharmacology has been advocated.[6] This classification scheme, rather than the more traditional schemes, i.e., chemical classification (e.g., "thiazide" diuretic), site of action (e.g., "loop" diuretics), or efficacy and clinical outcome (e.g., "high-ceiling" and "potassium-sparing" diuretics), will be used throughout this chapter.

Functional Regions of the Nephron

PROXIMAL TUBULE.

Fluid resorption across the proximal tubule is isosmotic and accounts for approximately two-thirds of the resorption of filtered Na^+ and H_2O. Resorption of sodium bicarbonate from the tubular lumen is facilitated by the action of luminal and cytosolic carbonic anhydrase in proximal tubular epithelial cells. This substance raises the intraluminal chloride concentration and thereby allows further isosmotic resorption of NaCl along the proximal tubule. In addition to Na^+, Cl^{--}, and HCO_3^{--}, this segment of the nephron resorbs most of the K^+ and two-thirds of the Ca^{2+} filtered at the glomerulus, as well as most of the inorganic phosphate.

Agents that alter intrarenal regulation of the formation of glomerular filtrate, such as renin-angiotensin antagonists, may enhance the delivery of solute and water to more distal segments of the nephron that are sensitive to diuretics that inhibit ion transport. Predictably, other drugs, such as nonsteroidal antiinflammatory drugs (NSAIDs), may diminish glomerular filtrate formation, thus reducing the flow of urine to distal diuretic-sensitive portions of the nephron. Many diuretics that are not freely filtered at the glomerulus obtain access to the tubular lumen by organic ion transport proteins in the distal *pars recta* portion of the proximal tubule.

THE LOOP OF HENLE.

About one-third of the glomerular filtrate arrives at the descending limb of Henle's loop; however, no active transport of solute occurs here. The tubular epithelium in Henle's loop is highly permeable to water, which leaves the nephron and passes into the hyperosmotic medullary interstitium. Most of the solute transport responsible for maintaining the hypertonicity of the medullary interstitium occurs in the urea- and water-impermeable thick ascending limb of Henle's loop. Here, the Na^+ /K^+ /$2Cl^{--}$ cotransporter, which resides in the luminal membrane, facilitates electroneutral ionic transport. The Na^+ /K^+ /$2Cl^{--}$ cotransporter is the "receptor" for loop diuretics (e.g., furosemide, bumetanide, torsemide, and probably ethacrynic acid).

Before reaching the distal convoluted tubule, the thick ascending limb of the loop of Henle passes near the afferent arteriole of its own glomerulus in a specialized epithelium known as the macula densa. These epithelial cells release locally acting autacoids that regulate afferent arteriolar tone and therefore glomerular perfusion pressure and the filtration fraction in accordance with the volume and solute concentration of the luminal fluid reaching this portion of the glomerulus (i.e., "tubuloglomerular feedback"). Drugs that inhibit the Na^+ /K^+ /$2Cl^-$ cotransporter in the

epithelial cell of the macula densa, such as furosemide, ablate this "sensing" mechanism of the macula densa, thereby preventing a rapid feedback decline in the GFR despite large increases in solute delivery out of the loop of Henle.

DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT.

Like the ascending limb of the loop of Henle, the distal convoluted tubule is impervious to water; therefore, luminal fluid is hypotonic. Na^+ - and Cl^- -facilitated transport is mediated by the thiazide diuretic-sensitive Na^+ /Cl^- cotransporter in the apical membranes of epithelial cells in this segment. Increased delivery of Na^+ and luminal fluid to the distal nephron, after the administration of furosemide or a thiazide diuretic, for example, directly enhances K^+ and H^+ secretion by this portion of the nephron. Importantly, the number and activities of the apical membrane epithelial Na^+ channels and H^+ ,K^+ -ATPase, as well as basolateral membrane Na^+ /K^+ -ATPase, are increased by the mineralocorticoid aldosterone.

CLASSES OF DIURETICS

Inhibitors of the Na+/K+/2Cl- Cotransporter (Loop Diuretics)

The agents traditionally classified as loop or high-ceiling diuretics, including furosemide, bumetanide, and torasemide (torsemide), have been known for over a decade to reversibly inhibit the Na^+ /K^+ /2Cl^- symporter (cotransporter) when applied to the luminal, but not the basolateral membranes of epithelial cells of the thick ascending limb of the loop of Henle. A second functional class of these drugs, typified by ethacrynic acid, are also effective only from the tubule lumen but exhibit a slower onset of action and delayed and only partial reversibility. Individual agents that act as Na^+ /K^+ /2Cl^- cotransporter inhibitors are listed in Table 18-2 .

The molecular targets of these drugs have recently been cloned and sequenced and were found to encompass a family of cation chloride symporters that have now been described in a number of cell types and tissues.[7] Within the

TABLE 18-2 -- COMMON DIURETICS USED IN THE TREATMENT OF CONGESTIVE

DIURETIC	BRAND NAME	PRINCIPAL SITE AND MECHANISM OF ACTION	EFFECTS ON URINARY ELECTROLYTES	EFFECTS ON BLOOD ELECTROLYTES AND ACID-BASE BALANCE	EXTRARENA EFFECTS

Carbonic Anhydrase Inhibitors

Acetazolamide	Diamox	Proximal tubule	Na+, K+, HCO_3 --	Metabolic acidosis	Ventilatory dri
Dichlorphenamide	Daranide	Carbonic anhydrase inhibition			Intraocular pressure
Methazolamide	Neptazane				

Na+/K+/2Cl-- Cotransporter Inhibitors (Loop Diuretics)

Furosemide	Lasix	Thick ascending limb of the loop of Henle: Inhibition of the Na+/K+/2Cl-- cotransporter	Na+	Hypochloremic alkalosis HCO_3 -- K+, Na+ Cl--, Mg^{2+} Uric acid	Acute: Venous capacitance, systemic vascular resistance
Bumetanide	Bumex		Cl--		
Ethacrynic acid	Edecrin				Chronic: Cardiac preload, ototoxicity
Torsemide	Demadex				

Na+/Cl-- Cotransporter Inhibitors (Thiazide and Thiazide-like Diuretics)

Chlorothiazide	Diuril	Distal tubule: Inhibit Na+/Cl-- cotransporter	Na+, Cl--, K+	Na+, particularly in elderly patients	Glucose
Hydrochlorothiazide	Hydrodiuril				LDL/triglyceri (may be dose related)

Chlorthalidone	Hygroton		Mg^{2+} , Ca^{2+}	Cl--, HCO_3 -- (mild alkalosis)	
Metolazone	Mykrox			Uric acid, Ca^{2+}	
	Zaroxolyn			K+, Mg^{2+}	
Indapamide	Lozol				
Epithelial Na+ Channel Inhibitors (K+-Sparing Diuretics)					
Triamterene	Dyrenium	Collecting duct: Inhibit apical membrane Na+ conductance	HCO_3 --	GFR; metabolic acidosis	
Amiloride	Midamor			Mg^{2+}	
Type I Mineralocorticoid Receptor Antagonists (K+-Sparing Diuretics)					
Spironolactone	Aldactone	Collecting duct: Aldosterone antagonists	K+, Na+, Cl--	K+	Gynecomastia

Not yet licensed in the United States.

ACE=angiotensin-converting enzyme; GFR=glomerular filtration rate; LDL=low-density lipoprotein.

Vasodilator prostaglandins VENODILATION ARTERIOLAR DILATION

*Dosages are approximate (p.o.).

mammalian kidney, three alternatively spliced variants with approximately 60 percent overall amino acid homology have been described that encode proteins with 12 membrane-spanning domains and large cytosolic N-terminal and C-terminal regions.

These cytosolic regions contain amino acid sequences that serve as potential sites of posttranslational modification, thereby resulting in the regulation of cotransporter activity within the tubular epithelial cell.

Inhibition of this cotransporter results in a marked increase in the fractional excretion of Na^+ and Cl^- and indirectly results in the fractional excretion of Ca^{2+} and Mg^{2+} . By inhibiting the concentration of solute within the medullary interstitium, these drugs also reduce the driving force for water resorption in the collecting duct, regardless of the presence of AVP; the decreased resorption of water in turn results in the production of urine that is nearly isotonic with that of plasma at the height of the diuresis. The delivery of large amounts of Na^+ and fluid to the distal nephron increases both K^+ and H^+ secretion, a process that is accelerated by aldosterone.

Na^+ /K^+ /2Cl^- cotransporter inhibitors also exhibit several characteristic effects on intracardiac pressure and systemic hemodynamics. An increase in venous capacitance and lowering of pulmonary capillary wedge pressure within minutes of a bolus infusion of intravenous furosemide (0.5 to 1.0 mg/kg) have been well documented in patients with congestive symptoms following acute myocardial infarction or in those with valvular heart disease.[8] [9] Some increase in pulmonary venous compliance probably occurs as well. Similar data, although not as extensive, have accumulated for bumetanide and torsemide.[10] Despite the fall in left ventricular end-diastolic filling pressure, systemic vascular resistance often increases acutely in response to loop diuretics, an effect that has been attributed to transient activation of the systemic or intravascular RAS. The net effect of these actions of cardiac function may contribute to some improvement in congestive HF systems. However, the potentially deleterious rise in left ventricular afterload reinforces the importance of initiating vasodilator therapy with diuretics in patients with acute pulmonary edema and adequate blood pressure.

All the rapid hemodynamic actions of Na^+ /K^+ /2Cl^- cotransporter inhibitors are attenuated in patients with chronic congestive HF. Although most of these effects have been attributed in the past to activation of the RAS by the kidney in response to a loop diuretic, with subsequent release of renal and intravascular prostaglandins, recent evidence indicates that these drugs have direct effects on endothelial cells and vascular smooth muscle. In in vitro experiments, furosemide stimulates the release of prostacyclin and endothelium-derived relaxing factor (EDRF, now known to be nitrogen oxide and related congeners) by increasing the release of vasoactive kinins, presumably after inhibition of Na^+ /K^+ /2Cl^- cotransporter function in endothelial cells in vitro.[11] Furosemide has also been shown to relax precontracted pulmonary venous rings by a direct effect on smooth muscle that was dependent on inhibition of vascular smooth muscle Na^+ /K^+ /2Cl^- cotransporter function in these cells.[12] Interestingly, this effect was apparent only on pulmonary venous, not arterial vascular tissue and was apparent in these in vitro studies only at drug concentrations achievable transiently after bolus infusions.[12]

Inhibitors of the Na+/Cl- Cotransporter (Thiazide and Thiazide-Like Diuretics)

This class of diuretic, of which chlorothiazide is the prototype, includes the first effective orally bioavailable diuretics with acceptable safety profiles to become widely used in

clinical practice, and they supplemented the much more toxic mercurial diuretics in the 1950s. A number of these agents are now available for clinical use in the United States (see Table 18-2) . Although not all are technically benzothiadiazine derivatives, they are often collectively referred to as "thiazide" diuretics. The site of action of these drugs within the distal convoluted tubule has been identified at a molecular level as being the Na^+ /Cl^- cotransporter of the distal convoluted tubule.[13] It has 12 membrane-spanning domains and shares 60 percent amino acid homology with the Na^+ /K^+ /2Cl^- cotransporter of the ascending limb of the loop of Henle; however, it is insensitive to the effects of furosemide. This cotransporter (or related isoforms) is also present on cells within the vasculature and many cell types within other organs and tissues and may contribute to some of the other actions of these agents.

By blocking solute uptake in the distal convoluted tube, Na^+ /Cl^- cotransporter inhibitors prevent maximal dilution of urine, decrease the kidney's ability to increase free water clearance, and may contribute to the development of hyponatremia. Thiazides increase Ca^{2+} resorption in the distal nephron by several mechanisms, occasionally resulting in a small increase in serum Ca^{2+} levels. In contrast, Mg^{2+} resorption is diminished and hypomagnesemia may occur with prolonged use. Increased delivery of NaCl and fluid into the collecting duct directly enhances K^+ and H^+ secretion by this segment of the nephron and may lead to clinically important hypokalemia.

Inhibitors of Epithelial Na+ Channels (Potassium-Sparing Diuretics)

The apical (luminal) membranes of the principal cells of the late distal convoluted tubule and the cortical collecting duct contain Na^+ -selective channels that permit Na^+ entry from within the tubular lumen, driven by the electrochemical gradient established by Na,K-ATPase in the basolateral membranes of these cells.[14] The number of epithelial Na^+ channels available for entry into tubular epithelial membranes is regulated in part by mineralocorticoid levels. The activity (conductance) of these Na^+ channels appears to be regulated by both protein kinase A-mediated phosphorylation and guanosine triphosphate (GTP)-binding proteins (i.e., G_{alphal}). [15] Na^+ conductance by these channels is inhibited by *amiloride* and by *triamterene*, which subsequently diminishes the electrochemical potential for K^+ secretion into the urine. Thus, these agents, along with mineralocorticoid inhibitors (see below), are commonly referred to as "potassium-sparing" diuretics.

Neither amiloride nor triamterene is effective in achieving a net negative Na^+ balance when given alone. Amiloride and its congeners also inhibit Na^+ /H^+ antiporters in renal epithelial cells and in many other cell types, but only at concentrations that are higher than those used clinically. Both amiloride and triamterene affect cardiac repolarization, possibly by inhibiting delayed rectifier K^+ currents (I_K), and may exaggerate the prolonged repolarization observed with Singh-Vaughan Williams class IA antiarrhythmics[16] [17] (e.g., quinidine).

Inhibitors of Mineralocorticoid/Glucocorticoid Receptors (Spironolactone)

Spironolactone and its active metabolites canrenone and potassium canrenoate have been known for over two decades to competitively inhibit the binding of aldosterone to mineralocorticoid or type I receptors in many tissues, including epithelial cells of the distal convoluted tubule and collecting duct.[18] These cytosolic receptors are members of a "superfamily" of cytosolic proteins that are ligand-dependent transcription factors, which upon ligand binding translocate to the cell nucleus, where they bind to specific DNA sequences and regulate the transcription and synthesis of a number of gene products, including apical membrane Na^+ channels, H^+ ,K^+ -ATPase, and Na^+ ,K^+ -ATPase, among others.[19]

The spironolactone-bound type I receptor complex is inactive and diminishes K^+ and H^+ secretion by this portion of the nephron, particularly in patients with high plasma aldosterone levels, as in HF.[20] [20A] Hyperkalemia and, unusually, a metabolic acidosis may result from the use of these drugs. In addition, gynecomastia may be observed in male patients. It is now recognized that the molecular pharmacology of steroid receptors is complex and relatively poorly understood. Endogenous glucocorticoids appear to be the principal ligand for the type I "mineralocorticoid" receptor in most cell types, for example.[21] [22] Additional information may clarify the mechanism of some of the side effects of spironolactone and its metabolites, such as gynecomastia, as well as their potential beneficial effects in nonrenal tissue.

Recently, spironolactone has been shown to markedly decrease mortality in subjects with stage C, advanced HF,[23] as further discussed in the section on neurohormonal inhibitors.

VASOPRESSIN ANTAGONISTS

Increased levels of circulating AVP (antidiuretic hormone) contribute to the increased systemic vascular resistance and positive solute and water balance in patients with advanced HF.[24] Physiologically, a primary site of action of AVP is the renal collecting duct, where it acts to increase water permeability (see below); however, it is clear that AVP has a number of nonrenal effects on the cardiovascular and central nervous system and on blood coagulation.

Vasopressin receptors have been divided into V_1 and V_2 receptor subtypes, which exhibit different ligand-binding specificities. V_{1a} (vascular/hepatic) and V_{1b} (anterior pituitary) receptors, like angiotensin II (AT_1) and $alpha_1$ -adrenergic receptors, are coupled via the G_{alpha} q subtype of G proteins to activation of phospholipase C in the plasma membranes of vascular smooth muscle cells and other tissues. Stimulation of V_1 receptors results in vasoconstriction, platelet activation, glycogenolysis, and adrenocorticotropic hormone release, as well as stimulation of the transcription factors c-fos and c-jun, which ultimately results in cell growth. In contrast, V_2 receptors, found

largely in distal nephron segments within the kidney, are coupled through stimulatory G_{alpha} s proteins to the stimulation of adenylyl cyclase activity, increased production of the second messenger cyclic adenosine monophosphate (cAMP), and activation of protein kinase A. By interrupting this phosphorylation cascade, V_2 -selective receptor antagonists inhibit recruitment of aquaporin-CD water channels,[25] amiloride-sensitive Na^+ channels, and urea transporters into the apical membranes of collecting duct epithelial cells. Therefore, the ability of the collecting duct to resorb water is reduced.

The prototypical orally bioavailable nonpeptide V_2 -selective antagonist is OPC-31260.[25] In general, this agent increases free water clearance, thereby increasing plasma osmolality as well as increasing the serum Na^+ concentration. A general consensus from studies in animal models with both the V_1 -selective antagonist OPC-21268[26] and OPC-31260[27] suggests that AVP contributes to the development of HF more through the actions of V_2 receptor-mediated fluid retention and less so through alterations in systemic hemodynamics.[28] More recently, other V_2 -selective antagonists such as WAY-VPA-985[29] or nonselective antagonists such as YM087[30] have been developed. In a clinical trial of WAY-VPA-985 in HF patients with dilutional hyponatremia, a significant increase in solute-free water clearance was demonstrated.[31] Clinical trials with YM087 are currently ongoing.

While the pharmacology of these drugs will undoubtedly prove to be complex in patients with HF, most of whom will be receiving other vasodilators and natriuretic aquatic drugs and in whom AVP levels will vary as a function of plasma osmolality and cardiac output among other factors, these agents may prove to be valuable adjuncts to the treatment of HF.

NATRIURETIC PEPTIDES (ANP AND BNP)

The contribution of the natriuretic peptides ANP, BNP, and related proteins, including urodilatin and fragments of the pro-ANP protein, to the physiological adaptations that accompany HF and their potential role in pharmacotherapy for this syndrome have been the subject of intensive research efforts by cardiovascular and renal pharmacologists in academia and by the pharmaceutical industry for more than a decade.[32] [33] Apart from C-type natriuretic peptide, which is synthesized in endothelial (and other) cells in a number of organs and tissues and has limited natriuretic activity, plasma levels of these peptides are increased in most patients with HF[34] and exhibit a direct natriuretic effect on the kidney.[35]

The natriuretic peptides act at both particulate (i.e., membrane-bound) guanylyl cyclase-linked (GC-A and GC-B or NPR-A and NPR-B) receptors and so-called clearance receptors (NPR-C) that are linked through inhibitory GTP-binding proteins to adenylyl cyclase or through stimulatory GTP-binding proteins to phospholipase C. For a complete discussion of the complex pharmacology of natriuretic peptides, the reader is referred to recent comprehensive reviews.[36] [37] Aside from actions that indirectly affect renal function, such as inhibition of AVP release by the pituitary, inhibition of aldosterone synthesis by adrenal zona glomerulosa cells, sympathoinhibitory effects,

and relaxant effects on systemic vascular resistance and venous capacitance, natriuretic peptides directly affect renal solute and water homeostasis. Acting predominantly through guanylyl cyclase (GC-A and GC-B)-linked receptors, natriuretic peptides alter the hemodynamic forces regulating glomerular filtration and tubular Na^+ resorption, particularly in the distal nephron.

Infusions of ANP have been shown to cause afferent arteriolar dilation and efferent arteriolar constriction, which result in an increase in the GFR.[5] Even when infused at concentrations that do not affect the GFR, ANP induces natriuresis by inhibiting the resorptive capacity of the proximal tubular epithelium largely by inhibiting the actions of locally acting antinatriuretic agents such as angiotensin II and by augmenting the activity of intrarenal dopamine. In the distal nephron, particularly in the medullary portion of the collecting duct, there is evidence that natriuretic peptides acting through GC-A receptors decrease Na^+ influx from the tubular lumen through amiloride-sensitive epithelial Na^+ channels. The result is a natriuresis with minimal effect on urinary potassium excretion. ANP, which is likewise synthesized and released by vascular endothelial cells,[38] may also be important in regulating blood pressure, particularly during physiological stress. For example, the blood pressure of mice that have had their pro-ANP gene disrupted by gene-targeting techniques--and therefore have no detectable circulating ANP--is very sensitive to dietary salt intake.[39] Very little evidence has been presented for any clinically significant direct effect of ANP[40] or BNP[41] on ventricular function.

BRAIN NATRIURETIC PEPTIDE.

While ANP would appear to have a favorable pharmacological profile in HF, therapeutic trials with ANP have been disappointing because of its short biological half-life, end-organ resistance, the development of pharmacological tolerance, and undesirable hemodynamic effects.[42] [43] [44] [424A] However, results with BNP have been more promising.[44] [45] [46] When infused continuously into patients with HF, recombinant human BNP (hBNP, nesiritide, Natrecor) produces vasodilator and cardiac output-increasing effects[45] [46] Although BNP was natriuretic and diuretic in two studies,[44] [45] in another study, approximately half the subjects were resistant to the natriuretic effects of BNP. Moreover, the diuretic and natriuretic effects of BNP were either absent or not very pronounced in the two studies conducted in moderate or advanced HF.[45] [46] In addition, episodes of bradycardia noted previously with ANP have been observed with BNP.[46] It therefore appears that hBNP will be useful primarily as a vasodilator, and it continues to be evaluated in phase III trials.

NEUTRAL ENDOPEPTIDASE.

Since receptor-mediated clearance and metabolism by the zinc metallopeptidase neutral endopeptidase (NEP) are the two predominant mechanisms for natriuretic peptide inactivation and removal, two approaches have been taken to lengthening the biological half-life of endogenous and exogenously infused natriuretic peptides.[42] Analogs of ANP have been developed that bind to ANP-R_2 receptors with high affinity but exhibit little biological activity. Several classes of NEP inhibitors have also been developed that alone or in combination with ANP-R_2 antagonists induce natriuresis and

delay the clearance of exogenously infused ANP. NEP antagonists have been shown to increase plasma ANP levels and induce natriuresis with little effect on potassium excretion in patients with HF. However, in limited clinical trials in patients with HF, NEP inhibitors had relatively little efficacy.[47] [48]

NEP-ACE INHIBITION.

The combination of an NEP antagonist with an angiotensin-converting enzyme (ACE) inhibitor has been shown to result in more sustained natriuretic effects than has an NEP antagonist alone in experimental animal models of HF, in part because of the inhibition of angiotensin II-mediated effects but also because of the fact that both NEP and ACE degrade bradykinin, a vasodilatory and natriuretic peptide.[49] [50]

Some evidence has shown that ACE inhibition in HF patients may favorably affect the release and/or clearance of endogenous ANP, but not BNP, by resetting the relationship between ANP levels and atrial pressure, although confirmation will require additional studies.[51] With these actions in mind, single agents with dual metalloproteinase inhibitor activity (i.e., NEP and ACE inhibition) have been developed that address the mechanisms contributing to both pharmacological tolerance and end-organ resistance to natriuretic peptides in HF.[52] [53] Indeed, both renal (natriuresis) and humoral (decrease in renin) responses to omapatrilat are superior to an ACE inhibitor in subjects with HF.[54] Moreover, omapatrilat was compared with the ACE inhibitor lisinopril in two recently completed phase II trials, and the results are quite promising.[55] In fact, if the two medium-sized trials with omapatrilat are combined, a statistically significant reduction in mortality (by 28 percent) in comparison to 20 mg/day of lisinopril was noted.[55] It therefore seems likely that this form of therapy will prove to be useful in the treatment of chronic HF.

Carbonic Anhydrase Inhibitors

The representative of this class of agents is acetazolamide (Diamox), whose use as a diuretic in HF patients is confined

to temporary administration to correct the metabolic alkalosis that occurs as a "contraction" phenomenon in response to the administration of other diuretics.

DIURETIC RESISTANCE AND MANAGEMENT

Inhibitors of the Na^+ /K^+ /2Cl^- cotransporter (loop diuretics) have been the only class of diuretics that are effective as single agents in moderate and advanced HF. The rationale for this assumption was the magnitude of their maximal ("ceiling") natriuretic effect and the fact that the natriuretic effect of more distally acting drugs may be limited by the increased resorption of solute and water by proximal nephron segments in individuals

with HF. However, even the effectiveness of potent loop diuretics can decrease with worsening HF. Although the bioavailability of these drugs is not generally decreased in HF, the potential delay in their rate of absorption may result in peak drug levels within the tubular lumen in the ascending loop of Henle that are insufficient to induce maximal natriuresis.[56] [57] Resorting to an intravenous formulation typically obviates this problem. However, even with intravenous dosing, a rightward shift of the dose-response curve is observed between the diuretic concentration in the tubular lumen and its natriuretic effect in HF; in addition, the maximal effect or "ceiling" is lower. This rightward shift has been termed "diuretic resistance" and can be due to several contributing factors.[58] A point of distinction is that diuretic resistance should be distinguished from "diuretic adaptation" or the "breaking" phenomenon that is observed even in normal subjects given multiple doses of a short-acting loop diuretic.[59]

Diuretic-induced alterations in intrarenal hemodynamics, caused by tubuloglomerular feedback and increased sympathetic nerve activity among other possible mechanisms (see below), result in avid renal sodium retention by all nephron segments as intraluminal drug levels decline. If dietary salt intake is sufficiently high, as in many Western diets, a daily net negative sodium balance may not be achieved despite several daily intravenous doses of a loop diuretic. *These data imply that salt intake must be restricted in normal subjects and particularly in patients with HF to obtain a negative sodium balance*. The data also indicate that short-acting diuretics, particularly furosemide and bumetanide, must be administered several times per day to obtain consistent daily salt and water loss unless dietary sodium intake is severely restricted. An alternative strategy in hospitalized patients is to administer the same daily parenteral dose of a loop diuretic by continuous intravenous infusion,[60] which leads to sustained natriuresis from the continuous presence of high drug levels within the tubular lumen. This approach requires the use of a constant-infusion pump but permits more precise control over the natriuretic effect achieved over time, particularly in carefully monitored patients. It also diminishes the potential for a too rapid decline in intravascular volume and hypotension, as well as the risk of ototoxicity in patients given large bolus intravenous doses of a loop diuretic. A typical continuous furosemide infusion is initiated with a 20- to 40-mg intravenous loading dose as a bolus injection, followed by a continuous infusion of 5 to 10 mg/hr for a patient who had been receiving 200 mg of oral furosemide (or 100 mg of intravenous drug) per day in divided doses.

Even in normal subjects with an Na^+ -restricted diet, the natriuretic effect of diuretics will decline with time; that is, a rightward and downward shift will been seen in the sigmoidal concentration-effect relationship as a result of the "braking phenomenon." This effect is now known to be due in large part to compensatory hypertrophy of the tubular epithelium distal to the site of action of the Na^+ /K^+ /2Cl^- cotransporter inhibitor, which increases the solute resorptive capacity of the kidney, as well as other adaptive mechanisms.[58] [61] In this context, Morsing and colleagues demonstrated that chronic and perhaps even acute treatment with loop diuretics causes rapid (60 minutes) upregulation of the thiazide-sensitive Na^+ /Cl^- cotransporter in the distal tubule (as measured by increased ^{3}H-metolazone binding). [61] In addition, many patients with HF also manifest some degree of renal impairment, which also shifts the diuretic concentration-effect relationship downward and to the right. While the maximum effect expressed as the fractional excretion of sodium may be unchanged in patients with some degree of intrinsic renal disease, the absolute natriuretic effect will be limited

by the reduced filtered load of sodium into the remaining functional nephrons.

The cause of apparent resistance to diuretics in patients who initially achieve an acceptable natriuretic and diuretic response may be multifactorial, as indicated. In the absence of an abrupt decline in cardiac or renal function or noncompliance with either the drug regimen or dietary salt restriction, *the usual reason for diuretic resistance is the concurrent administration of other drugs*. In this regard, one of the biggest offending classes of agents is NSAIDs, which reduce renal function by decreasing the renal synthesis of vasodilator prostaglandins.[62] All NSAIDs, including aspirin, can diminish diuretic efficacy. Rarely, drugs such as probenecid or high plasma concentrations of some antibiotics may compete with the organic ion transporters in the proximal tubule responsible for the transfer of most diuretics from the recirculation into the tubular lumen.

The use of increasing doses of vasodilators, with or without a marked decline in intravascular volume as a result of concomitant diuretic therapy, is a common cause of diuretic resistance. It is often difficult to clinically distinguish between intravascular volume depletion following aggressive diuretic and vasodilator therapy and a decrease in cardiac output caused by primary HF, although a more marked decline in urea clearance than in creatinine clearance suggests intravascular volume depletion. Pulmonary arterial and venous or left atrial pressure monitoring may be required to make this distinction. In addition, all vasodilators commonly used as afterload-reducing agents in HF dilate a number of central and peripheral vascular beds. Therefore, renal blood flow may be reduced despite an increase in cardiac output, and the effectiveness of the diuretic declines. Vasodilator therapy also may lower renal perfusion pressure below that necessary to maintain normal autoregulation and glomerular filtration in patients with renal artery stenosis from atherosclerotic disease.

Treatment of Diuretic Resistance

Among the vasodilators, RAS antagonists can uniquely augment the effectiveness of diuretics by mechanisms that are independent of their ability to reduce systemic vascular resistance (see below).[63] However, by reducing efferent arteriolar tone, these drugs may also diminish diuretic effectiveness by reducing the transglomerular perfusion pressure to the point that the GFR declines abruptly. This response is most commonly observed in patients with decreased renal arterial perfusion pressure caused either by renal artery stenosis or by limited cardiac output; in these patients, high efferent arteriolar tone mediated by angiotensin II is necessary to maintain glomerular filtration. This cause of diuretic resistance is usually characterized by an abrupt rise in the serum creatinine concentration and should be distinguished from the more common, limited increases in serum creatinine levels that often accompany initiation of ACE inhibitor therapy. In addition to ACE inhibitors, the $alpha_1$ -adrenergic antagonist prazosin has been shown to have direct tubular action in reducing sodium resorption at doses below those necessary to lower arterial pressure (e.g., 0.50 mg).[64]

With a cardiac output and mean arterial pressure adequate to sustain autoregulation of glomerular filtration, diuretic resistance can be managed by increasing the frequency

of loop diuretic dosing or by switching to a continuous intravenous infusion. If this treatment is ineffective, concomitant administration of a more distally acting diuretic, usually an Na/Cl symport inhibitor (e.g., a thiazide or thiazide-like diuretic such as intravenous chlorothiazide or oral metolazone), will usually result in substantial natriuresis.[58] [65] [66] While effective, this diuretic combination may cause profound intravascular volume depletion, hypotension, renal potassium wasting, hyponatremia, and eventually a fall in cardiac output and GFR. Accordingly, this combination should be used cautiously and with careful monitoring of renal function and serum potassium and sodium, especially in outpatients. A type I mineralocorticoid receptor antagonist (e.g., spironolactone) may also be capable of increasing the diuretic effectiveness of more proximally acting diuretics, although patients are at increased risk for hyperkalemia if they are concomitantly receiving another renin-angiotensin-aldosterone system (RAAS) antagonist. Despite this possibility, to reduce the oral KCl requirement and to maintain potassium serum levels well in the normal range, most subjects receiving large doses of loop diuretics or loop diuretics plus thiazides benefit from a potassium-sparing diuretic. If tolerated, spironolactone should be the potassium-sparing diuretic used because of its mortality-reducing effects.

In hospitalized patients, as discussed below, dopamine administered at doses that cause selective dopaminergic receptor stimulation may increase renal blood flow and decrease tubular solute resorption (i.e.,
2 mug/kg/min, based on estimated lean body weight). Assuming that it will ultimately be approved by the Food and Drug Administration (FDA), in some subjects a short-term infusion of hBNP may be beneficial. In addition, selective V_1 and V_2 vasopressin receptor antagonists, once approved, may individually or in combination increase the efficacy of Na^+ /K^+ /2Cl^- symporter inhibitors based on experimental animal data and preliminary evidence in humans. Finally, mechanical circulatory support may become necessary in patients with marginal cardiac output for diuretics to be effective, particularly in patients recovering from cardiac surgery or myocarditis or as a "bridge" to transplantation. Discrete renal arterial stenoses that limit renal blood flow and systemic vasodilator therapy may be amenable to percutaneous angioplasty in patients with adequate cardiac output and diuretic resistance from marginal renal perfusion.

Electrolyte and Metabolic Disorders in Heart Failure: Complications of Diuretic Therapy

POTASSIUM HOMEOSTASIS.

All the diuretics discussed in this chapter, with the possible exceptions of V_2 vasopressin receptor antagonists and hBNP, affect renal K^+ handling.[66] [67] In patients with chronic HF, both hypokalemia caused by K^+ -wasting diuretics and hyperkalemia caused by K^+ supplements administered with a K^+ -sparing diuretic or an RAS antagonist may contribute to morbidity and mortality. Renal K^+ losses from diuretic use can be exacerbated by the hyperaldosteronism characteristic of patients with untreated HF and

by the persistent chloride depletion and metabolic alkalosis that follow chronic use of Na^+ /K^+ /2Cl^- cotransporter inhibitors. The level of dietary salt intake may also contribute to the extent of renal K^+ wasting with diuretics. High-salt diets increase delivery of NaCl to distal tubular K^+ secretory sites, while very low salt diets may stimulate aldosterone-induced K^+ secretion. Extrarenal regulators of the serum K^+ concentration may also produce effects additive to renal losses of K^+ , such as the shift of K^+ into cells accompanying the release of epinephrine in response to stress, myocardial ischemia, pulmonary edema, or the administration of insulin, regardless of whether glucose is given concurrently. Long-term infusion of heparin, conversely, reduces aldosterone synthesis and may cause hyperkalemia, particularly in patients with insulin-dependent diabetes and in patients receiving potassium replacement and/or potassium-sparing drugs.[67] Importantly, any beta-agonist or phosphodiesterase inhibitor (PDEI) will lower potassium levels by shifting potassium into skeletal muscle, which is a $beta_2$ -adrenergic/cAMP pathway effect.[68] [69]

Despite the absence of conclusive data to determine whether routine administration of K supplements and/or K-sparing diuretics reduces serious morbidity or mortality in the treatment of patients with either primary hypertension or chronic HF, it is recommended that serum K^+ be maintained between 3.5 and 5.0 mEq/L.[70] [71] However, for patients with HF, the recommendation is to maintain serum K^+ between 4.3 and 5.0 mEq/L. One of the reasons for the higher serum K^+ is that HF subjects are often being treated with agents in which the proarrhythmic effects are exacerbated by hypokalemia, including digoxin, type III antiarrhythmics, and beta-agonists or PDEIs. Since chronic HF patients are at much higher risk for malignant ventricular arrhythmias and sudden death than are hypertension patients, it is sound clinical practice to monitor K^+ levels frequently and maintain them well up in the normal range.

The metabolic consequences of diuretic therapy must be established from limited and potentially biased data. Despite this limitation, the majority of the data that are available, much of it obtained from retrospective or subgroup analysis of clinical trials evaluating diuretic use in hypertension, are reassuring.[70] [71] Even when thiazide diuretic use was associated with a higher risk of primary cardiac arrest in a retrospective, case-control study, concomitant administration of a potassium-sparing diuretic lowered this risk below that of control patients receiving a beta-adrenergic antagonist.[71]

If supplementation is necessary, oral K supplements in the form of KCl extended-release tablets or liquid concentrate should be used whenever possible. Intravenous K is potentially hazardous and should be avoided except in emergencies. The routine use of "sliding scales" for intravenous K administration in hospitalized patients is also potentially dangerous and should be discouraged.

OTHER METABOLIC AND ELECTROLYTE DISTURBANCES.

Diuretics may be associated with multiple other metabolic and electrolyte disturbances, including hypomagnesemia, hyponatremia, metabolic alkalosis, hyperglycemia, hyperlipidemia, and hyperuricemia.[72] None of these disturbances are limiting in the usual patient with HF. Hypomagnesemia can be caused by both loop and thiazide

diuretics, but its detection (because of the poor correlation of total serum magnesium levels with either ionized levels or total-body stores) is difficult and its impact is uncertain. Magnesium replacement should be given for signs or symptoms that could be due to hypomagnesemia (arrhythmias, muscle cramps), and it can be routinely given (with uncertain benefit) to all subjects receiving large doses of diuretics or requiring large amounts of K^+ replacement. Hyponatremia is usually a manifestation of advanced HF with very high degrees of activation of the vasopressin system and/or inadequate RAS inhibition. Hyponatremia can typically be treated by more stringent water restriction and/or an increase in RAS inhibition. Once V_2 receptor antagonists are available as diuretics, this problem will probably be eliminated.

Metabolic alkalosis can generally be treated by increasing KCl supplementation, lowering diuretic doses, and/or transiently treating with acetazolamide as discussed above. The small level of glucose intolerance and/or hyperlipidemia produced by thiazide diuretics is not usually clinically important, and blood glucose and lipids should be controlled according to standard guidelines regardless of the presence of any perceived diuretic effect. Hyperuricemia from thiazide diuretics is occasionally a problem and may precipitate gout, particularly in predisposed subjects or in the presence of renal dysfunction. If a thiazide diuretic is absolutely necessary in such patients, allopurinol can be administered to reduce uric acid synthesis.

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Vasodilators

The rationale for the use of vasodilators grew out of experience with parenteral sympatholytic agents and nitroprusside in patients with severe HF. Cohn and Franciosa, in an influential 1977 article, reviewed the evidence and advocated the use of these drugs in decompensated HF.[73] As originally conceived, the pharmacological rationale for the use of vasodilators in HF was purely hemodynamic and based on the application of Ohm's law to blood flow: Flow=DeltaP/R, where DeltaP is the difference between arterial and venous pressure and R is resistance across the vascular bed. Since systemic vascular resistance is usually increased in HF as a result of neurohormonal activation, vasodilation of resistance vessels will increase central cardiac output and flow to some organs. Figure 18-1 illustrates this point: Activation of the adrenergic and RAS systems results in multiple effects that are detrimental to the natural history of HF, including vasoconstriction.

Vasoconstriction serves the short-term purpose of redistributing blood flow to the brain and the heart because these organs exhibit autoregulatory control of flow. When neurohormonal-mediated vasoconstriction occurs in peripheral vascular beds, the brain and heart, the first priorities in the homeostatic hierarchy, will receive redistributed flow because their resistance vessels are maximally vasodilated as a result of local regulation. This short-term strategy is effective for dealing with trauma and blood loss, but because the function of important organs such as the kidney, skeletal muscle, liver, and splanchnic beds is ultimately compromised, this strategy is not the optimal way to deal with the blood flow compromise associated with chronic HF. Thus, the vasodilator approach to treating HF was and is well grounded in targeting the correction of a basic

abnormality afflicting patients with HF.

VENTRICULAR-VASCULAR COUPLING.

As described in Chapters 14 and 15 , myocardial function is dependent on loading conditions. From the point of view of the ventricles, *afterload* is the force opposing contraction and *preload* is the amount of stretch applied to ventricular myocardium before contraction. Vasodilator-mediated arteriolar relaxation reduces vascular resistance, which is a major component of afterload.[74] From a biomechanical point of view, the circulatory system is defined by *ventricular-vascular coupling*. [75] The force ejecting blood from the ventricle is known as end-systolic elastance, a load-independent measure of contractility, and the force resisting ejection of blood is termed vascular elastance. When end-systolic elastance overcomes vascular elastance, blood is ejected as stroke volume. For a given end-diastolic volume, the major determinants of the size of the stroke volume are the velocity of shortening of ventricular contraction and the amount of vascular elastance.[76] For the left ventricle, systemic vascular resistance is a major component of vascular elastance.[77] From these relationships it is obvious that stroke volume can be increased by increasing the velocity of shortening (positive inotropic effect) or by decreasing systemic vascular resistance (vasodilator effect) to overcome the abnormal respective decreases and increases in these parameters inherent in HF resulting from systolic dysfunction.

EFFECTS ON DIFFERENT VASCULAR BEDS.

An extremely important aspect of vasodilator use in chronic HF is that the potential exists to affect different types of vascular beds. The original concept of vasodilator use was based on small arteriolar dilatation since this is the biggest contribution to systemic vascular resistance. However, perhaps even more important is the ability of certain classes of agents to effect venodilation of "capacitance" vessels, which will reduce venous return by enlarging the effective blood volume reservoir and will therefore reduce end-diastolic, pulmonary, and systemic venous pressure. The clinical consequence of this reduction in preload is to reduce pulmonary and hepatic congestion and, more importantly, diastolic wall stress. As described in Chapter 21 , increased wall stress is a major signaling pathway for hypertrophy and other changes in gene expression that are important in producing the dilated cardiomyopathy phenotype of ventricular dilatation and systolic dysfunction. Since a chronically failing heart is usually operating on a flat portion of the preload-performance relationship (see Fig. 18-2), pharmacological reduction in preload will not ordinarily reduce cardiac output in that setting, but it may do so in acute situations. The hemodynamic consequences of alterations in preload and afterload by vasodilators are described in Figure 18-2 , and the vasodilator profiles of individual agents or classes are given in Table 18-3 .

V-HEFT-I.

Studies of vasodilators in the 1980s demonstrated that they were well tolerated and effective in improving symptoms in patients with HF. These short-term trials eventually led to the first mortality-based clinical trial in chronic HF, V-HeFT-I (Vasodilator HF

Trial).[77] V-HeFT-I was a comparison of the alpha$_1$ -adrenergic receptor blocking agent prazosin, the combination of isosorbide dinitrate and hydralazine, and placebo for their effects on total mortality.[78] In this trial, prazosin was not different from placebo, but isosorbide dinitrate-hydralazine reduced mortality at 2 years by 34 percent ($p < 0.03$) but did not reduce mortality over the entire period of follow-up by the log-rank test (p=0.09). Based on these statistically marginal results (because of a relatively underpowered sample size as opposed to an inadequate effect size), the FDA has not approved the hydralazine-isosorbide dinitrate combination for the treatment of HF.

V-HeFT-I served to introduce the idea that the natural history of HF could be favorably influenced by medical therapy, and it also provided strong support to the vasodilator approach to treating HF. However, subsequent clinical trials with "pure" (i.e., that are not also neurohumoral inhibitors) vasodilating agents have not demonstrated a reduction in mortality, and in fact, the powerful vasodilators flosequinan[79] and epoprostenol[80] markedly (by respective values of 43 and 29 percent) *increased mortality* despite salutary effects on exercise tolerance in smaller studies.[81] [82] [83] Therefore, vasodilation per se is not a particularly effective method for improving the natural history of chronic HF, but it is an important strategy for dealing with acute, decompensated HF.

NITROVASODILATORS

Despite the fact that nitrovasodilators are among the oldest vasodilators in common clinical practice, the cellular mechanisms by which these drugs lead to the relaxation of vascular smooth muscle has only become apparent since 1990. It is now understood that these drugs mimic the activity of nitric oxide and its congeners. These autocrine and paracrine signaling autacoids are formed in endothelial and smooth muscle cells throughout the vasculature, as well as in many other cell types, including cardiac muscle cells[84] [85] [86] (see also Chap. 34) . Nitrogen oxides were originally identified as the bioactive factor(s) ("EDRF") responsible for endothelium-dependent relaxation of blood vessels.[87] Their primary mechanism of action in vascular smooth muscle cells is based on their ability to bind to a heme moiety in soluble guanylyl cyclase, with a subsequent increase in intracellular cyclic guanosine monophosphate. The pharmacological activity of each of the nitrovasodilators

TABLE 18-3 -- PROFILE OF VARIOUS VASODILATOR CLASSES FOR PRODUCING VENOUS OR ARTERIOLAR DILATION

CLASS/COMPOUND	VENODILATION	ARTERIOLAR DILATION
Nitrovasodilators	+++	+
Hydralazine	+	+++
Flosequinan	++	+++
Calcium channel blockers	+	+++
K+ channel activators	++	+++
Vasodilator prostaglandins	+++	++
Natriuretic peptides	++	+

Neurohormonal inhibitors	++	+

depends on their biotransformation into nitrogen oxides within the blood and vascular tissue.[84]

Nitroprusside

Intravenous nitroprusside is an effective venous and arterial vasodilator and acts to reduce both ventricular preload and afterload. Because of the fact that it is quickly metabolized to cyanide and nitric oxide, its onset of action is rapid and upward titration can usually be achieved expeditiously to produce an optimal and predictable hemodynamic effect. For these reasons, nitroprusside is commonly used in intensive care settings for the management of acutely decompensated HF when blood pressure is adequate to maintain cerebral, coronary, and renal perfusion. Nitroprusside has balanced effects on afterload and preload, and ventricular filling pressures are rapidly reduced by an increase in venous compliance.[88]

Nitroprusside is among the most effective afterload-reducing agents because of its spectrum of vasodilating activity on different vascular beds. It reduces systemic vascular resistance, increases aortic wall compliance, and at optimal doses, improves ventricular-vascular coupling. Nitroprusside also decreases pulmonary vascular resistance, as well as improves other components of right ventricular afterload, including the amplitude and timing of reflected pressure waves during ejection.[89]

Hydrocyanic acid and cyanide are byproducts of the biotransformation of nitroprusside. However, cyanide toxicity is uncommon because cyanide is rapidly metabolized by the liver to thiocyanate, which is cleared by the kidney. Thiocyanate and/or cyanide toxicity may occur in the presence of hepatic or renal failure and after prolonged infusions of nitroprusside in patients with marginal cardiac output or passive congestion of the liver. Thiocyanate toxicity, which is more common in patients with renal insufficiency, should be suspected in any patient receiving this drug who has unexplained abdominal pain, mental status changes, or convulsions. Clinical manifestations of cyanide toxicity are more subtle in onset and are usually manifested as a decline in cardiac output accompanied by metabolic acidosis from the accumulation of lactic acid.

Nitroprusside should not be used in active ischemia because its powerful intramyocardial afterload-reducing effects may "steal" coronary blood flow from segments of myocardium supplied by epicardial vessels with high-grade lesions.[90] This phenomenon is probably the reason why nitroprusside increased mortality in an acute myocardial infarction study.[91] In the setting of ischemia, any indicated vasodilator therapy should be delivered by organic nitrates, which are less powerful intramyocardial afterload reducers than nitroprusside is and which produce greater epicardial

vasodilation.

Organic Nitrates and Molsidomine*

The organic nitrates and molsidomine are powerful venodilators and mild arteriolar vasodilators and produce the most extensive epicardial coronary vasodilation of any class of vasodilator. Because of their relatively selective vasodilating effects on the epicardial coronary vasculature, organic nitrates may directly increase systolic and diastolic ventricular function by improving coronary flow in patients with ischemic cardiomyopathy, in addition to their activity in reducing ventricular filling pressure, wall stress, and oxygen consumption.[92] In acute myocardial infarction, however, the effect of the routine use of nitrovasodilators on mortality remains controversial.[93] [94]

Experience with the newer nitrovasodilators, including isosorbide mononitrates and molsidomine, in the treatment of HF is limited in comparison to their use in the treatment of angina. Molsidomine, after formation of its active metabolite linsidomine (SIN-1) in the liver, does not require the intermediate biotransformation with sulfhydryl groups needed to form nitric oxide in vascular smooth muscle that is required of organic nitrates. Molsidomine given intravenously or orally is effective in reducing systemic vascular resistance, pulmonary capillary wedge pressure, and right atrial pressure.[95] Tolerance to the arteriolar and venular vasodilating effects of molsidomine does develop, although its extent and time course may differ from that of tolerance associated with organic nitrates. The spectrum of activity of 5-isosorbide mononitrate would not be expected to differ from that of isosorbide dinitrate in HF. Although isosorbide mononitrate's greater bioavailability and longer elimination half-life may provide a convenient pharmacokinetic profile, only isosorbide dinitrate among the nitrate formulations has been shown to increase exercise tolerance[96] and, in combination with hydralazine, may have prolonged survival in patients with HF.[77]

TOLERANCE.

The main problem with longer-term (>24 hours) use of organic nitrates and molsidomine is the development of tolerance (see Chap. 37) . Rapid development of tolerance to the venous and arteriolar dilating effects of organic nitrates has been known for over a century.[97] While well documented, the mechanism(s) responsible for nitrate tolerance are not clearly understood. It is likely that several mechanisms contribute to decreased responsiveness to nitrovasodilators with time and that the importance of the relative contribution of each potential mechanism differs with the specific drug used, the underlying disease (HF vs. angina), and the specific vascular bed.[97]

Most of the data on the efficacy of intermittent versus continuous nitroglycerin dosing protocols have been obtained in patients with angina rather than chronic congestive HF symptoms.[98] Indeed, it is somewhat controversial whether HF patients should be exposed to a long nitrate-free period. Nevertheless, it seems prudent to recommend nitrate-free intervals in patients receiving chronic doses of isosorbide dinitrate, which can usually be achieved by providing the last dose of isosorbide dinitrate in the early

evening.

"DIRECTLY ACTING" AND OTHER VASODILATORS (see also Chap. 29)

Hydralazine

Hydralazine, an effective afterload-reducing agent whose cellular mechanism of action remains poorly understood, is best used in chronic HF when combined with isosorbide dinitrate to provide more effective venodilation.[77] This combination produces a more balanced form of vasodilation, and in addition, some evidence indicates that hydralazine can attenuate nitrate tolerance.[99] In HF, hydralazine reduces right and left ventricular afterload by reducing systemic as well as pulmonary artery input impedance and vascular resistance.[100] Unlike the use of hydralazine to treat hypertension, this reduction in afterload is usually accompanied by only minor reflex increases in sympathetic nervous system activity unless symptomatic hypotension occurs. These hemodynamic changes result in an increase in forward stroke volume and reductions in ventricular systolic wall stress and the regurgitant fraction in mitral or aortic regurgitation. Hydralazine's effects on regional blood flow consist of an increase in renal and skeletal muscle blood flow.[101]

One of the problems with the use of hydralazine is its short half-life, which necessitates dosing four times daily. In addition, side effects that may necessitate dose adjustment or withdrawal of hydralazine therapy are common. For example, in the V-HeFT-I Trial, 20 percent of patients complained of symptoms that could have been related to hydralazine. The most common complaints--headache and dizziness--could also have been due to the concomitantly administered nitrates. However, with time, the symptoms diminish or respond to a reduction in dose.

Hydralazine metabolism is primarily via hepatic acetylation, although many additional potential metabolic pathways

have been described.[102] Therefore, patients with a "slow-acetylater" phenotype will have a prolonged elimination half-life of the drug. At the usual doses and dosing intervals of hydralazine, these patients are at greater risk of arthritis or other components of a lupus-like syndrome.

Because of the somewhat equivocal results of hydralazine-isosorbide dinitrate in V-HeFT-I[100] and the superiority of the ACE inhibitor enalapril to this combination in V-HeFT-II,[103] hydralazine-isosorbide dinitrate is reserved for subjects who cannot tolerate ACE inhibitors or who have need for additional afterload reduction (blood pressure remaining high normal or greater in the face of full-dose ACE inhibition). Another potential use for hydralazine-isosorbide dinitrate is in American blacks, who in V-HeFT-II had better clinical responses to the combination than to enalapril.[104]

Flosequinan

Flosequinan is a powerful balanced vasodilator with an unknown mechanism of action that was FDA approved briefly for the treatment of HF and then withdrawn from the market by the sponsor because of a substantial increase in mortality[79] in a study that was not completed at the time of approval. Although flosequinan has weak positive inotropic effects in isolated human heart preparations,[105] the major pharmacological property of this compound is vasodilation. The flosequinan "story" is described here because of its multiple important lessons in HF therapy and drug development.

The hemodynamic effects of flosequinan are sustained[106] and associated with a consistent and impressive increase in maximum exercise tolerance.[81] [82] Although flosequinan produced an excess of deaths when compared with placebo in medium-sized phase III trials,[81] [82] this result was initially disregarded because it was not statistically significant and the agent's vasodilator class was not thought to confer high risk for increasing mortality. However, the Prospective Randomized Flosequinan Longevity Evaluation (PROFILE) mortality trial[79] confirmed the increased mortality, with a nearly identical percent increase in death in comparison to placebo as occurred in the exercise trials.[81] [82] In retrospect, one clue to the mortality-enhancing potential of flosequinan was its positive chronotropic effects in that the drug increased the resting heart rate by an average of 7 beats/min in earlier phase II and III trials. In general, compounds that increase the heart rate increase mortality and vice versa.[107]

The clinical trial results with flosequinan demonstrated that sustained vasodilation without concomitant neurohormonal antagonism has an adverse, rather than favorable effect on the natural history of HF. This observation, coupled with the results of V-HeFT-II,[103] spelled the end of the "vasodilator era" of therapy for chronic HF. Moreover, the flosequinan results, combined with the adverse survival results seen with higher doses of inotropic agents, ended the pure hemodynamic approach to the treatment of HF or the notion that simple pharmacological correction of hemodynamic abnormalities would improve the natural history.[108]

Calcium Channel Antagonists

Although all three classes of calcium channel antagonists (i.e., phenylalkylamines such as verapamil; benzothiazepines such as diltiazem; and dihydropyridines such as nifedipine, nitrendipine, felodipine, nicardipine, isradipine, or amlodipine) are effective arteriolar vasodilators, none has been shown to produce sustained improvement in symptoms or natural history in HF patients with predominant systolic ventricular dysfunction. Indeed, some of these agents appear to worsen symptoms and may increase mortality in patients with systolic dysfunction.[109] The reason for these adverse effects or lack of efficacy of calcium channel blockers in HF is unclear. It may be related to the known negative inotropic effects of these drugs, to reflex neurohumoral activation, or a combination of these and other effects.

Second-generation calcium channel antagonists of the dihydropyridine class, such as

amlodipine, nicardipine, and felodipine, have fewer negatively inotropic effects than do earlier drugs of this class as a result of their higher degrees of vasoselectivity. All three have recently been evaluated in medium or large-scale randomized trials.[110] [111] [112] In V-HeFT-III,[110] felodipine and, in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) Study,[111] amlodipine did not increase mortality, thus indicating that these agents and probably nicardipine[112] are safe for use in treating angina in subjects with HF.

K+ CHANNEL ACTIVATORS

K^+ channels are composed of diverse families of integral plasma membrane proteins, the K^+ conductance of which is specific to each family. [113] K^+ channels are regulated by a number of mechanisms, including changes in transmembrane voltage, intracellular Ca^{2+} activity, intracellular adenosine triphosphate (ATP) levels, and other mechanisms.[114] [115] The distribution of K^+ channel isoforms is tissue and cell type specific, [116] which permits the possibility of relatively selective tissue pharmacological activity of drugs acting on a specific family of K^+ channels. In vascular smooth muscle, increased outward K^+ conductance causes cellular hyperpolarization and decreased Ca^{2+} entry, thereby resulting in vasorelaxation. Diazoxide and minoxidil, classic "directly" acting vasodilators, are now known to act at ATP-regulated K^+ channels.

Nicorandil*, pinacidil,* and cromakalim* are representatives of a new class of ATP-regulated K^+ channel activators that exhibit a unique spectrum of activity among vasodilator drugs. Like minoxidil, nicorandil is primarily an arteriolar vasodilator, but it is also effective in dilating epicardial coronary arteries and in reducing preload in experimental animals and patients with HF.[117] Nicorandil, pinacidil, and cromakalim have been tested in humans, primarily for hypertension and angina, and are effective and relatively well tolerated with fewer adverse effects than seen with the older vasodilators of this class. In addition, ATP-regulated K^+ channel activators may have cardioprotective effects in terms of preventing ischemic damage.[118] More recently, the calcium-sensitizing inotrope-vasodilator levosimendan, which is in phase III HF clinical trials in both intravenous and oral form, has been shown to be an activator of ATP-regulated K^+ channels at higher doses (see below).

The experience to date with these agents in patients with HF has not been extensive. Unlike nitrovasodilators, tolerance to nicorandil has not been observed in angina studies.[119] As with any novel class of vasodilator, the utility of nicorandil and other ATP-regulated K^+ channel activators must await the design and completion of large controlled efficacy and survival trials.

Vasodilator Prostaglandins

Prostaglandins are biologically active eicosanoids that produce either vasodilation (e.g., prostaglandin E_1 , prostacyclin) or vasoconstriction (e.g., thromboxane). One of them, prostacyclin (epoprostenol), has been developed as an intravenous vasodilator and has been used in clinical trials in right ventricular failure from primary pulmonary

hypertension (PPH)[120] (see Chap. 53) and in advanced chronic biventricular failure.[80] In both trials, prostacyclin was given intravenously by continuous infusion. The remarkable finding in these two clinical trials was that prostacyclin *decreased* mortality in PPH[120] but *increased* it in biventricular failure.[80] These findings initially seem paradoxical until the underlying pathophysiology of the two disorders is examined. In PPH, the pathophysiology is dominated by a marked increase in right ventricular afterload to levels that are severalfold above normal. The natural history of PPH is dependent on the ability of the right ventricle to withstand this insult, and any measure that can reduce afterload, such as prostacyclin, can improve the natural history of PPH. In contrast, in biventricular failure from a dilated cardiomyopathy phenotype, elevated left or right ventricular afterload is not usually the dominant pathophysiology. Rather, the natural history is related to the vicious cycle of contractile dysfunction and remodeling described in Chapter 16 . When a powerful vasodilator such as prostacyclin is administered, neurohormonal signaling pathways are probably progressively activated, thereby leading to an increase in mortality and generally worsening the natural history of HF. Indeed, results of the prostacyclin chronic HF ("Flolan International Randomized Survival Trial" [FIRST]) trial are part of the evidence that vasodilation per se is not a beneficial approach to the treatment of chronic HF.[108]

Natriuretic Peptides

As discussed above in the section on diuretics, the natriuretic peptides are hormones that are produced by the heart in response to increased wall stress and are secreted into the circulation as a marker of hypertrophy or failure. In fact, one of them, BNP, has promise as a blood test for HF or left ventricular dysfunction.[121] [122] Natriuretic peptides are not simply markers of myocardial hypertrophy and failure; they are also vasodilators and are natriuretic and diuretic in some patients.[45] [46] The vasodilator properties are both venous and arteriolar.[45] [46]

Because of these favorable vascular and renal effects, recombinant natriuretic peptides have been evaluated as intravenous therapy in decompensated HF, and one of them, hBNP, is in phase III clinical development. In subjects with HF, intravenous BNP increases cardiac output and lowers pulmonary wedge mean and mean pulmonary

artery pressure without increasing the heart rate.[45] [46] The latter is probably due to the sympathoinhibitory properties of BNP[123] because systemic norepinephrine levels actually decrease[46] despite the vasodilator effects of the compound. The unique combination of vasodilation and diuresis/natriuresis creates a potentially useful acute HF treatment for certain subjects.

Another approach to the use of natriuretic peptides is to deliver them subcutaneously, where they could then be used to treat chronic HF.[124] Thus far, proof of concept for the route of administration[124] has been accomplished, but no controlled trial data are

available.

Neurohormonal/Cyokine Inhibitors

Although initially investigated within the vasodilator paradigm, inhibitors of vasoconstrictor neurohormones or cytokines do far more than produce vasodilation. That is, inhibitors of the renin-angiotensin, adrenergic, and endothelin systems probably exert their primary action on the heart in that they attenuate or even reverse the dysfunction/remodeling process, as discussed in Chapter 16 . However, their vasodilator properties are also useful because they tend to improve rather than worsen hemodynamics. Inhibitors of neurohormonal or cytokine systems are discussed in detail in a later section.

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Positive Inotropic Agents

CARDIAC GLYCOSIDES

Cardiac glycosides are used to treat chronic HF in patients in sinus rhythm and to control the response of the ventricular rate to supraventricular arrhythmias, including atrial fibrillation.[124A] The first drug used to treat chronic HF was digitalis, an extract of the common foxglove plant *Digitalis purpurea*. Digoxin is now the most commonly prescribed cardiac glycoside because of its convenient pharmacokinetics, alternative routes of administration, and the widespread availability of serum drug level measurements. Both deslanoside, a rapidly acting agent available only for parenteral use, and digitoxin continue to be marketed in the United States. The discussion is confined to digoxin since it is the cardiac glycoside of choice worldwide.

MOLECULAR MECHANISM OF ACTION.

Digoxin is an extremely complex agent in that its mode of action, inhibition of Na^+ ,K^+ -ATPase, affects multiple cellular processes, including several critical to cardiac myocyte function (see Chap. 14) . Digoxin is also extremely toxic, not surprising in view of its role in nature. Cardiac glycosides bind to a specific high-affinity site on the extracytoplasmic face of the alpha subunit of Na^+ ,K^+ -ATPase, the enzymatic equivalent of the cellular "sodium pump."[125] The affinity of the subunit for cardiac glycosides varies among species and among the three known mammalian subunit isoforms, each of which is encoded by a separate gene.[125]

Cardiac glycoside binding to and inhibition of the Na^+ ,K^+ -ATPase sodium pump are reversible and entropically driven. Under physiological conditions, these drugs preferentially bind to the enzyme after phosphorylation of a beta-aspartate on the

cytoplasmic face of the alpha subunit, thus stabilizing this "E_2 P" conformation.[125] [126] Extracellular K^+ promotes dephosphorylation at this site, resulting in a decrease in the cardiac glycoside binding affinity for the enzyme.[126] This action presumably explains why increased extracellular K^+ tends to reverse some manifestations of digitalis toxicity.

POSITIVE INOTROPIC EFFECT.

Cardiac glycosides increase the velocity and extent of shortening of cardiac muscle, thereby resulting in an upward and left shift of the ventricular function curve (Frank-Starling) relating cardiac performance to filling volume or pressure (see Fig. 18-2) . This process occurs in normal as well as failing myocardium and in atrial as well as ventricular muscle. The effect appears to be sustained for periods of weeks or months without evidence of desensitization or tolerance.[127] The positive inotropic effect is due to an increase in the availability of cytosolic Ca^{2+} during systole, thus increasing the velocity and extent of sarcomere shortening. The increase in intracellular Ca^{2+} is a consequence of cardiac glycoside-induced inhibition of sarcolemmal Na^+ ,K^+ -ATPase.[125] [126] Inhibition of Na^+ ,K^+ -ATPase causes intracellular Na^+ to increase, which is then exchanged for extracellular Ca^{2+} via the Na^+ -Ca^{2+} exchanger.[128] The net effect of these adjustments is to increase intracellular Ca^{2+} during systole, which increases systolic function.

In part because cardiac glycosides produce an increase in contractile function without increasing the heart rate, the positive inotropic effects are more energetically efficient than are the effects of beta-adrenergic agonists and higher doses of PDEIs.[129] This difference may be one of the reasons why low-dose digoxin does not increase mortality in patients with HF.[130]

ANTIADRENERGIC PROPERTIES.

Na^+ ,K^+ -ATPase is involved in baroreflex afferent signaling and may be upregulated in the carotid sinus in HF.[131] Decreased baroreflex control[132] is one of the mechanisms responsible for an increase in generalized and cardiac[133] adrenergic activity in HF. Inhibition of Na^+ ,K^+ -ATPase by ouabain modulates baroreflex function toward normal in HF animal models,[131] which is likely to be the mechanism by which cardiac glycosides inhibit adrenergic activity in HF. Ferguson and colleagues demonstrated in patients with moderate to severe HF that infusion of the cardiac glycoside deslanoside increases forearm blood flow and the cardiac index and decreases the heart rate, concomitant with a marked decrease in skeletal muscle sympathetic nerve activity measured as an indicator of centrally mediated sympathetic nervous system activity.[134] In addition, controlled clinical trial data have indicated that digoxin reduces systemic[135] and cardiac[136] norepinephrine levels in subjects with chronic HF. This reduction in adrenergic activity may be another reason why digoxin does not increase mortality when used in low doses in patients with chronic HF.

ELECTROPHYSIOLOGICAL ACTIONS.

Cardiac glycosides have complex electrophysiological effects that are a combination of indirect, parasympathetic, and direct effects of specialized cardiac pacemaker and conduction tissue.[137] At low to moderate therapeutic serum concentrations (0.5 to 1.9 ng/ml), digoxin usually decreases automaticity and increases maximal diastolic resting membrane potential in atrial and atrioventricular (AV) nodal cells as a result of augmented vagal tone and decreased sympathetic nervous system activity. These effects are accompanied by prolongation of the effective refractory period and decreased AV nodal conduction velocity. At higher, toxic digoxin levels or in the presence of underlying disease, patients are susceptible to sinus bradycardia or arrest, prolongation of AV conduction, or heart block. At toxic levels, cardiac glycosides can also increase sympathetic nervous system activity, potentially contributing to the generation of arrhythmias. Increased intracellular Ca^{2+} loading and increased sympathetic tone both contribute to an increased rate of spontaneous (phase 4) diastolic depolarization and also to delayed afterdepolarizations that may reach threshold and generate propagated action potentials. The combination of increased automaticity and depressed conduction in the His-Purkinje network predisposes to arrhythmias, including ventricular tachycardia and fibrillation. Recent data from the Digitalis Investigation Group (DIG) Trial[138] suggest that the increase in ventricular arrhythmia manifested in chronic HF as an increase in sudden death extends down to digoxin serum levels of 1.0 ng/ml, inasmuch as higher concentrations were associated with an increase in mortality.

Clinical Trial Results

Despite its use for over 200 years in the treatment of HF, the debate over the use of cardiac glycosides in chronic HF continues. Small and medium-size trials conducted in the 1970s and 1980s yielded equivocal results, with some apparently

demonstrating efficacy[139] [140] [141] and some not.[142] [143] [144] In the early 1990s, two relatively large digoxin withdrawal studies, the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE)[145] [146] and the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED),[146] [147] provided strong support for clinical benefit from digoxin in that worsening HF developed in more patients and they had to be hospitalized if digoxin therapy was withdrawn than in patients who had placebo withdrawn and were maintained on a regimen of digoxin. However, withdrawal studies are difficult to interpret, so a large placebo-controlled mortality trial, the DIG Trial, was conducted.[130]

The DIG Trial had all-cause mortality as its primary endpoint and had secondary endpoints of hospitalization and worsening HF.[130] This trial enrolled 6800 Class I to III HF patients with an average left ventricular ejection fraction of 28 percent and monitored them for an average of 37 months. Remarkably, the DIG Trial finished with a relative risk ratio of 1.00 (confidence intervals of 0.91 and 1.07, p=0.80), which indicates that at

the doses (0.125 to 0.375 mg/d, with 70 percent receiving 0.25 mg/d) and serum levels of digoxin studied, this positive inotrope does *not* increase mortality in chronic HF. The data indicated a strong trend (p=0.06) toward a decrease in deaths assigned to a progressive pump failure etiology, balanced by an increase in sudden and other non-pump failure cardiac deaths (p=0.04). [130] The number of patients hospitalized was statistically significantly reduced (by 4 percent) by digoxin therapy, and the total number of hospitalizations per subject was significantly reduced by 6 percent.[130] Therefore, evidence of efficacy was seen in the DIG Trial, but in view of its large size and power, this evidence is modest.

One of the most important findings to emerge from the DIG Trial was that mortality was directly related to the digoxin serum level.[138] In addition, data from other studies have demonstrated that the beneficial effects of digoxin on ventricular function[148] and neurohormonal activation[148] [149] occur at the "safe" lower serum levels of 0.5 to 1.0 ng/ml. This information means that if digoxin is used in subjects with HF, *trough levels should be kept between 0.5 and 1.0 ng/ml.*

Overall, these clinical trial results support the routine use of digoxin in patients in sinus rhythm who have mild to moderate HF, which is why most HF practice guidelines recommend the use of digoxin. Because the DIG Trial,[130] as well as RADIANCE[145] and PROVED,[147] were conducted in patients with Class II to III HF, no firm recommendation is possible for more advanced HF patients in sinus rhythm. In addition, digoxin is indicated in all HF patients with atrial fibrillation in whom ventricular response slowing is required. However, in both the sinus rhythm and atrial fibrillation settings, digoxin must be used in such a way to avoid overt toxicity or an increase in sudden death without obvious toxicity.

PHARMACOKINETICS AND DOSING

Orally administered digoxin is variably absorbed, depending on the preparation, but Lanoxin is 60 to 80 percent absorbed. Digoxin is approximately 25 percent protein bound in plasma, has a large volume of distribution (4 to 7 liter/kg), and crosses both the blood-brain barrier and the placenta. Digoxin is eliminated primarily by renal mechanisms, both glomerular filtration and tubular secretion. Tubular excretion is via the energy-dependent membrane-bound efflux pump/transport enzyme P-glycoprotein, which is modulated by many other drugs. Digoxin is largely excreted in the urine unchanged with a clearance rate proportional to the GFR, which results in the excretion of approximately one-third of body stores daily. The half-life for digoxin elimination of 36 to 48 hours in patients with normal or near-normal renal function permits once-daily or every-other-day dosing.[150]

In the presence of an elevated blood urea nitrogen-to-creatinine ratio (i.e., "prerenal azotemia"), digoxin clearance more closely parallels urea clearance, thus indicating that under these circumstances some drug filtered at the glomerulus undergoes tubular reabsorption.[150] In patients with HF, increased cardiac output and renal blood flow in response to treatment with vasodilators or sympathomimetic agents may increase renal digoxin clearance and necessitate dosage adjustment. Digoxin is not removed effectively by peritoneal dialysis or hemodialysis because of its large volume of

distribution.[150] The principal body reservoir is skeletal muscle and not adipose tissue. Accordingly, dosing should be based on estimated lean body mass. Although neonates and infants tolerate and may require higher doses of digoxin (e.g., 0.01 mg/kg/d) for a therapeutic effect equivalent to that of older children or adults, once-daily dosing appears to be as effective as twice-daily dosing in this population.[151]

Digoxin can be loaded at a dose of 0.75 to 1.25 mg orally (or intravenously at doses 25 percent lower) over a 24-hour period in three to four divided doses and then given at a maintenance dose, or a daily maintenance dose of 0.0625 to 0.25 mg/d orally can be started, depending on renal function, body size, and the presence or absence of coadministered drugs causing pharmacokinetic interactions. In the absence of loading doses, nearly steady-state blood levels are achieved in four to five half-lives, or about 1 week after initiation of maintenance therapy if normal renal function is present. If given intravenously, administration should be carried out over at least 15 minutes to avoid vasoconstrictor responses to more rapid injection. Intramuscular digoxin is absorbed unpredictably, causes local pain, and is not recommended.

Patients with HF usually have a reduced volume of distribution and reduced renal function, and both may be influenced by other treatment and by the ebb and flow of the HF. Although nomograms on digoxin dosing have been published, these nomograms should not be used in patients with HF because of the narrow therapeutic index and the unpredictability of the numerous factors that can alter digoxin pharmacokinetics. Instead, patients should be started on a dose as described above and trough levels (see below) measured 1 to 2 weeks later and at frequent intervals (every 1 to 3 months) thereafter.

DRUG INTERACTIONS WITH DIGOXIN.

Multiple drugs interact with digoxin at multiple levels, including reduced renal tubular excretion by drugs inhibiting P-glycoprotein renal tubular transport,[152] induction of gut P-glycoprotein,[153] alterations in gut flora by antibiotics causing less gut metabolism of digoxin before absorption, displacement from plasma protein-binding sites, or reduction in renal function. A partial list of these interactions is given in Table 18-4 .

THERAPEUTIC DRUG MONITORING

Digoxin has an extremely low therapeutic index, and its use should be carefully monitored by serum blood levels. The various clinical conditions and drug interactions that can alter digoxin's pharmacokinetics are also reflected in the serum digoxin level. Reduced thyroid function and renal function both decrease the volume of distribution of digoxin and thus necessitate downward adjustments in loading and maintenance doses. Hypochlorhydria (i.e., gastric pH >7), which is common in elderly patients and patients receiving histamine H_2 receptor antagonists or gastric H^+ ,K^+ -ATPase inhibitors, reduces gastric metabolism of digoxin and nonrenal clearance of the drug.[154] This abnormality may lead to higher steady-state blood levels in these patients with reduced renal function, particularly in the elderly. Both hypokalemia and hypercalcemia can independently increase ventricular automaticity and lower the threshold for

digoxin-induced cardiac arrhythmias. Hypomagnesemia may also contribute to arrhythmias with digoxin. Hyperkalemia may exacerbate digoxin-induced conduction disorders and cause high-grade AV nodal block.

Studies using noninvasive indices of ventricular function suggest a nonlinear relationship between the serum digoxin concentration and observed inotropic or neurohormonal antagonism, with the majority of the increase in contractility[148] or neurohormonal effects[148] [149] occurring by the time that steady-state levels around 1.4 ng/ml are reached. *This information, plus DIG Trial mortality data, indicates that the optimal trough digoxin serum level is 0.5 to 1.0 ng/ml.* This concentration range is also the one that should be used to control the ventricular rate response to atrial fibrillation in HF patients, particularly since digoxin is not a very effective agent in this regard in the setting of high amounts of adrenergic activity.[155] Blood samples for measurement of serum digoxin levels should be taken at least 6 to 8 hours following the last digoxin dose.

Digitalis Toxicity

In patients with HF, overt clinical toxicity tends to emerge at serum concentrations greater than 2.0 ng/ml, but it must always be remembered that substantial overlap in serum levels exists among patients exhibiting symptoms and signs of toxicity and those with no clinical evidence of intoxication.[156] Disturbances in cardiac impulse formation, conduction, or both are the hallmarks of digitalis toxicity.[157] Among the common electrocardiographic manifestations are ectopic beats of AV junctional or ventricular origin, first-degree AV block, an excessively slow ventricular rate response to atrial fibrillation, or an accelerated AV junctional pacemaker. These manifestations may require only dosage adjustment and monitoring as clinically appropriate. Sinus bradycardia, sinoatrial arrest or exit block, and second- or third-degree AV conduction delay often respond to atropine, but temporary ventricular pacing is sometimes necessary and should be available.

TABLE 18-4 -- PARTIAL LIST OF DRUG INTERACTIONS WITH DIGOXIN

DRUG	EFFECT ON SERUM DIGOXIN LEVEL	MECHANISM
Amiodarone	Increases	? Renal clearance
Verapamil	Increases	Renal clearance
Nifedipine	Increases	Renal clearance

Diltiazem	Increases	Renal clearance
Quinidine	Increases	Displacement of protein binding, renal clearance
Propafenone	Increases	Renal clearance
Captopril	? Increases	? Renal clearance
Carvedilol	Increases	Oral bioavailability
Spironolactone	Increases	Renal clearance
Amiloride	Increases	Renal clearance
Triamterene	Increases	Renal clearance
Salbutamol	Decreases	Unknown
Macrolide antibiotics (erythromycin, clarithromycin)	Increases	Altered gut flora, renal clearance
Tetracycline	Increases	Altered gut flora
Indomethacin	Increases	Renal clearance
Alprazolam	Increases	? Renal clearance
Itraconazole	Increases	Renal clearance
Rifampin	Decreases	Induction of gut P-glycoprotein
Sucralfate	Decreases	Decreased gut absorption
Cholestyramine	Decreases	Decreased gut absorption
Cyclosporine	Increases	Renal clearance
Saint Johns wort	Increases	Renal clearance

MANAGEMENT.

Oral potassium administration is often useful for atrial, AV junctional, or ventricular ectopic rhythms, even when the serum potassium is in the normal range, unless

high-grade AV block is also present. However, [K^+] must be monitored carefully to avoid hyperkalemia, especially in patients with renal failure. Magnesium may be useful in patients with atrial fibrillation and an accessory pathway in whom digoxin administration has facilitated a rapid accessory pathway-mediated ventricular response; again, careful monitoring is required to avoid hypermagnesemia.[158] Lidocaine and phenytoin, which in conventional doses have minimal effects on AV conduction, are useful in the management of worsening ventricular arrhythmias that threaten hemodynamic compromise. Electrical cardioversion can precipitate severe rhythm disturbances in patients with overt digitalis toxicity and should be used with particular caution. Neurological or gastrointestinal complaints can also be manifestations of digitalis toxicity. Occasionally, gynecomastia results from digoxin administration, apparently because of the similarity of the glycoside structure to that of estrogens.

ANTIDIGOXIN IMMUNOTHERAPY.

Potentially life-threatening digoxin or digitoxin toxicity can be reversed by antidigoxin immunotherapy. Purified Fab fragments from digoxin-specific antisera are available at most poison control centers and larger hospitals in North America and Europe. The smaller (molecular weight 50,000) Fab fragments have a larger volume of distribution, more rapid onset of action, and more rapid clearance, as well as reduced immunogenicity in comparison to intact IgG.[159] Clinical experience in adults and children has established the effectiveness and safety of antidigoxin Fab in treating life-threatening digoxin toxicity, including cases of massive ingestion with suicidal intent.[160] Doses of Fab are calculated by using a simple formula based on either the estimated dose of drug ingested or the total-body digoxin burden (Table 18-5) and are administered intravenously in saline over a period of 30 to 60 minutes. Recrudescent digoxin toxicity is unusual but can occur 24 to 48 hours after Fab administration in patients with normal renal function or later in patients with renal impairment. Determination of the efficacy and cost-effectiveness of less than complete neutralizing doses of digoxin-specific Fab fragments for suspected or moderate cases of digoxin toxicity awaits further assessment.[159] [161]

ADRENERGIC AGONISTS

The most powerful way to increase contractility in the human heart is by a beta-adrenergic receptor agonist. Beta-agonists operate through the mechanism that regulates contractility and heart rate on a beat-to-beat basis in the intact heart, the cardiac myocyte beta receptor pathways (see

TABLE 18-5 -- DOSES OF FAB CALCULATED ON THE BASIS OF THE AMOUNT OF INGESTED DIGOXIN OR THE TOTAL-BODY DIGOXIN BURDEN

Estimation of Total-Body Digoxin Burden (mg)
Total drug ingested following acute digoxin poisoning (i.e., amount ingested×0.80 [average oral bioavailability of tablet formulations])
or

Known or suspected toxicity during chronic digoxin therapy:

Serum digoxin concentration×volume of distribution (5.6 liter/kg)×weight in kg ÷ 1000

Calculation of Fab Fragment Dose

Molecular mass of Fab fragments =50,000×64×total-body digoxin content (mg) ÷ Molecular mass of digoxin=781

=dose of Fab fragments (mg)

or

Use a standard formulation (e.g., Digibind [Burroughs Wellcome])

Estimated total-body load of digoxin (mg) ÷ 0.6 (mg/vial) =Digibind dose in numbers of vials

For reversal of digitoxin toxicity, substitute 1.0 for oral bioavailability and 0.56 liter/kg for volume of distribution in the formulas above.

Figure 18-3 Beta-adrenergic signal transduction in human cardiac myocytes. AC=adenylyl cyclase; AMP=adenosine monophosphate; $beta_1$ AR=$beta_1$ -adrenergic receptor; $beta_2$ AR=$beta_2$ -adrenergic receptor; ATP=adenosine triphosphate; CAMK=calmodulin-activated kinase; cAMP=cyclic adenosine monophosphate; G_i =inhibitory G protein with alpha, beta, and gamma subunits; G_s =stimulatory G protein with alpha, beta, and gamma subunits; PDE_c =cytosolic phosphodiesterases; PDE_p =particulate, SR-associated PDE III; PHLMBN=phospholamban; PKA=cAMP-dependent protein kinase A; SR=sarcoplasmic reticulum.

Chap. 14) . As depicted in Figure 18-3 , this system is composed of two cell surface membrane receptors ($beta_1$ and $beta_2$), two G proteins (the "stimulatory G protein G_{alpha} s and the inhibitory G protein G_{alpha} i), the adenylyl cyclase enzyme (which converts Mg-ATP to cAMP), cAMP-activated protein kinase (protein kinase A), and target structures whose phosphorylation leads to a positive inotropic effect by changes in Ca^{2+} handling (phospholamban, the ryanodine release channel, and slow inward current calcium channels). The end result is a powerful positive inotropic as well as positive chronotropic effect.

In the failing human heart, beta-adrenergic pathways undergo *desensitization*, a pharmacological term encompassing the regulatory changes that occur in receptors, G proteins, and adenylyl cyclase.[162] [163] In advanced HF, the degree of desensitization approaches 50 to 60 percent of the maximum capacity of signal transduction,[164] [165] and in severe HF, beta-agonists may no longer be able to support myocardial function.[166] The degree of desensitization present in end-stage HF patients who underwent cardiac

transplantation can be appreciated in Figure 18-4 , which gives maximum responses to the full, nonselective beta-agonist isoproterenol and other agents in isolated right ventricular trabeculae removed from nonfailing and failing human hearts. However, the vast majority of patients with advanced HF still exhibit a substantial inotropic response to beta-agonists,[165] which is the basis for their usefulness as inotropic agents in the treatment of decompensated HF.

All beta-agonists are given intravenously for short-term support in decompensated HF. They are all arrhythmogenic

Figure 18-4 Effects of various inotropic agents on the systolic tension response in nonfailing and failing human right ventricular trabeculae, mean+SEM. OPC 8212=vesnarinone; FLSQ=flosequinan; ENOX=enoximone; MIL=milrinone; ISO=isoproterenol.

to some extent via direct mechanisms, as well as through increasing the skeletal muscle deposition of potassium[68] and decreasing serum magnesium.[167] Obviously, their administration should be carefully monitored and the lowest possible effective doses used. In addition, all beta-agonists are subject to the development of desensitization phenomena when used continuously, another reason to keep the doses low and the use short term or intermittent. Beta-agonists all have short (in minutes) half-lives, which is an advantage for powerful inotropes that may have adverse effects. As shown in Table 18-6 , from a therapeutic standpoint it is important to understand how beta-agonists differ from one another with respect to intrinsic activity; affinity for binding to $beta_1$, $beta_2$, and $alpha_1$ receptors; and affinity for the cardiac adrenergic neuronal reuptake system ($uptake_1$).[168] Neuronal reuptake is an important consideration in the heart, which has the most active $uptake_1$ system of any organ and uses neuronal reuptake to terminate the majority of the action of released norepinephrine.[173] [174]

Although $beta_1$ - and $beta_2$ -adrenergic receptors are both coupled to positive inotropic and chronotropic responses via cAMP-dependent mechanisms, these two receptors have important differences. For one thing, $beta_1$ receptors are positioned inside or near the synaptic cleft area to mediate the effects of released norepinephrine,[176] which also means that catecholamines that have high affinity for $uptake_1$ will not reach myocardial $beta_1$ receptors unless neuronal reuptake is functionally decreased (as it is myocardial failure) or absent (as it is in a recently [<2 years] transplanted heart). In addition, a growing body of evidence indicates that chronic $beta_1$ receptor agonist occupancy and/or pathway activation is more deleterious than $beta_2$ receptor activation.[177] However, from an acute support standpoint, both receptors can be used in supporting cardiac function in decompensated patients.

NEURONAL AFFINITIES FOR SYMPATHOMIMETIC AMINES.

Table 18-6 lists the adrenergic receptor and neuronal uptake (uptake$_1$) affinities for catecholamines that are used therapeutically to increase cardiac performance and/or increase systemic vascular resistance or blood pressure. Although the primary action of uptake$_1$ is to terminate the action of norepinephrine, the functional status of uptake$_1$ is also an important determinant of catecholamine therapeutic action when these agents are administered exogenously. For example, epinephrine, which has an affinity for uptake$_1$ that is slightly lower than that of norepinephrine, is a much more potent therapeutic catecholamine when administered to denervated cardiac transplant hearts than to innervated hearts.[178] [179] When the heart is innervated, uptake$_1$ removes much of the systemically administered epinephrine before it can reach myocardial beta$_1$ -adrenergic receptors, which are preferentially located within the synaptic cleft area.[176] In contrast, isoproterenol, which has essentially no affinity for uptake$_1$, is equally effective in innervated and denervated hearts.[178] [179]

The failing human heart has a functional impairment in uptake$_1$ that essentially creates functional denervation, which in the case of catecholamines with higher affinity for uptake$_1$, can offset some of the postsynaptic desensitization changes. Another way in which uptake$_1$ can influence drug action is to compete with neurotransmitter norepinephrine for neuronal reuptake, which will increase the amount of norepinephrine available in the synaptic cleft area. As can be observed in Table 18-6 , the substituted synthetic catecholamine dobutamine and the endogenous catecholamine dopamine have even higher affinity for uptake$_1$ than norepinephrine does, and at least in the case of dopamine, this higher affinity contributes to its predominant inotropic action, which is to potentiate norepinephrine release.

Dobutamine

Dobutamine is an extremely useful inotropic agent for moderately decompensated HF.[179A] As available clinically, dobutamine is a racemic mixture that stimulates both beta$_1$ - and beta$_2$ -adrenergic receptor subtypes (binding at an approximately 3:1 ratio)[180] and either binds to but does not activate alpha-adrenergic receptors ([+] enantiomer) or stimulates alpha$_1$ and alpha$_2$ receptor subtypes ([-] enantiomer). As discussed above, dobutamine also has relatively high affinity for uptake$_1$. The affinity constants for racemic dobutamine binding to beta$_1$, beta$_2$, and alpha$_{1B}$ receptors are given in Table 18-6 , where it can seen that dobutamine is relatively nonselective for binding to beta$_1$ vs. beta$_2$ receptors and binds to alpha$_1$ receptors and uptake$_1$ at slightly higher affinity. When compared with isoproterenol, in human cardiac preparations dobutamine is a partial beta-agonist with an intrinsic activity of approximately 0.5.[181] The binding to alpha receptors by each isomer of dobutamine results in a mixture of antagonist and agonist action that when coupled with some peripheral vascular beta$_2$ -agonism, usually produces a net mild degree of vasodilation at lower (

5 mug/kg/min) doses. At these doses, dobutamine reduces aortic impedance and systemic vascular resistance, thus reducing afterload and improving ventricular-vascular coupling by reducing aortic impedance.[182] [183] In contrast, dopamine (see below) may have either no effect or increase ventricular afterload by increasing systemic vascular resistance and causing more rapid return of reflected aortic pressure waves, depending on the infusion rate. Therefore, dobutamine is preferable to dopamine for most patients with advanced decompensated HF who have not responded adequately to intravenous diuretics.

The neuronal uptake inhibition of dobutamine means that in subjects with preserved neuronal uptake mechanisms, dobutamine may increase synaptic cleft area norepinephrine concentrations in the heart, in addition to its intrinsic receptor-mediated actions. Dobutamine does not stimulate dopaminergic receptors and, unlike dopamine,

TABLE 18-6 -- PHARMACOLOGICAL CHARACTERISTICS OF VARIOUS ADRENERGIC AGONISTS USED TO TREAT DECOMPENSATED HEART FAILURE

AGENT	$BETA_1$ RECEPTOR AFFINITY (K_d , nM)	$BETA_2$ RECEPTOR AFFINITY (K_d , nM)	$ALPHA_1$ RECEPTOR AFFINITY (K_d , nM)	$UPTAKE_1$ AFFINITY (nM)	INTRINSIC ACTIVITY* FOR HUMAN $BETA_1$ RECEPTORS
Dobutamine	470	570	130	190,330	0.5
Dopamine	25,000	100,000	36,000	130,230	0.2
Epinephrine	30	30	160	1400	1.0
Isoproterenol	30	30	>10,000	9000	1.0
Norepinephrine	10-30	250-750	200	500,670	1.0
Phenylephrine	>10,000	>10,000	1000	>10,000	0

*Relative to isoproterenol=1.0 in nonfailing isolated human right ventricular trabeculae. Affinity data are based on radioligand-cold ligand competition curves in (1) human ventricular myocardial membrane preparations ($beta_1$, in nonfailing hearts with greater than 80 percent $beta_1$ receptors; $alpha_1$, norepinephrine, epinephrine [168]), (2) human recombinant $beta_2$ receptors in COS cell membranes (isoproterenol, norepinephrine, and epinephrine), (3) DTT_1 cell membranes ($beta_2$, dobutamine and dopamine), and (4) rat heart membranes ($alpha_1$, dobutamine).[169] Additional $alpha_1$ -agonist affinity data are derived from irreversible dibenamine antagonism in rabbit aorta, with relative affinities corrected for human/rabbit $alpha_1$ receptor-norepinephrine *K* values (dopamine, phenylephrine, epinephrine).[170] $Uptake_1$ data are from the human recombinant protein cloned from SK-N-SH neuroblastoma cells (norepinephrine, dopamine),[171] rabbit brain synaptosomes (dobutamine, dopamine, isoproterenol),[172] or the original data in rat heart (epinephrine, norepinephrine, phenylephrine) from Iversen.[173] [174] Data on concentrations inhibiting 50 percent (IC_{50}) were converted to affinity constants by using the Cheng-Prusoff equation.[175]

does not selectively alter renal blood flow.[184] The importance of the vascular effects of dobutamine has been demonstrated by experiments in animals[185] [186] with artificial hearts. Even in the presence of a mechanical heart, dobutamine increased cardiac output by 10 to 15 percent and decreased systemic vascular resistance. Interestingly, dobutamine also decreased venous capacitance and increased right atrial pressure, possibly as a result of alpha$_1$ -adrenergic agonism of the (-) enantiomer.[186] These experiments also demonstrated that the (+) enantiomer is responsible for the racemic drug's effects on aortic input impedance, wave reflectance, and systemic vascular resistance.[185] These favorable actions on left ventricular afterload are also responsible for the reduction in functional mitral regurgitation often observed with dobutamine infusions in patients with large dilated ventricles and high left ventricular end-diastolic pressure.[187] Dobutamine also causes a mild decline in pulmonary vascular resistance that is present regardless of chronic background vasodilator therapy.

At higher doses, the (-) isomer of dobutamine begins to exert alpha$_1$ -adrenergic agonist action, thereby preventing progressive vasodilation and usually leading to only minimal changes in afterload and preload. The advantage of this alpha-adrenergic effect of dobutamine is that since preload and afterload do not change dramatically, dobutamine can be administered without pulmonary artery catheter monitoring of left ventricular filling pressure. Another advantage of the relative lack of vasodilation coupled to the partial agonist action is that dobutamine does not produce much increase in the heart rate at doses of 10 mug/kg/min or less. Because of its partial agonist activity, desensitization to prolonged infusions of dobutamine is not pronounced.[188] Dobutamine infusions are initiated at 2 to 3 mug/kg/min and are titrated upward according to the patient's hemodynamic response (usually not higher than 20 mug/kg/min).[183] [184]

The limitations of dobutamine are that it (1) is a relatively weak beta-agonist,[181] (2) only modestly lowers elevated pulmonary artery pressure, (3) eventually produces desensitization phenomena when used chronically,[188] [190] and (4) cannot be effectively used in the presence of high levels of beta-adrenergic receptor blockade.[190] The first three of these limitations can be overcome by combining dobutamine with a PDEI, which results in additive effects on myocardial performance,[191] [192] substantial reductions in pulmonary wedge and pulmonary artery pressure,[191] [192] and a protective effect on desensitization [190] related to being able to lower the dobutamine dose.

Dopamine

Dopamine is an endogenous catecholamine that is the precursor to norepinephrine in the catecholamine synthetic pathway. When administered therapeutically, dopamine is a complex agent. Dopamine through its direct effects is a weak partial agonist. When initially administered, it releases norepinephrine through a tyramine-like effect.[192] It is a potent (relative to its receptor affinities) neuronal uptake inhibitor and by direct action acts as an agonist at dopamine D_1 postsynaptic vasodilator receptors[193] and D_2 presynaptic receptors on blood vessels and in the kidney.[194] The affinities for beta$_1$,

$beta_2$, and $alpha_{1B}$ receptors are shown in Table 18-6 , where it can be seen that dopamine has extremely low affinity for all three adrenergic receptors.

At lower doses (
2 mug/kg/min), dopamine causes relatively selective vasodilation of splanchnic and renal arterial beds. This effect may be useful in promoting renal blood flow and maintaining the GFR in selected patients who become refractory to diuretics, especially when caused by marginal renal perfusion. Dopamine also has direct renal tubular effects that promote natriuresis. At intermediate (2 to 10 mug/kg/min) infusion rates, dopamine, by virtue of its tyramine and neuronal uptake-inhibiting properties, enhances norepinephrine release from vascular and myocardial adrenergic neurons, thereby resulting in increased cardiac beta-adrenergic receptor activation and an increase in peripheral vascular resistance. In patients with advanced HF, who often have depleted intracardiac norepinephrine stores, dopamine is a less effective positive inotropic drug than other "directly" acting inotropes are.[184] [185] At higher infusion rates (5 to 20 mug/kg/min), peripheral vasoconstriction occurs as a result of direct alpha-adrenergic receptor stimulation. Increases in systemic vascular resistance are common even at intermediate infusion rates. On initial administration, tachycardia and arrhythmia tend to be more pronounced than with dobutamine[184] and are related to cardiac norepinephrine release.[192] [195]

In patients with advanced, decompensated HF, dopamine should not be used as a positive inotropic agent, but rather used in low doses for renal perfusion and in intermediate to high doses to increase peripheral resistance. The latter property is often necessary for a variety of reasons, including sepsis, iatrogenic overvasodilation, and brain injury.

Epinephrine

Epinephrine is an endogenous full beta-agonist catecholamine that like dobutamine, produces relatively balanced effects between vasodilation and vasoconstriction. This balance between vasodilation and vasoconstriction occurs because epinephrine has relatively equal high affinities for $beta_1$, $beta_2$, and $alpha_1$ receptors (see Table 18-6) . Epinephrine has moderately high affinity for neuronal reuptake, which means that the majority of administered drug may not reach $beta_1$ -adrenergic receptors in the normal heart. However, neuronal reuptake is markedly reduced in the failing heart,[196] [197] which will allow epinephrine to reach more $beta_1$ -adrenergic receptors in this setting. Epinephrine is an excellent positive inotropic agent in the denervated, transplanted heart[178] [179] because neuronal reuptake is no longer a factor. The dose of epinephrine usually ranges from 0.05 to 0.50 mug/kg/min.

When cardiogenic shock is profound, calcium is often added to an epinephrine infusion to produce synergistic increases in contractility[198] and an increase in vascular tone. This combination, made by adding 1 gm of $CaCl_2$ to 250 ml of intravenous solution containing epinephrine and called "Epi-Cal," has never been subjected to a clinical trial and should be used in resuscitative settings only.

Isoproterenol

Isoproterenol is a full, nonselective beta-agonist that produces powerful positive chronotropic, inotropic, and vasodilator responses. At therapeutic doses, isoproterenol does not bind to the neuronal uptake system (see Table 18-6) . As a therapeutic inotrope, isoproterenol has only one indication--postoperatively after heart transplantation. Isoproterenol is useful in this setting because an increase in heart rate is not a problem in the presence of normal coronary arteries, and the chronotropic stimulation is useful in the newly transplanted heart, which often has a sluggish sinus node mechanism. The pulmonary vasodilator properties of isoproterenol are also useful in this setting, where pulmonary artery pressure and pulmonary vascular resistance are usually elevated.

The dose of isoproterenol ranges from 0.005 to 0.05 mug/kg/min.

Norepinephrine

As shown in Table 18-6 , norepinephrine is a mildly (10- to 30-fold) $beta_1$ vs. $beta_2$ receptor-selective agonist with relatively high affinity for $alpha_1$ receptors and for $uptake_1$. This constellation of properties means that norepinephrine will be a powerful vasoconstrictor, but not a very powerful

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inotrope in hearts with functioning neuronal uptake. Norepinephrine does not have any recommended uses in subjects with cardiac decompensation; subjects who need peripheral vascular resistance support (such as in sepsis, iatrogenic overvasodilation, or brain injury) are served better by dopamine or dopamine plus phenylephrine administration.

Phenylephrine

Phenylephrine is a pure alpha-agonist with no beta-agonist activity and low affinity for $uptake_1$. Even though $alpha_1$ receptors can mediate a small inotropic response in the human heart, phenylephrine should be used only to increase systemic vascular resistance in settings in which dopamine is not effective. The usual dose of phenylephrine ranges from 0.3 to 3 mug/kg/min.

PHOSPHODIESTERASE INHIBITORS

MECHANISMS OF ACTION.

As shown in Figure 18-3 , the enzyme phosphodiesterase type III is associated with the

sarcoplasmic reticulum (SR) in human cardiac myocytes[199] and vascular smooth muscle, where it breaks down cAMP into AMP. Type III phosphodiesterase is also found in platelets. It has an SR-anchoring moiety[200] that accounts for its compartmentation in cardiac myocytes and vascular smooth muscle. Elevations in cAMP in the vicinity of the SR can then activate locally compartmentalized[201] protein kinase A, which will phosphorylate phospholamban[197] and relieve this molecule's inhibition of SR function.[203] Thus, specific type III PDEIs, particularly at low doses, may have a relatively selective effect on phospholamban phosphorylation[202] [204] and SR function, which explains why they lower diastolic Ca^{2+} and increase systolic Ca^{2+} in cultured cardiac myocytes.[205] This SR-selective effect is probably the reason why highly type III-specific PDEIs increase contractile function without much increase in the heart rate,[206] similar to transgenic mice with phospholamban knockout, which exhibit an increase in contractility without an increase in heart rate.[207] However, PDEIs also increase the calcium channel current,[208] and higher doses increase the phosphorylation of sarcolemmal proteins, similar to beta-agonists.[209]

Type III PDEIs are also potent vasodilators, particularly on venous capacitance and pulmonary vascular beds. The vasodilator properties of PDEIs substantially exceed that of beta-agonists,[191] [210] including isoproterenol.[210] The reason for this superior vasodilation appears to be that in vascular smooth muscle, PDEI-induced elevations in cAMP activate protein kinase G,[211] [212] which leads to prominent vasodilation that is not unlike a nitrovasodilator effect in its regional distribution. PDEIs are among the best agents for lowering pulmonary artery pressure and pulmonary vascular resistance, which is why they have assumed an important role in postoperative cardiac surgical regimens, including cardiac transplantation.[213] [214] [215]

Type III PDEIs inhibit platelet aggregation[216] [217] and dilate epicardial coronary arteries and bypass grafts,[218] [219] and at least one of them has been shown to have potent antiischemic effects.[220] [221] In addition, type III PDEIs inhibit neointimal formation after vascular injury,[222] [223] and they inhibit proinflammatory cytokine formation[224] and the effects of endotoxin.[225] Thus, type III PDEIs have multiple properties that might prove valuable in the setting of advanced or severe HF.

Similar to beta-agonists, a PDEI's inotropic response is blunted in failing versus nonfailing hearts[191] [226] (see Fig. 18-5) . In a failing human heart the reason for blunting of the response to PDEIs is not an alteration in myocardial type III phosphodiesterase,[199] but rather upregulation of the inhibitory G protein $G_{alpha\ i}$[227] [228] [229] because a decrease in $G_{alpha\ i}$[230] leads to augmentation of the PDEI response.[231] However, when compared with beta-agonists, little or no subsensitivity develops to the inotrope-vasodilator effects of more potent type III PDEIs such as milrinone[232] and enoximone.[190] [233] [234]

HEMODYNAMIC EFFECTS.

As discussed above, the substantial preload- and pulmonary artery pressure-reducing properties of PDEIs are both a strength and a weakness of this class of agents, inasmuch as before their acute intravenous administration, it is necessary to be certain of an elevated left ventricular filling pressure. Therefore, in the absence of elevated

right-sided venous pressure in a subject with biventricular failure, pulmonary artery catheter-determined documentation of a pulmonary wedge mean pressure greater than 15 mm Hg is desirable before administering a PDEI intravenously. Otherwise, a precipitous drop in blood pressure may accompany drug administration.

PDEIs are absorbed orally, and their attractive hemodynamic profile has led to multiple clinical trials in chronic HF. The increase in cardiac output from PDEIs is preferentially distributed to skeletal muscle,[235] [236] which should theoretically increase maximum exercise responses. Such does appear to be the case.[234] [237] In addition, in a dilated, failing heart, PDEIs have a favorable energetic effect,[238] [239] and PDEIs improve diastolic[240] [241] as well as systolic[242] [243] function. All these observations suggest that PDEIs would be useful in the long-term treatment of chronic HF.

CLINICAL EFFECTS.

However, when subjected to placebo-controlled clinical trials, selective type III PDEIs given in doses that produce large hemodynamic effects have increased mortality.[244] [245] [246] Moreover, agents with PDEI activity and K^+ channel antagonism (vesnarinone), [247] as well PDEI activity and Ca^{2+} sensitization (pimobendan),[248] are also associated with increased mortality. The basis for the increase in mortality is increased sudden death,[246] [249] presumably on an arrhythmic basis.

Despite these discouraging results, PDEIs continue in development for the treatment of chronic HF via two new approaches. One is a "low-dose" approach[250] that takes advantage of the fact that doses that are one-sixth to one-third those used in earlier clinical trials are hemodynamically active,[251] increase exercise tolerance,[234] do not increase the heart rate, [234] are not proarrhythmic,[234] and apparently do not increase mortality.[190] [234] That a positive inotropic agent can increase mortality at higher doses but be safely given at low doses has been established by the DIG Trial, but it remains to be seen whether the same will be true for PDEIs. The second approach to the safe, long-term use of PDEIs in chronic HF is to combine them with a beta-blocking agent.[252] [253] This combination is possible because the site of action of PDEIs is beyond the beta-adrenergic receptor (see Fig. 18-3) and the combination appears to produce additive efficacy and subtractive adverse effects.[252] Treatment with beta-blocking agents actually enhances the hemodynamic effects of PDEIs[231] [246] [254] because of a beta blocker-related reduction in upregulated G_{alpha} i. [230] One practical consequence of these findings and realizations is that subjects chronically receiving beta-blocking agents who decompensate to the point of needing positive inotropic support should be treated with a PDEI rather than dobutamine or some other beta-agonist. [252]

Individual PDEIs available for use or in late-stage development will now be discussed.

AMRINONE.

Originally, the mechanism of action of amrinone and its more potent analog milrinone was unkown,[255] then ascribed to a direct effect on Ca^{2+} influx,[256] [257] and ultimately attributed to type III phosphodiesterase inhibition.[258] [259] Because amrinone causes

thrombocytopenia[260] and may be associated with rapid subsensitivity in subjects with advanced HF,[261] it is no longer widely used to treat decompensated heart failure.

MILRINONE.

Unlike amrinone, milrinone does not commonly cause thrombocytopenia.[262] The incidence of thrombocytopenia reported with milrinone use is 0.4 percent.[263] Although milrinone is a highly selective type III PDEI,[258] [259] other actions capable of producing an inotropic effect have been described, including stimulation of the Ca^{2+} release channel,[264] Ca^{2+} channel agonism,[257] and effects on sarcolemmal Ca^{2+} -ATPase.[265]

Milrinone produces sustained inotropic and vasodilator effects when administered intravenously.[266] [266A] The elimination half-life is 2.3 hours, and milrinone is usually administered as a 25- to 75-mug/kg bolus over a 10- to 20-minute period, followed by a 0.375- to 0.75-mug/kg/min continuous infusion.[263] Development of oral milrinone has been abandoned because of the increase in mortality in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) Trial,[244] which was conducted at doses that are at least four times higher than the minimum effective hemodynamic dose.[267] Milrinone is mostly (80 percent) excreted by the kidney unchanged, and in renal failure, the continuous-infusion dose should be decreased by 50 percent.

ENOXIMONE.*

Enoximone is approved for intravenous use in Europe and is in development in the United States for oral use as both low-dose enoximone alone and in combination with $beta_1$ -selective blockade. Enoximone is a highly selective type III PDEI[268] with no other known pharmacological actions at therapeutic plasma concentrations. Enoximone rarely causes thrombocytopenia and produces sustained hemodynamic effects with intravenous[269] or oral[233] [234] administration.

Enoximone is about one-tenth as potent as milrinone for inhibiting type III phosphodiesterase, which translates to oral and intravenous doses of enoximone being approximately 10 times those of milrinone. The intravenous loading dose is 0.25 to 0.75 mg/kg, with the continuous infusion rate being 1.25 to 7.5 mug/kg/min. Enoximone is extensively metabolized by the liver to sulfoxide derivatives, including at least one active metabolite.[270] [271] Sulfoxide metabolites (about 75 percent within 24 hours in HF subjects) are eliminated by the kidney, and dose reductions in renal failure are the same as with milrinone.[272] Enoximone doses should also be reduced in patients with hepatic failure.

VESNARINONE AND OTHER QUINOLINONE INOTROPES.*

This class of compounds has recently had members in development in the United

States for advanced, chronic HF in oral (vesnarinone) and intravenous (toborinone) formulations. Vesnarinone is approved for the treatment of HF in Japan. Several unique features about the pharmacology and clinical trial experience are associated with these agents. In human myocardium, therapeutic concentrations of these agents produces phosphodiesterase inhibition and K^+ channel (delayed rectifier current) antagonism.[273] This action results in a hemodynamic profile similar to that of enoximone or milrinone, but coupled with type III antiarrhythmic properties. The benefit of this combination is that the heart rate will not be increased and may even decrease slightly in response to treatment, thus providing an energetic advantage.[274] The disadvantage of this combination of properties is that the quinolinone inotropic agents have two potentially proarrhythmic properties, and in fact, *torsades de pointes* was a frequent adverse event with higher doses of these agents.[275] Evidence has also been presented that members of this class have more potent anti-proinflammatory cytokine properties than other PDEIs do,[276] but such did not prove to be the case when subjected to testing in a large multicenter trial.[277]

In the first phase III trial conducted in the United States, vesnarinone lowered the primary endpoint of mortality plus HF hospitalization requiring intravenous inotropic agents by 50 percent and also lowered mortality alone.[278] Unfortunately, this experience could not be repeated in a subsequent mortality trial (Vesnarinone Survival Trial [VEST]) that had longer follow-up.[247] VEST demonstrated that vesnarinone produced small, but dose-related increases in mortality at 30 mg (by 11 percent) and 60 mg (by 21 percent) orally daily.[247] After these results, vesnarinone's development in the United States was discontinued. The fact that two consecutive HF trials can result in diametrically opposite effects on mortality with the same drug dose (60 mg/d) highlights the vagaries of HF clinical trials, where patient selection, subtle details of ancillary treatment, length of follow-up, and other factors can greatly influence results.

PHOSPHODIESTERASE INHIBITORS WITH CALCIUM SENSITIZER ACTIVITY

These positive inotropic agents act in part by increasing the sensitivity of troponin C or some other part of the myofibrillar Ca^{2+} -binding apparatus to ionized calcium. This property alone would prolong contraction time and decrease diastolic function, which would not be desirable in an inotropic agent. However, all agents that have gone on to clinical development are also PDEIs, and this property will "cancel" the increased contraction time and provide favorable effects on diastolic function.[279] Under these circumstances, the advantage of calcium sensitization is that the pharmacological effect of the drug does not rely on increasing systolic calcium concentrations, although this action will occur if the compound also has PDEI activity. Another advantage would be in not increasing the heart rate, but again, PDEI activity would lead to a chronotropic effect at higher doses. The combination of not increasing intracellular Ca^{2+} or the heart rate would confer an energetic advantage to Ca^{2+} sensitizers.

The mixed-action Ca^{2+} sensitizers levosimendan and pimobendan have undergone the most clinical experience, and their hemodynamic profile,[280] [281] including increasing the heart rate at higher doses, does not differ from that of milrinone and enoximone. This similarity occurs because, as discussed below, the dominant pharmacological action of

both compounds is type III phosphodiesterase inhibition.

PIMOBENDAN.

Pimobendan is available in oral form for the treatment of HF only in Japan. Pimobendan has weak Ca^{2+} -sensitizing properties through facilitating the interaction of Ca^{2+} with troponin C,[282] but its major mechanism of action is phosphodiesterase inhibition.[283] In several medium-sized trials, pimobendan increased exercise performance and/or improved quality of life,[284] [285] [286] but its development in the Unites States and Europe was put on hold when a strong trend (relative risk 1.8, confidence interval 0.9 to 3.5) toward an increase in mortality was noted in the Pimobendan in Congestive Heart Failure (PICO) Trial, which was conducted in subjects with mild to moderate HF.[248]

LEVOSIMENDAN.

Levosimendan was discovered as part of a screening strategy for identifying compounds that bind to a troponin C affinity column,[287] and levosimendan does bind to free troponin C.[288] However, recent data indicate that levosimendan does not bind to the human troponin C-troponin I complex,[289] which is the natural state of the regulatory thin filament proteins.

Pharmacological studies clearly demonstrate that levosimendan is a potent (IC_{50} of 25 nM) and specific type III PDEI.[290] In model systems, the positive inotropic effects of levosimendan have been shown to be exclusively via phosphodiesterase inhibition[289] or through a combination of phosphodiesterase inhibition and calcium sensitization.[291] [292] In human ventricular myocardium, one study has found evidence of calcium sensitization at smaller inotropic effects of levosimendan, with evidence of positive inotropy via phosphodiesterase inhibition for larger increases in inotropic response.[293] However, another study in isolated human ventricular myocardium found no evidence of calcium sensitization for an inotropic effect that was associated with phosphodiesterase inhibition.[294] Finally, very recent work in isolated human heart preparations has demonstrated that levosimendan stimulates L-type Ca^{2+} current at low concentrations (10 nM), which indicates that it is acting as a type III PDEI at concentrations that produce positive inotropic effects.[295] Thus, without question, levosimendan is a potent and selective type III PDEI, but it is not clear whether calcium sensitization is contributing to its inotropic action in the human heart.

Levosimendan is a potent vasodilator that also increases heart rate at higher doses.[296] While these effects may well be due to phosphodiesterase inhibition, levosimendan has also recently been found at somewhat higher concentrations than those that produce phosphodiesterase inhibition to activate vascular smooth muscle ATP-sensitive K^+ channels [297] in a manner similar to cromakalim, nicorandil, or diazoxide. These effects also occur in the heart,[298] which appeared to explain why levosimendan reduced infarct size in a dog model.[299] However, other studies of levosimendan's vasodilator effects have not found evidence for ATP-sensitive K^+ channel activity while demonstrating phosphodiesterase inhibition, [300] and in human cardiac cells, activation of ATP-sensitive K^+ channels by levosimendan occurs at substantially higher concentrations (10 muM)

than therapeutic concentrations (
20 nM).[295] In addition, other PDEIs have reduced infarct size in model systems,[301] and a direct comparison of levosimendan to milrinone and amrinone in an infarct rabbit model found no difference in the antiischemic effects of the three agents.[302] Thus, ATP-sensitive K^+ channel activation, the newest addition to the pharmacological profile of levosimendan, is an unproved candidate for the mechanism of vasodilation and for protection against ischemic damage. Since it is not operative in the human heart at therapeutic concentrations, it is unlikely that this mechanism will provide cardioprotection from ischemic injury.

Levosimendan is in clinical development in both oral and intravenous forms. In intravenous form, levosimendan has been evaluated in two clinical trials that have been presented at national meetings but not yet published. In an acute myocardial infarction study conducted in Russia, levosimendan was randomized against placebo, and not surprisingly, the positive inotropic agent produced better circulatory support.[303] In another study where approximately 40 percent of the subjects were taking beta blockers, levosimendan performed better than dobutamine in hemodynamic response.[304] This result is also expected

*Not approved by the FDA.

since by virtue of their respective sites of action, beta blockade would inhibit the response to dobutamine but not to levosimendan. These studies do not provide evidence that levosimendan is superior to other PDEI-positive inotropic agents currently available in intravenous form.

CALCIUM SENSITIZERS

Some compounds are in development whose principal or dominant action is calcium sensitization, and they may have potential as positive inotropic agents, provided that diastolic function is not adversely affected and that vasoconstriction is not part of their pharmacological profile. One such compound is CGP 48506,[294] and another is EMD 57033.[305] EMD 57033 is the (+) enantiomer of EMD 53998, a racemic thiadiazinone compound whose other, (-) isomer (EMD 57439) is a pure type III PDEI.[305] In model systems, EMD 57033 increases systolic function without affecting blood pressure or the heart rate, which are respectively decreased and increased by EMD 57439.[305] Moreover, EMD 57033 binds to the human troponin I-troponin C complex.[289] The problem is that EMD 57033 causes diastolic dysfunction in human ventricular myocardium, with failing hearts much more adversely affected than nonfailing hearts.[306] Moreover, the racemic compound EMD 53998, even though it contains the phosphodiesterase III enantiomer, causes diastolic dysfunction that becomes more pronounced in ischemia.[307] However, some evidence indicates that the calcium sensitizer CGP 48506 does not inhibit relaxation.[308] Thus, it is unclear whether pure calcium sensitizers will have a therapeutic role as positive inotropic agents.

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Neurohormonal Cytokine Inhibitors

Without question, the greatest advance in the treatment of chronic HF has been the application of agents that inhibit harmful neurohormonal systems that are activated to support the failing heart (see Chaps. 16 and 21) . This generally useful paradigm had multiple origins, including work done by the Minnesota group in the late 1970s and early 1980s that documented the nature and extent of neurohormonal activation in chronic HF,[309] [310] the association of systemic neurohormonal activation with adverse outcomes,[311] [312] observations in the failing human heart that excessive adrenergic activation produces harmful biological effects,[164] [313] and astute clinical observations regarding the degree of improvement effected by inhibitors of the adrenergic[314] [315] [316] and renin-angiotensin[317] [318] [319] systems. By the mid to late 1980s, influential commentaries on the validity of the "neurohormonal hypothesis" were being articulated,[309] [320] [321] [322] and all these developments ultimately culminated in the performance of large-scale clinical trials that demonstrated that inhibition of the renin-angiotensin[323] [324] and adrenergic[325] [326] [327] [328] [329] systems improved the natural history of chronic HF caused by a dilated cardiomyopathy (primary or secondary) phenotype. The success with inhibition of the adrenergic and renin-angiotensin systems has led to extension of the general paradigm to other neurohormonal or cytokine systems that promote growth and remodeling in the failing heart, such as endothelin antagonists and inhibitors of tumor necrosis factor-alpha (TNF-alpha).

The general mechanisms by which neurohormonal activation worsens and neurohormonal inhibition improves the natural history of myocardial dysfunction and remodeling are discussed in Chapter 21 . In essence, multiple neurohormonal signaling pathways, such as $beta_1$ -, $beta_2$ -, and $alpha_1$ -adrenergic receptor,[177] angiotensin II AT_1 receptor,[330] endothelin-1 ET_A receptor,[331] and TNF-alpha receptor pathways,[332] are activated in the failing heart and promote maladaptive growth, remodeling, and

progressive myocardial dysfunction.[108] Inhibition of these systems prevents or reverses these adverse biological processes, thereby leading to improvement in the natural history of HF. Therapy targeting individual neurohormonal or cytokine systems will now be discussed.

INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (See also Chap. 29)

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors were the first consistent and substantial success story for medical therapy to improve the natural history of chronic HF, and this class of neurohormonal inhibitors remains a mainstay in HF treatment. ACE inhibitors were originally developed within the vasodilator paradigm,[317] but when their clinical results proved to be out of proportion to their relatively weak vasodilator effects (see Table 18-3) , it became apparent that another mechanism was operative. That mechanism, as elucidated by the Pfeffers' laboratory in elegant studies in myocardial infarction animal models[333] [334] and humans[318] [319] and then confirmed in chronic HF,[335] is the prevention of angiotensin II-mediated remodeling.[108]

MECHANISMS OF ACTION.

Figure 18-5 shows the pathways for angiotensin II formation, which occurs systemically as well as locally in cardiac and vascular tissue. Note that generation of angiotensin II is accomplished by two pathways, one that uses converting enzyme found in high abundance in endothelium and one that uses the protease chymase, which is found in interstitial cells. Transmyocardial studies in the intact human heart have indicated that greater than 80 percent of the generation of angiotensin II is via the ACE pathway,[336] but studies in isolated human heart preparations[337] and in model systems[338] have emphasized the contribution of the chymase pathway. If the chymase pathway is important in producing ventricular remodeling in the failing heart, angiotensin receptor-blocking agents (ARBs) would be more effective than ACE inhibitors in decreasing angiotensin II signaling. If, on the other hand, ACE inhibitors are just as effective clinically as ARBs, by inference, the ACE pathway is the dominant mechanism for generating angiotensin II in the failing heart. Finally, if ACE inhibitors are superior to ARBs, additional properties of

Figure 18-5 Pathways of angiotensin II formation. ACE=angiotensin-converting enzyme; Ang-1=angiotensin I; AT_1 R=angiotensin II type 1 receptor; NE=norepinephrine.

TABLE 18-7 -- BIOLOGICAL RESPONSES MEDIATED BY ANGIOTENSIN II RECEPTORS IN THE HUMAN CARDIOVASCULAR SYSTEM

BIOLOGICAL RESPONSE	RECEPTOR MEDIATION
Cardiac myocyte growth	AT_1
Positive inotropic response (minimal)	AT_1
Myocyte apoptosis	AT_1 , AT_2
Aldosterone release	AT_1
Norepinephrine release	AT_1
Cardiac myocyte toxicity	Beta-adrenergic via norepinephrine release
Fibroblast proliferation	AT_1
Smooth muscle proliferation	AT_1
Vasoconstriction	AT_1

ACE inhibitors, such as increasing bradykinin,[339] are presumably responsible. Based on the results of the Evaluation of Losartan in the Elderly Study II (ELITE-II, see below), at present it would seem that the ACE pathway is the predominant means of generating angiotensin II in the human heart and that enhancement of bradykinin levels may well be important.

Studies in the failing human heart indicate that ACE gene[340] [341] and protein[341] expression and enzyme activity [336] [341] are increased, but chymase gene expression is not.[340] Systemically increased renin is taken up by failing human ventricles in larger amounts than by nonfailing ventricles,[342] and failing human hearts also exhibit lower angiotensinogen protein levels compatible with substrate depletion.[342] Finally, angiotensin II type 1 (AT_1) receptors are selectively downregulated in the failing human heart at the protein[343] and mRNA[344] levels, probably as a result of increased exposure to angiotensin II. These data indicate that the local myocardial renin-augiotensin system (RAS) is induced in the failing human heart, which adds to the increased systemic activation. No such induction seems to occur with the chymase system.

As shown in Table 18-7 , increased levels of angiotensin II have several adverse effects on the cardiovascular system, including cardiac myocyte hypertrophy, myocyte apoptosis, presynaptic facilitation of norepinephrine release, and mitogenic effects on fibroblasts. Most, if not all of these effects are mediated via the AT_1 subtype. In addition, most of these biological effects of angiotensin II contribute to the development of hypertrophy and remodeling.

CLINICAL OBSERVATIONS.

Two types of studies demonstrate the consistent efficacy of ACE inhibitors in HF: post-myocardial infarction studies and clinical trials in chronic HF. As shown in Table

18-8 , more of the former studies than the latter have been conducted. All placebo-controlled chronic HF trials, with the exception of the "asymptomatic" Studies of Left Ventricular Dysfunction (SOLVD) Prevention Study,[345] demonstrated a reduction in mortality. As can be observed in Table 18-8 , the Class IV Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I) had a much larger effect size than did the SOLVD Treatment Trial (Fig. 18-6) , which in turn had a larger effect size than the SOLVD Prevention Trial did. Although only these three placebo-controlled mortality trials have been conducted in patients with chronic HF, it seems obvious that ACE inhibitors reduce mortality in direct relation to the degree of severity of chronic HF. Although not placebo controlled, the V-HeFT-II Trial provided evidence that ACE inhibitors improve the natural history of HF through mechanisms other than vasodilation, inasmuch as subjects treated with enalapril had significantly lower mortality than did subjects treated with the nonneurohormonal inhibitor-vasodilator combination of hydralazine plus isosorbide dinitrate.[103]

Although only one ACE inhibitor, enalapril, has been used in placebo-controlled mortality trials in chronic HF, as can be observed in Table 18-8 , multiple ACE inhibitors have proved to be more or less equally effective when administered in oral form within the first week of the ischemic event in post-myocardial infarction trials.[346] [347] [348] This observation leads to the conclusion that the effects of ACE inhibition on the natural history of chronic HF or post-myocardial infarction left ventricular dysfunction are class effects.

In summary, an ACE inhibitor is considered mandatory treatment in chronic HF or in asymptomatic left ventricular systolic dysfunction. The doses employed should be at least the average dose used to lower mortality in heart failure or post-myocardial infarction trials. The only consistent adverse effect noted with ACE inhibitors is a low-level (5 percent greater than placebo) increase in cough. In such patients, an angiotensin II AT_1 receptor-blocking agent can be substituted.

Aldosterone Antagonists

It has been shown in numerous studies that ACE inhibitors do not completely inhibit tissue-based RAS systems[349] [350] [350A] and that after several months of treatment, "escape" can

TABLE 18-8 -- COMPARISON OF CRUDE, ANNUALIZED MORTALITY RATES IN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR TRIALS*

TRIAL NAME	AGENT	NYHA CLASS	SUBJECTS ENROLLED (N)	12-MO PLACEBO MORTALITY (%)	12-MO EFFECT SIZE (%)	*P* VALUE AT 12 MO (FULL FOLLOW-UP)
Chronic Heart Failure						
CONSENSUS-I[323]	Enalapril	IV	253	52	31	0.01 (0.003)

SOLVD-Rx[324]	Enalapril	I-III	2569	15	21	0.02 (0.004)
SOLVD-Asx[345]	Enalapril	I, II	4228	5	0	0.82 (0.30)
Totals		I-IV	7050	11	16	0.02
Post-Myocardial Infarction						
SAVE[346]	Captopril	--	2231	12	18	0.11 (0.02)
AIRE[347]	Ramipril	--	1986	20	22	0.01 (0.002)
TRACE[348]	Trandolapril	--	1749	26	16	0.046 (0.001)
Totals			5966	19	18	0.001

AIRE=Acute Infarction Ramipril Efficacy; CONSENSUS=Cooperative North Scandinavian Enalapril Survival Study; SAVE=Survival and Ventricular Enlargement; SOLVD=Studies of Left Ventricular Dysfunction; SOLVD-Asx=SOLVD Asymptomatic LV Dysfunction Trial; SOLVD-Rx=SOLVD Treatment Trial; TRACE=Trandolapril Cardiac Evaluation.

*The trials were conducted in post-myocardial infarction or chronic heart failure subjects, with 12-month mortality rates taken from survival curves when data were not directly available in published material.

Figure 18-6 Cumulative probability of death in the placebo and enalapril groups in the CONSENSUS Trial *(A)* and in the SOLVD Trial *(B).* (From Smith TW, Kelly RA, Stevenson LW, Braunwald E: Management of heart failure. *In* Braunwald E (ed): Heart Disease, 5th ed. Philadelphia, WB Saunders, 1997, pp 492-514. *A,* Modified from CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure; results of the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS]. N Engl J Med 316:1429, 1987. *B,* Modified from SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293, 1991.)

occur with an increase in systemic angiotensin II[351] or aldosterone[352] levels. These observations set the stage for additional RAS inhibitor strategies, and one of them was addition of the competitive nanomolar-affinity aldosterone antagonist spironolactone[18] to ACE inhibitor therapy. This combination was used in the Randomized Aldactone Evaluation Study (RALES) Trial, which evaluated the addition of 25 mg of spironolactone vs. placebo to standard HF therapy

Figure 18-7 Results of the RALES Trial. (Reprinted, by permission, from Pitt B, Zannad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709-717, 1999.)

in stage C (New York Heart Association [NYHA] Class III or IV) patients, with a primary endpoint of all-cause mortality.[23] As can be observed in Figure 18-7 , in RALES, spironolactone produced a 31 percent reduction in total mortality when compared with placebo (p=0.001). The beneficial effect of spironolactone appeared to be on both sudden and pump failure deaths. Although the mechanism behind the benefit of spironolactone has not been elucidated, prevention of extracellular matrix remodeling[353] and/or prevention of increasing potassium levels are leading contenders. In RALES, serum potassium levels were 0.3 mEq/liter higher in the spironolactone group than in the placebo group (p=0.001), [23] which could have played a major role in reducing sudden or even pump failure deaths.

Although spironolactone was well tolerated in RALES, it is associated with a small incidence of gynecomastia, which may lead to discontinuation. Some newer-generation aldosterone antagonists have a much lower incidence of this adverse effect, and one of them, eplerenone, is currently being evaluated in a large-scale post-myocardial infarction clinical trial.

Angiotensin II AT_1 Receptor-Blocking Agents

Six angiotensin receptor blockers (ARBs) approved for the treatment of hypertension are now on the market in the United States. However, none of them has received approval for the treatment of HF. The rationale for the use of these agents is derived from information presented in Table 18-7 , which is that virtually all the adverse biological effects relevant to a failing, remodeled heart are mediated by the AT_1 receptor. Moreover, ARBs antagonize the effects of

angiotensin II regardless of its origin (via the ACE or chymase pathway). All these compounds are selective, high-affinity antagonists of AT_1 receptors.

Hemodynamic studies and studies with ARBs in HF have demonstrated effects that are similar to those of ACE inhibitors; that is, these agents reduce pulmonary wedge and pulmonary artery pressure moderately, are mild preload reducers, and increase cardiac output.[354] [355] [356] The heart rate is not affected unless baroreflexes are excessively activated by hypotension. Maximum exercise time is also improved to a similar degree with each type of RAS inhibitor.[356A] [357] [358]

Clinical trial data on ARBs are emerging, but the results thus far are limited and mixed. The initial comparison of an ARB (losartan) to an ACE inhibitor (captopril) was in ELITE (or ELITE-I); no difference in the primary endpoint of renal function was found in an elderly HF population, but unexpectedly, a 46 percent reduction in mortality (p=0.035) was noted in losartan-treated patients.[359] These results led to a mortality trial, ELITE-II, to test the hypothesis that losartan reduces mortality in comparison to captopril-treated patients. The results of ELITE-II are *not* consistent with ELITE-I in that losartan tended to *increase* mortality when compared with captopril.[359A] At this juncture, there is no reason to believe that ARBs will prove superior to ACE inhibitors in patients with HF, with the exception of the side effect of cough (4 percent with captopril, 0 percent with losartan in ELITE-I).[359] Moreover, based on bradykinin enhancement by ACE inhibitors, it is possible that ARBs will, in fact, be inferior to ACE inhibitors.

The future of ARB treatment in chronic HF would appear to be in combination with ACE inhibitors (and potentially spironolactone) to provide more complete inhibition of the RAAS. This view is supported by the observation that the combination of an ACE inhibitor and an ARB produces additive hemodynamic effects.[360] [361] Recently reported clinical trial data also support this concept. The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Trial[362] compared enalapril, the ARB candesartan, and a combination of the two for their effects on remodeling and clinical parameters. In this trial, the combination of an ACE inhibitor plus an ARB produced the greatest degree of inhibition of remodeling.[362] Other studies investigating the combination of an ACE inhibitor and an ARB that have clinical primary endpoints (such as the Valsartan in Heart Failure Trial[363] [Val-HeFT]) are under way, and they will yield a definitive answer regarding ARBs in combination with ACE inhibitors.

For the time being, recommendations for the use of ARBs in chronic HF are limited to patients who are ACE inhibitor intolerant, particularly those with an ACE inhibitor-induced cough.

ANTIADRENERGIC AGENTS

Beta-Adrenegic Receptor-Blocking Agents (See also Chap. 37)

The failing human heart is adrenergically activated[364] [365] to maintain cardiac performance over the short term by increasing contractility[366] and heart rate. In contrast, in the resting state, no adrenergic support occurs in normally functioning human left ventricles.[366] Multiple lines of evidence[367] [368] [369] indicate that it is increased cardiac adrenergic drive rather than an increase in circulating norepinephrine that is both initially supportive and then ultimately damaging to the failing human heart.

BETA-ADRENERGIC RECEPTORS.

As shown in Table 18-9 , human cardiac myocytes have three adrenergic receptors (beta$_1$, beta$_2$, and alpha$_1$) that are coupled to a positive

TABLE 18-9 -- BIOLOGICAL RESPONSES MEDIATED BY ADRENERGIC RECEPTORS IN THE HUMAN HEART

BIOLOGICAL RESPONSE	ADRENERGIC RECEPTOR MEDIATION
Cardiac myocyte growth	$beta_1$, $beta_2$, $alpha_1$
Positive inotropic response	$beta_1$, $beta_2$, $alpha_1$ (minimal)
Positive chronotropic response	$beta_1$, $beta_2$
Myocyte toxicity	$beta_1$, $beta_2$ (?<$beta_1$)
Myocyte apoptosis	$beta_1$

inotropic response and cell growth.[162] [163] [177] [370] [371] Beta-adrenergic receptors are coupled via the "stimulatory" G protein G_s to the effector enzyme adenylyl cyclase, which converts the substrate Mg-ATP to cAMP. cAMP is a positive inotropic and chronotropic second messenger and is also strongly growth promoting. In younger (<50 years) nonfailing human left or right ventricles, the $beta_1$ /$beta_2$ ratio is 70 to 80/30 to 20,[313] but in failing[162] [370] [371] or older[372] human ventricles, 35 to 40 percent of the total number of beta receptors are $beta_2$ as a result of selective downregulation in the $beta_1$ subtype. $Alpha_1$ receptors are coupled via a different G protein (G_q) to the effector enzyme phospholipase C, which through the second messenger diacylglycerol activates the growth-promoting protein kinase C family. Because $alpha_1$ receptors are upregulated in the failing heart, [373] [374] the cardiac myocyte adrenergic receptor profile changes from predominantly (>70 percent of the total adrenergic receptor population) $beta_1$ to more of a mixed, 2:1:1 ratio in end-stage HF.[162] [163] [177] $Beta_2$ receptors are also present on adrenergic nerve terminals in the heart, where they facilitate norepinephrine release.[375] The $beta_3$ receptor may also be present in the human heart as a counterregulatory receptor coupled to the "inhibitory" G protein G_i ,[376] and evidence also exists for a "$beta_4$ " receptor.[377]

CARDIAC DAMAGE INDUCED BY RECEPTOR ACTIVATION.

Norepinephrine is an exceptionally cardiotoxic substance that produces cardiac myocyte injury[378] in concentrations found in the failing human heart. Norepinephrine is mildly (10- to 30-fold when compared with the binding affinity to $beta_2$ receptors) $beta_1$ receptor selective, and its cytotoxicity appears to be mediated through beta- rather than alpha-adrenergic receptors.[378] In transgenic mice, cardiac overexpression of human $beta_1$ receptors,[379] [380] [381] $beta_2$ receptors,[382] G_{alpha} s, [383] or G_{alpha} q[384] produces an overtly cardiomyopathic phenotype and, ultimately, chamber dilatation and systolic dysfunction. Although direct comparisons have yet to be made, it appears that higher levels of expression of human $beta_2$ versus $beta_1$ receptors are required to produce histopathology.[379] [380] [381] [382] Overexpression of G_{alpha} s is also associated with increased markers of apoptosis,[385] which can be produced in cardiac myocytes by norepinephrine exposure.[386] [387] [388] Norepinephrine-mediated apoptosis is mediated

through $beta_1$ receptors,[388] and apoptosis is prominent in cardiac $beta_1$ receptor-overexpressing mice.[389] Finally, cardiac expression of a constitutively activated $alpha_1$ receptor produces concentric hypertrophy. [70] These data from model systems incontrovertibly indicate that chronic adrenergic signaling is a harmful compensatory mechanism in the failing human heart. The data are extremely convincing for chronic $beta_1$ receptor signaling and less convincing, but likely for chronic $beta_2$ and $alpha_1$ receptor pathway activation. The compensatory as well as adverse effects of adrenergic signaling pathways are summarized in Figure 18-1 and Table 18-9 .

Interestingly, when components of the beta-adrenergic-adenylyl cyclase-phospholamban phosphorylation pathway are transgenically manipulated beyond the level of G_{alpha} s, no overt pathology is apparent despite marked and sustained

increases in contractility.[207] [390] This finding may mean that G_{alpha} s-coupled cAMP-independent pathways mediate the majority of myocardial damage in beta-adrenergic receptor- and G_{alpha} s-overexpressing animals.

In the failing heart, beta-adrenergic signal transduction is reduced secondary to desensitization changes at the level of $beta_1$ and $beta_2$ receptors, the inhibitory G protein (G_i), and an enzyme responsible for modulating receptor activity by phosphorylation (beta-adrenergic receptor kinase), as well as by changes in expression of the adenylyl cyclase enzyme itself.[162] [177] [227] [228] [229] [370] [371] [391] [392] In an end-stage failing heart, 50 to 60 percent of the total signal transducing potential is lost, but substantial signaling capacity remains.[165] These and other data from model systems[378] [393] suggest that the beta-adrenergic receptor pathway desensitization changes present in the failing human heart are adaptive changes and that a potentially effective therapeutic strategy would be to add to this endogenous antiadrenergic strategy by inhibiting receptor signal transduction.[163] [177] [313] [394] [395] [396]

Thus, the chronically increased adrenergic drive present in the failing human heart delivers adverse biological signals to the cardiac myocyte via $beta_1$ -, $beta_2$ -, and possibly $alpha_1$ -adrenergic receptors. Elimination of these adverse signals is the fundamental reason for using antiadrenergic agents in the treatment of chronic HF.

TREATMENT OF HEART FAILURE.

Because of their availability, beta-adrenergic blocking agents were the first antiadrenergic agents used to treat chronic HF.[314] Although three classes of beta blockers are now available for clinical use, only the "second-generation," $beta_1$ receptor-selective antagonists or the "third-generation," beta blocker-vasodilators are tolerated to an acceptable degree by subjects with chronic HF.[397] Second-generation

compounds are tolerated because they do not block cardiac presynaptic or postsynaptic $beta_2$ receptors,[177] [375] [397] [398] while third-generation compounds are tolerated because their afterload-reducing properties mitigate the cardiac output-reducing effects of beta-adrenergic withdrawal.[177] [397] [399] The receptor-binding profiles of beta-blocking agents that have been used successfully to treat HF are given in Table 18-10 .

Regardless of the type of beta-blocking agent used, the treatment approach that must be taken in subjects with chronic HF is to start with extremely low (one-eighth to one-sixteenth of the target dose) doses and gradually increase the dose every 1 to 2 weeks to full beta-blocking doses.[397] [397A] When this approach is taken, over 90 percent of subjects with mild to moderate or stage B HF can tolerate beta blockade.[397]

The general mechanism of action of beta blockade in the failing, remodeled heart has been extensively reviewed.[108] [163] [177] [401] Both second- and third-generation beta-blocking agents improve intrinsic systolic function and reverse remodeling in primary or secondary cardiomyopathy in a time-dependent fashion that begins after an initial period of myocardial depression related to withdrawal of beta-adrenergic support.[108] [163] [177] However, these effects are not uniform across all treated subjects, and some subjects may deteriorate and have an adverse clinical response to beta blockade.[402]

The various beta blockers that have had substantial clinical trial experience in chronic HF or that are in development will now be reviewed.

Metoprolol

As can be observed in Table 18-10 , metoprolol is a second-generation, $beta_1$ receptor-selective blocking agent with an approximately 75-fold higher affinity for human $beta_1$ versus $beta_2$ receptors. Metoprolol is not yet approved for the treatment of HF in the United States but is approved for hypertension and ischemic heart disease indications. Metoprolol is approved in some European countries for an HF indication. The first placebo-controlled multicenter trial with a beta-blocking agent was the Metoprolol in Dilated Cardiomyopathy (MDC) Trial.[325] The MDC Trial compared metoprolol tartrate with placebo in subjects with symptomatic HF caused by idiopathic dilated cardiomyopathy. The sample size estimate was based on an expected 50 percent reduction by metoprolol in the combined endpoint of all-cause mortality and deterioration of the patient to the point of requiring listing for heart transplantation. The MDC Trial also had numerous prespecified secondary endpoints, including mortality alone, number of hospitalizations, left ventricular function, quality of life, and exercise tolerance.[325] In the MDC Trial, metoprolol at an average dose of 108 mg/d reduced the prevalence of the primary endpoint by 34 percent, which was not quite statistically significant (p=0.058). [325] The benefit was entirely due to a reduction by metoprolol in the morbidity endpoint (a reduction of 90 percent), inasmuch as a greater trend toward all-cause mortality was in fact seen in the metoprolol-treated group.[326] In addition, when compared with placebo, metoprolol improved left ventricular function, quality of life, number of hospitalizations, and exercise tolerance at 12 months.[325]

The encouraging results of the MDC Trial led to a more traditional placebo-controlled mortality

TABLE 18-10 -- ADRENERGIC RECEPTOR-BLOCKING AFFINITIES OF BETA-BLOCKING AGENTS IN HUMAN RECEPTORS

GENERATION/CLASS	COMPOUND	*K*(beta$_1$)(nM)	*K*(beta$_2$)(nM)	beta$_1$/beta$_2$ SELECTIVITY	*K*(alpha$_1$)(nM)	beta$_1$/alpha$_1$ SELECTIVITY
1st/Nonselective	* Propranolol	4.1	8.5	2.1	--	--
2nd/Selective beta$_1$	Metoprolol	45	3345	74	--	--
	Bisoprolol	121	14,390	119	--	--
3rd/Beta blocker-	* Carvedilol	4.0	29	7.3	--	--
	* Bucindolol	3.6	5.0	1.4	238	66 (19)
	Nebivolol	5.8	1700	293	--	--

K(alpha$_1$)=dissociation constant determined from ^{125}I-BE2254 competition curves in human ventricular myocardial membranes. *K*(beta$_1$)=average of the high-affinity dissociation constant determined from ^{125}I-CYP competition curves in human ventricular myocardial membranes, the dissociation constant determined from competition curves in transfected cells expressing recombinant human beta$_1$ receptors, and the dissociation constant determined from inhibition of isoproterenol-mediated stimulation of muscle contraction in preparations of nonfailing human heart. *K*(beta$_2$)=average of the low-affinity dissociation constant determined from ^{125}I-CYP competition curves, the dissociation constant determined from simple curve fitting in transfected cells expressing recombinant human beta$_2$ receptors, and the dissociation constant determined from inhibition of isoproterenol-mediated stimulation of adenylyl cyclase in membrane preparations of human heart.

*Beta receptors are the average of data from radiological binding data in myocardial membranes and recombinant receptors and inhibition in functional assays; alpha$_1$ receptors are from myocardial membranes. Metoprolol and bisoprolol data are from radiological binding data in myocardial membranes. Nebivolol data are from another laboratory in guinea pig receptor preparations.[400]

Based on an alpha$_1$ K_i of 69 nM in human saphenous vein ring segments (Tackett RL, personal communication, 1999).

trial, the Metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure

(MERIT-HF), which was stopped prematurely because of a 34 percent reduction in mortality in the metoprolol arm[329] (Fig. 18-8). The MERIT-HF Trial enrolled 3991 subjects with ischemic and nonischemic dilated cardiomyopathy who had Class II to IV HF, and the metoprolol preparation used was a continuous-release (CR), single-daily dose formulation of coated metoprolol succinate pellets.[329] Importantly, the average dose of metoprolol achieved in MERIT-HF was larger than in the MDC Trial, 159 versus 108 mg. The majority (97 percent) of patients enrolled in MERIT-HF were categorized as having Class II or III HF, and based on the annualized mortality of 11 percent in the placebo group and the baseline left ventricular ejection fraction of 28 percent, this landmark clinical trial enrolled subjects with mild to moderate HF and moderate to severe systolic dysfunction. Importantly, in the MERIT-HF, mortality from sudden death or progressive pump failure was reduced.[326] In addition, mortality was reduced across most demographic groups, including older versus younger subjects, nonischemic versus ischemic etiology, and lower versus higher ejection fractions.[329] However, almost no mortality reduction was noted in the relatively small number of female subjects enrolled (23 percent of the total),[329] which suggests that gender may influence the response to beta blockade in HF populations.

The CR preparation used in MERIT-HF produces a relatively constant blood level of metoprolol for 24 hours.[403] The bioavailability of the CR preparation is approximately 70 percent of the conventional formulation.[403] However, when compared with 50 mg twice daily of the conventional formulation, 100 mg/day of the CR preparation produces similar trough levels and degrees of reduction in the exercise heart rate, thus indicating bioequivalence of the two preparations.[403] The reduced fluctuation in blood levels for the CR versus the conventional formulation provides the potential for improved tolerability of the CR formulation in patients with HF, but no direct comparison studies have been performed. In addition, the much more shallow slope of the CR plasma concentration curve at the end of the dosing interval would theoretically reduce the potential of producing a beta blocker withdrawal effect[404] if doses are missed or dosing intervals are prolonged. Although these differences in pharmacokinetics could account for a greater efficacy of the CR preparation in reducing mortality, in the absence of direct comparison data demonstrating superiority of the CR formulation in HF populations, it is reasonable to assume that twice-daily dosing of the conventional tartrate metoprolol preparation is clinically equivalent to the same daily dose of the CR formulation. Indeed, recent data comparing metoprolol tartrate with the CR succinate preparation in subjects with chronic HF indicate no obvious difference in efficacy between the two preparations.[405] However, therapy can be initiated with 12.5 or 25 mg of metoprolol succinate

Figure 18-8 Kaplan-Meier curves of the cumulative percentage of total mortality *(A)*, sudden deaths *(B)*, and deaths from worsening heart failure *(C)* in the MERIT-HF Trial. (From MERIT-HF Study Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure [MERIT-HF]. Lancet 353:2001-2007, 1999. © by The Lancet Ltd., 1999.)6

CR by simply halving the scored 50-mg tablet,[405] which is an advantage when compared with specially preparing 6.25-mg capsules of the tartrate.

Bisoprolol

Bisoprolol is a second-generation, $beta_1$ receptor-selective blocking agent with an approximately 120-fold higher affinity for human $beta_1$ versus $beta_2$ receptors (Table 18-10) . Bisoprolol is approved for the treatment of hypertension but not HF in the United States; however, it was recently approved for HF treatment in Europe. The first trial performed with bisoprolol was the Cardiac Insufficiency Bisoprolol Study I (CIBIS-I) Trial, which was a placebo-controlled trial of the effects of bisoprolol on mortality in symptomatic ischemic or nonischemic cardiomyopathy subjects treated for an average follow-up of 22.8 months[406] (Fig. 18-9) . This trial, sample-sized on an unrealistically high expected event rate in the control group, ended up with a statistically insignificant, 20 percent mortality reduction.[406] In addition, the benefit in this trial was confined to subjects with nonischemic cardiomyopathy, who had a 47 percent reduction (p=0.01) in mortality in comparison to placebo.[406] Despite the lack of overall statistical significance in CIBIS-I, the reduction in mortality was similar to what has been accomplished with ACE inhibitors and was viewed as encouraging. The results prompted a follow-up trial, CIBIS-II,[328] with more conservative effect size estimates and sample size calculations.

The CIBIS-II Trial was stopped by the Data and Safety Monitoring Committee 18 months early because of a 32 percent reduction ($p < 0.001$) in all-cause mortality (see

Figure 18-9 *A,* Survival curves in the CIBIS-II Trial. *B,* Relative risk of treatment effect on mortality by etiology and functional class at baseline in the CIBIS-II Trial. Horizontal bars represent 95% confidence intervals. (From CIBIS-II Investigators and Committees: The Cardiac Insufficiency Bisoprolol Study II [CIBIS II]: A randomized trial. Lancet 353:9-13, 1999. © by The Lancet Ltd., 1999.)

Table 18-4) in the bisoprolol-treated group.[328] CIBIS-II enrolled 2647 patients with Class III or IV HF caused by ischemic and nonischemic cardiomyopathy; the median follow-up was 1.3 years. In addition to the reduction in mortality, bisoprolol also reduced the number of hospitalizations (by 20 percent) and cardiovascular deaths (by 29 percent).[328] In CIBIS-II,[328] deaths classified as sudden were statistically reduced (by 44 percent) in the bisoprolol group, whereas pump failure deaths were nonsignificantly reduced by 26 percent.

This trend toward a greater reduction in sudden versus pump failure deaths was opposite that obtained in CIBIS-I.[406] Another difference between CIBIS-I and CIBIS-II was the effect on ischemic versus nonischemic cardiomyopathy, which also demonstrated opposite trends. In CIBIS-I,[406] the reduction in mortality in the nonischemic group was 47 percent (p=0.01), whereas in patients with a history of

myocardial infarction, a trend toward an increase in mortality (by 11 percent) was noted in the bisoprolol group. One possible explanation for the differences between the CIBIS-I and CIBIS-II trials is the average dose of bisoprolol used; in CIBIS-II the target dose was 10 mg/day,[328] whereas in CIBIS-I it was 5 mg/day.[406]

Although CIBIS-II enrolled patients with Class III (>90 percent of the total) or Class IV symptoms, the annualized placebo mortality was only 13.2 percent[328] (Table 18-11) . This mortality rate is similar to that found in the enalapril arm of the SOLVD Treatment Trial,[324] which was composed of 68 percent Class I and II patients. In addition, the average blood pressure of patients enrolled in CIBIS-II was 130/80, which is higher than the blood pressures of the SOLVD patients[324] or the patients enrolled in the U.S. Carvedilol Trials, who were approximately 50/50 Class II/III.[326] A relatively large proportion of CIBIS-II patients were enrolled in Eastern Europe and Russia, where practice patterns, HF etiology, or symptom interpretation may not be comparable to that in Western Europe and the United States. Nevertheless, the results of CIBIS-II were internally consistent through all major demographic groups,[328] and the impressive results constitute a landmark clinical trial in the development of beta blockade as therapy for chronic HF.

Carvedilol

As may be noted in Table 18-10 , carvedilol is a minimally $beta_1$ receptor-selective beta-blocking agent that also has high affinity for $alpha_1$ receptors and antioxidant action.[406A] Because carvedilol is a potent vasodilator, its side effect profile on initiation of therapy and during uptitration is different from that of highly $beta_1$ -selective second-generation agents, with orthostatic symptoms being more prominent.[397] At low doses (
6.25 mg twice daily) carvedilol may exhibit some $beta_1$ selectivity in humans with HF. [407] At higher target doses, carvedilol blocks all three adrenergic receptors coupled to hypertrophy and other adverse biological effects (see Table 18-9) that contribute to remodeling and myocardial dysfunction in the failing human heart. The idea that a comprehensive antiadrenergic profile is desirable is supported by the results of the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) Trial, which demonstrated left ventricular functional and clinical superiority of 25 mg carvedilol twice daily over 6.25 mg twice daily.[327] In addition, because it blocks presynaptic $beta_2$ receptors, carvedilol mildly reduces cardiac adrenergic drive.[408] Because of its potent, comprehensive antiadrenergic action, the beneficial effects of carvedilol on myocardial function and reversal of remodeling tend to be greater than for $beta_1$ -selective compounds.[408] [409] [410] [411] [412] [412A] [412B] However, it is not yet clear whether this superiority translates into better clinical results in view of the excellent results of $beta_1$ -selective compounds in the MERIT-HF[329] and CIBIS-II[328] trials. The answer to this question will be given by the outcome of the Carvedilol and Metroprolol European Trial (COMET) which is comparing the effects of metoprolol and carvedilol on all-cause mortality.

Carvedilol is currently the only beta blocker approved for the treatment of chronic HF in the United States, and it is also approved in most other countries. The controlled clinical

trial data base for carvedilol is extensive. To date, 1748 patients have been enrolled in eight randomized, placebo-controlled phase II and III clinical trials with carvedilol. [326] [327] [413] [414] [415] [416] [417] [418] [419] [420] Although data on carvedilol are not yet

TABLE 18-11 -- COMPARISON OF CRUDE, ANNUALIZED MORTALITY RATES IN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR AND BETA BLOCKER TRIALS CONDUCTED IN CHRONIC HEART FAILURE*

TRIAL NAME	AGENT	NYHA CLASS	HEART FAILURE STAGE,A-D	SUBJECTS ENROLLED (N)	12-MO PLACEBO MORTALITY (%)	12-MO EFFECT SIZE(%)
Angiotensin-Converting Enzyme Inhibitors						
CONSENSUS-I[323]	Enalapril	IV	D	253	52	31
SOLVD-Rx[324]	Enalapril	I-III	B	2569	15	21
SOLVD-Asx[325]	Enalapril	I, II	A	4228	5	0
Totals		I-IV		7050	11	16
Beta Blockers						
Stage B patient populations						
CIBIS-I[406]	Bisoprolol	III, IV	B	641	11	20
Carvedilol U.S.[326]	Carvedilol	II, III	B	1094	10	66
CIBIS-II[328]	Bisoprolol	III, IV	B	2647	13	33
MERIT-HF[329]	Metoprolol CR	II-IV	B	3991	11	35
Stage C patient population						
BEST[424]	Bucindolol	III, IV	C	2708	17	10
Totals		II-IV		11,081	13	30
Combined mortality reduction				18,131	12	41

BEST=beta-Blocker Evaluation Survival Trial; CIBIS=Cardiac Insufficiency Bisoprolol Study; CONSENSUS=Cooperative North Scandinavian Enalapril Survival Study; CR=continuous release; MERIT-HF=Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; SOLVD=Studies of Left Ventricular Function; SOLVD-Asx=SOLVD Asymptomatic LV Dysfunction Trial; SOLVD-Rx=SOLVD Treatment Trial.

*Twelve-month mortality rates were taken from survival curves when data were not directly available in published material.

See Chapter 21 .

Effect size at 2 years.

available from prospectively designed placebo-controlled mortality trials (one such trial, the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS), is in progress), the phase III U.S. Carvedilol Trials Program was stopped prematurely by the Data and Safety Committee monitoring all four trials because of a highly significant ($p < 0.0001$) 65 percent reduction in mortality by carvedilol versus placebo.[326] In addition, one individual trial (MOCHA) demonstrated a highly statistically significant 73 percent reduction in mortality.[327] However, because these trials were relatively short-term and the number of events was small, the data from MOCHA or the rest of the U.S. Carvedilol Trials Program were not considered by the FDA to be conclusive for an indication of mortality reduction. Carvedilol has been approved by the FDA for delaying progression of the myocardial disease process and lowering the combined risk of morbidity plus mortality.[421] Approval was based on (1) results from the "Mild" HF trial,[417] which demonstrated that carvedilol reduced the probability of development of the combined endpoint of mortality, cardiovascular hospitalization, or an increase in associated HF medical treatment when compared with placebo, and (2) grouped analysis of all four U.S. trials[327] [416] [417] [418] and one conducted in Australia-New Zealand[420] in which carvedilol reduced the combined endpoint of mortality or cardiovascular hospitalization.

To date, all the reported trials demonstrating unequivocal efficacy with carvedilol have been in stage A (asymptomatic to mild symptoms) or B (mild to moderate symptoms) HF. The two trials conducted in more advanced HF either had too many subjects eliminated up-front by carvedilol challenge[415] or were too small to reach conclusions.[418] The COPERNICUS mortality trial is investigating Class III to IV (stage C) HF, and this trial plus the Beta-Blocker Evaluation Survival Trial (BEST, see below) will provide the answer to whether beta blockers are indicated in patients with more advanced HF.

BUCINDOLOL

Bucindolol is a completely nonselective third-generation beta-blocking agent with mild vasodilator activity that is probably due to weak alpha$_1$ receptor-blocking properties.[177] The mild vasodilator properties of bucindolol coupled with its low "inverse-agonist" profile[177] [422] [423] make this beta blocker extremely well tolerated in HF subjects,[397] including those with advanced HF.[424] Inverse agonism is the ability of a receptor antagonist to inactivate "active-state" receptors that are precoupled to G proteins and

capable of transducing signals without agonist occupancy.[163] In the human heart, the percentage of such precoupled beta-adrenergic receptors identified by high-affinity agonist binding is on the order of 10 to 30 percent of the total. Antagonists such as metoprolol and to a lesser extent carvedilol have a greater ability than bucindolol to inactivate these active-state receptors, which is probably why bucindolol is associated with less intrinsic myocardial depression and lowers 24-hour Holter-monitored heart rates less than metoprolol or carvedilol does.[399] The latter property translates into less symptomatic bradycardia with bucindolol, which is why the BEST Trial had a much lower heart rate exclusion criterion (50 beats/min)[425] than other beta blocker HF trials did (typically 68 beats/min). Thus, a low inverse-agonist profile is a property that increases the tolerability of a beta blocker in subjects with HF.

Although bucindolol has intrinsic sympathomimetic activity in some smaller animal species,[426] [427] because of differences in the stoichiometry of receptor-G protein coupling between animal models and humans, bucindolol has no intrinsic sympathomimetic activity in failing[315] [399] [428] [429] or nonfailing[430] human hearts. Finally, because of its potent beta$_2$ receptor-blocking properties coupled with only mild vasodilation, bucindolol is the only beta-blocking agent that has been shown to lower systemic adrenergic activity in subjects with HF.[315] [424] Thus, the unique pharmacological profile of bucindolol allows an agent with comprehensive antiadrenergic activity to be given to patients with advanced, stage C HF.[424] [425]

CLINICAL OBSERVATIONS.

The third-generation nonselective compound bucindolol was the first beta-blocking agent shown to improve left ventricular function in a placebo-controlled trial,[315] and it was the first beta-blocking agent shown to improve load-independent, intrinsic systolic function.[316] In those[315] and subsequent phase II trials, [431] [432] bucindolol was well tolerated, in marked contrast to previous[433] [434] and subsequent[435] experience with the nonselective first-generation agent propranolol. Bucindolol was the second beta-blocking agent to be evaluated in a multicenter trial in which bucindolol produced a dose-related improvement in left ventricular function and a dose-unrelated prevention of deterioration in left ventricular function in subjects with symptomatic ischemic and nonischemic cardiomyopathy treated for a 12-week period.[432] Based on these data, doses of bucindolol with very high degrees of beta blockade[432] (100 mg twice daily for subjects heavier than 75 kg, 50 mg twice daily for subjects less than 75 kg) were chosen for use in phase III trials.

THE BEST TRIAL.

The largest of these phase III trials, the recently completed BEST Trial[419] randomized 2708 subjects with advanced (Class III and IV) HF to placebo or bucindolol. As can be observed by the 12-month placebo mortality rates in Table 18-11 , the BEST Trial was conducted in subjects with much more advanced HF than the subjects enrolled in other beta blocker trials where mortality was reported. A 12-month mortality of 17 percent was observed in comparison

to 10 percent for the U.S. Carvedilol Trials, for example. Note in Table 18-11 that the CIBIS-II Trial, which purported to enroll subjects with NYHA Class III or IV symptoms, had a 12-month placebo mortality that is substantially less than that in BEST, which had internal controls to ensure that subjects with advanced HF were being enrolled.

In the BEST subject population as a whole, bucindolol produced a statistically nonsignificant (p=0.10), 10 percent reduction in total mortality that was heterogeneous with respect to race.[424] That is, the 76 percent of subjects in BEST who were not black had a statistically significant (p=0.01), 19 percent reduction in mortality, whereas the 24 percent who were black had a nonsignificant trend for an increase (by 17 percent) in mortality (interaction p value <0.05). Since BEST was the first beta blocker mortality trial to enroll a substantial percentage of black patients and it is the first reported beta blocker study in advanced HF, it is uncertain whether the demographically heterogeneous findings can be extrapolated to other beta-blocking agents or to less advanced HF. Of note is that in the U.S. Carvedilol Trials conducted in mild to moderate HF, an agent with a similar pharmacological profile produced a similar degree of improvement in left ventricular function and clinical parameters in blacks and nonblacks.[436] In addition, in a small single-center experience, metoprolol appeared to improve left ventricular function in blacks with HF similar to that produced in whites.[437] Therefore, the apparent lack of favorable effect of bucindolol in blacks in BEST may be due to the more advanced nature of HF investigated in BEST or the unique characteristics of the black patient population in this trial. However, there are also potential drug-specific explanations for the bucindolol versus carvedilol or metoprolol data in blacks, including the greater degree of vasodilation in carvedilol being beneficial in an HF population with a high incidence of a history of hypertension, the $beta_1$ selectivity of metoprolol, or the norepinephrine-lowering property of bucindolol producing too much withdrawal of adrenergic support (see below for moxonidine) in the black population of BEST. Norepinephrine lowering is a $beta_2$ receptor blockade-mediated response, and the black population of BEST had higher baseline systemic norepinephrine levels than the other subjects did.[424]

From previous trials it is known that black hypertensives respond less well to beta-blocking agents or ACE inhibitors[438] than do nonblacks and that blacks with HF also do not respond well to ACE inhibitors.[439] Thus, the most beneficial therapy for favorably affecting the natural history of HF, ACE inhibitors and beta-blocking agents, may be less effective or even ineffective in a population group that represents 12 percent of the U.S. population. This obviously major problem will be commented on further below.

In the BEST population as a whole, bucindolol produced statistically favorable effects on multiple secondary endpoints, including cardiovascular deaths, heart failure hospitalizations, the combined endpoint of mortality plus hospitalization, the need for cardiac transplantation, left and right ventricular function, and the incidence of myocardial infarction.[424] Despite the advanced nature of the HF patients enrolled in BEST, bucindolol was well tolerated and slightly more subjects were receiving active

drug than placebo when the trial was concluded.[424] The BEST Trial therefore demonstrates that a comprehensive antiadrenergic beta-blocking agent can be used in patients with advanced HF to lower morbidity but that beta-blocking agents should be used with caution or not at all in black patients who have advanced HF with the demographic characteristics of those enrolled in BEST. When the COPERNICUS Trial is completed, drug-specific versus degree-of-HF issues can, it is hoped, be determined.

NEBIVOLOL

Nebivolol is another third-generation beta-blocker-vasodilator with limited but favorable experience[440] [441] in HF trials. As can be observed in Table 18-10 , nebivolol is markedly $beta_1$ -selective,[442] and as such it is unique among third-generation compounds available or in development for HF. Another unique feature of nebivolol is its vasodilatory action appears to be due to the generation of nitric oxide.[443] Interestingly, in a small study comparing nebivolol and placebo, nebivolol improved intrinsic systolic function and resulted in regression of hypertrophy in South African blacks with mild to moderate HF.[440] Although it is likely that the patient populations differ substantially (such as more subjects with a history of hypertension in the carvedilol/U.S. data), it is worth noting that carvedilol and nebivolol, both of which have substantial vasodilator properties, have shown some success in black populations with mild to moderate HF. Nebivolol will be starting one phase II and then two phase III trials in 2000-2001.

Conclusions Regarding Beta Blockers as a Class

As can be observed in Table 18-11 , based on comparison of clinical trial data between ACE inhibitors and beta blockers, it appears that in mild to moderate HF (stage B; see p. 562) placebo annual mortality of 5 to 15 percent), beta blockers produce a much larger effect size than ACE inhibitors do (respective average mortality reduction of 36 vs. 21 percent). On the other hand, in stage C or D HF, ACE inhibitors[323] or aldosterone inhibition plus ACE inhibition[23] may produce a greater reduction in mortality than achieved with beta blockade[424] (respective mortality reduction of 31 vs. 10 percent). In other words, the effect size (degree of mortality reduction) increases with increasing severity of HF for agents acting by inhibiting the renin-angiotensin-aldosterone system (RAAS), and it decreases with increasing degree of HF for beta-blocking agents. The likely explanation for this difference is that patients with more advanced HF have a greater dependency on beta-adrenergic support of myocardial function; it becomes increasingly difficult to withdraw them from it, or withdrawal of adrenergic support may even be undesirable in many stage C patients. ACE inhibitors, on the other hand, have overall favorable effects on hemodynamics when administered to patients with advanced HF, which allows this type of treatment to take therapeutic advantage of inhibition of the high degree of activation of the RAAS in advanced HF.

Summary Recommendations for the Use of Beta-Blocking Agents

Patients with mild to moderate compensated HF from nonischemic or ischemic dilated cardiomyopathy and NYHA Class II to III symptoms (stage B subjects) who are receiving standard treatment, including diuretics and ACE inhibitors, and who do not

have a contraindication to beta blockade are candidates for treatment with a beta-blocking agent.[397A] [424A] For the present, this group would include black patients, although the data supporting use in such patients are confined to carvedilol. Patients who are treated with beta-blocking agents should not have decompensated HF because the myocardial depression that accompanies initiation of therapy can be life threatening in such individuals. At present, the only FDA-approved agent is carvedilol, but metoprolol and bisoprolol are approved for other cardiovascular indications. For now, patients with advanced, Class III or IV (stage C) HF should not be routinely treated with beta-blocking agents pending the availability of bucindolol (in nonblack populations), demonstration of a favorable effect of carvedilol in the COPERNICUS Trial, or demonstration of benefit by metoprolol, bisoprolol, or nebivolol in such patients. Until a trial has demonstrated efficacy and safety, blacks with Class III or IV HF fitting the demographic characteristics of the BEST Trial population should not be treated with a beta-blocking agent. For patients in Class IV, beta blockers remain contraindicated, but this position could change pending the outcome of current trials such as Enoximone Plus Metoprolol in Subjects With Advanced Chronic Heart Failure (EMPOWER), which are combining PDEIs with beta blockers on the basis of encouraging phase II data.[253]

Once patients with HF reach a maintenance dose of a beta blocker, treatment should be maintained indefinitely because of the risk of deterioration after drug withdrawal.[444] As discussed in the section Positive Inotropic Agents, if it is necessary to treat a decompensated patient receiving maintenance beta blockade with a positive inotropic agent, a PDEI rather than a beta-agonist should be used because the hemodynamic effects of PDEIs are not antagonized by beta blockade.[231] [252] [254]

Limitations of Beta Blocker Therapy in Chronic Heart Failure

Despite their proven efficacy in mild to moderate HF in patients with primary or secondary dilated cardiomyopathy, it is important to emphasize that beta blockers have limitations to general application in HF populations. First and foremost is that many HF patients have contraindications to beta blockade, such as reactive airway disease, sinus node or conduction system disease with bradycardia,

and advanced HF with hemodynamic decompensation. Another problem is that even in mild to moderate HF, initiation of therapy and uptitration of beta-blocking agents can be difficult and require both persistence and a knowledge of management maneuvers[397] that allow target doses to be achieved. A third problem is that for reasons that are not yet clear, some patients do not respond to beta blockade in terms of favorable effects on myocardial function, and these individuals may have a worse outcome than patients treated with placebo.[402] Some, but not all of these problems might be overcome by the development of more efficacious or better-tolerated compounds, the use of other, more effective types of antiadrenergic therapy, or the use of a combination of beta blockers with positive inotropic agents.[252] [253] The importance of the beta blocker data set is not that it demonstrates a "cure" for chronic HF, but rather that it has now been shown that in some patients, the prognosis can be substantially improved by medical therapy. This

observation should provide an impetus to develop further types of treatment that improve the biological properties of the failing heart.

Other Antiadrenergic Agents

The success of beta-blocking agents and the realization that many subjects have contraindications to them has prompted attempts to develop other antiadrenergic agents. Two of them, the dopamine beta-hydroxylase inhibitor nepicastat[445] and the imidazoline receptor agonist moxonidine,[446] * have had clinical trials conducted in chronic HF patients. A phase III trial of moxonidine (MOXCON) was recently stopped because of an increase in mortality, indicating that a drug that powerfully lowers adrenergic activity in a potentially irreversible manner is not a good strategy in the treatment of chronic stable heart failure.

Endothelin Antagonists

Endothelin-1, a peptide synthesized in endothelium and secreted on the abluminal side of the vascular wall, acts as an autocrine or paracrine substance[447] [448] (see also Chap. 21) . Although circulating endothelin levels are increased in patients with HF,[449] the half-life of endothelin is only a few minutes because of its rapid clearance by the lung.[450] Therefore, endothelin is an autocrine or paracrine cytokine, not a hormone.

Endothelin has powerful biological effects that are mediated through two receptors, ET_A and ET_B .[451] In human ventricular myocardium, the ET_A receptor gene is expressed in vascular endothelial and smooth muscle media and in cardiac myocytes, where expression is increased in myocardial failure.[452] The ET_A receptor is G_q and protein kinase C-coupled to vasoconstriction, a weak positive inotropic effect, as well as coupled to the indication of cardiac myocyte hypertrophy and fibroblast or smooth muscle cell hyperplasia.[447] [448] These biological/physiological effects are similar to those of the angiotensin II AT_1 receptor. The ET_B receptor is expressed in human ventricular myocardium in endothelium, cardiac myocytes, and fibroblasts, but not in vascular smooth muscle.[452] The ET_B receptor is coupled to nitric oxide generation and vasodilation and possibly to antiproliferative responses in cardiac myocytes and fibroblasts.[447] [448] The ET_B receptor is also a clearance receptor in the lung[453] and probably in myocardium. [454] In human myocardial failure, tissue concentrations of endothelin are increased,[452] [455] the ET_A receptor population is upregulated from 60 to 80 percent of the total,[452] and the ET_B population is downregulated from 40 to 20 percent of the total. [452] These data suggest that the endothelin-1 system is quite activated in the failing human heart and that it contributes to the progression of remodeling. This hypothesis is strongly supported by data from HF animal models, where nonselective ET_A /ET_B [442] or selective ET_A [456] [458] antagonists prevent remodeling.

CLINICAL OBSERVATIONS.

Clinical experience with ET receptor antagonists in HF is limited to acute hemodynamic studies, where both nonselective[459] and ET_A -selective[460] [461] compounds produce the expected vasodilator effects with an increase in cardiac output and little or no increase in heart rate, as well as one clinical trial with clinical endpoints.[461] The one reported phase II trial[462] was stopped early for hepatotoxicity, but in the evaluable patients, clinical improvement was observed more frequently with the nonselective antagonist bosentan than with placebo. Bosentan continues in development at a lower dose in an attempt to mitigate its adverse effects on liver function. Hepatotoxicity has also been observed for some other members of this class, and teratogenicity is a general problem with all ET antagonists. Another potential issue with this class of compounds is that endothelin gene expression is stimulated by both angiotensin II[463] and norepinephrine,[464] and in the presence of full inhibition of the RAS and adrenergic systems, it is not clear how much additional benefit will be conferred by endothelin antagonists. Nevertheless, endothelin receptor antagonists remain a very promising potential treatment of HF.

Tumor Necrosis Factor-Alpha Inhibitors

Another promising treatment of HF that is entering phase III trials is TNF-alpha inhibition.[465] [466] The hypertrophic/remodeling response of failing myocardium incorporates features of a generalized inflammatory response, with increased systemic[467] and/or myocardial levels[468] [469] of the proinflammatory cytokines TNF-alpha and interleukin-1 (IL-1) contributing to growth signaling. TNF-alpha is a 17-kDa protein that acts through two distinct receptors, TNFR1 and TNFR2. TNF-alpha produces a series of powerful biological effects, including immunostimulation, mediation of host resistance to bacteria, activation of protein kinase C, and activation of expression of a wide variety of genes generally involved in inflammation or cell growth.[470] In an acute or subacute setting, most of these biological effects of TNF-alpha are helpful in combating infection or responding to injury.

TNF-alpha[471] as well as IL-1beta[472] can produce an increase in cardiac protein synthesis and cardiac myocyte hypertrophy. Moreover, Mann's laboratory has shown that in the failing human heart, TNF-alpha production is induced in cardiac myocytes[473] and that chronic infusion of TNF-alpha in rats produces left ventricular contractile dysfunction and dilatation.[474] Therefore, local myocardial production of TNF-alpha becomes, along with neurotransmitter-derived norepinephrine, autocrine- or paracrine-produced endothelin and hormonally or cytokine-derived angiotensin II, a serious candidate for mediation of the progression in myocardial dysfunction and remodeling that is part of the natural history of chronic HF. As is the case for angiotensin II, endothelin-1, and norepinephrine, the maladaptive aspect of TNF-alpha in the failing heart is the sustained production and chronic cell signaling. Finally, transgenic models of cardiac overexpression of TNF-alpha have unequivocally demonstrated that this cytokine can produce a dilated cardiomyopathy phenotype.[475] [476] Therefore, TNF-alpha appears to be involved in the progression of remodeling and myocardial dysfunction that characterizes the natural history of HF.

CLINICAL OBSERVATIONS.

On this impressive pathobiological background, inhibitors of TNF-alpha are just beginning to be evaluated in chronic HF. The first compound to enter phase III trials is etanercept, a soluble TNF-alpha receptor fusion protein that binds to and inactivates TNF-alpha. This compound was recently reported to improve left ventricular function and ameliorate symptoms and exercise intolerance in subjects with chronic HF.[477] In addition, a small-molecule TNF-alpha inhibitor[478] that is used to treat other disorders, pentoxifylline, was recently shown to increase left ventricular function in a controlled clinical trial.[479] Etanercept has recently entered phase III testing in a subcutaneous, twice-per-week dosing regimen that has been shown to be effective in rheumatoid arthritis.[480] This approach to the treatment of chronic HF is obviously quite rational and promising.

THE NEXT GENERATION OF HEART FAILURE TREATMENT

As can be observed by the effects of ACE inhibitor and beta blocker therapy (see Table 18-11) , medical therapy of HF has improved substantially since 1990. Moreover, as discussed above, in the near future there will likely be additional neurohormonal/cytokine inhibitors that will further improve the natural history of chronic HF. New drug classes, such as compounds that improve myocardial metabolism, may be added to the HF armamentarium in the next several years. In addition, because of the potential market size, the full force of the "high-technology revolution" of drug development is being applied to HF. Gene therapy, drugs designed to specifically reverse abnormalities in gene expression, and novel targets identified by transcriptomics and proteomics will probably emerge as effective HF therapies. Accordingly, we look forward to substantial expansion of Table 18-1 in the next edition of this textbook.

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Chapter 19 - Treatment of Heart Failure: Assisted Circulation

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Up to 4.9 million Americans suffer from congestive heart failure, with over 400,000 new cases diagnosed each year.[1] [2] The incidence of advanced heart failure rises dramatically with increasing age, accounting for approximately 80 percent of hospital discharges in patients older than 60 years of age.[2] Patients with New York Heart Association (NYHA) functional Class IV heart failure have a reported 1-year mortality of 33 to 37 percent.[3] According to the Framingham Heart Study, the 5-year mortality rate for patients with congestive heart failure is 75 percent in men and 62 percent in women.[4] Two hundred thousand patients with heart failure die annually at a cost estimated at $8 to $20 billion per year.[1] [2] Standard medical and surgical therapies benefit only a small percentage of patients with ventricular dysfunction. Cardiac transplantation (see Chap. 20) , the therapeutic mainstay for end-stage cardiomyopathic patients, has been performed with decreasing frequency worldwide for each of the past 4 years.[5] The decline in heart transplant volume is attributed to limited donor heart availability.

Two distinct patient populations benefit from mechanical circulatory support. Potential

cardiac transplant recipients with hemodynamic instability may receive temporary mechanical circulatory support as a bridge to transplantation. The second patient group includes patients with reversible ventricular dysfunction. Two to 6 percent of patients who undergo an open-heart operation develop postcardiotomy cardiogenic shock.[6] Aggressive medical management, including intraaortic balloon (IAB) counterpulsation, allows 75 to 85 percent of these patients to be weaned from cardiopulmonary bypass. Thus, approximately 1 percent of patients who undergo an open-heart procedure would benefit from interval support with a mechanical blood pump.[7]

An evolving, third indication for blood pump insertion is as a permanent form of mechanical circulatory support. Best estimates suggest that 17,000 to 66,000 patients in the United States each year may benefit from a permanent implantable blood pump.[8] Not only will mechanical blood pumps be immediately accessible, but they will ultimately provide a cost-effective alternative to cardiac transplantation or long-term medical treatment of patients in NYHA functional Class III or IV.[9]

Patients with cardiovascular disease whose condition deteriorates hemodynamically first receive conventional medical therapy. Conventional management is directed toward correction of any electrolyte or acid-base imbalance, hypoxemia, rhythm disturbance, or hypovolemic state. Cardiogenic shock, as defined in Table 19-1 , is next treated with inotropes and, if systemic blood pressure permits, afterload reducing agents (see also Chap. 35) . Patients who manifest ongoing hemodynamic instability, and who fulfill the selection criteria outlined in Table 19-2 , may qualify for an advanced form of mechanical circulatory support.

Mechanical circulatory support devices can be divided into three major groups. The IAB is a readily available, catheter-mounted intravascular device designed to improve the balance between myocardial oxygen supply and demand while increasing systemic perfusion to a modest degree. The ventricular assist device (VAD) is a blood pump that is designed to assist or replace the function of either the right or left ventricle. A right VAD supports the pulmonary circulation, whereas a left VAD provides systemic perfusion, in the absence of adequate right or left ventricular ejection, respectively. Implantable VADs are positioned intracorporeally, under the anterior abdominal wall or within the thorax or abdomen. Extracorporeal VADs may be located in a paracorporeal position, on the patient's anterior abdomen, or externally, at the patient's bedside. Five pulsatile VAD systems have approval by the U.S. Food and Drug Administration (FDA) for clinical use. The total artificial heart (TAH) is an orthotopically positioned cardiac replacement device. The pneumatic TAH is used infrequently, and only with FDA approval, as a mechanical bridge to cardiac transplantation. Completely implantable electric VADs and artificial hearts that do not employ a percutaneous drive line have been successfully implanted in experimental animals and are expected to reach the clinical arena in the near future.

HISTORY

Extracorporeal counterpulsation was introduced by Clauss and coworkers in 1961.[10] The concept was modified by Moulopolous and colleagues, who described an intravascular counterpulsation balloon in 1962.[11] The first successful clinical application

of balloon counterpulsation was reported by Kantrowitz and associates in 1968.[12] IAB insertion originally required a surgical procedure. In 1980, Bregman and coworkers described percutaneous IAB insertion using a sheath and dilators.[13] The IAB is now a standard form of therapy for a variety

TABLE 19-1 -- DEFINITION OF CARDIOGENIC SHOCK

Cardiac output index	<2.0 liters/min/m^2
Systolic blood pressure	<90 mm Hg
Left or right atrial pressure	>20 mm Hg
Urine output	<20 ml/hr
Systemic vascular resistance	>2100 dynes-secccm^{-5}

TABLE 19-2 -- MECHANICAL CIRCULATORY SUPPORT SELECTION CRITERIA

Patient fulfills hemodynamic criteria (see Table 19-1)
Maximal inotropic support and intraaortic balloon counterpulsation
Exclude patient if:
Blood urea nitrogen >100 mg/dl
Serum creatinine >5.0 mg/dl
Chronic lung disease
Chronic liver disease
Metastatic cancer
Systemic sepsis
Neurological deficit
Technically incomplete cardiac operative procedure (if postcardiotomy cardiogenic shock)
Age >65 yr (if bridge to transplant)

of patients with cardiovascular disease. In 1993, nearly 100,000 IABs were inserted in the United States alone.[14]

The dawn of complete, clinical mechanical circulatory support occurred on May 6, 1953, when Gibbon successfully closed a secundum atrial septal defect in a patient supported with cardiopulmonary bypass.[15] The majority of patients with ventricular dysfunction, however, do not require pulmonary support with an in-line oxygenator. Roller pump left ventricular assistance using atrial transseptal uptake and femoral arterial return was

introduced by Dennis and colleagues in 1962.[16] Subsequently, DeBakey successfully employed left atrial to aortic bypass in patients who could not be weaned from cardiopulmonary bypass.[17] By the late 1970s, a variety of intracorporeal and extracorporeal mechanical blood pumps were being tested for both "support to weaning"[18] and "bridge to transplant"[19] indications. Patient selection and hemodynamic criteria were developed, and cannulation techniques, blood-biomaterial interactions, and control strategies were evaluated. During the 1980s, patient management techniques were refined and clinical results improved. Advances in myocardial preservation resulted in fewer blood pumps being required for postcardiotomy cardiogenic shock. However, a disparity in the ratio of cardiac donors to recipients increased the need for long-term circulatory support in patients requiring a bridge to cardiac transplantation. Results in this patient population proved gratifying, with survival statistics approaching those achieved with conventional cardiac transplantation.[20] The 1990s saw research efforts focus on the development of implantable VADs suitable for permanent implantation in patients with end-stage cardiomyopathy.

While IAB and VAD development were in their infancy, investigators also initiated laboratory efforts to develop a cardiac replacement device. In 1958, Akutsu and Kolff described an experiment in which a pneumatic TAH was implanted in a dog.[21] By the mid 1960s, Nose and coworkers had achieved 24-hour survival with sac-type hearts implanted in calves.[22] By the end of the decade survival times approached 3 to 5 days.[23] Experimental animals with TAHs have now lived for up to 1 year. The TAH entered the clinical arena in 1969 when Cooley and associates introduced the concept of staged cardiac replacement.[24] Joyce and coworkers were the first to implant a TAH as a permanent cardiac replacement.[25]

INTRAAORTIC BALLOON COUNTERPULSATION

The design and function of the IAB has not changed substantially during the past three decades. The IAB is an intravascular, catheter-mounted, counterpulsation device with a balloon volume between 30 and 50 ml. A central lumen allows passage of the balloon catheter over a small diameter guidewire and subsequent monitoring of central blood pressure. The IAB is attached to a small bedside console and timed to the patient's arterial pressure curve or electrocardiogram. The shuttle gas is helium, as its viscosity allows rapid balloon inflation and deflation, which facilitates counterpulsation in patients with tachyarrhythmias.

The IAB is positioned in the descending thoracic aorta and set to inflate at the dicrotic notch of the arterial pressure waveform when monitoring the aortic pressure (Fig. 19-1) . The diastolic rise in aortic root pressure augments coronary blood flow and myocardial oxygen supply. The increase in systemic perfusion may be less than 0.5 liter/min. The IAB is deflated during the isovolumetric phase of left ventricular contraction. The reduction in the afterload component of cardiac work decreases peak left ventricular pressure and myocardial oxygen consumption. The net effect is a favorable shift in the myocardial oxygen supply/demand ratio, with a small increase in systemic perfusion.

Indications and Results of Clinical Use

Traditional indications for IAB counterpulsation include refractory cardiogenic shock after cardiac surgery or acute myocardial infarction (Table 19-3) . The latter indication includes patients suffering from primary pump failure in addition to those with mechanical complications, such as acute mitral regurgitation or a postinfarction ventricular septal defect.

Five to 10 percent of patients who suffer an acute myocardial infarction develop cardiogenic shock.[26] Seventy-five percent of patients with an acute myocardial infarction who develop cardiogenic shock not amenable to conventional medical therapy will improve hemodynamically with IAB

Figure 19-1 The intraaortic balloon is inserted through the common femoral artery and positioned in the descending thoracic aorta. The tip is located just distal to the left subclavian artery. The balloon is inflated during cardiac diastole thereby increasing coronary artery perfusion *(A).* Left ventricular afterload is decreased as the balloon is deflated during cardiac systole *(B).* Proper balloon timing improves the ratio between myocardial oxygen supply and demand. (From Richenbacher WE: Intraaortic balloon counterpulsation. *In* Richenbacher WE [ed]: Mechanical Circulatory Support. Georgetown, TX, Landes Bioscience, 1999, p 33.).

TABLE 19-3 -- INDICATIONS FOR INTRAAORTIC BALLOON COUNTERPULSATION

Cardiogenic shock
Postcardiotomy
Associated with an acute myocardial infarction
Mechanical complication of an acute myocardial infarction
Mitral regurgitation
Ventricular septal defect
In association with coronary artery bypass surgery
Preoperative insertion
Patients with severe left ventricular dysfunction
Patients undergoing repeat bypass surgery
Postoperative insertion
Postcardiotomy cardiogenic shock
In association with nonsurgical revascularization
Hemodynamically unstable infarct patients
High-risk coronary angioplasty

Patients with severe left ventricular dysfunction
Complex coronary artery disease
Stabilization of cardiac transplant recipient before insertion of ventricular assist device
Postinfarction angina
Ventricular arrhythmias related to ischemia

counterpulsation.[27] Although it has been suggested that prolonged IAB support in such patients may improve hospital and long-term survival rates,[28] the role of IAB counterpulsation in this patient population is to facilitate early catheterization and reperfusion strategies. Patients with an acute myocardial infarction complicated by cardiogenic shock have a hospital survival rate of 5 to 21 percent.[26] If such patients can be revascularized either by coronary artery bypass or by thrombolysis and percutaneous transluminal coronary angioplasty, survival rates improve dramatically. Patients with an acute myocardial infarction and cardiogenic shock who are treated with early IAB counterpulsation and coronary artery bypass grafting achieve an early survival rate of 88 to 93 percent.[26] [29]

Patients who develop a mechanical complication after an acute myocardial infarction are best managed with IAB counterpulsation, urgent cardiac catheterization, and immediate surgical repair. IAB counterpulsation reduces the left-to-right shunt and maintains coronary perfusion in patients with a postinfarction ventricular septal defect. Hospital mortality in patients managed with an IAB and urgent operation is 25 to 47 percent.[30] [31] [32] Patients with postinfarction mitral regurgitation secondary to papillary muscle dysfunction or rupture also benefit from IAB insertion. IAB counterpulsation increases coronary perfusion and reduces ischemic ventricular dysfunction, mitral regurgitation, and the pulmonary capillary wedge pressure. Outcome is related to the extent of cardiac dysfunction, with surgical mortality approaching 55 percent.[33]

POSTCARDIOTOMY CARDIOGENIC SHOCK.

IAB counterpulsation is employed in association with coronary artery bypass surgery in up to 13 percent of cases.[34] Preoperative IAB insertion is thought to be efficacious in patients with profound left ventricular dysfunction and in certain patients who have had previous bypass surgery.[35] [36] Refractory postcardiotomy cardiogenic shock is related to preoperative left ventricular dysfunction, inadequate myocardial preservation, intraoperative myocardial infarction, prolonged cardiopulmonary bypass and intraoperative ischemic times, or technical difficulties with the conduct of the operation. With maximal medical support and IAB counterpulsation, survival rates average 52 to 66 percent.[37] Predictors of death with intraoperative or postoperative IAB use include age, mitral valve replacement, urgent or emergent operation, preoperative renal dysfunction, complex ventricular ectopy, right ventricular failure, and transthoracic IAB insertion.[38]

IAB counterpulsation has also been used in conjunction with nonsurgical revascularization. In addition to the use of the IAB in hemodynamically unstable infarct patients just described, IAB counterpulsation has been employed prophylactically in patients requiring high-risk coronary angioplasty.[39] Prophylactic IAB support has been

used in patients with severe left ventricular dysfunction and complex coronary artery disease, a population that comprises 1 to 2 percent of the total number of angioplasty procedures. Using this management algorithm, successful angioplasty has been performed in 86 to 100 percent of patients, with a hospital mortality of 6 to 19 percent.[39]

HEART FAILURE.

The use of IAB counterpulsation in heart failure patients awaiting cardiac transplantation has decreased as the waiting time for donor hearts has increased. The rationale for IAB counterpulsation in this clinical setting is to maintain systemic perfusion and preserve end organ function until cardiac transplantation occurs. Long-term IAB use is, however, impractical because patients are not afforded an opportunity for rehabilitation and the IAB represents a significant ongoing infection risk. VAD support is now the standard of care in the patient requiring a bridge to transplantation. The role of IAB counterpulsation in this patient population has now been reduced to stabilization of the occasional patient with marked hemodynamic instability to allow time for VAD insertion.

UNSTABLE ANGINA (See also Chap. 36) .

IAB support has also been offered to patients who do not fulfill hemodynamic selection criteria but who suffer from unstable angina or malignant ventricular tachyarrhythmias. Although nonrandomized trials suggest that IAB counterpulsation and subsequent myocardial revascularization may be of some benefit in patients with unstable angina,[40] aggressive preoperative medical management and a judicious cardiac anesthetic may eliminate the need for an IAB with equally good results. The role of IAB counterpulsation in patients with postinfarction angina is equally controversial.[41] In general, IAB support is reserved for patients with deteriorating hemodynamics or ongoing ischemia, as evidenced by rest pain or electrocardiogram changes in the region of the infarct, prior to myocardial revascularization. IAB counterpulsation may be beneficial in patients with ventricular tachyarrhythmias, particularly when the ventricular tachyarrhythmias are related to ischemia.[42] Ectopic impulses originate in the ischemic area surrounding an infarct zone, and the IAB may reduce the frequency of such arrhythmias by increasing myocardial perfusion and oxygenation in the ischemic zone.

The use of IAB counterpulsation in the pediatric patient population remains problematic. Balloon catheters and consoles have been modified for use in children. However, the complex anatomy associated with congenital cardiac anomalies often results in biventricular failure for which IAB counterpulsation is not particularly effective. Even so, survival rates exceeding 50 percent in children supported with an IAB after a cardiac operation have been reported.[43]

CONTRAINDICATIONS.

Absolute contraindications to IAB counterpulsation include aortic insufficiency and aortic dissection (Table 19-4) . Contraindications to IAB insertion through the femoral arterial route include the presence of an abdominal aortic aneurysm or severe calcific aortoiliac or femoral arterial disease. The percutaneous insertion technique should not be

employed in patients who have a recent groin incision with violation of the subcutaneous tissue at the proposed puncture site. The percutaneous insertion technique should be used with caution in the morbidly obese patient because the peritoneal reflection may be quite caudad, resulting in transperitoneal passage of the balloon catheter.

INSERTION TECHNIQUE

The IAB is most commonly inserted in a percutaneous fashion through the common femoral artery.[44] Preinsertion evaluation of the

TABLE 19-4 -- CONTRAINDICATIONS TO THE USE OF INTRAAORTIC BALLOON COUNTERPULSATION

Absolute Contraindications
Aortic valve insufficiency
Aortic dissection
Relative Contraindications
Femoral arterial insertion
Abdominal aortic aneurysm
Severe calcific aortoiliac or femoral arterial disease
Percutaneous insertion
Recent ipsilateral groin incision
Morbid obesity

patient's femoral arterial and pedal pulses facilitates rapid recognition of limb ischemia after balloon insertion. With the use of strict aseptic technique the femoral artery is accessed using the Seldinger technique. The femoral arterial puncture should occur below the inguinal ligament, to avoid a transperitoneal puncture, and above the profunda femoris artery, to reduce the potential for superficial femoral arterial cannulation.

The common femoral artery is dilated, and the final dilator and sheath are advanced over a guidewire into the descending thoracic aorta. The final dilator is withdrawn, and the IAB is inserted into the introducer sheath. The radiopaque tip of the IAB is positioned just distal to the left subclavian artery. The balloon is unwound, purged, connected to the bedside console, and pulsed. Proper augmentation is best accomplished with the IAB synchronized 1:2 with the patient's arterial pressure trace. Once inflation and deflation times are determined, augmentation is set at 1:1. Postinsertion anticoagulation is usually accomplished with a continuous heparin sodium infusion (1000 U heparin sodium in 500 ml normal saline, 3 ml/hr). Heparin sodium

administration is not necessary in postcardiotomy patients.

Alternatively, the IAB may be inserted into the femoral artery using an open technique. The femoral artery is exposed, and a 5-cm segment of an 8- to 10-mm diameter vascular graft is anastomosed, at a 45-degree angle, to the common femoral artery. The IAB is passed through the vascular graft and into the artery and positioned as described previously. The IAB is fixed in position by tying umbilical tapes around the vascular graft.

When an abdominal aortic aneurysm or severe peripheral vascular disease precludes femoral arterial insertion, the IAB may be inserted directly into the ascending aorta or transverse arch.[45] Access is obtained through a median sternotomy, usually at the time of cardiotomy. The balloon is inserted through a vascular graft in a manner identical to that described in the open femoral arterial technique. The balloon is advanced across the transverse arch into the descending thoracic aorta. Alternatively, the IAB can simply be inserted through two concentric pursestring sutures.

A "sheathless" insertion technique may be employed in the nonanticoagulated patient. With this technique, the IAB is inserted into the common femoral artery after dilation with the small diameter dilator. The large dilator and sheath assembly are not employed. This technique minimizes the obstruction to blood flow in the common femoral artery facilitating IAB use in patients with a small body habitus and in those with known or suspected peripheral vascular disease.

REMOVAL TECHNIQUE

As the patient's hemodynamic status improves, balloon augmentation is serially decreased. If the patient tolerates augmentation of every third to eighth cardiac cycle (1:3 to 1:8), the IAB can be safely withdrawn.[44] Balloon inflation is discontinued and the balloon aspirated to ensure deflation is complete. The balloon is withdrawn until it touches the sheath. Manual pressure is applied to the femoral artery distal to the insertion site, and the balloon and insertion sheath are withdrawn as a single unit. Blood is permitted to eject from the insertion site for one or two heartbeats to clear any thrombotic debris from the vascular space. Pressure is then applied to the insertion site: manually for 30 minutes and with a sandbag for an additional 8 hours. One must make certain the limb is adequately perfused during IAB removal. Withdrawal of an IAB inserted by the open technique requires surgical groin exploration, balloon and vascular graft removal, and femoral artery repair, usually with a vein patch. Open removal is also recommended when there has been a high (proximal) percutaneous insertion in morbidly obese patients, and in patients who develop limb ischemia after percutaneous insertion.

Balloons inserted into the ascending aorta can be removed under local anesthesia if the side arm graft is brought into the subcutaneous space.[46] The authors, however, recommend a repeat sternotomy with direct visualization of the insertion site.

COMPLICATIONS OF IAB USE

The complication rate from IAB counterpulsation ranges from 5 to 47 percent.[47] [48] Major complications, including limb ischemia necessitating thrombectomy or amputation, aortic dissection, aortoiliac laceration or perforation, and deep wound infection requiring debridement, occur in 4 to 17 percent of patients.[49] Major complications lead to an additional operative procedure, prolonged hospitalization, long-term morbidity, or death. Minor complications, including bleeding at the insertion site, superficial wound infections, asymptomatic loss of peripheral pulse or lymphocele, occur in 7 to 42 percent of patients.[49] Minor complications are usually self-limited or resolve after IAB removal. Although the overall complication rate has not changed appreciably in the recent past, it appears that the severity of complications and the mortality directly attributable to IAB insertion have decreased significantly.[50]

The most common complications related to femoral IAB use are vascular.[47] [48] [50] [51] [52] [53] [54] Vascular complication rates vary from 8 to 20 percent and are related to mechanical trauma to the vessel wall during IAB insertion, flow obstruction by the balloon catheter, and low cardiac output with peripheral vasoconstriction.[47] [50] [51] [52] [53] Risk factors for developing a major vascular complication after femoral IAB insertion are controversial but generally include peripheral vascular disease, diabetes mellitus, female gender, and small body surface area. In the past few years there has been a trend toward a lower incidence of limb ischemia associated with IAB use. This trend may be explained by an increased use of small-diameter balloon catheters. When percutaneous IAB insertion was introduced, a sheath as large as 12.5F was employed. Currently, sheaths as small as 8.5F to 9.5F are used, whereas sheath pull-back insertion techniques reduce the cross-sectional area of the catheter within the vascular space. These improvements in catheter design and insertion technique should have a significant positive impact on the vascular complication rate. Unfortunately, some series report no improvement in the vascular complication rate when a smaller catheter is employed[54] or when a sheathless insertion technique is used.[53]

LEG ISCHEMIA.

When a patient develops leg ischemia after femoral IAB insertion, the IAB should be removed. Persistent limb ischemia after IAB removal requires emergent femoral arterial exploration, thrombectomy, and vein patch angioplasty. Balloon-dependent patients with limb ischemia benefit from moving the IAB to the contralateral leg or undergoing a femoral-femoral crossover graft.[55]

The reported complication rate of transthoracic IAB counterpulsation is 0 to 13 percent.[49] [56] Complications associated with IAB insertion in the ascending aorta include bleeding at the insertion site, mediastinitis, transient ischemic attack, cerebrovascular accident, and an inability to close the sternum secondary to mechanical tamponade. Proponents of this route for IAB insertion note that the problem with leg ischemia is eliminated and placement of the IAB under direct vision reduces the potential for vessel

perforation and risk of aortic dissection.[56]

VENTRICULAR ASSIST DEVICES

Unlike the IAB, which is designed to improve the ratio between myocardial oxygen supply and demand while supporting systemic perfusion to only a modest degree, ventricular assist devices (VADs) are designed to effectively unload either the right or left ventricle while completely supporting the pulmonary or systemic circulation. The term VAD describes any of a variety of mechanical blood pumps that are employed singly to replace the function of either the right or the left ventricle. Two blood pumps can be used for biventricular support. For right ventricular assistance, blood is withdrawn from the right atrium and returned to the main pulmonary artery. For left ventricular assistance, blood is withdrawn from either the left atrium or the apex of the left ventricle. The blood passes through the left VAD and is returned to the ascending aorta.

There is a wealth of information in the literature regarding the advantages and disadvantages of left atrial versus left ventricular inflow (with respect to the VAD) cannulation.[57] [58] In general, left atrial inflow cannulation is technically easier to perform, may employ cannulas readily available to any open-heart surgical team, but is thought to provide incomplete ventricular decompression. Left ventricular inflow cannulation requires a custom-designed cannula but provides very effective left ventricular decompression. The reduction in myocardial oxygen demand is offset by the fact that left ventricular apical cannulation damages the myocardium, an important consideration in a patient with marginal ventricular function. A left ventricular apex cannula is, however, ideally suited to patients who receive

TABLE 19-5 -- COMPARISON OF VENTRICULAR ASSIST PUMPS

VAD Type	Advantage	Disadvantage
Centrifugal	Readily available Simple to use Relatively inexpensive	Nonpulsatile Systemic anticoagulation Constant supervision required Not FDA approved as a VAD
Pneumatic pulsatile	No blood trauma ±anticoagulation Pulsatile flow Minimal supervision required	Limited patient mobility with current approved drive consoles Expensive
Electric pulsatile	Same as pneumatic pulsatile	Highly portable Hospital discharge permittted

VAD=ventricular assist device; FDA=Food and Drug Administration.

mechanical circulatory support as a bridge to cardiac transplantation. In this patient population, ventricular recovery is not expected and the apical cannula is removed in its entirety at the time of recipient cardiectomy.

REGULATORY AFFAIRS

To better understand the enormous amount of effort that has been expended developing mechanical blood pumps, and limitations imposed on clinicians who desire access to a VAD, it is important to become familiar with the process by which medical devices are evaluated and approved for clinical use.[59] [60] The Medical Device Amendment of 1976 amended the federal Food, Drug and Cosmetic Act to require the FDA to approve clinical investigation of new medical devices and to approve new medical devices before they could be sold for general use. To prove that a new medical device is both safe and effective, the device must be the subject of a carefully controlled clinical trial.

An investigator/manufacturer first conducts extensive in vitro device testing followed by in vivo animal experimentation. The data derived from the preclinical evaluation are submitted to the FDA along with results, if any, from foreign clinical trials. The investigator must also submit a formal clinical protocol and informed consent material that have been approved by the Institutional Review Board at the site of the proposed clinical trial. If the application for clinical investigation of the device is deemed satisfactory by the FDA, an Investigational Device Exemption (IDE) is granted to the investigator. It is expected that the clinical protocol will answer specific questions concerning the proposed indications and contraindications for use of the device.

Because of the inordinate expense of device research and development, and the cost incurred during the conduct of a clinical trial (under an approved IDE), most investigators have an industrial partner. Assuming the clinical trial shows the device to be safe and effective for a well-defined set of indications, the next step will be to seek approval from the FDA for commercial sale of the device. In general, the industrial partner will submit a Pre-Market Approval (PMA) request to the FDA. The focus of the PMA application is to provide more extensive durability testing, an important consideration in devices intended for long-term clinical use.

Durability testing is most often accomplished by accelerated in vitro experimentation, frequently performed under conditions more severe than those experienced when the device is in actual clinical use. Approval of a PMA by the FDA allows the manufacturer to release the medical device for commercial sale.

Description of Devices

Mechanical blood pumps capable of replacing the function of a single ventricle can be divided into three categories. The advantages and disadvantages of each category of blood pump are summarized in Table 19-5 . Representative members of each class of VAD are listed in Table 19-6 . Specific design features and functional characteristics of each VAD are described here. Specific details regarding implantation and explantation

technique are described in the section entitled Management Considerations.

Centrifugal Pumps

Centrifugal pumps are simple to use and readily available to most cardiac surgeons.[61] [62] [63] [64] Standard cardiopulmonary bypass atrial and arterial cannulas are connected to the centrifugal head by short lengths of medical grade polyvinyl chloride tubing. The centrifugal head imparts forward flow to blood by creating a vortex with a rapidly spinning series of cones or impeller blades that are located within the rigid pump housing. The nonocclusive pump head has excellent blood handling characteristics, and the system is pressure limited, virtually eliminating the potential for air embolus or tubing disruption.[63] [65] Centrifugal blood pumps provide nonpulsatile blood flow and require full systemic anticoagulation and constant driver supervision.[66] The centrifugal pump can provide left- or right-sided heart support, or two pumps can be used for biventricular assistance. Centrifugal pumps entered the clinical arena before the Medical Device Amendment of 1976. However, centrifugal blood pumps are considered a Class III medical device, subject to the constraints imposed by this amendment to the federal Food, Drug and Cosmetic Act. Currently, the three centrifugal blood pumps available in the United States are approved by the FDA for only up to 6 hours of use, which makes them suitable for cardiopulmonary bypass but not

TABLE 19-6 -- REPRESENTATIVE MEMBERS OF EACH VAD TYPE

VAD Type	Name	Manufacturer
Centrifugal	BioPump Sarns Lifestream	Medtronic BioMedicus, Inc. 3M Health Care St. Jude Medical, Inc.
Pneumatic pulsatile	BVS 5000 biventricular support system Thoratec VAD system HeartMate 1000 IP LVAS	Abiomed, Inc. Thoratec Laboratories Corp. Thermo Cardiosystems, Inc.
Electric pulsatile	Novacor N100 LVAS HeartMate VE LVAS LionHeart	Novacor Medical Division, Baxter Healthcare Corp. Thermo Cardiosystems, Inc. Arrow International, Inc.

VAD=ventricular assist device.

for short-term temporary ventricular assistance (see Table 19-6) .

Pneumatic Pulsatile Blood Pumps

Complex, air-driven, pulsatile VADs are considerably more expensive than a centrifugal

pump but are capable of producing pulsatile flow with no trauma to formed blood elements. Furthermore, integral sophisticated control systems are largely self regulating, and beyond the first few days after device insertion minimal supervision is required. As drive units become more refined and portable drivers are developed, patient mobility and lifestyle will improve dramatically.

ABIOMED BVS 5000 BIVENTRICULAR SUPPORT SYSTEM.

The Abiomed BVS 5000 Biventricular Support System (Abiomed, Inc., Danvers, MA) received PMA approval from the FDA for the treatment of patients with postcardiotomy cardiogenic shock.[67] [68] [69] The BVS 5000 blood pump is an external, dual-chamber device that is capable of providing short-term univentricular or biventricular circulatory support. Each chamber contains a 100-ml polyurethane blood sac. Trileaflet polyurethane valves are located at the inlet and outlet side of the ventricular chamber. The atrial chamber fills passively throughout pump systole and diastole while the ventricular chamber is intermittently pulsed with air from the drive console. Custom-designed cannulas provide right or left atrial inflow. The distal portion of the outlet cannula is a coated vascular prosthesis that is anastomosed to either the pulmonary artery or aorta. The cannulas traverse the skin subcostally. The drive unit functions asynchronously with respect to the patient's native cardiac rhythm. The control system maintains a constant 80-ml stroke volume by automatically adjusting the duration of pump systole and diastole in response to changes in preload and afterload.

HEARTMATE 1000 IP LVAS.

The Heart.Mate 1000 IP LVAS (Thermo Cardiosystems, Inc., Woburn, MA) has received PMA approval from the FDA for use as a mechanical bridge to cardiac transplantation.[70] [71] [72] [72A] This implantable blood pump is connected to an external drive unit by a percutaneous air drive line. The titanium VAD housing contains a flexible segmented polyurethane diaphragm that is bonded to a rigid pusher plate. The unique, textured blood contacting surface promotes the formation of a stable neointima.[73] Patients do not require systemic anticoagulation and instead receive only antiplatelet agents. Intermittent air pulses from the external drive console actuate the pusher-plate diaphragm, and eject blood from the VAD housing. The pump has a maximum stroke volume of 83 ml and a maximum pump output of 10 liters/min. Valved conduits containing 25-mm porcine valves are located at the inlet and outlet ports of the VAD housing. The VAD is only designed for left ventricular support, withdrawing blood from the left ventricular apex. Blood is returned to the ascending aorta. The device may be implanted intraperitoneally, but more typically it is positioned preperitoneally, in the patient's abdominal wall.[74] When the blood pump is placed in a preperitoneal position, the potential visceral complications associated with peritoneal implantation are avoided. The drive console runs on standard alternating current, as well as internal rechargeable batteries. The batteries provide up to 40 minutes of support. The control system allows the VAD to function in a fixed rate or pump-on-full mode. The latter is a rate-responsive mode in which the VAD is automatically pulsed when the pump chamber is approximately 90 percent filled.

THORATEC VAD SYSTEM.

The Thoratec VAD System (Thoratec Laboratories Corp., Berkeley, CA, Fig. 19-2) is the only VAD approved by the FDA both for the treatment of postcardiotomy cardiogenic shock and as a bridge to cardiac transplantation.[75] [76] [77] [77A] This versatile paracorporeal blood pump can be used for right, left, or biventricular assistance. In the case of left ventricular assistance, custom-designed cannulas allow blood to be withdrawn from either

Figure 19-2 The paracorporeal Thoratec ventricular assist device is located on the patient's anterior abdominal wall. The inlet and outlet cannulas traverse the skin in the subcostal region. The biventricular assistance configuration shown here would be used in a patient requiring a bridge to cardiac transplantation. The left ventricular assist device inflow cannula is inserted into the left ventricular apex. The left ventricular assist device outflow graft is sutured to the ascending aorta. The right ventricular assist device withdraws blood from the right atrium. Right ventricular assist device outflow is to the main pulmonary artery. (From Richenbacher WE: Ventricular assistance as a bridge to cardiac transplantation. *In* Richenbacher WE [ed]: Mechanical Circulatory Support. Georgetown, TX, Landes Bioscience, 1999, p 125.)

the left atrium or the apex of the left ventricle. The blood pump consists of a machined polycarbonate housing that contains a polyurethane blood sac and Bjork-Shiley monostrut inlet and outlet valves (Shiley, Inc., Irvine, CA). Patients are maintained on sodium warfarin. The blood pump has a stroke volume of 65 ml with a dynamic ejection fraction of approximately 0.75. Air pulses from the drive unit intermittently compress the flexible blood sac ejecting blood from the VAD housing. The control system allows the device to function in one of three modes: a manual fixed-rate mode, a synchronized mode in which the R-wave of the patient's electrocardiogram serves as an electronic trigger, and an asynchronous full-to-empty mode in which the VAD enters systole each time the blood sac fills. The latter mode maximizes cardiac output by allowing the VAD pump rate to be determined by preload.

Electric Pulsatile Blood Pumps

In the past few years great progress has been made in the development and clinical application of electric VADs. The current generation of electric blood pumps are intracorporeal devices that are capable of providing months, or even 1 or 2 years, of ventricular support. These devices provide left ventricular apex-to-aortic left ventricular assistance and are not designed for right ventricular assistance. Electric VADs are powered by a highly portable external controller and battery pack. In 1998, two electric VAD systems were approved by the FDA for the bridge to transplant application. Both approved systems employ a percutaneous drive line that connects the intracorporeal blood pump to the external electronics. Patients may now be discharged from the

hospital to await their cardiac transplant at home.[78] [79] The conversion from a bulky external pneumatic drive unit to a small portable battery pack, with the possibility of hospital discharge, represents a dramatic improvement in the quality of life experienced by the patients who require mechanical circulatory support as a bridge to cardiac transplantation.

The next-generation electric VAD will be completely implantable and capable of providing years of tether-free left ventricular support. The electric VAD system will have an implantable controller and backup battery. An external, portable battery pack will serve as the primary power source. The external battery pack will be carried in a shoulder bag and transfer energy to the implantable controller and blood pump using transcutaneous energy transmission.[80] Energy will be passed from an external primary coil located on the surface of the skin to a subcutaneous secondary coil by inductive coupling. There will be no break in the integument, eliminating the potential for an ascending drive line infection. The internal, rechargeable battery will allow brief periods of entirely tether-free VAD function. Because these systems will be completely sealed, air displaced from the blood pump housing during VAD diastole will move to an implanted reservoir known as a compliance chamber.[81] As the final technological barriers to the development of implantable electric VADs are overcome, these systems will be permanently implanted in patients with unreconstructable coronary artery disease or end-stage cardiomyopathy not amenable to cardiac transplantation.

Recently, a clinical trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure [REMATCH]) was initiated.[82] The trial seeks to enroll patients with NYHA functional Class IV heart failure who are not candidates for cardiac transplantation. Patients are randomized to one of two treatment arms: medical therapy or permanent electric VAD insertion. The purpose of the study is to evaluate the efficacy, safety, and cost effectiveness of wearable VADs versus optimal medical therapy in the treatment of end-stage heart failure. As implantable VAD systems reach the clinical arena the goal of using mechanical blood pumps as an alternate to transplant will be realized.[83]

NOVACOR N100 LVAS.

The Novacor N100 LVAS (Novacor Medical Division, Baxter Healthcare Corporation, Oakland, CA) was approved by the FDA for the bridge to transplant application (Fig. 19-3) . This ventricular assist system contains a polyurethane blood sac that is compressed by dual, symmetrically opposed pusher plates.[84] The pump is actuated by a spring-decoupled solenoid energy converter. The blood pump and energy converter are contained within a lightweight fiberglass/epoxy housing that is implanted in a preperitoneal position in the left upper quadrant of the patient's abdomen.[84] [85] The inflow and outflow conduits each contain a bioprosthetic, pericardial valve. Patients require full anticoagulation with sodium warfarin.

The Novacor blood pump has a maximum stroke volume of 67 ml. The tethered configuration employs a percutaneous vented tube containing power and control wires.[84] The external console-based controller typically allows the device to function in a fill-rate trigger mode that provides synchronized counterpulsation to the native heart.

The device may also be powered by a wearable, microprocessor-based controller and external batteries.[86] [87] [88] The compact controller and rechargeable batteries are worn as a belt and can support the blood pump for up to 6 hours.

HEARTMATE VE LVAS.

The HeartMate VE LVAS (Thermo Cardiosystems, Inc., Woburn, MA) has been approved by the FDA for the bridge to transplant application (Fig. 19-4) . This left ventricular assist system utilizes a

Figure 19-3 The implantable Novacor N100 LVAS. The blood pump is located in the preperitoneal position in the left upper quadrant of the patient's abdomen. The device is designed to provide left-sided heart support. Blood is withdrawn from the left ventricular apex and is returned to the ascending aorta. The percutaneous drive line connects the blood pump to the external controller and primary and reserve power packs. (Courtesy of the Novacor Division, Cardiovascular Group, Baxter Healthcare Corporation, Oakland, CA.)

Figure 19-4 The implantable Thermo Cardiosystems VE LVAS. The blood pump is positioned preperitoneally in the left upper quadrant of the patient's abdomen. The device is configured for left ventricular assistance with a left ventricular apex inflow cannula and an aortic outflow graft. The percutaneous drive line exits the skin in the right upper quadrant. The external controller is clipped to a belt. The two batteries are worn in shoulder holsters. (From Richenbacher WE: Ventricular assistance as a bridge to cardiac transplantation. *In* Richenbacher WE [ed]: Mechanical Circulatory Support. Georgetown, TX, Landes Bioscience, 1999, p 123.)

blood pump similar to that employed in the pneumatically powered ventricular assist system produced by the same manufacturer.[71] [72] [89] In the vented electric version, however, the diaphragm pusher-plate mechanism is pulsed by a low-speed high-torque motor. The percutaneous electrical leads connect the blood pump to the external controller and batteries. The rechargeable batteries, capable of providing 4 to 6 hours of tether-free operation, are carried in a shoulder holster, or the device may be connected to a stationary power base unit.

ARROW LIONHEART LVAS.

The completely implantable, sealed system being developed at The Pennsylvania State University and Arrow International (Arrow International, Inc, Reading, PA) contains a segmented polyurethane blood sac that is contained in a rigid housing.[90] [91] Bjork-Shiley monostrut inlet and outlet valves provide unidirectional blood flow. The blood sac is compressed by a pusher plate driven by a brushless direct current motor. Air displaced from the pump housing during VAD diastole is managed by a polyurethane

compliance chamber.[81] Control electronics and a 30-minute battery pack are contained in an implantable cannister that receives power from a subcutaneous energy transmission coil. The external battery pack carried by the patient transfers energy to the implanted coil using transcutaneous energy transmission.[80] The device has a stroke volume of 62 ml and can pump up to 8.5 liters/min. The controller adjusts the VAD beat rate in response to physiologic conditions, ensuring that the blood pump functions in a full-to-empty mode.

The Pennsylvania State University electric VAD has run continuously for more than 1 year on a mock circulatory system.[90] The system has been tested in vivo for up to 90 days.[92] Clinical implants began in Europe in the fall of 1999. An IDE has been submitted to the FDA in preparation for the initial feasibility study in the United States.

Indications and Results of Clinical Use

POSTCARDIOTOMY CARDIOGENIC SHOCK.

The original indication for VAD support was postcardiotomy cardiogenic shock. Approximately 1 percent of patients cannot be separated from cardiopulmonary bypass after an open-heart operation despite maximum medical therapy and IAB counterpulsation.[7] [93] [94] These patients are considered potential candidates for VAD insertion. The goal of mechanical circulatory support in this clinical setting is to alter the balance between myocardial oxygen supply and demand to create a milieu that favors myocardial recovery. At the same time, systemic perfusion is maintained. The end point in this scenario is a return of ventricular function, with the expectation that following a few days of mechanical circulatory support the VAD(s) could be removed.

The results achieved with mechanical blood pump support for postcardiotomy cardiogenic shock are summarized in Table 19-7 . The Combined Registry for the Clinical Use of Mechanical Ventricular Assist Devices and the Total Artificial Heart was developed in 1988 under the auspices of the International Society for Heart Transplantation and the American Society for Artificial Internal Organs.[7] The responsibility for the Registry was transferred to the Society of Thoracic Surgery in 1993. Clinicians from 62 centers worldwide voluntarily submit data to this registry.

Postcardiotomy cardiogenic shock remains the most frequent indication for mechanical circulatory support, although the number of blood pumps implanted for this clinical indication has declined steadily during the past decade.[7] Whether this reflects more strict implantation criteria, advances in myocardial preservation, improved medical

TABLE 19-7 -- RESULTS OF MECHANICAL BLOOD PUMP SUPPORT FOR POSTCARDIOTOMY CARDIOGENIC SHOCK

Author	Device	No. of Patients	Weaned	Survived*
Golding, et al[95]	BioPump	79	49 (62%)	20 (25%)
Lee, et al[96]	BioPump	28	N/A	9 (32%)

Curtis, et al[64]	Sarns			
	1986-1989	33	11 (33%)	5 (15%)
	1989-1994	32	17 (53%)	9 (28%)
	Overall	65	28 (43%)	14 (22%)
Mehta, et al[7]	Centrifugal	905	422 (47%)	236 (26%)
Korfer, et al[94]	Abiomed BVS 5000	50	N/A	25 (50%)
Gray and Champsaur[67]	Abiomed BVS 5000	211	87 (41%)	N/A
Guyton, et al[68]	Abiomed BVS 5000	31	17 (55%)	9 (29%)
Thoratec[97]	Thoratec	158	59 (37%)	33 (21%)
Mehta, et al[7]	Pneumatic	335	152 (45%)	82 (25%)

*Successfully weaned and survived to hospital discharge.

management of postcardiotomy heart failure, or underreporting to the voluntary registry is unknown. Mechanical circulatory support for postcardiotomy cardiogenic shock is most frequently required after coronary revascularization. The duration of support is brief, varying between 1.4 and 5.7 days.[7] [64] [98] Recent trends suggest that the duration of support required is independent of the need for left, right, or biventricular assistance.[7]

In general, lower survival is associated with an unsuccessful operation,[93] perioperative myocardial infarction,[93] advanced age,[7] renal failure,[7] [93] [95] neurologic complications,[7] biventricular failure,[7] [95] multisystem organ failure,[98] and sepsis.[98] Patients who are subjected to prolonged cardiopulmonary bypass times or who require late VAD insertion (hemodynamic collapse after having been moved out of the operating room) have very poor survival rates.[7] [93] Survival does not appear to be influenced by the type of operation performed before VAD insertion, the need for right versus left versus biventricular support, or the type of device used.[7] Survival is similar regardless of whether the patient receives a centrifugal or pulsatile blood pump. Although an overall salvage rate of approximately 25 percent seems low, it must be understood that without mechanical circulatory support, patients with refractory postcardiotomy cardiogenic shock would die. Although registry data show that weaning and survival rates have not improved in the past decade, Curtis and colleagues have shown that there is a trend toward increased hospital survival when an early versus recent cohort of patients at a single institution are compared.[64] Recently, Korfer and associates described 50 patients who received mechanical circulatory support for postcardiotomy cardiogenic shock with a hospital discharge rate of 50 percent.[98] Of note, the survival curve levels off after hospital discharge. The Registry reports a 24 percent 6-month survival and a 22 percent 5-year survival.[7] The majority of long-term survivors achieve NYHA functional Class II

or better.[64]

ADJUNCT TO CARDIAC TRANSPLANTATION (See alsoChap. 20) .

With the introduction of cyclosporine-based immunosuppressive regimens, and the resurgence of interest in cardiac transplantation in the early 1980s, a second patient population that could potentially benefit from mechanical ventricular assistance was identified. The number of patients with end-stage cardiomyopathy quickly exceeded the number of donor hearts available. The list of approved cardiac transplant candidates grew, and the time a patient spent waiting for a donor heart increased. At year-end 1998, 4185 potential cardiac transplant recipients were listed with the United Network for Organ Sharing (UNOS).[99] During the same year, 767 potential cardiac transplant recipients died while on the UNOS waiting list.[99] Cardiac transplant recipients who decompensate hemodynamically before the availability of a donor heart are potential candidates for VAD implantation. The role of mechanical circulatory support in this clinical setting is to maintain systemic perfusion and end organ function until a donor heart is available. The recipient's heart and VAD are removed at the time of cardiac transplantation.[99A]

Results of mechanical blood pump support as a bridge to cardiac transplantation are summarized in Table 19-8 . Although the length of time a cardiac transplant candidate waits for a suitable donor heart varies with UNOS status, blood type, and weight, the average waiting time is a number of months and can be as long as 1 to 2 years. Pulsatile devices, in particular implantable VADs, are designed to provide long-term support. The average duration of support for the series summarized in Table 19-8 varied between 41 and 108 days.[71] [72] [76] [98] [103] Fifty-five percent of patients who receive support with a pulsatile device that is approved by the FDA for the bridge application survive to hospital discharge after cardiac transplantation.[76] [97] [98] [101] [102] [103] Some would question the wisdom of allocating hearts to this critically ill patient population when the 1-year survival after conventional heart transplantation now exceeds 80 percent.[5] It has been suggested that VAD support intensifies the donor shortage by including recipients who otherwise would not have survived to transplantation.[104] The Registry of the International Society for Heart and Lung Transplantation notes that VAD support before transplantation is a recipient factor that has a significant negative impact on 1-year patient survival after transplantation.[5] If the cumulative experience of the bridge patients is reviewed, approximately two thirds of patients requiring VAD support survive to transplantation. More importantly, 86 percent of patients who require VAD support, and who are successfully transplanted, will survive to hospital discharge.[76] [97] [98] [101] [102] [103] Others have shown that posttransplant survival in bridge patients meets,[101] [102] [104] or exceeds,[105] the survival rate in non-bridge patients.

Risk factors associated with reduced survival in patients requiring VAD support as a bridge to cardiac transplantation include a preoperative need for mechanical ventilation; significant end organ dysfunction as evidenced by an elevated blood urea nitrogen, creatinine (with or without the need for dialysis), or bilirubin level; the need for a reoperation for bleeding after VAD insertion; right-sided heart failure requiring mechanical right ventricular assistance in addition to left VAD insertion; infection; and device failure.[71] [103] [106] The incidence of device failure is low, a tribute to extensive

preclinical device testing. Technical refinements in device design have largely eliminated the causes of device malfunction that appeared in the early clinical experience. [71] [107] [108]

The benefits of an extended period of VAD support are well defined. Patients undergo vigorous nutritional and physical rehabilitation.[109] Hemodynamic parameters, exercise tolerance, and end organ function improve.[110] [111] [112] [113] The recent approval by the FDA of two intracorporeal, electric VAD systems now allows VAD supported patients to be

TABLE 19-8 -- RESULTS OF MECHANICAL BLOOD PUMP SUPPORT AS A BRIDGE TO CARDIAC TRANSPLANTATION

Author	Device	No. of Patients	Transplanted	Survived*	Survival after Transplant
McBride[100]	Centrifugal	77	56 (73%)	36 (47%)	36/56 (64%)
Gray and Champsaur[67]	Abiomed BVS 5000	94	66 (70%)	39 (41%)	39/66 (59%)
Kormos, et al[101]	Novacor N100	43	30 (70%)	28 (65%)	28/30 (93%)
McCarthy, et al[71]	HeartMate	97	74 (76%)	N/A	N/A
Sun, et al[72]	HeartMate	95	62/88 (70%)	N/A	N/A
Frazier, et al[89]	HeartMate	1387	810/1214 (67%)	N/A	N/A
Hill, et al[102]	Thoratec	300	187/287 (65%)	159/287 (55%)	159/187 (85%)
McBride, et al[76]	Thoratec	67	39/64 (61%)	39/64 (61%)	39/39 (100%)
Korfer, et al[98]	Thoratec	84	56 (74%)	51 (61%)	51/56 (91%)
Thoratec[97]	Thoratec	608	365 (60%)	315 (52%)	315/365 (86%)
Mehta, et al[103]	Pulsatile	315	221 (70%)	183 (58%)	183/221 (83%)

*= Survived to successful transplanatation;

= survived to hospital discharge after transplantation.

discharged from the hospital. Home-based care has significant psychological and

emotional benefits for patients and their families.[114] [115] Outpatient VAD care also has a positive impact on health care economics.[116]

Mechanical circulatory support has been employed in two additional subpopulations of patients requiring cardiac transplantation: both after donor heart implantation. According to the Registry, 40 patients have been treated with circulatory support during a rejection episode complicated by hemodynamic compromise.[117] Only 23 of the patients (58 percent) underwent a second cardiac transplant. Eight of the 23 patients (35 percent) were discharged from the hospital. This represents an absolute salvage rate of 20 percent. Sixty-eight other posttransplant patients suffered from presumed reversible cardiogenic shock unrelated to rejection.[117] VAD support in this patient population resulted in an absolute salvage rate of 19 percent, statistically equal to the survival rate when ventricular assistance was employed in patients with postcardiotomy cardiogenic shock after other types of procedures.

ACUTE MYOCARDIAL INFARCTION (See also Chap. 35) .

Patients in cardiogenic shock after acute myocardial infarction treated with mechanical circulatory support alone have a mortality rate of 80 percent, the same as patients treated medically.[118] Ventricular assistance has been used in this patient population to stabilize the patient's condition to allow cardiac catheterization and emergent revascularization, treat cardiogenic shock after urgent revascularization, or support patients with irreparable cardiac damage until cardiac transplantation can be performed.[119] Mortality in certain subsets of patients may be reduced to 25 to 40 percent.[118] [119] [120] Because the therapeutic end point is unknown, proper device selection can be problematic. If ventricular apex cannulation is employed, the surgical technique must be modified when dealing with necrotic myocardium.[121] In general, less than optimal results leave the role for mechanical circulatory support in this clinical setting poorly defined.

LONG-TERM BRIDGE TO RECOVERY.

Most large series in which a pulsatile VAD has been inserted as a bridge to cardiac transplantation include patients who have recovered ventricular function after a protracted period of mechanical circulatory support.[72] [76] [89] [122] [123] [123A] In this situation the VAD is removed, obviating the need for cardiac transplantation. In most instances the VAD is removed when the patient develops a contraindication to transplantation or device malfunction. Observational studies describe a variety of morphological and physiological changes that are associated with chronic ventricular unloading.[124] [125] Indicators of ventricular recovery, however, are unknown. It is also unclear if the improvement in left ventricular function is sustained after VAD explantation. At this time, the role of ventricular assistance in the management of the patient with chronic heart failure, other than as a bridge to transplantation, must be considered experimental.

Complications Associated with VAD Use

Hemorrhage, usually defined as the need for a reexploration for bleeding, occurs in 14

to 50 percent of patients who require mechanical ventricular assistance.[64] [71] [76] [77] [89] [98] [103] Postimplant bleeding occurs more frequently in patients who receive a VAD for postcardiotomy cardiogenic shock versus a VAD as a bridge to transplant.[126] There is also a device-related prevalence in that bleeding occurs more frequently in the patients supported with a centrifugal pump for postcardiotomy cardiogenic shock than in patients supported with a pulsatile device for the same indication.[7] The etiology of bleeding associated with VAD implantation is multifactorial and includes preoperative hepatic failure or coagulopathy, technical surgical ability, hematologic abnormalities related to a prolonged cardiopulmonary bypass time, hypothermia, hemodilution, and platelet activation or disseminated intravascular coagulation secondary to blood-biomaterial interaction in the heart-lung machine or VAD.[126] [127] Use of the bovine serine protease inhibitor aprotinin has reduced blood loss associated with VAD implantation.[128]

Stasis of blood within the blood pump and inadequate anticoagulation may lead to thrombus deposition.[129] Thromboembolic complications occur in 6 to 47 percent of patients.[64] [72] [76] [98] [103] [130] Not all thromboembolic events result in a neurological deficit, and, in fact, many thromboembolic events are not clinically evident.[64] [130] [131] Multisystem organ failure is usually related to preimplantation end organ hypoperfusion but may be exacerbated by postimplantation low-flow states. Renal failure, in most instances defined as the need for dialysis, occurs in 5 to 29 percent of patients.[64] [76] [77] [98] [103] After left VAD insertion, systemic hypoperfusion is most often related to right ventricular failure and inadequate left VAD filling. Right ventricular dysfunction secondary to pulmonary hypertension is most effectively treated with inhaled nitric oxide.[132] [133] Medically refractory right-sided heart failure requiring right VAD insertion occurs in 11 to 37 percent of patients.[71] [72] [77]

Infection occurs in up to 59 percent of patients receiving mechanical circulatory support.[64] [71] [72] [76] [98] [103] Infection is often attributed to prolonged hospitalization, indwelling lines and catheters, and percutaneous drive lines or cannulas. Device-related infections occur in 11 to 27 percent of patients.[71] [72] [76] Device-related infections include percutaneous drive line colonization, intracorporeal VAD pocket infections, and VAD endocarditis. VAD endocarditis, best treated with chronic antibiotic therapy and early VAD removal, is associated with a poor outcome.[134] [135] Septic complications in the patient receiving VAD support as a bridge to transplantation should not influence the decision to proceed with transplantation. Transplantation in the face of infection is the most effective treatment option because survival rates are not significantly different in patients who are transplanted with or without an infectious complication during the period of VAD support.[134] [136]

Management Considerations

POSTCARDIOTOMY CARDIOGENIC SHOCK.

Patients who have preexisting ventricular dysfunction and who are at risk for intractable heart failure after an open-heart procedure have a femoral arterial line placed before the initiation of cardiopulmonary bypass. The presence of a femoral arterial line facilitates subsequent IAB insertion. Selected patients also undergo a cursory pretransplant evaluation. Of 965 postcardiotomy cardiogenic shock patients reported to the Registry

for Mechanical Circulatory Support, 43 patients (4.5 percent) were activated as potential cardiac transplant recipients when they developed device dependency and had no contraindication to transplant.[6]

On completion of the cardiac operation, acid-base balance and electrolyte abnormalities are corrected. A functional cardiac rhythm is restored utilizing temporary cardiac pacing, if necessary. A patient is considered a candidate for VAD insertion when he or she fulfills the hemodynamic criteria outlined in Table 19-1 , has no contraindication to VAD insertion as outlined in Table 19-2 , and cannot be weaned from cardiopulmonary bypass despite moderate inotropic support and IAB counterpulsation. It is imperative that operative decision-making be performed rapidly, and VAD insertion undertaken expeditiously, to avoid the complications associated with a prolonged cardiopulmonary bypass time.[137]

Standard cardiopulmonary bypass cannulas are employed for centrifugal VAD support.[138] [139] [140] Custom-designed cannulas are used with pulsatile VADs. For left ventricular

TABLE 19-9 -- HEMODYNAMIC STATUS DURING MECHANICAL LEFT VENTRICULAR ASSISTANCE

CVP (mm Hg)	LAP (mm Hg)	Systolic AoP (mm Hg)	CI (liters/min/m[2])	Diagnosis
15-20	<15	>90	>2.0	Satisfactory pumping
<15	<15	<90	<2.0	Hypovolemia
15-20	>20	<90	<2.0	Inlet cannula obstruction
>20	<15	<90	<2.0	Right ventricular failure

CVP=central venous pressure; LAP=left atrial pressure; AoP=aortic pressure; CI=cardiac output index.

assistance, left atrial cannulation is preferred as myocardium is spared and decannulation, after a return of ventricular function, can be performed without cardiopulmonary bypass. With a left VAD in place, cardiopulmonary bypass is discontinued. Simultaneous monitoring of left and right atrial pressures aids in the distinction between inflow cannula obstruction, hypovolemia, and right ventricular failure should left VAD filling be less than satisfactory (Table 19-9) . Right ventricular failure is managed with judicious volume loading, intravenous isoproterenol, or inhaled nitric oxide. Intractable right-sided heart failure mandates insertion of a right VAD. The goal is to achieve a cardiac index greater than 2.2 liters/min/m[2] . The IAB may be left in place to impart a degree of pulsatility to nonpulsatile centrifugal left ventricular assistance. To

avoid septic complications, however, the IAB is usually withdrawn in the immediate postoperative period.

Postoperatively, abnormal coagulation studies are aggressively corrected with protamine sulfate and blood product administration. When mediastinal tube drainage slows, patients are anticoagulated with continuous intravenous heparin sodium. Sodium warfarin is not usually employed as the time course for ventricular recovery is measured in days. A variety of weaning protocols have been employed.[141] In general, ventricular support is periodically decreased to assess a patient's native ventricular function. This can be accomplished with pulmonary arterial catheter measurements of cardiac output or observations of wall motion using transesophageal echocardiography.[142] When ventricular recovery is complete, the patient is returned to the operating room for device explantation. Management is conventional thereafter.[142A]

BRIDGE TO CARDIAC TRANSPLANTATION.

To be considered for mechanical circulatory support before cardiac transplantation, patients must not only fulfill VAD selection criteria but must also meet cardiac transplant selection and exclusion criteria (see Chap. 20) . The timing of VAD insertion is critical. When an inotrope-dependent cardiac transplant candidate deteriorates to the point where IAB counterpulsation is required, VAD implantation should follow within 24 to 48 hours. VAD insertion as a bridge to transplant is rarely an emergent procedure. However, inordinate delays in device implantation only result in progressive end organ deterioration and an increased risk of infectious complications.

Pulsatile devices are most frequently employed in this clinical setting. Implantation techniques are highly specialized but well documented.[74] [85] [140] [141] [143] [144] Cardiopulmonary bypass times are often brief, but postoperative bleeding can be troublesome. Aprotinin is used routinely.[128] Because aprotinin may have been used during a previous open heart operation, appropriate precautions should be taken as the patient may have been sensitized during the previous exposure. Should a right VAD be necessary, device selection is limited. The versatile Thoratec device can be employed for either right- or left-sided support.[76] [77] [140] If an implantable device is employed on the left, right ventricular support can only be provided with a hybrid pump configuration using a paracorporeal Thoratec VAD. The Abiomed BVS 5000, or a nonpulsatile pump, may also be used for right-sided heart support, although neither is approved by the FDA as a bridge to cardiac transplantation.

Postoperatively, the patient should be rapidly extubated and all invasive monitoring lines and tubes removed as soon as medically allowed to avoid nosocomial infection.[135] Fastidious cannula/drive line care and immobilization of the drive line reduces the potential for tract colonization.[145] Blood transfusions should be minimized and only leukocyte-depleted blood administered. Interval panel reactive antibody determinations will detect the presence of preformed antibodies to human lymphocyte antigens and determine the need for a prospective crossmatch with the cardiac donor or perioperative plasmapheresis at the time of transplant.[146] Aggressive nutritional and physical rehabilitation will prepare the patient for the subsequent cardiac transplant.[109] [147] Cardiac transplantation should be delayed for at least 2 to 4 weeks after VAD insertion

to allow time for the patient to convalesce from the VAD implant, rehabilitate, and recover end organ function.[110] [111] [148] The VAD is explanted at the time of recipient cardiectomy.[149]

THE ARTIFICIAL HEART

The total artificial heart (TAH) is a biventricular device capable of supporting both the pulmonary and systemic circulations. The TAH is implanted within the patient's pericardium (orthotopic position) in a manner very similar to donor heart implantation at the time of cardiac transplantation. The TAH must be compact and possess a control system capable of balancing the output of the two prosthetic ventricles, while varying cardiac output with physiological need.

Pneumatic Total Artificial Heart

At least 11 different TAHs have been employed clinically worldwide.[150] All possess similar design characteristics. Each prosthetic ventricle contains a flexible blood sac that is housed in a rigid case. Air pulses generated by a bedside drive unit are transmitted through small diameter percutaneous drive lines and periodically compress the flexible blood sacs. Inlet and outlet valves ensure a unidirectional flow of blood through the prosthetic ventricle. Cardiac output and output balance between the ventricles are achieved with a sophisticated control system. A manual, fixed rate control system functions using the Starling mechanism. The prosthetic ventricles completely empty during systole but heart rate and diastolic fill time are modified to limit diastolic filling. Any increase in preload results in more complete ventricular filling, a higher stroke volume, and increased cardiac output. An automatic control system employs two negative feedback servomechanisms.[151] The left ventricle pumps a full stroke with each beat, varying the rate to maintain systemic pressure within normal limits. The right ventricular beat rate varies to maintain a left atrial pressure of 5 to 12 mm Hg.

TAH implantation is carried out using cardiopulmonary bypass, with bicaval venous and aortic cannulation.[152] The patient's heart is excised by transecting the great vessels just distal to the semilunar valves and the atria along the atrioventricular groove. Prosthetic atrial cuffs are sutured to the atrial remnants. Vascular grafts are anastomosed to the aorta and pulmonary artery. The prosthetic ventricles are attached to the atrial cuffs and outlet grafts with snap-on quick connects or a threaded union nut. The ventricles are de-aired, pumping initiated, and cardiopulmonary bypass discontinued.

The pneumatic TAH has been employed extensively as a mechanical bridge to transplantation. Patient selection criteria are identical to those outlined in the VAD section. The sole exception is patient size. Patients must weigh at least 150 pounds and have an adequate anteroposterior thoracic dimension to avoid atrial compression and inflow obstruction at the time of sternal closure. The most recent Registry report includes 191 patients who received TAH support as a bridge to cardiac

transplantation.[103] One hundred and thirty-five patients (71 percent) underwent transplantation, of whom 66 (49 percent) were discharged from the hospital. The posttransplant discharge rate is 49 percent (66/135 patients). Transplantation rates were statistically equal regardless of whether the patient was supported with a left VAD, two VADs, or the TAH.[103] However, there was a highly statistically significant difference in posttransplant discharge rate, with the best outcome seen with left-sided heart support and least favorable outcome with the TAH. The only pneumatic TAH still employed as a bridge to transplantation under an IDE in the United States is the CardioWest (Jarvik) Total Artificial Heart (CardioWest, Tucson, AZ). Since 1993 the CardioWest TAH has been implanted in 100 patients.[153] [154] Sixty-seven patients subsequently underwent a cardiac transplant. Sixty-one patients (61 percent) were discharged to home, for a posttransplant discharge rate of 91 percent.

Of historical interest, four patients received the Jarvik-7-100 TAH under an FDA-approved protocol as a permanent form of circulatory replacement.[155] The longest survivor lived for 620 days, whereas all four patients succumbed to hematologic, thromboembolic, and infectious complications. Currently, infectious complications secondary to percutaneous drive lines and lifestyle issues related to the requisite bulky external drive unit preclude the use of pneumatic TAHs as a permanent form of circulatory support. Although the TAH can provide safe and effective hemodynamic support to a precardiac transplant patient, the TAH is more expensive and technically more difficult to implant than a VAD. Furthermore, univentricular support will suffice in the majority of patients who require a mechanical bridge to cardiac transplantation. We believe that transplant recipients who decompensate hemodynamically before cardiac transplantation are best served by VAD insertion. The TAH, if available, should be reserved for selected patients with a postinfarction ventricular septal defect, valvular heart disease, or intractable arrhythmias.

Electric Total Artificial Heart

When available for clinical use, the electric TAH will serve as a readily available cardiac replacement for patients with irreparable acute or chronic heart failure (Fig. 19-5) . The electric TAH is designed for permanent use and, as such, will be completely implantable. Size constraints represent the most significant hurdle to device development. Two blood pumps are located within the pericardium and, unlike the pneumatic TAH that employs a separate external drive unit for each ventricle, the electric TAH uses a single implantable energy converter to drive both ventricles, greatly increasing the complexity of device control. The electric TAH has a minimum energy requirement of 14 watts. Implantable batteries cannot provide the power required. Thus, currently available electric TAHs will rely on an external power source and transcutaneous energy transmission, with a small rechargeable implantable backup battery capable of serving as a power source for 30 to 60 minutes. In the future, higher-energy density batteries may reduce or eliminate the need for a primary external power source altogether.[156]

Two research teams are developing an electric TAH under a contract program established by the National Heart, Lung, and Blood Institute in 1988.[157] The Abiomed

TAH

Figure 19-5 The completely implantable electric motor-driven artificial heart being developed at The Pennsylvania State University. The artificial heart is positioned within the pericardium. The implanted controller and rechargeable reserve battery are powered by an external battery pack. Energy passes from the superficial primary coil to the subcutaneous secondary coil using inductive coupling (TETS). Air displaced from the blood pump housing enters the intrathoracic compliance chamber. Air that diffuses out of the compliance chamber over time is replenished using the subcutaneous access port. SVC=superior vena cava, PA=pulmonary artery, Ao=aorta. (From Corry DC, Richenbacher WE: Mechanical circulatory support: Past, present and future. Surgical Rounds 21:426, 1998.)

(Abiomed, Inc., Danvers, MA) is an electrohydraulically actuated device capable of providing a cardiac output in excess of 10 liters/min.[158] [159] An atrial flow balancing chamber is used to control the left-right blood flow balance.[160] Preclinical device testing is in progress with the expectation that the device will be implanted clinically within the next year.

The Pennsylvania State University/Benecor Heart Systems (Benecor Heart Systems, Inc., Ann Arbor, MI) TAH employs a dual pusher plate rollerscrew energy converter.[161] Left-right output balance is achieved with an implanted control algorithm that adjusts the left pump diastolic fill time and speed of systole, to just barely allow complete left pump filling while maximizing pump rate.[151] Extensive mock loop testing is being performed at this time as required by the FDA before clinical trials. The completely implanted system has been tested in vivo in 5 acute and 37 chronic studies.[162] The blood pump has now functioned in a calf for over 1 year without evidence of thromboembolic complications.

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Chapter 20 - Heart and Heart-Lung Transplantation

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Although cardiac transplantation in humans was first carried out in 1967, it is only since the early 1980s that it has been established as an accepted treatment for end-stage heart disease. The advances in immunosuppression and management that have made this possible also have led to successful heart-lung and lung transplantation. The increasingly widespread application of thoracic organ transplantation has brought this therapy to many centers around the world and to an ever-increasing patient population.

The Registry of the International Society for Heart Transplantation in 1999 listed a cumulative total of 48,541 cardiac transplantation procedures performed in 304 transplant centers.[1] The expansion of heart transplantation is emphasized by the fact that before 1980, fewer than 360 transplantations had been performed. The 30-year cardiac transplantation experience with approximately 1000 patients at Stanford University was reviewed and published.[2] The management philosophies and strategies discussed in this chapter are based in part on this experience.

HISTORY

There are several mentions of heart transplantation in ancient Chinese mythology and biblical reference, but not until the pioneering work of Alexis Carrel at the beginning of the 20th century did surgeons have the ability to transplant organs such as the heart.[3] In a number of imaginative experiments, Carrel demonstrated that a heart could be transplanted and resume functioning in the new host. Carrel not only transplanted hearts but also suggested and performed the en bloc transplantation of heart and lungs,[4] both of these procedures being heterotopic transplants into the necks of recipient dogs.

With the advent of techniques for successful cardiac surgery in the 1950s, major attention was finally directed to the problem of transplantation of the heart in the chest in the normal, or orthotopic, position. The current most commonly used surgical technique for heart transplantation originated with the work of Lower and Shumway in 1959.[5] A number of important questions about transplants, including protocols for immunosuppression,[6] correlation of the surface electrocardiogram with allograft rejection,[7] and reversal of these changes with augmented immunosuppression, were subjects of early laboratory study. Despite this prior laboratory work, many were surprised when the first human heart transplant was performed by Christiaan Barnard in Capetown, South Africa, in December 1967.[8] This transplant initiated a great amount of interest at other centers around the world, and 170 transplants were performed by 65 surgical teams between December 1967 and March 1971. The 1-year survival was only 15 percent, and because of this, enthusiasm for heart transplantation rapidly waned by the end of 1971.

Only at Stanford University and the Medical College of Virginia did surgical teams continue with programs in heart transplantation. Working virtually alone through the decade of the 1970s, these investigators refined recipient selection criteria,[9] saw the development of the transvenous endomyocardial biopsy for diagnosing rejection,[10] developed rabbit antithymocyte globulin as an effective treatment of acute rejection,[11] and defined many of the late posttransplant complications and management principles.[12]

IMMUNOSUPPRESSIVE THERAPY.

Widespread application of heart transplantation depended on the development of better immunosuppressive therapy (see pp. 178 , 179 , and 180). This goal was reached with the discovery that cyclosporin A (cyclosporine), a novel cyclic undecapeptide of fungal origin, could selectively block the effect of interleukin 2 (IL-2) in stimulating T cells.[13] [14] [15] [16] [17]

Heart and lung transplantation has been extended to a large number of additional recipients, including neonates with hypoplastic left heart syndrome, the elderly (age 60 to 70), and patients with primary lung disease, such as emphysema, cystic fibrosis, or primary pulmonary hypertension.

In 1999, there were 304 centers performing cardiac transplantation worldwide. Experience has shown that a successful program depends on both institutional commitment and participation of many professional groups within the institution that must work together in caring for patients. Careful attention to detail in organizing a transplant program is crucial in obtaining and sustaining good outcomes in transplant recipients.

The development of an effective cardiac transplant program requires careful organization and cooperation from both clinical and nonclinical personnel. Some but not all states require a certificate of need to initiate a new program of heart transplantation. The National Organ Transplantation Act of 1984 established certain minimum criteria for transplant programs to enroll in the nationwide computerized matching system.[18] To encourage excellent patient care and to discourage transplantation in centers with suboptimal results, the act established the United Network for Organ Sharing (UNOS), with membership limited to those centers that perform a minimum of 12 transplant procedures per year and that obtain a 1-year survival rate of at least 70 percent. In addition to these performance criteria, the center must have adequate operating room facilities and trained physicians and nursing personnel and must be a participating member in a local organ procurement organization. The program must have established protocols and procedures for the selection of patients, the evaluation and distribution of donor organs, postoperative management, and long-term follow-up. Both surgeons and physicians involved in the care of patients must meet certain criteria in terms of training and prior experience. The ability of an individual center to obtain funding from Medicare depends on similar criteria.[19]

RECIPIENT SELECTION

With improved outcomes in both quality of life and percentage of patients surviving, cardiac transplantation has become accepted therapy for many patients with end-stage

Figure 20-1 Adult heart transplantation indications. (From Hosenpud JD, Bennett LE, Keck BM, et al: The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report--1999. J Heart Lung Transplant 18:613, 1999. Reprinted with permission from Elsevier Science Ltd.)

heart disease. A fairly rigid selection process is required in order to obtain excellent results in individual patients. Although a tendency has been to relax these criteria in an effort to extend the benefits of transplantation to a larger number of patients, this has heightened the problem of donor scarcity. The number of potential recipients rises

exponentially with an extension of the upper age accepted. The indications for heart transplantation are listed in Figure 20-1 . The most frequent indications are equally divided between ischemic heart disease and cardiomyopathy. Contraindications (Table 20-1) vary somewhat by program.

An important aspect of evaluation is a comprehensive psychosocial evaluation by a clinical social worker or psychologist. Patients' ability to follow a complex medical regimen is extremely important, as is family support necessary to help patients through numerous medical procedures and evaluations and to maintain the essential medical regimen after transplantation.

All conventional medical or surgical therapies should be used before consideration of transplantation. Evaluation might reasonably include endomyocardial biopsy to rule out other treatable causes of cardiomyopathy, especially for patients without ischemic heart disease. Unsuspected sarcoidosis or myocarditis is occasionally detected and might respond favorably to an alternative therapy, and some patients with recurrent life-threatening arrhythmias may be best treated initially by placement of an automatic implantable cardiac defibrillator.

Although it may be easy to identify the most severely ill

TABLE 20-1 -- CONTRAINDICATIONS TO HEART TRANSPLANTATION

Advanced age (>70 yr)
Irreversible hepatic, renal, or pulmonary dysfunction
Severe peripheral vascular or cerebrovascular disease
Insulin-requiring diabetes mellitus with end-organ damage
Active infection
Recent cancer with uncertain status
Psychiatric illness, poor medical compliance
Systemic disease that would significantly limit survival or rehabilitation
Pulmonary hypertension with pulmonary vascular resistance
>6 Wood units or 3 Wood units after treatment with vasodilators

patients with a poor prognosis for 6-month survival, for a large group of patients with symptomatic cardiomyopathy and ominous objective findings (ejection fraction <20 percent, stroke volume
40 ml, severe ventricular arrhythmias), timing may be somewhat difficult. A further consideration may be the quality of life, which is a judgment made by patients and the physicians caring for them. This comes into play in patients with intractable angina and coronary vessels that cannot be bypassed.

Clinical Considerations

The selection of a candidate for heart transplantation ultimately results from a clinical assessment that a patient free of established contraindications (see Table 20-1) suffers severe cardiac disability refractory to expert management. The pathophysiology usually encompasses congestive heart failure but is occasionally dominated by recurrent lethal

arrhythmias or intolerable ischemic symptoms. Consideration based solely on a low (<20 percent) ejection fraction has become less reliable since the introduction of aggressive vasodilator therapy. Some patients with extensive left ventricular dysfunction are remarkably symptom free. Even symptomatic patients, when using the appropriate selection criteria, can experience 1- and 4-year survivals of 98 and 84 percent when treated medically,[20] and patients who are removed from the list of candidates because of clinical improvement have been shown to have similar symptoms and survival data as those going on to transplantation.[21]

INITIAL SCREENING.

The fine line between medical therapy and transplantation is often drawn with the help of physiological data that numerous studies have proved to be adequate predictors of short- and long-term survival. Several authorities have noted the value of peak exercise oxygen consumption (dot(V)$_{O_2}$) and cardiac output response to exercise in delineating which patients should be listed for transplantation.[22] [23] [24] [25] In considering peak dot(V)$_{O_2}$, however, it has been noted that many patients may terminate exercise for reasons other than a cardiopulmonary limitation (e.g., leg fatigue). As such, provided that the patient has reached the anaerobic threshold, there is near consensus that either a peak dot(V)$_{O_2}$ of less than 15 ml/kg/min or less than 55 percent of predicted peak dot(V)$_{O_2}$ should result in strong consideration of listing for transplantation. A peak dot(V)$_{O_2}$ of less than 12 ml/kg/min augurs a very poor 1-year survival rate and warrants listing in nearly all contraindication-free cases.[26]

UPPER AGE LIMIT.

One of the most controversial aspects of patient selection is the upper age limit for cardiac transplantation. The initial Stanford University criteria considered an upper age limit of 50 years. This was modified to include patients older than 55 and then up to age 60 during the era of improving results because of cyclosporine therapy in the early 1980's. Sufficient additional experience has now been reported in patients older than 60 to indicate that a strict chronological age criterion is not appropriate.[27] [28] In fact, one study used organs considered marginal for an alternate list of patients who would not have otherwise been considered for transplantation owing to age or need for a third transplant. The investigators found no significant difference in early and medium-term outcomes in comparison with patients on the standard list.[29] At Stanford, 65 years currently is considered the general upper age limit, although successful cardiac transplantations have been performed in patients up to 70 years old. Some evidence has suggested that older patients experience less rejection than younger patients.[30] Patients older than 50 years may warrant additional screening for comorbid conditions, and the concurrent relative contraindications of diabetes or other systemic disease, such as chronic pulmonary disease, probably would eliminate most patients older than 60 years as potential candidates.

PULMONARY VASCULAR DISEASE.

This is an important consideration. Orthotopic cardiac transplantation requires that the pulmonary vascular resistance be low, so that the normal right ventricle of the donor heart can adequately support the recipient's circulation after transplantation. A great deal of controversy has developed over the optimal measure of pulmonary vascular resistance. Most programs use the measurement of the traditional Wood unit and limit the value to 6 units or less at rest or less than 3 with maximal vasodilation. Other centers use the pulmonary vascular resistance index (Wood units × body surface area) or transpulmonary pressure gradient (mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) of 15 mm Hg or less.[31] Whatever measure of resistance is used, in those patients with values toward the upper limits, it is imperative to demonstrate in the catheterization laboratory that the resistance can be manipulated with oxygen, vasodilators, inhaled nitric oxide, or intravenous or inhaled prostacyclin.[32] [33] [34] If the pulmonary vascular resistance measurements remain elevated, strong consideration should be given to heart-lung transplantation. Because patients may remain on a waiting list for more than 6 months, repeat cardiac catheterization may be necessary semiannually to determine if the pulmonary vascular resistance has increased. Significantly elevated pulmonary vascular resistance and right-sided heart failure remain problems after orthotopic cardiac transplantation and are major causes of early postoperative mortality.

COEXISTING DISEASES.

Patients with involvement of other organs that precluded selection in the past but that now respond to transplantation may be considered candidates for *dual organ transplantation.* In addition to heart-lung, these include heart-kidney (notably for retransplantation in heart transplant recipients who have developed cyclosporine nephrotoxicity) and heart-liver (for homozygous familial hypercholesterolemia). Dual organ candidacy does not change a patient's status or position on the waiting list, but when patients become eligible for a heart or liver based on standard criteria, the second required organ may be allocated from the same donor.[35] The ethical dilemma of improving one life instead of two remains unresolved.

Patients with infective endocarditis (without metastatic infection) and patients with malignancy without evidence of recurrence (often with anthracycline cardiomyopathy) have successfully received heart transplants. All patients, however, should have at least several stool guaiac tests; mammograms, and Papanicolaou (PAP) smears, or prostate-specific antigen tests; and chest radiographs, to screen for cancer. Obesity (>140 percent of ideal body weight), which carries risks of worse graft coronary disease, hypertension, and wound infection, is a relative contraindication. Osteoporosis may contribute to spontaneous fractures associated with prednisone use, so candidates at risk should be evaluated with a bone density study. Sarcoidosis and some types of muscular dystrophy are considered a contraindication to transplantation. Systemic amyloidosis, because of its frequent multiorgan involvement as well as documented recurrence in the allograft, remains an unlikely condition for permitting transplantation at

most centers.

All programs inevitably exercise some subjectivity in the selection process, determined by the prior experience of the transplant team with the many clinical, physiological, and social variables involved. Although the evaluation of potential candidates for cardiac transplantation is difficult, these established criteria have led to certain predictable outcomes in terms of quality of life and actuarial survival. Deviations from these protocols usually produce less favorable results. As with any medical or surgical procedure, the final decision ultimately rests with the patient, in accordance with the concept of informed consent.

TREATMENT OF PATIENTS AWAITING TRANSPLANTATION

Because a number of patients are awaiting transplantation at any point in time, their management is important. The UNOS patient waiting list for needed organs in October 1998 totaled nearly 4000 patients awaiting heart transplantation worldwide.[26] Because approximately 3400 procedures were performed per year during 1997 to 1999, a number of awaiting recipients will not survive to receive a needed organ. Most centers experience between 10 and 20 percent mortality of patients on the waiting list. Worldwide heart-lung transplantations, after peaking at 241 in 1990, have declined to an average of 130 per year 1997 to 1999, while lung transplantations have steadily risen and stabilized at an annual rate of close to 1200.[1]

The management of end-stage congestive heart failure is described in Chapter 18 . Although digitalis remains the only generally available oral inotropic agent, the use of intravenous low-dose dopamine or dobutamine has been a helpful tool for treating some of these patients.[36] Some controversy surrounds the use of outpatient inotrope infusion, because some studies have noted increased mortality,[37] especially with higher doses.[38] More recent reports, however, have demonstrated safe and effective use of these agents.[39] [40] [41] With brief hospitalizations for hemodynamic monitoring to optimize use of vasodilators, diuretics, and intravenous inotropes, patients often sustain improvement lasting for weeks or even months. The use of anticoagulants as prophylaxis against systemic or pulmonary thromboembolism is practiced routinely at some centers. Finally, beta blockers have produced hemodynamic and symptomatic improvement in chronic heart failure and have been demonstrated to decrease mortality in patients who are also taking digoxin, diuretics, and an angiotensin-converting enzyme (ACE)-inhibitor (see Chap. 18).[42]

MECHANICAL DEVICES FOR BRIDGING.

Patients in whom conventional medical therapy fails may require intraaortic balloon counterpulsation or possibly a mechanical assist device for bridging to transplantation (see Chap. 19). The major devices currently being used all have been recently reviewed and include the total artificial heart (TAH, CardioWest, Tucson, AZ),[43] [44] Thoratec (Thoratec Laboratories, Pleasanton, CA),[45] TCI Heartmate (Thermo Cardiosystems, Woburn, MA),[46] [47] [48] [49] and Novacor Left Ventricular Assist System (Baxter Healthcare, Oakland, CA).[50] [51] In addition, the Arrow Lionheart and the Abiomed Abiocor will soon be clinically available as destination therapy for patients who

are not candidates for cardiac transplantation. More than 2000 ventricular assist devices have been implanted,

TABLE 20-2 -- ADULT THORACIC TRANSPLANTATION CANDIDATE STATUS

STATUS	CRITERIA
1A	Inpatient+ MCS (VAD 30 d; TAH; IABP; ECMO) *or* MCS >30 days+significant device-related complications *or* Mechanical ventilation *or* Continuous infusion of one high-dose or multiple IV inotropes*or* Life expectancy <7 d without transplant
1B	VAD>30 d *or* Continuous infusion of IV inotropes *or* Justified exceptional case
2	Does not meet status 1A or 1B criteria
7	Temporarily unsuitable to receive organ

MCS=mechanical circulatory support; VAD=ventricular assist device; TAH=total artificial heart; IABP=intraaortic balloon pump; ECMO=extracorporeal membrane oxygenation; IV=intravenous.

and more than 500 have been used as a bridge to transplantation.[52] Although bleeding and thromboembolism remain important complications, 69 percent of intention-to-bridge patients go on to successful transplantation. For patients requiring only left-sided support, the short- and long-term transplantation survival is comparable to that of nonbridged transplant recipients. Over time, more compact systems for outpatient management have developed, and the use of all of these devices as portable bridges to transplantation, to recovery, or as permanent replacement therapy has become a more real possibility.

Once selected, patients are categorized on the basis of size, ABO blood group, time on the waiting list, and clinical status. Clinical status divisions include IA, IB, 2, and 7 and are described in Table 20-2 . Patients are "delisted" if they improve or if they suffer complications (e.g., cerebral or pulmonary embolism) or superimposed illnesses (e.g., infections, gastrointestinal bleeding), which increase the risk of operation and immunosuppression or which compromise rehabilitation or survival. They are reactivated when clinically appropriate. Current UNOS policy allows for all time accumulated on the waiting list to be held forever by a patient and to be accrued if the

patient is delisted and reactivated.

EVALUATION AND TREATMENT OF THE HEART DONOR

The factor limiting the number of heart transplant performed is the availability of donor organs. Thus, it is imperative to obtain as high a percentage of potential donor organs as possible by increasing the donation rate and to consider all donor organs that might possibly be suitable for transplantation. Cardiologists frequently are asked to take part in the donor evaluation process so that the adequate function of the graft can be predicted before transplantation.

Brain death has been accepted as the legal definition of death throughout the United States.[53] The diagnosis should not involve physicians caring for a potential candidate, and it requires the absence of hypothermia (core temperature >32.5°C) or drugs capable of altering neurological or neuromuscular function.[54]

The specific neurological catastrophe that has resulted in brain death may include blunt traumatic injury to the head, intracranial hemorrhage, or penetrating traumatic injury. The characteristics of all organ donors are listed in Table 20-3 . Heart and heart-lung transplant donor criteria once were very selective. The upper age limit was usually 35 years, and there were a number of other criteria. With the need to increase the number of transplants, these criteria have been modified. Most centers evaluate any potential donor up to as old as 55 years of age. Especially with older or suboptimal donors, a careful cardiac history must be obtained from the next of kin and adequate cardiac function ensured, including potential evaluation with coronary arteriography for men older than 40 or women older than 45 years. Sweeney and colleagues reported on the use of hearts from donors who did not meet the standard criteria.[55] Recipients received grafts from older donors (> age 40) or from patients with a history of prolonged cardiac arrest or septicemia. Their results indicate that selective use of such donors is possible, with reasonable outcomes. In addition, Drinkwater and associates[56] demonstrated similar early and late outcomes when using organs with a mean donor age of 51 years compared with younger donors. In some cases, the older donor organs simultaneously received bypass grafts, and incidence of rejection, infection, and graft coronary artery disease were similar between the two groups.[56] The most recent Registry of the International Society of Heart and Lung Transplantation, however, includes increasing donor age among risk factors for 1- and 5-year mortality and demonstrates a significant interaction between ischemic time and donor age.[1] Hearts from older donors should, whenever possible, be reserved for older recipients because of inherent loss of function with age.

The evaluation of potential donors includes obtaining adequate background data, a physical examination, a 12-lead electrocardiogram, and an echocardiogram. Brain death and increased intracranial pressure often result in nonspecific ST and T wave changes. These also may be seen with hypothermia. The echocardiogram has assumed an even greater role in evaluating cardiac function. This evaluation should be done at a time when doses of intravenous inotropic agents have been lowered to as low as is compatible with adequate blood pressure and cardiac output, and after adequate fluid

resuscitation.

Current matching criteria of donors and recipients include only ABO compatibility and appropriate size match. A prospective specific crossmatch between donor and recipient is performed only where recipients have been identified as having more than 5 percent of reactivity when evaluated against a panel of random donors. A recent large multicenter retrospective analysis showed modest predictive value of HLA mismatch on survival of cardiac allografts.[56A]

With respect to size, fairly wide limits are acceptable, although donors who weigh less than 80 percent of the recipient's weight should not be accepted for those patients who have higher levels of pulmonary vascular resistance.

Vital signs in patients with brain death frequently are unstable, and close attention to fluid balance is required, owing to diabetes insipidus. This necessitates monitoring of central venous pressure and adequate fluid resuscitation, administration of vasopressin, and replacement of fluid lost

TABLE 20-3 -- CALIFORNIA TRANSPLANT DONOR NETWORK DONOR CHARACTERISTICS (1995-1998)*

CAUSE OF DEATH	NUMBER OF DONORS	%
Intracranial bleed	356	44.3
Motor vehicle accident	144	17.9
Gunshot wound	116	14.4
Closed head injury	87	10.8
Anoxia	68	8.5
Other medical	33	4.1
Total	804	100

*Mean age 36.7 years (0.3-78.0); 59.5% male, 40.5% female.

through urine output. If hypotension occurs despite adequate volume replacement, a vasopressor is infused. Dopamine is the standard inotropic agent used, but some donors are better maintained on an alpha-adrenergic agent.

Donor evaluation currently also includes various serology results. These are for human immunodeficiency virus (HIV), hepatitis B antigen, cytomegalovirus (CMV), and toxoplasmosis. The finding of HIV antibody rules out a potential donor, and the presence of CMV antibody may disqualify a potential heart-lung donor for a

CMV-negative recipient at some centers. Present consensus also excludes donors with carbon monoxide-hemoglobin levels above 20 percent, arterial oxygen saturation less than 80 percent, previous myocardial infarction, or severe coronary or structural heart disease. The presence of metastatic malignancy is also an exclusion at many centers, although those with primary brain tumors and skin cancers may be excepted. Relative contraindications include sepsis, prolonged (>6 hours) severe (<60 mm Hg) hypotension, noncritical coronary disease, hepatitis B surface antigen or hepatitis C antibodies (unless the organs are destined for recipients with the same serology), repeated resuscitations, severe left ventricular hypertrophy, or the need for inotropic support (dopamine >20 mug/kg/min) for 24 hours.[53]

Distant procurement of the heart and heart-lung for transplantation is now routine in almost all transplant centers. The technique for heart preservation remains simple, with cold crystalloid or blood cardioplegia infusion combined with topical cold for extended preservation. Average ischemic times are between 3 and 4 hours, with excellent function in most cases. Data from the Registry of the International Society for Heart Transplantation show some relation between ischemic time and survival, although most experienced centers see no particular relation for up to 6 hours of ischemia.[1]

Techniques for distant heart-lung procurement and preservation of isolated lung grafts include flush solutions in the pulmonary artery with potent pulmonary vasodilators,[57] the use of cold blood for flush, [58] placing the donor on cardiopulmonary bypass,[59] and the use of an autoperfusing heart-lung preparation for maintaining the organs at normothermia in a working state.[60] Again, distant procurement is limited to 6 hours or less, with most procurements having an ischemic period between 3 and 4 hours.

This length of allowable ischemic time has usually kept procurement between centers of not more than 1000 miles distance. The tendency to use donor organs within the local region also has limited times.

Allocation of organs begins with status 1 patients in ever-widening zones. It is offered first to candidates in the local Organ Procurement Organization (OPO) and then to patients within a 500-mile and then 1000-mile radius. If no recipient is found, the process is repeated for the status 2 list.

Regional OPOs are available to assist doctors and hospitals with all medical and legal considerations involved in organ donation. A listing of OPOs with contact information can be found via the Association of Organ Procurement Organizations (website *www.aopo.org*).

OPERATIVE TECHNIQUE

The current technique for orthotopic heart transplantation was described in 1960 by Lower and Shumway.[5] The method involves retaining a large portion of the posterior wall of the right and left atrium in the recipient and implanting the donor heart with relatively long suture lines in the atria, together with direct end-to-end anastomoses of the aorta and the pulmonary artery. Modification of this technique with venous anastomoses at the level of the cavae and the pulmonary veins permits a more

physiological atrial contribution to ventricular fitting and causes less distortion of the mitral and tricuspid annuli, with less tendency to atrioventricular valve regurgitation and rhythm disturbances.[61] [62] In addition, Blanche and colleagues demonstrated significantly greater short- and long-term survival using this total reimplantation technique.[63] This technique is reviewed by Trento and associates[64] and is illustrated in Figure 20-2 .

Many types of congenital anomalies have been dealt with during cardiac transplantation. For example, absence of the right superior vena cava or persistent left superior vena cava can easily be accommodated.[65] Corrected transposition of the great vessels requires extra length of the donor aorta and pulmonary artery.[66]

The operation is performed by way of a median sternotomy incision, with routine cannulation of the aorta and both venae cavae. Cardiopulmonary bypass is usually performed with moderate hypothermia of between 28° and 30°C. The implantation procedure usually requires from 45 to 80 minutes, and after careful attention to de-airing maneuvers and resuscitation of the heart, cardiopulmonary bypass is weaned. The incision is closed after placement of temporary pacing wires and chest drainage catheters.

PHYSIOLOGY OF THE TRANSPLANTED HEART

The transplanted heart initially is completely denervated. It is generally believed that partial reinnervation of the transplanted

Figure 20-2 Total heart replacement by pulmonary venous anastomoses on right or left and caval anastomosis at the superior and inferior vena cava. Aorta and pulmonary artery attached as in the previous biatrial transplantation technique.

heart begins within 1 year. Evidence exists for both sympathetic[67] [68] and parasympathetic[69] function, but most authorities agree that these phenomena are incomplete and variable from patient to patient, and the data are less clear for the parasympathetic system in particular.[70] [71] Various studies document the transplanted cardiac response to exercise or stress, which is less than normal but adequate for almost all activities (Fig. 20-3) . The heart rate accelerates slowly during the first stages of exercise, accompanied by an immediate increase in filling pressures as a result of augmented venous return from exercising muscles and decreased compliance. The latter may result from rejection, arteriopathy, arterial hypertension, small donor heart size, or cyclosporine use. Atrial contribution to end-diastolic filling is compromised by the dissociation between host and donor atrial contractions. The midatrial anastomosis may partially deform the atrioventricular annuli, leading to mitral and tricuspid regurgitation. In the absence of hypertension or rejection, ventricular ejection fractions

are normal to high.[72] [73]

Incomplete innervation abolishes or blunts the heart's anatomically mediated reflexes while enhancing its sensitivity to circulating norepinephrine. The resting heart rate is generally higher owing to absence of vagal tone. Respiratory sinus arrhythmia and carotid sinus-mediated reflex bradycardia are absent. The more gradual increase of heart rate with exercise parallels the rise in circulating catecholamines, which also leads to an increase in the inotropic state of the myocardium. With augmented venous return and higher filling pressures, the stroke volume increases, contributing to the necessary increase in cardiac output during exercise.

Figure 20-3 The relationship between cardiac output (C.O.) and oxygen consumption in seven patients 1 year after cardiac transplantation (*dots and solid line*) and in 27 normal subjects ages 14 to 41 (*dashed line*). (From Hosenpud JD, Novick RJ, Breen TJ, Daily OP: The Registry of the International Society for Heart and Lung Transplantation Eleventh Official Report--1994. J Heart Lung Transplant 13:561, 1994. Reprinted with permission from Mosby-Year Book.)

Cardiac denervation results in an increase in beta-adrenergic receptor density.[74] In laboratory animals, denervation results in increased responsiveness to noradrenaline and isoproterenol. This supersensitivity appears to be due both to upregulation of beta receptors and to a loss of norepinephrine uptake in postganglionic sympathetic neurons. In a study by Borow and associates, the heart rate response to dobutamine was compared with that of normal subjects pretreated with atropine and found to be greater in the group of transplant recipients.[75] In other studies, infusions of isoproterenol produced a greater increase in heart rate than in normal controls.[76] This slight supersensitivity of the chronically denervated heart may be important in maintaining the necessary inotropic and chronotropic response to exercise and other stresses. All of the mechanisms underlying this supersensitivity have not been fully defined. Denervation of the allograft also blunts systemic responses to volume changes. Failure to reduce sympathetic tone during hypervolemia may contribute to hypertension and persistence of edema,[77] and blunted rate response to hypovolemia may predispose to orthostatic hypotension.

Arrhythmias are uncommon. Sinus node dysfunction occurs in 10 to 20 percent of patients in the immediate perioperative period but is readily repaired in most cases with theophylline.[78] When this falls, permanent pacing may be necessary. With the adoption of the bicaval anastomosis technique there has been a trend toward decreased requirements for permanent pacemaker insertions.

Pronounced sinus tachycardia (<120) at rest in an a febrile patient without obvious cause suggests physiological distress and warrants a search for hypovolemia, hypoglycemia, rejection, silent myocardial infarction, pulmonary emboli, adrenal insufficiency, tamponade, or abdominal catastrophe masked by corticosteroids.

Atrial arrhythmias--particularly atrial flutter--may signal rejection and are a sufficient indication for heart biopsy. Ventricular arrhythmias are uncommon except with ischemic

disease or severe rejection. Ventricular fibrillation is often refractory to resuscitation.

With respect to the coronary circulation, the coronary vasodilator reserve of the transplanted heart is normal in the absence of rejection, hypertrophy, or regional wall motion abnormalities. During periods of acute rejection, coronary flow reserve is impaired.

EARLY POSTOPERATIVE RECOVERY

Much of the early postoperative treatment is similar to that of other patients recovering from cardiac surgical procedures. Strict isolation precautions are no longer considered mandatory. Patients are weaned from the ventilator and from inotropic drugs, as tolerated. Mobilization and use of physical therapy are begun as soon as tolerated.

RIGHT VENTRICULAR FAILURE.

Because the pulmonary vascular resistance of the recipient may be elevated, acute right ventricular failure is a frequent cause of early morbidity and mortality. The normal donor right ventricle may be unable to meet the elevated resistance, and there may be a high degree of both pulmonary and tricuspid valve regurgitation in the early posttransplant period.[79] This problem may be exacerbated by a relatively long ischemic time or by a donor heart somewhat smaller than that of the recipient. Therapy for right ventricular failure has included ventricular assist devices,[80] [81] intravenous or inhaled prostacyclin, inhaled nitric oxide,[82] [83] and extracorporeal membrane oxygenation. [84] [85]

IMMUNOSUPPRESSION.

The most important feature of early management is the institution of the immunosuppressive regimen, which will be continued throughout the patient's lifetime. Numerous protocols exist for maintenance immunosuppression and evolve continually. Most patients receive cyclosporine in combination with several other medications. The most common protocol currently involves triple-drug therapy of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil (MMF), and prednisone. They are usually given in higher doses in the early posttransplant period, with weaning to lower and less toxic levels for long-term administration. A typical protocol for immunosuppression is shown in Table 20-4 .

Withdrawal or marked reduction of corticosteroids is of particular benefit in diabetic patients and in the presence of severe osteoporosis or aseptic necrosis of bone. In children, a corticosteroid-free regimen permits normal axial growth and prevents the development of the cushingoid features and acne that contribute to noncompliance in adolescents.[86]

Figure 20-4 represents an overview of the site and mechanism of action of immunosuppressive agents based

TABLE 20-4 -- IMMUNOSUPPRESSION FOR HEART TRANSPLANTATION PROTOCOLS

DRUG	EARLY	LATE
Methylprednisolone	500 mg IV intraoperatively then 125 mg IV q8hr×3	
OKT3 induction	5 mg/d IV×7	
Cyclosporine	6-10 mg/kg/d PO* or 0.5-2 mg/kg/d IV	3-6 mg/kg/d PO
or		
Tacrolimus (FK506)	0.15-0.30 mg/kg/d PO	0.15-0.30 mg/kg/d PO
Azathioprine	2 mg/kg/d PO	1-2 mg/kg/d PO
or		
Mycophenolate mofetil	3000 mg/d PO	3000 mg/d PO
Prednisone	1 mg/kg/d PO tapered to 0.4 mg/kg/d	0.1-0.2 mg/kg/d PO

*Omit if preoperative serum creatinine level is >1.5 mg/dl and use IV.

Or as modified by blood levels.

Omit if white blood count <4000/mm^3 .

on the immune response signals of antigen recognition, co-stimulation, and T-cell activation. Corticosteroids have many potential immunosuppressive effects, including suppressing activation of the transcriptional regulator nuclear factor kappa B (NF-kappaB). By regulating the promoter of the inhibitory factor intracellular kappa B (IkappaB) and increasing IkappaB levels, steroids reduce transcription of many genes involved in inflammation and immunity.[87] In addition, steroids can alter the transcription of some cytokine genes, inhibiting cytokine production.[88]

Cyclosporine binds to cyclophilin, which inhibits IL-2 expression by blocking calcium-dependent signal transduction via calcineurin. Cyclosporine also inhibits IL-2 receptor expression on T-helper and cytotoxic T lymphocytes. These two actions limit the differentiation into and proliferation of cytotoxic T lymphocytes. Although the advent of cyclosporine significantly improved transplantation outcomes, major toxicities

mandated the search for better agents. These toxicities include renal dysfunction, neurotoxicity, hypertension, gingival hyperplasia, hirsutism, and others. Renal dysfunction is the most frequent side effect, occurring in 40 to 70 percent of patients. The microemulsion formulation of cyclosporine, Neoral, has increased bioavailability and has more favorable pharmacokinetics.[89] [89A]

Tacrolimus (FK-506) also inhibits calcineurin but by forming a complex with an FK-binding protein distinct from cyclophilin. Randomized trials indicate that tacrolimus prophylaxis is comparable to cyclosporine in survival and incidence of rejection but may have more severe side effects, in particular nephrotoxicity and hyperglycemia.[89]

Azathioprine, one of the first agents used for immunosuppression, blocks proliferation of replicating cells, including lymphocytes, by inhibiting synthesis of inosinic acid, a precursor of purine synthesis. Although an effective component of triple-drug therapy together with cyclosporine and steroids, azathioprine can cause important side effects. These unwanted actions include hepatotoxicity and severe myelosuppression, especially in patients deficient in thiopurine methyltransferase, an enzyme important in azathioprine metabolism.[90]

MMF inhibits inosine monophosphate dehydrogenase and guanylate synthetase, enzymes in the de novo pathway of purine synthesis. Because proliferating B and T lymphocytes rely primarily on this pathway for purine synthesis, MMF more specifically inhibits cells of these lineages. This drug may also reduce recruitment of monocytes and lymphocytes by reducing guanosine triphosphate (GTP) production, which slows the transfer of saccharide moieties to the glycoproteins expressed on some adhesion molecules.[91] Comparison studies have shown that MMF prophylaxis reduced

Figure 20-4 Overview of the site and mechanism of action of immunosuppressive agents based on signals required for the immune response. APC, antigen-presenting cell; ATGAM, antithymyocyte gamma-globulin; DSG, 15-deoxyspergualin; TCR, T-cell receptor; IL-2R, interleukin-2 receptor; CyA, cyclosporine; FK506, tacrolimus; NFAT, nuclear factor of activated T cells; TOR, target of rapamycin; MMF, mycophenolate mofetil; Aza, azathioprine. (From Halloran PF, Miller LW: In vivo immunosuppressive mechanisms. J Heart Lung Transplant. 15:967, 1995. Reprinted with permission from Elsevier Science Ltd.)

1-year mortality and the need for antirejection therapy but also was associated with an increased incidence of opportunistic infections compared with azathioprine.[92] Additional studies have indicated that MMF causes little renal, hepatic, and bone marrow toxicity. The most common side effects are gastrointestinal and include nausea, diarrhea, and abdominal cramping.[91]

OKT3 is used as induction therapy for heart transplantation recipients at Stanford University and has also been used as treatment for severe rejection. This monoclonal

murine antibody against the CD3 antigen causes T-lymphocyte cell lysis, which can cause severe systemic effects due to release of multiple cytokines. Premedication including acetaminophen, diphenhydramine, and hydrocortisone can ameliorate these effects. OKT3 induction can be advantageous, especially in cases of critically ill patients with renal dysfunction, by allowing for a delay in the initiation of cyclosporine therapy.

Interleukin-2 receptor antagonism with a monoclonal antibody has shown reduction in the frequency and severity of rejection in early post-cardiac transplantation.[91A]

ACUTE REJECTION

Immunosuppression to prevent allograft rejection continues from the time of implantation. Although a number of strategies, including those described earlier, are being developed to enhance immunosuppression and to maximize development of tolerance in recipients, virtually every patient experiences some acute allograft rejection during the first transplant year.

According to a report from the Cardiac Transplant Research Database, risk of acute rejection in patients receiving heart transplants in 30 institutions from January 1990 to July 1993 peaked at approximately 1 month after transplantation then rapidly decreased.[93] That study found a mean of 1.25 episodes of rejection per patient during the first year, 0.18 episodes per patient in the second year, and 0.13 and 0.02 episodes per patient in the third and fourth years, respectively. Risk factors for recurrent rejection included female gender, black race, recipient positive CMV serology and CMV infection, shorter time since previous rejection, and more prior rejection episodes.

Acute rejection continues to contribute significantly to early morbidity and mortality of heart transplant recipients. Detection and treatment of acute rejection remain crucial aspects of transplant management.

Detection of Acute Rejection

NONINVASIVE TECHNIQUES

The most reliable and frequently used technique to assess allograft rejection is endomyocardial biopsy. Many less invasive modalities have been suggested but have yet to be developed for use in humans. Noninvasive techniques reported to have clinical potential include intramyocardial electrograms, serum troponin measurement, radionuclide scanning, and antimyosin antibody binding.

HIGH-RESOLUTION INTRAMYOCARDIAL ELECTROGRAMS.

In a multiinstitutional U.S. study, measurement of the ventricular evoked response during ventricular pacing using epimyocardial leads and high-resolution telemetry pacemakers allowed detection of significant rejection, with a negative predictive value of 98 percent.[94] In another study of pediatric patients, intramyocardial electrograms successfully indicated acute rejection and allowed for improvement in long-term

survival.[95]

SERUM TROPONIN.

Cardiac troponin T is detectable in the circulation only after myocyte damage, which is likely to occur in acute rejection. Dengler and colleagues demonstrated that serum troponin T concentrations increased in parallel with severity of graft rejection in endomyocardial biopsy samples and that severe rejection would have been detected before the development of clinical symptoms.[96]

RADIONUCLIDE SCANNING.

Technetium 99m-labeled annexin V has been shown to concentrate at sites of apoptotic cell death and to correlate with acute rejection in animal studies.[97] [98] [99] [99A] A multiinstitutional clinical trial using annexin V imaging to detect acute heart transplant rejection in humans is currently under way.

ANTIMYOSIN ANTIBODIES.

These monoclonal Fab fragments directed against myosin can be used to evaluate myosin exposure during the cell death associated with cardiac rejection.[100]

Endomyocardial Biopsy

With the inadequacy of these noninvasive tests, the endomyocardial biopsy remains the standard method for the detection of rejection and its effective treatment with augmented immunosuppression. The technique was introduced for cardiac transplantation by Caves and associates in 1973.[10] The relatively diffuse interstitial infiltrate associated with rejection renders the focal biopsy a useful reflection of events throughout the myocardium.[101] Although an invasive procedure, endomyocardial biopsy seems relatively well tolerated and can be performed sequentially. Complications are usually mild and include pneumothoraces, transient rhythm disturbances, a rare instance of myocardial perforation, or tricuspid regurgitation due to chordal interruption.

A study at Stanford University showed that severe tricuspid regurgitation can occur after repeated biopsies and entails substantial morbidity. In this series, 6 of 336 patients required tricuspid valve replacement.[102] Because endomyocardial biopsy is a percutaneous and transvenous technique, it requires only local anesthetic. The procedure is rapidly performed, usually through the right internal jugular vein, and can be repeated on many occasions through the same access site. It can also be accomplished from the left jugular vein, the subclavian vein, or the femoral veins, as shown in Figure 20-5 . Fluoroscopy is usually used, although

Figure 20-5 Positioning of the bioptome for endomyocardial biopsy. (1) Bioptome is inserted with the tip pointed toward the lateral wall of the right atrium. (2) At the level of the mid-right atrium, the bioptome is

rotated anteriorly about 180 degrees and is advanced through the tricuspid valve apparatus toward the right ventricle. (3) The bioptome is advanced to the interventricular septum with the jaws opened. (From Baughman KL: History and current techniques of endomyocardial biopsy. *In* Baumgartner WA, Reitz BA, Achuff SA [eds]: Heart and Heart-Lung Transplantation. Philadelphia, WB Saunders, 1990.)

TABLE 20-5 -- RECOMMENDED FREQUENCY OF ENDOMYOCARDIAL BIOPSY FOR ROUTINE MONITORING OF HEART TRANSPLANT REJECTION*

TIME AFTER TRANSPLANT	INTERVAL	NO. BIOPSIES
Day 14	First biopsy	1
1-4 wk	Every week	3
5-12 wk	Every 2 wk	4
3-6 mo	Every mo	3
6 mo to indefinite	Every 3 mo	

*Rebiopsy if indeterminate and 10 d after conclusion of rejection treatment.

the use of echocardiography for bioptome guidance is increasing.

To get an adequate sample for examination, four to six biopsy specimens are taken at each examination.[101] A typical posttransplant biopsy schedule is shown in Table 20-5 . Based on our experience with OKT3 induction therapy, the need for endomyocardial biopsy during the first week after transplantation has been eliminated. Patients who demonstrate allograft rejection are treated with an appropriate immunosuppressive regimen (discussed later), and repeat endomyocardial biopsy is performed again after an interval of 10 to 14 days. The effect of treatment during this time is usually monitored by echocardiographic and clinical assessment.

The variety and significance of the observed histological changes in cardiac allografts have now been reasonably well defined. Many grading systems have been advocated by different transplant groups, but the International Society for Heart and Lung Tranplantation has used uniform criteria since 1989.[103] The tissue fragments are embedded together in a single block, processed, and sectioned. Most specimens are assessed using standard hematoxylin and eosin stains, but other special stains may be useful for gaining additional information, such as the amount of collagen present or identification of specific subtypes of infiltrating lymphocytes.

The most important feature of most posttransplant biopsy specimens is the detection of lymphocyte infiltration and the presence of myocyte necrosis. The continuum of histological findings from a normal specimen to one showing severe acute rejection

includes various subtle findings (Table 20-6) . Figure 20-6 shows examples of acute rejection of various grades.

A certain number of confusing histopathological changes can be seen in some biopsy specimens and can be unrelated to rejection. For example, specimens taken early after

TABLE 20-6 -- STANDARDIZED CARDIAC BIOPSY GRADING (ISHLT SCALE)

GRADE	FINDINGS
0	No rejection
1	A Focal (perivascular or interstitial) infiltrate without necrosis B Diffuse but sparse infiltrate without necrosis
2	One focus only with aggressive infiltration and/or focal myocyte damage
3	A Multifocal aggressive infiltrates and/or myocyte damage B Diffuse inflammatory process with necrosis
4	Diffuse aggressive polymorphous infiltrate, ±edema, ±hemorrhage, ±vasculitis, with necrosis

ISHLT=International Society for Heart and Lung Transplantation.

Modified from Miller LW, Schlant RC, Kobashigawa J, et al: Task Force 5: Complications. J Am Coll Cardiol 22:43, 1993. Reprinted with permission from the American College of Cardiology.

transplantation may reveal necrotic myocytes undergoing macrophagic removal because of ischemia at the time of the transplant procedure itself. Necrosis may also be secondary to infectious agents, such as CMV and toxoplasmosis. Occasional infections with these agents have been first diagnosed by endomyocardial biopsy. Perhaps the most frequent abnormality is a sample taken from a previous biopsy site that may contain contraction bands and evidence of inflammation and collagen formation as a result of healing of the previous biopsy site. The findings associated with

Figure 20-6 Composite photomicrograph showing different stages of acute cardiac rejection: *A,* Mild acute rejection, with a sparse interstitial lymphocytic infiltrate (grade 1B, ISHLT) (hematoxylin and eosin, original magnification × 200). *B,* Moderate acute rejection with islands of lymphocytes replacing myocardial tissue (grade 3A, ISHLT) (hematoxylin and eosin, original magnification ×200). *C,* Severe acute rejection with marked myocyte damage and a mixed inflammatory infiltrate (grade 4, ISHLT) (hematoxylin and eosin, original magnification × 300). (Courtesy of Dr. Margaret Billingham).

previous biopsy site histology are described in more detail elsewhere.[104]

In addition to classical cell-mediated rejection, occasional cases of hyperacute rejection due to preformed circulating antibodies from prior transfusion, pregnancy, or ABO incompatibility may occur within hours of surgery and require prompt retransplantation. In established allografts, vascular damage in the absence of lymphocytic infiltration has been accompanied by deposition of complement and IgG on endothelial cells that are swollen or disrupted.[105] The specificity of these findings remains controversial[106] ; however, when they are accompanied by clinical deterioration, treatment with an augmented immunosuppressive regimen and plasmapheresis has been used successfully.[107]

Treatment of Acute Rejection

Although a number of new immunosuppressive agents have become available, acute rejection episodes are still treated by a relatively small number of standard therapies.

The timing and severity of rejection episodes dictate the appropriate therapy. A representative algorithm for treatment is shown in Figure 20-7 . Episodes that occur within the first 3 months or that are moderate to severe are best treated by pulse therapy with methylprednisolone. Methylprednisolone sodium succinate is administered intravenously at a dose of 1000 mg/d for 3 consecutive days. Rejection that occurs after more than 1 month may be treated by augmenting oral steroid intake to 100 mg of prednisone per day for 3 consecutive days, tapered gradually back to baseline over 2 weeks. Several studies have demonstrated that an equivalent oral dose of prednisone may be as effective as intravenous methylprednisolone in early acute rejection.[108] In children or small adults, the dose of methylprednisolone and prednisone should be decreased in proportion to body size. Because of the side effects of increased corticosteroid therapy, patients should be carefully monitored for infections, increased fluid retention. glucose intolerance, and psychological or mood changes.

SEVERE REJECTION.

When prednisone treatment is ineffective or in particularly severe cases of rejection associated with hemodynamic changes, more aggressive therapy is given. The use of ATGAM (horse antithymocyte globulin), rabbit ATG, or OKT3 monoclonal antibody constitutes rescue therapy after unsuccessful use of prednisone or methylprednisolone. Unfortunately, the availability of commercial preparations of ATGAM is limited. Similarly, the availability of rabbit ATG preparations is erratic because such preparations are not commercially available and require special local arrangements for preparation. Consequently, OKT3 therapy is probably the most frequent type of rescue therapy being used and is an effective treatment for most resistant rejection episodes.[109] Treatment with OKT3 is costly ($3000 for a 10-day coure). Precautions to limit OKT3 toxicity are described later (see p. 183).

MILD REJECTION.

Additional strategies for treatment of early or mild rejection have been advocated.

Kobashigawa and associates treated patients with mild acute rejection with increases in oral cyclosporine, treating 40 episodes in 28 patients.[110] In their study of those patients with an actual increase in serum cyclosporine levels, 90 percent had no progression of rejection or clearing of rejection, whereas 37 percent of those who had no increase in levels had increasing evidence of acute rejection requiring treatment. An alternative approach is simply to observe patients in cases of grade IA or IB rejection and rebiopsy in 2 weeks, because almost two thirds of patients with stable cyclosporine levels reverted to normal spontaneously.

PERSISTENT OR RECURRENT REJECTION.

For patients with persistent recurrent rejection episodes despite repeated courses of conventional therapy, Hunt and colleagues at Stanford University[111] and Kirklin's group at Alabama[112] have supported the use of total lymphoid irradiation (TLI). It was administered according to standard protocols. Total doses varied from 240 to 1200 cGy (rads) over 5 to 10 weeks and were adjusted in response to leukopenia and thrombocytopenia. Measurement of absolute T-cell counts may also be helpful. The frequency of rejection episodes eventually fell to 5 percent of the pretreatment rate. Azathioprine and MMF should be discontinued or diminished

Figure 20-7 Algorithm for treating acute allograft rejection. EMB = endomyocardial biopsy; ATG = antithymocyte globulin.

during TLI. Olsen and coworkers from the University of Utah reported using methotrexate in the treatment of persistent low-grade rejection.[113] Methotrexate was given three times a week for an average of 8 weeks to 16 patients. All rejections were reversed, and the dose of prednisone could be reduced. Although there were no infections, azathioprine dose had to be reduced in 10 patients because of leukopenia. Methotrexate has also been advocated for recurrent acute, as well as refractory rejection in doses up to 15 mg/wk.[114]

In addition to these therapies, if a patient is receiving a traditional triple-drug regimen, consideration should be given to switching from cyclosporine to tacrolimus and from azathioprine to MMF.[115] [116] Finally, some authorities have advocated plasmapheresis in refractory cases.[117] [118] [119]

NEW AND FUTURE IMMUNOSUPPRESSIVE AGENTS

The availability of many agents for selective immunosuppression will almost certainly enhance the early and late acceptance of cardiac allografts, minimize toxicities, and increase the safety of cardiac transplantation.

SIROLIMUS.

Like tacrolimus, this investigative compound of fungal origin also binds to the FK-binding protein; however, its mode of action is not linked to calcineurin. Instead, it interferes with the action of growth factors on T cells. It selectively targets only those cells responsive to IL-2 and similar lymphokines and does not inhibit the replication of other rapidly dividing cells. Its mechanism complements that of cyclosporine and tacrolimus.[120]

Sirolimus (rapamycin) has been studied in a randomized trial of heart transplant recipients with acute moderate rejection. The investigators concluded that this agent effectively treats rejection in a dose-dependent manner and that adverse events, including thrombocytopenia, neutropenia, infection, and nausea/vomiting, were also dose related.[121] Ongoing clinical trials will define the use of sirolimus as maintenance immunosuppression with or without cyclosporine.

IL-2 RECEPTOR (CD25) MONOCLONAL ANTIBODIES.

Daclizimab (humanized monoclonal) and basiliximab (chimeric, murine variable region and human constant region) are anti-IL-2 receptor antibodies that have been efficacious in treating acute rejection in renal tranplant recipients.[122] [123] Their effectiveness in heart transplantation has recently been demonstrated.[91A]

HYDROXYMETHYLGLUTARYL-COENZYME A REDUCTASE INHIBITORS.

Kobashigawa and colleagues found that the lipid-lowering agent pravastatin not only lowered mean cholesterol levels compared with no treatment controls but also reduced cardiac rejection with hemodynamic compromise and graft coronary artery disease and improved 1-year survival (94 vs. 78 percent).[124] Other HMG-CoA reductase inhibitors have been shown to inhibit natural killer cells in vitro,[125] so it is possible that these agents have some unexpected immunosuppressive effect that remains to be elucidated.

OTHERS.

Additional promising approaches to the treatment of acute rejection include strategies for blockade of costimulation such as CTLA4Ig and monoclonal antibodies to B7 or CD40 ligand, and antisense oligonucleotides, in particular to intercellular adhesion molecule-1, all of which have shown success in animal models.

COMPLICATIONS OF IMMUNOSUPPRESSION

Along with the benefits of immunosuppressive drugs come numerous complications. All of the commonly used drugs cause side effects, increase the risk of infection, and are associated with neoplasia.

DRUG-SPECIFIC TOXICITIES

CYCLOSPORINE TOXICITY.

Cyclosporine is associated with a number of complications. The most clinically significant effect of cyclosporine involves the kidneys. Almost all patient groups receiving cyclosporine have a fall in creatinine clearance, an increase in serum creatinine level, and hypertension.[126] [127] Histopathological changes after long-term administration are found in the proximal convoluted tubule and in the distal tubules and consist of vacuotion of cells, epithelial swelling, hydropic degeneration, and necrosis, increasing clinical and experimental evidence shows that cyclosporine produces a derangement in the prostaglandin system in the renal tubules. Indomethacin exacerbates renal dysfunction after cyclosporine administration.

Cyclosporine may act by increasing urinary thromboxane B_2 levels in a dose-dependent manner, with local vasoconstriction, platelet aggregation, and release of platelet-produced thromboxane. This may explain the development of hypertension, renal ischemia, and the dysfunction that is seen clinically, although azotemia and hypertension are occasionally independent of each other.[128] Acute elevation of cyclosporine to three to four times customary maintenance levels may cause acute oliguria and rapid decline in renal function. This is probably due to vasoconstriction and is promptly reversible with adjustment of dose or removal of drugs hindering cyclosporine catabolism. Chronic interstitial fibrosis and nephron loss is common but is usually stable, it may be intermittently exacerbated by nephrotoxins used for therapy (e.g., amphotericin B, nonsteroidal antiinflammatory drugs) or diagnosis (radiographics contrast agents).

Early after transplant, many patients have oliguria. Thus, many transplant groups restrict the use of cyclosporine to continuous intravenous administration with careful control of circulating levels during the early posttransplant period, or they omit cyclosporine altogether and use induction therapy with OKT3 until serum creatinine level is normal and the patient has recovered from the effects of cardiopulmonary bypass.[127] [129] [130]

Hepatotoxicity, although uncommon, is usually acute and secondary to exceptionally high levels of cyclosporine. It is evidenced by an increase in bilirubin and by increases in serum liver enzyme levels. There are no characteristic cellular pathological alterations except for centrilobular fatty changes. The hepatotoxicity is dose related and reverts to normal after the dose of cyclosporine is lowered or eliminated. In general, hepatotoxicity is uncommon after cardiac transplantation, and so far, no long-term sequelae of cyclosporine on liver function have been reported.

Neurotoxic reactions are manifested by a fine tremor, paresthesias, and occasionally seizures. Most of these events are dose related and reversible. Other unusual side effects include the development of hirsutism or hypertrichosis, observed in almost all patients who receive cyclosporine. These effects tend to regress as the dose of cyclosporine is lowered. Similarly, gingival hyperplasia has been observed. A

combination of cyclosporine and nifedipine has resulted in an increased rate of gingival hyperplasia (51 percent) when compared with cyclosporine alone (8 percent).[131] Because cyclosporine is metabolized almost exclusively by the liver, hepatic dysfunction can cause abrupt elevations of blood levels of cyclosporine, precipitating renal dysfunction. Many commonly used compounds can influence the hepatic P450 cytochrome system, which is responsible for cyclosporine catabolism. Drugs that raise cyclosporine levels include the antimicrobials erythromycin, doxycycline, imipenem, cilastatin, ticarcillin, norfloxacin, ketoconazole, and itraconazole; the calcium channel blockers diltiazem, verapamil, nifedipine, and nicardipine; hormone products such as danazol, androgens, estradiol, and oral contraceptives, as well as other commonly used medications such as cimetidine, ranitidine, warfarin, acetazolamide, metoclopramide, and amiodarone. (Diltiazem and ketoconazole have been used adjunctively to lower the dose and cost of cyclosporine maintenance.[132])

Conversely, a decline in circulating cyclosporine levels, with the danger of causing rejection, may be precipitated by omeprazole, by the antibiotics rifampin and nafcillin, and by the anticonvulsants phenytoin, carbamazepine, valproic acid, primidone, and methsuximide.[133] [134] The use of lovastatin to control hypercholesterolemia in patients receiving cyclosporine has rarely been associated with rhabdomyolysis.[135]

CORTICOSTEROID TOXICITY.

Perhaps the most troublesome side effects of immunosuppressive therapy are associated with long-term administration of corticosteroids. In patients who require relatively high doses of steroids, these can be especially severe and include adrenal cortical atrophy, cushingold appearance, cataracts, skin fragility, severe osteoporosis, peptic ulcers, aseptic necrosis of bone, weight gain, psychiatric effects, diabetes, elevated serum lipid levels, and heightened susceptibility to infection of all types. In children, axial growth may be impaired. Perhaps the major advance in transplantation will come when corticosteroid therapy can be completely eliminated, a strategy under investigation.[136]

AZATHIOPRINE TOXICITY.

The major morbidity of long-term azathioprine administration is bone marrow suppression. Severe granulocytopenia has resulted from inadvertent coadministration of allopurinol for the treatment of CyA-induced hyperuricemia and gout and has been life threatening. In some patients, azathioprine also causes hepatotoxicity that may be so severe that the drug must be discontinued with substitution of an alkylating agent, such as cyclophosphamide.

TACROLIMUS TOXICITY.

Tacrolimus is nephrotoxic and should not be used simultaneously with cyclosporine. In addition, mild to severe hyperkalemia has been noted with its use. Serum potassium levels should be monitored, and potassium-sparing diuretic therapy should be avoided. Hyperglycemia requiring insulin therapy has also been noted with its use. Neurotoxicity,

including tremor, headache, coma, and delirium have been associated with high blood levels of tacrolimus. The most commonly associated neoplasms are lymphomas and skin carcinomas.

MYCOPHENOLATE MOFETIL TOXICITY.

MMF has been most frequently associated with gastrointestinal adverse events, from dyspepsia and diarrhea to gastrointestinal tract ulceration and hemorrhage. In addition, up to 2 percent of patients receiving MMF can develop severe neutropenia, and mild to moderate hypertension has been reported. Finally, lymphoproliferative (approximately 1 percent) and skin malignancies can also occur.

OKT3 TOXICITY.

Many patients develop cytokine release syndrome 30 to 60 minutes after administration OKT3, with frequency and severity increased with the first dose. The syndrome ranges from a mild, self-limited flulike illness to a less frequently reported severe, life-threatening

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shocklike reaction. Most patients experience fever and chills, and fewer report rash, pruritus, and noncardiac pulmonary edema. Transient rise in serum creatinine and hepatic transaminases may also be noted with the initial doses. Premedication with acetominophen 650 mg orally, ranitidine 100 mg intravenously, diphenhydramine 25 mg intravenously, and hydrocortisone 100 mg intravenously given 30 minutes before the OKT3 dose during the first 3 days of therapy serves as cytokine release syndrome prophylaxis.

Infection

In most centers, infectious complications are the most common cause of death after transplantation. Despite the fact that more effective immunosuppressive therapy has reduced the incidence and severity of infections, they still remain a major problem.[137] The overall incidence of infections ranges from 41 to 71 percent in various series, and repeated infections are frequent. In a multicenter analysis of 814 consecutive patients undergoing primary heart transplantation between 1990 and 1991, approximately half suffered acute infection at 6 months. This rose to almost two thirds by 1 year.[138]

With the extensive experience now available from both kidney, liver, and heart transplant recipients, certain typical infection patterns can be described. Infections in the first postoperative month tend to involve bacterial pathogens encountered in surgical patients in general. Infections in the time from 1 to 4 months after surgery usually involve opportunistic pathogens, especially CMV. After this period, both conventional

and opportunistic infections occur.

In contrast to renal transplant recipients, cardiac recipients must receive somewhat higher levels of pharmacological immunosuppression, which cannot be reduced appreciably at the time of infectious complications, hence the need for early diagnosis and aggressive therapy for any type of infection.

The role of immunization in preventing posttransplant infections is too often overlooked. If given before the institution of immunosuppressive regimens, immunization is more likely to be successful. Pretransplant inoculation with pneumococcal and hepatitis B vaccines, boosters for diphtheria-pertussis-tetanus, and, for young people not previously immunized, measles-mumps-rubella and polio vaccines are recommended. Because these last two are live virus vaccines, they should be avoided by patients (and immediate family members) after transplantation, when immunosuppression may enhance their virulence. Regular use of influenza vaccine every 2 years is controversial but has been advocated for HIV-infected patients and may be useful in transplant recipients as well.

EARLY INFECTION.

Infections in the first month after transplantation are commonly bacterial and most frequently pulmonary. This is especially true of patients with lung transplants in addition to heart. Nosocomial organisms, such as *Legionella, Staphylococcus epidermidis, Pseudomonas aeruginosa, Proteus, Klebsiella,* and *Escherichia coli* are typically encountered. The incidence of significant mediastinitis is between 0.4 and 4.5 percent in heart transplant recipients. Treatment includes prolonged courses of antibiotics, debridement of devitalized bone, and the use of vascularized muscle flaps for subsequent wound closure. Other typical causes of early postoperative infection, such as urinary tract infections, bacteremias, and pneumonia, should be suspected. The clinical diagnosis of pneumonia is made on the basis of typical clinical features, including cough, fever, sputum production, and chest radiographs showing a new pulmonary infiltrate. An aggressive approach to early diagnosis is recommended. This may include bronchoscopy with washings and culture. The results of these cultures will determine specific antibiotic therapy, but early broad-spectrum coverage started immediately after obtaining appropriate cultures is recommended.

LATE INFECTION.

Late posttransplant infections are more diverse. These are frequently of the opportunistic variety, including viruses (CMV, herpes), *Pneumocystis carinii,* and other fungi (e.g., *Candida* and *Aspergillus*), as well as more exotic varieties. *Nocardia* or *Toxoplasma gondii* is occasionally encountered. The variety of late posttransplant pneumonias may vary from center to center, depending on local prevalences and the use of prophylactic treatments. For example, in some series, *P. carinii* is the most common late pulmonary infection, whereas in other series it is absent. Regular prophylactic administration of trimethoprim-sulfamethoxazole (TMP-SMZ) three times per week on a long-term basis is now routinely recommended by most transplant programs to prevent *P. carinii* pneumonia (PCP) and *Toxoplasma* infection (or if

TMP-SMZ is not tolerated, monthly pentamidine aerosol inhalation for PCP prophylaxis).[139]

CYTOMEGALOVIRUS INFECTION.

CMV infection is the most frequent and important viral infection in transplant recipients, with an incidence in cardiac recipients of between 73 and 100 percent.[140] [141] CMV is the single most frequent infecting organism, accounting for 26 percent of all infections in a large cooperative study.[137] This can be minimized in CMV-negative patients by the use of CMV-negative blood products, but a CMV-positive donor almost invariably transmits infection. It may be detected in some patients only by seroconversion or, if they are seropositive preoperatively, by a rise in IgG titers or the appearance of an IgM antibody. Some infections remain subclinical. When clinical disease is present, it may present as leukopenia, pneumonia, gastroenteritis, hepatitis, or retinitis in various combinations. Of these, pneumonia is the most lethal (13 percent mortality), whereas retinitis is the most refractory and requires indefinite maintenance therapy. Most cases are responsive to ganciclovir (DHPG) or foscarnet. The addition of hyperimmune globulin has further improved therapeutic outcome and decreased mortality, particularly from CMV pneumonia. Although seronegative recipients who accept allografts from CMV-positive donors are the most vulnerable, prior seropositivity does not offer protection from infection (15 percent disease frequency), and late reactivation, reflecting the persistence of this member of the herpesvirus family, may occur.

Unfortunately, results of diagnostic tests are not always positive. Viral cultures may be negative in the presence of infection, and serological responses may be diminished owing to immunosuppression. The addition of polymerase chain reaction (PCR) technology for the detection of CMV viremia has added a more sensitive diagnostic method.[142] Because of these limitations, CMV should always be suspected in the event of unexplained fevers, gastroenteritis, or culture-negative interstitial pneumonitis. Endoscopy with biopsy may establish the diagnosis promptly in these latter cases.[143] Early prophylaxis with ganciclovir in the setting of positive CMV graft into a negative recipient includes the use of ganciclovir and hyperimmune globulin for 6 to 8 weeks after transplantation. Prophylaxis against CMV infection decreased the incidence of CMV disease in recipients who were seropositive before transplantation but not in those who were seronegative.[144]

The importance of CMV infection cannot be overemphasized because of its relation to the development of late graft arteriosclerosis. The availability of newer antiviral treatments may help to minimize the complications of this particular infection in the future.

FUNGAL INFECTIONS.

Although less common than viral and bacterial infections, fungal infections are more serious, less responsive to therapy, and more likely to be lethal. (*P. carinii,* originally thought to be a protozoan, has now been reclassified as fungus). *Candida* and *Aspergillus* are the most commonly encountered pathogens. Treatment with imidazoles

is often effective for *Candida* and coccidioidomycosis,

but their use may raise cyclosporine levels. Infections of vital organs usually require amphotericin B and flucytosine, which compromise renal function and potentiate leukopenia, respectively.

Toxoplasmosis is uncommon but responds to pyrimethamine.[145]

NEOPLASMS

Chronic immunosuppression can predispose to certain malignancies. In general, transplant recipients have a threefold increase in the incidence of various cancers when compared with age-matched controls. Some specific cancers are more than 100 times more frequent in immunosuppressed patients than in the general population. For all tumors, the average time of appearance of the cancer after transplantation is 58 months, although some tumors may characteristically appear at other intervals. Cardiac transplant recipients have a somewhat higher incidence of cancer than do renal transplant recipients, perhaps because of the higher levels of immunosuppression. The most common tumors among transplant recipients are those of the skin and lips, non-Hodgkin lymphomas, Kaposi sarcomas, and uterine, cervical, vulval, and perineal neoplasms. The frequency of common adenocarcinomas, such as those of breast, lung, prostate, and colon, does not exceed that in the general population.[146]

Perhaps the most important neoplasms are the lymphoproliferative tumors that occur early after transplantation, more frequently in younger recipients. Most of these tumors are thought to be the result of Epstein-Barr viral infection and consist of B-cell proliferation that is unchecked because of T-cell suppression or depletion.[147] The recurrent use of OKT3 has been identified as a risk factor in some programs,[148] but this has not been confirmed by others.[149] Approximately 15 percent are of T-cell origin, and some of these tumors also carry Epstein-Barr virus markers.[146] [150]

The tumors typically arise in extranodal sites, such as lung, gut, or central nervous system. Treatment has included diminishing immunosuppression, adding antiviral therapy with acyclovir or ganciclovir,[151] and irradiation or surgical removal for monofocal tumor. Closer surveillance by cardiac echocardiography and biopsy is essential during this period. If rejection occurs or if the tumor is refractory, additional therapy with alfa-interferon chemotherapy, and monoclonal B-cell antibodies have been used with success.[152] Roughly one-third of patients will respond, and recurrence is uncommon.

GRAFT CORONARY ARTERY DISEASE

The major long-term problem after cardiac transplantation, assuming greater importance as the number of survivors increases, is the development of coronary artery disease in the transplanted heart. Graft coronary artery disease was first observed by Thomson in

1969 in the first long-term survivor reported from South Africa.[153] Nineteen months after transplantation for ischemic cardiomyopathy, the patient died with extensive coronary artery disease. Various reports describe an incidence of between 20 and 50 percent at 5 years.[154] [155] [156] [157] [158] [158A]

With the advent of protocols using cyclosporine for immunosuppression, there has been no significant decline in the incidence of this disease.[159]

Graft coronary artery disease has been observed as an incidental finding at autopsy as early as 3 months after transplantation. Significant coronary disease may produce arrhythmias, myocardial infarction, sudden death, or impaired left ventricular function with congestive heart failure.[160] Angina pectoris is rare because the cardiac allograft remains essentially denervated, so patients may present with sudden and severe cardiac dysfunction. The disease tends to be diffuse and concentric, and coronary angiograms must be closely inspected and compared with previous studies to appreciate the reduction in coronary diameter. The introduction of intravascular ultrasound to assess thickness and composition of the coronary arterial wall, as well as to provide precise measurement of lumen diameter, has demonstrated the presence of disease that was not visible angiographically (Fig. 20-8 *B*). Definite intimal thickening was present in one quarter of patients at Stanford University at 1 year, and its prevalence increased to approximately 80 percent at 5 years after transplantation. Multivessel intracoronary ultrasound interrogation increases the sensitivity for detection of graft coronary disease.[160A] Calcification was uncommon (<10 percent) up to 5 years but approached 25 percent at 6 to 10 years and 50 percent at 11 to 15 years.[161] Electron beam computed tomography may aid detection of coronary calcification in this context.[161A]

Noninvasive stress imaging with thallium and sestaMIBI scans has been generally disappointing, probably because of the diffuse nature of the vascular lesion, which affects the intramyocardial as well as epicardial coronary arteries.

PATHOGENESIS.

The cause of graft coronary artery disease remains controversial and is probably multifactorial (see also Chap. 30) . Vascular endothelium is known to be immunologically active, and similar vascular changes are seen late after kidney and liver transplantation. The early stages of cardiac allograft rejection are characterized by lymphocytic perivascular infiltration, and vasculitis frequently is a prominent part of moderate to severe allograft rejection. Vascular changes with deposition of immunoglobulin, complement, and fibrin occur in both patients and animals. Current data strongly support a complex immune mechanism for the development of graft coronary artery disease. Histological features of graft arteriopathy demonstrate extensive concentric intimal proliferation (Fig. 20-9) with hyperplasia of smooth muscle and lipid-laden macrophages. [162] Grossly, the vessels show diffuse disease extending symmetrically into distal branches with few collateral

Figure 20-8 *A,* Intravascular ultrasound examination of the left anterior descending coronary artery in a transplant recipient at the site shown at A in the middle panel depicting the coronary angiogram. *B,* Intravascular ultrasound in the proximal circumflex coronary artery at the point marked in the coronary angiogram in the central panel at B. Arrowheads show thickened intima. (Courtesy of Dr. Peter Fitzgerald.)

Figure 20-9 *A,* Histological section of the left main coronary artery showing concentric atheromatous plaque composed of a fibrous cap overlying a basal layer of cellular and intracellular lipid. (Original magnification ×15.) *B,* Coronary arteriogram performed 4 days before death, 14 months after transplantation. Arrow indicates the site of the histological section shown in panel A. (From Johnson DE, Alderman EL, Schroeder JS, et al: Transplant coronary artery disease: Histopathologic correlations with angiographic morphology. J Am Coll Cardiol 17:449, 1991. Reprinted with permission from the American College of Cardiology.)

vessels. Proximal stenoses occur rarely.[163] Angiography may not be sensitive enough to show this disease (see Fig. 20-9 *B*).

RISK FACTORS.

Both alloantigen-dependent and alloantigen-independent factors contribute to coronary artery endothelial damage, which results in graft coronary artery disease. The association of episodes of acute rejection with later development of the graft coronary artery disease points toward immune-mediated mechanisms.[164] Additional alloantigen-independent risk factors could contribute to the progression of graft coronary artery disease. Recipient characteristics (age, gender, obesity, hypertension, hyperlipidemia, insulin resistance, and CMV infection) and donor characteristics (age, gender, preexisting coronary disease, and donor ischemic time) may have such a role.[165] Chang and colleagues, for example, have demonstrated increased recipient triglyceride levels and older donor age, but not lipoprotein(a) levels, to significantly predict development of the disease.[166] In addition, the ischemia-reperfusion injury inherent to the transplantation procedure activates the microvascular endothelium, leading to release of reactive oxygen species and inflammatory mediators, which may have long-term consequences.[167]

CYTOMEGALOVIRUS INFECTION.

Several reports emphasize the possible role of CMV infection in graft coronary artery disease. CMV may contribute to the pathogenesis of graft coronary artery disease by inducing molecular events that serve to promote mononuclear adhesion, activation, and transendothelial migration within the allograft vasculature.[168] In addition, intimal proliferation has been linked to the inactivation of p53 (a tumor suppressor) by CMV, permitting enhanced proliferation of smooth muscle cells.[169] Hosenpud has shown that CMV infection alters the expression of major histocompatibility complex type I molecules

as well as cytokine gene transcription in smooth muscle cells, favoring a proinflammatory milieu.[170] Finally, a study from Stanford has shown a decreased incidence of graft coronary artery disease in patients treated with ganciclovir (CMV prophylaxis) when not concurrently taking a calcium channel blocker.[171] The mechanistic implications of this investigation have yet to be elucidated.

PREVENTION.

Most centers use some preventive measures in the hope of reducing the incidence of graft arteriosclerosis. In addition to measures to limit CMV, strategies have been directed toward limiting the amount of steroid administered. Hypercholesterolemia is a known risk factor for the development of coronary artery disease in general, and the use of prednisone[172] and cyclosporine[173] is correlated with elevated serum cholesterol levels in cardiac transplant recipients. Other modifications of known risk factors include maintenance of ideal body weight through dietary restriction, reduced intake of cholesterol and saturated fats, the use of lipid-lowering agents such as pravastatin or simvastatin,[173A] [173B] cessation of smoking, regular exercise, and the use of an antiplatelet agent such as low-dose aspirin. Doses of statins should be chosen recognizing the potential for interaction with cyclosporine. The addition of diltiazem to the posttransplant regimen has retarded progression of allograft coronary disease, and its cyclosporine-sparing effect has also reduced costs.[174]

TREATMENT.

The existence of more discrete proximal lesions has been treated by percutaneous transluminal coronary angioplasty in some cases, and even coronary artery bypass grafting has been reported.[175] [176] [177] [178] However, retransplantation is the major alternative once diffuse graft atherosclerosis develops. The results of retransplantation are worse than for the primary procedure, with a reported patient survival rate of approximately 48 percent at 1 year (n = 449) reported by the International Society for Heart and Lung Transplantation. Uncontrolled rejection and an interval of less than 6 months between operation and the need for pretransplant mechanical support were listed as risk factors.[179]

LATE FOLLOW-UP

Late follow-up of cardiac transplant recipients requires a coordinated and systematic approach. The drug regimen for late follow-up is shown in Table 20-7 . MMF therapy is supplanting azathioprine use in some centers, including Stanford University. The two leading causes of early morbidity

TABLE 20-7 -- DRUG REGIMEN FOR LONG-TERM RECIPIENT

Prednisone 0.1-0.2 mg/kg/d
Cyclosporine 3-6 mg/kg/d
Diltiazem 120-240 mg/kg/d
Sulfamethoxazole-trimethoprim b.i.d. 3 d/wk
Azathioprine 1-2 mg/kg/d
Pravastatin 20 mg/d
Miscellaneous
Furosemide
Potassium supplements
Antacids
Aspirin
Additional antihypertensives p.r.n.

and mortality are rejection and infection. Later surveillance should focus also on graft arteriosclerosis and cancer. The frequency and timing of transplant follow-up visits are determined by the general condition of the patient and the time after transplant. Endomyocardial biopsy remains a necessity and is performed every 3 to 4 months indefinitely. We currently recommend performing coronary arteriography on a yearly basis, although some programs alternate this with noninvasive studies of myocardial function or ischemia.

In addition to the objective laboratory data, a detailed interval history and physical examination are important to detect other complicating illnesses at an early stage. Patients may minimize new symptoms, and physicians must be constantly alert to the possibility of an occult but potentially life-threatening infectious complication. A detailed inquiry into all medications that the patient is taking should be performed to avoid errors of omission, dosage misunderstanding, or unexplained additions that might alter the metabolism or excretion of immunosuppressive drugs, potentially causing rejection (e.g., rifampin), nephropathy (e.g., erythromycin), or bone marrow suppression (e.g., allopurinol). A sampling of other late problems routinely encountered includes aseptic necrosis of bone, azotemia, cataracts, cholelithiasis, gout, heart failure, herpes zoster, impotence, obesity, rejection, vertebral compression fractures, and an assortment of skin lesions.

SURVIVAL EXPECTATIONS

Long-term survival and complete rehabilitation can be attained by most patients currently undergoing heart transplantation. Three-year actuarial survival data from the Registry of the International Society of Heart and Lung Transplantation, broken down by four time periods, is shown in Figure 20-10. From 1991 onward, even though significant changes in donor and recipient characteristics such as increased age in both have occurred, overall survival is maintained at approximately 82 percent for 1 year and 74 percent for 3 years.[1] At Stanford, patients receiving a cardiac transplant in the past

year had a 1-year survival of 91 percent.

Longer-term data are given by the recent Stanford 30-year report. For patients receiving transplants in the past decade (1988 to 1998), the 1-, 5-, and 10-year survival is 85, 68, and 46 percent. With improved immunosuppression, deaths due to rejection and infection have declined

Figure 20-10 Heart transplantation actuarial survival by era for all patients reported to the Registry of the International Society for Heart and Lung Transplantation from 1980 to 1998. (From Hosenpud JD, Bennett LE, Keck BM, et al: The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report--1999. J Heart Lung Transplant 18:614, 1999. Reprinted with permission from Elsevier Science Ltd.)

and freedom from graft coronary artery disease has increased. These improvements occurred despite older organ donors, longer graft ischemic times, and longer waiting periods on the transplantation list for the group in the later treatment era.[2]

Quality-of-life studies, both short and long term, indicate overall good physical status and well-being in the majority of patients.[180] [181] The majority of heart transplant recipients report no activity limitations, but less than 40 percent are working. This may reflect planned early retirement, unwillingness to give up disability and insurance benefits, or the employer's resistance to hiring someone with a chronic disorder, rather than any real physical limitation.[1] Structured cardiac rehabilitation programs are common and can improve exercise capabilities.[182]

COST CONSIDERATIONS

The cost of care has been divided into pretransplantation, evaluation and candidacy, transplantation, and posttransplantation by Evans.[183] Pretransplantation costs derive from the care needs of patients with end-stage heart disease and are multiplied by the steadily increasing time spent on waiting lists, which reached a median in 1993 of 208 days (22 percent waited 6 to 12 months and 42 percent waited more than a year).[184] Depending on the need for hospitalization, intensive care, or mechanical support, such costs easily exceed $100,000. These costs are considerably higher for status I patients.[185]

The cost of candidacy, including catheterization, myocardial biopsy, social service evaluation, special studies,[186] and professional fees, totals $10,000 to $20,000.

The median charge for a heart transplant in 1993 dollars was $123,000, with a median length of hospital stay of 23 days (range 1 to 554). The charge, when separated into its components, was distributed as follows: hospital charges $84,000, donor organ acquisition $17,000, surgeons' fees $13,000, and other professional fees $9000. The extremes for these figures varied by factors of 5 to 10.[183] In 1993, charges for the entire first year were estimated at $209,000. Efforts to reform the health care system have focused on cost, quality, and access, and growing involvement of managed care has

reduced this expenditure to less than $100,000.[187] Yearly follow-up thereafter, including angiography and regular biopsies (three to four per year), probably exceeds $15,000, with immunosuppressive drugs alone costing $4000 to $6000 annually.[188]

The majority of private insurers[189] and, by 1990, 78 percent of state Medicaid programs[190] cover heart transplantation. Medicare also pays for care at designated centers that meet federal operational criteria.[19]

Reimbursement is usually less than 80 percent of charges, and long-term medication costs are not always recovered.[190] Insurance contracts that pay ongoing costs only when linked to claims of continued disability necessarily inhibit return to work.

HEART TRANSPLANTATION IN CHILDREN

The annual number of pediatric heart transplantations performed worldwide peaked at 395 in 1993 and since then has averaged approximately 340 per year. Overall, congenital heart disease and cardiomyopathy are the most common indications for transplantation in children younger than 1 year and 1 year and older, respectively. Various other indications have included failed Fontan procedure, severe Ebstein anomaly, single ventricle, and tricuspid and pulmonary atresia with coronary artery sinusoids.[191]

International Society of Heart and Lung Transplantation Registry data indicate an actuarial 1- and 5-year survival of approximately 78 and 65 percent. Children ages 11 to 17 have survival nearly identical to adults, whereas those younger than 1 year fare worse.[1] Some evidence

shows that rejection complications are less frequent in children in whom transplantation occurs before 1 month of age. After that time, rejection is clearly common and appears to be no less than in adult patients.

A major drawback to transplantation in children is the need for invasive endomyocardial biopsy to monitor the function of the transplanted heart. A report by Braunlin and colleagues suggests that episodes of rejection are relatively uncommon with triple-drug immunosuppression and that surveillance biopsies more than 6 months after transplantation are unlikely to show rejection in the absence of symptoms or an abnormal echocardiogram.[192] Rejection in neonatal patients may be associated with fever, irritability, and difficulty feeding. Emerging noninvasive techniques of detecting rejection were discussed earlier in this chapter and may someday greatly benefit the management of pediatric patients.

With continual improvements in immmunosuppression, the consequence of long-term administration of these drugs may be lessened, and the need for retransplantation later in life may also be alleviated. These issues, together with limited donor resources,

remain the major stumbling blocks to more widespread use of transplantation in infants and children.

RETRANSPLANTATION

An important consideration in cardiac transplantation is the question of retransplantation. The major indications are (1) the development of graft coronary artery disease, (2) treatment of severe acute early rejection, and (3) treatment of early acute right-sided heart failure. All of these patient groups are less desirable potential recipients than are primary transplant candidates, either because of chronic immunosuppression or the circumstances surrounding early graft failure.

These patients should meet the same standard criteria as initial candidates. These include a lack of evidence of systemic infection, no other irreversible major organ system failure, and the potential for adequate rehabilitation. Recipients should be screened for the presence of preexisting cytotoxic antibodies. If a sufficient percentage is determined against a panel of random donor cells, a specific crossmatch will be required for the retransplantation procedure.

Although some reports demonstrate worse survival after retransplantation, others indicate that long-term survival and survival after an interval between procedures of at least 2 years approximate that of primary transplantation.[1] [193] [194] [195] In the largest report, 67 patients underwent 69 retransplantations out of 954 total procedures at the Stanford University

Figure 20-11 Adult heart retransplantation actuarial survival based on length of time since primary transplantation, as reported to the Registry of the International Society for Heart and Lung Transplantation. (From Hosenpud JD, Bennett LE, Keck BM, et al: The Registry of the International Society for Heart and Lung Transplantation: Fifteenth Official Report--1998. J Heart Lung Transplant 17:658, 1998. Reprinted with permission from Elsevier Science Ltd.)

Medical Center. Twenty-three patients received retransplantation for early rejection and 43 patients for development of coronary artery disease. Causes of death were similar to those for other transplant recipients, and survival was 49, 27, and 15 percent at 1, 5, and 10 years after operation.[2] Actuarial survival of patients undergoing retransplant procedures reported to the Registry of the International Society of Heart and Lung Transplantation is shown in Figure 20-11. A clear benefit is seen in patients undergoing retransplantation more than 9 months after the initial transplantation. Because of the scarcity of donor organs and experiences with worse outcomes, most authorities agree that candidates for retransplantation must be carefully selected.

HEART-LUNG TRANSPLANTATION

Transplantation of the entire cardiopulmonary axis was accomplished experimentally even before orthotopic heart transplantation.[196] Despite early experimental attempts, it was a difficult clinical endeavor because of problems inherent in lung transplantation.

The nonspecific immunosuppression available before cyclosporine therapy led to major problems with pulmonary infections and delayed healing of the trachea or bronchus, such that no truly therapeutic and extended lung transplant had been reported.[197] The availability of cyclosporine-based protocols led to success in primate allografts in the laboratory[198] and then a clinical series initiated at Stanford University Medical Center. The first reported therapeutic success in heart-lung transplantation was reported in 1981.[16]

The indications for heart-lung transplantation initially were severe pulmonary vascular disease, either primary or secondary to congenital heart disease. Later, heart-lung transplantation was extended to patients with various diffuse pulmonary diseases, such as emphysema, lymphangioleiomyomatosis, diffuse pulmonary atriovenous fistulas, and cystic fibrosis. Heart-lung transplantation currently is mainly performed for patients with complex congenital heart disease and Eisenmenger syndrome. Patients with cystic fibrosis and primary pulmonary hypertension are preferentially treated with bilateral lung transplantation; in cases of these conditions complicated by severe right or left ventricular failure, heart-lung transplantation may be indicated. Long-term survival figures for heart-lung transplantation (Fig. 20-12) are not as favorable as for heart transplantation (see Fig. 20-10).

Figure 20-12 Survival of patients receiving heart-lung transplants, as reported to the Registry of the International Society for Heart and Lung Transplantation. (From Hosenpud JD, Bennett LE, Keck BM, et al: The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report--1999. J Heart Lung Transplant 18:620, 1999. Reprinted with permission from Elsevier Science Ltd.)

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Chapter 21 - Management of Heart Failure

MICHAEL R. BRISTOW

INTRODUCTION

DEFINITION OF HEART FAILURE AND RELATED DISORDERS (see also Chaps. 16 and 18).

Heart failure (HF) is a specific term used to define the clinical syndrome that ensues when the heart is unable to pump enough blood to supply the metabolic needs of the body. The clinical syndrome of HF is caused by *cardiac failure*, a term used to define the various types of pump dysfunction that may cause HF. Cardiac failure may be produced by processes involving the pericardium, heart valves, coronary circulation, or myocardium (Table 21-1) . Of these etiologies, the most common cause of chronic HF is myocardial dysfunction, termed *myocardial failure*. Myocardial failure is usually divided into two general types, *systolic dysfunction* and *diastolic dysfunction,* to reflect the dominant abnormalities of contraction and relaxation, respectively. Subjects with myocardial failure can have symptomatic HF or asymptomatic ventricular dysfunction.

As typically used, HF generally refers to the chronic syndrome, or *chronic HF*. The qualifier "congestive" should not be used in association with HF inasmuch as many HF patients receiving modern medical treatment do not manifest congestive symptoms or

signs. Rather, HF symptoms usually relate to impaired exercise tolerance, plus or minus symptoms related to fluid overload. Symptoms of exercise intolerance are typically assessed by the New York Heart Association (NYHA) functional classification,[1] where I=no symptoms, II=symptoms with moderate or marked levels of activity, III=symptoms with mild activity, and IV=symptoms at rest (see also Chap. 3).

CLINICAL IMPORTANCE (see also Chap. 17).

Because of its high prevalence (1 to 2 percent of the adult population)[2] and frequent hospitalizations, the clinical syndrome of HF is among the most costly medical problems in the United States.[3] Despite improvements in the treatment of HF introduced since the early 1980s, including the general availability of cardiac transplantation and better medical treatment, clinical outcome following the onset of symptoms remains characterized by high mortality, morbidity, and progression of symptoms. For example, even in recent clinical trials showing benefit of new agents superimposed on successful older treatment, annualized mortality (percent) and hospitalization rates (number of hospitalizations per patient per year) in the active treatment groups have been respectively 5 to 9 percent and 0.3 to 0.4 in Classes II and III[4] [5] [6] and 14 to 18 percent and 0.6 to 0.8 in Classes III and IV HF.[7] [8] Furthermore, HF is the only cardiovascular disorder in the United States that is increasing in prevalence,[9] and since the prevalence is directly related to age,[10] the incidence and prevalence of HF will continue to increase on the basis of population demographics (Fig. 21-1) . At present, an estimated 4.5 million patients have HF in the United States,[9] plus at least as many additional subjects with asymptomatic left ventricular dysfunction.[11] As can be observed in Figure 21-1 , by 2050 the number of subjects with symptomatic HF will increase to over 7 million on the basis of an increase in the number of persons older than 65 years,[12] in whom the prevalence of HF is 6 percent.[10]

PHENOTYPIC CLASSIFICATION OF HEART MUSCLE DISEASE (see also Chap. 48)

Heart muscle disease, or cardiomyopathy, is classified by a system developed by a World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) task force. This committee recently revised the original classification,[13] which dealt with only "unknown cause" cardiomyopathies, and included all cardiomyopathies regardless of whether the cause is known.[14] The reasons for this change were the desire to be able to classify all cardiomyopathies within one classification and the developing reality that many previously unknown types of cardiomyopathy, such as hypertrophic cardiomyopathies, now have known molecular causes.

Within the current WHO/ISFC classification[14] (see Table 48-1) of cardiomyopathy, the most common cause of the clinical syndrome of chronic HF is a secondary (e.g., ischemic, valvular, hypertensive) or a primary (e.g., idiopathic or familial) dilated cardiomyopathy, defined as a ventricular chamber exhibiting increased diastolic and systolic volume and a low (<0.40) ejection fraction. However, all types of cardiomyopathy listed in Table 48-1 can cause chronic HF.

As shown in Table 48-1 , the WHO/ISFC cardiomyopathy classification[14] uses two

separate methods to define the individual categories. The first is based on the global anatomical description of chamber dimensions in systole and diastole. Thus, the dilated and restrictive

TABLE 21-1 -- GENERAL ETIOLOGIES OF CARDIAC FAILURE

GENERAL CAUSE	SPECIFIC EXAMPLES
Pericardial	Tamponade, pericardial constriction
Valvular	Aortic or mitral regurgitation
Myocardial	Idiopathic dilated cardiomyopthy, familial dilated cardiomyopathy, ischemic cardiomyopathy, valvular cardiomyopathy
Coronary vascular	Acute ischemic episodes
Rhythm disturbances	Tachycardia-induced heart failure

Figure 21-1 Effect of the aging population on the prevalence of heart failure. *(Based on data from Phase I of the National Health and Nutrition Examination Survey III 1980 and U.S. Bureau of the Census data and projections appearing in Hayflick L: How and Why We Age. New York, Ballantine, 1994.)*

categories have definitions based on left ventricular dimension or volume, which also defines function via the calculated ejection fraction. The justification for classification is that these two groups have distinct natural histories and may respond differently to medical treatment. The second method of creating individual categories within the WHO/ISFC classification is for cardiomyopathies that are genetically based, have unique myocardial phenotypic features, and do not exhibit extracardiac phenotypes. Thus, hypertrophic cardiomyopathy caused by mutations in sarcomeric proteins and manifested as a unique phenotype (see Chap. 48) merits a separate category. The same is true for arrhythmogenic right ventricular dysplasia, which also has a unique phenotype and will probably turn out to be completely genetic in basis, as has hypertrophic cardiomyopathy. On the other hand, genetic cardiomyopathies without unique phenotypes, such as the X-linked dilated cardiomyopathy of Becker-Duchenne muscular dystrophy (see Chap. 71), are included as one type of the anatomical/chamber dimension category (category I).

SECONDARY (SPECIFIC) CARDIOMYOPATHIES.

The WHO/ISFC classification includes another assignment of nomenclature in "secondary" cardiomyopathies, i.e., those associated with known cardiac or systemic

processes. These conditions are referred to as "specific cardiomyopathies" and are named for the disease process with which they are associated. Thus, an ischemic cardiomyopathy would be a specific cardiomyopathy related to previous myocardial infarctions and the subsequent remodeling process and would usually fall within the dilated class. On the other hand, a hypertensive cardiomyopathy might be classified as either dilated or restrictive, depending on chamber dimensions. Therefore, the correct term for these cardiomyopathies would be "ischemic dilated cardiomyopathy" and "hypertensive dilated (or restrictive) cardiomyopathy."

PATHOPHYSIOLOGY OF HEART FAILURE DUE TO PRIMARY OR SECONDARY DILATED CARDIOMYOPATHIES (see also Chap. 16)

HF caused by pericardial, valvular, and acute coronary circulation problems is discussed elsewhere. The discussion here is confined to the pathophysiology of primary and secondary dilated cardiomyopathy, the cause of the majority of cases of HF, as it may relate to medical therapy. More detailed discussion of the pathophysiology of myocardial failure is given in Chapter 16 .

As depicted in Figure 21-2 , two interrelated processes, chamber remodeling and myocardial systolic dysfunction, are thought to play critical roles in the development and progression of primary and secondary dilated cardiomyopathy.[15] [16] Although both are the products of changes that occur at the cardiac myocyte level, changes in the interstitium also contribute.[17] In the remodeling process, cardiac myocytes become longer without a proportional increase in transverse diameter, which explains the increase in chamber diameter without an increase in wall thickness.[18] [19] Although this adjustment does increase the number of contractile elements as new sarcomeres are laid down in series, the law of Laplace dictates that diastolic wall stress will be markedly increased (see also Chap. 14). Also, the elongated and remodeled cardiac myocyte is poorly contractile.[20] The end result of these processes is a poorly contractile, dilated ventricular chamber that at some point can no longer adequately support the circulatory requirements of daily living.

As originally described in rat models,[21] the process of hypertrophy is accompanied by a qualitative change in the expression of genes regulating cell growth and contractile function. This constellation of changes in myocardial gene expression resembles the prenatal pattern of expression, and hence the term *induction of fetal gene expression* is used to describe these changes. Some of the specific changes are shown in Table 21-2 . Several of the fetal gene program changes can depress contractile function, such as the decrease in alpha-myosin heavy chain (alpha-MyHC) and sarcoplasmic reticulum Ca^{2+} ATPase and the increase in beta-MyHC. For many years, human ventricular myocardium

Figure 21-2 Relationship between remodeling and dysfunction.

TABLE 21-2 -- FETAL GENE PROGRAM INDUCTION IN HYPERTROPHIED, FAILING HUMAN VENTRICULAR MYOCARDIUM, DEGREE OF EXPRESSION (0-4+)

GENE EXPRESSED	ADULT PATTERN	FETAL PATTERN	HYPERTROPHY/FAILURE	BIOLOGICAL EFFECT IN HYPERTROPHY
alpha-MyHC	++	0-+	0-+	Contractile function
beta-MyHC	+++	++++	++++	Contractile function Cell growth
SR Ca^{2+} ATPase	+++	++	++	Contractile function
Natriuretic peptides (ANP, BNP)	0-+	+++	+++	? Cell growth
Skeletal actin	+++	++++	?	--
Cardiac actin	+	0-+	?	--

ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; MyHC=alpha-myosin heavy chain; SR=sarcoplasmic reticulum.

was not thought to undergo the full pattern of fetal induction, but recent data indicate that failing human ventricular myocardium qualitatively resembles rodent models of fetal gene induction.[22] [23] [24] [25] Hypertrophied and failing human ventricular myocardium undergoes changes in expression of MyHC isoforms and sarcoplasmic reticulum Ca^{2+} handling proteins that summate to decrease systolic and diastolic function; on the basis of work done in rodent models,[21] [26] [27] it is likely that this mechanism of fetal gene induction contributes to the development of myocardial failure in the context of pathological hypertrophy, as depicted in Figure 21-2 .

VENTRICULAR REMODELING AND SYSTOLIC DYSFUNCTION.

These processes are progressive in most patients with established chronic HF,[28] and the pace [29] and degree[30] of this progression are directly related to the prognosis. It is therefore not surprising that two of the most effective treatments for chronic HF, inhibition of the renin-angiotensin and adrenergic nervous systems, act by attenuating or

partially reversing these processes.[16] This mechanism implies that activation of the renin-angiotensin and adrenergic nervous systems is in part responsible for progressive remodeling and myocardial dysfunction, as depicted in Figure 21-3 and Table 21-3 . As shown in Figure 21-3 , after a myocardial insult sufficient to reduce pump function, only a limited number of compensatory options are available to stabilize cardiac output. As described in Table 21-3 , these options are an increase in heart rate and contractility, volume expansion to increase preload and thereby reach a higher position on the Frank-Starling curve, and an increase in the number of contractile elements through cell and chamber hypertrophy. As can be observed in Table 21-3 , the renin-angiotensin and adrenergic mechanisms are involved

Figure 21-3 Activation of compensatory mechanisms leads to a decrease in intrinsic and modulatable myocardial function.

TABLE 21-3 -- COMPENSATORY MECHANISMS ACTIVATED WHEN THE HEART BEGINS TO FAIL

PROCESS	MECHANISM PRIMARILY RESPONSIBLE
Heart rate	Beta-adrenergic
Contractility	Beta-adrenergic
Preload	Renin-angiotensin, beta-adrenergic
Hypertrophy	Renin-angiotensin, alpha- and beta-adrenergic, endothelin, cytokines (TNF-alpha, interleukin-1 beta) stretch-activated pathways

TNF=tumor necrosis factor.

in several of these mechanisms. The compensatory adjustments listed do stabilize myocardial pump performance in most subjects for a period. However, as implied in Figure 21-3 , ultimately, continuous activation of compensatory mechanisms produces additional myocardial damage in the context of the remodeling process. Some of the ways in which this additional damage occurs are given in Figure 21-4 .

The heart is unique among critical organs in that it has the ability to rapidly and markedly increase its performance

Figure 21-4 Harmful effects of neurohormonal, cytokine, and wall stress (mechanical stretch) signaling in the failing heart.

above a basal level of function. This specialized property, termed "modulatable function" in Figure 21-3 , can account for a twofold to fivefold increase in cardiac output in response to stress or exercise, which allows normal individuals to routinely increase workloads in the course of their daily activities. The specialized mechanisms that are responsible for modulatable function are the beta-adrenergic pathways, or the same mechanisms used as compensatory mechanisms when the heart begins to fail.[31] As shown in Figure 21-3 , because these mechanisms are continuously used to support the failing heart, some of their signal transduction capacity is lost through desensitization changes, thereby resulting in attenuation of exercise responses. [31] [32]

Thus, activation of compensatory neurohormonal/cytokine mechanisms contributes to progression in myocardial dysfunction and remodeling, as well as the HF syndrome, including fluid retention and loss of exercise capacity. Therefore, the most effective therapies in HF associated with primary or secondary dilated cardiomyopathy are neurohormonal antagonists.

DIAGNOSIS OF HEART FAILURE: DETERMINATION OF ETIOLOGY AND PROGNOSIS (see also Chap. 17)

One of the major problems in HF is its initial diagnosis, since the earliest symptoms of HF are often mistaken for other medical problems, including reactive airway disease, chronic obstructive pulmonary disease, pneumonia, and other pulmonary and nonpulmonary problems. Numerous studies have documented the lack of sensitivity and specificity of HF signs and symptoms,[33] [34] and the initial diagnosis is often first made by the radiologist from a chest radiograph demonstrating pulmonary edema and cardiomegaly. Because of these realities, alternative means of initially diagnosing HF are needed, such as a point-of-care blood test. One such test, brain natriuretic peptide, is promising in this regard.[35]

ECHOCARDIOGRAPHY.

If HF is suspected because of symptoms (dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, easy fatigability, or other radiographic or biochemical data), an echocardiogram needs to be obtained. In the limited number of subjects who cannot be imaged by ultrasound for technical reasons, radionuclide ventriculography or magnetic resonance imaging (MRI) can be used to detect ventricular systolic dysfunction. An echocardiogram is the initial test of choice because it evaluates valvular and pericardial causes of HF, as well as being able to detect systolic dysfunction, and it may also be able to detect diastolic dysfunction. An echocardiogram (see Chap. 7) provides immediate information about whether the etiology is a pericardial, valvular, or myocardial process. It is important to emphasize that HF needs to be diagnosed as early as possible so that mortality- and morbidity-lowering treatment can be initiated.

If impaired left ventricular systolic function is detected by echocardiography, more precise measurement of the function of both ventricles may be indicated via radionuclide ventriculography (see Chap. 9). This imaging modality is able to measure left ventricular systolic function more precisely, which is important from a prognostic standpoint,[29] [30] and for monitoring the response to beta-blocker therapy, a treatment that favorably affects systolic function (see below).[16] Radionuclide ventriculography can also measure right ventricular function, which is another prognostic index in chronic HF.[36] As shown in Table 21-4 , when right ventricular structural abnormalities are suspected, cardiac MRI is indicated (see Chap. 10) because this modality is currently the best available imaging method for visualizing right ventricular pathology and function.

DIASTOLIC DYSFUNCTION (see Chaps. 15 and 16).

The diagnosis of diastolic dysfunction is largely one of exclusion. That is, to make the diagnosis of diastolic dysfunction, two pieces of data are required: documentation of normal or near-normal systolic function and unequivocal evidence of HF. The latter may be provided by unambiguous documentation of acute episodes of decompensation (e.g., pulmonary edema on a chest radiograph plus symptoms of breathlessness or right-sided failure) or chronic myocardial dysfunction resulting in high filling pressure, decreased cardiac output, and impaired functional capacity. Although echocardiographic and radionuclide ventriculographic data can contribute to a diagnosis of diastolic dysfunction, neither are considered sufficiently definitive to establish the diagnosis on the basis of isolated measurements. Finally, diastolic dysfunction as the cause of HF in a relatively young (<60 years) patient suggests an infiltrative process, and an endomyocardial biopsy may be indicated.

Once the diagnosis of HF has been established, additional data need to be gathered. In general, the goals of this additional work-up are to determine the etiology and establish a general prognosis. The diagnostic work-up of HF should seek to determine the etiology, as outlined in Table 21-1 , unless the patient is so infirm that no form of intervention would be possible. Figure 21-5 gives an algorithm for a work-up of confirmed or suspected cases of HF. Cardiac catheterization is often indicated, as discussed in Table 21-4 .

ENDOMYOCARDIAL BIOPSY.

Perhaps the most controversial diagnostic test in the work-up of heart muscle disease is endomyocardial biopsy (see Chap. 11). This procedure in inexperienced hands can be associated with complications, including death in rare cases (
1 percent). On the other hand, recent data indicate that in the presence of

TABLE 21-4 -- INDICATIONS FOR CARDIAC CATHETERIZATION AFTER EVALUATION FOR HEART FAILURE AND PERFORMANCE OF AN ECHOCARDIOGRAM

ECHOCARDIOGRAPHY, CLINICAL FINDINGS	CARDIAC CATHETERIZATION OR OTHER PROCEDURE
Significant pericardial effusion, evidence of tamponade	Right-heart catheterization, pericardiocentesis
Thickened pericardium, evidence of cardiac compression	Right- and left-heart catheterization, with or without endomyocardial biopsy if restriction suspected
Severe aortic or mitral regurgitation, LV enlargement with decreased systolic function	Right- and left-heart catheterization, coronary angiography in anticipation of possible surgery
Aortic stenosis	Right-heart catheterization, coronary angiography in anticipation of surgery
Mitral stenosis	Right- and left-heart catheterization, coronary angiography in anticipation of possible surgery
LV enlargement, decreased systolic function with valvular abnormalities less than severe	Right- and left-heart catheterization, coronary angiography, possible endomyocardial biopsy if coronaries normal
Normal LV size, function	Right- and left-heart catheterization, coronary angiography, possible endomyocardial biopsy if coronaries normal to rule out an infiltrative process
Hypertrophic cardiomyopathy with ASH, with or without mitral regurgitation	Coronary angiography if surgery (myectomy with or without mitral valve replacement) contemplated
Normal LV size, decreased systolic function, no history of anthracycline use	Right- and left-heart catheterization, coronary angiography, endomyocardial biopsy if coronaries normal to rule out inflammatory heart disease
RV dysfunction, arrhythmia	MRI (to rule out ARVD)
RV dysfunction, isolated	Right-heart catheterization (to rule out PPH)
ARVD=arrhythmogenic right ventricular dysplasia; ASH=asymmetrical septal hypertrophy; LV=left ventricular; MRI=magnetic resonance imaging; PPH=primary pulmonary hypertension; RV=right ventricular	

Figure 21-5 Algorithm for establishing the diagnosis of heart failure and determining etiology and prognosis. LV=left ventricular; MR=magnetic resonance imaging; RV=right ventricular.

unexplained heart muscle disease, endomyocardial biopsy yields important diagnostic/prognostic information in 11 percent of patients,[37] a figure high enough to justify biopsy provided that experienced personnel are available to perform it and interpret the results.

In cases of systolic dysfunction caused by a primary or secondary dilated cardiomyopathy, precise determination of the degree of left and right ventricular dysfunction will have important prognostic value. Additional clinical characteristics that may have an impact on the prognosis are the degree of pulmonary hypertension, the presence or absence of high-grade ventricular arrhythmia, and the extent of coronary artery disease. Importantly, valuable prognostic information can be gained by measuring peak oxygen consumption (V_{O_2}), which in chronic HF correlates with prognosis independently of left ventricular function.[38]

MANAGEMENT OF ACUTE, NEW-ONSET HEART FAILURE

TRANSIENT HEART FAILURE.

Although chronic HF is the most commonly encountered form of symptomatic myocardial dysfunction, HF may also be acute and not superimposed on chronic pump dysfunction (see also Chap. 18). Such manifestations can occur in the postoperative state following cardiac surgery,[39] in the setting of severe brain injury,[40] secondary to ischemic insults, or after the sudden onset of an inflammatory process or any pathophysiological mechanism that rapidly produces myocardial injury. The general pathophysiological mechanism involved is either some form of "stunning" of functional myocardium (see Chap. 14) or abrupt loss of functioning tissue that occurs before compensatory mechanisms can stabilize function. In both of these situations, myocardial function is adequate to support the circulation once recovery has occurred, and in the case of mechanisms that may produce stunning, such as cardiopulmonary bypass, other ischemic insults, and severe brain injury (where the stunning is probably related to massive release of catecholamines[40]), myocardial function may be completely normal on recovery.

Treatment.

Management of episodes of acute HF caused by an evanescent process depressing myocardial function is support of pump function with positive inotropic agents (see Chap. 18) and/or, if extremely severe, with mechanical devices (see Chap. 19) to the extent necessary to provide adequate perfusion of critical organs. Once function has recovered, no further treatment may be necessary. In the case of ischemia caused by coronary artery disease or another mechanism that may persist to cause recurrent problems, treatment of the underlying process is the management goal. Further details of the treatment of transient myocardial failure are given below under the treatment of decompensated chronic HF.

NEW-ONSET, PERSISTENT HEART FAILURE.

The most common manifestation of acute, new-onset HF is superimposition on a chronic process that has previously been subclinical and in which myocardial function has been supported by the compensatory mechanisms described in Table 21-3 . Therefore, most episodes of new-onset HF are actually the first episode of decompensation, similar to what occurs in established chronic HF.

How much myocardial functional loss can be countered by compensatory mechanisms? The quantitative relationship between degree of myocardial loss and development of myocardial pump dysfunction has been examined in two settings, following myocardial infarction[41] [42] and after individual cardiac myocyte "dropout" from anthracycline cardiotoxicity.[43] The experimental model data from acute myocardial infarction[41] [42] are more relevant to acute-onset HF superimposed on previously normal cardiac function, while the anthracycline data generated in patients represent decompensation superimposed on a chronic myocardial process that has previously been stabilized by compensatory mechanisms. The conclusion from the myocardial infarction studies conducted in animal models was that loss of 30 percent or less of the left ventricle in rats[41] and 25 percent or less in dogs[42] is relatively well tolerated, whereas in rats,[41] infarcts in excess of 46 percent were associated with severe hemodynamic compromise.

Investigation of the structure-function relationship in anthracycline-induced cardiomyopathy (see Chap. 69) was conducted in the intact human heart in patients receiving

Figure 21-6 Relationship of the degree of myocardial damage to myocardial dysfunction in anthracycline-induced cardiomyopathy in 15 subjects who underwent serial biopsy. Myocardial damage is assessed semiquantitatively by the Billingham scale according to the percentage of cells exhibiting an anthracycline effect on endomyocardial biopsy (biopsy score).[43] [44] [45] Myocardial dysfunction is assessed by a "catheterization score" based on abnormalities detected by right-heart catheterization with exercise.[43] [44] [45]

the antitumor agent doxorubicin (Adriamycin). Myocardial damage in this unique form of drug-induced heart disease consists of vacuolization and myofibrillar loss in individual cardiac myocytes, which are typically surrounded by myocytes that are unaffected.[43] By morphometrically counting the number of affected myocytes relative to the total in a field of endomyocardial biopsy material, it is possible to determine the percentage of cells that are nonfunctional because of the anthracycline process.[44] [45] The percentage of affected cells is converted to a semiquantitative score, as described in Figure 21-6 . The degree of myocardial damage can then be related to the degree of myocardial dysfunction, as assessed by right-heart catheterization performed at rest and with exercise.[43] [44] [45] As shown in Figure 21-6 , it is not until more than 15 percent of cells are damaged that detectable myocardial dysfunction develops, and moderate

dysfunction (grade 2 catheterization abnormalities in Fig. 21-6) does not develop until more than 25 percent of cardiac myocytes are involved. In other words, as in myocardial infarction, in anthracycline-associated cardiomyopathy a certain amount of myocardial damage can be tolerated with the aid of compensatory mechanisms. In anthracycline cardiomyopathy, these compensatory mechanisms rely heavily on adrenergic stimulation, since hypertrophy is inhibited by the effects of anthracyclines on myocardial protein synthesis.[46] [47]

Therefore, data from these model systems suggest that the initial, sudden onset of HF will occur when compensatory mechanisms can no longer sustain normal myocardial function. Consequently, myocardial function and structure usually indicate a chronic remodeling process at the initial evaluation for HF.

Treatment of acute, new-onset myocardial failure does not differ from that of decompensated chronic HF, which is discussed in detail below.

MANAGEMENT OF CHRONIC HEART FAILURE

Pharmacological Therapy for Chronic Heart Failure Caused by Systolic Dysfunction

The pharmacological treatment of chronic HF is best understood by subdividing the patient population into four groups as described in Table 21-5 . This "HF stage" classification system reflects the average symptomatic status of the patient inasmuch as patients typically move from one NYHA class to another within the stage groups. In general, the average symptomatic status is directly related to hospitalization frequency and is also related to mortality risk as demonstrated in Figure 21-7 and described in Table 21-5 . Important differences between the HF stage-ordered classification and the NYHA functional class are that the stage classification (1) begins with some level of disability as opposed to asymptomatic status, (2) ends with a more advanced level of disability than is generally reflected by the NYHA Class IV category, and (3) recognizes the reality that patients with HF often move from one level of symptoms to another, for example, typically exhibiting Class III symptoms that transiently increase to Class IV depending on medical management and other factors.

As outlined in Table 21-6 , the goals of treatment for chronic HF are to (1) relieve symptoms, (2) improve functional capacity and reduce disability, (3) decrease the intensity of medical care and reduce economic cost, (4) delay progression of or reverse remodeling and myocardial dysfunction, and (5) reduce mortality. Depending on the stage that a particular HF patient is in, one or more of these goals may be more important than the others and dictate the type of agent to be developed or used once efficacy and safety are established.

TABLE 21-5 -- CLINICAL STAGES OF CHRONIC HEART FAILURE ASSOCIATED WITH SYSTOLIC DYSFUNCTION BASED ON SYMPTOMS AND HOSPITALIZATION REQUIREMENT

STAGE	DESCRIPTION	NYHA CLASS	ANNUALIZED MORTALITY (%)*	HOSPITALIZATIONS/YEAR
A (asymptomatic-mild)	Asymptomatic or only minimal symptoms, rare hospitalizations	I-II	2-5	<0.25
B (mild-moderate)	Mild-moderate symptoms, infrequent hospitalizations	II-III	5-15	0.25-0.75
C (advanced)	Moderate-severe symptoms, frequent hospitalizations	III-IV	15-25	0.75-2
D (severe)	Persistent, severe symptoms; frequent prolonged or continuous hospitalizations	IV	>25	>2

*Risk also depends on the degree of myocardial dysfunction and other factors.

Figure 21-7 Plot of the relationship between survival or hospitalization frequency and New York Heart Association Class in chronic heart failure.

STAGE A (NO OR MILD HEART FAILURE, NYHA CLASS I/II SYMPTOMS).

As for any chronic disease process, the most effective way to deal with the HF problem is to treat it early, before irreversible damage has developed. The goals of treatment of stage A HF (see Table 21-6) are to prevent progression of the underlying pathophysiological processes of remodeling and dysfunction and thereby prevent disease progression and overt development of the HF syndrome. However, only limited data actually support this generally accepted belief. Clinical trial experience is confined to one study, the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial.[48] That trial demonstrated that the angiotensin-converting enzyme (ACE) inhibitor enalapril reduced the probability of development of overt HF by 37 percent and reduced the

combined endpoint of mortality plus HF hospitalizations by 20 percent.[48]

TABLE 21-6 -- GOALS AND PHARMACOLOGICAL TREATMENT FOR VARIOUS STAGES OF HEART FAILURE

STAGE	GOALS (IN ORDER OF IMPORTANCE)	TREATMENT
A (asymptomatic-mild)	Reverse or prevent progressive remodeling and dysfunction	ACE inhibitors
		? Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
	Prevent overt heart failure or progressive symptoms	ACE inhibitors
		? Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
B (mild-moderate)	Reverse or prevent progressive remodeling and dysfunction	ACE inhibitors
		Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
	Improve symptoms and functional capacity	Diuretics
		ACE inhibitors
		Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
		Digoxin
		Reduce dietary Na
	Reduce disability and hospitalizations	Diuretics
		ACE inhibitors
		Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
		? Digoxin
		Reduce dietary Na
	Reduce mortality	ACE inhibitors

		Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
C (advanced)	Reduce mortality	ACE inhibitors
		Spironolactone
		? Beta-blocking agents
		? Other neurohormonal or cytokine antagonists
	Reduce disability and hospitalizations	Reduce dietary Na
		Diuretics
		ACE inhibitors
		Beta blockers
		Spironolactone
		? Other neurohormonal or cytokine antagonists
		? Positive inotropic agents
	Improve symptoms and functional capacity	Reduce dietary Na
		Diuretics
		ACE inhibitors
		Spironolactone
		? Other neurohormonal or cytokine antagonists
		? Positive inotropic agents

ACE=angiotensin-converting enzyme.

TABLE 21-7 -- CLINICAL TRIALS OF MEDICAL THERAPY FOR MILD TO MODERATE HEART

TRIAL (YEAR OF PUBLICATION)	ENTRY CRITERIA	n	THERAPY	FOLLOW-UP	PRIMARY ENDPOINT	
ANTIARRHYTHMICS						

GESICA[142] (1994)	NYHA II-IV LVEF <35%	516	Amiodarone vs. placebo	--	Amiodarone decreased mortality
CHF-STAT[143] (1995)	History of CHF PVC 10/hr EF 40%	674	Amiodarone vs. placebo	45 mo	Neutral for mortality
BETABLOCKERS					
U.S. Carvedilol Program[4] (1996)	NYHA II-IV LVEF <35%	1094	Carvedilol vs. placebo	6 mo	
CIBIS-II[5] (1999)	NYHA III-IV	2647	Bisoprolol vs. placebo	16 mo	Favorable for mortality

MERIT-HF[6] (1999)	NYHA II-IV	3991	Metoprolol CR/XL vs. placebo	12-mo mean	Favorable for mortality and morbidity/mortality combined
COPERNICUS (ongoing)	NYHA IIIB-IV LVEF <25%	1800	Carvedilol vs. placebo	--	Mortality
VASODILATORS					
V-HeFT-1[144] (1986)	NYHA II-III LVEF <45% CTR >0.55	642	Hyd-Isdn vs. placebo, prazosin vs. placebo	2.5-yr mean	Decreased mortality (Hyd-Isdn); no mortality effect with prazosin
V-HeFT-II[145] (1991)	NYHA II-III LVEF <45% CTR >0.55	804	Enalapril vs. Hyd-Isdn	2.5-yr mean	Decreased mortality with enalapril
CALCIUM ANTAGONISTS					
PRAISE-I[146] (1996)	NYHA III-IV LVEF <30%	1094	Amlodipine. vs. placebo (background ACE inhibitors, digitalis, diuretics)	14.5-mo mean	Neutral for mortality and life-threatening hospitalization

PRAISE-II (ongoing)	NYHA III-IV Nonischemic cardiomyopathy	1800	Amlodipine vs. placebo (background ACE inhibitors, diuretics, digoxin)	--	Mortality
RENIN-ANGIOTENSIN INHIBITORS					
CONSENSUS[59] (1987)	NYHA IV	253	Enalapril vs. placebo	Early termination	Decreased mortality
SOLVD Treatment[49] (1991)	NYHA II-III LVEF <35%	2569	Enalapril vs. placebo	41.4-mo average	Decreased mortality
SOLVD Prevention[48] (1992)	Asymptomatic LVEF <35%	4228	Enalapril vs. placebo	37.4 mo	Equivocal mortality; decreased progression of HF or hospitalization combined with deaths
ATLAS[50] (1998)	NYHA II-IV LVEF <30%	3000	High-dose lisinopril vs. low-dose lisinopril	3 yr	Neutral for mortality
VALHeFT (ongoing)	NYHA II-IV LVEF <40%	5000	Valsartan vs. placebo+standard therapy	--	Mortality/morbidity and mortality

CHARM (ongoing) Preserved systolic function Additive therapy ACE inhibitor intolerant	NYHA II-IV LVEF >40% LVEF <40% LVEF <40%	6500 2800 2700 1000	Candesartan vs. placebo	--	HF mortality and HF hospitalization
INOTROPIC AGENTS					
DIG[147] (1997)	NYHA II-IV, stratified LVEF <45% LVEF >45%	7788	Digoxin vs. placebo	37 mo	Neutral mortality; decreased HF and hospitalization
RALES[7] (1999)	NYHA III-IV LVEF <35%	1663	Spironolactone vs. placebo	34 mo	Decreased mortality and cardiovascular morbidity

ACE=angiotensin-converting enzyme; CTR=cardiothoracic ratio; EF=ejection fraction; HF=heart failur
Hyd-Isdn=hydralazine-isosorbide dinitrate; LVEF=left ventricular EF; NYHA=New York Heart Associat
PVC=premature ventricular contractions.

Adapted from Carson P: Current review of heart failure trials. Cardiology, Vol 5, 1999.

Although it is likely that beta-adrenergic blocking agents will reduce mortality in stage A HF, because of the sample size and therefore the cost considerations of performing placebo-controlled trials in this patient population, to date no beta blocker clinical trial has examined this patient population. Similarly, trials with other neurohormonal antagonists will probably not be performed until efficacy has been demonstrated in later stage HF.

STAGE B (MILD TO MODERATE HEART FAILURE, NYHA CLASS II/III SYMPTOMS).

This stage of HF is the stage in which the majority of clinical trial data are available

because of the prevalence, relative stability, and sample size considerations in these patients (Table 21-7) . As a result, recommendations for medical therapy for Class II to III or stage B HF can be given with a high degree of certainty. The goals of therapy in this stage are, similar to stage A, centered around reversal or prevention of progression of remodeling and dysfunction because the potential for reversibility of the dilated cardiomyopathy phenotype still exists. As remodeling/dysfunction is attenuated or reversed, the other treatment goals outlined in Table 21-6 will be realized, and all are important in stage B HF.

ACE inhibitors[49] and beta-blocking agents[4] [6] [50] have been shown to reduce mortality and hospitalizations in patients with stage B HF (see Figs. 18-6 , 18-8 , and 18-9). ACE inhibitors also improve symptoms and tend to improve functional capacity in this stage of HF,[51] while beta-blocking agents have produced variable results on symptoms and functional capacity.[52] On balance, digoxin has generally improved symptoms and functional capacity in mild to moderate HF,[53] and other, nonapproved positive inotropic agents have as well.[54] [55] [56] However, positive inotropic agents other than digoxin are associated with increased mortality when used chronically in HF, and it is unclear whether newer strategies such as low-dose administration[56] [57] or combination with beta-blocking agents [58] will mitigate theses adverse effects.

Although never subjected to large-scale trials, diuretics are a cornerstone of symptomatic HF treatment beginning in stage B.[58A] The goals of diuretic therapy are to reduce congestive symptoms, reduce wall stress, and attenuate the harmful signaling of remodeling/dysfunction mechanisms outlined in Figure 21-2 . In stage B, a loop diuretic alone will usually suffice, along with potassium replacement to maintain serum levels well into the normal range. Diuretics should be used in conjunction with dietary salt restriction, initially avoiding added salt and then avoiding foods prepared with salt such as canned foods and processed foods.

The majority of patients in stages B and C (described next) should be treated with an ACE inhibitor, a beta-adrenergic blocker, digoxin, a diuretic, and sodium restriction.

STAGE C (ADVANCED HEART FAILURE, NYHA CLASS III/IV SYMPTOMS).

As shown in Figure 21-7 , in this stage of HF the hospitalization rate and mortality begin to markedly increase. Therefore, the main goal of therapy in advanced, stage C HF is to lower the probability of HF-related hospitalization and mortality. ACE inhibitors[59] and the aldosterone antagonist spironolactone[7] have been shown to be effective in this regard. Beta-blocking agents, which are quantitatively more effective than ACE inhibitors in stage B HF, appear to be less effective in reducing mortality and hospitalizations in more advanced HF.[8] However, in a recent trial conducted in stage C patients, the third-generation beta blocker bucindolol did reduce mortality by 10 percent and HF-associated hospitalizations by 14 percent[8] (see also Chap. 18).

In terms of symptom relief and improvement of functional capacity in stage C patients, inhibitors of the renin-angiotensin system, diuretics, and possibly positive inotropic agents have had some success in controlled trials. For diuretics, in stage C HF it is often necessary to add the powerful thiazide diuretic metolazone plus a K^+ -sparing

compound (spironolactone if it is tolerated) to control fluid retention. Dietary salt restriction should be intensified. Trials of inotropic agents in this patient population have not prolonged survival thus far,[60] [61] [62] but promising low-dose and combined beta blocker-inotrope approaches are currently being evaluated.[57] [58]

STAGE D (SEVERE HEART FAILURE, CLASS III/IV SYMPTOMS WITH FREQUENT OR SUSTAINED DECOMPENSATION).

When subjects progress to stage D, i.e., severe HF despite optimal medical management, the goals of therapy change to include palliation of symptoms, reducing rates of hospitalization, and in subjects who are eligible, bridging to cardiac transplantation (see also Chap. 20). In general, reversal of the intrinsic biological processes of remodeling and dysfunction are not possible in this stage. The only treatment shown to be effective in lowering mortality in this stage of HF is ACE inhibition,[59] but despite this treatment, when subjects reach stage D HF, the possibility of salvage by medical therapy is indeed remote.

Although for ethical reasons no randomized study has provided convincing proof, in subjects who periodically decompensate to incipient or overt cardiogenic shock, the administration of non-glycoside-positive inotropic agents is life saving. Currently, no orally administered positive inotropic agents are approved for palliation of advanced HF, but investigational agents[63] [64] have shown enough promise to instigate phase III clinical trials in this regard. Until an oral agent is available, the standard treatment for palliation of advanced HF will remain intermittent or continuous administration of intravenous inotropic agents such as dobutamine,[65] milrinone,[66] or enoximone.[67]

PHARMACOLOGICAL THERAPY IN SUBGROUPS.

Two HF demographic groups have exhibited a response to pharmacological treatment that appears to be different from that of other groups or the population as a whole. The first is American blacks, who in the beta-Blocker Evaluation of Survival Trial[8] (BEST) exhibited a worse response to beta blockade than did the rest of the population (see also Chap. 18). American blacks treated with bucindolol had a statistically insignificant 17 percent increase in mortality as compared with a statistically significant 19 percent reduction in mortality in the rest of the population.[8] A statistical test for interaction between blacks and the remainder of the population was significant, which suggests that this disparity in clinical response was not due to chance.[8] The poorer response of blacks to beta blockade in BEST is reminiscent of the reduced efficacy of beta blockers in treating hypertension in blacks[68] and less efficacy of ACE inhibitors in treating hypertension[68] or HF[69] in blacks.

However, blacks treated with carvedilol in the U.S. Carvedilol Trials fared as well as the rest of the population,[70] perhaps because they had only stage B HF as opposed to the stage C subjects in BEST. Another possibility for the difference in response to beta blockade in BEST and the U.S. Carvedilol Trials is that the more powerful vasodilator properties of carvedilol were beneficial in a population enriched in hypertensive heart disease.[8] [70] What is certain is that blacks with HF have very different associated demographics, including a lower prevalence of ischemic cardiomyopathy, more hypertension by history, a higher prevalence of diabetes, and a younger subject

population.[8] [70] [71] Thus, it is not clear whether race per se or associated demographic modifiers account for the difference in response to beta blockers and ACE inhibitors that has been noted in clinical trials. The scientific basis for these differences needs to be elucidated, and more effective treatment of blacks with HF needs to be developed. For the present, it is prudent to avoid beta blockers in black patients with stage C HF and to consider the alternative of hydralazine/isosorbide dinitrate instead of ACE inhibitor treatment.[69]

Women with HF may also have special characteristics that can influence pharmacological treatment.[72] [73] [74] These characteristics include a better prognosis than men,[10] greater functional incapacity for the same degree of left ventricular dysfunction,[72] a higher prevalence of diastolic dysfunction,[73] and a higher percentage of elderly individuals.[73] Some or all of these factors may contribute to the tendency for lower effect sizes in women versus men in the few clinical trials that have enrolled enough women to report differences in response versus men.[6] [8]

Pharmacological Therapy for Chronic Heart Failure Caused by Diastolic Dysfunction (Table 21-8)

As many as 30 to 40 percent of patients with symptomatic HF exhibit diastolic rather than systolic dysfunction (see also Chaps. 15 , 16 , and 17).[74] [75] Diastolic dysfunction is much more common in women[73] and the elderly,[76] and in the latter it may be the dominant form of HF.[76] Additional risk factors for diastolic dysfunction include a history of hypertension[77] or diabetes mellitus.[78] Most studies indicate that that patients with diastolic dysfunction as the primary cause of HF have a better prognosis than do controls with systolic dysfunction.[74] Importantly, as discussed above, predominantly diastolic dysfunction in a younger (<60 years) patient suggests an infiltrative cardiomyopathic process.

Unlike systolic dysfunction, no definitive pharmacological therapy for diastolic dysfunction is available. The cornerstone of treatment is careful regulation of ventricular filling pressure by diuretics, in a range that prevents excessive dyspnea and liver congestion but allows for adequate cardiac output. ACE inhibitors and/or spironolactone may make diuretic management easier by preventing excessive activation of the renin-angiotensin-aldosterone system. In addition, in limited settings some evidence indicates that ACE inhibitors improve ventricular relaxation,[79] but this improvement does not seem to be translated into benefit in subjects with diastolic HF.[80] Beta blockers may be used to slow the heart rate and prolong filling time, and beta blockers or amiodarone may be required to control and prevent

TABLE 21-8 -- DIASTOLIC DYSFUNCTION: TREATMENT GOALS AND METHODS

REDUCE THE CONGESTIVE STATE
Salt restriction, diuretics, ACE inhibitors
Dialysis or plasmapheresis

Maintain Atrial Contraction
Direct-current or pharmacological cardioversion
Sequential atrioventricular pacing
Prevent Tachycardia and Promote Bradycardia
Beta blockers
Radiofrequency ablation and pacing
Treat and Prevent Myocardial Ischemia
Nitrates, beta blockers, calcium blockers
Bypass surgery, angioplasty
Control Hypertension and Promote Regression of Hypertrophy
Antihypertensive agents
Attenuate Neurohormonal Activation
Beta blockers, ACE inhibitors
Prevent Fibrosis and Promote Regression of Fibrosis
ACE inhibitors, spironolactone
Antiischemic agents
Improve Ventricular Relaxation
Phosphodiesterase inhibitors
Systolic unloading
Treat ischemia
Calcium blockers (in hypertrophic cardiomyopathy)
ACE=angiotensin-converting enzyme.
From Smith TW (ed): Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1996, p 241.

supraventricular arrhythmias. Finally, phosphodiesterase inhibitors (PDEIs) have been shown to improve diastolic function acutely,[81] but there has been no controlled experience with these agents in chronic therapy.

Adjunctive Pharmacological Therapy

ANTIARRHYTHMIC AGENTS (see also Chap. 23).

In general, antiarrhythmic therapy in HF patients is reserved for symptomatic arrhythmias or for control of ventricular responses to atrial fibrillation. With regard to treatment of ventricular arrhythmias, the Cardiac Arrhythmia Suppression Trial (CAST),[82] [83] which was conducted not in an HF population but in subjects with left

ventricular dysfunction after myocardial infarction, convincingly demonstrated that type 1 antiarrhythmic agents (i.e., Na channel blockers) increase mortality when used to suppress ventricular premature contractions. The Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM)[84] extended the evidence for adverse effects of type 1 agents in subjects with left ventricular dysfunction and Holter monitor-documented ventricular arrhythmias or inducible sustained ventricular tachycardia. In the ESVEM trial, sotalol, a beta-blocking agent with type III antiarrhythmic properties, was the most effective agent. However, ESVEM had no placebo control, so it was not possible to precisely measure the efficacy and adverse effects of sotalol.

The antiarrhythmic agent that has undergone the most extensive evaluation for efficacy and safety in populations with HF or left ventricular dysfunction is amiodarone. Similar to sotalol, amiodarone is a type III antiarrhythmic with antiadrenergic properties[85] (see Chap. 23). In controlled clinical trials in HF or asymptomatic left ventricular dysfunction, amiodarone either has been associated with reduced mortality[86] or has been equivalent to placebo. [87] In other words, amiodarone is the one antiarrhythmic agent that appears to be safe in patients with left ventricular dysfunction and HF. However, amiodarone has pulmonary, thyroid, liver, and other toxicities, and its use should be accompanied by careful surveillance for adverse effects. Additionally, as for all antiarrhythmic agents, amiodarone has negative inotropic effects and may be poorly tolerated by patients with advanced HF.

Treatment of arrhythmias has evolved to catheter-based ablation (see Chap. 23) and implantable defibrillators (see Chap. 24). Current indications for device therapy for ventricular arrhythmias are given below.

ANTICOAGULATION (see also Chap. 62).

An area of considerable controversy is the use of anticoagulation in the form of warfarin in patients with normal sinus rhythm and severe left ventricular dysfunction. In controlled clinical trials, the risk of arterial thromboembolic events, most of which are stroke, ranges from 0.9 to 5.5 per 100 patient-years.[88] [89] Since warfarin convincingly lowers thromboembolism and stroke risk in atrial fibrillation,[90] it is logical that this benefit would extend to subjects with severe left ventricular dysfunction. Such benefit may be particularly true in nonischemic cardiomyopathies, which are associated with a relatively high incidence of left ventricular thrombus.[91] On the basis of these considerations, many, but not all HF centers routinely administer anticoagulants to all patients with moderate or severe left ventricular dysfunction who do not have a contraindication. However, anticoagulation with warfarin is not without risk, and it must be carefully monitored. In chronic HF, a firm indication for anticoagulation can be made in patients with atrial fibrillation, those with a visualized left ventricular thrombus, and those with a history of a thromboembolic event.[92] Anticoagulation in left ventricular dysfunction with normal sinus

rhythm should be considered optional, with the issue to be settled by ongoing clinical trials.

Device Therapy

IMPLANTABLE CARDIAC DEFIBRILLATORS (see also Chap. 24).

Implantable cardiac defibrillators are now the treatment of choice in patients with left ventricular dysfunction who have survived sudden cardiac death,[93] have symptomatic sustained ventricular tachycardia,[93] or have asymptomatic nonsustained but inducible ventricular tachycardia.[94] [95] Data supporting these recommendations are derived from the Antiarrhythmic Versus Implantable Defibrillator Trial[93] (AVID), the Multicenter Automatic Defibrillator Implantation Trial[94] (MADIT), and the Multicenter Unsustained Tachycardia Trial[95] (MUSTT). At this point, the major question is whether implantable defibrillators can reduce mortality in other left ventricular dysfunction or HF populations, such as patients with nonsustained and noninducible ventricular tachycardia, large numbers of premature ventricular contractions, intraventricular conduction delays, and abnormal signal-averaged electrocardiograms, or even in subjects with no evidence of electrophysiological abnormalities.

BIVENTRICULAR PACING.

One of the more interesting developments in HF is the concept that left ventricular or biventricular pacing may be beneficial in a subset of subjects with intraventricular conduction delay, which may include 30 to 50 percent of subjects with advanced left ventricular dysfunction.[96] The biventricular pacing strategy is based on the fact that most subjects with intraventricular conduction delay have asynchronous left ventricular contraction, which results in a reduction in ventricular performance and an increase in regional wall stress.[97] There is no question that, acutely, biventricular or left ventricular pacing can, by synchronizing left ventricular contraction, improve left ventricular dP/dT, ejection fraction,[97] and cardiac index[98] ; reduce wall stress[97] ; and decrease left ventricular filling pressure.[97] [98] These favorable myocardial functional effects contribute to a short-term reduction in neurohormonal activation.[99] If these salutary effects can be sustained in the long term, biventricular pacing would be expected to improve functional capacity and clinical outcomes. Such hypotheses are being tested by the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and the Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trials.

VENTRICULAR ASSIST DEVICES (see also Chap. 19).

Ventricular assist devices have emerged as a potential treatment of chronic HF, beyond their traditional role as a bridge to transplantation. A randomized, controlled clinical trial[100] (the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure [REMATCH] Trial) to test one device is under way in patients

who are not transplant eligible. This trial has, as a control group, optimal medical therapy, and the endpoints are clinically meaningful. If the left ventricular assist device proves superior to medical therapy in this stage C to D HF population and is cost-effective, mechanical device implantation will have a role in the treatment of a subset of ultraadvanced HF patients.

OTHER INVESTIGATIONAL DEVICES.

Several other devices in development may have a role in the treatment of HF. For example, external pneumatic counterpulsation, shown to be effective in treating angina,[101] may have a role in treating HF.[102] One of the more interesting approaches to preventing progressive remodeling is a device (the "Acorn" device) that physically prevents ventricular dilatation in animal models.[103] Clearly, devices of various types will increasingly contribute to HF treatment in the future.

Surgical Therapy

CARDIAC TRANSPLANTATION (see also Chap. 20).

This procedure was the first definitive treatment developed for HF, that is, the first treatment that lowered mortality.[104] The treatment is so successful in advanced or severe stage C or D HF that to this point no randomized study could have been ethically justified. The current survival of severe HF stage D subjects from the enalapril arm of the Cooperative New Scandinavian Enalapril Survival (CONSENSUS) Trial,[59] a cohort of stage C subjects from 1980 prior to ACE inhibitor treatment, is shown in Figure 47-7 . Survival after transplantation is superior to that with medical therapy. However, survival with medical therapy is improving,[52] and with another incremental improvement it will rival transplantation for outcomes in stage C patients.

The biggest limitation of cardiac transplantation is not efficacy or safety, but rather the limited supply of donors available to apply the treatment. It has been estimated that less than 10 percent of subjects who would benefit from cardiac transplantation can actually receive it on the basis of the upward limit of 2000 to 3000 donors per year in the United States.[105] Therefore, transplantation is reserved for subjects who have reached stage D or late stage C HF and are progressing despite application of all medical therapy of proven benefit.

CORONARY ARTERY BYPASS GRAFTING (see also Chap. 37).

Over 15 years ago, the Coronary Artery Surgery Study (CASS)[106] demonstrated that coronary artery bypass grafting (CABG) is superior to medical therapy from a survival standpoint in subjects with symptomatic three-vessel coronary artery disease and reduced but not severely depressed left ventricular ejection fractions (LVEFs). In recent years, the benefit of CABG has been extended to patients with LVEFs lower than the 0.35 cutoff in CASS. Many centers have successfully extended CABG therapy to stage C HF subjects with LVEFs less than 0.30,[107] [108] but no large controlled trials have compared CABG with current recommended standard medical therapy, including beta

blockers. Such trials need to be conducted.

MITRAL VALVE RECONSTRUCTION IN LEFT VENTRICULAR DYSFUNCTION (see also Chap. 46).

Mitral regurgitation occurs to a greater or lesser degree in the remodeled, dilated ventricle. Recently, surgical approaches to correction of mitral regurgitation without valve replacement have been applied to the failing, remodeled ventricle with low operative mortality and impressive early clinical outcomes.[109] However, no prospective controlled/randomized studies have compared mitral valve reconstruction with the best available medical therapy, which itself can reverse remodeling.[16] Thus, the role of mitral valve reconstruction in the setting of remodeling and mitral regurgitation is somewhat unclear and at the moment should be conservatively confined to cases of severe mitral regurgitation with some preservation of left ventricular function, i.e., with ejection fractions over 0.30.

VENTRICULAR REDUCTION SURGERY.

The most controversial treatment of HF developed in recent years is ventricular reduction surgery, originally known as the Batista procedure after the surgeon who developed and popularized it.[110] This procedure involves a direct, surgical approach to reversing remodeling by simply removing a large (20 to 40 percent) amount of the left ventricle and reshaping it.[110] Later approaches have also included mitral valve reconstruction.[111] Despite the considerable initial fanfare of this approach to HF, enthusiasm quickly waned when it was appreciated that the combined rate of mortality, cardiac transplantation, or need for a left ventricular assist device was on the order of 30 percent.[111]

The basic flaw with this approach is represented in Figure 21-2 . Ventricular remodeling is caused by cardiac myocyte lengthening as part of the hypertrophic response. Much of the signaling for myocyte hypertrophy and sarcomeric assembly in series derives from myocardial dysfunction, which in most cases of primary or secondary dilated cardiomyopathy precedes the remodeling process. For example, after myocardial infarction, gradual ventricular dilatation and shape change, i.e., remodeling, take place in a subset of patients over several months to years. This response, which occurs more frequently in patients who have had a large anterior infarction, serves the compensatory role of increasing stroke volume by increasing end-diastolic volume. When a substantial amount of functioning myocardium is surgically removed, even though the ejection fraction may temporarily rise because end-diastolic volume is reduced, on average, stroke volume will not increase and may even decrease to the point of circulatory compromise in many subjects.[111] This process leads to further activation of the signaling mechanisms responsible for remodeling and myocyte dysfunction outlined in Figure 21-2 . Therefore, clinical results with ventricular reduction surgery indicate that in most patients, the bioenergetic benefit of reducing ventricular size does not outweigh

the deleterious consequences of removing functioning myocardium.

The latest direct surgical approach to ventricular remodeling is to not remove functioning myocardium, but to surgically reshape the ventricle off bypass in a minimally invasive approach.[112] While this procedure is more rational than removing functioning myocardium, no controlled data have yet documented its usefulness.

Health Care Delivery Strategies

HEART FAILURE CENTERS.

The number of therapeutic options for the care of HF patients is extensive, and access to investigational agents or complex approaches limited to specialized centers, such as transplantation, are often required. Numerous outcomes studies[113] [114] [115] have documented the utility of such centers, and there is good argument[116] for federal support of such a mechanism analogous to what was done in the United States in the early 1970s for cancer. However, it must be appreciated that the majority of patients are cared for by primary care physicians rather than HF specialists or general cardiologists.[117] The sheer number of HF patients dictates that primary care physicians will continue to care for these patients, but it is likely that specialized centers will have an increasing role as treatment becomes even more complex.

HEART FAILURE CLINICS.

It is evident that a substantial and perhaps a majority of HF patients are not being optimally treated with the most basic medications, much less given more aggressive treatment options such as some of the surgical approaches described above. For example, the latest estimates on the number of HF patients being treated with ACE inhibitors are between 50 percent[118] and 71 percent,[119] whereas on the basis of what is achieved in controlled clinical trials, it should be over 90 percent.[4] [7] [8] For beta blockers, the results are even more dismal, with estimates of 5 percent of the HF population receiving therapy (Kwasha D, personal communication, 1999) as compared with the ideal figure of greater than 25 percent. Inadequate medical treatment of HF no doubt extends beyond the appropriate use of ACE inhibitors or beta blockers and probably includes failure to consistently adhere to a low-salt diet, suboptimal use of diuretics, failure to maintain digoxin levels lower than 1.0 ng/ml, inadequate interval follow-up, and numerous other important factors.

The failure to deliver optimal medical care to HF patients is multifactorial. As for other medical conditions, optimal care includes a health care provider with knowledge and the ability to communicate that knowledge, a method of ensuring that the patient has received and understood the knowledge, a system of encouraging adherence to the recommended regimen, and patient compliance. The elderly nature of many HF patients and the incapacitating nature of the disease syndrome present special challenges to caregivers in this setting. However, many of the challenges to delivering optimal care to HF patients can be met through an integrated specialized clinic approach that uses nurse and physician extender personnel to deliver and ensure the implementation of

care. This approach has been shown to reduce hospitalizations and increase the percentage of patients receiving ideal, guideline-recommended therapy.[120] The end result is lowered cost of HF treatment and probably improved survival.

The biggest challenge to this obvious solution to the delivery of HF care is how to support the additional personnel required in the "HF clinic" model. In specialized centers, the costs are usually supported by sponsored research, and in the community, some health care maintenance organizations or hospitals have seen the wisdom of this cost-reducing approach. This model will probably be adopted in direct relation to the availability of support for it, which in turn is dependent on the health care system.

Exercise

Until recently, HF patients were instructed to avoid exercise, and at one point, bed rest was offered as a treatment of HF.[121] Bed rest is no longer prescribed, and in fact, exercise now appears to be promising as a treatment of HF. It is not surprising that an exercise regimen can increase functional capacity in subjects with HF, as documented in numerous studies.[122] [123] [124] [125] [126] [127] What is surprising is that in small controlled studies, various other aspects of HF thought to be important in prognosis, such as neurohormonal activation,[122] [125] symptoms,[126] resting cardiac function,[127] and quality of life,[122] appear to be improved by exercise. What is lacking is a large, well-controlled clinical outcomes trial to test the hypothesis that moderate levels of exercise improve the natural history of HF. Until such a trial is available, it seems prudent to suggest to patients that they maintain at least some level of conditioning with mild to moderate regimens of aerobic exercise in view of the lack of evidence that such exercise is harmful and the potential beneficial effect on symptoms and individual psychology.

Treatment of Episodes of Decompensation

As discussed above, acute manifestations of HF can either be in the context of new onset or be in subjects with established chronic HF. Treatment of acute episodes of HF are similar in these two scenarios, with the exception that a diagnostic work-up potentially leading to definitive therapy should be done in new cases. Since multiple treatment modalities may be brought to bear on acute HF episodes, the discussion will be divided into pharmacological and nonpharmacological forms of therapy.

Pharmacological Therapy (see also Chap. 18)

Table 21-9 gives the standard treatment modalities typically used to treat acute episodes of HF with advanced,

TABLE 21-9 -- PHARMACOLOGICAL THERAPY FOR ACUTE, DECOMPENSATED HEART FAILURE

TREATMENT MODALITY	SPECIFIC EXAMPLES
Intravenous diuretics	Furosemide, bumetanide, torsemide
Intravenous positive inotropic agents	Dobutamine, milrinone, enoximone
Intravenous afterload reducers	Nitroprusside, nitroglycerin, brain natriuretic peptide*
Blood pressure, renal perfusion support	Intravenous dopamine

*Not yet approved in the United States.

Class IV symptoms. In general, treatment begins with intravenous diuretics, which in subjects with adequate organ perfusion often suffice to produce diuresis accompanied by a prompt drop in preload and relief of symptoms related to pulmonary edema. If peripheral perfusion is compromised or diuresis does not ensue, intravenous dobutamine, an inotropic beta/alpha-adrenergic agonist that produces an increase in cardiac output without substantially dropping preload or blood pressure,[128] can be added via a well-secured peripheral line. A PDEI such as milrinone[129] [130] or enoximone[131] [132] can also be used to treat decompensated HF, but a PDEI should not be administered without pulmonary artery pressure monitoring unless it is certain that left ventricular filling pressure is high (>16 mm Hg). The reason for this precaution is that PDEIs are such potent venodilators that in patients with normal or low filling pressure, they can drop preload to undesirably low levels. Finally, in decompensated subjects who are still receiving beta-blocking agents, a PDEI rather than a beta blocker is the treatment of choice because PDEIs retain full or even have enhanced activity in the presence of beta blockade.[133]

If the situation has not stabilized, additional inotropic support with or without supplemental afterload reduction is indicated and best delivered with the aid of pulmonary artery catheter monitoring (Table 21-10) . The combination of dobutamine and a PDEI is additive for effects on cardiac output and, via the PDEI, will produce a reduction in pulmonary artery and left ventricular filling pressure.[134] [135] The latter may provide welcome unloading of the right ventricle inasmuch as high pulmonary artery pressure can produce limiting right ventricular dysfunction in some patients.

Once optimal inotropic therapy is being delivered, pure vasodilators can be additionally administered to subjects with persistently high systemic or pulmonary vascular resistance.

TABLE 21-10 -- SUGGESTED INDICATIONS FOR HEMODYNAMIC MONITORING DURING THERAPY FOR DECOMPENSATED HEART FAILURE

PRESENCE OF HYPOPERFUSION SUSPECTED FROM :

Narrow pulse pressure
Mental obtundation
Declining renal function with high volume status
Intense Neurohormonal Activation Suggested by :
Serum sodium below 133 mEq/L
Persistent systemic hypotension with low doses of ACE inhibitors
Symptoms of Congestion at Rest in the Presence of :
Frequent angina or other evidence of ischemia
Frequent symptomatic ventricular arrhythmias
Baseline impairment in renal function
Severe intrinsic pulmonary disease
Persistent or Recurrent Symptoms of Congestion at Rest or During Minimal Exertion Despite :
Administration of high doses of loop diuretics
Addition of metolazone or hydrochlorothiazide
Salt and fluid restriction
ACE=angiotensin-converting enzyme.
Modified from Smith TW (ed): Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1996, p 201.

Vasodilators such as nitroprusside or nitroglycerin can also be used in lieu of a positive inotropic agent, particularly in patients with higher systemic vascular resistance. In addition to more traditional vasodilators, brain natriuretic peptide is a novel, mild vasodilator with the unique property of preferentially increasing renal blood flow.[136] [137] However, brain natriuretic peptide is still undergoing clinical trials and is not yet approved by the Food and Drug Administration.

Finally, in patients with blood pressure so low that renal perfusion is compromised, dopamine may be added to increase perfusion pressure and renal blood flow via this agent's alpha-adrenergic and dopaminergic properties. However, dopamine should not be considered an effective positive inotropic agent because the majority of its weak, partial beta-agonist effect is mediated by norepinephrine release,[138] which results in tachyphylaxis within 12 hours of administration.[139]

Nonpharmacological Therapy

Table 21-11 lists some nonpharmacological therapies that can be used to treat acute episodes of HF. In general, nonpharmacological therapy is used only if drug therapy does not stabilize the patient. Although its effectiveness has never been demonstrated in a controlled clinical trial, use of an intraaortic balloon pump (IABP) can increase

cardiac output modestly while increasing effective coronary perfusion pressure (see Chap. 19). This benefit and the ease of use of this device make it an attractive adjunct in myocardial failure occurring in the context of ischemia. The IABP is also helpful in nonischemic myocardial failure. However, contraindications to IABP use include significant aortic regurgitation and severe peripheral vascular disease. If pharmacological therapy plus IABP does not stabilize the patient, a ventricular assist device should be used in selected individuals, as discussed in Chapter 19 .

Because of the success of treating acute myocardial infarction by primary angioplasty[140] with stenting [141] (see Chap. 35), percutaneous coronary intervention techniques (see Chap. 38) have assumed an important role in treating the most common cause of new-onset acute HF, that arising in the setting of myocardial infarction. In general, the primary goal of treating myocardial failure in the setting of infarction is to establish and maintain patency of the infarct artery in the most expeditious manner possible. The catheterization laboratory is also an ideal setting in which to initiate adjunctive treatment such as an IABP, mechanical ventilation, and optimal pharmacological support guided by hemodynamic monitoring. Other catheterization techniques used in acute HF treatment include pericardiocentesis for tamponade (see Chap. 50) and relief of severe mitral stenosis by balloon valvuloplasty (see Chap. 46) (see Table 21-11).

Occasionally, urgent cardiac surgery is required for the treatment of acute HF. As outlined in Table 21-11 , these procedures include CABG in acute ischemic disorders involving left main disease or in patients in whom percutaneous coronary intervention is not a technical option, acute aortic or mitral valve surgery, and on rare occasion, transplantation. In general, it is neither desirable nor feasible to

TABLE 21-11 -- NONPHARMACOLOGICAL THERAPY FOR ACUTE, DECOMPENSATED HEART FAILURE

TREATMENT MODALITY	SPECIFIC EXAMPLES
Oxygenation	Supplemental oxygen, mechanical ventilation
Balloon counterpulsation	Intraaortic balloon pump
Ventricular assist device	Pulsatile-flow LVAD
Pacing	AV sequential pacemaker
Urgent cardiac catheterization	PTCA, mitral valvuloplasty, pericardiocentesis
Urgent cardiac surgery	CABG, AVR, MV repair or replacement, transplantation

AV=atrioventricular; AVR=aortic valve replacement; CABG=coronary artery bypass grafting; LVAD=left ventricular assist device; MV=mitral valve; PTCA=percutaneous transluminal coronary angioplasty.

perform cardiac transplantation on someone during their initial experience with HF.

Investigational Treatment and Future Directions

In the last 10 years, major progress has been made in the medical treatment of HF. In mild to moderate stage B HF, the use of ACE inhibitors and beta-adrenergic blocking agents has reduced mortality by nearly 50 percent.[52] The degree of the remaining challenge and the size of the pharmaceutical market will ensure that medical therapy will continue to improve for all degrees of HF. However, to attain such progress, subjects with HF will need to continue to be enrolled in investigational protocols, typically available at larger, well-organized HF centers. In addition, left ventricular assist devices will continue to become more practical and economical and will probably soon become standard treatment of advanced HF in selected individuals.

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GUIDELINES
MANAGEMENT OF HEART FAILURE

Thomas H. Lee

Heart failure guidelines were published by the Agency for Health Care Policy and Research (AHCPR) in 1994,[1] by an American College of Cardiology/American Heart Association (ACC/AHA) task force in 1995,[2] and by a task force of the Heart Failure Society of America in 1999.[3] These guidelines preceded research on new strategies for heart failure, such as beta-blockers, spironolactone, angiotensin receptor blockers, and left ventriculoplasty, and therefore do not comment on their role. The guidelines are consistent and, in some ways, complementary. The ACC/AHA guidelines contain detailed information on management of acute syndromes, such as cardiogenic shock. In contrast, a focus of the AHCPR guidelines is improving care by reducing common errors in diagnosis and chronic management.

Among the common errors in management and testing cited by the AHCPR panel are

- Overuse of testing technologies
- Inadequate treatment of coexistent hypertension
- Inadequate education for patient, family, and caregivers
- Inappropriate treatment of heart failure not due to systolic dysfunction
- Suboptimal patient involvement in care and compliance

Delayed referral for transplantation

Underutilization of exercise prescriptions

Underutilization of angiotensin-converting enzyme (ACE) inhibitors

Inadequate dosing of diuretics in patients with persistent volume overload

Failure of clinicians to appreciate adverse effects of medications

To reduce the frequency of these errors, the AHCPR panel formulated recommendations for a wide range of topics (excerpted in Table 21-G-1). [1] The multidisciplinary group that developed these guidelines used an A-B-C system to grade the strength of evidence in support of their recommendations. The focus of the AHCPR guidelines were patients with left ventricular systolic dysfunction leading to volume overload or inadequate tissue perfusion, but one of their most specific recommendations was aimed at preventing this syndrome: The guidelines recommend use of ACE inhibitors in patients with moderately or severely reduced left ventricular systolic function even if they are asymptomatic.

TABLE 21--G-1 -- SELECTED RECOMMENDATIONS FROM GUIDELINES FOR HEART FAILURE

Topic	**Recommendation**	**Strength of Evidence**
Prevention in asymptomatic patients	Asymptomatic patients with moderately or severely reduced left-ventricular systolic function (ejection fraction <35--40 percent) should be treated with an angiotensin-converting enzyme (ACE) inhibitor to reduce the chance of developing clinical heart failure.	A
Initial evaluation	Patients with symptoms that are highly suggestive of heart failure should undergo echocardiography or radionuclide ventriculography to measure left ventricular function even if physical signs of heart failure are absent.	C

Diagnostic testing	Practitioners should perform a chest x-ray; electrocardiography (ECG); complete blood count (CBC); serum electrolytes, serum creatinine, serum albumin, liver function tests; and urinalysis for all patients with suspected or clinically evident heart failure. A T4 and thyroid-stimulating hormone (TSH) level should also be checked in all patients over the age of 65 with heart failure and no obvious etiology and in patients who have atrial fibrillation or other signs of symptoms of thyroid disease. Routine use of myocardial biopsy is not recommended.	C
Screening for arrhythmias	Screening evaluation for arrhythmias such as ambulatory ECG is not routinely warranted.	A
Hospital admission criteria	Presence of suspicion of heart failure and any of the following findings usually indicates a need for hospitalization: Clinical or ECG evidence of acute myocardial ischemia. Pulmonary edema or severe respiratory distress. Oxygen saturation below 90 percent (not due to pulmonary disease). Severe complicating medical illness (e.g., pneumonia). Anasarca. Symptomatic hypotension or syncope. Heart failure refractory to outpatient therapy. Inadequate social support for safe outpatient management	C

Hospital discharge criteria	Patients with heart failure should be discharged from the hospital only when: Symptoms of heart failure have been adequately controlled. All reversible causes of morbidity have been treated or stabilized. Patients and caregivers have been educated about medications, diet, activity and exercise recommendations, and symptoms of worsening heart failure. Adequate outpatient support and follow-up care have been arranged.	C
Activity recommendations	Regular exercise should be encouraged for all patients with stable NYHA Class I-III heart failure.	B
Cardiac rehabilitation	There is insufficient evidence at this time to recommend the routine use of supervised rehabilitation programs for patients with heart failure.	C
Diet	Dietary sodium should be restricted to as close to 2 grams per day as possible.	C
	People who drink alcohol should be advised to consume no more than one drink per day.	C
Discussion of prognosis	All patients should be encouraged to complete a durable power of attorney for health care or another form of advanced directive.	N/A
Initial pharmacological management	Patients with heart failure and signs of significant volume overload should be started immediately on a diuretic. Patients with mild volume overload can be managed adequately on thiazide diuretics, whereas those with more severe volume overload should be started on a loop diuretic.	C

ACE inhibitors	Patients with heart failure due to left-ventricular systolic dysfunction should be given a trial of ACE inhibitors unless specific contraindications exist: (1) history of intolerance or adverse reactions to these agents, (2) serum potassium greater than 5.5 mEq/liter that cannot be reduced, or (3) symptomatic hypertension. Patients with systolic blood pressure less than 90 mm Hg have a higher risk of complications and should be managed by a physician experienced in utilizing ACE inhibitors in such patients. Caution and close monitoring are also required for patients who have a serum creatinine level greater than 3.0 mg/dL or an estimated creatinine clearance of less than 30 mL/min; half the usual dose should be used in this setting.	B
Digoxin	Digoxin should be used routinely in patients with severe heart failure and should be added to the medical regimen of patients with mild or moderate heart failure who remain symptomatic after optimal management with ACE inhibitors and diuretics.	C
Hydralazine/isosorbide dinitrate	Isosorbide dinitrate and hydralazine is an appropriate alternative in patients with contraindications for intolerance to ACE inhibitors.	B
Anticoagulation	Routine anticoagulation is not recommended.	C
Patient follow-up	Patients should be instructed to call if they experience an unexplained weight gain greater than 3--5 pounds since their last clinical evaluation.	C

Strength of Evidence: A = strongest, B = intermediate; C = weakest on consensus of expert opinion.

From Konstam M, Dracup K, Baker D, et al: Heart Failure: Evaluation and Care of Patients with Left-Ventricular Systolic Dysfunction. Clinical Practice Guidelines No. 11. AHCPR Publication No. 94-0612. Rockville, MD, Agency for Health Care Policy and Research, NHLBI Public Health Service, U.S. Department of Health and Human Services, June 1994.

INITIAL EVALUATION

The AHCPR guidelines identify symptoms that should trigger consideration of an evaluation for heart failure, the most critical of which are paroxysmal nocturnal dyspnea, orthopnea, or new-onset dyspnea on exertion. Unless the patient has clear evidence of a noncardiac cause for these symptoms, the AHCPR guidelines indicate that echocardiography or radionuclide ventriculography should be used to evaluate left

ventricular function, even if physical signs of heart failure are not present. Other symptoms that suggest this diagnosis are lower extremity edema, decreased exercise tolerance, unexplained confusion or fatigue, and abdominal symptoms associated with ascites, hepatic engorgement, or both.

Similar recommendations are given for tests in the initial evaluation of heart failure in both the AHCPR and the ACC/AHA guidelines (Table 21-G-2); also see Table 21-G-1). The goals of this testing include assessment of severity and identification of causes of the myocardial dysfunction. However, both sets of guidelines emphasize that screening evaluation, such as ambulatory electrocardiography, for arrhythmias should not be performed routinely for all patients with heart failure; instead, this test should be reserved for patients with histories of syncope, near syncope, or other symptoms suggestive of arrhythmia.

One arrhythmia that may be *undertreated* in this population is atrial fibrillation. The AHCPR guidelines recommend attempting cardioversion for patients with left atrial diameters less than 50 mm and with less than a 1-year history of atrial fibrillation. No recommendations are offered on the drug of choice, although the guidelines comment that amiodarone may emerge as the preferred agent. The ACC/AHA guidelines do not address this issue.

Routine use of myocardial biopsy is not supported by either set of guidelines because of a lack of evidence that the information from this procedure leads to improved management or outcomes.

INPATIENT AND OUTPATIENT MANAGEMENT

The AHCPR guidelines give specific criteria for admission to the hospital and also offer standards for outcomes to be achieved before patients with heart failure are discharged to home (see Table 21-G-1). These recommendations reflect the importance of discharge planning and an adequate system of outpatient care, including patient and family education and counseling. Many of these interventions, such as support groups, have not been part of the traditional focus of physicians; hence, these guidelines imply close collaboration of a team of providers for patients with heart failure. Among the topics for patient education specifically cited are

- Nature of heart failure
- Drug regimens
- Dietary restrictions
- What to do if symptoms occur
- Prognosis

Completion of advanced directives

Smoking and chewing of tobacco

Importance of influenza and pneumococcal vaccination

Sexual activity

Alcohol use

Regular physical activity programs are recommended for all patients except those with New York Heart Association (NYHA) Class IV heart failure, but the guidelines do not explicitly endorse the use of cardiac rehabilitation programs for all patients with heart failure.

MANAGEMENT

Both the AHCPR and the ACC/AHA guidelines provide a strong endorsement of the use of ACE inhibitors for patients with left ventricular systolic dysfunction in the absence of specific contraindications (see Tables 21-G-1 and 21-G-2) and make recommendations regarding several other medications. Diuretic use for patients with signs of volume overload should be immediate, according to the guidelines, which also suggest that patients with mild volume overload can be managed adequately on thiazide diuretics, which cause less acute diuresis than does furosemide. For patients without volume overload, ACE inhibitors may be considered as the sole initial therapy. The prominent roles of ACE inhibitors and diuretics in the AHCPR guidelines are reflected in its flowsheet summarizing pharmacological management.

TABLE 21--G-2 -- ACC/AHA GUIDELINES FOR MANAGEMENT OF CONGESTIVE HEART F

INDICATION	CLASS I (INDICATED)	CLASS II (PROBABLY/POSSIBLY INDICATED)	CLASS INDIC

Initial Diagnostic Evaluation of Acute Pulmonary Edema	1. Focused history/physical examination 2. Twelve-lead ECG 3. Continuous ECG monitoring 4. Blood--serum studies: complete blood count (CBC); electrolytes, blood urea nitrogen (BUN), creatinine and cardiac enzyme levels 5. Digital pulse oximetry/arterial blood gases 6. Chest radiography 7. Transthoracic Doppler--two-dimensional echocardiography 8. Cardiac catheterization/coronary arteriography for suspected coronary artery disease (1) if acute intervention for myocardial injury/infarction is anticipated; (2) to determine the cause(s) of refractory acute pulmonary edema	1. Indwelling arterial cannula 2. Transesophageal echocardiography 3. Tabulation of fluid volume intake and urine output	1. Extensiv (e.g., ca catheter coronar arteriog patient concom illness c not be c candida necessa cardiova interven

Therapeutic Management of Acute Pulmonary Edema	1. Oxygen therapy 2. Nitroglycerin, sublingually or intravenously 3. Intravenous administration of a diuretic (e.g., furosemide) 4. Morphine sulfate 5. Administration of cardiovascular support drugs to attain and stablize clinical-hemodynamic status (e.g., intravenous infusion of nitroprusside, dobutamine, dopamine) 6. Thrombolytic therapy or urgent revascularization (angioplasty or coronary artery bypass surgery) for acute myocardial injury/farction 7. Intubation and mechanicaSl ventilation for severe hypoxia that does not respond rapidly to therapy and for respiratory acidosis 8. Definitive correction of the underlying cause (e.g., mitral valve replacement or repair of acute severe mitral regurgitation) when indicated and clinically feasible		

Initial Diagnostic Evaluation of Cardiogenic Shock/Near Shock	1. Focused history--physical examination 2. Twelve-lead ECG (plus occasional right-sided leads) 3. Continuous ECG monitoring 4. Blood--serum studies; complete blood count, platelet count, clotting studies, electrolytes, BUN, creatinine, glucose, and cardiac and liver enzymes 5. Arterial blood gases and lactate concentration 6. Chest radiograph 7. Transthoracic Doppler--two-dimensional echocardiography 8. Indwelling arterial cannula for continuous monitoring of systemic blood pressure and for arterial blood gas sampling 9. Tabulation of fluid volume intake, urine output, and other fluid volume loss 10. Cardiac catheterization/coronary arteriography if acute revascularization for acute myocardial injury/infarction is anticipated	1. Transesophageal echocardiography	1. Extensiv in a pati concom illness c candida cardiova interven

Therapeutic Management of Cardiogenic Shock/Near Shock	1. Oxygen therapy 2. In the absence of obvious intravascular volume overload, brisk intravenous administration of fluid volume 3. In the presence of intravascular volume overload or after adequate intravenous fluid volume therapy, intravenous administration of cardiovascular support drugs (e.g., dopamine, dobutamine, norepinephrine) to attain and maintain stable clinical-hemodynamic status 4. Urgent coronary artery revascularization for acute myocardial injury/infarction, if readily available	1. Thrombolytic therapy in the setting of acute myocardial injury/infarction if a cardiac catheterization/coronary arteriography/revascularization procedure is not readily available 2. Ventricular assist device in patients who respond inadequately to the aforementioned interventions and who are reasonable candidates for heart transplantation	1. Extensiv and maj interven patients concom illness, t with an underlyi those w candida correcti interven transpla

Recommendations for Intraaortic Balloon Counterpulsation in Heart Failure	1. Cardiogenic shock, pulmonary edema and other acute heart failure conditions not responding to the proper administration of fluid volume or pharmacological therapy, or both, in patients with potentially reversible heart failure or as a bridge to heart transplantation 2. Acute heart failure accompanied by refractory ischemia, in preparation for cardiac catheterization/coronary arteriography and definitive intervention 3. Acute heart failure complicated by significant mitral regurgitation of rupture of the ventricular septum, to obtain hemodynamic stabilization for definitive diagnostic studies or intervention, or both	1. Progressive, chronic heart failure, if necessary to allow for a proper diagnostic approach, time to consider treatment options and definitive intervention (e.g., cardiac surgery, heart transplantation)	1. Significa insuffici 2. Aortic d 3. Patients unrespo therapy cause is uncorre irreversi are not transpla 4. Patients stage of illness 5. Bleedin severe thrombo

Recommendations for Placement of Pulmonary Artery Balloon Catheter in Heart Failure	1. Cardiogenic shock or near shock that does not respond promptly to the proper administration of fluid volume 2. Acute pulmonary edema that does not respond to appropriate intervention or is complicated by systemic hypotension or shock/near shock 3. As a diagnostic tool to resolve any uncertainty of whether pulmonary edema is cardiogenic or noncardiogenic in origin	1. Assessment of the status of intravascular volume, ventricular filling pressures, and overall cardiac function in a patient whose decompensated chronic heart failure is not responding appropriately to standard therapy 2. Evaluation of overall cardiachemodynamic status and exclusion of left heart failure in a patient with decompensated chronic lung disease 3. As a diagnostic tool to assess the origin and clinical and hemodynamic significance of a new systolic murmur in acute heart failure	1. As a rou approac assessm diagnos treatme failure
Recommended Routine Diagnostic Studies for Adult Patients With Chronic Heart Failure or Stabilized Acute Heart Failure Not Previously Performed	1. CBC and urinalysis 2. Blood--serum: electrolytes, BUN, creatinine, glucose, phosphorus, magnesium, calcium and albumin levels 3. Thyroid-stimulating hormone levels in patients with atrial fibrillation and unexplained heart failure 4. Chest radiograph and ECG 5. Transthoracic Doppler--two-dimensio nal echocardiography 6. Noninvasive stress testing to detect ischemia in patients without angina but with a high probability of coronary artery disease who would be candidates for revascularization 7. Noninvasive testing to detect ischemia and	1. Serum iron and ferritin 2. Noninvasive stress testing to detect ischemia in all patients with unexplained heart failure who are potential candidates for revascularization 3. Coronary arteriography in all patients with unexplained heart failure who are potential candidates for revascularization 4. Endomyocardial biopsy in patients (a) with recent onset of rapidly deteriorating cardiac function or other clinical indications of myocarditis; (b) receiving chemotherapy with Adriamycin or similar myocardial toxic agents; (c) with a systemic disease and possible cardiac involvement (hemochromatosis, sarcoid, amyloid, Loeffler endocarditis, endomyocardial fibroelastosis)	1. Repeat catheter ary arte stress te patients coronar disease left vent dysfunc exclude and no evidenc intercur or infarc occurre 2. Endomy biopsy i evaluati with chr failure 3. Multiple echocar radionu in the ro follow-u with hea respond 4. Routine monitori

	a high probability of coronary artery disease who would be candidates for revascularization 7. Noninvasive testing to detect ischemia and assess myocardial viability or coronary arteriography in patients with a previous infarction but with no angina who would be candidates for revascularization 8. Cardiac catheterization/coronary arteriography in patients with angina or large areas of ischemic or hibernating myocardium; also in patients at risk for coronary artery disease who are to undergo surgical correction of noncoronary cardiac lesions	possible cardiac involvement (hemochromatosis, sarcoid, amyloid, Loeffler endocarditis, endomyocardial fibroelastosis) 5. Thyroid-stimulating hormone levels in patients with sinus rhythm and unexplained heart failure	in the ro follow-u with hea respond 4. Routine monitori signal-a electroc 5. Cardiac catheter ary arte patients candida revascu valve su heart tra
Recommendations for Assessment of Functional Capacity in Heart Failure	1. Patient interview or questionnaire at each clinic visit 2. Exercise testing, usually with respiratory gas analysis, to determine potential candidacy for heart transplantation	1. Exercise testing to more definitively assess functional capacity and symptomatic limitations in patients in whom a disparity exists between symptoms expressed and clinical assessment 2. Exercise testing to address specific clinical questions and issues. Examples include: (a) ventricular rate changes and control during atrial fibrillation or after pacemaker placement; (b) blood pressure control in a patient with heart failure with a history of hypertension; (c) exercise-induced arrhythmias; (d) quantitative evaluation of degree of disability; and (e) assessing a change in functional capacity or response to therapy	1. Exercise routine perform followin ventricu dysfunc clinically unless u assess

Pharmacologic Treatment of Left Ventricular Systolic Dysfunction	1. ACE inhibitors for all patients with significantly reduced left ventricular ejection fraction unless contraindicated 2. Hydralazine and isosorbide dinitrate in patients who cannot take ACE inhibitors 3. Digoxin in patients with heart failure due to systolic dysfunction not adequately responsive to ACE inhibitors and diuretic drugs 4. Digoxin in patients with atrial fibrillation and rapid ventricular rates 5. Diuretic drugs for patients with fluid overload 6. Anticoagulation in patients with atrial fibrillation, or a previous history of systemic or pulmonary embolism 7. Beta blockers for high-risk patients after an acute myocardial infarction	1. 1. Digoxin for all patients with heart failure due to left ventricular systolic dysfunction 2. Addition of hydralazine and isosorbide dinitrate for patients who do not respond adequately to ACE inhibitors 3. Beta blockers for patients with dilated cardiomyopathy 4. Anticoagulation in patients with sinus rhythm with a very low eject fraction or intracardiac thrombi 5. Outpatient low-dose dobutamine infusion for refractory heart failure	1. Calcium blockers absence angina hyperte 2. Treatme asympto ventricu arrhythm
Pharmacologic Treatment of Left Ventricular Diastolic Dysfunction	1. Diuretic drugs 2. Nitrates 3. Drugs suppressing AV conduction to control ventricular rate in patients with atrial fibrillation 4. Anticoagulation in patients with atrial fibrillation or previous systemic or pulmonary embolization	1. Calcium channel blockers 2. Beta blockers 3. ACE inhibitors 4. Anticoagulation in patients with intracardiac thrombus	1. Drugs w inotropic absence dysfunc 2. Treatme asympto arrhythm

Recommendations for Hospital Admission of Patients with Heart Failure	1. Patients experiencing moderate to severe heart failure for the first time 2. Patients with recurrent heart failure complicated by acutely threatening events of clinical situations (e.g., recent myocardial ischemia/infarction, acute pulmonary edema, hypotension, pulmonary or systemic embolus, symptomatic arrhythmias, or other severe medical illnesses)	1. Mild to moderate decompensation of chronic heart failure 2. Patients experiencing mild heart failure for the first time

From Williams JF Jr, Hlatky MA, Bristow MR, et al: Guidelines for the Evaluation and Management of
Report of the American College of Cardiology/American Heart Association Task Force on Practice Gu
(Committee on Evaluation and Management of Heart Failure). J Am Coll Cardiol 26:1376--1398, 1996

ECG = electrocardiogram; ACE = angiotensin-converting enzyme.

The guidelines also support use of digoxin, despite the uncertainty regarding its impact on mortality.[4] [5] [6] Because of data demonstrating that digoxin can improve physical function and decrease symptoms in at least some patients with heart failure, the guidelines recommend that it be used routinely for patients with severe heart failure and added to the regimen of patients with mild or moderate heart failure that remain symptomatic despite the use of diuretics and ACE inhibitors.

The AHCPR task force concluded that anticoagulation was not justifiable as part of routine therapy for heart failure but should be reserved for patients with thromboembolic disease, atrial fibrillation, or mobile left ventricular thrombi. The guidelines also do not clearly support use of beta-adrenergic blockers, despite the promising findings from studies. This recommendation can be expected to change in future revisions.

Revascularization of ischemic myocardium either by percutaneous transluminal coronary angioplasty (PTCA) or by coronary artery bypass grafting (CABG) does not directly improve heart failure in most patients, but this strategy can improve survival, inasmuch as patients with severe coronary disease and left ventricular dysfunction have a poor prognosis with medical therapy alone. Therefore, the guidelines support performance of coronary angiography in patients with heart failure and with exercise-limiting angina, rest angina, or recurrent episodes of acute pulmonary edema.

Should left ventricular function be irreversibly and severely damaged, patients may be considered for cardiac transplantation. The AHCPR guidelines do not provide

recommendations for the evaluation of this patient population.

OUTCOMES ASSESSMENT AND FOLLOW-UP

The most important judge of whether therapeutic interventions have led to improvement is the patient, not a noninvasive test. Therefore, the AHCPR guidelines emphasize the importance of follow-up of patient data such as physical functioning, mental health, sexual function, and ability to perform usual work and social activities. Between visits to their physicians, patients should keep track of their own weights, and contact their provider if their weight goes up more than 3 to 5 pounds.

More recent guidelines for management of heart failure that reflect findings from randomized trials in the late 1990s were published by the Heart Failure Society of America (HFSA) in 1999.[3] These guidelines focus on issues related to the use of pharmaceutical agents and use the same approach for evaluating the strength of evidence in support of recommendations (A, B, and C).

BETA ADRENERGIC BLOCKERS

The most prominent differences in the HFSA statement in comparison with prior guidelines are regarding use of beta-adrenergic receptor blockers. Whereas the AHCPR and ACC/AHA guidelines consider this strategy experimental, the HFSA statement recommends that beta-blocker therapy be *routinely administered to stable patients with left ventricular systolic dysfunction and mild-to-moderate symptoms* and considered for asymptomatic patients. The guidelines recommend that physicians initiate beta blockers cautiously, and this therapy is not endorsed in patients with symptoms of heart failure at rest.

The HFSA guidelines acknowledge some unresolved therapeutic issues related to use of beta blockers in patients with heart failure. These issues include the safety of combining beta-blocking agents with amiodarone therapy, because both may induce bradycardia; implantation of cardiac pacemakers to provide protection from symptomatic bradycardia; and whether therapy with beta blockers should be continued indefinitely.

DIGOXIN

Use of digoxin for patients with symptomatic heart failure is endorsed by the HFSA guidelines, which reflects evidence of efficacy from trials unavailable to committees developing prior guidelines.[4] [5] [6] [7] Evidence for digoxin's use is considered stronger for patients with NYHA Classes II and III (strength of evidence=A) than for NYHA Class IV patients (strength of evidence=C). The HFSA committee recommends dosages of digoxin of 0.125 to 0.25 mg per day in most patients without use of a loading dose. (Patients with abnormal renal function should begin on 0.125 mg per day.) Higher dosages for patients with atrial fibrillation are not supported; instead, if necessary, rate

control should be achieved with amiodarone or beta-blocker therapy.

WARFARIN

The HFSA guidelines[3] support use of warfarin therapy for anticoagulation in patients with heart failure and atrial fibrillation who do not have contraindications, and they urge consideration of warfarin for patients with a left ventricular ejection fraction of 35% or less. The committee did not consider evidence for potentially negative interactions between ACE inhibitors and acetylsalicylic acid sufficiently strong to advise against their use in combination.

ANGIOTENSIN II RECEPTOR BLOCKERS

The HFSA committee emphasized that angiotensin II receptor blockers (ARBs) were not first-line therapies for heart failure and that ACE inhibitors should be used if at all possible. The guidelines indicate that the strength of evidence supporting ARBs as an alternative to ACE inhibitors is less than that for use of the combination of hydralazine and isosorbide dinitrate. The impact of combined use of ACE inhibitors and ARBs was considered an unresolved issue.

ANTIARRHYTHMIC THERAPY

For patients with life-threatening ventricular arrhythmias, implantable cardioverter defibrillators were recommended. Amiodarone therapy was not recommended for primary prevention of sudden death in patients with heart failure except in patients who were not candidates for implantable cardioverter-defibrillators. However, amiodarone was considered the preferred drug for supraventricular tachycardia not controlled with digoxin or beta blockers.

OTHER

The HFSA guidelines were able to reflect the results of the Randomized Aldactone Evaluation Study trial[8] and recommended that spironolactone be considered for patients with severe heart failure. Cautions regarding the danger of hyperkalemia are included in the recommendations.

Finally, these guidelines do not support use of immunosuppressive therapy for patients with myocarditis.

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Chapter 22 - Genesis of Cardiac Arrhythmias: Electrophysiological Considerations

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ANATOMY OF THE CARDIAC CONDUCTION SYSTEM

Sinus Node

In humans, the sinus node is a spindle-shaped structure composed of a fibrous tissue matrix with closely packed cells. It is 10 to 20 mm long, 2 to 3 mm wide, and thick, tending to narrow caudally toward the inferior vena cava. It lies less than 1 mm from the epicardial surface, laterally in the right atrial sulcus terminalis at the junction of the superior vena cava and right atrium (Figs. 22-1 and 22-2). The artery supplying the sinus node branches from the right (55 to 60 percent of the time) or the left circumflex (40 to 45 percent) coronary artery and approaches the node from a clockwise or counterclockwise direction around the superior vena caval-right atrial junction.

CELLULAR STRUCTURE.

Cell types in the sinus node include nodal cells, transitional cells, and atrial muscle cells. *Nodal cells,* also called "P cells" and thought to be the source of normal impulse formation, are small (5 to 10 mum), ovoid, primitive-appearing cells with relatively few organelles, mitochondria, and myofibrils. They are grouped in elongated clusters located centrally in the sinus node. No transverse tubular system exists. Contact between nodal cells appears to occur via nexus connections.

TRANSITIONAL CELLS.

Also known as "T cells," these elongated cells are intermediate in size and complexity between nodal cells and atrial muscle cells. T cells near nodal cells have simple intercellular connections, while more fully developed intercalated discs exist between T cells and atrial myocardium. Since nodal cells make contact only with each other or T cells, the latter may provide the only functional pathway for distribution of the sinus impulse formed in the nodal cells to the rest of the atrial myocardium.

ATRIAL MYOCARDIAL CELLS.

These cells extend as peninsulas into the nodal boundaries, with overlapping zones of sinus and atrial cells most prominent on the nodal surface that abuts the crista terminalis.

GAP JUNCTIONS.

Gap junctional channels (see p. 669) formed by connexin 45, 43, and 40, depending on the species and tissue type, electrically couple sinus node cells and probably account for their synchronized electrical activity.[1] [2] [3] [4] [5] [14A] [43A] [43B] [48A] [154A] [157A] [157B] [159A] The relative paucity and small size of gap junctions may account for slow conduction in the sinus node.[3] Few gap junctions may be required for frequency entrainment.[4] Although most gap junctions contain connexin 40, 43, and 45, the sinus and atrioventricular (AV) nodes are virtually devoid of connexin 43 but contain connexin 40 and connexin 45.[5] [6] [7] [61A] Abnormalities in gap junctions can cause arrhythmias.[8]

FUNCTION.

Very probably, no single cell in the sinus node serves as *the* pacemaker. Rather, sinus nodal cells function as electrically coupled oscillators that discharge synchronously because of mutual entrainment. Thus, faster-discharging cells are slowed by cells firing more slowly, while they themselves are sped so that a "democratically derived" discharge rate occurs.[9] In humans, sinus rhythm may result from impulse origin at widely separated sites, with two or three individual wavefronts created that merge to form a single, widely disseminated wavefront.[10] Modulated parasystole can occur.[9]

Figure 22-1 The human sinus node. This photograph, taken in the operating room, shows the location of the normal cigar-shaped sinus node along the lateral border of the terminal groove at the superior vena cava-atrial junction *(arrowheads)*. (From Anderson RH, Wilcox BR, Becker AE: Anatomy of the normal heart. *In* Hurst JW, Anderson RH, Becker AE, Wilcox BR [eds]: Atlas of the Heart. New York, Gower, 1988, p 1.2.)

Figure 22-2 Histological section taken at right angles to the cigar-shaped sinus node shows how in short axis, the node is a wedge-shaped structure located between the wall of the superior vena cava and the terminal crest. Discrete boundaries between the sinus node and atrial muscle are noted *(arrowheads)*. The node is penetrated by the sinus nodal artery. (From Anderson RH, Wilcox BR, Becker AE: Anatomy of the normal heart. *In* Hurst JW, Anderson RH, Becker AE, Wilcox BR [eds]: Atlas of the Heart. New York, Gower, 1988, p 1.2.)

INNERVATION.

The sinus node is richly innervated with postganglionic adrenergic and cholinergic nerve terminals.[11] [12] [13] [14] [14A] [15] [16] [154A] [157A] [157B] [159A] Discrete vagal efferent pathways innervate both the sinus and AV regions of the dog and nonhuman primate. Most efferent vagal fibers to the atria appear to converge first at a single fat pad that is located between the medial portion of the superior vena cava and the aortic root, superior to the right pulmonary artery; the fibers then project onto two other fat pads found at the inferior vena cava-left atrial junction and the right pulmonary vein-atrial junction and subsequently project to both atria. Vagal fibers to the sinus and AV nodes also converge at the superior vena cava-aortic root fat pad before projection to the right pulmonary vein and inferior vena cava fat pads.[17] The concentration of norepinephrine is two to four times higher in atrial than in ventricular tissue in canine and guinea pig hearts. Although the sinus nodal region contains amounts of norepinephrine equivalent to those in other parts of the right atrium, acetylcholine, acetylcholinesterase, and choline acetyltransferase (the enzyme necessary for the synthesis of acetylcholine) have all been found in greatest concentration in the sinus node, with the next highest concentration in the right and then the left atrium. The concentration of acetylcholine in the ventricles is only 20 to 50 percent of that in the atria.

Vagal stimulation, by releasing acetylcholine, slows the sinus nodal discharge rate and prolongs intranodal conduction time, at times to the point of sinus nodal exit block. Acetylcholine increases and norepinephrine decreases refractoriness in the center of the sinus node. Adrenergic stimulation speeds the sinus discharge rate. The phase (timing) in the cardiac cycle at which vagal discharge occurs and the background sympathetic tone importantly influence vagal effects on the sinus rate and conduction (see below). The negative chronotropic effects of acetylcholine are due to inhibition of the hyperpolarization-activated pacemaker current I_f ,[18] [19] [20] [21] [22] probably mediated by a G protein (see Chap. 14) . Acetylcholine also activates the muscarinic m_2 receptor in the pacemaker cell. The activated receptor in turn activates a specific G protein (G_1)

that activates the K channel ($I_{K.G}$), which also modulates the discharge rate.[23] The m_2 receptor also inhibits adenylate cyclase via G_1 to antagonize adrenergic effects on the sinus node. After cessation of vagal stimulation, sinus nodal automatically may accelerate transiently (postvagal tachycardia).

INTERNODAL AND INTRAATRIAL CONDUCTION

Whether impulses travel from the sinus to the AV node over preferentially conducting pathways has been contested. Anatomical evidence has been interpreted to indicate the presence of three intraatrial pathways. The *anterior internodal pathway* begins at the anterior margin of the sinus node and curves anteriorly around the superior vena cava to enter the anterior interatrial band, called the *Bachmann bundle.* This band continues to the left atrium, with the anterior internodal pathway entering the superior margin of the AV node. the *Bachmann bundle* is a large muscle bundle that appears to conduct the cardiac impulse preferentially from the right to the left atrium. The *middle internodal tract* begins at the superior and posterior margins of the sinus node, travels behind the superior vena cava to the crest of the interatrial septum, and descends in the interatrial septum to the superior margin of the AV node. The *posterior internodal tract* starts at the posterior margin of the sinus node and travels posteriorly around the superior vena cava and along the crista terminalis to the eustachian ridge and then into the interatrial septum above the coronary sinus, where it joins the posterior portion of the AV node. Some fibers from all three tracts bypass the crest of the AV node and enter its more distal segment. These groups of internodal tissue are best referred to as *internodal atrial myocardium,* not tracts, because they do not appear to be histologically discrete specialized tracts, only plain atrial myocardium.

Preferential internodal conduction, i.e., more rapid conduction velocity between the nodes in some parts of the atrium than in other parts, does exist and may be due to fiber orientation, size, geometry, or other factors rather than to specialized tracts located between the nodes. Importantly, the atrial anterosuperior and posteroinferior inputs or approaches to the AV node may be the anatomical substrates constituting the fast and anterograde slow pathways of AV nodal reentry, the upper end of the retrograde fast pathway being located at the apex of the Koch triangle, near the His bundle, and the upper end of the anterograde pathway being located near the coronary sinus os.[24] [25] [26] The term "*triangle of Koch,*" however, has to be used with caution since recent histological studies of anatomically normal adult hearts demonstrated that the tendon of Todaro, which forms one side of the triangle of Koch, is absent in about two-thirds of hearts.[27]

The Atrioventricular Junctional Area and Intraventricular Conduction System

The normal AV junctional area (Figs. 22-3 and 22-4) can be divided into distinct regions: the transitional cell zone,

Figure 22-3 Photograph of a normal human heart showing the anatomical landmarks of the triangle of Koch. This triangle is delimited by the tendon of Todaro superiorly, which is the fibrous commissure of the flap guarding the openings of the inferior vena cava and coronary sinus, by the attachment of the septal leaflet of the tricuspid valve inferiorly, and by the mouth of the coronary sinus at the base. The stippled area adjacent to the central fibrous body is the approximate site of the compact atrioventricular node. (From Janse MJ, Anderson RH, McGuire MA, et al: "AV nodal" reentry: I. "AV nodal" reentry revisited. J Cardiovasc Electrophysiol 4:561, 1993.)

also called nodal approaches; the compact portion, or the AV node itself; and the penetrating part of the AV bundle (His bundle), which continues as a nonbranching portion.

TRANSITIONAL CELL ZONE.

In the rabbit AV node, the transitional cells or nodal approaches are located in posterior, superficial, and deep groups of cells. They differ histologically from atrial myocardium and connect the latter with the compact portion of the AV node. Some fibers may pass from the posterior internodal tract to the distal portion of the AV node or His bundle and provide the anatomical substrate for conduction to bypass AV nodal slowing. However, the importance of this structure is unclear.

THE AV NODE.

The compact portion of the AV node is a superficial structure lying just beneath the right atrial endocardium, anterior to the ostium of the coronary sinus, and directly above the insertion of the sepal leaflet of the tricuspid valve. It is at the apex of a triangle formed by the tricuspid annulus and the tendon of Todaro, which originates in the central fibrous body and passes posteriorly through the atrial septum to continue with the eustachian valve[24] [25] [28] [29] (Figs. 22-3 and 22-4; however, see comments on the triangle of Koch above). The compact portion of the AV node is divided from and becomes the penetrating portion of the His bundle at the point where it enters the central fibrous body. In 85 to 90 percent of human hearts, the arterial supply to the AV node is a branch from the right coronary artery that originates at the posterior intersection of the AV and interventricular grooves (crux). A branch of the circumflex coronary artery provides the AV nodal artery in the remaining hearts. Fibers in the lower part of the AV node may exhibit automatic impulse formation.

THE BUNDLE OF HIS, OR PENETRATING PORTION OF THE AV BUNDLE.

This structure connects with the distal part of the compact AV node, perforates the central fibrous body, and continues through the annulus fibrosis, where it is called the nonbranching portion as it penetrates the membranous septum (see Fig. 22-4) . Proximal cells of the penetrating portion are heterogeneous and resemble those of the compact AV node, while distal cells are similar to cells in the proximal bundle branches. Connective tissue of the central fibrous body and membranous septum encloses the

penetrating portion of the AV bundle, which may send out extensions into the central fibrous body.[24] [25] [28] [29] However, large well-formed fasciculoventricular connections between the penetrating portion of the AV bundle and the ventricular septal crest are rarely found in adult hearts. Branches from the anterior and posterior descending coronary arteries supply the upper muscular interventricular septum with blood, which makes the conduction system at this site more impervious to ischemic damage unless the ischemia is extensive.

THE BUNDLE BRANCHES, OR BRANCHING PORTION OF THE AV BUNDLE.

These structures begin at the superior margin of the muscular interventricular septum, immediately beneath the membranous septum, with the cells of the left bundle branch cascading downward as a continuous sheet onto the septum beneath the noncoronary aortic cusp (Fig. 22-5) . The AV bundle may then give off other left bundle branches, sometimes constituting a true bifascicular system with an anterosuperior branch, in other hearts giving rise to a group of central fibers, and in still others appearing more as a network without a clear division into a fascicular system. The right bundle branch continues intramyocardially as an unbranched extension of the AV bundle down the right side of the interventricular septum to the apex of the right ventricle and base of the anterior papillary muscle. In some human hearts, the His bundle traverses the right interventricular crest and gives rise to a right-sided narrow stem origin of the left bundle branch. The anatomy of the left bundle branch system may be variable and may not conform to a constant bifascicular division. However, the concept of a trifascicular system remains useful to both the electrocardiographer and the clinician (Fig. 22-5)

TERMINAL PURKINJE FIBERS.

These fibers connect with the ends of the bundle branches to form interweaving networks on the endocardial surface of both ventricles that transmit the cardiac impulse almost simultaneously to the entire right and left ventricular endocardium. Purkinje fibers tend to be less concentrated at the base of the ventricle and at the papillary muscle tips. They penetrate the myocardium for varying distances depending on the animal species: In humans, they apparently penetrate only the inner third of the endocardium, while in the pig they almost reach the epicardium. Such variations could influence changes produced by myocardial ischemia, for example, since Purkinje fibers appear to be more resistant to ischemia than ordinary myocardial fibers are.

CELLULAR COMPOSITION OF THE AV JUNCTIONAL AREA.

Transitional cells in the rabbit are elongated and smaller than atrial cells, stain more palely, and are separated by numerous strands of connective tissue. They merge at the entrance of the compact portion of the AV node, where the cells are small and spherical, not separated by muscle or connective tissue, and have very few nexuses. They interweave in interconnecting whorls of fasciculi. The AV node is divided on the basis of electrophysiological characteristics into AN, N, and NH regions[30] (Fig. 22-6) .

In the rabbit, the AN region corresponds to the transitional cell groups of the posterior

portion of the node, the NH region to the anterior portion of the bundle of lower nodal cells, and the N region to the small enclosed node where transitional cells merge with midnodal cells. *Dead-end pathways*--groups of cells that form an apparent

Figure 22-4 Sections through the atrioventricular (AV) junction show the position of the AV node *(arrowhead)* within the triangle of Koch (*A*) and the penetrating AV bundle of His (*arrowheads*) within the central fibrous body (*B*). (From Anderson RH, Wilcox BR, Becker AE: Anatomy of the normal heart. *In* Hurst JW, Anderson RH, Becker AE, Wilcox BR [eds]. Atlas of the Heart. New York, Gower, 1988, p 1.2.)

Figure 22-5 Schematic representation of the trifascicular bundle branch system. A = anterosuperior fascicle of the left bundle; AVN = atrioventricular node; HB = His bundle; LBB = main left bundle branch; P = posteroinferior fascicle of the left bundle branch; RBB = right bundle branch. (Modified from Rosenbaum MB, Elizari MV, Lazzari JO: The Hemiblocks. Oldsmar, FL, Tampa Tracings, 1970, cover illustration.)

electrophysiological cul-de-sac that does not contribute to overall conduction in the node--are also found at several sites. Cells in the penetrating bundle remain similar to compact AV nodal cells. In the dog, P cells, similar to those found in the sinus node, and several types of transitional cells have been noted and related to the automaticity and conduction properties of the AV node.[24] [25]

Purkinje cells are found in the His bundle and bundle branches, cover much of the endocardium of both ventricles, and align to form multicellular bundles in longitudinal strands separated by collagen. They are large, clear cells (10 to 30mum in diameter, 20 to 50mum long) with loosely arrayed mitochondria distributed between few linearly aligned myofibrils that have few myofilaments. Round nuclei occupy the center of the cell. Although conduction of the cardiac impulse appears to be their major function, free-running Purkinje fibers, sometimes called *false tendons,* which are composed of many Purkinje cells in a series, are capable of contraction (Fig. 22-7). Extensive lateral and end-to-end gap junctions, made up primarily of connexin 43, apparently transform the individual Purkinje cells into functioning like a cable.[5] [6] [7] [31]

Innervation of the AV Node and His Bundle

PATHWAYS OF INNERVATION.

The AV node and His bundle region are innervated by a rich supply of cholinergic and adrenergic fibers with a density exceeding that found in the ventricular myocardium. Ganglia, nerve fibers, and nerve nets lie close to the AV node. Parasympathetic nerves to the AV node region enter the canine heart at the junction of the inferior vena cava and the inferior aspect of the left atrium, adjacent to the coronary sinus entrance.

Nerves in direct contact with AV nodal fibers have been noted, along with agranular and granular vesicular processes, presumably representing cholinergic and adrenergic processes. Acetylcholine release may be concentrated around the N region of the AV node.[13] [14] [14A] [15]

In general, autonomic neural input to the heart exhibits some degree of "sidedness," with the right sympathetic and vagal nerves affecting the sinus node more than the AV node and the left sympathetic and vagal nerves affecting the AV node more than the sinus node. The distribution of the neural input to the sinus and AV nodes is complex because of substantial overlapping innervation. Despite the overlap, specific branches of the vagal and sympathetic nerves can be shown to innervate certain regions preferentially, and sympathetic or vagal nerves to the sinus node can be interrupted discretely without affecting AV nodal innervation. Similarly, vagal or sympathetic neural input to the AV node can be interrupted without affecting sinus innervation. Supersensitivity to acetylcholine follows vagal denervation.

Figure 22-6 Diagram showing the distribution of morphologically different cell types in the atrioventricular (AV) node. *Upper panel,* Transverse section showing the trilaminar appearance of the interior part of the node. The level of sectioning is indicated by the vertical dark line in the *lower panel. Lower panel,* Diagram of the AV node indicating the different sites identified histologically after recording typical action potentials. (From Janse MJ, van Capelle FJL, Anderson RH, et al: Electrophysiology and structure of the atrioventricular node of the isolated rabbit heart. *In* Wellens JHH, Lie KI, Janse MJ [eds]: The Conduction System of the Heart. Philadelphia, Lea & Febiger, 1976, p 296.)

Stimulation of the right stellate ganglion produces sinus tachycardia with less effect on AV nodal conduction, while stimulation of the left stellate ganglion generally produces a shift in the sinus pacemaker to an ectopic site and consistently shortens AV nodal conduction time and refractoriness but inconsistently speeds the sinus nodal discharge rate. Stimulation of the right cervical vagus nerve primarily slows the sinus nodal discharge rate, while stimulation of the left vagus primarily prolongs AV nodal conduction time and refractoriness when "sidedness" is present. While neither sympathetic nor vagal stimulation affects normal conduction in the His bundle, either can affect abnormal AV conduction.

Most efferent sympathetic impulses reach the canine ventricles over the ansae subclaviae, branches from the stellate ganglia. Sympathetic nerves then synapse primarily in the caudal cervical ganglia and form individual cardiac nerves that innervate relatively localized parts of the ventricles. On the right side, the major route to the heart is the recurrent cardiac nerve, and on the left, the ventrolateral cardiac nerve. In general, the right sympathetic chain shortens refractoriness primarily of the anterior portion of the ventricles, while the left affects primarily the posterior surface of the ventricles, although overlapping areas of distribution occur.

The intraventricular route of sympathetic nerves generally follows coronary arteries. Functional data suggest that afferent and efferent sympathetic nerves travel in the superficial layers of the epicardium and dive to innervate the endocardium, and anatomical observations support this conclusion. Vagal fibers travel intramurally or subendocardially and rise to the epicardium at the AV groove[13] [14] [14A] [15] [32] (see Fig. 22-7) .

EFFECTS OF VAGAL STIMULATION.

The vagus modulates cardiac sympathetic activity at prejunctional and postjunctional sites by regulating the amount of norepinephrine released and by inhibiting cyclic adenosine monophosphate (cAMP)-induced phosphorylation of cardiac proteins such as phospholamban.[23] The latter inhibition occurs at more than one level in the series of reactions constituting the adenylate cyclase-, AMP-dependent protein kinase system. Neuropeptides released from nerve fibers of both autonomic limbs also modulate autonomic responses. For example, neuropeptide Y released from sympathetic nerve terminals inhibits cardiac vagal effects.[11] [12]

Tonic vagal stimulation produces a greater absolute reduction in sinus rate in the presence of tonic background sympathetic stimulation, a sympathetic-parasympathetic interaction termed *accentuated antagonism.* In contrast, changes in AV conduction during concomitant sympathetic and vagal stimulation are essentially the *algebraic sum* of the individual AV conduction responses to tonic vagal and sympathetic stimulation alone. Cardiac responses to brief vagal bursts begin after a short latency and dissipate quickly; in contrast, cardiac responses to sympathetic stimulation commence and dissipate slowly. The rapid onset and offset of responses to vagal stimulation allow for dynamic beat-to-beat vagal modulation of heart rate and AV conduction, whereas the slow temporal response to sympathetic stimulation precludes any beat-to-beat regulation by sympathetic activity. Periodic vagal bursting (as may occur each time a systolic pressure wave arrives at the baroreceptor regions in the aortic and carotid sinuses) induces phasic changes in sinus cycle length and can entrain the sinus node to discharge faster or slower at periods that are identical to those of the vagal burst. In a similar phasic manner, vagal bursts prolong AV nodal conduction time and are influenced by background levels of sympathetic tone. Because the peak vagal effects on sinus rate and AV nodal conduction occur at different times in the cardiac cycle, a brief vagal burst can slow the sinus rate without affecting AV nodal conduction or can prolong AV nodal conduction time and not slow the sinus rate.[9] [11] [12]

EFFECTS OF SYMPATHETIC STIMULATION.

Stimulation of sympathetic ganglia shortens the refractory period equally in the epicardium and underlying endocardium of the left ventricular free wall, although dispersion of recovery properties occurs, i.e., different degrees of shortening of refractoriness occur when measured at different epicardial sites. Nonuniform distribution of norepinephrine may, in part, contribute to some of the nonuniform electrophysiological effects since the ventricular content of norepinephrine is greater at the base than at the apex of the heart, with greater distribution to muscle than to

Purkinje fibers. Afferent vagal activity appears to be greater in the posterior ventricular myocardium, which may account for the vagomimetic effects of inferior myocardial infarction.[13] [14] [14A] [15]

The vagi exert minimal but measurable effects on ventricular tissue: decreasing the strength of myocardial contraction and prolonging refractoriness. Under some circumstances, acetylcholine can cause a positive inotropic effect. It is now clear that the vagus (acetylcholine) can exert direct effects on some types of ventricular fibers, as well as exert indirect effects by modulating sympathetic influences.[14] [14A] [33]

ARRHYTHMIAS AND THE AUTONOMIC NERVOUS SYSTEM.

Alterations in vagal and sympathetic innervation can influence the development of arrhythmias.[14] [14A] [34] Damage to nerves extrinsic to the heart, such as the stellate ganglia, as well as to intrinsic cardiac nerves from diseases that may affect nerves primarily, e.g., viral infections, or secondarily, from diseases that cause cardiac damage, may produce cardioneuropathy. Such neural changes may create electrical instability via a variety of electrophysiological mechanisms. For example, myocardial infarction can interrupt afferent and efferent neural transmission and create areas of sympathetic supersensitivity that may be conducive to the development of arrhythmias.[13] [14]

Figure 22-7 *Left panel,* Intraventricular route of sympathetic and vagal nerves to the left ventricle. *Right panel,* Schematic of the transverse views of the right ventricular (RV) wall showing functional pathways of the efferent sympathetic and vagal nerves. *Top right,* Transverse view of the RV outflow tract at the upper horizontal line on the left. *Bottom right,* Transverse view of the anterolateral wall at the lower horizontal line on the left. The *vertical solid line* indicates the center of the RV anterolateral wall. Closed circles indicate positions of plunge electrodes labeled 1 to 6. IVS = interventricular septum; LAD = left anterior descending coronary artery; RA = right atrium; RCA = right coronary artery. (From Ito M, Zipes DP: Efferent sympathetic and vagal innervation of the canine right ventricle. Circulation *90:*1459, 1994. By permission of the American Heart Association, Inc.)

Figure 22-8 Structure of ion channels. *A,* Subunit of a voltage-gated potassium channel containing six membrane-spanning domains (S1 through S6) linked by intracellular and extracellular sequences of hydrophilic amino acids. One of the subunits (S4) has positively charged lysine and arginine residues, and this region is thought to form the voltage sensor of the channel. Transmembrane segments S5 and S6, along with the intervening peptide chain (H), line the pore through which ions pass into the lipid bilayer. Voltage-dependent "fast" or N-type inactivation is mediated by an N-terminal particle that binds to the activated channel and plugs the permeation pathway. Both the COOH-terminus and the NH_2 -terminus have phosphorylation sites (P) that are potential targets for a variety of protein kinases and protein phosphatases. A change in phosphorylation status may then result in altered gating and/or permeation properties of the channel. *B,* Voltage-gated Na+ and Ca^{2+} channels are composed of a *single* tetramer consisting of four covalently linked repeats of the six-transmembrane-spanning motifs, whereas voltage-gated K+ channels are composed of four *separate* subunits, each containing a single

six-transmembrane-spanning motif. (Modified from Katz AM: Molecular biology in cardiology, a paradigmatic shift. J Mol Cell Cardiol 20:355, 1988.)

BASIC ELECTROPHYSIOLOGICAL PRINCIPLES

Physiology of Ion Channels

Electrical signaling in the heart involves the passage of ions through ionic channels. The Na+, K+, Ca^{2+} , and Cl-- ions are the major charge carriers, and their movement across the cell membrane creates a flow of current that generates excitation and signals in cardiac myocytes. Ion channels are macromolecular pores that span the lipid bilayer of the cell membrane (Fig. 22-8). Conformational transitions change (gate) a single ion channel from closed to open, which allows selected ions to flow passively down the electrochemical activity gradient at a very high rate (>10^{6} ions per second). The high transfer rates and restriction to "downhill" fluxes not stoichiometrically coupled to the hydrolysis of energy-rich phosphates distinguish ionic channel mechanisms from those of other ion-transporting structures such as the sarcolemmal Na+, K+-adenosine triphosphatase (ATPase) or the sarcoplasmic reticular Mg^{2+} , Ca^{2+} -ATPase. Ion channels may be gated by extracellular and intracellular ligands, changes in transmembrane voltage, or mechanical stress. Gating of single ion channels can best be studied by means of the patch-clamp technique, as illustrated in Figure 22-9 , with the voltage-gated Ca^{2+} channel used as an example.

Ion channels are usually named after the strongest permeant ion--Na+, Ca^{2+} , K+, Cl----but some channels are less or not selective, as in gap junctional channels. Channels have also been named after neurotransmitters, as in acetylcholine-sensitive K+ channels, $I_{K.Ach}$.

The ionic permeability ratio is a commonly used quantitative index of a channel's selectivity. It is defined as the ratio of the permeability of one ion type to that of the main permeant ion type. Permeability ratios of voltage-gated K+ and Na+ channels for monovalent and divalent (e.g., Ca^{2+}) cations are usually less than 1:10.[34] Voltage-gated Ca^{2+} channels exhibit a more than thousand-fold discrimination against Na+ and K+ ions (e.g., P_K /P_{Ca} = 1/3000) and are impermeable to anions.

Because ions are charged, net ionic flux through an open channel is determined by both the concentration and electrical gradient across the membrane. According to the Goldman-Hodgkin-Katz (GHK) *current* equation, the current i carried by an ion S is equal to the permeability of the channel to that ion, P_S , multiplied by a nonlinear function of voltage, V.

Figure 22-10 demonstrates that the GHK theory predicts nonlinear single-channel current (i)-voltage (V) relationships whenever permeant ion concentrations are unequal

on the two sides of the membrane; i.e., channel conductance (which equals the slope of the i-V curve) is larger when ions flow from the more concentrated side (rectification). The intercept of the i-V curve with the voltage axis indicates the reversal potential of the channel. At this point, the passive flux of ions along the chemical driving force is exactly balanced by the electrical driving force. In the case of a channel that is perfectly selective for one ion species (as illustrated in Fig. 22-10*A* for a K+-selective channel), the reversal potential equals the Nernst or thermodynamic equilibrium potential of that ion, E_S , which is given by the Nernst equation in the form

where S_i and S_o are the intracellular and extracellular concentrations of the permeant ion, respectively, z is the valence of the ion, R is the gas constant, F is Faraday constant, T is the temperature in Kelvin, and ln is the logarithm to the base *e*. If the current through an open channel is carried by more than one permeant ion, the reversal potential becomes a weighted mean of all Nernst potentials, as illustrated in Figure 22-10 (insert), with a Ca^{2+} channel weakly permeable to K+ used as an example.

As shown in Figure 22-15 and Table 22-2 , membrane voltages during a cardiac action potential are in the range of -95 to +30 mV. With physiological external K+ (4 mM; see Table 22-1) , E_K is approximately -91 mV, and passive K+ movement is out of the cell. K+ efflux through a single K+ channel, or the single-channel current i, *increases* with membrane depolarization over the range of physiological membrane potentials (Fig. 22-10 *A*). On the other hand, since the calculated reversal potential of a Ca^{2+} channel is +64 mV (P_K /P_{Ca} = 1/3000, K_i =150 mM, K_o =4 mM, Ca_i =100 nM, Ca_o =2 mM), passive Ca^{2+} flux is into the cell. Ca^{2+} influx through a single open Ca^{2+} channel *decreases* with membrane depolarization in a nonlinear fashion (see Fig 22-10 *A*). With physiological internal and external chloride concentrations (see Table 22-1) , E_{Cl} is -80 to -35 mV, and passive movement of Cl-- ions

Figure 22-9 Patch-clamp measurements of ion channel activity, with the voltage-dependent Ca^{2+} channel used as an example. *A,* Open-closed gating of a single L-type Ca^{2+} channel. A glass pipette filled with an electrolyte solution is pressed against the cell surface, suction is applied, and a tight electrical seal is formed between the pipette rim and cell membrane. This high-resistance seal ensures that the recording circuit measures only ionic currents flowing through the 1 to 3 $mum^{[2]}$ of membrane that is encircled by the pipette tip. In this way, the ionic current passing through a single open channel can be measured ("cell-attached" mode). The pipette is filled with 5 mM Ca^{2+} . To activate the channel, step depolarization (500 milliseconds) to -40 mV from a holding potential of -70 mV is applied, followed by repolarization to -70 mV. (The square wave-shaped tracing at the top indicates voltage changes.) During the step depolarization, brief openings (downward current deflections) and closings of one channel appear as discrete changes in the record. At the -40-mV applied membrane potential, an open channel passes -0.25 pA, which corresponds to a flux of approximately 750,000 Ca^{2+} ions per second through a single open pore. Note that the depolarization causes the channel to open only occasionally, with seven brief openings of a single channel in this example. *B,* In the whole-cell mode, after a cell-attached patch has been formed, a brief pulse of suction disrupts the membrane underneath the pipette tip and creates low-resistance access to the entire intracellular space. While in this configuration, current passing through the whole cell can be measured. In this example, step depolarization to +20 mV from a holding potential of -40 mV causes an inward Ca^{2+} current of several hundreds of picoamperes that subsides upon

repolarization to the holding potential.

through open chloride channels can be both inward and outward at membrane potentials typically occurring during a cardiac action potential. In more general terms, the direction and magnitude of passive ion flux through a single open channel at any given transmembrane voltage is governed by the reversal potential of that ion and its concentration on the two sides of the membrane, with the net flux being larger when ions move from the more concentrated side.

ION FLUX THROUGH VOLTAGE-GATED CHANNELS

Changes in transmembrane potential determine ion flux through voltage-gated channels not only through the voltage dependence of the electrochemical driving force on the permeant ion but also through the voltage dependence of the open-state probability of that channel. If the probability of a channel being activated, P_{act} (or the fraction of time that it permits ions to permeate), exhibits voltage-dependent activation, as is the case, for example, with the L-type Ca^{2+} channel or voltage-dependent K+ channels in cardiac myocytes, P_{act} would increase with membrane depolarization. Hypothetical examples

Figure 22-10 Relationship between channel properties and whole-cell ionic currents. *A,* Hypothetical single-channel current (i)-voltage (V_m) relationships of a potassium and a calcium channel. The relationships were generated from the Goldman-Hodgkin-Katz *current* equation (see the text), assuming that the K+ channel is perfectly selective for K+ and the Ca^{2+} is weakly permeable to K+ (P_K P_{Ca} = 1/3000). Intracellular and extracellular concentrations of Ca^{2+} and K+ are those given in Table 22-1. The thermodynamic equilibrium potentials or Nernst potentials for Ca^{2+} (E_{Ca}) and K+ (E_K) were therefore +124 mV and -91 mV, respectively (at T = 294.16 K). P is a constant and was scaled so that i=0.3 pA (K+ channel) and -0.5 pA (Ca^{2+} channel) at -20 mV. Despite their low permeability, K+ ions generate a significant outward current through open Ca^{2+} channels, as reflected in the negative shift of the reversal potential in the single open channel i-V relationship. *B*, Hypothetical voltage dependence of single-channel current activation, measured as single-channel open-state probability or the probability of being activated, P_{act}. The relations were obtained from Boltzmann activation curves with the following parameters: Ca^{2+} channel: V_{half} =+5 mV, k=+7 mV; K+ channel: V_{half} =+5 mV, k=+13 mV. *C,* Hypothetical whole-cell current-voltage relationships. At each membrane potential, the whole cell current (I) equals the product of the single-channel current (i) and P_{act} multiplied by the number of channels (N): 5000 and 45,000 for the K+ and Ca^{2+} channel, respectively.

based on data from cardiac myocytes are shown in Figure 22-10 *B.* The dependence of the single-channel open-state probability (or the probability of being activated, P_{act}) on membrane potential is sigmoidal and usually described by a Boltzmann distribution equation of the form

where V_{half} is the membrane potential at which P_{act} is half-maximal and k is a steepness factor that indicates the sensitivity of channel activation to changes in membrane potential. Note that channels do not have a sharp voltage threshold for opening. The open probability of channels is a continuous function of voltage as formalized in the Boltzmann distribution equation above. Thus, even at membrane potentials well hyperpolarized to the midpoint of activation, voltage-gated Ca^{2+} (K+, Na+) channels would have a finite, albeit extremely small open probability. Cardiac myocytes, though, show a sharp threshold for firing an action potential. This characteristic, however, reflects reversal of net membrane current and not a threshold for channel opening. An action potential develops when a depolarizing stimulus increases the open-state probability of a sufficient number of Na+ channels (or Ca^{2+} channels in slow tissue) to generate an inward current that opposes the outward current carried by K+ or CI-- ions.

Whole-cell ionic currents, I, are related to the single-channel current i and the open state probability P_{act} by

where N is the number of functional channels in the plasma membrane. Whole-cell currents can be measured by using the patch-clamp technique (see Fig. 22-9 *B*).

TABLE 22-1 -- INTRACELLULAR AND EXTRACELLULAR ION CONCENTRATIONS IN CARDIAC MUSCLE

ION	EXTRACELLULAR CONCENTRATION (mM)	INTRACELLULAR CONCENTRATION	RATIO OF EXTRACELLULAR TO INTRACELLULAR CONCENTRATION	E_i (mV)
Na	145	15 mM	9.7	+60
K	4	150 mM	0.027	-94
Cl	120	5-30 mM	4-24	-83 to -36
Ca	2	10^{-7} M	2×10^{4}	+129

Although intracellular Ca content is about 2 mM, most of this Ca is bound or sequestered in intracellular organelles (mitochondria and sarcoplasmic reticulum).

E_1 =equilibrium potential for a particular ion at 37°C.

Modified after Sperelakis N: Origin of the cardiac resting potential. In Berne RM, Sperelakis N, Geiger SR (eds): Handbook of Physiology, The Cardiovascular System. Bethesda, MD, American Physiological Society, 1979, p 193.

The I-V relationships for hypothetical voltage-gated K+ and Ca^{2+} channels are illustrated in Figure 22-10 *C*. The voltage dependence of the macroscopic Ca^{2+} current has a different shape than that of the single-channel current (i) because it is determined by i N P_{act} . Thus, this relationship is bell shaped, i.e., near zero at threshold (large i but small P_{act}), maximal at V_{peak} (
+10 mV; intermediate i and large P_{act}), and smaller at more positive potentials (small i, maximal P_{act}). In contrast, the I-V relationship of the voltage-dependent K+ channel is similar to the single-channel current (i)-voltage (V) relationship because i increases with membrane depolarization.

As indicated in Figure 22-11 , open channels enter a nonconducting conformation after a depolarizing change in membrane potential, a process termed *inactivation.* Channel inactivation increases with membrane depolarization. The voltage dependence of channel inactivation is expressed by plotting the availability of the channel to open (equal to 1 - P_{inact} [the probability for a channel being in the inactivated state]) against membrane potential. The relationship between membrane potential and channel inactivation is sigmoidal and usually described by a Boltzmann equation of the same form as given above (Equation 2). Hypothetical Boltzmann activation and inactivation curves for a voltage-gated Ca^{2+} channel are shown in Figure 22-12 .

From overlap of the activation and inactivation curves it is predicted that a potential range exists where P_{act} (1 P_{inact}) 0, and a steady-state or noninactivating current with the approximate amplitude P_{act} (1 P_{inact}) I (V_{peak}) will flow. The existence of such a window current has been verified for both the voltage-gated Na+ current[35] and the L-type Ca^{2+} current.[36] A role of the L-type window current has been implicated in the genesis of early afterdepolarizations (EADs).

Channels recover from inactivation and then enter the closed state from which they can be reactivated (see Fig. 22-11) . Rates of recovery from inactivation vary among the different types of voltage-dependent channels and usually follow monoexponential or multiexponential time courses, with the longest time constants ranging from a few milliseconds, as, for example, for the fast sodium channel, to hundreds of milliseconds, as for the transient outward potassium current.

PRINCIPLES OF IONIC CURRENT MODULATION

According to Equation 3, modulation of whole-cell current amplitudes may be due to changes in i (e.g., changes in charge carrier concentration or temperature), number of functional channels in the cell membrane (e.g., changes in ion channel gene

expression), and/or P_{act} (e.g., modulation of the voltage dependence of single-channel gating by

Figure 22-11 Simplest scheme for gating of voltage-gated ion channels.

intracellular second messengers). Changes in single-channel open-state probability underlie most of the second messenger effects on voltage-gated channels. Intracellular second messengers may act through (1) change in the channel's closed and open time, (2) shift in the membrane potential dependence of a channel's activation and/or availability curve, (3) modification of the sensitivity of channel activation/inactivation to changes in membrane potential, and (4) any combination of the above. An example of a second messenger-induced change in a channel's open and closed time is given in Figure 22-13 . The consequences of a negative shift in the channel's activation curve on the whole-cell Ca^{2+} current are simulated in Figure 22-13 *C*. At activating potentials below V_{peak} , the percent increase in macroscopic current is larger than at V_{peak} or more positive potentials, where P_{act} approaches its saturating value.

MOLECULAR STRUCTURE OF ION CHANNELS.

Voltage-gated potassium channels are composed of four *separate* subunits, each containing six regions of hydrophobic amino acids (S1 through S6) that are thought to form membrane-spanning domains, and these hydrophobic regions are linked by sequences of hydrophilic amino acids that are exposed to the intracellular or extracellular space (see Fig. 22-8 *A*). One of the membrane-spanning subunits (S4) is positively charged, having a cluster of basic amino acids (lysine or arginine), and this region is thought to be part of the voltage sensor. The peptide chain linking S5 and S6

Figure 22-12 Hypothetical Boltzmann activation and inactivation curves of a voltage-gated channel. Inactivation and activation curves were constructed by using the Boltzmann distribution equation (see the text), with midpoints of activation and inactivation (V_{half}) of +5 mV and -10 mV, respectively. The slope of each curve (k) was assumed to not be different and was 7 mV. Inactivation and activation curves overlap over a potential range from approximately -30 to about +30 mV. Over this range, the product of the probability of being activated and of not being inactivated is nonzero, P_{act} - (1 P_{inact}) 0, thus indicating that a steady-state or noninactivating current will flow.

Figure 22-13 On-cell recording from a guinea pig ventricular cell patch containing one L-type Ca^{2+} channel. Panels show currents during eight consecutive applications of a 190-millisecond depolarizing voltage-clamp pulse to +20 mV and the average current *(below)* of about 500 sweeps. Charge carrier: 70

mM Ba^{2+} . *A*, Control conditions. Many sweeps are blank or show brief openings. One sweep contains repeated openings. *B,* After bath application of a membrane-permeable cyclic adenosine monophosphate analog, the channel opens more often and the open times become longer. (From Yue DT, Herzig S, Marban E: beta-Adrenergic stimulation of calcium channels occurs by potentiation of high-activity gating modes. Proc Natl Acad Sci 87:753, 1990.) Simulation of the effects of a hypothetical Ca^{2+} current modulator on the channel's activation curve and the whole-cell Ca^{2+} currents, assuming that the effect is through a negative shift of the membrane potential dependence of single-channel open-state probability. *Dotted line* = presence of channel modulator; *solid line* = control conditions.

(H5 loop) lines the water-filled pore. Voltage-dependent "fast" inactivation of the channel is mediated by a tethered N-terminal particle ("inactivation ball") that binds to the activated channel and occludes the intracellular mouth of the permeation pathway (see Fig. 22-8 *A*). Voltage-gated Na+ and Ca^{2+} channels have a basic structure similar to voltage-dependent potassium channels, although unlike K+ channels, each Ca^{2+} or Na+ channel consists of a single (alpha) subunit containing the four repeats of the six transmembrane-spanning domains (Fig. 22-8 *B*).

A structurally different family of potassium channels is that containing the inwardly rectifying potassium-selective channels (Kir). Kir channels in cardiac myocytes, as in other cells, conduct inward current at membrane potentials negative to E_K and smaller outward currents at membrane potentials positive to E_K . The activity of Kir channels is a function of both the membrane potential and the extracellular K+ concentration ($[K+]_o$). As $[K+]_o$ changes, the channel conducts inward current at potentials negative to the new E_K while a small outward current within a certain potential range positive to the new E_K remains. Structurally, Kir channels resemble voltage-gated K+ channels, but the subunits lack the S1 to S4 domains, whereas the pore-forming domains and the H5 region are conserved. Kir channel subunits can form heteromultimeric complexes with other proteins, which adds considerable complexity to the behavior of Kir channels. For example, the ATP-sensitive K+ channel $I_{K.ATP}$ is a heteromeric complex of inwardly rectifying potassium channel subunits and the sulfonylurea receptor. Drugs such as nicorandil, pinacidil, and diaxozide open ATP-sensitive K+ channels, while sulfonylurea compounds (such as glibenclamide) inhibit the activity of $I_{K.ATP}$.

The molecular basis of the acetylcholine-activated potassium channel $I_{K.Ach}$ is a heteromultimer of two inwardly rectifying potassium channel subunits. This channel is activated after direct binding of the beta-gamma subunits of G protein. Stimulation of $I_{K.Ach}$ by vagally secreted acetylcholine decreases spontaneous depolarization in the sinus node and slows the velocity of conduction in the AV node.[37] Adenosine, via type 1 purinergic receptor-mediated G protein activation, also increases $I_{K.Ach}$ activity in atrial, sinus node, and AV node cells, thus making this compound a treatment of choice for AV reentry tachycardia.

INTERCALATED DISCS

Another family of ion channel proteins is that containing the gap junctional channels. These dodecameric channels are found in the intercalated discs between adjacent cells.

Three types of specialized junctions make up each intercalated disc. The macula adherens or desmosome and fascia adherens form areas of strong adhesion between cells and may provide a linkage for the transfer of mechanical energy from one cell to the next. The *nexus,* also called the *tight* or *gap junction,* is a region in the intercalated disc where cells are in functional contact with each other. Membranes at these junctions are separated by only about 10 to 20 A and are connected by a series of hexagonally packed subunit bridges. Gap junctions provide low-resistance electrical coupling between adjacent cells by establishing aqueous pores that directly link the cytoplasm of these adjacent cells. Gap junctions allow movement of ions and small molecules between cells, thereby linking the interiors of adjacent cells.

Gap junctions permit a multicellular structure such as the heart to function electrically like an orderly, synchronized, interconnected unit and are probably responsible in part for the fact that conduction in the myocardium is *anisotropic,* i.e., its anatomical and biophysical properties vary according to the direction in which they are measured. Usually, conduction velocity is two to three times faster longitudinally, i.e., in the direction of the long axis of the fiber, than it is

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Figure 22-14 Model of the structure of a gap junction based on results of x-ray diffraction studies. Individual channels are composed of paired hexamers that travel in the membranes of adjacent cells and adjoin in the extracellular gap to form an aqueous pore that provides continuity of the cytoplasm of the two cells. (*From Saffitz JE: Cell-to-cell communication in the heart. Cardiol Rev 3:86, 1995.*)

transversely, i.e., in the direction perpendicular to this long axis. Resistivity is lower longitudinally than transversely. Interestingly, the safety factor for propagation is greater transversely than horizontally. Conduction delay or block occurs more commonly in the longitudinal direction than it does transversely. Cardiac conduction is discontinuous because of resistive discontinuities created by the gap junctions, which have anisotropic distribution on the cell surface.[38] Because of anisotropy, propagation is discontinuous and can be a cause of reentry.

Gap junctions may also provide "biochemical coupling" that might permit cell-to-cell movement of ATP on other high-energy phosphates. Gap junctions can also change their electrical resistance. When intracellular calcium rises, as in myocardial infarction, the gap junction may close to help "seal off" the effects of injured from noninjured cells. Acidosis increases and alkalosis decreases gap junctional resistance. Increased gap junctional resistance tends to slow the rate of action potential propagation, a condition that could lead to conduction delay or block.[5] [6] [7] [8] [61A] [39] [40] [41] [42] [43] [43A] [43B]

Connexins are the proteins that form the intercellular channels of gap junctions. An individual channel (connexin) is created by two hemichannels, each located in the plasma membrane of adjacent cells and composed of six integral membrane protein subunits (connexins). The hemichannels surround an aqueous pore and thereby create

a transmembrane channel (Fig. 22-14). . Connexin 43, a 43-kp polypeptide, is the most abundant cardiac connexin, with connexin 40 and 45 found in smaller amounts. Gap junctions in the distal His bundle and proximal bundle branches have large amounts of connexin 40 and 43. Atrial gap junctions have large amounts of all three connexins, while ventricular gap junctions have large amounts of connexin 43 and 45 and much less connexin 40 (see p. 659) [3] [6]

Phases of the Cardiac Action Potential

The cardiac transmembrane potential consists of five phases: phase 0--upstroke or rapid depolarization; phase 1--early rapid repolarization; phase 2--plateau; phase 3 final rapid repolarization; and phase 4--resting membrane potential and diastolic depolarization (see Fig. 20-17). These phases are the result of passive ion fluxes moving down electrochemical gradients established by active ion pumps and exchange mechanisms. Each ion moves primarily through its own ion-specific channel. Impulses spread from one cell to the next without requiring neural input. The transplanted heart dramatically demonstrates this fact. The following discussion will explain the electrogenesis of each of these phases. For in-depth coverage, the reader is referred to other reference sources.[44] [45]

General Considerations

Having a basic understanding of how transmembrane voltage controls ionic fluxes through ionic channels, we now ask the question how ionic fluxes regulate membrane potential in cardiac myocytes. When only one type of ion channel opens, assuming that this channel is perfectly selective for that ion, the membrane potential of the entire cell would equal the Nernst potential of that ion. Solving the Nernst equation for the four major ions across the plasma membrane, one obtains the following equilibrium potentials: sodium, +60 mV; potassium, -94 mV; calcium, +129 mV; and chloride, -80 to -35 mV. Therefore, if a single K^+ -selective channel opens, such as the inwardly rectifying K^+ channel, the membrane potential will approach E_K (-94 mV). If a single Na^+ -selective channel opens, the transmembrane potential will become E_{Na} (+60 mV). A quiescent cardiac myocyte (phase 4) has many more open potassium than sodium channels, and the cell's transmembrane potential is close to E_K (Table 22-2) . When two or more types of ion channel open simultaneously, each type will try to make the membrane potential go to the equilibrium potential of that channel. The contribution of each ion type to the overall membrane potential at any

TABLE 22-2 -- PROPERTIES OF TRANSMEMBRANE POTENTIALS IN MAMMALIAN HEARTS

	SINUS NODAL CELL	ATRIAL MUSCLE CELL	AV NODAL CELL	PURKINJE FIBER	VENTRICULAR MUSCLE CELL
Resting potential (mV)	-50 to -60	-80 to -90	-60 to -70	-90 to -95	-80 to -90

Action potential					
Amplitude (mV)	60-70	110-120	70-80	120	110-120
Overshoot (mV)	0-10	30	5-15	30	30
Duration (msec)	100-300	100-300	100-300	300-500	200-300
V_{max} (V/S)	1-10	100-200	5-15	500-700	100-200
Propagation velocity (M/sec)	<0.05	0.3-0.4	0.1	2-3	0.3-0.4
Fiber diameter (mum)	5-10	10-15	1-10	100	10-16

Modified from Sperelakis N: Origin of the cardiac resting potential. In Berne RM, Sperelakis N, Geiger SR (eds): Handbook of Physiology. The Cardiovascular System. Bethesda, MD, American Psychological Society, 1979, p 190.

Figure 22-15 *Left,* Demonstration of action potentials recorded during impalement of a cardiac cell. The upper row of diagrams shows a cell (circle), two microelectrodes, and stages during impalement of the cell and its activation and recovery. *A,* Both microelectrodes are extracellular, and no difference in potential exists between them (0 potential). The environment inside the cell is negative and the outside is positive since the cell is polarized. *B,* One microelectrode has pierced the cell membrane to record the intracellular resting membrane potential, which is -90 mV with respect to the outside of the cell. *C,* The cell has depolarized and the upstroke of the action potential is recorded. At its peak voltage, the inside of the cell is about +30 mV with respect to the outside of the cell. *D,* Phase of repolarization, with the membrane returning to its former resting potential (*E*) (From Cranefield PF: The Conduction of the Cardiac Impulse. Mt Kisco, NY, Futura, 1975.)

given moment is determined by the instantaneous permeability of the plasma membrane to that ion. For example, deviation of the measured resting membrane potential from E_K (see Table 22-1) would predict that other ion types with equilibrium potentials positive to E_K contribute to the resting membrane potential in cardiac myocytes. If it is assumed that Na^+ , K^+ , and Cl^- are the permeant ions at resting potential, their individual contributions to the resting membrane potential V_r can be quantified by the GHK *voltage* equation of the form

where the symbols have the meanings as outlined above. With only one permeant ion,

V_r becomes the Nernst potential for that ion. With several permeant ion types, V_r is a weighted mean of all the Nernst potentials.

Intracellular electrical activity can be recorded by inserting a glass microelectrode filled with an electrolyte solution and having a tip diameter less than 0.5 mum into a single cell. The electrode produces minimal damage, its entry point apparently being sealed by the cell. The transmembrane potential is recorded by using this electrode in reference to an extracellular ground electrode placed in the tissue bath near the cell membrane and represents the potential difference between intracellular and extracellular voltage (Fig. 22-15) . Alternatively, the patch-clamp technique in current clamp mode can be used to measure transmembrane potentials.

Phase 4--The Resting Membrane Potential

Intracellular potential during electrical quiescence in diastole is 50 to 95 mV, depending on the cell type (see Table 22-2) . Therefore, the inside of the cell is 50 to 95 mV negative relative to the outside of the cell because of the distribution of ions such as K^+ , Na^+ , and Cl^- .

Because cardiac myocytes have an abundance of open K^+ channels at rest, the cardiac transmembrane potential (in phase 4) is close to E_K . Potassium outward current through open, inwardly rectifying K^+ channels, I_{Kl} , mainly contributes to the resting membrane potential in atrial and ventricular myocytes, as well as in Purkinje cells, under normal conditions. Deviation of the resting membrane potential from E_K is due to movement of monovalent ions with an equilibrium potential greater than E_K , e.g. Cl^- efflux through activated chloride channels, such as $I_{Cl.cAMP}$, $I_{Cl.Ca}$, and $I_{Cl.swell}$. [46] Calcium does not contribute directly to the resting membrane potential, but changes in intracellular free calcium concentration can affect other membrane conductance values. For instance, an increase in sarcoplasmic reticulum Ca^{2+} load can cause spontaneous intracellular Ca^{2+} waves,[47] which in turn activate the Ca^{2+} -dependent chloride conductance $I_{Cl.Ca}$ and thereby lead to spontaneous transient inward currents and concomitant membrane depolarization. Increases in $[Ca^{2+}]_i$ may also stimulate the Na^+/Ca^{2+} exchanger $I_{Na/Ca}$. This protein exchanges three Na^+ ions for one Ca^{2+} ion, the direction being dependent on the sodium and calcium concentrations on the two sides of the membrane and the transmembrane potential difference. At resting membrane potential and during a spontaneous sarcoplasmic reticulum Ca^{2+} release event, this exchanger would generate a net Na^+ influx, possibly causing transient membrane depolarizations. [48] $[Ca^{2+}]_i$ has also been shown to activate the activity of I_{Kl} in cardiac myocytes, thereby indirectly contributing to cardiac resting membrane potential. Because of the Na-K pump, which pumps Na^+ out of the cell against its electrochemical gradient and simultaneously pumps K^+ into the cell against its chemical gradient, the intracellular K^+ concentration remains high and the intracellular

Figure 22-16 Currents and channels involved in generating resting and action potentials. The time course of a stylized action potential of atrial and ventricular cells is shown on the left, and that of sinoatrial node cells is on the right. Above and below are the various channels and pumps that contribute the currents underlying the electrical events. See Table 22-3 for identification of the symbols and description of the channels or currents. Where possible, the approximate time courses of the currents associated with the channels or pumps are shown symbolically without an effort to represent their magnitudes relative to each other. I_K incorporates at least two currents, I_{K-R} and I_{K-S} . There appears to be an ultrarapid component as well, designated I_{K-UR} . The heavy bars for I_{Cl} , I_{pump} , and $I_{K(ATP)}$ indicate only the presence of these channels or pump without implying magnitude of currents since that would vary with physiological and pathophysiological conditions. The channels identified by brackets (I_{NS} and $I_{K(ATP)}$) imply that they are active only under pathological conditions. I_{NS} may represent a swelling-activated cation current. For the sinoatrial node cells, I_{NS} and I_{K1} are small or absent. Question marks indicate that experimental evidence is not yet available to determine the presence of these channels in sinoatrial cell membranes. Although it is likely that other ionic current mechanisms exist, they are not shown here because their roles in electrogenesis are not sufficiently well defined. (From Members of the Sicilian Gambit: Antiarrhythmic Therapy: A Pathophysiologic Approach. Mt Kisco, NY, Futura, 1994, p 13.)

Na^+ concentration remains low. This pump, fueled by an Na^+ , K^+ -ATPase enzyme that hydrolyzes ATP for energy, is bound to the membrane. It requires both Na^+ and K^+ to function and can transport three Na^+ ions outward for two K^+ ions inward. Therefore, the pump can be electrogenic and generate a net outward movement of positive charges. The rate of Na^+ -K^+ pumping to maintain the same ionic gradients must increase as the heart rate increases since the cell gains a slight amount of Na^+ and loses a slight amount of K^+ with each depolarization. Cardiac glycosides block this pump.

Phase 0--Upstroke or Rapid Depolarization

A stimulus delivered to excitable tissue evokes an action potential characterized by a sudden voltage change caused by transient depolarization followed by repolarization. The action potential is conducted throughout the heart and is responsible for initiating each "heartbeat." Electrical changes in action potential follow a relatively fixed time and voltage relationship that differs according to specific cell types (Figs. 22-16 and 22-17). In nerve, the entire process takes several milliseconds, while action potentials in cardiac fibers last several hundred milliseconds. Normally, the action potential is independent of the size of the depolarizing stimulus, if the latter exceeds a certain threshold potential. Small subthreshold depolarizing stimuli depolarize the membrane in proportion to the strength of the stimulus. However, once the stimulus is sufficiently intense to reduce membrane potential to a threshold value in the range of -70 to -65 mV for normal Purkinje fibers, more intense stimuli do not produce larger action potential responses, and an "all-or-none" response results. In contrast, hyperpolarizing pulses, i.e., stimuli that render the membrane potential more negative, elicit a response proportional to the strength of the stimulus.

MECHANISM OF PHASE 0.

The upstroke of the cardiac action potential in atrial and ventricular muscle and His-Purkinje fibers is due to a sudden increase in membrane conductance to Na^+ . An externally applied stimulus or a spontaneously generated local membrane circuit current in advance of a propagating action potential depolarizes a sufficiently large area of membrane at a sufficiently rapid rate to open the Na^+ channels and depolarize the membrane further. When the stimulus activates enough sodium channels, Na^+ rushes into the cell, down its electrochemical gradient. The excited membrane no longer behaves like a K^+ electrode, i.e., exclusively permeable to K^+ , but more closely approximates an Na^+ electrode, and the membrane moves toward the Na^+ equilibrium potential.

The rate at which depolarization occurs during phase 0, i.e., the maximum rate of change of voltage over time, is indicated by the expression dv/dtma or Vmax (see Table 22-2) , which is a reasonable approximation of the rate and magnitude of Na^+ entry into the cell and a determinant of conduction velocity for the propagated action potential. The transient increase in sodium conductance lasts 1 to 2 milliseconds. The action potential, or more properly the Na^+ current (I_{Na}), is said to be regenerative; that is, intracellular movement of a little Na^+ depolarizes the membrane more, which increases conductance to Na^+ more, which allows more Na^+ to enter, and so on. As this process is occurring, however, $[Na^+]_1$ and positive intracellular charges increase and reduce the driving force for Na^+ . When the equilibrium potential for Na^+ (E_{Na}) is reached, Na^+ no longer enters the cell; i.e., when the driving force acting on the ion to enter the cell balances the driving force acting on the ion to exit the cell, no current will flow. In addition, Na^+ conductance is time dependent, so when the membrane spends some time at voltages less negative than the resting potential, Na^+ conductance decreases (in activation). Therefore, an intervention that reduces membrane potential for a time--but not to threshold--partially inactivates Na^+ channels, and if threshold is now achieved, the magnitude and rate of Na^+ influx are reduced.

The probability of a voltage-gated channel not being inactivated, 1 - P_{inact} , is given by the Boltzmann distribution equation of the form

Figure 22-17 Action potentials recorded from different tissues in the heart (*left*) remounted along with a His bundle recording and scalar electrocardiogram from a patient (*right*) to illustrate the timing during a single cardiac cycle. In panels *A* to *F,* the top tracing is dV/dt of phase 0 and the second tracing is the action potential. For each panel the numbers (from left to right) indicate maximum diastolic potential (mV), action potential amplitude (mV), action potential duration at 90 percent of repolarization (milliseconds), and Vmax of phase 0 (V/sec). Zero potential is indicated by the short horizontal line next to the zero on the upper left of each action potential. *A,* Rabbit sinoatrial node; *B,* canine atrial muscle; *C,* rabbit atrioventricular node; *D,* canine ventricular muscle; *E,* canine Purkinje fiber; *F,* diseased human ventricle. Note that the action potentials recorded in *A, C,* and *F* have reduced resting membrane potentials, amplitudes, and Vmax when compared with the other action potentials. In the *right panel,* A = atrial

muscle potential; AVN = atrioventricular nodal potential; HB = His bundle recording; II = lead II; PF = Purkinje fiber potential; SN = sinus nodal potential; V = ventricular muscle potential. Horizontal calibration on the left: 50 milliseconds for *A* and *C,* 100 milliseconds for *B, D, E,* and *F;* 200 milliseconds on the right. Vertical calibration on the left: 50 mV. Horizontal calibration on the right: 200 milliseconds (Modified from Gilmour RF Jr, Zipes DP: Basic electrophysiology of the slow inward current. *In* Antman E, Stone PH (Eds.) Calcium Blocking Agents in the Treatment of Cardiovascular Disorders. Mt Kisco, NY, Futura, 1983, pp 1-37.)

Figure 22-18 Schematic representation of membrane channels for rapid and slow inward currents at resting membrane potential *(top row)*, during the activated state *(middle row)*, and during the inactivated state *(bottom row)*. Vertically separated panels depict fibers with a normal resting potential of -90 mV *(left)*, with resting membrane potential reduced to less than -60 mV *(middle)*, and after stimulation of the cell with catecholamines *(right)*. The activation (m) and inactivation (h) gates of the fast channel and the activation (d) and inactivation (f) gates of the slow channel are depicted. During the resting state *(left panel)*, the activation gates of both channels are closed while the inactivation gates are open. When the cell is stimulated, the m gates of the fast channel open, and for a brief period, the open m gates and h gates allow inward sodium current to flow, depolarize the cell, and produce its upstroke. The action potential is depicted below. The h gates then close the channel and inactivate sodium conductance. Membrane depolarization also activates voltage-gated Ca^{2+} channels (d gates open), allowing influx of Ca^{2+} that contributes to the plateau phase of the action potential. The inactivation gates of the slow Ca^{2+} channel are both voltage and $[Ca^{2+}]_i$ dependent. High and low levels of intracellular free calcium ions respectively accelerate and slow inactivation, thereby functioning as a negative feed-back mechanism to control intracellular calcium content. When the upstroke of the action potential exceeds the threshold for activation of the slow inward current, the d gates open and allow ingress of the slow inward current that contributes to the plateau phase of the action potential. The f gates of the slow channel close more slowly than the h gates. Although the slow inward channel remains open longer than the fast channel does, less total current flows. When the resting membrane potential is reduced below -60 mV by increasing $[K]_o$ from 4.0 to 14.0 mm *(middle panel)*, the cell depolarizes to -60 mV and the fast channel becomes inactivated because the h gates remain closed. Even though the m gate may open during activation, the amount of sodium current is too small to elicit an action potential. The inactivation gates of the slow channel (f gates) remain open, and when the cell is excited after the addition of catecholamine *(right panel),* the d gates open and permit flow of a slow inward current that causes a slow-response action potential. This action potential resembles those in panels *A, C,* and *F* of Figure 22-17. (From Wit AL, Bigger JT Jr: Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 52(Suppl 3):96, 1975. By permission of the American Heart Association, Inc.)

(for symbols see Equation 2). If it is assumed that the midpoint of half-inactivation is -60 mV and the steepness of the inactivation curve of the voltage-gated Na^+ channel is -3 mV, sustained membrane depolarization from -90 to -65 mV would decrease steady-state Na^+ channel availability from approximately 1 to 0.84.

In cardiac Purkinje fibers and to a lesser extent in ventricular muscle, two different populations of Na+ channels exist, or two different modes of operation of the same Na+ channel. One is responsible for the brief Na+ current of phase 0, while the other, which is longer lasting, participates in the action potential plateau (Steady-state or "window" current, see Fig. 22-12). Tetrodotoxin (TTX) and local anesthetics block both types of channels, thereby diminishing the rate of rise of phase 0 and shortening the action

potential duration.[49] Furthermore, there may be a background Na+ current ($I_{Na\text{-}B}$) through a voltage-independent channel in sinus nodal cells that contributes to pacemaker behavior.[50]

THE GATED SYSTEM--A HYPOTHETICAL MODEL.

In this hypothetical model, three m (activation) gates and one h (inactivation) gate can be considered to be lined up in series in the membrane Na+ channel (Fig. 22-18), , with the m gate on the extracellular side and the h gate on the intracellular side of the membrane. When the membrane is in a resting polarized state, the m gates are almost completely closed, the h gate is open, and no Na+ can cross the membrane. Although depolarization of the membrane opens the m gates and closes the h gate, the m gates open faster than the h gate closes; i.e., activation of the channel proceeds faster than inactivation can occur, and Na+ flows through the Na+ channel for about 1 millisecond while both gates are open simultaneously (Fig. 22-18*left panel,* red arrow).

When the membrane repolarizes to fairly high negative values, i.e., the membrane potential becomes more negative than about -60 mV, the m gates shut rapidly, the h gate opens more slowly (reactivation or recovery from inactivation), and the membrane is once again capable of depolarization. Until that time, the cell is absolutely refractory; i.e., no stimulus, regardless of intensity, can activate the cell. If the membrane is activated a second time before reaching a large negative value, all the h gates have not yet reopened and the maximum number of Na+ channels that can open is reduced. The

Figure 22-19 Mechanism of fast inactivation of sodium channels. The hinged-lid mechanism of sodium channel inactivation is illustrated. The intracellular loop connecting domains III and IV of the sodium channel is depicted as forming a hinged lid. The critical residue (Phe1489F) is shown as occluding the intracellular mouth of the pore. (From Catteral WA: Molecular analysis of voltage gated sodium channels in the heart and other tissues. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. 2nd ed. Philadelphia, WB Saunders, 1994, p 1.)

resulting action potential will have reduced Vmax, amplitude, duration, and conduction velocity. The state of the gates at any time depends on the membrane potential and the length of time that the potential has been maintained.[49]

A cluster of positively charged arginine and lysine residues in the S4 domain is thought to function as the voltage sensor (m gate), while the peptide loop connecting repeats S3 and S4 binds to the activated channel and occludes the intracellular mouth of the channel pore (h gate; see Fig. 22-19). This loop could be regarded as analogous to the N-terminal peptide chain of inactivating voltage-gated potassium channels (see Fig. 22-8*A*).

A Hodgkin-Huxley formalism has been used to describe the voltage dependence of single-channel permeability to sodium, with four hypothetical gating particles making independent transitions between conducting and nonconducting positions to control ion flux. Three m particles control activation and one h particle controls inactivation. The probability that they are all in a position where the channel conducts is $m^{[3]}$ h, and for the Na+ channel,

where P_{Na} is the permeability of the sodium channel at a given voltage, $P_{Na,max}$ is the maximal possible permeability of the channel, $m^{[3]}$ represents the probability that all three activation particles are in a position to make up an open channel (m = 1, gate is permissive; m = 0, gate is nonpermissive), whereas h represents the probability that the Na+ channel is not inactivated ([1 - P_{inact}], h = 1, gate is open; h = 0, gate is shut; see Fig. 22-12) . Since opening and closing of the gates are voltage *and* time dependent, the permeability of the channel (P_{Na}) will be some fraction of the maximum possible permeability ($P_{Na,max}$), depending on membrane potential and the period that the membrane has been at that voltage.

TABLE 22-3 -- SYNOPSIS OF IONIC CURRENTS IN MAMMALIAN CARDIAC MYOCYTES

I_{Na}	Tetrodotoxin-sensitive voltage-gated Na^+ current
I_{Na-B}	Proposed background Na^+ current through a voltage-independent channel in sinus nodal cells
$I_{Ca.L}$	L-type (*l*ong lasting, *l*arge conductance) Ca^{2+} currents through voltage-gated channels blocked by dihydropyridine-type antagonists (e.g., nifedipine), phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and a variety of divalent ions (e.g., Cd^{2+}), activated by dihydropyridine-type agonists (e.g., Bay K 8644), responsible for phase 0 depolarization and propagation in sinoatrial and AV nodal tissue, and contributing to the plateau of atrial, His-Purkinje, and ventricular cells; main trigger of Ca^{2+} release from the sarcoplasmic reticulum (Ca^{2+} -induced Ca^{2+} release); a noninactivating or "window" component may underlie early afterdepolarizations
$I_{Ca.T}$	T-type (*t*ransient current, *t*iny conductance) Ca^{2+} currents through voltage-gated channels blocked by mibefradil but insensitive to dihydropyridines; may contribute inward current to the later phase of phase 4 depolarization in pacemaker cells
I_f	Hyperpolarization-activated current carried by Na^+ and K^+ in sinoatrial and AV nodal cells and His-Purkinje cells and involved in generating phase 4 depolarization; increases rate of impulse initiation in pacemaker cells

I_{K1}	Inward rectifier K^+ current, voltage-dependent block by Ba^{2+} at micromolar concentrations; responsible for maintaining resting membrane potential in atrial, His-Purkinje, and ventricular cells; channel activity is a function of both membrane potential and $[K^+]_0$; inward rectification appears to result from depolarization-induced internal block by Mg^{2+}
$I_{K.G}$ ($I_{K.Ach}$, $I_{K.Ade}$)	Inwardly rectifying K^+ current activated by muscarinic (M_2) and purinergic (type 1) receptor stimulation via GTP regulatory (G) protein signal transduction; expressed in sinoatrial and AV nodal cells and atrial cells, where it causes hyperpolarization and action potential shortening; activation causes negative chronotropic and dromotropic effects
I_K	K^+ current carried by a voltage-gated K^+ channel (delayed rectifier K^+ channel); composed of the rapid (I_{Kr}) and slow (I_{Ks}) component. I_{Kr} is specifically blocked by dofetilide and sotalol in a reverse-use-dependent manner; inward rectification of I_{Kr} results from depolarization-induced fast inactivation; plays a major role in determining action potential duration
$I_{K,ur}$	K^+ current through a voltage-gated channel with ultrarapid activation, but ultraslow inactivation kinetics; expressed in atrial myocytes; determines action potential duration
I_{to} (I_{to1} , I_A)	Transient outward K^+ current through voltage-gated channels; exhibits fast activation and inactivation kinetics; blocked by 4-aminopyridine in a reverse-use-dependent manner; determines time course of phase 1 repolarization
$I_{Cl.Ca}$ (I_{to2})	4-Aminopyridine-resistant transient outward current carried by Cl^{-} ions; activated by rises in intracellular calcium; blocked by stilbene derivatives (SITS, DIDS); determines time course of phase 1 repolarization; may underlie spontaneous transient inward currents under conditions of Ca^{2+} overload
$I_{Cl.cAMP}$	Time-independent chloride current regulated by the cAMP/adenylate cyclase pathway; slightly depolarizes resting membrane potential and significantly shortens action potential duration; antagonizes action potential prolongation associated with beta-adrenergic stimulation of $I_{Ca.L}$
$I_{Cl.swell}$	Outwardly rectifying, swelling-activated Cl^{-} current; inhibited by 9-anthracene carboxylic acid; activation causes resting membrane depolarization and action potential shortening
$I_{K.ATP}$	Time-independent K^+ current through channels activated by a fall in intracellular ATP concentration; inhibited by sulfonylurea drugs, such as glibenclamide; activated by pinacidil, nicorandil, cromakalim; causes shortening of action potential duration during myocardial ischemia or hypoxia
$I_{Cir.swell}$	Inwardly rectifying, swelling-activated cation current; permeable to Na^+ and K^+ (P_{Na}/P_K =8); inhibited by Gd^{3+} ; depolarizes resting membrane potential and prolongs terminal (phase 3) repolarization

$I_{Na/Ca}$	Current carried by the Na/Ca exchanger; causes a net Na^+ outward current and a Ca^{2+} inward current (reverse mode) or a net Na^+ inward and Ca^{2+} outward current (3 Na^+ for 1 Ca^{2+}), the direction of Na^+ flux being dependent on membrane potential and intracellular and extracellular concentrations of Na^+ and Ca^{2+} ; Ca^{2+} influx mediated by $I_{Na/Ca}$ can trigger SR Ca^{2+} release; underlies I_{ti} (transient inward current) under conditions of intracellular Ca^{2+} overload
$I_{Na/K}$	Na^+ outward current generated by Na^+ , K^+ -ATPase (stoichiometry: 3 Na^+ leave and 2 K^+ enter); inhibited by digitalis
ELECTRONEUTRAL ION-EXCHANGING PROTEINS	
Ca^{2+} -ATPase	Extrudes cytosolic calcium
Na/H	Exchanges intracellular H^+ for extracellular Na^+ ; cardiac myocytes express isoform NHE 1; specifically inhibited by the benzoylguanidine derivatives HOE 694 and HOE 642; inhibition causes intracellular acidification
Cl^{--} -HCO_3^{--}	Exchanges intracellular HCO_3^{--} for external Cl^{--} ; inhibited by SITS
Na^+ -K^+ -2Cl^{--}	Cotransporter blocked by amiloride

ATP=adenosine triphosphate; AV=atrioventricular; cAMP=cyclic adenosine monophosphate; DIDS=4,4
-diisothiocyanatostilbene-2,2
-disulfonic acid; GTP=guanosine triphosphate; SITS=4-acetamido-4
-isothiocyanatostilbene-2,2
-disulfonic acid; SR=sarcoplasmic reticulum.

UPSTROKE OF THE ACTION POTENTIAL.

In normal atrial and ventricular muscle and in fibers in the His-Purkinje system, action potentials have very rapid upstrokes with a large Vmax and are called *fast responses.* Action potentials in the normal sinus and AV nodes have very slow upstrokes with a reduced Vmax and are called *slow responses* [31] (see Fig. 22-17 and Table 22-3) . Upstrokes of "slow responses" are mediated by a slow inward, predominantly Ca^{2+} current (I_{Ca}) rather than the fast inward I_{Na} (Table 22-4) . These potentials received the name *slow response* because the time required for activation and inactivation of the slow inward current ($I_{Ca.L}$) is approximately an order of magnitude slower than that for the fast inward Na+ current (I_{Na}). Recovery from inactivation also takes longer. Calcium entry and $[Ca^{2+}]_i$ help promote inactivation. Thus, the slow channel opens (activation

gates d) and closes (inactivation gates f) more slowly than the fast channel does, remains open for a longer time, and requires more time following a stimulus to be reactivated (see Fig. 22-18) . In fact, recovery of excitability outlasts full restoration of maximum diastolic potential, which means that even though the membrane potential has returned to normal, the cell has not recovered excitability completely because the latter depends on elapse of a certain amount of time (i.e., is time dependent) and not just on recovery of a particular membrane potential (i.e., voltage dependence).

The threshold for activation of $I_{Ca.L}$ i.e., the voltage that the cell must reach to "turn on" the slow inward current, is about -30 to -40 mV. In fast-response-type fibers, $I_{Ca.L}$ is normally activated during phase 0 by the regenerative depolarization caused by the fast sodium current. Current flows through both fast and slow channels during the latter part of the action potential upstroke. However, $I_{Ca.L}$ is much smaller than the peak Na+ current and therefore contributes little to the action potential until the fast Na+ current is inactivated, after completion of phase 0. Thus, $I_{Ca.L}$ affects mainly the plateau of action potentials recorded in atrial and ventricular muscle and His-Purkinje fibers. When the fast Na+ current is inactivated rapidly, such as in frog ventricle, $I_{Ca.L}$ may contribute noticeably to the peak of phase 0. In addition, $I_{Ca.L}$ can be activated and may play a prominent role in partially depolarized cells in which the fast Na+ channels have been inactivated, if conditions are appropriate for slow-channel activation.

At least two types of calcium current exist in cardiac myocytes: a slowly inactivating dihydropyridine-sensitive current $I_{Ca.L}$ and a fast inactivating dihydropyridine-insensitive current ($I_{Ca.T}$). $I_{Ca.L}$ produces repolarization and propagation in sinus and AV nodal cells and contributes to the plateau by triggering calcium release from the sarcoplasmic reticulum in atrial, ventricular, and His-Purkinje cells. Calcium channel blockers block this channel, which is strongly modulated by neurotransmitters. $I_{Ca.T}$ is activated at membrane potentials intermediate between I_{Na} and $I_{Ca.L}$ and probably contributes inward current to the later stages of phase 4 depolarizations in the sinus node and His-Purkinje cells.[51] [52] [53] [54] [55] [56] [57] [58] [59] A functional role of $I_{Ca.T}$ in atrial and ventricular myocytes is less certain. Whether Ca^{2+} influx through open T-type channels provides a sufficient trigger for Ca^{2+} release from the sarcoplasmic reticulum is controversial. The density of T-type Ca^{2+} channels has been found to be increased in myocytes from hearts with experimentally induced hypertrophy,[60] but the role of enhanced T-type channel density under these conditions remains to be determined.

Other significant differences exist between the fast and slow channels (see Table 22-4) . Drugs that elevate cAMP levels such as beta-adrenoceptor agonists, phosphodiesterase inhibitors such as theophylline, and the lipid-soluble derivative of cAMP dibutyryl cAMP, increase $I_{Ca.L}$. Binding of the beta-adrenoceptor agonist to specific sarcolemmal receptors facilitates the dissociation of two subunits of a regulatory protein (G protein, see Chap. 14) , one of which (C_s) activates adenylate cyclase and thus increases intracellular levels of cAMP. The latter binds to a regulatory subunit of a cAMP-dependent protein kinase that promotes phosphorylation of specific

phosphorylation sites on the channel protein (see Fig. 22-8 *A*), ultimately resulting

TABLE 22-4 -- CHARACTERISTICS OF FAST AND SLOW INWARD CURRENTS IN CARDIAC TISSUE

CHARACTERISTIC	FAST	SLOW
Primary charge carrier	Na	Ca (Na)
Activation threshold* (mV)	-70 to -55	-55 to -30
Magnitude (muA)	1-30	0.1-3.0
Time constant of		
Activation (msec)	<1	<5
Inactivation (msec)	<1	3-80
Inhibitors	Tetrodotoxin, local anesthetics, sustained depolarization at less than -40 mV	Verapamil, D-600, nifedipine, diltiazem, Mn, Co, Ni, La, Ca^{2+}
Resting membrane potential (mV)	-80 to -95	-40 to -70
Conduction velocity (M/sec)	0.3-3.0	0.01-0.10
Rate of rise (V_{max}) of action potential upstroke (V/sec)	200-1000	1-10
Action potential amplitude (mV)	100-130	35-75
Response to stimulus	All or none	Affected by characteristics of stimulus
Recovery of excitability	Prompt, ends with repolarization	Delayed, outlasts full repolarization
Safety factor for conduction	High	Low
Major current of action potential upstroke in the following:		
SA node	-	+
Atrial myocardium	+	-
AV node (N region)	-	+
His-Purkinje system	+	-

Ventricular myocardium	+	-
Neurotransmitter influence		
Beta-adrenergic	-	
Alpha-adrenergic	-	
Muscarinic, cholinergic	-	
		In atrium
		In ventricle

AV=atrioventricular; SA=sinoatrial.

*Note that the term "threshold" does not stand for a sharp voltage threshold for channel opening but a threshold for reversal of the net membrane current. This situation occurs when the membrane potential reaches a range where just enough Na^{1} (or Ca^{2+}) channels open to make an inward current that opposes the sum of outward currents carried by K^{+} and other ions.

in enhanced open-state probability of the channel (see Fig. 22-13 *A* and *B*).

Acetylcholine reduces $I_{Ca.L}$ by decreasing adenylate cyclase activity. However, acetylcholine stimulates cyclic guanosine monophosphate (cGMP) accumulation. cGMP has negligible effects on basal $I_{Ca.L}$ but decreases $I_{Ca.L}$ levels that have been elevated by beta-adrenoceptor agonists. This effect is mediated by cAMP hydrolysis via a cGMP-stimulated cyclic nucleotide phosphodiesterase.[23]

DIFFERENCES BETWEEN CHANNELS.

Fast and slow channels can be differentiated on the basis of their pharmacological sensitivity. Drugs that block the slow channel with a *fair* degree of specificity include verapamil, nifedipine, diltiazem, and D-600 (a methoxy derivative of verapamil). Antiarrhythmic agents such as lidocaine, quinidine, procainamide, and disopyramide (see Chap. 23) affect the fast channel and not the slow channel. The puffer fish poison TTX, which is too toxic to be used clinically, blocks the fast channel with considerable specificity (see Table 22-4).

While fast-response action potentials are characteristic of atrial and ventricular muscle and His-Purkinje tissue, slow-response-type action potentials are found in the normal sinus and AV nodes and many kinds of diseased tissue (see Table 22-4) . Normal action

potentials recorded from the sinus node and the N region of the AV node have a reduced resting membrane potential, action potential amplitude, overshoot, upstroke, and conduction velocity when compared with action potentials in muscle or Purkinje fibers (see Fig. 22-17) .

Slow-channel blockers, but not TTX, suppress sinus and AV nodal action potentials. The prolonged time for reactivation of $I_{Ca.L}$ probably accounts for the fact that sinus and AV nodal cells remain refractory longer than the time that it takes for full voltage repolarization to occur. Thus, premature stimulation immediately after the membrane potential reaches full repolarization leads to action potentials with reduced amplitudes and upstroke velocities. Therefore, slow conduction and prolonged refractoriness are characteristic features of nodal cells. These cells also have a reduced "safety factor for conduction," which means that the stimulating efficacy of the propagating impulse is low and conduction block occurs easily. Membranes of nodal cells probably do have Na channels that are inactivated by the relatively depolarized range of potentials over which activity takes place. Hyperpolarization exposes a fast TTX-sensitive sodium current in nodal cells.

INWARD CURRENTS.

Thus, I_{Na} and I_{Ca} represent two important inward currents. Another important inward current is I_f , also called the *pacemaker current.* [18] [19] [20] [21] [22] This current is activated by hyperpolarization and is carried by Na+ and K+. It generates phase 4 diastolic depolarization in the sinus node. I_f activation is the major mechanism by which beta-adrenergic and cholinergic neurotransmitters regulate cardiac rhythm under physiological conditions. Catecholamines increase the probability of channel opening, with no change in single-channel amplitude, and increase the discharge rate, with cholinergic action, in general, having an opposite effect.

A variety of manipulations, including those that block or inactivate I_{Na} (such as administration of TTX or sustained depolarization of the cell membrane with submillimolar concentrations of external Ba^{2+} to block K+ efflux through I_{kl} channels), combined with those that increase $I_{Ca.L}$ (such as administration of catecholamines), can transform a fast-channel-dependent fiber (e.g., a Purkinje fiber) to a slow-channel-dependent fiber. Whether these artificial in vitro alterations have clinical relevance is not known, but it is possible that myocardial ischemia or infarction, for example, can produce this transformation (see Fig. 22-17 *F*).

The electrophysiological changes accompanying *acute* myocardial ischemia may represent a depressed form of a fast response in the center of the ischemic zone and a slow response in the border area. Probable slow-response activity has been shown in myocardium resected from patients undergoing surgery for recurrent ventricular tachyarrhythmias. Whether and how slow responses play a role in the genesis of ventricular arrhythmias in these patients have not been established.

Phase 1--Early Rapid Repolarization

Following phase 0, the membrane repolarizes rapidly and transiently to nearly 0 mV, partly because of inactivation of I_{Na} and concomitant activation of several outward currents:

1. The 4-aminopyridine-sensitive transient outward K+ current, commonly termed I_{to} , turns on rapidly by depolarization and is then rapidly inactivated. Both the density and recovery of I_{to} from inactivation exhibit transmural gradients in the left ventricular free wall, with the density decreasing (Fig. 22-20) and reactivation becoming progressively prolonged from epicardium to endocardium.[61] It is currently unknown whether these nonuniformities in I_{to} recovery reflect transmural differences in channel subunit composition or in posttranslational modification of channel proteins that are thought to underlie I_{to} (Kv4.2 and Kv4.3). Gradients in I_{to} channel density and reactivation kinetics give rise to regional differences in action potential shape, with increasingly slower phase 1 restitution kinetics along the transmural axis. These regional differences might create transmural voltage gradients, specifically at higher rates, thereby increasing dispersion of repolarization, a putative arrhythmogenic factor. Since I_{to} overlaps I_{Na} , changes in I_{to} density or properties may also affect cellular excitability.
2. The 4-aminopyridine-resistant, Ca^{2+} -activated chloride current $I_{Cl.Ca}$ also contributes a significant outward current during phase 1 repolarization. This current is activated by the action potential-evoked intracellular Ca^{2+} transient. Therefore, interventions that augment the amplitude of the Ca^{2+} transient associated with the twitch (such as beta-adrenergic receptor stimulation) also enhance outward $IC_{l.Ca}$. It is not currently known whether human cardiac myocytes express Ca^{2+} -activated chloride channels. Other, time-*in*dependent chloride currents may also play a role in determining the time course of early repolarization, such as the cAMP- or swelling-activated chloride conductances $I_{Cl.cAMP}$ and $I_{Cl.swell}$.
3. A third current contributing to early repolarization is Na+ outward movement through the Na/Ca exchanger operating in reverse mode (see Fig. 22-16) . Overexpression of the exchanger in transgenic mice causes accentuation of the early "notch" in left ventricular myocytes.[61A]

Sometimes, a transient depolarization follows phase 1 repolarization. This "notch" is well defined and separated from phase 2 in Purkinje fibers and left ventricular epicardial and midmyocardial myocytes (see Fig. 22-20) .

Phase 2--Plateau

During the plateau phase, which may last several hundred milliseconds, membrane conductance to all ions falls to rather low values. Thus, less change in current is required near plateau levels than near resting potential levels to produce the same

changes in transmembrane potential. The plateau is maintained by the competition between outward current carried by K+ and Cl-- ions and inward current carried by Ca^{2+} moving through open L-type Ca^{2+} channels and Na+ being exchanged for internal Ca^{2+} by the Na/Ca exchanger operating in forward mode. After depolarization, potassium conductance falls to plateau levels as a result of inward rectification, in spite of the large electrochemical driving force on K+ ions,

Rectification simply means that membrane conductance changes with voltage. Specifically, inward rectification means that K+ channels are open at negative potentials but shut at less negative or positive voltages. Membrane depolarization-induced internal block by intracellular ionized magnesium is thought to underlie inward rectification of cardiac I_{Kl} channels. The mechanism underlying rectification of the rapid component of the delayed rectifier K+ current (I_{Kr}) in cardiac cells is the inactivation that channels rapidly undergo during depolarizing pulses. More I_{Kr} channels enter the inactivated state with stronger depolarizations, thereby causing inward rectification. This fast inactivation mechanism is sensitive to changes in extracellular K+ in the physiological range, with inactivation more accentuated at low extracellular K+ concentrations.[62] Thus, hypokalemia would decrease outward I_{Kr} , thereby prolonging action potential duration.

Outward K+ movement carried by the slow component of the delayed rectifier K+ current (I_{Ks}) also contributes to plateau duration since (1) I_{Ks} density has been shown to be correlated with action potential duration[63] and (2) isolated defects in the KvLQT1 subunit, which in combination with the IsK subunit (minK) reconstitutes the cardiac I_{Ks} current, is associated with abnormally prolonged ventricular repolarization (long QT syndrome type 1; see Chap. 25) . Although I_{Ks} activates slowly in comparison to action potential duration, it also does not or is only very slowly inactivated. Therefore, increases in heart rate can cause this activation to accumulate during successive depolarizations. Thus, cumulative activation can determine the contribution to repolarization of K+ currents that are active during the plateau of the action potential. In conditions of reduced intracellular ATP concentration (hypoxia, ischemia), K+ efflux through activated K_{ATP} channels is enhanced, thereby shortening the plateau phase of the action potential. Other ionic mechanisms that control plateau potential and duration include the kinetics of inactivation of the L-type Ca^{2+} current. Reduced efficiency of intracellular free Ca^{2+} to induce

Figure 22-20 Action potential plots demonstrating differences in the action potential shape of human ventricular myocytes of subepicardial *(A)* and subendocardial *(B)* origin. Subepicardial myocytes present a prominent notch during phase 1 repolarization of the action potential, most likely caused by a larger I_{to} in these cells. The notch is absent in subendocardial cells. The peak plateau potential is higher in subendocardial than in subepicardial myocytes, and the action potential duration tends to be shorter in subepicardial cells. Recording temperature = 35°C; V_m = membrane potential. *C* and *D,* Voltage

dependence of the current density of I_{to} . Panels denote voltage-clamp protocol *(top)*, original current recordings *(middle)*, and mean peak current densities (pA/pF) in subepicardial and subendocardial myocytes. Upon depolarization, myocytes from both nonpaced and paced hearts displayed a rapidly activating outward current, which then decayed to nonzero steady-state current levels. As cells were depolarized to more and more positive potentials, the transient outward current became larger and peaked sooner. At each voltage, the peak I_{to} amplitude was quantified as the difference between the maximum and steady-state current at the end of the test pulse and normalized to cell capacitance to obtain the peak I_{to} density. Endocardial cells exhibit a significantly smaller peak I_{to} amplitude than epicardial cells do. (From Nabauer M, Beuckelmann DJ, Uberfuhr P, Steinbeck G: Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. Circulation 93:168-177, 1996. By permission of the American Heart Association, Inc.)

Ca^{2+} -dependent inactivation, such as in myocytes from hypertrophic hearts, may result in delayed repolarization. Steady-state components of both I_{Na} and $I_{Ca.L}$ may shape the plateau phase (see Fig. 22-12) .

One type of the long QT syndrome, LQT3, is caused by a defective sodium channel gene, *SCN5A.* One mutation in patients with LQT3 involves a deletion of three amino acids in the S3-S4 cytoplasmic linker loop (see Fig. 22-19), which is thought to mediate inactivation. The mutant sodium channel is inactivated only incompletely, which results in prolonged depolarizations. Na, K-ATPase generates a net outward current by pumping out three Na+ ions in exchange for 2 K+. Noninactivating chloride currents, such as $I_{Cl.swell}$ and $I_{Cl.cAMP}$, may produce significant outward currents during the plateau phase under certain conditions, thereby significantly shortening action potential duration. A recently discovered, nonselective, swelling-induced cation current has been shown to cause action potential prolongation in myocytes from failing ventricles.[64]

Phase 3--Final Rapid Repolarization

In this portion of the action potential, repolarization proceeds rapidly owing at least in part to two currents: time-dependent inactivation of $I_{Ca.L}$, with a decrease in the intracellular movement of positive charges, and activation of repolarizing K+ currents, including the slow and rapid components of the delayed rectifier K+ current I_{Ks} and I_{Kr} and the inwardly rectifying K+ currents I_{Kl} and $I_{K.Ach}$, with an increase in the movement of positive charges out of the cell. The net membrane current becomes more outward, and the membrane potential shifts to the resting potential. Mutations in the human ether-a-go-go-related gene (*HERG*), which is responsible for I_{Kr} , prolong phase 3 repolarization, thereby predisposing to the development of torsades de pointes. Macrolide antibiotics such as erythromycin, antihistamines such as terfenadine, and antifungal drugs such as ketoconazole all inhibit I_{Kr} and have been implicated in the acquired form of long QT syndrome. A decrease in I_{Kl} activity, as is the case in left ventricular myocytes from

Figure 22-21 Differences in action potential characteristics and whole-cell I_{Kl} activity in left ventricular myocytes isolated from patients with ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM). *A,* Transmembrane action potential recordings. Late phase 3 repolarization was slowed and resting membrane potential was depolarized for DCM when compared with ICM. *B,* Whole-cell I_{Kl} recordings in ventricular myocytes from patients with ICM and DCM. A test pulse (TP) was applied for 300 milliseconds to the potential indicated. The current magnitude for DCM was smaller than that for ICM. *C,* Average I_{Kl} -voltage relationship in ventricular myocytes from patients with ICM and DCM. The whole cell current slope conductance at E_K for DCM was smaller (41 pS) than that for ICM (81 pS). (From Koumi S, Backer CL, Arentzen CE: Molecular and cellular cardiology: Characterization of inwardly rectifying K+ channel in human cardiac myocytes: Alterations in channel behavior in myocytes isolated from patients with idiopathic dilated cardiomyopathy. Circulation 92:164-174, 1995. By permission of the American Heart Association, Inc.)

patients with dilated cardiomyopathy,[65] causes action potential prolongation via slowing of phase 3 repolarization and resting membrane depolarization (Fig. 22-21) .

Phase 4--Diastolic Depolarization (see also p. 680)

Under normal conditions, the membrane potential of atrial and ventricular muscle cells remains steady throughout diastole. I_{Kl} is the current responsible for maintaining the resting potential near the K+ equilibrium potential in atrial, AV nodal, His-Purkinje, and ventricular cells. I_{Kl} is the inward rectifier and shuts off during depolarization. It is absent in sinus nodal and AV nodal cells. In other fibers found in certain parts of the atria, in the muscle of the mitral and tricuspid valves, in His-Purkinje fibers, and in the sinus node and distal portion of the AV node, the resting membrane potential does not remain constant in diastole but gradually depolarizes (see Fig. 22-17 *A*). If a propagating impulse does not depolarize the cell or group of cells, it may reach threshold by itself and produce a spontaneous action potential. The property possessed by spontaneously discharging cells is called *phase 4 diastolic depolarization;* when it leads to initiation of action potentials, automaticity results. The discharge rate of the sinus node normally exceeds the discharge rate of other potentially automatic pacemaker sites and thus maintains dominance of the cardiac rhythm. The discharge rate of the sinus node is more sensitive to the effects of norepinephrine and acetylcholine than is the discharge rate of ventricular muscle cells (Fig. 22-22) . Normal or abnormal automaticity at other sites can cause discharge at rates faster than the sinus nodal discharge rate and can usurp control of the cardiac rhythm for one cycle or many.

Normal Automaticity

The ionic basis of automaticity is explained by a net gain in intracellular positive charges during diastole. Contributing to this change is a voltage-dependent channel activated by potentials negative to -50 to -60 mV, i.e., a hyperpolarization-activated inward pacemaker current. At this potential an inward current called I_f becomes activated and is carried by a channel relatively nonselective for monovalent cations. Hyperpolarization increases its rate of activation, and at -70 mV, the time constant of activation ranges

from 2 to 4 seconds. I_f probably underlies the slow diastolic depolarization that occurs between -90 and -60 mV in Purkinje fibers. Although either K+ or Na+ can serve as ion transporters, I_f carries largely Na+ at the more negative intracellular voltages. Extracellular K+ ions activate I_f , but $[Na+]_o$ does not influence its conductance.[18] [19] [20] [21] [22]

AUTOMATICITY IN SINUS NODAL CELLS.

At the reduced membrane potentials of sinus nodal cells, I_f contributes only about 20 percent of the pacemaker current, and automaticity is primarily dependent on I_K and $I_{Ca.L}$. However,

Figure 22-22 Effects of different doses of acetylcholine (ACh) on spontaneous activity in a single sinoatrial node cell. *A-D,* Activity in the control Tyrode solution *(C)* is compared with that in the presence of 0.01, 0.1, 1.0, and 10 muM ACh, respectively. Each concentration of ACh was perfused for about 20 seconds. Note that slowing occurred with 0.01 and 0.1 muM ACh and that the cell ceased to beat at higher concentrations, at which point hyperpolarization of the maximum diastolic depolarization also clearly appeared. (From DiFrancisco D: Current i_f and the neuronal modulation of heart rate. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology. From Cell to Bedside. Philadelphia, WB Saunders, 1990.)

sinus nodal cells exhibit significant I_f current if they are hyperpolarized in the range of -50 to -100 mV. Conversely, I_K in normally polarized Purkinje fibers adds little to the pacemaker current. Deactivation of I_K , the presence of an unidentified background inward current, deactivation of $I_{Ca.T}$, and activation of $I_{Ca.L}$ are the essential processes governing the rate of pacemaker depolarization in sinus and AV nodal cells and in Purkinje fibers whose membrane potential has been depolarized to voltages largely positive to the activation range of I_f .[66]

The sinus nodal discharge rate maintains dominance over latent pacemaker sites because it depolarizes more rapidly and because of the mechanism called *overdrive suppression,* a phenomenon characterized by prolonged suppression of normal pacemakers in proportion to the duration and rate of stimulation by a more rapidly discharging pacemaker. The mechanism may relate to active Na extrusion during the more rapid rate that maintains diastolic depolarization of latent pacemakers at a level more negative than the threshold potential for automatic discharge.

The rate of sinus nodal discharge can be varied by several mechanisms in response to autonomic or other influences. The pacemaker locus can shift within or outside the sinus node to cells discharging faster or more slowly. If the pacemaker site remains the same, alterations in the slope of the diastolic depolarization, maximum diastolic potential, or

threshold potential can speed or slow the discharge rate (see Fig. 22-22) . For example, if the slope of diastolic depolarization steepens and if the resting membrane potential becomes less negative or the threshold potential more negative (within limits), discharge rate increases. Opposite changes slow the discharge rate.

Acetylcholine activates K+ efflux through acetylcholine-sensitive inward rectifier K+ channels, which are expressed in both sinus nodal and AV nodal cells, thereby shifting the maximum diastolic potential to more negative values. The same mechanism reduces input resistance at diastolic potentials, which means that a greater depolarizing current would be required to achieve "threshold" for firing an action potential.

Passive Membrane Electrical Properties

We have just discussed many of the features of active membrane properties. In addition, it is important to be aware of some features of the passive membrane properties of cardiac myocytes, such as membrane resistance, capacitance, and cable properties.[44] [49]

Although the cardiac cell membrane is resistant to current flow, it also has capacitative properties, which means that it behaves like a battery and can store charges of opposite sign on its two sides: an excess of negative charges inside the membrane balanced by equivalent positive charges outside the membrane. These resistive and capacitative properties cause the membrane to take a certain amount of time to respond to an applied stimulus, rather than responding instantly, because the charges across the capacitative membrane must be altered first. A subthreshold rectangular-shaped current pulse applied to the membrane produces a slowly rising and decaying membrane voltage change rather than a rectangular voltage change. A value called the *time constant of the membrane* reflects this property. The time constant tau is equal to the product of membrane resistance R_m and cell capacitance C_m ,

and is the time taken by the membrane voltage to reach 63 percent of its final value after application of a steady current.

When aligned end to end, cardiac cells, particularly the His-Purkinje system, behave like a long cable in which current flows more easily inside the cell and to the adjacent cell across the gap junction than it does across the cell membrane to the outside. When current is injected at a point, most of it flows along the cell, but some leaks out. Because of this loss of current, the voltage change of a cell at a site distant from the point of applied current is less than the change in membrane voltage where the stimulus was given. A measure of this property of a cable is called the space or length constant lambda, which is the distance along the cable from the point of stimulation that the voltage at steady state is 1/e (37 percent) of its value at the point of introduction.

Restated, lambda describes how far current flows before leaking passively across the surface membrane to a value about one-third its initial value. This distance is normally about 2 mm for Purkinje fibers, 0.5 mm for the sinus node, and 0.8 mm for ventricular

muscle fibers. Lambda is about 10 times the length of an individual cell. As an example, if e is about 2.7 and a hyperpolarizing current pulse in a Purkinje fiber produces a membrane voltage change of 15 mV at the site of current injection, the membrane potential change one space constant (2 mm) away would be 15/2.7=5.5 mV.

Since the current loop in any circuit must be closed, current must flow back to its point of origin. Local circuit currents pass across gap junctions between cells and exit across the sarcolemmal membrane to close the loop and complete the circuit. Inward excitation currents in one area (carried by Na+ in most regions) flow intracellularly along the length of the tissue (carried mostly by K+), escape across the membrane, and flow extracellularly in a longitudinal direction. The outside local circuit current is the current recorded in an electrocardiogram (ECG). Through these local circuit currents the transmembrane potential of each cell influences the transmembrane potential of its neighbor because of the passive flow of current from one segment of the fiber to another across the low-resistance gap junctions.

If two cells having different resting membrane potentials are coupled to one another, the resting potentials of each cell will equalize; i.e., one cell will depolarize and the other will hyperpolarize. This "electrotonic" influence of neighboring cells on each other is determined chiefly by the length constant of the fiber and is due to the passive spread of current.

As discussed earlier, the speed of conduction depends on active membrane properties such as the magnitude of the Na+ current, a measure of which is Vmax. Passive membrane properties also contribute to conduction velocity and include excitability threshold, which influences the capability of cells adjacent to the one that has been discharged to reach threshold; the intracellular resistance of the cell, which is determined by the free ions in the cytoplasm; the resistance of the gap junction; and the cross-sectional area of the cell. Direction of propagation is crucial because of the influence of anisotropy, as mentioned earlier.

Loss of Membrane Potential and Arrhythmia Development

Most acquired abnormalities of cardiac muscle or specialized fibers that result in arrhythmias produce a loss of

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membrane potential; i.e., maximum diastolic potential becomes less negative. This change should be viewed as a symptom of an underlying abnormality, analogous to fever or jaundice, rather than as a diagnostic category in and of itself because both the ionic changes resulting in cellular depolarization and the more fundamental biochemical or metabolic abnormalities responsible for the ionic alterations are probably multicausal. Cellular depolarization can result from elevated $[K+]_o$ or decreased $[K+]_o$, an increase in membrane permeability to Na+ (P_{Na} increases), or a decrease in membrane

permeability to K+ (P_K decreases). Reference to Equation 4 (see p 670) illustrates that these changes alone or in combination make V_r less negative.

Normal cells perfused by an abnormal milieu (e.g., hyperkalemia), abnormal cells perfused by a normal milieu (e.g., healed myocardial infarction), or abnormal cells perfused by an abnormal milieu (e.g., acute myocardial ischemia and infarction) may exist alone or in combination and reduce resting membrane voltage. Each of these changes can have one or more biochemical or metabolic causes. For example, acute myocardial ischemia results in decreased $[K+]_i$ [67] [68] [69] and increased $[K+]_o$, norepinephrine release, and acidosis that may be related to an increase in intracellular Ca^{2+} and Ca^{2+} induced transient inward currents and accumulation of amphipathic lipid metabolites and oxygen free radicals. All these changes can contribute to the development of an abnormal electrophysiological environment and arrhythmias during ischemia and reperfusion. Knowledge of these changes may provide insight into therapy that actually reverses basic defects and restores membrane potential or other abnormalities to normal.

Figure 22-23 Rate-dependent conduction from the normal zone into the abnormal zone. When the pacing cycle length in the normal zone was shortened from 1200 to 400 milliseconds (panels *A* to *F*), increasing degrees of entrance block into the abnormal area occurred and progressed from 1:1 conduction at a cycle length of 1200 milliseconds to 4:3 conduction at 1100 milliseconds, 3:2 conduction at 1000 milliseconds, 2:1 conduction at 900 milliseconds, 3:1 conduction at 600 milliseconds, and 4:1 conduction at 400 milliseconds. Pacing the abnormal zone (not shown) resulted in block to the normal zone (unidirectional propagation). Vertical calibration: 50 mV. Horizontal calibration: 4 seconds in *A* and *B* and 2 seconds in *C* to *F*. (From Gilmour RF Jr, Heger JJ, Prystowsky EN, et al: Cellular electrophysiologic abnormalities of diseased human ventricular myocardium. Am J Cardiol 51:137, 1983.)

EFFECTS OF REDUCED RESTING POTENTIAL.

The reduced resting membrane potential alters the depolarization and repolarization phases of the cardiac action potential. For example, partial membrane depolarization causes a decrease in the steady-state availability of fast sodium channels (see Fig. 22-12) , thereby reducing the magnitude of peak I_{Na} during phase 0 of the action potential. The subsequent reduction in V_{max} and action potential amplitude prolongs the conduction time of the propagated impulse, at times to the point of block.

Action potentials with reduced upstroke velocity resulting from partial inactivation of I_{Na} are called depressed fast responses (see Fig. 22-21 *C*). Their contours often resemble and may be difficult to distinguish from slow responses, in which upstrokes are due to $I_{Ca.L}$ (see Fig. 22-19 *F*). Membrane depolarization to levels of -60 to -70 mV may inactivate half the Na+ channels, while depolarization to -50 mV or less may inactivate all the Na+ channels. At membrane potentials positive to -50 mV, $I_{Ca.L}$ can be activated to generate phase 0 if conditions are appropriate. These action potential changes are likely to be heterogeneous, with unequal degrees of Na+ inactivation that create areas with minimally reduced velocity, more severely depressed zones, and areas of complete

block. These uneven changes are propitious for the development of arrhythmias (Fig. 22-23) .

In these cells with reduced membrane potential, refractoriness may outlast voltage recovery of the action potential; i.e., the cell may still be refractory or partially refractory after the resting membrane potential returns to its most negative value. Furthermore, if block of the cardiac impulse occurs in a fairly localized area without significant slowing of conduction proximal to the site of block, cells in this proximal zone exhibit short action potentials and refractory periods because unexcited cells distal to the block (still in a polarized state) electrotonically speed recovery in cells proximal to the site of block.

If conduction slows gradually proximal to the site of block, the duration of these action potentials and their refractory periods may be prolonged. Some cells may exhibit abnormal electrophysiological properties even though they have a relatively normal resting membrane potential.

MECHANISMS OF ARRHYTHMOGENESIS (Table 22-5)

The mechanisms responsible for cardiac arrhythmias are generally divided into categories of disorders of impulse formation, disorders of impulse conduction, or combinations of both.[45] [70] [71] [72] [73] It is important to realize, however, that our present diagnostic tools do not permit unequivocal determination of the electrophysiological mechanisms responsible for many clinically occurring arrhythmias or their ionic bases. This is especially true for ventricular arrhythmias. It may be very difficult to separate reentry from automaticity clinically, and often, one is left with a postulate that a particular arrhythmia is "most consistent with" or "best explained by" one or the other electrophysiological mechanism. Some tachyarrhythmias can be started by one mechanism and perpetuated by another. An episode of tachycardia caused by one mechanism can precipitate another episode caused by a different mechanism.[74] For example, an initiating tachycardia or premature complex caused by abnormal automaticity can precipitate an episode of tachycardia sustained by reentry. However, by using the features of entrainment (see below), arrhythmias caused by macro-reentry circuits can be identified.

TABLE 22-5 -- MECHANISMS OF ARRHYTHMOGENESIS

Disorders of Impulse Formation
Automaticity
Normal automaticity

Experimental examples--Normal in vivo or in vitro in sinus node, Purkinje fibers, others
Clinical examples--Sinus tachycardia or bradycardia inappropriate for the clinical situation, possibly ventricular parasystole

Abnormal automaticity

Experimental example--Depolarization-induced automaticity in Purkinje fibers or ventricular muscle
Clinical example--Possibly accelerated ventricular rhythms after myocardial infarction

Triggered activity

Early afterdepolarizations

Experimental examples--EADs produced by barium, hypoxia, high concentrations of catecholamines, drugs such as sotalol, *N*-acetylprocainamide, cesium
Clinical examples--Possibly idiopathic and acquired long QT syndromes and associated ventricular arrhythmias

Delayed afterdepolarizations

Experimental example--DADs produced in Purkinje fibers by digitalis
Clinical example--Possibly some digitalis-induced arrhythmias

Disorders of Impulse Conduction

Block

Bidirectional or unidirectional without reentry

Experimental example--SA, AV, bundle branch, Purkinje-muscle, others
Clinical example--SA, AV, bundle branch, others

Unidirectional block with reentry

Experimental examples--AV node, Purkinje-muscle junction, infarcted myocardium, others
Clinical examples--Reciprocating tachycardia in WPW syndrome, AV nodal reentry, VT due to bundle branch reentry, others

Reflection

Experimental example--Purkinje fiber with area of inexcitability
Clinical example--Unknown

Combined Disorders

Interactions between automatic foci

Experimental examples--Depolarizing or hyperpolarizing subthreshold stimuli speed or slow automatic discharge rate
Clinical examples--Modulated parasystole

Interactions between automaticity and conduction

Experimental examples--Deceleration-dependent block, overdrive suppression of conduction, entrance and exit block
Clinical examples--Similar to experimental

AV=atrioventricular; SA=sinoatrial; WPW=Wolfe-Parkinson-White.

Disorders of Impulse Formation

Disorders in this category are characterized by an inappropriate discharge rate of the normal pacemaker, the sinus node (e.g., sinus rates too fast or too slow for the physiological needs of the patient), or discharge of an ectopic pacemaker that controls atrial or ventricular rhythm. Pacemaker discharge from ectopic sites, often called *latent* or *subsidiary pacemakers,* can occur in fibers located in several parts of the atria, the coronary sinus and pulmonary veins, AV valves, portions of the AV junction, and the His-Purkinje system. Ordinarily kept from reaching the level of threshold potential because of overdrive suppression by the more rapidly firing sinus node or electrotonic depression from contiguous fibers, ectopic pacemaker activity at one of these latent sites can become manifested when the sinus nodal discharge rate slows or block occurs at some level between the sinus node and the ectopic pacemaker site and permits *escape* of the latent pacemaker at the latter's normal discharge rate. A clinical example would be sinus bradycardia to a rate of 45 beats/min that permits an AV junctional escape complex to occur at a rate of 50 beats/min.

Alternatively, the discharge rate of the latent pacemaker can speed up inappropriately and usurp control of cardiac rhythm from the sinus node, which has been discharging at a normal rate. A clinical example would be interruption of normal sinus rhythm by a premature ventricular complex or a burst of ventricular tachycardia. It is important to remember that such disorders of impulse formation can be due to speeding or slowing of a *normal* pacemaker mechanism (e.g., phase 4 diastolic depolarization that is ionically normal for the sinus node or for an ectopic site such as a Purkinje fiber but occurs inappropriately fast or slow) or due to an ionically *abnormal* pacemaker mechanism.

A patient with persistent sinus tachycardia at rest or sinus bradycardia during exertion exhibits inappropriate sinus nodal discharge rates, but the ionic mechanisms responsible for sinus nodal discharge may still be normal, although the kinetics or magnitude of the currents may be altered. Conversely, when a patient experiences ventricular tachycardia during an acute myocardial infarction, ionic mechanisms ordinarily not involved in formation of spontaneous impulses for this fiber type may be operative and generate this tachycardia. For example, although pacemaker activity is not generally found in ordinary working myocardium, the effects of myocardial infarction can perhaps depolarize these cells to membrane potentials at which inactivation of I_K and activation of $I_{Ca.L}$ cause automatic discharge. Because the maximum rate that can be achieved by adrenergic stimulation of normal automaticity is generally less than 200 beats/min, it is likely that episodes of faster tachycardia are not due to enhanced normal automaticity.

ABNORMAL AUTOMATICITY.

Mechanisms responsible for *normal* automaticity were described earlier (see p. 677).

Abnormal automaticity can arise from cells that have reduced maximum diastolic potentials, often at membrane potentials positive to -50 mV, when I_K and $I_{Ca.L}$ may be operative.

Automaticity at membrane potentials more negative than -70 mV may be due to I_f . When the membrane potential is between -50 and -70 mV, the cell may be quiescent. Electrotonic effects from surrounding normally polarized or more depolarized myocardium will influence the development of automaticity. Abnormal automaticity has been found in Purkinje fibers removed from dogs subjected to myocardial infarction, in rat myocardium damaged by epinephrine, in human atrial samples, and in ventricular myocardial specimens from patients undergoing aneurysmectomy and endocardial resection for recurrent ventricular tachyarrhythmias.

Abnormal automaticity can be produced in normal muscle or Purkinje fibers by appropriate interventions such as current passage that reduces diastolic potential. An automatic discharge rate speeds up with progressive depolarization, while hyperpolarizing pulses slow the spontaneous firing. It is possible that partial depolarization and failure to reach normal maximal diastolic potential can induce automatic discharge in most if not all cardiac fibers. Although this type of spontaneous automatic activity has been found in human atrial and ventricular fibers, its relationship to the genesis of clinical arrhythmias has not been established.

Rhythms resulting from automaticity may be slow atrial, junctional, and ventricular escape rhythms; certain types of atrial tachycardias (such as those produced by digitalis or perhaps those coming from the pulmonary veins); accelerated junctional (nonparoxysmal junctional tachycardia) and idioventricular rhythms; and parasystole (see Chap. 25) .

Triggered Activity

Automaticity is the property of a fiber to initiate an impulse *spontaneously,* without need for prior stimulation, so that electrical quiescence does not occur. *Triggered activity* is initiated by afterdepolarizations, which are depolarizing oscillations in membrane voltage induced by one or more

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Figure 22-24 Early afterdepolarizations (EADs). EADs occur spontaneously in an isolated canine cardiac Purkinje fiber when exposed to a reduced extracellular potassium concentration. Note that spontaneous phase 4 diastolic depolarization is present. In the initial two action potentials, a series of spontaneous depolarizations (EADs) result before the membrane returns to its maximum diastolic potential. Following the second series of EADs, pacing is begun (S) and normal action potentials follow. Horizontal calibration bar = 5 seconds; vertical bar =2 mV. (From Kovacs RJ, Bailey JC, Zipes DP: Mechanisms of cardiac arrhythmias. *In* Parmley WW, Chatterjee K, Cheitlin M, et al (eds): Cardiology. Philadelphia, JB Lippincott,

1989.)

preceding action potentials. Thus, triggered activity is pacemaker activity that results *consequent* to a preceding impulse or series of impulses, without which electrical quiescence occurs (Figs. 22-24 and 22-25) . This triggering activity is not caused by an automatic self-generating mechanism, and the term *triggered automaticity* is therefore contradictory. These depolarizations can occur before (Fig. 22-24) or after (Fig. 22-25) full repolarization of the fiber and are best termed *early afterdepolarizations* [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] when they arise from a reduced level of membrane potential during phases 2 (type 1) and 3 (type 2) of the cardiac action potential and called *late* or *delayed afterdepolarizations* (DADs) when they occur after completion of repolarization (phase 4), generally at a more negative membrane potential than that from which EADs arise[89] (Table 22-6) . All afterdepolarizations may not reach threshold potential, but if they do, they can trigger another afterdepolarization and thus self-perpetuate.

Early Afterdepolarizations

A variety of interventions, each of which results in an increase in intracellular positivity, can cause EADs.[75] [76] [77] [78] [79] EADs may be responsible for the lengthened repolarization time and ventricular tachyarrhythmias in several clinical situations, such as the acquired and congenital forms of the long QT syndrome.[80] [81] [82] [83] [84] [85] [86] [87] [88] Left ansae subclaviae stimulation (Fig. 22-26) increases the amplitude of cesium-induced EADs in dogs and the prevalence of ventricular tachyarrhythmias more than does right ansae subclaviae stimulation, possibly because of a greater quantitative effect of the left than the right stellate ganglion on the left ventricle.

TABLE 22-6 -- DETERMINANTS OF THE AMPLITUDE OF AFTERDEPOLARIZATIONS

	EFFECT ON AMPLITUDE OF	
INTERVENTION	**EADs**	**DADs**
Long cycles (basic and premature)		
Long action potential duration		
Reduced membrane potential		
Na channel blockers	No effect	
Ca channel blockers		

Catecholamines		

=increase amplitude;
=decrease amplitude; DADs=delayed afterdepolarizations; EADs=early afterdepolarizations.

Figure 22-25 Triggered sustained rhythmic activity and delayed afterdepolarizations in diseased human ventricle. *A,* Spontaneous activity triggered by a series of driven action potentials *(indicated by the dots)* at recording site X1. Note the gradual increase in size of the delayed afterdepolarizations *(arrows)* until the afterdepolarizations reach threshold and maintain sustained rhythmic activity after cessation of pacing. The sustained rhythmic activity finally terminates when the last afterdepolarization fails to reach threshold *(arrow)*. *B,* Initiation of triggered activity by intracellular current injection *(indicated by dots beneath the respective action potential recordings)* at sites X1 and X2, which lie along the same trabeculum. Although sites X1 and X2 were only about 4 mm apart, triggered sustained rhythmic activity from one site did not propagate to the other site, thus indicating complete dissociation between these two sites. For current pulses, cycle length = 2000 milliseconds; pulse duration = 10 milliseconds; pulse intensity=200 nA. Vertical calibration: 50 mV; horizontal calibration: 10 seconds (From Gilmour RF Jr, Heger JJ, Prystowsky EN, et al: Cellular electrophysiological abnormalities of diseased human ventricular myocardium. Am J Cardiol 51:137, 1983.)

Figure 22-26 Following cesium administration during left ansae subclaviae stimulation (LAS), early afterdepolarizations increase in amplitude *(arrows)* and culminate in a short run of nonsustained ventricular tachycardia. LVEG = left ventricular electrograms; LVMAP = left ventricular monophasic action potential recording; RVMAP = right ventricular monophasic action potential recording; time lines-1 second. (From Ben-David J, Zipes DP: Differential response to right and left stellate stimulation of early afterdepolarizations and ventricular tachycardia in the dog. Circulation 78:1241, 1988. By permission of the American Heart Association, Inc.)

Patients with the heritable long QT syndrome have either potassium channel defects (LQT1 and LQT2) or sodium channel-linked defects (LQT3) and, consequently, an abnormally prolonged cardiac action potential duration. In patients with the long QT syndrome, T wave morphology is often abnormal, and the QT interval corrected for heart rate (QTc) is prolonged. The genesis of long QT syndrome-associated ventricular tachycardia/fibrillation is uncertain. Experimental observations[90] suggest an important role of transmural heterogeneity of repolarization. Multiple studies in isolated ventricular myocytes or in tissue preparations have demonstrated spatial dispersion of repolarization along the transmural axes of the left and right ventricular free wall (Fig. 22-27) . A prominent spike and dome is apparent in myocytes from epicardium and the M region but not in myocytes from endocardium. Action potential duration-rate relationships are considerably more pronounced in cells isolated from the M region. The ionic basis for electrophysiological distinctions among epicardial, midmyocardial, and

endocardial myocytes is a large gradient in both the density- and rate-dependent properties of the transient outward K+ current[91] and a smaller density of the slow component of the delayed rectifier K+ current I_{Ks} in midmyocardial cells than in myocytes of endocardial and epicardial origin.[63]

Marked transmural dispersion of repolarization can create a vulnerable window for the development of reentry. EADs arising from M cells may underlie the premature beat that initiates polymorphic ventricular

Figure 22-27 Comparison of the electrophysiological characteristics of myocytes isolated from the epicardial, midmyocardial (M cell), and endocardial regions of the canine left ventricular free wall. Each panel shows superimposed action potentials recorded at basic cycle lengths of 300 to 8000 milliseconds. An increase in basic cycle length leads to progressive accentuation of the spike-and-dome configuration of the action potential in epicardial and midmyocardial cells. In cells from the M region, but not in those from the epicardial and endocardial regions, deceleration causes remarkable prolongation in action potential duration (APD). Thus, a much steeper APD-rate relationship is observed in myocytes from the M region. (From Liu DW, Antzelevitch C: Characteristics of the delayed rectifier current (I_{Kr} and I_{Ks}) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. Circ Res 76:351, 1995. By permission of the American Heart Association, Inc.)

tachycardia (torsades de pointes; see Fig 22-29) in patients with the long QT syndrome.

Sympathetic stimulation, primarily left, could periodically increase the EAD amplitude to provoke ventricular tachyarrhythmias (Fig. 22-26) .

Figure 22-28 Isoproterenol and elevated external calcium activate a transient inward current in canine left ventricular myocytes in the absence of sodium and potassium. *A,* Whole-cell current recordings in the presence of isoproterenol and 5 mM $CaCl_2$. Spontaneous transient inward currents were recorded at a potential of -80 mV following a short depolarizing pulse to 0 mV. *B,* Inward current transients disappeared when holding potential was made equal to E_{Cl} (-50 mV; see Table 22-3) . (From Zygmunt AC: Intracellular calcium activates a chloride current in canine ventricular myocytes. Am J Physiol 267:H1984-H1995, 1994.)

Figure 22-29 Torsades de pointes. Ventricular tachycardia with varying morphology is characteristic of torsades de pointes. A continuous recording of lead II is shown. (From Zipes DP, Ben-David J: Autonomic neural modulation of cardiac rhythm: 2. Mechanisms and examples. Mod Concepts Cardiovasc Dis 57:47, 1988. By permission of the American Heart Association, Inc.)

Alpha-adrenoceptor stimulation also increases the amplitude of cesium-induced EADs and the prevalence of ventricular tachyarrhythmias, both of which are suppressed by

magnesium.

The ionic basis of EADs is unclear but may be via the L-type calcium channel.[75] [76] [79] [89] [92] [93] [94] EADs that arise at voltages close to the plateau (phase 2) appear to result from time- and voltage-dependent reactivation of L-type Ca^{2+} channels. Lengthening the action potential by a variety of ways allows the development of this type of EAD. They may occur preferentially in Purkinje cells and M cells of ventricular myocardium.[77] EADs that arise at voltages negative to the action potential plateau appear to have separable time- and voltage-dependent properties, but the mechanism is uncertain. Short coupling intervals and rapid rates suppress EADs.

In patients with the acquired long QT syndrome and torsades de pointes from drugs such as quinidine, *N*-acetylprocainamide, cisapride, erythromycin,[95] and some class III antiarrhythmic agents, EADs may also be responsible. Such drugs easily elicit EADs experimentally and clinically, while magnesium suppresses them. It is possible that multiple drugs can cause summating effects to provoke EADs and torsades de pointes in patients.[96] Activators of ATP-dependent potassium channels, such as pinacidil and cromakalim, can eliminate EADs.

Delayed Afterdepolarizations

DADs and triggered activity have been demonstrated in Purkinje fibers, specialized atrial fibers and ventricular muscle fibers exposed to digitalis preparations, normal Purkinje fibers exposed to Na-free superfusates from the endocardium of the intact heart, ventricular myocardial cells,[97] and endocardial preparations 1 day after a myocardial infarction. When fibers in the rabbit, canine, simian, and human mitral valves and in the canine tricuspid valve and coronary sinus are superfused with norepinephrine, they exhibit the capacity for sustained triggered rhythmic activity.

Triggered activity caused by DADs has also been noted in diseased human atrial and ventricular fibers (see Fig. 22-25) studied in vitro. Left stellate ganglion stimulation can elicit DADs in canine ventricles. In vivo, atrial and ventricular arrhythmias apparently caused by triggered activity have been reported in the dog and possibly in humans. It is tempting to ascribe certain clinical arrhythmias to DADs, such as some arrhythmias precipitated by digitalis. The accelerated idloventricular rhythm 1 day after experimental canine myocardial infarction may be due to DADs, and some evidence suggests that certain ventricular tachycardias, such as those arising in the right ventricular outflow tract, may be due to DADs,[98] while other data suggest that EADs[99] are responsible.

IONIC BASIS OF DELAYED AFTERDEPOLARIZATIONS.

DADs appear to be caused by a transient inward current (I_{ti}) that is small or absent under normal physiological conditions.

When intracellular Ca^{2+} overload occurs, as is the case during adrenergic stimulation, elevated extracellular Ca^{2+} levels, prolonged action potentials, and rapid repetitive stimulation or after large doses of digitalis, spontaneous release of Ca^{2+} from the

sarcoplasmic reticulum can activate Cl-- currents[100] (Fig. 22-28) or the Na/Ca exchanger [48] [48A] and result in transient inward currents and brief membrane depolarizations. Compounds that reduce the sarcoplasmic Ca^{2+} load (L-type Ca^{2+} channel antagonists, beta-adrenergic receptor blocker) or inhibit sarcoplasmic Ca^{2+} release (thapsigargin, ryanodine, cyclopiazonic acid) suppress DADs. Inhibitors of calmodulin kinase eliminated I_{ti} carried by inward $I_{Na/Ca}$ in isolated rabbit ventricular myocytes,[48] thus indicating that activation of this enzyme appears to play an important role in cardiac arrhythmogenesis. In addition, drugs that reduce I_{Na} also reduce $[Na+]_{ti}$, relieve Ca^{2+} overload, and can also abolish DADs.

DADs caused by *digitalis toxicity* (see Chap. 18) behave differently from DADs caused by catecholamines. Catecholamine-induced triggering often slows slightly after initiation, then regularizes, but slows still further prior to termination, without a progressive increase in maximum diastolic potential. A subthreshold DAD often follows termination of triggered activity. Spontaneous termination may be due in part to an increase in the rate of electrogenic sodium extrusion.

Figure 22-30 *Left,* Modulation of pacemaker activity by subthreshold current pulses in diseased human ventricle. *A,* Two recording sites along the same trabeculum in a spontaneously active preparation. Current pulses *(indicated by the dots)* 30 milliseconds in duration were injected through the lower microelectrode at various times. The interval between the spontaneous action potentials is given in milliseconds above each cycle. Injection of a subthreshold current pulse through the lower microelectrode relatively early in the spontaneous cycle (about 680 milliseconds after initiation of the rapid portion of the preceding action potential upstroke) produced a subthreshold depolarization in the upper recording and delayed the next spontaneous discharge by 400 to 1900 milliseconds. This response curve would fall in the first half of the curve indicated in *C.* A current pulse of the same intensity and duration delivered later in the spontaneous cycle (950 milliseconds after the preceding upstroke) accelerated the next discharge by 210 to 1390 milliseconds relative to the previous two action potentials. The response to this current injection falls in the second half of the graph depicted in *C. B,* A stimulus at a precise interval in the cardiac cycle (called the singular point, in this example, 930 milliseconds after the preceding action potential upstroke) abolishes pacemaker activity. (From Gilmour RF Jr, Heger JJ, Prystowsky EN, et al: Cellular electrophysiological abnormalities of diseased human ventricular myocardium. Am J Cardiol 51:137, 1983.) *C,* Phase-response curves from experimental data obtained in canine Purkinje fibers in a manner similar to the human experiment shown in *A* and *B.* Two different runs are shown. Ordinate = percent increase or decrease in spontaneous cycle length of the "parasystolic focus" (control cycle length equals 100 percent); abscissa = percentage of the "parasystolic focus" spontaneous cycle length during which stimulation was performed. The spontaneous cycle length was maximally prolonged (by 26 percent) or shortened (by 20 percent) by subthreshold depolarizations that entered the "parasystolic focus" after approximately 50 and 60 percent of the cycle had elapsed, respectively. Very similar curves can be plotted for patients with parasystole (for example, see Figs. 9 and 10 from Zipes DP: Plenary lecture. Cardiac electrophysiology: Promises and contributions. J Am Coll Cardiol 13:1329, 1989). (*From Jalife J, Moe GK: Effect of electronic potentials on pacemaker activity of canine Purkinje fibers and relation to parasystole. Circ Res 39:801, 1976. By permission of the American Heart Association, Inc.*)

Termination of digitalis-induced triggering is often characterized by speeding of the rate, a decrease in action potential amplitude, and a decrease in membrane potential,

possibly because of $[Na^+]_1$ or $[Ca^{2+}]_1$, accumulation.

Short coupling intervals or pacing at rates more rapid than the triggered activity rate (overdrive pacing) increases the amplitude and shortens the cycle length of the DAD following cessation of pacing (overdrive acceleration) rather than suppressing and delaying the escape rate of the afterdepolarization, as in normal automatic mechanisms. Premature stimulation exerts a similar effect; the shorter the premature interval, the larger the amplitude and shorter the escape interval of the triggered event.

The clinical implication might be that tachyarrhythmias caused by DAD-triggered activity may not be suppressed easily or, indeed, may be precipitated by rapid rates, either spontaneous (such as a sinus tachycardia) or pacing induced. Finally, because a single premature stimulus can both initiate and terminate triggered activity, differentiation from reentry (see below) becomes quite difficult. The response to overdrive pacing may help separate triggered arrhythmias from reentrant ones.

Parasystole (See also Chap. 25)

Classically, parasystole has been likened to the function of a fixed-rate asynchronously discharging pacemaker: Its timing is not altered by the dominant rhythm, it produces depolarization when the myocardium is excitable, and the intervals between discharges are multiples of a basic interval.[101] Complete *entrance block,* constant or intermittent, insulates and protects the parasystolic focus from surrounding electrical events and accounts for such behavior. Occasionally, the focus may exhibit *exit block,* during which it may fail to depolarize excitable myocardium. In fact, the dominant cardiac rhythm may modulate parasystolic discharge to speed up or slow down its rate. Experimental simulations of parasystole demonstrate that the discharge rate of an isolated, "protected" focus can be modulated by electrotonic interactions with the dominant rhythm across an area of depressed excitability. Brief subthreshold depolarizations induced during the first half of the cardiac cycle of a spontaneously discharging pacemaker will delay the subsequent discharge, while similar depolarizations induced in the second half of the cardiac cycle will accelerate it (Fig. 22-30) .

The ionic basis for these rate changes is not totally established, but it is probable that early depolarizing stimuli reactivate outward potassium currents and retard depolarization while late stimuli contribute depolarizing current that enables the cell to reach threshold more quickly. Early hyperpolarizing subthreshold stimuli accelerate while late hyperpolarizing stimuli retard discharge. Similar examples have been noted in human ventricular tissue, and interactions may be predicted according to the general rules of biological oscillators. Numerous clinical examples have been published to support these experimental observations.

DISORDERS OF IMPULSE CONDUCTION

Conduction delay and block[102] can result in bradyarrhythmias or tachyarrhythmias, the former when the propagating impulse is blocked and is followed by asystole or a slow escape rhythm and the latter when the delay and block produce reentrant excitation

(see below). Various factors involving both active and passive membrane properties determine the conduction velocity of an impulse and whether conduction is successful. Among these factors are the stimulating efficacy of the propagating impulse, which is related to the amplitude and rate of rise of phase 0, the excitability of the tissue into which the impulse is conducted, and the geometry of the tissue.

DECELERATION-DEPENDENT BLOCK.

Diastolic depolarization has been suggested as a cause of conduction block at slow rates, so-called bradycardia- or deceleration-dependent block (see Chap. 25) . Yet excitability *increases* as the membrane depolarizes until about -70 mV, despite a reduction in action potential amplitude and V_{max} . Evidently, depolarization-induced inactivation of fast Na+ channels is offset by other factors such as reduction in the difference between membrane potential and threshold potential. A more probable explanation of deceleration-dependent block is the reduction in action potential amplitude and excitability at long diastolic intervals. Rapid pacing can also produce overdrive suppression of conduction, with a similar mechanism related to the depression of action potential amplitude and excitability.

PHASE 3 OR TACHYCARDIA-DEPENDENT BLOCK.

More commonly, impulses are blocked at rapid rates or short cycle lengths as a result of incomplete recovery of refractoriness caused by incomplete time- or voltage-dependent recovery of excitability (see Chap. 5) . For example, such incomplete recovery is the usual mechanism responsible for a nonconducted premature P wave or one that conducts with a functional bundle branch block.

DECREMENTAL CONDUCTION.

Decremental conduction is used commonly in the clinical literature but is often misapplied to describe any Wenckebach-like conduction block, i.e., responses similar to block in the AV node during which progressive conduction delay precedes the nonconducted impulse. Correctly used, *decremental conduction* refers to a situation in which the properties of the fiber change along its length so that the action potential loses its efficacy as a stimulus to excite the fiber ahead of it. Thus, the stimulating efficacy of the propagating action potential diminishes progressively, possibly as a result of its decreasing amplitude and V_{max} .

Reentry

Electrical activity during each normal cardiac cycle begins in the sinus node and continues until the entire heart has been activated. Each cell becomes activated in turn, and the cardiac impulse dies out when all fibers have been discharged and are completely refractory. During this absolute refractory period, the cardiac impulse has "no place to go." It must be extinguished and restarted by the next sinus impulse. If, however, a group of fibers not activated during the initial wave of depolarization recover excitability in time to be discharged before the impulse dies out, they may serve as a

link to reexcite areas that were just discharged and have now recovered from the initial depolarization. Such a process is given various names, all meaning approximately the same thing: reentry, reentrant excitation, circus movement, reciprocal or echo beat, or reciprocating tachycardia.

ANATOMICAL REENTRY.

The earliest studies on reentry were with models that had anatomically defined separate pathways in which it could be shown that they had (1) an area of unidirectional block, (2) recirculation of the impulse to its point of origin, and (3) elimination of the arrhythmia by cutting the pathway. In models with anatomically defined pathways, because the two (or more) pathways have different electrophysiological properties, e.g., a refractory period longer in one pathway than the other, the impulse (1) is blocked in one pathway (site A in Fig. 22-31 *A*) and (2) propagates slowly in the adjacent pathway (serpentine arrow, D to C, Fig. 22-31 *A*). If conduction in this alternative route is sufficiently depressed, the slowly propagating impulse excites tissue beyond the blocked pathway (horizontal lined area in Fig. 22-31 *A*) and returns in a reversed direction along the pathway initially blocked (B to A in Fig. 22-31 *A*) to (3) reexcite tissue proximal to the site of block (A to D in Fig. 22-31 *A*). A clinical arrhythmia caused by anatomical reentry is most likely to have a monomorphic contour.

Figure 22-31 *A,* Diagram of reentry published by Schmitt and Erlanger in 1928. A Purkinje fiber (D) divides into two pathways (B and C), both of which join ventricular muscle. It is assumed that the original impulse travels down D, is blocked in its anterograde direction at site A *(arrow followed by a double bar)*, but continues slowly down C *(serpentine arrow)* to excite ventricular muscle. The impulse then reenters the Purkinje twig at B and retrogradely excites A and D. If the impulse continues to propagate through D to the ventricular myocardium and elicits ventricular depolarization, a reentrant ventricular extrasystole results. Continued reentry of this type would produce ventricular tachycardia. *B,* Schematic representation of intranodal dissociation responsible for an atrial echo *(left diagram).* A premature atrial response fails to penetrate the beta pathway, which exhibits a unidirectional block but propagates anterogradely through the alpha pathway. Once the final common pathway (FCP) is engaged, the impulse may return to the atrium via the now-recovered beta pathway to produce an atrial echo. The neighboring *(right)* diagram illustrates the pattern of propagation during generation of a ventricular echo. A premature response in the His bundle traverses the FCP, encounters a refractory beta pathway (unidirectional block), reaches the atrium over the alpha pathway, and returns through a now-recovered beta pathway to produce a ventricular echo. *C,* Actual recordings from the atrium *(top tracing)*, with cells impaled in the beta region *(second tracing)*, alpha region *(third tracing)*, and N portion of the atrioventricular (AV) node *(bottom tracing)* in an isolated rabbit preparation. The basic response to A_1 activated both alpha and beta pathways and the N cell (first tier of action potentials). The premature atrial response A_2 caused only a local response in the beta cell *(heavy arrow)*, was delayed in transmission to the alpha cell, and was further delayed in propagation to the N cell. Following the alpha response, a retrograde spontaneous response occurred in the beta cell and propagated to the atrium (E). This atrial response represents an atrial echo. The echo returned to stimulate the alpha cell but was not propagated to the N cell. It is important that while intranodal reentry has been shown to occur within the rabbit AV node, AV nodal reentry in humans probably occurs over extranodal pathways. (From Mendez C, Moe GK: Demonstrations of a dual AV nodal conduction system in the isolated rabbit heart. Circ Res 19:378, 1966.

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For reentry of this type to occur, the time for conduction within the depressed but unblocked area and for excitation of the distal segments must exceed the refractory period of the initially blocked pathway (A in Fig. 22-31 *A*) and the tissue proximal to the site of block (D in Fig. 22-31 *A*). Stated another way, continuous reentry requires the anatomical length of the circuit traveled to equal or exceed the reentrant wavelength. The latter is equal to the mean conduction velocity of the impulse multiplied by the longest refractory period of the elements in the circuit. Both values can be different at different points along the reentry pathway, and thus, the wavelength value is somewhat contrived.

CONDITIONS FOR REENTRY.

The length of the pathway is fixed and determined by the anatomy. Conditions that depress conduction velocity or abbreviate the refractory period will promote the development of reentry in this model, whereas prolonging refractoriness and speeding conduction velocity can hinder it. For example, if conduction velocity (0.30 m/sec) and refractoriness (350 m/sec) for ventricular muscle were normal, a pathway of 105 mm (0.30 milliseconds × 0.35 seconds) would be necessary for reentry to occur. However, under certain conditions, conduction velocity in ventricular muscle and

Purkinje fibers can be very slow (0.03 m/sec), and if refractoriness is not greatly prolonged (600 milliseconds), a pathway of only 18 mm (0.03 m/sec × 0.60 seconds) may be necessary. Such reentry frequently exhibits an excitable gap, i.e., a time interval between the end of refractoriness from one cycle and the beginning of depolarization in the next, when tissue in the circuit is excitable. This condition results because the wavelength of the reentrant circuit is less than the pathway length. Electrical stimulation during this time period can invade the reentrant circuit and reset its timing or terminate the tachycardia.

Rapid pacing can entrain the tachycardia, i.e., continuously reset it by entering the circuit and propagating around it in the same way as the reentrant impulse, which increases the tachycardia rate to the pacing rate without terminating the tachycardia. In reentrant circuits with an excitable gap, conduction velocity determines the revolution time of the impulse around the circuit and, hence, the rate of the tachycardia. Prolongation of refractoriness, unless it is great enough to eliminate the excitable gap and make the impulse propagate in relatively refractory tissue, will not influence the revolution time around the circuit or the rate of the tachycardia. Anatomical reentry occurs in patients with the Wolff-Parkinson-White syndrome, in AV nodal reentry, in some atrial flutters, and in some ventricular tachycardias.

FUNCTIONAL REENTRY.

Functional reentry lacks confining anatomical boundaries and can occur in contiguous fibers that exhibit functionally different electrophysiological properties caused by local differences in transmembrane action potential. Dispersion of excitability and/or refractoriness, as well as anisotropic distributions of intercellular resistance, permits initiation and maintenance of reentry.[103] [104] [105] A clinical arrhythmia caused by functional reentry is most likely to be polymorphic because of charging circuits.

Leading Circle Reentry.

Leading circle reentry, important in atrial fibrillation (AF), is reentrant excitation during which the reentrant circuit propagates around a functionally refractory core and follows a course along fibers that have a shorter refractory period so that the impulse is blocked in one direction in fibers with a longer refractory period (Fig. 22-32) .

The pathway length of a functional circuit is determined by the smallest circuit in which the leading wavefront is just able to excite tissue ahead that is still relatively refractory. If these parameters change, the size of the circuit may change also and alter the rate of the tachycardia. Shorter wavelengths may predispose to fibrillation. No or a very short excitable gap exists, and the duration of the refractory period of the tissue in the circuit primarily determines the

Figure 22-32 Functional models of reentry. *Leading circle model,* a diagrammatic representation of the leading circle model of reentry in isolated left atrium of the rabbit. The central area is activated by converging centripetal wavelets. (From Allessie MA, Bonke FIM, Schopman FJG: Circus movement in rabbit atrial muscle as a mechanism of tachycardia: III. The "leading circle" concept: A new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 41:9, 1977. By permission of the American Heart Association, Inc.) *Figure-of-8 model,* activation map (in 20 millisecond isochrones) of a figure-of-8 circuit in the surviving epicardial layer of a dog 4 days after ligation of the left anterior descending coronary artery (LAD). The circuit consists of clockwise and counterclockwise wavefronts around two functional arcs of block that coalesce into a central common front that usually represents the slow zone of the circuit. (From El-Sherif N: The figure 8 model of reentrant excitation in the canine post-infarction heart. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology and Arrhythmias. New York, Grune & Stratton, 1985, p 363.) *Anisotropic model* showing stimulation from the center of a multiple-electrode array (at the pulse symbol, *A*) on the epicardial border zone of a 4-day-old canine infarct producing an elliptical pattern of activation characteristic of conduction in an anisotropic medium. Arrows indicate the direction of the fast axes of conduction and the longitudinal orientation of the myocardial fibers. *B,* activation map of a reentrant circuit on the epicardial border obtained with the same electrode array during sustained ventricular tachycardia in the same heart. Arrows indicate the sequence of isochrones and thus the direction of movement of activation. (From Wit AL, Janse MJJ: The Ventricular Arrhythmias of Ischemia and Infarction: Electrophysiological Mechanisms. Mt Kisco, NY, Futura, 1992.) *Spiral wave model,* activation map of spiral wave activity in a thin slice of isolated ventricular muscle from a sheep heart *(right panel).* Isochrone lines were drawn from raw data by overlaying transparent paper on snapshots of video images during spiral wave activity (*left panel,* not from the same experiment). Each line represents consecutive positions of the activation front recorded every 16.6 milliseconds. (From Brugada J, Boersma L, Kirchhof C, et al: Sustained monomorphic ventricular tachycardia: A single electrocardiographic expression of different patterns of reentry. Pacing Clin Electrophysiol 14:1943-1946, 1991.)

cycle length of the tachycardia because the stimulating efficacy of the head of the next impulse is just sufficient to excite the relatively refractory tissue in the wake of the preceding impulse. Propagating impulses originating outside the circuit cannot easily enter the circuit to reset, entrain, or terminate the reentry.[106]

Theoretically, drugs that prolong refractoriness and do not delay conduction would slow tachycardia as a result of the leading circle mechanism and not affect tachycardia with an excitable gap until the prolongation of refractoriness exceeded the duration of the excitable gap. Drugs that primarily slow conduction would have major effects on tachycardia with an excitable gap and not on tachycardias resulting from the leading circle concept. Mixed circuits with both anatomical and functional pathways obfuscate these differences.

Random Reentry.

Random reentry, also important in AF, occurs when the reentry propagates continuously and randomly and reexcites areas that were excited shortly before by another wavelet.

ANISOTROPIC REENTRY.

Anisotropic reentry is due to the structural features responsible for variations in conduction velocity and the time course of repolarization, such as a concentration of gap junctions at the ends rather than on the side of cells, which can result in block and slowed conduction with subsequent reentry[95] [95A] (Fig. 22-32) . Even in normal cardiac tissue showing normal transmembrane potentials and uniform refractory periods, conduction can be blocked in the direction parallel to the long axis of fiber orientation, propagate slowly in the direction transverse to the long axis of fiber orientation, and reenter the area of block. Spatial differences in refractoriness may not be necessary for reentry to occur. Such anisotropic reentry has been shown in atrial and ventricular muscle and may be responsible for ventricular tachycardia in epicardial muscle surviving myocardial infarction. An excitable gap may be present.[105]

Figure-of-8 Reentry.

Figure-of-8 reentry consists of clockwise and counterclockwise wavefronts around two functional arcs of block that coalesce into a central common from commonly representing the slow zone of the circuit. Such reentry has been shown in both atrial and ventricular muscle[103] (Fig. 22-32) .

Spiral Wave Reentry.

Spiral waves of excitation have been demonstrated in cardiac muscle and represent a two-dimensional form of reentry; in three dimensions, spiral waves may be represented

by scroll waves. Spiral waves may be stationary when the shape, size, and location of the arc remain unchanged throughout the episode; drifting when the arc migrates away from its site of origin; or anchoring when the drifting core becomes anchored to some small obstacle, such as a blood vessel. One can speculate that a stationary spiral wave could be responsible for a monomorphic tachycardia, a drifting spiral wave responsible for rhythm with changing contours such as torsades de pointes, and an anchoring spiral wave responsible for the transition from a polymorphic to a monomorphic tachycardia[107] [108] [109] (Fig. 22-32) [32] . The use of voltage-sensitive probes in combination with high-resolution video imaging to record electrical wave propagation on the surface of the heart has recently provided experimental evidence for the role of spiral wave reentry in cardiac fibrillation. Experiments in isolated perfused hearts[110] [111] demonstrate that a single rapidly moving rotor or a small number of coexisting, but short-lived rotors give rise to ECG patterns of activity indistinguishable from ventricular fibrillation (VF). The rotors may drift and interact with each other and with boundaries in the heart and result in annihilation and/or formation of new, but also short-lived rotors.

REFLECTION.

Reflection can be considered a special subclass of reentry. As in reentry, an area of conduction delay is required, and the total time for the impulse to leave and return to its site of origin must exceed the refractory period of the proximal segment. Reflection differs from reentry in that the impulse does not require a circuit but appears to travel along the *same* pathway in both directions.

Tachycardias Caused by Reentry

Reentry is probably the cause of many tachyarrhythmias, including various kinds of supraventricular and ventricular tachycardias, flutter, and fibrillation. However, in complex preparations, such as large pieces of tissue in vitro or the intact heart, it becomes much more difficult to unequivocally prove that reentry exists.

BRUGADA SYNDROME.

A reentry mechanism has been implicated in the genesis of ventricular tachycardia/fibrillation associated with the inheritable Brugada syndrome, which is characterized by ST segment elevation (unrelated to ischemia, electrolyte abnormalities, or structural heart disease) in the right precordial (V_1 to V_3) ECG leads, often but not always accompanied by an apparent right bundle branch block. The Brugada syndrome appears to be a congenital ion channel disorder since mutations in the cardiac sodium channel gene *SCN5A* have been reported.[112] The gene defect caused either acceleration of recovery of the sodium channel from inactivation or a nonfunctional sodium channel. Inhibition of the sodium channel current causes heterogeneous loss of the action potential dome (plateau) in the right ventricular epicardium, which leads to a marked dispersion of repolarization and refractoriness and the potential for reentry. Whether transmural heterogeneity in Na+ channel recovery in the right ventricular free wall causes arrhythmia by a similar mechanism remains to be determined.

In addition, many other factors such as stretch, autonomic stimulation, and a host of modulating influences can act on these electrophysiological mechanisms and obscure the cause of many arrhythmias. Initiation or termination of tachycardia by pacing stimuli, the demonstration of electrical activity bridging diastole, fixed coupling, and a variety of other clinically used techniques such as entrainment and resetting curves, while consistent with reentry, do not constitute absolute proof of its existence. The most compelling evidence is probably provided by entrainment.[113]

ENTRAINMENT.

It has been shown that if one could entrain the tachycardia, that is, increase the rate of the tachycardia to a faster rate by pacing, with resumption of the intrinsic rate of the tachycardia when pacing was stopped, the presence of reentry could be established. (Fig. 22-33 *A*). Entrainment represents capture or continuous resetting of the reentrant circuit of the tachycardia by the pacing-induced activation. Each pacing stimulus creates a wavefront that travels in an anterograde direction (orthodromic) and resets the tachycardia to the pacing rate. A wavefront propagating retrogradely in the opposite direction (antidromic) collides with the orthodromic wavefront of the previous beat (Fig 22-33 *B*). These wavefront interactions create ECG and electrophysiological features that can be explained only by reentry. Therefore, the criteria of entrainment can be used to prove the reentrant mechanism of a clinical tachycardia and form the basis for localizing the pathway traveled by the tachycardia wavefront. Such localization is essential for ablation therapy.[114]

ATRIAL FLUTTER (see also Chap. 25) .

Reentry is the most likely cause of the usual form of atrial flutter, with the reentrant circuit confined to the right atrium, where it usually travels counterclockwise, in a caudocranial direction in the interatrial septum and in a craniocaudal direction in the right atrial free wall.[113] [115] [116] [117] [118] [119] [120] [121] [122] [123] [124] An area of slow conduction is present in the posterolateral to posteromedial inferior area of the right atrium with a central area of block that can include an anatomical (inferior vena cava) and functional component. It is possible that several different reentrant circuits exist in patients with atrial flutter (see Chap. 25) . However, this area of slow conduction is rather constant and represents the site of successful ablation of atrial flutter. Ablation results are consistent with a macro-reentry circuit.[125] [126] [127] [128] [129] [130] [131] [132]

VENTRICULAR FIBRILLATION (see also Chap. 25)

Electrical Restitution and Critical Mass.

Substantial experimental support has accumulated in favor of the concept that the onset of VF involves the disintegration of a single spiral wave into many self-perpetuating waves.[133] It has been proposed that the breakup of spiral waves is precipitated by oscillations of action potential duration that are of sufficiently large amplitude to cause

conduction block along the spiral wavefront.

Experimental support for this idea comes from most recent studies demonstrating that if action potential duration restitution (which relates action potential duration to the preceding diastolic interval) contains a region of slope greater than 1, action potential duration alternans is possible and can lead to the formation of reentrant waves.[134] [135] Reduction of the slope of the restitution relationship prevented the induction of VF, thus indicating that the kinetics of electrical restitution appears to be a key determinant of VF. The mass of the tissue appears to be another important factor in the development of fibrillation. In an isolated swine model, it was recently shown that tissue mass reduction resulted in the termination of VF when a critical mass (l9 gm) was reached.[136] In humans, this value appears to be much greater (>111 gm).[135] Similarly, partitioning the atrium into its small segments prevents AF, a concept that has led to a corrective surgical[137] [138] and ablation[139] [140] [141] procedure (see Chap. 23) .

Figure 22-33 *Top panel,* Illustrated criteria for entrainment exemplified in a case of postinfarct ventricular tachycardia (VT). *A, left,* Two electrocardiographic (ECG) leads of a VT and intracardiac recordings from a mapping catheter (*Map*) at a left ventricular site critical for VT continuation, as well as from the right ventricular apex (*RV*). Note the diastolic potential (*dark arrow*) during VT. Recordings are similarly arranged in all subsequent panels. *A, right,* RV pacing in the setting of sinus rhythm. *B,* RV pacing at a cycle length (CL) slightly shorter than VT produces a QRS complex that is a blend between fully VT and fully paced ("fusion") complexes. All recordings are accelerated to the paced CL, and after pacing ceases, the same VT resumes. Each fused QRS complex is identical and the last beat is entrained, but surface fusion is absent. *C* and *D,* The same phenomena, but at shorter-paced CL. Note that the fused QRS complex appears more similar to pacing than it does to VT as the pacing CL shortens. *B* through *D* thus illustrate a progressive degree of ECG fusion. The Map recording of *B* through *D* also shows a progression of fusion, with both the morphology and timing of a portion of the electrogram changing with faster pacing. *E,* Finally, a still shorter paced CL results in a sudden change in both the Map electrogram (block in the small diastolic potential, *white arrow*) and the surface ECG, which is now fully paced. When pacing ceases, VT has been interrupted. (From Zipes DP: A century of cardiac arrhythmia: In search of Jason's Golden Fleece. J Am Coll Cardiol 34:959-965, 1999). *Bottom panel,* Diagrammatic representation of the reentrant circuit during spontaneous atrial flutter (AFL) and during transient entrainment of the AFL. *Left,* The reentrant circuit during spontaneous type I AFL. *f* = circulating wavefront of the AFL. *Center,* Introduction of the first pacing impulse (X) during rapid pacing from a high atrial site during AFL. The *large arrow* indicates entry of the pacing impulse into the reentrant circuit, whereupon it is conducted orthodromically (*Ortho*) and antidromically (*Anti*). The antidromic wavefront of the pacing impulse (*X*) collides with the previous beat, in this case the circulating wavefront of the spontaneous AFL (*f*), which results in an atrial fusion beat and, in effect, terminates the AFL. However, the orthodromic wavefront from the pacing impulse (*X*) continues the tachycardia and resets it to the pacing rate. *Right,* Introduction of the next pacing impulse (*X* + 1) during rapid pacing from the same high atrial site. The large arrow again indicates the entry of the pacing impulse into the reentrant circuit, whereupon it is conducted orthodromically and antidromically. Once again, the antidromic wavefront from the pacing impulse (*X* + 1) collides with the orthodromic wavefront of the previous beat. In this case, it is the orthodromic wavefront of the previous paced beat (*X*), and an atrial fusion beat results. The orthodromic wavefront from the pacing impulse (*X* + 1) continues the tachycardia and resets it to the pacing rate. In all three parts, arrows indicate the direction of spread of the impulses; the serpentine line indicates slow conduction through a presumed area of slow conduction (stippled region) in the reentrant circuit, and the black dots with tails indicate bipolar electrodes at the high atrial pacing site, the

posteroinferior portion of the left atrium (PLA), and another atrial site. (From Waldo AL: Atrial flutter. Entrainment characteristics. J Cardiovasc Electrophysiol 8:337-352, 1997.)

Lower and Upper Limit of Vulnerability.

The cardiac response to electrical stimulation depends on the strength and timing of the stimulus relative to cardiac recovery (coupling interval). A vulnerable zone is present during which a stimulus with appropriate strength may induce VF. When the heart is beating spontaneously (e.g., during sinus rhythm), the timing of the vulnerable period corresponds to the T wave on the surface ECG, more precisely, to the latter part of its upslope and its peak.[142] The strength of a stimulus may not be either too low or too high. There is a lower limit of stimulus strength that can induce VF, as well as an upper limit of vulnerability, defined as a current strength at or above which VF cannot be induced.

Propagated graded responses may underlie the mechanisms of ventricular vulnerability to a single premature stimulus. A stimulus delivered during incomplete recovery evokes a gradual response that propagates slowly to neighboring recovered cells and, if its amplitude is large enough, may induce an all-or-none response. This all-or-none response spreads in all directions except into regions near the site of stimulus because of a graded response-induced increase in ERP at the latter site, which results in unidirectional block and reentry (propagated graded-response hypothesis of ventricular vulnerability). When the extrastimulus strength and thus the magnitude of gradual responses increase beyond a critical level, the increase in refractoriness at the site of the stimulus becomes so long that the unidirectional block becomes bidirectional and prevents the formation of reentry (upper limit of vulnerability).[142]

ATRIAL FIBRILLATION

Spatiotemporal Organization and Focal Discharge (see also Chap. 25) .

According to the multiple-wavelet hypothesis, AF is characterized by fragmentation of the wavefront

into multiple daughter wavelets that wander randomly throughout the atrium and give rise to new wavelets that collide with each other and are mutually annihilated or that give rise to new wavelets in a perpetual activity.

The randomness of the irregular electrical activity during AF has been disputed recently on the basis of both statistical methods and experimental studies. A combination of high-resolution video imaging, ECG recordings, and spectral analysis was used to demonstrate that reentry in anatomically or functionally determined circuits forms the basis of spatiotemporal periodicity during acute AF.[143] The cycle length of the source in the left atrium determines the dominant peak in the frequency spectra. The underlying

periodicity may stem from a repetitive focal source of activity propagated from an individual pulmonary vein to the remainder of the atrium as fibrillating waves.[144] If a single repetitive focal source(s) of activity that undergo(es) fractionation underlie(s) maintenance of AF, ablation of this focal source should interrupt AF. Indeed, delivery of radiofrequency energy to discrete sites in the distal pulmonary veins in humans has been shown to eliminate or reduce recurrence of AF.[145] Localization and subsequent ablation of sources of repetitive electrical activity may therefore represent a novel approach for future treatment of AF.

Electrical Remodeling of the Heart.

Electrical remodeling of the atria appears to be a key determinant for maintenance of AF. Prolonged rapid atrial pacing in goats[146] and dogs[147] [148] causes electrophysiological alterations of the atria, including shortening and loss of the physiological rate adaptation of refractoriness and decrease in conduction velocity. Since abbreviation of the atrial refractory period is disproportionally larger than reduction of conduction velocity, the wavelength of the reentrant wavelets shortens and thereby promotes reentrant activity (the wavelength is the distance traveled by the depolarization wavefront during the duration of its refractory period and equals conduction velocity time refractoriness).

The ionic basis of shortening of the refractory period and slowing of conduction may be a significant reduction in the density of both the L-type Ca^{2+} and the fast Na^{+} current. [147] [148] The electrophysiological changes are paralleled by similar decreases in mRNA levels of Ca^{2+} and Na^{+} channel genes, which suggests alterations in gene expression as the underlying molecular mechanisms of atrial electrical remodeling.[149] Changes in the density and/or spatial distribution of various connexin types may also cause alterations in atrial impulse propagation.[150] [151] [152] Autonomic remodeling also appears to play a key role in both triggering and maintaining AF. Long-term selective vagal denervation of the atria and sinus and AV nodes prevents induction of AF.[17] Heterogeneous sympathetic denervation of the atria favors the development of sustained AF.[154] [154A]

Prolonged rapid ventricular pacing reproducibly causes action potential prolongation in a variety of species, similar to what has been observed in cells isolated from human hearts with dilated cardiomyopathy. The ionic basis for these repolarization abnormalities varies among species, but a reduction in the density of L-type Ca^{2+} currents and downregulation and upregulation of I_{to} and $I_{Na/Ca}$, respectively, appear to be involved.[155] [156] [157] [157A] [157B] A change in ventricular rate, even of short duration, can cause lasting changes in cardiac electrophysiology. Transient superimposition of a fast ventricular rate on a slow rate was found to lengthen the QT interval and refractoriness for hours and to facilitate induction of torsades de pointes.[158] Action potential prolongation was still present in cells isolated from hearts subjected to transient tachycardia[159] and resulted from a reduction in I_{to} and enhanced $I_{Ca.L}$.[159A] Besides the rate, other factors have been found to electrically remodel the heart: Left ventricular hypertrophy reduced the expression of voltage-gated K^{+} channels,[160] and Na^{+} channel function was altered in myocytes from the epicardial border zone over an infarct.[161] Together, these results underline that the process of remodeling probably plays a role in

the pathogenesis of atrial and ventricular arrhythmias.

SINUS REENTRY (see also Chap. 25) .

The sinus node shares with the AV node electrophysiological features such as the potential for *dissociation of conduction;* i.e., an impulse can conduct in some nodal fibers but not in others, thereby permitting reentry to occur.[162] The reentrant circuit may be located entirely within the sinus node or involve both the sinus node and atrium. Supraventricular tachycardias caused by sinus node reentry may generally be less symptomatic than other supraventricular tachycardias because of slower rates. Ablation of the sinus node may be necessary in an occasional refractory tachycardia.[163]

ATRIAL REENTRY (see also Chap. 25) .

Reentry within the atrium, unrelated to the sinus node, may be a cause of supraventricular tachycardia in humans.[164] [165] [166] [167] [168] [169] Atrial reentry appears to be less frequently encountered than other types of supraventricular tachycardia.[167] It has been shown to be due to reentry,[164] [169] automaticity,[170] and afterdepolarizations causing triggered activity. Adenosine has been used to probe for the mechanism.[171] Distinguishing atrial tachycardia caused by automaticity from atrial tachycardia sustained by reentry over quite small areas, i.e., micro-reentry of the leading circle type, is difficult. Multiple foci can be present.[172]

AV NODAL REENTRY (see also Chap. 25) .

Longitudinal dissociation of the AV node into two or more pathways has been demonstrated in the isolated rabbit AV node, where cells in the upper portion of the AV node can be dissociated during propagation of premature stimuli so that one group of cells, called *alpha,* can discharge in response to a premature stimulus at a time when another group of cells, called *beta,* fails to discharge. The impulse can then turn around (without needing to activate the His bundle) to reexcite the beta group of cells and produce an atrial echo (see Fig. 22-31 *B*) or sustained tachycardia.

The presence of dual AV nodal pathways has also been supported by the finding that an impulse traveling from the ventricle to the atrium, if timed properly, can reach the atrium at the same time that another impulse is traveling from the atrium to the ventricle (Fig. 22-34) . For this event to occur, the impulses traveling in opposite directions without colliding must be conducting in different AV nodal pathways. Another convincing fact is the finding of two ventricular responses to a single atrial depolarization or two atrial responses to a single ventricular depolarization as a result of simultaneous transmission over both the slow and fast AV nodal pathways.[173] [174] Finally, the onset of AV of nodal reentry (AVNR) is consistent with dual AV nodal pathways.[175] [176] [177] [178] [179] [180] [181] [182] [183]

Usually, a premature atrial response can block anterogradely in one AV nodal pathway that conducts more rapidly (fast pathway, or beta pathway in Fig. 22-31 *B*), but has a longer refractory period than a second pathway (slow pathway, or alpha pathway in Fig.

22-31 *B*). The premature atrial response travels to the ventricle over the slow (alpha) pathway, thereby prolonging the A-H interval, and returns back to the atrium over the fast (beta) pathway with a short H-A interval, so-called slow-fast AVNR. Less commonly, the slow pathway has a long refractory period, and the premature atrial response can block anterogradely in the slow pathway and travel in the fast pathway by using the slow pathway retrogradely, so-called fast-slow AVNR. Finally, some patients can have both anterograde and retrograde conduction over slowly conducting AV nodal fibers, so-called slow-slow AVNR.[183] [184] Some patients may have more than two pathways. The nodal anatomical structure in patients with AVNR appears to be normal.[185] [186]

LOCATION OF AV NODAL PATHWAYS.

While the presence of dual AV nodal pathways in AVNR is indisputable,[24] [25] the question is where are they located--intranodal and caused by longitudinal dissociation or extranodal and involving separate atrial inputs into the AV node? The results of radiofrequency catheter abiation,[187] [188] [189] [190] [191] [192] [193] [194] [195] [196] [197] [198] [199] [200] [201] as well as surgery,[202] [203] [204] [205] [206] treating patients with AVNR leaves little doubt that the fast and slow pathways have their origins well outside the limits of the compact portion of the AV node and, at the point that they are interrupted, are composed of ordinary working atrial myocardium. The slow and fast pathways are likely to be atrionodal approaches or connections rather than discrete intranodal pathways.

During the common form of AVNR, anterograde conduction occurs over a posteroinferior atrial approach, or "slow" pathway, whose upper end is posteroinferior to the AV node, toward the coronary sinus orifice. Radiofrequency lesions in this area eliminate AVNR by selectively affecting conduction over the slow pathway. The lower end of this pathway enters the compact portion of the AV node, where the impulse is able to "turn around" and retrogradely enter the "fast" or anterosuperior atrial approach, whose upper end inserts at the apex of the Koch triangle near the His bundle. This pathway can also be selectively ablated (Fig. 22-35) .

During sinus rhythm, anterograde conduction probably occurs over the anterosuperior atrial approaches. A premature atrial impulse can be blocked in this pathway, because of its longer refractory period, and then conduct anterogradely

Figure 22-34 Atrial preexcitation during atrioventricular (AV) nodal reentry. AV nodal reentrant tachycardia is present with a cycle length of 410 milliseconds. A premature ventricular complex (S_2) from the right ventricular outflow tract with a coupling interval of 300 milliseconds is introduced during the tachycardia before His is activated and penetrates the AV node retrogradely to shorten the A-A interval to 395 milliseconds. Shorter V_1 -V_2 intervals decreased the A-A interval to 355 milliseconds. Dual AV nodal pathways best explain how two impulses can travel in opposite directions in the AV node, i.e., the impulse from the tachycardia traveling anterogradely and the impulse from premature ventricular stimulation traveling retrogradely, and not collide. Surface leads I, II, III, V_1 are displayed along with high right atrial

(HRA), His bundle (HBE), proximal coronary sinus (PCS), distal coronary sinus (DCS), and right ventricular (RV) electrograms. Numbers are milliseconds. Premature ventricular stimulus is indicated by S_2 . His bundle activation is indicated by H, and atrial activation is indicated by A. Large time = 50 milliseconds; small time = 10 milliseconds (From Miles WM, Yee R, Klein G, et al: The preexcitation index: An aid in determining the mechanism of supraventricular tachycardia and localizing accessory pathways. Circulation 74:493, 1986. By permission of the American Heart Association, Inc.)

Figure 22-35 Schematic diagram of atrial approaches to the atrioventricular (AV) node that constitute the fast and slow pathways. The AV node and pathways are greatly enlarged for graphic purposes. The lower catheter lies posteroinferiorly over the slow pathway, while the upper catheter lies anterosuperiorly over the His bundle. IVC = inferior vena cava; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

Figure 22-36 His-Purkinje block during atrioventricular (AV) nodal reentry. *A,* A spontaneous premature atrial complex (PAC) is followed by PR (A-H) prolongation and the initiation of AV nodal reentry. Retrograde atrial activation (A
) occurs simultaneously with onset of the QRS complex. *B,* A2:1 block distal to the His bundle recording site is present, with continuation of the AV nodal reentry, which indicates that activation of the ventricle is not required for perpetuation of the tachycardia. Such an event could not occur during reciprocating tachycardia with use of an accessory AV connection in the Wolff-Parkinson-White syndrome. Conventions are as listed in Figure 22-34 .

over the posteroinferior approaches and cause the "jump" in the A-H interval. At this point, AVNR can occur. In the less common form of AVNR, anterograde conduction occurs over the fast pathway and retrograde conduction over the slow pathway and, in the slow-slow form, over two slow pathways.

In patients who have dual AV nodal physiology, both pathways exhibit electrophysiological responses in the anterograde direction characteristic of AV nodal fibers. However, the electrophysiological features of the pathway conducting retrogradely during the tachycardia differ from those of the anterogradely conducting pathway in response not only to atrial or ventricular pacing but also to various drugs.[207] For example, drugs such as procainamide prolong conduction time in the retrogradely conducting but not in either anterogradely conducting pathway. Also, pacing at short cycle lengths prolongs anterograde, but not retrograde AV nodal conduction time. Yet verapamil prolongs retrograde AV nodal conduction time, consistent with an effect on nodal fibers. The area of slow conduction in AVNR is located in the same region as the area of slow conduction in atrial flutter.[208]

While it is clear that activation of the ventricle is not necessary for AVNR (Fig. 22-36) and activation of His bundle is also probably not required in some patients, the necessary role of atrial participation in the reentrant circuit is still debated,[175] [176] [182] and it is probably true that some patients have AVNR confined to reentry within the AV node.

The obligatory role of the atrium in the reentry is implicit in the diagram in Figure 22-31 *B*. Figure 22-37 provides an example *apparent* dissociation of the atrium with uninterrupted continuation of the supraventricular tachycardia, which leads to the conclusion that the atrium may *not* be a necessary part of the reentrant circuit in humans.

PREEXCITATION SYNDROME (see also Chap. 25) .

In most patients who have reciprocating tachycardias associated with Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than does the normal AV node but takes a longer time to recover excitability; i.e., the anterograde refractory period of the accessory pathway exceeds that of the AV node at long cycles.[209] [210] Consequently, a premature atrial complex that occurs sufficiently early is blocked anterogradely in the accessory pathway and continues to the ventricle over the normal AV node and His bundle. After the ventricles have been excited, the impulse is able to enter the accessory pathway retrogradely and return to the atrium. A continuous conduction loop of this kind establishes the circuit for the tachycardia. The usual (orthodromic) activation wave during such a reciprocating tachycardia in a patient with an accessory pathway occurs in the following manner: anterogradely over the normal AV node-His-Purkinje system and retrogradely over the accessory pathway, which results in a normal QRS complex (Fig. 22-38) .

Because the circuit requires both atria and ventricles, the term *supraventricular tachycardia* is not precisely correct, and the tachycardia is more accurately called *atrioventricular reciprocating tachycardia* (AVRT). The reentrant loop can be interrupted by ablation of the normal AV node-His bundle pathway *or* the accessory pathway.[211] [212] [213] [214] [215] [216] [217] [218] [219] [220] Occasionally, the activation wave travels in a reverse (antidromic) direction to the ventricles over the accessory pathway and to the atria retrogradely up the AV node.[209] [210] Two accessory pathways can form the circuit in some patients with antidromic AVRT. In some patients, the accessory pathway may be capable of only retrograde conduction ("concealed"), but the circuit and mechanism of AVRT remain the same. Less commonly, the accessory pathway may conduct only anterogradely. The pathway can be localized by analysis of the scalar ECG.[221] [222] [223] [224] [225] [226] [227] Patients can have AF as well as AVRT.[228]

Unusual accessory pathways with AV nodal-like electrophysiological properties, i.e., nodofascicular or nodoventricular fibers, can constitute the circuit for reciprocating tachycardias in patients who have some form of the Wolff-Parkinson-White

Figure 22-37 Dissociation of atria from ventricles without interrupting atrioventricular (AV) nodal reentrant supraventricular tachycardia. During sinus rhythm, a single premature atrial complex (S, *top panel*) was conducted with AV nodal delay (prolonged A-H interval) and initiated an AV nodal reentrant supraventricular tachycardia. Note that retrograde atrial activation (A

) occurred prior to onset of the QRS complex. Two premature atrial stimuli (S-S, *bottom panel*) captured the atria on both occasions without altering the regular cycle length of the AV nodal reentrant supraventricular tachycardia. Note that the QRS complex marked by an asterisk has no accompanying atrial complex, which suggests that atrial participation in the reentrant circuit was not required. CS = coronary sinus electrogram; H = His bundle electrogram; RA = right atrial electrogram; V_1 = scalar lead.

syndrome. Tachycardia in patients with nodoventricular fibers can be due to reentry with these fibers used as the anterograde pathway and the His-Purkinje fibers and a portion of the AV node used retrogradely.[210] [211] In the Lown-Ganong-Levine syndrome (short PR interval and normal QRS complex), conduction over a James fiber that connects the atrium to the distal portion of the AV node and His bundle has been *proposed,* although little functional evidence to support the presence of this entity exists.

VENTRICULAR TACHYCARDIA CAUSED BY REENTRY (see also Chap. 25) .

Reentry in the ventricle, both anatomical and functional, as a cause of sustained ventricular tachycardia has been supported by many animal[219] [220] [221] [222] [223] [224] [225] [226] [227] [228] [229] [230] [231] [232] [233] [234] [235] [236] and clinical[237] [238] [239] [240] studies (see Fig. 22-32). Reentry in ventricular muscle, with or without contribution from specialized tissue, is responsible for many or most ventricular tachycardias in patients with ischemic heart disease. The area of micro-reentry appears to be quite small, and less uncommonly, a macro-reentry is found around the infarct scar. Surviving myocardial tissue (Fig. 22-39) separated by connective tissue provides serpentine routes of activation traversing infarcted areas that can establish reentry pathways. Bundle branch reentry can cause sustained ventricular tachycardia, particularly in patients with dilated cardiomyopathy.[239] [241]

Both figure-of-8 [237] (see Fig. 22-32) and single-circle[234] (Fig. 22-40) reentrant loops have been described as circulating around an area of functional block in a manner consistent with the leading circle hypothesis or conducting slowly across an apparent area of block created by anisotropy.[231] When intramural myocardium survives, it may form part of the reentrant loop. Structural discontinuities that separate muscle bundles, e.g., as a result of naturally occurring myocardial fiber orientation and anisotropic conduction, as well as collagen matrices formed from the fibrosis after a myocardial infarction, establish the basis for slowed conduction, fragmented electrograms, and continuous electrical activity that can lead to reentry. After the infarction, action potential recordings from surviving cells return to normal, which suggests that depressed activity in these cells does not account for the slowed conduction. However, ventricular myocardium resected from humans with recurrent ventricular tachycardia demonstrates abnormal action potentials, thus suggesting that causes of depressed conduction in humans may be multifactorial (see Figs. 22-23 and 22-25) . During acute ischemia, a variety of factors, including elevated $[K]_o$ and reduced pH, combine to create depressed action potentials in ischemic cells that retard conduction and can lead to reentry.[231] [240]

Ventricular Tachycardias Caused by Nonreentrant Mechanisms

In some instances of ventricular tachycardia related to coronary artery disease, but especially in patients without coronary artery disease, nonreentrant mechanisms are

important causes of ventricular tachycardias. However, in many patients the mechanism of the ventricular tachycardia remains unknown.[242]

Figure 22-38 *A,* Wolff-Parkinson-White syndrome. Following high right atrial pacing at a cycle length of 500 milliseconds (S_1 -S_1), premature stimulation at a coupling interval of 300 milliseconds (S_1 -S_2) produces physiological delay in atrioventricular (AV) nodal conduction resulting in an increase in the A-H interval from 100 to 140 milliseconds but no delay in the AV interval. Consequently, activation of the His bundle occurs following activation of the QRS complex *(second interrupted line)*, and the QRS complex becomes more anomalous in appearance because of increased ventricular activation over the accessory pathway. I, II, III, and V_1 and scalar leads. DCS = distal coronary sinus electrogram; HBE = His bundle electrogram; HRA = high right atrium; PCS = proximal coronary sinus electrogram; RV = right ventricular electrogram. Time lines and 50- and 10-millisecond intervals. S_1 , stimulus of the drive train; S_2 , premature stimulus. A, H-V, atrial His bundle, and ventricular activation during the drive train; A_2 , H_2 , V_2 , atrial His bundle, and ventricular activation during the premature stimulus. *B,* Induction of reciprocating atrioventricular tachycardia. Premature stimulation at a coupling interval of 230 milliseconds prolongs the A-H interval to 230 milliseconds and results in anterograde block in the accessory pathway and normalization of the QRS complex (a slight functional aberrancy in the nature of incomplete right bundle branch block occurs). Note that H_2 precedes onset of the QRS complex *(interrupted line)*. Following V_2 , the atria are excited retrogradely (A
) beginning in the distal coronary sinus, followed by atrial activation in leads recording from the proximal coronary sinus, His bundle, and high right atrium. A supraventricular tachycardia is initiated at a cycle length of 330 milliseconds. Conventions are as in panel *A.* (From Zipes DP, Mahomed Y, King RD, et al: Wolff-Parkinson-White syndrome: Cryosurgical treatment. Indiana Med 89:432, 1986.)

TRIGGERED ACTIVITY.

EADs and triggered activity may be responsible for torsades de pointes.[243] A group of probably nonreentrant ventricular tachycardias occurring in the absence of structural heart disease can be initiated and terminated by programmed stimulation. They are catecholamine dependent and are terminated by the Valsalva maneuver, adenosine, and verapamil. These ventricular tachycardias are generally, but not exclusively located in the right ventricular outflow tract and may be due to triggered activity, possibly DADs that are cAMP dependent.[92] [98] [244] [245] [246] EADs have been recorded in this tachycardia as well.[99] Left ventricular fascicular tachycardias can be suppressed by verapamil but not generally by adenosine,[246] and some may be due to triggered activity[247] and others to reentry.[248]

AUTOMATICITY.

Automatic discharge can be responsible for some ventricular tachycardias[249] [250] and does not appear to be suppressed by adenosine.[98] Unless invasive studies are undertaken, mechanisms of ventricular tachycardia can only be conjectured.[251] [252] [253]

Figure 22-39 *Top panel,* Schematic drawing illustrating left ventricular myocardial sections of a human heart studied electrophysiologically and histologically after removal for a cardiac transplant. Dark areas mark surviving cardiac tissue, while light areas point to fibrotic and fatty tissue. Note the irregularity of the surviving cardiac tissue interspersed with fibrotic tissue. The lower two panels are schematic drawings of sections from the lateral left ventricular wall 500 *(left)* and 1000 *(right)* mum, respectively, beneath the level of those shown in the *top panel.* Note that the bulge of viable tissue at the left of the surviving posterior wall (arrow in the *top panel*) becomes isolated in the *lower left panel* (arrow). In the *lower right panel,* this isolated area merges with the bulk of surviving tissue in the lateral wall (arrow). (From deBakken JMT, Coronel R, Tisserons S, et al: Ventricular tachycardia in the infarcted Langendorff-perfused human heart: Role of the arrangement of surviving cardiac fibers. J Am Coll Cardiol 15:1594, 1990. Reprinted with permission from the American College of Cardiology.)

Figure 22-40 Model of anisotropic reentry in the epicardial border zone. *A,* The activation map of the single reentrant circuit is shown. The large arrows point out the general activation pattern; activation appears to occur around a long line of block. However, parallel isochrones adjacent to the line (isochrones 130 and 140) suggest that activation is also occurring across the line and thereby results in the smaller circuit shown by the small arrows. *B,* This circuit is shown enlarged. Rapid activation occurs parallel to the long axis of the fiber orientation (isochrones 10 to 40 and at 130 to 150), whereas very slow activation (closely bunched isochrones 50 to 120) occurs transverse to fiber orientation in the circuit. The dark black rectangle is an area of either functional or anatomical block that forms the fulcrum of the circuit. (From Wit AL, Dillon SM: Anisotropic reentry. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology. From Cell to Bedside. Philadelphia, WB Saunders, 1990.)

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Chapter 23 - Management of the Patient with Cardiac Arrhythmias

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Approach to the Diagnosis of Cardiac Arrhythmias

In the management of clinical arrhythmias, the physician must evaluate and treat the whole patient, not just the rhythm disturbance.[1] Some arrhythmias are hazardous to the patient regardless of the clinical setting (e.g., ventricular fibrillation), whereas others are hazardous because of the clinical setting (e.g., rapidly conducted atrial fibrillation in a patient with severe coronary artery stenoses). Evaluation of the patient begins with a careful history[2] and physical examination and should usually progress from the simplest to the most complex test, from the least invasive and safest to the most invasive and risky, and from the least expensive out-of-hospital evaluations to those that require hospitalization and sophisticated, costly procedures. Occasionally, depending on the clinical circumstances, the physician may wish to proceed directly to a high-risk, expensive procedure, such as an electrophysiological study (EPS), before obtaining a 24-hour electrocardiographic (ECG) recording.

Patients with cardiac rhythm disturbances can present with a variety of complaints, but commonly symptoms such as palpitations, syncope, presyncope, or congestive heart failure cause them to seek a physician's help.[3] Their awareness of palpitations and of a regular or irregular cardiac rhythm varies greatly. Some patients perceive slight variations in their heart rhythm with uncommon accuracy, whereas others are oblivious even to sustained episodes of ventricular tachycardia (VT); still others complain of palpitations when they actually have regular sinus rhythm. The following tests can be used to evaluate patients who have cardiac arrhythmias. The physician's choice of which test to use depends on the clinical circumstances. For instance, a patient with multiple daily episodes of presyncope is likely to have an event recorded on a 24-hour Holter monitor, whereas in a patient who complains of infrequent anxiety- or exercise-induced palpitations, exercise stress testing may be more likely to provide a diagnosis.

Exercise Testing (See also Chap. 6.)

Exercise can induce various types of supraventricular and ventricular tachyarrhythmias and, uncommonly, bradyarrhythmias.[4] [5] [6] [7] [8] [9] About one third of normal subjects develop ventricular ectopy in response to exercise testing. Ectopy is more likely to occur at faster heart rates, usually in the form of occasional premature ventricular complexes (PVCs) of constant morphology, or even pairs of PVCs, and is often not reproducible from one stress test to the next. Three to six beats of nonsustained VT can occur in normal patients, especially the elderly, and its occurrence does not establish the existence of ischemic or other forms of heart disease or predict increased cardiovascular morbidity or mortality. Premature supraventricular complexes are often more common during exercise than at rest and increase in frequency with age; their occurrence does not suggest the presence of structural heart disease.

Approximately 50 percent of patients who have coronary artery disease develop PVCs in response to exercise testing. Ventricular ectopy appears in these patients at lower heart rates (less than 130 beats/min) than in the normal population and often occurs in the early recovery period as well. In one study, exercise reproduced sustained VT or ventricular fibrillation (VF) in only 11 percent of patients with spontaneous VT or VF late after myocardial infarction,[5] but

those who had it experienced a worse outcome. The relation of exercise to ventricular arrhythmia in patients with structurally normal hearts has no prognostic implications.[6] Stress testing with Holter recording has been used to assess antiarrhythmic drug efficacy.[10] [11] [12]

Patients who have symptoms consistent with an arrhythmia induced by exercise (e.g., syncope, sustained palpitations) should be considered for stress testing. Stress testing may be indicated to uncover more complex grades of ventricular arrhythmia, to provoke

supraventricular arrhythmias, to determine the relationship of the arrhythmia to activity, to aid in choosing antiarrhythmic therapy and uncovering proarrhythmic responses, and possibly to provide some insight into the mechanism of the tachycardia. The test can be performed safely[7] and appears more sensitive than a standard 12-lead resting ECG to detect ventricular ectopy. However, prolonged ambulatory recording is more sensitive than exercise testing in detecting ventricular ectopy. Because either technique may uncover serious arrhythmias that the other technique misses, both examinations may be indicated for selected patients.

Long-Term Electrocardiographic Recording

Prolonged ECG recording in patients engaged in normal daily activities is the most useful noninvasive method to document and quantitate the frequency and complexity of an arrhythmia, correlate the arrhythmia with the patient's symptoms, and evaluate the effect of antiarrhythmic therapy on spontaneous arrhythmia. For example, recording normal sinus rhythm during the patient's typical symptomatic episode effectively excludes cardiac arrhythmia as a cause. In addition, some recorders can document alterations in QRS, ST, and T contours (Fig. 23-1) .

HOLTER RECORDING.

Continuous ECG tape recorders represent the traditional Holter "monitor" and typically record on tape two ECG channels for 24 hours.[13] Interpretative accuracy of long-term tape recordings varies with the system used, but most computers that scan the tapes are sufficiently accurate to meet clinical needs. All systems can potentially record more information than the physician needs or can assimilate.[14] As long as the system detects important episodes of ectopic activity, VT, or asystolic intervals and semiquantitates these abnormalities, the physician probably receives all the clinical information that is needed. Twenty-five to 50 percent of patients experience a complaint during a 24-hour recording, caused by an arrhythmia in 2 to 15 percent (see Fig. 23-1).

Significant rhythm disturbances are fairly uncommon in healthy young persons. However, sinus bradycardia with heart rates of 35 to 40 beats/min, sinus arrhythmia with pauses exceeding 3 seconds, sinoatrial exit block, Wenckebach's second-degree atrioventricular (AV) block (often during sleep), a wandering atrial pacemaker, junctional escape complexes, and premature atrial complexes (PACs) and PVCs are not necessarily abnormal. Frequent and complex atrial and ventricular rhythm disturbances are less commonly observed, however, and type II second-degree AV conduction disturbances (see Chap. 25) are not recorded in normal patients. Elderly patients may have a greater prevalence of arrhythmias, some of which may be responsible for neurological symptoms. The long-term prognosis in asymptomatic healthy subjects with frequent and complex PVCs resembles that of the healthy U.S. population without an increased risk of death.

A majority of patients who have ischemic heart disease, particularly those after myocardial infarction, exhibit PVCs when monitored for periods of 6 to 24 hours.[15] [16] The frequency of PVCs progressively increases over the first several weeks, decreasing

at about 6 months after infarction.

Figure 23-1 Long-term ECG recording in a patient with atypical angina. The top channel reflects an inferior lead, and the bottom channel records an anterior lead. Note progressive ST segment elevation in the inferior lead, eventually resembling a monophasic action potential. Bursts of nonsustained ventricular tachycardia result. Then, sinus slowing and Wenckebach's AV block occur from a vasodepressor reflex response elicited by ischemia of the inferior myocardial wall or possibly caused by ischemia of the sinus and AV nodes. In the bottom tracing, both AV block and ventricular arrhythmias are apparent. Numbers indicate time (e.g., 2:37 P.M.). (Tracing of a patient of D.A. Chilson, M.D.)

Frequent and complex PVCs constitute an independent risk factor and are associated with a two- to fivefold increased risk of cardiac or sudden death in patients after myocardial infarction. Evidence from the Cardiac Arrhythmia Suppression Trial (CAST) raises the possibility that the ventricular ectopy is a marker identifying the patient at risk rather than being causally related to sudden death, because PVC suppression with flecainide, encainide, or moricizine was associated with increased mortality compared with placebo.[17] [18] Thus the PVC may be an "innocent bystander," unrelated to the tachyarrhythmia producing sudden death. Although the mechanism responsible for the drug-induced exacerbation of mortality is not clear, it may relate to an increase in ischemia-produced conduction delay due to sodium channel blocking drugs.[19]

Holter recordings have been used to determine antiarrhythmic drug efficacy. In one study, Holter recordings led to predictions of antiarrhythmic drug efficacy more often than did electrophysiological testing in patients with sustained ventricular tachyarrhythmias, and there was no significant difference in the success of drug therapy as selected by the two methods.[10] The study also found sotalol to be the most efficacious of the seven antiarrhythmic drugs tested.[11] The beneficial results of noninvasive compared with invasive assessment of drug efficacy in this study have been challenged.[20] [21]

Long-term ECG recording also has exposed potentially serious arrhythmias and complex ventricular ectopy in patients with left ventricular hypertrophy,[22] in those with mitral valve prolapse (see Chap. 46), in those who have otherwise unexplained syncope (see Chap. 27) or transient vague cerebrovascular symptoms, and in those with conduction

disturbances, sinus node dysfunction, the bradycardia-tachycardia syndrome, the Wolff-Parkinson-White syndrome, increased QT dispersion,[23] pacemaker malfunction, and after thrombolytic therapy.[24] [25] It has shown that asymptomatic atrial fibrillation occurs far more often than symptomatic atrial fibrillation in patients with that arrhythmia.[26] This has important implications for deciding whether a patient needs chronic anticoagulation based only on recurrent symptoms.

Variations of Holter recording have been used for particular applications. Repeated 24-hour recording periods may be needed to obtain enough episodes of PAC triggering atrial fibrillation to warrant proceeding to EPS and catheter ablation. Some monitoring systems are able to "reconstruct" a full 12-lead ECG from a seven-electrode recording system. This is especially useful when trying to document the ECG morphology of VT before an ablation procedure or a consistent morphology of PACs that may arise from an ablatable focus of atrial fibrillation. Most Holter recording and analysis systems have the ability to place a clearly recognizable deflection on the recording when a pacemaker stimulus is detected. This greatly facilitates diagnosis of potential pacemaker malfunction. Occasionally, ECG artifacts due to alterations in tape recording or playback speed may mimic bradycardias or tachycardias and lead to erroneous therapy. Newer digital Holter systems are less subject to this phenomenon.

EVENT RECORDING.

In many patients, the 24-hour "snapshot" provided by the Holter recording is incapable of documenting the cause of the patient's symptoms. Still longer-term monitoring is necessary in these cases, which occur frequently. This could be effected by simply repeating many 24-hour Holter recordings until symptoms occur, but this is costly, inefficient, and cumbersome. Instead, a transient-event recorder can be used.[27] [28] These devices are roughly the size of a pager and are kept by the patient for 30 days. During that time, digital recordings can be made during symptomatic episodes and transmitted to a receiving station over standard telephone lines at the patient's convenience. Some of these recorders store up to 30 seconds of ECG before the time when the patient activates the recording. These "loop" recorders[29] record continuously but only a small window of time is present in memory at any time; when the event button is pressed by the patient, the current window is "frozen" while the device continues recording for another 30 to 60 seconds, depending on how it is configured. Event recorders are very effective in documenting infrequent events, but the quality of the recordings is more variable than Holter recorders and only one channel can be recorded. In addition, the patient must be able to press the event button to begin recording; if syncope occurs without warning and the patient is not able to actuate the device, it cannot provide diagnostic information.

Some pacemakers and implantable defibrillators are capable of providing Holter-like data on occurrence of premature beats but cannot store ECGs of these events. Some pacemakers have a feature in which the patient waves a special magnet over the device, causing it to freeze 1 to 3 minutes of the intracardiac electrogram corresponding to the symptoms, much as a loop recorder does. The device can then be interrogated later and the electrograms printed for analysis.

IMPLANTABLE LOOP RECORDER.

For patients with very infrequent and transient symptoms, neither Holter recorders nor 30-day event recorders may yield diagnostic information. In such patients, implantable loop recorders may be used. This device (about the size of a pack of chewing gum) is inserted under the skin at about the second rib on the left and is activated by waving a

special magnet over the device. It is capable of recording up to 42 minutes of a single ECG channel that can be partitioned for 1 to 3 episodes, with up to 20 minutes of preactivation ECG saved for subsequent downloading to a programming unit for analysis. Both P waves and QRS complexes can usually be identified. In a recent report, this device was implanted in 24 patients with recurrent syncope who had undergone extensive evaluation without determining a cause of syncope. Over a mean 5-month period after implant, 21 patients had recurrent syncope; the device was instrumental in establishing the diagnosis in 18.[30] [30A]

Other Noninvasive Tests

HEART RATE VARIABILITY.

Heart rate variability is used to evaluate vagal and sympathetic influences on the heart and to identify patients at risk for a cardiovascular event or death.[31] [32] [33] [34] [35] [36] [37] [38] Frequency domain analysis resolves parasympathetic and sympathetic influences better than does time domain analysis, but both types of analysis are useful. RR variability predicts all-cause mortality as well as does left ventricular ejection fraction or nonsustained VT in patients after myocardial infarction[39] [40] [41] [42] [43] and can be added to other measures of risk to enhance predictive accuracy.[44] [45] [46] [47] [48] [49] [50] [51] [52] Perceived high- and low-frequency components of RR interval variability suggest that both vagal and sympathetic activities, respectively, are at physiological levels. However, reduced RR interval variability, the marker of increased risk,[53] merely indicates loss or reduction of the physiological periodic fluctuations, which can be due to many different influences and cannot necessarily be interpreted to represent a particular shift in autonomic modulation.[54]

QT DISPERSION.

Heterogeneity in refractoriness and conduction velocity is a hallmark of reentrant arrhythmias. One index of heterogeneity of ventricular refractoriness can be found in differences in length of the QT interval in surface ECG leads.[55] The most commonly used index to calculate this QT dispersion has been the difference between the longest and shortest QT intervals on the 12-lead ECG, which is often adjusted for heart rate as well as number of leads sampled (when the T wave is flat in some). Other indices have been developed. Abnormally high QT dispersion has been correlated with risk of arrhythmic death in a variety of disorders,[55] [56] [57] although results are not consistent.[58] QT dispersion has been correlated with efficacy and proarrhythmic potential of drug therapy.[59] [60] Different techniques exist for determining dispersion (including automated algorithms), and the results of one study are often difficult to compare with those of another.[23] It remains to be seen whether QT dispersion will be a useful clinical tool.[61] [62]

SIGNAL-AVERAGING TECHNIQUES.

Signal averaging is a method that improves signal-to-noise ratio when signals are recurrent and the noise is random.[63] In conjunction with appropriate filtering and other

methods of noise reduction, signal averaging can detect cardiac signals of a few microvolts in amplitude, reducing noise amplitude, such as muscle potentials that are typically 5 to 25 muV, to less than 1 muV. With this method, very low-amplitude electrical potentials generated by the sinus and AV nodes, His bundle, and bundle branches are detectable at the body surface.

One of the hallmarks of reentrant ventricular arrhythmias in patients with prior myocardial damage is slow conduction. Direct cardiac mapping techniques can record myocardial activation from damaged areas that occurs after the end of the surface QRS complex. These delayed signals have very low amplitude that cannot be discerned on routine electrocardiography and correspond to the delayed and fragmented conduction in the ventricles recorded with direct mapping techniques[64] [65] [66] [67] (Fig. 23-2) . Signal averaging has been applied clinically most often to detect such late ventricular potentials of 1 to 25 muV. Criteria for late potentials are (1) filtered QRS complex duration greater than 114 to 120 milliseconds, (2) less than 20 muV of signal in the last 40 milliseconds of the filtered QRS complex, and (3) the terminal filtered QRS complex remains below 40 muV for

Figure 23-2 Signal-averaged ECG showing the presence of prolonged QRS duration due to late potentials (dark-filled components in the terminal portion of the complex) present preoperatively but not postoperatively. RMS = root mean square (in muV); IN = integral of waveform delineated by the onset and offset markers; LAS = low amplitude signal; MN = mean value in the terminal QRS. Arrow indicates the 40-muV mark, after which the presence of low-amplitude signals is determined. Scale = number of muV per notch.

longer than 39 milliseconds. These late potentials have been recorded in 70 to 90 percent of patients with sustained and inducible VT after myocardial infarction, in only 0 to 6 percent of normal volunteers, and in 7 to 15 percent of patients after myocardial infarction who do not have VT. Late potentials can be detected as early as 3 hours after the onset of chest pain, increase in prevalence in the first week after infarction, and disappear in some patients after 1 year. If not present initially, late potentials usually do not appear later. Early use of thrombolytic agents may reduce the prevalence of late potentials after coronary occlusion.

Late potentials also have been recorded in patients with VT not related to ischemia, such as dilated cardiomyopathies. Successful surgical resection of the VT can eliminate late potentials but is not necessary to cause tachycardia suppression. Antiarrhythmic drug therapy, on the other hand, decreases the amplitude of the late potentials without abolishing them. Late potentials after myocardial infarction constitute an independent risk factor that identifies patients prone to develop VT and can be combined with other data, such as ejection fraction, spontaneous ventricular ectopy on a 24-hour ECG recording, or response to stress testing, to recognize with high sensitivity and specificity patients at risk for VT or sudden cardiac death. It also can be used to identify patients

with nonsustained VT or syncope who may develop sustained VT at EPS.

The high-pass filtering used to record late potentials meeting the criteria just noted is called time domain analysis because the filter output corresponds in time to the input signal. Because late potentials are high-frequency signals, Fourier transform can be applied to extract high-frequency content from the signal-averaged ECG, called frequency domain analysis. Some data suggest that frequency domain analysis provides useful information not available in the time domain analysis. The preferable choice has not been determined.[68] [69]

Signal averaging has been applied to the P wave to determine risk for developing postoperative atrial fibrillation[70] as well as maintenance of sinus rhythm after cardioversion.[71] The overall use of the technique remains limited at present.

T WAVE ALTERNANS.

Beat-to-beat alternation in the amplitude and/or morphology of the ECG measurement of repolarization, the ST segment and T wave, has been found in conditions favoring the development of ventricular tachyarrhythmias such as ischemia[72] [73] [74] [75] [76] and long QT interval syndrome[77] [78] [79] [80] and in patients with ventricular arrhythmias.[75] [76] The electrophysiological basis of the alternation is not entirely clear. In the presence of a long QT interval, the cellular basis of alternation has been shown to be due to beat-to-beat repolarization changes in midmyocardial cells (M cells).[81] Whether this mechanism applies to different disease states is not known. T wave alternans may represent a fundamental marker of an electrically unstable myocardium prone to developing VT or VF, and, as such, ST-T wave analysis for alternans may be useful in the future as a method to risk-stratify patients (Fig. 23-3) .

BARORECEPTOR REFLEX SENSITIVITY TESTING.

Acute blood pressure elevation triggers a baroreceptor reflex that augments vagal "tone" to the heart and slows the sinus rate. The increase in sinus cycle length per millimeter of

Figure 23-3 T wave alternans. Reports of T wave alternans analysis from two patients are shown, displaying heart rate (HR) in beats per minute (BPM), proportion of beats rejected from analysis (% Bad), ECG noise level (in muV), and selected precordial leads (V_2 and V_3) as a function of time. Records in the left panel are from a patient with no structural heart disease; the amplitude of T wave alternans was minimal. The study in the right panel, from a patient hospitalized for sustained ventricular tachycardia after myocardial infarction, shows T wave alternans (shaded area, arrow).

mercury systolic blood pressure increase is a measure of the sensitivity of the

baroreceptor reflex and, when reduced, identifies patients susceptible to developing VT and VF.[31] [77] The mechanism of the reduction in baroreceptor reflex sensitivity is not known. However, this test may be useful to identify patients at risk for developing a serious ventricular arrhythmia after myocardial infarction.

BODY SURFACE MAPPING.

Isopotential body surface maps are used to provide a complete picture of the effects of the currents from the heart on the body surface. The potential distributions are represented by contour lines of equal potential, and each distribution is displayed instant by instant throughout activation or recovery, or both.[82] [83] [84]

Body surface maps have been used clinically to localize and size areas of myocardial ischemia, localize ectopic foci or accessory pathways, differentiate aberrant supraventricular conduction from ventricular origin, recognize the patient prone to developing arrhythmias, and possibly understand the mechanisms involved.[85] [86] [87] [88] [89] [90] [91] [92] [93] Although these procedures are of interest, their clinical utility has not yet been established. In addition, the technique is cumbersome and the analysis is complex.

UPRIGHT TILT-TABLE TESTING (see also Chap. 27).

The tilt-table test is used to identify patients who have a vasodepressor and/or a cardioinhibitory response as a cause of syncope.[94] [95] Patients are positioned on a tilt table in the supine position and are tilted upright to a maximum of 60 to 80 degrees for 20 to 45 minutes, or longer if necessary (Fig. 23-4) . Isoproterenol, [96] [97] [98] as a bolus or an infusion, may provoke syncope in patients asymptomatic after initial upright tilt-table testing or after just several minutes of tilt to shorten the time of the test necessary to produce a positive response. An initial intravenous isoproterenol dose of 1 mug/min can be increased in 0.5-mug/min steps until symptoms occur or a maximum of 4 mug/min is given. Isoproterenol induces a vasodepressor response in upright, susceptible patients generally consisting of a decrease in heart rate and blood pressure along with near-syncope or syncope. Intravenous edrophonium chloride,[99] nitroglycerin,[95] and esmolol withdrawal[100] have been used. Atropine can block the early bradycardia but not the hypotension. Beta blockers[101] [102] can inhibit the latter. Tilt-table test results are positive in two thirds to three fourths of patients susceptible to neurally mediated syncope and are reproducible in about 80 percent,[103] [104] [105] [106] but have a 10 to 15 percent false-positive response rate. Repeating an initially negative tilt-table test on a subsequent day rarely yields a positive result.[107] Positive responses can be divided into cardioinhibitory, vasodepressor, and mixed categories.[108] Therapy with beta blockers,[101] [102] [109] disopyramide,[110] theophylline, midodrine,[111] and salt loading or fludrocortisone[112] have each been reported to be successful.

MECHANISM.[113]

Vasodepressor reactions, which are thought to be caused by activation of unmyelinated left ventricular vagal C fibers, can be triggered by a variety of events, including

increased left ventricular pressure. Stimulation of C fibers from vigorous left ventricular contraction on a relatively empty cavity reduces efferent sympathetic tone while increasing efferent vagal tone, possibly producing vasodepression and paradoxical bradycardia. Isoproterenol increases left ventricular contractility while reducing left ventricular volume. A passive upright tilt exaggerates these responses because the tilt also reduces venous return and prevents isoproterenol from increasing cardiac output. Some patients may experience profound bradycardia, whereas others may have a prominent vasodepressor component (see Chap. 27). Dual-chamber pacing has been shown to benefit some patients with refractory neurocardiogenic syncope.[114] [115] Before pacemaker implantation, some investigators have advocated performing a tilt-table test with temporary pacing catheters in place to simulate how a permanent pacing system would perform; however, correlation between this type of acute testing and long-term pacing results has not been proven.

A variant of the neurocardiogenic response, the postural orthostatic tachycardia syndrome, is characterized by dramatic increases in heart rate during the first 10 minutes of tilt-table testing.[116] This syndrome appears to be distinct from simple orthostatic hypotension as well as standard neurocardiogenic responses and is thought to be due to various forms of autonomic imbalance. Relief of symptoms has been effected with fludrocortisone, beta blockers, or combinations.

ESOPHAGEAL ELECTROCARDIOGRAPHY.

Esophageal electrocardiography is a useful noninvasive technique to diagnose arrhythmias.[117] [118] The esophagus is located immediately behind the left atrium, between the left and right pulmonary veins. An electrode in the lumen of the esophagus can record atrial potentials. Bipolar recording is superior to unipolar recording because the former can record far-field ventricular events that can lead to possible diagnostic confusion. In addition, atrial and occasionally ventricular

Figure 23-4 Head-up tilt-table testing. Surface ECG leads and an arterial blood pressure (BP) tracing are shown. After 8 minutes of head-up tilt at 80 degrees *(left)*, heart rate and BP were normal and the patient was asymptomatic. Four minutes later *(right)*, systolic BP dropped precipitously to 80 mm Hg, the heart rate fell to 50/min, and the patient lost consciousness. ECG artifact at right is seizure activity.

pacing can be performed by means of a catheter electrode inserted into the esophagus, and initiation and termination of tachycardias can be accomplished. Optimal electrode position for atrial pacing correlates with patient height and is within about 1 cm of the site at which the maximum amplitude of the atrial electrogram is recorded. No serious immediate complications of transesophageal pacing have been reported. A capsule electrode that is easily swallowed has been used to record continuous atrial electrograms from the esophagus.

When recorded simultaneously with the surface ECG, the esophageal atrial electrogram can be used to differentiate supraventricular tachycardia (SVT) with aberrancy from VT and to define the mechanism of SVTs. For example, if atrial and ventricular depolarizations occur simultaneously during a narrow QRS tachycardia, reentry utilizing an accessory AV pathway (Wolff-Parkinson-White syndrome) can be excluded, and AV nodal reentry is the most likely mechanism for the tachycardia (see Chap. 25).

Invasive Electrophysiological Studies

An invasive EPS involves introducing multipolar catheter electrodes into the venous and/or arterial system and positioning the electrodes at various intracardiac sites to record electrical activity. The heart is stimulated from portions of the atria or ventricles and from the region of the His bundle, bundle branches, accessory pathways, and other structures. Such studies are performed diagnostically to provide information on the type of rhythm disturbance and insight into its electrophysiological mechanism. They are used therapeutically to terminate a tachycardia by electrical stimulation or electroshock, to evaluate the effects of therapy by determining whether a particular intervention modifies or prevents electrical induction of a tachycardia or whether an electrical device properly senses and terminates an induced tachyarrhythmia, and to ablate myocardium involved in the tachycardia to prevent further episodes. Finally, these tests have been used prognostically to identify patients at risk for sudden cardiac death. The study may be helpful in patients who have AV block, intraventricular conduction disturbance, sinus node dysfunction, tachycardia, and unexplained syncope or palpitations.[119]

The EPS is quite good at initiating VT or SVT when these have occurred spontaneously. This enables the use of similar stimulation techniques after an intervention (drug therapy or surgical or catheter ablation) to assess treatment efficacy. However, false-negative responses (not finding a particular electrical abnormality known to be present) as well as false-positive ones (induction of a nonclinical arrhythmia) may complicate interpretation of the results, as many lack reproducibility. Altered autonomic tone in a supine patient undergoing study, hemodynamic or ischemic influences, changing anatomy (e.g., new infarction) after the study, day-to-day variability, and the fact that the test employs

an artificial "trigger" (electrical stimulation) to induce the arrhythmia are several of many factors that may explain the occasional disparity between test results and spontaneous clinical occurrences. Overall, the diagnostic validity and reproducibility of these studies are quite good, and they are very safe when performed by skilled clinical electrophysiologists.

AV Block (See also Chap. 25.)

In patients with AV block, the site of block usually dictates the clinical course of the patient and whether a pacemaker is needed.[120] Generally, the site of AV block can be

determined from an analysis of the scalar ECG. When the site of block cannot be determined from such an analysis, and when knowing the site of block is imperative for patient management, an invasive EPS is indicated. Candidates include symptomatic patients in whom His-Purkinje block is suspected but not established and patients with AV block treated with a pacemaker who continue to be symptomatic in whom a causal ventricular tachyarrhythmia is sought. Possible candidates are those with second- or third-degree AV block in whom knowledge of the site of block or its mechanism may help direct therapy or assess prognosis and patients suspected of having concealed His bundle extrasystoles. Patients with block in the His-Purkinje system more commonly become symptomatic because of periods of bradycardia or asystole and more commonly require pacemaker implantation than do patients who have AV nodal block.[121] Wenckebach's (type I) AV block in older patients may have clinical implications similar to type II AV block. The results of EPS for evaluating the conduction system must be interpreted with caution, however. In rare cases, the process of recording conduction intervals alters their values. For instance, catheter pressure on the AV node or His bundle can cause a prolongation of the atrial-His (AH) or His-ventricular (HV) interval and lead to erroneous diagnosis and therapy.

Intraventricular Conduction Disturbance

For patients with an intraventricular conduction disturbance, an EPS provides information on the duration of the HV interval, which can be prolonged with a normal PR interval or normal with a prolonged PR interval. A prolonged HV interval (>55 msec) is associated with a greater likelihood of developing trifascicular block (but the rate of progression is slow, 2 to 3 percent annually), having structural disease, and higher mortality. Finding very long HV intervals (>80 to 90 msec) identifies patients at increased risk of developing AV block. The HV interval has a high specificity (about 80 percent) but low sensitivity (about 66 percent) for predicting the development of complete AV block. During the study, atrial pacing is used to uncover abnormal His-Purkinje conduction.[122] A positive response is provocation of distal His block during 1:1 AV node conduction. Once again, sensitivity is low but specificity is high. Functional His-Purkinje block due to normal HisPurkinje refractoriness is not a positive response. Drug infusion, such as that with procainamide or ajmaline, sometimes exposes abnormal His-Purkinje conduction (Fig. 23-5) . Ajmaline (not available in the United States) can cause arrhythmias and should be used cautiously.

An EPS is indicated in the patient with symptoms (syncope or presyncope) that appear to be related to a bradyarrhythmia or tachyarrhythmia when no other cause of symptoms

Figure 23-5 Testing the His-Purkinje system. A 43-year-old woman with sarcoid underwent electrophysiological study after a syncopal episode. Surface leads 1, 2, V_1 , and V_6 are shown with intracardiac recordings from catheters in the high right atrium (HRA), proximal (prox) and distal (dist) electrode pairs of a catheter at the atrioventricular junction to record the His potential, and right ventricular apex (RVA). A = atrial electrogram; H = His potential; V = ventricular electrogram. During baseline recording, the HV interval is only slightly prolonged (62 msec). After infusion of intravenous procainamide, the HV is longer and infra-His Wenckebach is present. Arrow denotes "missing" QRS complex due to

infra-His block.

is found. For many of these patients, ventricular tachyarrhythmias rather than AV block can be the cause of their symptoms.[123]

Sinus Node Dysfunction

The demonstration of slow sinus rates, sinus exit block, or sinus pauses temporally related to symptoms suggests a causal relationship and usually obviates further diagnostic studies.[124] [125] [126] [127] [128] Carotid sinus pressure that results in several seconds of complete cardiac asystole or AV block and reproduces the patient's usual symptoms exposes the presence of a hypersensitive carotid sinus reflex (see Chap. 22). Carotid sinus massage must be done cautiously. Rarely, carotid sinus massage can precipitate a stroke. Neurohumoral agents, adenosine,[129] or stress testing can be employed to evaluate the effects of autonomic tone on sinus node automaticity and sinoatrial conduction time. EPS should be considered in patients who have symptoms attributable to bradycardia or asystole, such as presyncope or syncope, and for whom noninvasive approaches have provided no explanation for the symptoms.[130]

SINUS NODE RECOVERY TIME (SNRT).

This technique can be a useful test to evaluate sinus node function. The interval between the last paced high right atrial response and the first spontaneous (sinus) high right atrial response after termination of pacing is measured to determine the SNRT. Because the spontaneous sinus rate influences the SNRT, the value is corrected by subtracting the spontaneous sinus node cycle length (C) (before pacing) from the SNRT (Fig. 23-6) . This value, the CSNRT, is generally less than 525 milliseconds. Prolonged CSNRT has been found in patients suspected of having sinus node dysfunction. Direct recordings of the sinus node electrogram have documented that SNRT is influenced by prolongation of sinoatrial conduction time (the time from the onset of the sinus impulse to the onset of activation of surrounding atrial myocardium), as well as by changes in sinus node automaticity, especially in the first beat after cessation of pacing. After cessation of pacing, the first return sinus cycle can be normal and can be followed by secondary pauses. Secondary pauses appear to be more common in patients whose sinus node dysfunction is caused by sinoatrial exit block. Sinoatrial exit block can cause some sinus pauses. Finally, it is important to evaluate AV node and His-Purkinje function in patients with sinus node dysfunction, because many also exhibit impaired AV conduction.

SINOATRIAL CONDUCTION TIME (SACT).

This time can be estimated using simple pacing techniques based on the assumptions that (1) conduction times into and out of the sinus node are equal, (2) no depression of sinus node automaticity occurs, and (3) the pacemaker site does not shift after

premature stimulation. These assumptions may be erroneous, particularly in patients with sinus node dysfunction. SACT can also be measured directly with extracellular electrodes placed in the region of the sinus node. This direct measurement correlates well with the SACT measured indirectly in patients with normal sinus node function. The sensitivity of the SACT and SNRT tests is only about 50 percent for each test alone and about 65 percent when combined. The specificity, when combined, is about 88 percent, with a low predictive value. Thus, if they are abnormal, the likelihood of the patient having sinus node dysfunction is great. However, if they are normal, that does not exclude the possibility of sinus node disease. Candidates for invasive EPS to evaluate sinus node function are symptomatic patients in whom sinus node dysfunction has not been established as a cause of the symptoms. Potential candidates are those requiring pacemakers to determine the pacing modality, patients with sinus node dysfunction to determine the mechanism and response to therapy, and patients

Figure 23-6 Abnormal sinus node function. Recordings are similar to those in Figure 23-3 . The last five complexes of a 1-minute burst of atrial pacing (S) at a cycle length of 400 msec are shown, after which pacing is stopped. The sinus node does not spontaneously discharge (sinus node recovery time) until 6.2 seconds later (arrow). Three junctional escape beats occurred before this time.

in whom other causes of symptoms (e.g., tachyarrhythmias) are to be excluded.

Tachycardia

In patients with tachycardias, an EPS may be used to diagnose the arrhythmia, determine and deliver therapy, determine the anatomical site(s) involved in the tachycardia, identify patients at high risk for developing serious arrhythmias, and gain insights into mechanisms responsible for the arrhythmia. The study can differentiate aberrant supraventricular conduction from ventricular tachyarrhythmias when standard ECG criteria are equivocal in making the differentiation.[131] [132]

An SVT is recognized electrophysiologically by the presence of an HV interval equaling or exceeding that recorded during normal sinus rhythm (Fig. 23-7) . In contrast, during VT, the HV interval is shorter than normal or the His deflection cannot be recorded clearly owing to superimposition of the larger ventricular electrogram. Only two situations exist when a consistently short HV interval occurs: during retrograde activation of the His bundle from activation originating in the ventricle (i.e., PVC or tachycardia) (see Chap. 25) or during conduction over an accessory pathway (preexcitation syndrome; see Chap. 25). Atrial pacing at rates exceeding the tachycardia rate can demonstrate the ventricular origin of the wide QRS tachycardia by producing fusion and capture beats and normalization of the HV interval. The only VT that exhibits an HV interval equal to or slightly exceeding the normal sinus HV interval is bundle branch reentry (see Chap. 25), but His activation will be in the retrograde

direction.

INDICATIONS FOR EPS IN PATIENTS WITH TACHYCARDIA.

An EPS should be considered (1) in patients who have symptomatic, recurrent, or drug-resistant supraventricular or ventricular tachyarrhythmias to help select optimal therapy; (2) in patients with tachyarrhythmias occurring too

Figure 23-7 Bundle of His recordings in different situations. Recordings similar to prior figures; CS = coronary sinus. *A,* Baseline sinus rhythm with normal AV conduction. *B,* Orthodromic supraventricular tachycardia with retrograde conduction over a left-sided accessory pathway throughout the tracing. The first three beats have a narrow QRS complex with a normal HV interval; the last three QRS complexes represent a fusion of conduction over the AV node-His and a slowly conducting right-sided accessory pathway. The His potential occurs after the onset of the wide QRS complex (dashed lines). In *C,* three paced ventricular beats are shown with a retrograde His potential (H
), followed by initiation of AV node reentrant supraventricular tachycardia (atrial depolarization near the end of the QRS complex, as seen in HRA tracing). *D,* Ventricular tachycardia with delayed activation of the His potential and complete retrograde AV node block (dissociated atrial complexes).

infrequently to permit adequate diagnostic or therapeutic assessment; (3) to differentiate SVT and aberrant conduction from VT; (4) whenever nonpharmacological therapy such as the use of electrical devices, catheter ablation, or surgery is contemplated; (5) in patients surviving an episode of cardiac arrest (occurring 48 hours after an acute myocardial infarction or without evidence of an acute Q-wave myocardial infarction); and (6) in assessing risk of sustained VT in patients with a prior myocardial infarction, ejection fraction less than 0.4 and nonsustained VT on ECG.[133] Generally, EPS is not indicated in patients with the long QT syndrome and torsades de pointes, although recent information about early afterdepolarizations (see Chap. 22) may make such studies useful in the future.

The process of initiation and termination of SVT or VT with programmed electrical stimulation to test the potential efficacy of pharmacological, electrical, or surgical therapy represents an important application of EPS in patients with tachycardia. Arrhythmia-free survival is higher among patients in whom a drug prevents electrical reinitiation of a sustained monomorphic VT that was induced during the predrug control state. Among patients in whom VT remains inducible, characteristics of the induced arrhythmia predict features of future recurrences. When the tachycardia and its hemodynamic response are not altered, an adverse risk for recurrence and mortality is predicted. When the tachycardia cycle length is prolonged more than 100 milliseconds and stable hemodynamics result, survival improves.[134]

Determination of drug efficacy based on results from long-term ECG recordings may be insufficient to predict a patient's therapeutic response when a low frequency of

spontaneous ventricular arrhythmias is present. Two studies have concluded that noninvasive assessment of drug efficacy testing using beta blockers[135] or amiodarone[136] may be superior to the results of programmed electrical stimulation using conventional antiarrhythmic agents. Another controlled, randomized study comparing invasive and noninvasive assessments of conventional drugs[11] found both techniques to be equivalent.[10] Both invasive and noninvasive methods should be considered appropriate approaches for guiding drug therapy.

Patients with Unexplained Syncope (See Chap. 27.)

The three common arrhythmic causes of syncope include sinus node dysfunction, tachyarrhythmias, and AV block. Of the three, tachyarrhythmias are most reliably initiated in the electrophysiology laboratory, followed by sinus node abnormalities and then His-Purkinje block.[137]

The cause of syncope goes undetected in up to 50 percent of patients, depending in part on the extent of the evaluation. A careful, accurately performed history and physical examination begin the evaluation,[1] [138] [139] followed by noninvasive tests, including a 12-lead and 24-hour ECG recording, and can lead to a diagnosis in half or more of the patients.[137] [140] [141] [142] [143] The 1-year mortality is about 6 percent in patients with unknown causes, and 1 to 12 percent in patients with noncardiovascular causes but 19 to 30 percent in patients with cardiovascular causes. The incidence of sudden death is also higher in patients with a cardiovascular cause of syncope. A small percentage (< 5 percent) of patients develop an arrhythmia coincident with syncope or presyncope during a 24-hour ECG recording, whereas a larger percentage (15 percent) have symptoms without an arrhythmia, excluding an arrhythmic cause. Prolonged ECG monitoring with patient-activated transtelephonic event recorders that have memory loops may increase the yield. Signal averaging has a high sensitivity (about 75 percent) and specificity (about 90 percent) for predicting patients with syncope in whom VT can be induced at EPS.[144] Tilt-table testing[108] [145] [146] [147] and stress testing[148] can be useful in some patients, as can long-term ECG recordings.[149]

The EPS helps explain the cause of syncope or palpitations when it induces an arrhythmia that replicates the patient's symptoms. Syncopal patients with a nondiagnostic EPS have a low incidence of sudden death and 80 percent remission rate. In those with recurrent syncope, the test is falsely negative in 20 percent, owing to failure to find AV block or sinus node dysfunction. On the other hand, in many patients with structural heart disease, several abnormalities that could account for syncope may be diagnosed at EPS. Deciding which among these abnormalities is responsible for syncope and therefore requires therapy can be difficult. Mortality and incidence of sudden cardiac death are mainly determined by the presence of underlying heart disease.[150]

Syncopal patients considered for EPS are those whose spells remain undiagnosed despite general, neurological, and noninvasive cardiac evaluation, particularly if the patient has structural heart disease. The diagnostic yield is about 70 percent in that group but only about 12 percent in patients without structural heart disease. Therapy for a putative cause found during EPS prevents recurrence of syncope in about 80 percent

of patients. Among arrhythmic causes of syncope, intermittent conduction disturbances are the most difficult to diagnose. EPS is poor at establishing this diagnosis despite an array of provocative tests that can be applied. When tachyarrhythmias have been thoroughly sought and excluded and the clinical suspicion of intermittent heart block is high (e.g., bundle branch block or long HV interval), empirical pacing may be justified.

Palpitations

An EPS is indicated in patients with palpitations[2] [3] [151] who have had a pulse documented by medical personnel to be inappropriately rapid without ECG recording or in those suspected of having clinically significant palpitations without ECG documentation.

In patients with syncope or palpitation, the sensitivity of the EPS may be very low but may be increased at the expense of specificity. For example, more aggressive pacing techniques (e.g., using three or four premature stimuli), administration of drugs (e.g., isoproterenol), or left ventricular pacing can increase the success rate of VT induction, but by precipitating nonclinical ventricular tachyarrhythmias such as nonsustained polymorphic or monomorphic VT or VF. Similarly, aggressive techniques during atrial pacing can induce nonspecific episodes of atrial flutter or atrial fibrillation. A diagnostic dilemma arises when the patient's clinical, symptom-producing arrhythmia is one of these nonspecific arrhythmias that can be produced in the normal patient who has no arrhythmia. In most patients, these arrhythmias are regarded as "nonclinical" (i.e., nonspecific responses to intense stimulation). In other patients, such as those with hypertrophic or dilated nonischemic cardiomyopathy, these may be clinically relevant arrhythmias. Induction of sustained SVT (e.g., AV nodal reentry, AV reciprocating tachycardia) or monomorphic VT in patients who are not subject to the spontaneous development of the tachycardia appears to be uncommon and provides important information that the induced tachyarrhythmia may be clinically significant and responsible for the patient's symptoms. Generally, other abnormalities, such as prolonged sinus pauses after overdrive atrial pacing or His-Purkinje AV block, are not induced in patients who do not or may not experience these abnormalities spontaneously. Induction of these arrhythmias has a high degree of specificity.

Direct Cardiac Mapping: Recording Potentials Directly from the Heart

Cardiac mapping is a method whereby potentials recorded directly from the heart are spatially depicted as a function

Figure 23-8 Endocardial catheter recordings during ventricular tachycardia (VT) in two patients. Dashed lines denote onset of QRS complexes. In *A,* a woman without structural heart disease had a sustained VT arising from the left ventricular outflow tract (LVOT). Note unipolar (uni) electrogram with a sharp "QS"

complex and the onset (arrow) distal bipolar recording ($LVOT_{1-2}$) preceding right ventricular recordings. They also precede recordings from a multielectrode catheter advanced along the coronary sinus and down the great cardiac vein (GCV) on the epicardial surface opposite the endocardial recording. Retrograde 1:1 conduction is present. Ablation at this site (LVOT) terminated the VT. In *B,* a patient with reentrant VT due to a prior inferior wall infarction underwent mapping. The ablation catheter on the inferomedial wall shows a very prolonged, fragmented electrogram indicative of slow conduction. The electrogram spans all of the diastolic interval between QRS complexes. Ablation at this site eliminated the VT.

of time in an integrated manner (Fig. 23-8) . The location of recording electrodes (epicardial, intramural, or endocardial) and the recording mode used (unipolar vs. bipolar) as well as the method of display (isopotential vs. isochrone maps) depend on the problem under consideration. Special electrodes can record monophasic action potentials.[152]

Direct cardiac mapping by means of catheter electrodes or at the time of cardiac surgery can be used to identify and localize the areas responsible for rhythm disturbances in patients with supraventricular and ventricular tachyarrhythmias for electrical or surgical ablation, isolation, or resection. Disorders amenable to this approach include accessory pathways associated with the Wolff-Parkinson-White syndrome, the pathway(s) in AV node reentry, His bundle ablation, sites of origin of automatic atrial and VTs, and isolated pathways essential for maintenance of reentrant atrial or ventricular tachycardias. Mapping can also be used to delineate the anatomical course of the His bundle to avoid injury during open-heart surgery (usually for congenital heart surgery or septal accessory pathway ablation). These approaches are discussed in greater detail later in this chapter and in Chapter 25 under the individual arrhythmias.

Complications of Electrophysiological Studies

The risks of undergoing only an EPS are small.[153] Because most procedures do not involve left-sided heart access, risk of stroke, systemic embolism, or myocardial infarction is less than that of coronary arteriography. Myocardial perforation with cardiac tamponade, pseudoaneurysms at arterial access sites, and provocation of nonclinical arrhythmias can occur, each with less than 1/500 incidence. Adding therapeutic maneuvers (e.g., ablation) to the procedure increases the incidence of complications.[153A] In a European survey[154] based on 4398 patients reported from 68 institutions, procedure-related complications ranged from 3.2 to 8 percent. Five deaths occurred within the perioperative period of the ablation. In a North American Society of Pacing and Electrophysiology (NASPE) survey[155] of 164 hospitals reporting in 1994 on over 10,000 patients who received RF ablation, complications ranged from 1 to 3 percent, with procedure-related deaths of about 0.2 percent. The most recent data come from a multicenter study using a single type of temperature-controlled ablation system. In this study of 1050 patients undergoing ablation for supraventricular arrhythmias, 32 (3%) had a major complication. Predictors of major complications were ejection fraction less than 0.35 and multiple ablation targets.[156] The improvement in the complication rate probably reflects the learning curve for radio frequency ablation.

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Therapy for Cardiac Arrhythmias

PHARMACOLOGICAL THERAPY

PRINCIPLES OF CLINICAL PHARMACOKINETICS

Pharmacological treatment of a patient with a cardiac arrhythmia has as its primary objective to reach an effective and well-tolerated plasma drug concentration as rapidly as possible and to maintain this concentration for as long as required without producing adverse effects. In many but not all situations and not with all drugs, plasma concentration after equilibration correlates with the pharmacodynamic as well as adverse effects of the drug. Therapeutic serum concentrations for the most important available antiarrhythmic agents are listed in Table 23-1 and are based on concentrations of drugs that exert therapeutic effects on often benign arrhythmias such as PVCs without adverse effects in a majority of patients. However, the therapeutic concentration for any individual patient is the amount of drug required *for that patient* to suppress or terminate the specific cardiac arrhythmia requiring treatment without producing adverse effects.

For a specific patient, one must consider the response both of the patient and of the arrhythmia to the drug; the actual plasma concentration of the drug is often of secondary importance. Low drug concentrations can exert a therapeutic or toxic effect in some patients, whereas drug concentrations higher than the normal range may be needed and tolerated in other patients. In some patients, measured plasma concentrations can be useful to establish concentrations needed for arrhythmia prophylaxis, to judge the sensitivity or resistance of the arrhythmia to the drug, and to evaluate symptoms that suggest drug toxicity. Plasma concentrations also can be used to determine the effects of changing physiological states on drug concentrations, establish drug compliance or

abuse, search for drug interactions that affect the pharmacokinetics, and establish the importance of physiologically active metabolites of the parent compound.[157] [158] Active metabolites may be suspected when the clinical effect of the drug outlasts the therapeutic serum concentration of the parent compound or when results immediately after intravenous drug administration differ from those after oral administration of the drug.

Normally, because antiarrhythmic agents have a narrow toxic-therapeutic relationship, important complications of therapy can result from amounts of drug that only slightly exceed the amount necessary to produce beneficial effects; lesser concentrations are often subtherapeutic. It is obvious that careful dosing with these agents is essential to maintain adequate but nontoxic amounts of drug in the body, a task facilitated by understanding drug *pharmacokinetics.*[159] [160] [161] The latter consists of a quantitative assessment of drug dose concentration factors, including drug absorption, distribution, metabolism, and excretion. Alterations in the rate of any of these processes can account for significant intrapatient and interpatient variations in plasma concentrations. In addition, changes in the functional status of any of the organs involved (e.g., the heart, liver, or kidneys) can significantly alter dose requirements in a given patient. The latter concerns a study of *pharmacodynamics,* or drug concentration response issues.[158] [162] *Pharmacogenetics* refers to the influence of genetics on drug metabolism and action. Examples of pharmacogenetic effects include whether procainamide is extensively metabolized to *N*-acetylprocainamide (NAPA), as well as the bimodal population distribution of the oxidative cytochrome P450 enzyme (important in antiarrhythmic drug metabolism). The low activity of this enzyme leads to accumulation of the parent compound, whereas patients with high enzyme activity metabolize drugs more extensively, leading to an altered drug effect.

ABSORPTION.

Drug absorption from the intestinal tract occurs for most drugs with a half-life of absorption in the range of 20 to 30 minutes. completeness of absorption can vary between 50 and over 90 percent, depending on the drug, with most absorption occurring in the small intestine. Different preparations of the same drug can undergo different rates of absorption in the same patient because the tablet preparations have different dissolution rates. Thus, different brands of drug may not result in the same serum concentration. By altering the properties of the tablet, a slow-release form of a drug ordinarily rapidly absorbed and metabolized, such as procainamide, can be developed. Large amounts of some orally administered drugs, such as propranolol or verapamil, are transformed into inactive metabolites in the liver before they reach the systemic circulation (the so-called first-pass hepatic effect).[161] For such an agent, much more drug must be administered orally than intravenously to achieve the same physiological effect.

Absorption Abnormalities.

Disease states and other factors can alter the rate and completeness of drug absorption. For example, heart failure can cause mucosal edema of the gut and impair absorption of orally administered drugs, as can decreased intestinal blood flow. Renal or

hepatic hypoperfusion can reduce drug elimination and metabolism. Reduced volume of distribution and impaired clearance can increase elimination half-life, requiring a reduction in loading and maintenance doses (see Tables 23-1 and 23-2). Malabsorption syndromes, concomitant use of other drugs, or changes in gut motility or flora caused by diarrheal states, antibiotics, or the use of cathartics can alter absorption. Because most antiarrhythmic agents are basic compounds, they are ionized and poorly absorbed at normal gastric pH, and some drugs can decompose at gastric pH. Conditions that delay gastric emptying increase the absorption lag phase between ingestion of these drugs and their arrival in the small intestine, where most absorption takes place, and therefore can delay absorption. In patients with severe hypotension, shock, or cardiac arrest, impaired tissue perfusion prevents reliable absorption of intramuscularly administered agents; these patients should receive all medications by the intravenous (IV) route.

BIOAVAILABILITY.

The rate of drug absorption, which is determined by the time required to achieve maximum plasma concentration, and the fraction of drug absorbed influence the drug's *bioavailability,* which is a measure of the amount of drug that reaches the systemic circulation intact. Bioavailability of a drug is influenced by factors such as pill dissolution, absorption, metabolism by gut mucosa, hepatic metabolism, and plasma protein binding.

The fraction of an orally administered drug reaching the systemic circulation intact, or *systemic availability,* can be calculated (assuming equal clearances for IV and oral forms of drug) by comparing the areas under the plasma concentration curve achieved with oral and IV administrations using the following relationship. Systemic availability equals the area under the plasma concentration curve after oral administration divided by the area under the plasma concentration curve after IV administration times 100 (assuming equal IV and oral doses).

DRUG DISTRIBUTION

Most antiarrhythmic drugs in the therapeutic range are eliminated according to *first-order kinetics,* which means that the amount of drug eliminated per unit of time is directly proportional to the amount (or concentration) of drug in the body. More drug in the body results in more drug excreted by the kidneys or metabolized by the liver so that the *fraction* of drug eliminated per unit of time remains constant regardless of the amount of drug in the body. For example, one half the drug may be eliminated in 6 hours whether the total amount of drug in the body is 4 g or 10 g, resulting in elimination of 2 g in the first example and 5 g in the second. As a consequence, the elimination half-life, or time required to eliminate half the body load (or to halve the plasma concentration) of such a drug, is constant and independent of the total-body load. The following discussion will assume first-order kinetics unless otherwise stated. (*Zero-order kinetics* indicates that the reaction occurs at a constant, usually maximal, rate and cannot increase further despite increased drug concentrations. Such nonlinear or saturable kinetics can occur at high concentrations of a drug that at usual concentrations exhibits first-order kinetics.[158])

THE ONE-COMPARTMENT MODEL.

Generally, two models, a *one-compartment open model* and a *two-compartment open model,* are used with relative accuracy to describe and predict serum concentrations at a given time for a variety of dose regimens. Even though these models are oversimplified representations of drug disposition, they provide guidelines for choosing loading doses and maintenance dose schedules for a given patient. In the one-compartment open model, drugs are considered to enter and to be eliminated from a single homogeneous unit that represents the entire body. Drugs entering the compartment are considered to be distributed immediately throughout the compartment, making the concentration of the drug equal to the amount of drug in the compartment divided by the volume of the compartment. The latter equals the amount of the drug in the compartment divided by the drug concentration.

In reality, a one-compartment open model is not entirely appropriate because a certain amount of time is needed to distribute the drug throughout the volume of the compartment. However, the one-compartment model predicts plasma concentration as a function of time and dose if distribution is significantly faster than the rate of administration or excretion, which is the case for many antiarrhythmic drugs.

THE TWO-COMPARTMENT MODEL.

If the rate of drug administration is rapid in relation to drug distribution (e.g., IV administration), a two-compartment open model more accurately predicts drug concentrations (Fig. 23-9) . In this model the drug enters the system by the central compartment and can leave the system only by distribution into a peripheral compartment or elimination from the central compartment. The central compartment, in dynamic equilibrium with the more slowly equilibrating peripheral compartment, is assumed to consist of the blood volume and extracellular fluid of highly perfused tissues such as the heart, lungs, kidneys, and liver, whereas the peripheral compartment, acting as a reservoir, consists of less well perfused tissue such as muscle, skin, and adipose tissue. The first-order

TABLE 23-1 -- DOSAGE AND THERAPEUTIC CONCENTRATIONS FO

DRUG	USUAL DOSAGE RANGES				TIME TO PEAK PLASMA CONCENTRATION (ORAL) (HR)
	Intravenous		Oral		
	Loading	*Maintenance*	*Loading*	*Maintenance*	

Quinidine	6-10 mg/kg at 0.3-0.5 mg/kg/min	--	800-1000 mg	300-600 mg q 6 hr	1.5-3.0
Procainamide	6-13 mg/kg at 0.2-0.5 mg/kg/min	2-6 mg/min	500-1000 mg	250-1000 mg q 4-6 hr	1
Disopyramide	1-2 mg/kg over 15-45 min*	1 mg/kg/hr		100-300 mg q 6-8 hr	1-2
Lidocaine	1-3 mg/kg at 20-50 mg/min	1-4 mg/min	N/A	N/A	N/A
Mexiletine	500 mg*	0.5-1.0 gm/24 hr	400-600 mg	150-300 mg q 8-12 hr	2-4
Phenytoin	100 mg q 5 min for 1000 mg		1000 mg	100-400 mg q 12-24 hr	8-12
Flecainide	2 mg/kg*	100-200 mg q 12 hr		50-200 mg q 12 hr	3-4
Propafenone	1-2 mg/kg		600-900 mg	150-300 mg q 8-12 hr	1-3
Moricizine	N/A	N/A	300 mg	100-400 mg q 8 hr	1-3
Propranolol	0.25-0.5 mg q 5 min to 0.20 mg/kg			10-200 mg q 6-8 hr	4
Amiodarone	15 mg/kg for 10 min, 1 mg/kg for 3 hr, 0.5 mg/kg thereafter	1 mg/min	800-1600 mg q.d. for 7-14 days	200-600 mg q.d.	
Bretylium	5-10 mg/kg at 1-2 mg/kg/min	0.5-2 mg/min	N/A	4 mg/kg/day	2-4

Sotalol	10 mg over 1-2 min			80-320 mg q 12 hr	2.5-4
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	N/A
Dofetilide	2-5 mug/kg infusion	N/A	N/A	0.1-0.5 mg q 12 hr	
Azimilide	N/A	N/A	N/A	100-200 mg q.d.	
Verapamil	5-10 mg over 1-2 min	0.005 mg/kg/min		80-120 mg q 6-8 hr	1-2
Adenosine	6-18 mg (rapidly)	N/A	N/A	N/A	N/A
Digoxin	0.5-1.0 mg	0.125-0.25 mg q.d.	0.5-1.0 mg	0.125-0.25 mg q.d.	2-6

Investigational only.

N/A = not applicable.

Results presented may vary according to doses, disease state, and intravenous or oral administration

*Intravenous use investigational.

TABLE 23-2 -- KNOWN INFLUENCE OF DISEASE STATES AND OTHER CONDITIONS ON ANTIARRHYTHMIC DRUG PHARMACOKINETICS

DISEASE OR CONDITION	EFFECTS
Congestive heart failure	Reduced clearance of:
	Lidocaine
	Procainamide
	Flecainide
	Reduced volume of distribution of:
	Lidocaine

Liver disease	Reduced clearance of:
	Lidocaine
	Disopyramide
	Phenytoin
	Propranolol
Renal disease	Reduced clearance of:
	Disopyramide
	Procainamide
	Bretylium
	Flecainide
	Altered protein binding (with usually unchanged drug requirements) of:
	Phenytoin
Post-myocardial infarction	Reduced clearance of:
	Procainamide
	Altered protein binding of:
	Lidocaine
	Quinidine
Prolonged administration	Reduced clearance of:
	Lidocaine
Obesity	Increased volume of distribution of:
	Lidocaine

From Roden D: New concepts in antiarrhythmic drug pharmacokinetics. Prog Cardiovasc Dis 15:19, 1987.

rate constants $K_{1\text{-}2}$ and $K_{2\text{-}1}$ determine the rate of transfer of drug between the central and peripheral compartments or vice versa, with Ke representing the overall elimination rate constant. Ke relates the sum of all methods of irreversible drug elimination from the central compartment to the concentration of drug in that compartment (see Fig. 23-9).

For antiarrhythmic drugs, the peripheral compartment is generally larger than the central compartment. The concepts of distribution volumes and drug movement are more complex in the two-compartment open model than in the one-compartment open model. The two-compartment model may behave similarly to the one-compartment model when drugs are infused slowly or given orally and K_1 approximates K_2 , but pronounced differences exist when injections are given rapidly.

DISTRIBUTION AND ELIMINATION PHASES.

After administration of drugs for which the kinetics are described by a two-compartment

Figure 23-9 Two-compartment open model. A smaller central compartment into which drug is administered and from which it is eliminated (Ke) connects in dynamic equilibrium with a larger peripheral compartment.

model, the curve of plasma drug concentration demonstrates two distinct phases: (1) an early phase (alpha, or distribution, phase), characterized by rapidly falling plasma drug concentrations due to distribution between the central compartment and the peripheral compartment, and (2) a second phase (beta, or elimination, phase) of slower decline in plasma drug concentration, representing primarily elimination of drugs from the central compartment (Fig. 23-10) . *Alpha* is often referred to as the *rate constant for distribution* and *beta* as the *rate constant for elimination.* During the latter beta phase, when the drug is in distribution equilibrium, serum concentrations correlate with the pharmacological effects of the drug. The distribution of quinidine is shown in Figure 23-11 .

VOLUME OF DISTRIBUTION.

The extent of extravascular distribution of a drug is obtained by measuring the apparent *volume of distribution* (V_d), which is the hypothetical volume into which a dose of drug would have to be diluted to give the observed plasma concentration. It is determined by the dose administered divided by the plasma concentration at time 0. The latter equals the sum of A and B on the logarithmic plasma concentration axis obtained by extrapolating the alpha and beta phases back to 0 time (see Fig. 23-10). It is also calculated by dividing the systemic clearance of the drug by beta, the rate constant of elimination. A large volume of distribution indicates a wide distribution and extensive tissue uptake of the drug and often exceeds by several times the actual amount of total-body water. The large volume of distribution for most antiarrhythmic agents indicates that they are present in higher concentrations in some tissues than in the plasma. The volume of distribution is dependent on the relative serum and tissue binding characteristics of the drug and can be constricted in some patients, such as those with renal failure, during which a change in serum protein or tissue binding can occur. Quinidine decreases the volume of distribution of digoxin, probably as a result of a decrease in tissue binding of digoxin, and thereby causes an increase in serum digoxin concentration.

DRUG METABOLISM AND EXCRETION.

Serum elimination half-life is defined as the time interval for 50 percent of the drug present in the body at the beginning of the interval to be eliminated. After one half-life, 50 percent of the drug remains in the body (assuming no further drug is administered),

after two half-lives 25 percent remains, after three half-lives 12.5 percent remains, and so forth. Approximately 97 percent of the dose of any drug is removed from the body after five half-lives. Half-life is determined from the relationship $t_{1/2}$ = 0.693/beta for a two-compartment model (see Fig. 23-10). Because changes in drug distribution influence elimination half-life, the equation can be rewritten as

DRUG CLEARANCE.

This is analogous to renal clearance and is the volume of blood totally cleared of drug per unit of time. It is the sum of the clearances for each process by which the drug is eliminated and can be calculated from the relationship

Figure 23-10 Schematic diagram of the semilogarithmic plot of drug plasma concentration as a function of time after rapid intravenous injection, according to the principles outlined for a two-compartment open model. *(From Gibaldi M, Perrier D: Drugs and the pharmaceutical sciences. In Pharmacokinetics, vol 1. New York, Marcel Dekker, 1975.)*

Figure 23-11 *A,* Changes in plasma concentration over time after beginning treatment with quinidine. *Top,* Quinidine plasma concentration over time, with the dashed line indicating the therapeutic range. *Bottom,* The hatched bars represent the body load immediately after each dose of quinidine, expressed as a percentage of the load after a dose when a steady state has been achieved. Quinidine is administered every 6 hours (the half-life in this case). Four half-lives, or 24 hours, are required to achieve a body load of quinidine that exceeds 90 percent of the load at steady state. *B, top,* Plasma concentrations produced by administering a full intravenous loading dose of quinidine as a bolus, with the therapeutic range shown by a dashed line. *Bottom,* The numbered vertical boxes indicate the volume of distribution of quinidine. Just after the drug is given, it is dissolved only in the small central compartment, as in box 1, and very high peak concentrations are achieved (in the toxic range). The drug then distributes throughout the rest of the body. Distribution has a half-life of about 8 minutes and is complete by 30 minutes (box 3). Quinidine concentration is now in the therapeutic range, and further decreases in plasma concentration are due solely to drug elimination. *(From Nattel S, Zipes DP: Clinical pharmacology of old and new antiarrhythmic drugs. Cardiovasc Clin 11:221, 1980.)*

Expressed differently,

A larger volume of distribution increases the elimination half-life at a given clearance. The larger volume of distribution of antiarrhythmic drugs accounts for the relatively long half-life despite their high clearance rates. Administration of one drug may alter the half-life of another; for example, quinidine prolongs digoxin's half-life by decreasing total-body clearance. Clearance of drugs with high extraction ratios strongly depends on blood flow to the organ from which they are eliminated, such as propranolol, verapamil, or lidocaine in the liver. For antiarrhythmic drugs that have a high renal extraction ratio, such as procainamide and quinidine, reduction of renal flow decreases their clearance.

ELIMINATION HALF-LIFE.

The function of the organ system that eliminates a given drug from the body determines the elimination half-life. Primary routes of elimination are hepatic metabolism and renal clearance. The kidneys can remove unchanged drug or metabolites. For drugs rapidly metabolized in the liver, hepatic blood flow limits the rate of drug elimination. Disorders that reduce liver blood flow (e.g., low cardiac output, hepatic disease with portacaval shunting) markedly slow the elimination of such drugs. Drugs with a short half-life are convenient to use by intravenous infusion but not by chronic oral dosing, since the short half-life requires frequent oral doses to maintain a fairly constant plasma concentration. Generally, maintenance dosing involves giving a certain amount of the drug at a time interval that equals the elimination half-life. However, with drugs that have very long half-lives, such as 12 hours, this can result in excessive peak values shortly after administration and consequent side effects. Maintaining constant plasma concentrations is necessary because of the narrow toxic-therapeutic ratios exhibited by antiarrhythmic agents.

Some drugs have active metabolites with half-lives considerably longer than the parent compound, allowing dosing intervals to be more widely spaced than those predicted by the half-life of the parent drug. The active metabolite of procainamide, NAPA, is eliminated unchanged by the kidneys and can accumulate in high concentrations in patients with renal disease. The rate and extent of metabolism of the same drug can vary greatly from patient to patient owing to a variety of factors, including environment, genetics, age, disease states, and influence of other drugs given concomitantly. A genetically determined acetyltransferase enzyme system influences the metabolism of some drugs, making about half the American population "rapid" and half "slow acetylators." Rapid acetylators metabolize a greater proportion of a drug dose than do slow acetylators, who may require less drug to achieve any desired serum level or pharmacological effect. Also, rapid acetylators may be more prone to develop reactions from the metabolites of drugs or are less likely to develop side effects from the parent compound for a constant drug dose.

DRUG BINDING

Drugs exist in plasma both in the free form and bound to plasma proteins. Only free drug is capable of distributing into tissues and exerting a pharmacological action. Some drugs (e.g., verapamil, sotalol, and disopyramide) have optical isomers, with different potencies and effects. Virtually all assays for drug concentration in the blood measure *both* free and protein-bound drug. For antiarrhythmic drugs, the fraction of drug that is bound varies greatly among the different agents but is fairly constant for individual drugs over the clinically relevant range of plasma concentrations, with the exception of phenytoin, lidocaine, propafenone, and disopyramide. With these drugs, binding sites become saturated at high concentrations; therefore, a doubling of total drug concentration represents more than a doubling of unbound drug. Total plasma concentrations of a given drug generally correlate well with its clinical effects, and it has not been necessary to develop assays to measure free drug concentrations

for antiarrhythmic agents. Some drugs, such as quinidine and lidocaine, bind to an $alpha_1$ -acid glycoprotein that increases in acute disease states such as myocardial infarction, which may decrease the concentration of free drug.

When a constant dose of a drug is administered repeatedly (orally or parenterally) at a constant dosing interval, accumulation occurs until drug concentration approaches a constant steady-state level, at which time the rate of drug administration equals the rate of drug elimination. The time it takes to reach steady state is a function of the half-life of the drug; 94 percent of steady state is achieved after four half-lives and 99 percent after seven half-lives. A drug with a long half-life takes longer to reach steady state than does one with a short half-life. The average steady-state concentration of a drug equals the fraction of the dose absorbed (F) × the maintenance dose ($dose_m$) divided by the total-body clearance (Cl_s) × the dosing interval (tau).

If the drug is given intravenously,

Finally, it is important to stress that drug pharmacokinetics may differ in normal, healthy volunteers compared with patients who have a variety of illnesses. Therefore, information derived from patients as well as normal subjects must be considered when

one is planning dosing regimens.

General Considerations Regarding Antiarrhythmic Drugs

Most of the available antiarrhythmic drugs (Table 23-3) can be classified according to whether they exert blocking actions predominantly on sodium, potassium, or calcium channels and whether they block beta-adrenoceptors.[162] [163]

TABLE 23-3 -- CLASSIFICATION OF DRUG ACTIONS ON ARRHYTHMIAS BASED ON MODIFICATION OF VULNERABLE PARAMETER

MECHANISM	ARRHYTHMIA	VULNERABLE PARAMETER (EFFECT)	DRUGS (EFFECT)
Automaticity			
Enhanced normal	Inappropriate sinus tachycardia	Phase 4 depolarization (decrease)	Beta-adrenergic blocking agents
	Some idiopathic ventricular tachycardias		Na^+ channel blocking agents
Abnormal	Atrial tachycardia	Maximum diastolic potential (hyperpolarization)	M_2 agonist
		Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents
			M_2 agonist
	Accelerated idioventricular rhythms	Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents
Triggered Activity			
EAD	Torsades de pointes	Action potential duration (shorten)	Beta-adrenergic agonists; vagolytic agents (increase rate)
		EAD (suppress)	Ca^{2+} channel blocking agents; Mg^{2+} ; beta-adrenergic blocking agents
DAD	Digitalis-induced arrhythmias	Calcium overload (unload)	Ca^{2+} channel blocking agents
		DAD (suppress)	Na^+ channel blocking agents

	Right ventricular outflow tract ventricular tachycardia	Calcium overload (unload)	Beta-adrenergic blocking agents
		DAD (suppress)	Ca^{2+} channel blocking agents; adenosine
Reentry-Na^+ Channel-Dependent			
Long excitable gap	Typical atrial flutter	Conduction and excitability (depress)	Type IA, IC Na^+ channel blocking agents
	Circus movement tachycardia in WPW	Conduction and excitability (depress)	Type IA, IC Na^+ channel blocking agents
	Sustained uniform ventricular tachycardia	Conduction and excitability (depress)	Na^+ channel blocking agents
Short excitable gap	Atypical atrial flutter	Refractory period (prolong)	K^+ channel blocking agents
	Atrial fibrillation	Refractory period (prolong)	K^+ channel blocking agents
	Circus movement tachycardia in WPW	Refractory period (prolong)	Amiodarone, sotalol
	Polymorphic and uniform ventricular tachycardia	Refractory period (prolong)	Type IA Na^+ channel blocking agents
	Bundle branch reentry	Refractory period (prolong)	Type IA Na^+ channel blocking agents; bretylium
	Ventricular fibrillation	Refractory period (prolong)	
Reentry-Ca^{2+} Channel-Dependent			
	AV nodal reentrant tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Circus movement tachycardia in WPW	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Verapamil-sensitive ventricular tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents

WPW = Wolff-Parkinson-White syndrome.

Reproduced with permission from Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: The Sicilian Gambit: A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circulation 84:1831, 1991. Copyright 1991, American Heart Association.

The commonly used Vaughan Williams classification is limited because it is based on the electrophysiological effects exerted by an arbitrary concentration of the drug, generally on normal cardiac tissue. Actually, the actions of these drugs are quite complex and depend on tissue type, species, the degree of acute or chronic damage, heart rate, membrane potential, the ionic composition of the extracellular milieu, and other factors (see Table 23-3). Many drugs exhibit actions that belong in multiple categories or operate indirectly, such as by altering hemodynamics, myocardial metabolism, or autonomic neural transmission. Some drugs have active metabolites that exert effects different from those exerted by the parent compound. Not all drugs in the same class have identical effects (e.g., bretylium, sotalol, and amiodarone). Whereas all class III agents are dramatically different, some drugs in different classes have overlapping actions (e.g., Class IA and IC drugs). In vitro studies on healthy fibers usually establish the properties of antiarrhythmic agents rather than their actual antiarrhythmic properties.

Despite these limitations, the Vaughan Williams classification[164] is widely known and provides a useful communication shorthand. It is listed here, but the reader is cautioned that drug actions are more complex than those depicted by the classification. A more realistic view of antiarrhythmic agents is provided by the "Sicilian gambit."[165] [166] [167] This approach to drug classification is an attempt to identify the mechanisms of a particular arrhythmia, determine the vulnerable parameter of the arrhythmia most susceptible to modification, define the target most likely to affect the vulnerable parameter, and then select a drug that will modify the target. This concept provides a framework in which to consider antiarrhythmic drugs (see Tables 23-3 and 23-4).

DRUG CLASSIFICATION.

According to the Vaughan Williams classification, *Class I* drugs predominantly block the fast sodium channel (they can also block potassium channels). They, in turn, are divided into three subgroups:

Class IA. Drugs that reduce
max (rate of rise of action potential upstroke [phase 0]) and prolong action potential duration (see Chap. 22): quinidine, procainamide, disopyramide; kinetics of onset and offset in blocking the Na^+ ; channel are of intermediate rapidity (<5 seconds).

Class IB. Drugs that do not reduce
max and that shorten action potential duration: mexiletine, phenytoin, and lidocaine; fast onset and offset kinetics (<500 milliseconds).

Class IC. Drugs that reduce
max, primarily slow conduction, and can prolong refractoriness minimally: flecainide, propafenone, and moricizine; slow onset and offset kinetics (10 to 20 seconds).

Class II. Drugs that block beta-adrenergic receptors and include propranolol, timolol, metoprolol, and others.

Class III. Drugs that predominantly block potassium channels (such as I_{Kr}) and prolong repolarization. They include sotalol, amiodarone, bretylium, and NAPA.

Class IV. Drugs that predominantly block the slow calcium channel ($I_{Ca\text{-}L}$) and include verapamil, diltiazem, nifedipine, and others (felodipine blocks $I_{Ca\text{-}T}$).

A recently proposed model suggests that antiarrhythmic drugs cross the cell membrane and interact with receptors in the membrane channels when the latter are in the rested, activated, or inactivated state (see Table 23-4) and that each of these interactions is characterized by different association and dissociation rate constants (see Chap. 22) Such interactions are voltage and time dependent. Transitions among rested, activated, and inactivated states are governed by standard Hodgkin-Huxley-type equations. When the drug is bound (associated) to a receptor site at or very close to the ionic channel (the drug probably does not actually "plug" the channel), the latter cannot conduct, even in the activated state.

USE-DEPENDENCE.

Some drugs exert greater inhibitory effects on the upstroke of the action potential at more rapid rates of stimulation and after longer periods of stimulation, a characteristic called *use-dependence.* Use-dependence means that depression of
max is greater after the channel has been "used" (i.e., after action potential depolarization rather than after a rest period). It is possible that this use-dependence results from preferential interaction of the antiarrhythmic drug with either the open or the inactive channel, and there is little interaction with the resting channels of the unstimulated cell. Agents in Class IB exhibit fast kinetics of onset and offset or use-dependent block of the fast channel; that is, they bind and dissociate quickly from the receptors. Class IC drugs have slow kinetics, and Class IA drugs are intermediate. With increased time spent in diastole (slower rate), a greater proportion of receptors become drug free, and the drug exerts less effect. Cells with reduced membrane potentials recover more slowly from drug actions than cells with more negative membrane potentials (see Chap. 22).

REVERSE USE-DEPENDENCE.

Some drugs exert greater effects at slow rates than at fast rates, a property known as *reverse use-dependence.* This is particularly true for drugs that lengthen repolarization. The QT interval becomes prolonged more at slow than fast rates. This is opposite to what the ideal antiarrhythmic agent would do, because prolongation of refractoriness should be increased at fast rates so as to interrupt or prevent a tachycardia and should be minimal at slow rates to avoid precipitating torsades de pointes.[168]

MECHANISMS OF ARRHYTHMIA SUPPRESSION.

Given the fact that enhanced automaticity, triggered activity, or reentry can cause cardiac arrhythmias (see Chap. 22), mechanisms by which antiarrhythmic agents suppress arrhythmias can be postulated.[165] [166] Antiarrhythmic agents can slow the spontaneous discharge frequency of an automatic pacemaker by depressing the slope of diastolic depolarization, shifting the threshold voltage toward zero, or hyperpolarizing the resting membrane potential. Mechanisms by which different drugs suppress normal or abnormal automaticity may not be the same. In general, however, most antiarrhythmic agents in therapeutic doses depress the automatic firing rate of spontaneously discharging ectopic sites while minimally affecting the discharge rate of the normal sinus node. Slow-channel blockers like verapamil, beta blockers like propranolol, and some antiarrhythmic agents like amiodarone also depress spontaneous discharge of the normal sinus node, whereas drugs that exert vagolytic effects, such as disopyramide or quinidine, can increase the sinus discharge rate. Drugs can also suppress early or delayed afterdepolarizations (see Chap. 22) and eliminate triggered arrhythmias due to these mechanisms.

As mentioned earlier (see Chap. 22), reentry depends critically on the timing interrelationships between refractoriness and conduction velocity, the presence of unidirectional block in one of the pathways, and other factors that influence refractoriness and conduction, such as excitability. An antiarrhythmic agent can stop reentry that is already present or prevent it from starting if the drug improves or depresses conduction. For example, *improved conduction* can (1) eliminate the unidirectional block so that reentry cannot begin or (2) facilitate conduction in the reentrant loop so that the returning wavefront reenters too quickly, encroaches on fibers still refractory, and becomes extinguished. A drug that *depresses conduction* can transform the unidirectional block to bidirectional block and thus terminate reentry or prevent it from occurring by creating an area of complete block in the reentrant pathway.

TABLE 23-4 -- ACTIONS OF ANTIARRHYTHMIC DRUGS

DRUG	CHANNELS						RECEPTORS				PUMPS	CLINICAL EFFE	
	Na^+ *			Ca^{2+}	K_r^+	K_s^+							
	Fast	*Med*	*Slow*				alpha	beta	M_2	P	Na^+ ,K^+ - ATPase	LV Function	
Lidocaine												--	
Mexiletine												--	

Moricizine	I													
Procainamide		A												
Disopyramide		A												
Quinidine		A											--	
Propafenone		A												
Flecainide			A											
Verapamil														
Diltiazem														
Bretylium													--	
Sotalol														
Amiodarone													--	
Ibutilide													--	
Dofetilide													--	
Azimilide													--	
Nadolol														
Propranolol														
Atropine													--	
Adenosine													--	
Digoxin														

Relative potency of blockade or extracardiac side effect:
=low;
=moderate;
=high;
=agonist;
=agonist/antagonist.

A=activated state blocker; I=inactivated state blocker; --=minimal effect;
=increase;
=decrease; K^+_r = rapid component of delayed rectifier K^+ current; K_s =slow component of delayed rec
=muscarinic receptor subtype 2; P=A_1 purinergic receptor.

Adapted from Schwartz PJ, Zaza A: The Sicilian Gambit revisited--theory and practice. Eur Heart J 13

*Fast, Med (medium), and Slow refer to kinetics of recovery from sodium channel blockade.

Conversely, a drug that slows conduction without producing block or lengthening refractoriness significantly can promote reentry. Finally, most antiarrhythmic agents share the ability to prolong refractoriness relative to their effects on action potential duration (APD); that is, the ratio of effective refractory period (ERP) to APD exceeds 1.0. If a drug *prolongs refractoriness* of fibers in the reentrant pathway, the pathway may not recover excitability in time to be depolarized by the reentering impulse and the reentrant propagation ceases. The different types of reentry (see Chap. 22) influence the effects and effectiveness of a drug.

When one is discussing any of the properties of a drug, it is important that the situation and/or model from which conclusions are drawn be defined with care. Electrophysiological, hemodynamic, autonomic, pharmacokinetic, and adverse effects all may differ in normal subjects compared with patients, in normal tissue compared with abnormal tissue, in cardiac muscle compared with specialized conduction fibers, in atrium as opposed to ventricular muscle, and in different species.

STEREOSELECTIVITY.

Drug interactions with a channel, receptor, or enzyme may depend on the three-dimensional geometry of the drug.[169] Many drugs have stereoisomers (molecules with the same atomic composition but different spatial arrangement) that can influence drug effects, metabolism, binding, clearance, and excretion. Most drugs of this type are prescribed as 50/50 mixtures of their two forms (racemates), which may make 50 percent of the dose ineffective for some drugs. Except for timolol, virtually all beta blockers are racemates. *d*-Propranolol exerts antiarrhythmic actions unrelated to beta-adrenoceptor blockade, whereas *l*-propranolol blocks the beta receptor. Both enantiomers (mirror images) of sotalol block the potassium channel to prolong APD and

suppress arrhythmias equally, but *d*-sotalol does not block the beta adrenoceptor. Racemic propafenone exhibits beta-blocking actions due to the S enantiomer. Other drugs with notable stereoselective differences include disopyramide, with one form (S [+]) prolonging repolarization and having greater antiarrhythmic effects than R (-), which shortens repolarization. The latter form has fewer anticholinergic effects. The (-) enantiomer of verapamil exerts much more negative inotropic and dromotropic effects than does the (+) form and may have more potent antiarrhythmic actions. Stereoselectivity affects sodium channel blocking drugs less than it affects beta-adrenoceptor, potassium, and calcium blockers.

DRUG METABOLITES.

Drug metabolites may add to or alter the effects of the parent compound by exerting similar actions, competing with the parent compound, or mediating drug toxicity. Quinidine has at least four active metabolites but none with a potency exceeding the parent drug and none preliminarily implicated in causing torsades de pointes. About 50 percent of procainamide is metabolized to NAPA. Only the parent drug blocks cardiac sodium channels and slows impulse propagation in the His-Purkinje system. NAPA prolongs repolarization and is a less effective antiarrhythmic drug but competes with procainamide for renotubular secretory sites and can increase the parent drug's elimination half-life. Lidocaine's metabolite can compete with lidocaine for sodium channels and partially reverse block produced by lidocaine.

PHARMACOGENETICS.

Genetically determined metabolic pathways account for many of the differences in patients' responses to some drugs. The genetically determined activity of hepatic *N*-acetyltransferase regulates the development of antinuclear antibodies and development of the lupus syndrome in response to procainamide. Slow acetylator phenotypes appear more prone to develop lupus than do rapid acetylators.[170] [171] [172] About 7 percent of white and black subjects lack debrisoquin 4-hydroxylase. This enzyme is needed to metabolize debrisoquine (an antihypertensive drug) and propafenone, to hydroxylate several beta blockers, and to biotransform flecainide. The gene coding for this enzyme (termed $P450_{dbl}$) is on human chromosome 22. Lack of this enzyme reduces metabolism of the parent compound, leading to increased plasma concentrations of the parent drug and reduced concentrations of metabolites. Propafenone is metabolized by this enzyme to a compound with slightly less antiarrhythmic and beta-adrenergic blocking effects, as well as fewer central nervous system side effects. Thus, poor metabolizers may experience more heart rate slowing and neurotoxicity than extensive metabolizers. Quinidine in low doses can inhibit this enzyme and thereby alter concentrations of the drugs and metabolites given in combination that are affected by the $P450_{dbl}$ enzyme, such as propafenone or flecainide.

Understanding stereoselectivity and pharmacogenetics can provide major clues to understanding differences in drug efficacy and toxicity from one patient to the next. Cimetidine and ranitidine also affect drug metabolism, probably by inhibiting hepatic P450-metabolizing enzymes (Table 23-5) . Other commonly used noncardiovascular

medications affect this important metabolic pathway. Drugs such as rifampin, phenobarbital, and phenytoin induce synthesis of larger amounts of cytochrome $P450_{dbl}$, leading to lower concentrations of parent drugs that are extensively metabolized, whereas erythromycin, clarithromycin, fluoxetine, and grapefruit juice inhibit enzyme activity, leading to accumulation of the parent compound. This effect is thought to explain why cisapride, an agent used to increase gastric motility, can cause QT interval prolongation and torsades de pointes in isolated cases. Cisapride is a potent blocker of the delayed rectifier current I_{kr} but does not prolong the QT interval significantly in the majority of patients, presumably owing to extensive metabolism. In patients who take an inhibitor of cytochrome P450 (such as erythromycin) along with cisapride, the latter drug can accumulate, leading to QT prolongation and torsades de pointes.[173]

SIDE EFFECTS.

Antiarrhythmic drugs produce one group of side effects that relate to excessive dosage and plasma concentrations, resulting in both noncardiac (e.g., neurological defects) and cardiac (e.g., heart failure, some arrhythmias) toxicity and another group of side effects unrelated to plasma concentrations, which is termed *idiosyncratic.* Examples of the latter include procainamide-induced lupus syndrome, amiodarone-induced pulmonary toxicity (although some evidence relates maintenance dose to this side effect), and some arrhythmias such as quinidine-induced torsades de pointes. The latter phenomenon can occur in individuals with a "forme fruste" of the long QT syndrome (i.e., normal QT interval at rest but markedly prolonged in the presence of certain medications).[174]

PROARRHYTHMIA.

Drug-induced or drug-aggravated cardiac arrhythmias (proarrhythmia) constitute a major clinical

TABLE 23-5 -- SELECTED PHARMACOKINETIC INTERACTIONS OF ANTIARRHYTHMIC DRUGS

TYPE OF INTERACTION	EFFECTOR DRUG	AFFECTED DRUG
Increased Drug Concentration		
Decreased clearance	Quinidine	Propranolol, mexiletine, propafenone, phenothiazines, tricyclic antidepressants, haloperidol
	Propranolol	Quinidine, lidocaine
	Amiodarone	Quinidine, procainamide, digoxin, warfarin, phenytoin
	Quinidine, verapamil, amiodarone, Flecainide	Digoxin

	Cimetidine	Quinidine, lidocaine, procainamide, flecainide, moricizine
	Verapamil	Quinidine
Decreased volume of distribution	Propranolol	Quinidine
	Quinidine	Digoxin
Unknown mechanism	Quinidine	Warfarin
	Amiodarone	Flecainide
Decreased Drug Concentration		
Increased clearance	Phenytoin, phenobarbital, rifampin	Quinidine, disopyramide, mexiletine, digitoxin
Unknown mechanism	Disopyramide, nifedipine	Quinidine

problem. [175] [176] [177] [178] [179] [180] Proarrhythmia can be manifested as an increase in frequency of a preexisting arrhythmia, sustaining of a previously nonsustained arrhythmia (even making it incessant), or development of arrhythmias the patient has not previously experienced. Electrophysiological mechanisms probably relate to prolongation of repolarization, the development of early afterdepolarizations to cause torsades de pointes,[181] [182] [183] [184] [185] [186] [187] [188] [189] [190] and alterations in reentry pathways[191] to initiate or sustain ventricular tachyarrhythmias. Proarrhythmic events can occur in as many as 5 to 10 percent of patients. Heart failure increases proarrhythmic risk. Patients with atrial fibrillation treated with antiarrhythmic agents had a 4.7 relative risk of cardiac death if they had a history of heart failure compared with patients not so treated who had a 3.7 relative risk of arrhythmic death. Patients without a history of congestive heart failure had no increased risk of cardiac mortality during antiarrhythmic drug treatment.[192] Reduced left ventricular function, treatment with digitalis and diuretics, and longer pretreatment QT interval characterize patients who develop drug-induced VF. The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant VT, long QT syndrome, and torsades de pointes. However, in CAST,[18] [193] [194] researchers found that encainide and flecainide reduced spontaneous ventricular arrhythmias but were associated with a total mortality of 7.7 percent, in comparison with 3.0 percent of the group receiving placebo. Deaths were equally distributed throughout the treatment period, raising the important consideration that another kind of proarrhythmic response can occur some time after the beginning of drug therapy. Such late proarrhythmic effects may relate to drug-induced exacerbation of regional myocardial conduction delay due to ischemia and heterogeneous drug concentrations that may promote reentry. Moricizine also increased mortality, leading to

termination of CAST II.[17] [195]

CLASS IA ANTIARRHYTHMIC AGENTS

Quinidine

Quinidine and quinine are isomeric alkaloids isolated from the cinchona bark.[196] Although quinidine shares the antimalarial, antipyretic, and vagolytic actions of quinine, the latter lacks the significant electrophysiological and antiarrhythmic effects of quinidine.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Quinidine exerts little effect on automaticity of the isolated or denervated normal sinus node but suppresses automaticity in normal Purkinje fibers, especially in ectopic pacemakers, by decreasing the slope of phase 4 diastolic depolarization and shifting threshold voltage toward zero. In patients with the sick sinus syndrome, quinidine can depress sinus node automaticity. It does not affect abnormal automaticity in partially depolarized Purkinje fibers. Quinidine produces early afterdepolarizations in experimental preparations and in humans, which may be responsible for torsades de pointes.[181] [182] [183] [184] [185] [186] [187] [188] [189] [190] Because of its significant anticholinergic effect and reflex sympathetic stimulation resulting from alpha-adrenergic blockade that causes peripheral vasodilation, quinidine can increase sinus node discharge rate and can improve AV node conduction in the innervated heart in vivo. Direct myocardial effects can prolong AV node and His-Purkinje conduction times and refractoriness in an AV accessory pathway. Quinidine slightly prolongs the APD of atrial and ventricular muscle and Purkinje fibers (quinine shortens it) while also prolonging the ERP without significantly changing resting membrane potential. Prolongation of repolarization is more prominent at slow heart rates (reverse use-dependence)[197] [198] owing to block of I_{Kr} .[199] Action potential amplitude, overshoot, and
$\dot{V}_{max}$ of phase 0 are reduced, more so during ischemia, hypoxia, and in partially depolarized fibers, especially at fast rates. The open channel has a high affinity for quinidine, resulting in block of a fraction of sodium channels with each action potential upstroke.[200] The time for unblocking by Class IA drugs (about 4 seconds) is slower than for Class IB drugs but faster than for Class IC drugs. For the duration of the plateau of the action potential (inactivated state) or in depolarized fibers, the rate of unblocking is slow, proceeding much faster in polarized fibers. Therefore, faster rates result in more block of sodium channels and less unblocking because of a lesser percentage of time spent in a polarized state (use-dependence). Isoproterenol can modulate the effects of quinidine on reentrant circuits in humans.[201] [202] Quinidine's effect on I_{to} (but not I_k) varies according to patient age and may account for its lower efficacy in children than adults.[203]

TABLE 23-6 -- IN VIVO ELECTROPHYSIOLOGICAL CHARACTERISTICS OF ANTIARRHYTHMIC DRUGS

DRUG	ELECTROCARDIOGRAPHIC MEASUREMENTS						ELECTROPHYSIOLOGICAL INTERVALS				
	Sinus Rate	PR	QRS	QT	AH	HV	ERP-AVN	ERP-HPS	ERP-A	ERP-V	ERP-AP
Quinidine	0	0			0		0				
Procainamide	0	0			0		0				
Disopyramide	0	0			0		0				
Lidocaine	0	0	0	0	0	0	0	0	0	0	0
Mexiletine	0	0	0	0	0	0	0	0	0	0	0
Phenytoin	0	0	0	0	0	0	0		0	0	0
Flecainide	0			0							
Propafenone	0			0			0	0	0		
Moricizine	0	0	0	0			0	0	0	0	
Propranolol		0	0	0	0	0		0	0	0	0
Amiodarone		0									
Bretylium	0	0	0	0			0				0
Sotalol		0	0			0					
Ibutilide		0	0		0	0	0	0			
Dofetilide	0	0	0		0	0	0	0			
Azimilide	0	0	0		0	0	0	0			

Verapamil	0		0	0		0		0	0	0	0
Adenosine	then		0	0		0		0		0	0
Digoxin			0	0		0		0		0	

Results presented may vary according to tissue type, drug concentration, and autonomic tone.
=increase;
=decrease; 0=no change; 0
or 0
=slight or inconsistent increase or decrease, respectively; A=atrium; AVN=AV node; HPS=His-Purkinje system; V=ventricle; AP=accessory pathway (WPW); ERP=effective refractory period (longest S_1 -S_2 interval at which S_2 fails to produce a response).

TABLE 23-7 -- IN VITRO ELECTROPHYSIOLOGICAL CHARACTERISTICS OF ANTIARR

DRUG	APA	APD	dV/dt	MDP	ERP	CV	PF PHASE 4	SN AUTO	MEMB RES	ET	VFT	CONTR
Quinidine				0				0				0
Procainamide				0				0				0
Disopyramide				0				0				
Lidocaine	0		0	0		0		0	0	0		0
Mexiletine	0		0	0				0				
Phenytoin	0		0	0		0		0	0	0		
Flecainide		0		0				0				

Propafenone		0		0				0					
Moricizine				0			0	0			0		
Propranolol	0	0	0	0		0	*						
Amiodarone	0		0	0					0	0		0	
Brethylium	0		0	0		0	0 *	0	0	0	0		
Sotalol	0		0	0		0	0		0	0	0		
Ibutilide	0		0	0		0	0		0	0		0	
Dofetilide	0		0	0		0	0	0	0	0		0	
Azimilide	0		0	0		0	0	0	0	0		0	
Verapamil	0		0	0	0	0	*		0	0	0		
Adenosine	0		0	0		0	0		0	0	0	0	

APA=action potential amplitude; APD=action potential duration; dV/dt=rate of rise of action potential; potential; ERP=effective refractory period (longest S_1 -S_2 interval at which S_2 fails to produce a respor PF=Purkinje fiber; SN Auto=sinus node automaticity; Mem Res=membrane responsiveness; ET=exci VFT=ventricular fibrillation threshold; Contr=contractility; SI Curr=slow inward current; Local Anesth.=

*With a background of sympathetic activity.

HEMODYNAMIC EFFECTS.

Quinidine decreases peripheral vascular resistance and can cause significant hypotension because of its alpha-adrenergic receptor blocking effects. Concomitant administration of vasodilators can exaggerate the potential for hypotension. In some patients, quinidine can increase cardiac output, possibly by reducing afterload and preload. No significant direct myocardial depressant action occurs unless large doses

are given rapidly by intravenous infusion. Most of the adverse effects of intravenous quinidine are probably the result of excessive vasodilation.

PHARMACOKINETICS (see Table 23-1).

Although orally administered quinidine sulfate and quinidine gluconate exhibit similar degrees of systemic availability, plasma quinidine concentrations peak at about 90 minutes after oral administration of quinidine sulfate and at 3 to 4 hours after oral administration of quinidine gluconate. Intramuscular quinidine produces a higher and an earlier peak plasma concentration but results in incomplete absorption and tissue necrosis. Quinidine may be given intravenously if it is infused slowly. Approximately 80 percent of plasma quinidine is protein bound, especially to $alpha_1$ -acid glycoprotein, which increases in heart failure. Both the liver and the kidneys remove quinidine, and dose adjustments may be made according to the creatinine clearance.[204] [205] Metabolism is by means of the P450 cytochrome system. Approximately 20 percent is excreted unchanged in the urine. Because congestive heart failure, hepatic disease, or poor renal function can reduce quinidine elimination and increase plasma concentration, the dosage probably should be reduced and the drug given cautiously to patients with these disorders while serum quinidine concentration is monitored. Elimination half-life is 5 to 8 hours after oral administration. Quinidine can increase plasma concentrations of flecainide by inhibiting the P450 enzyme system.[169] Quinidine's effect on repolarization and overall efficacy vary directly with left ventricular function.[206]

DOSAGE AND ADMINISTRATION (see Table 23-1).

The usual oral dose of quinidine sulfate for an adult is 300 to 600 mg four times daily, which results in a steady-state level within about 24 hours. A loading dose of 600 to 1000 mg produces an earlier effective concentration. Similar doses of quinidine gluconate are used intramuscularly, whereas the IV dose of quinidine gluconate is about 10 mg/kg given at a rate of about 0.5 mg/kg/min as blood pressure and ECG parameters are checked frequently. Oral doses of the gluconate are about 30 percent greater than those of sulfate. Important interactions with other drugs occur (see Tables 23-2 and 23-5).

INDICATIONS.

Quinidine is a versatile antiarrhythmic agent, useful for treating premature supraventricular and ventricular complexes and sustained tachyarrhythmias. It may prevent spontaneous recurrences or electrical induction of AV node reentrant tachycardia (AVNRT) by prolonging atrial and ventricular refractoriness and depressing conduction in the retrograde fast pathway. In patients with the Wolff-Parkinson-White syndrome, quinidine prolongs the ERP of the accessory pathway and, by so doing, can prevent reciprocating tachycardias and slow the ventricular response from conduction over the accessory pathway during atrial flutter or atrial fibrillation. Quinidine and other antiarrhythmic agents also can prevent recurrences of tachycardia by suppressing the "trigger" (i.e., the PAC or PVC that initiates a sustained tachycardia).

Quinidine successfully terminates atrial flutter or atrial fibrillation in 20 to 60 percent of patients, with higher success rates if the arrhythmia is of more recent onset and if the atria are not enlarged.[207] Before quinidine is administered to these patients, the ventricular response should be slowed sufficiently with digitalis, propranolol, or verapamil, because quinidine-induced slowing of the atrial flutter rate (e.g., from 300 to 230 beats/min), and its vagolytic effect on AV node conduction may convert a 2:1 AV response (two atrial impulses for each QRS complex, ventricular rate 150 beats/min) to a 1:1 AV response, with an *increase* in the ventricular rate (to 230 beats/min). If quinidine is going to be used to try to maintain sinus rhythm after elective cardioversion of patients with atrial fibrillation, it probably should be given for 1 to 2 days before planned cardioversion, because this regimen restores sinus rhythm in some patients (thus obviating the need for direct-current cardioversion) and helps maintain sinus rhythm once it is achieved. In addition, early toxicity or patient intolerance to the drug may be observed and changes made in drug therapy before attempting cardioversion. A meta-analysis of six studies testing the effects of quinidine versus control in maintaining sinus rhythm in patients with atrial fibrillation showed that quinidine-treated patients remained in sinus rhythm longer than did the control group but had an increased total mortality over the same period. This important conclusion needs to be verified in a controlled, prospective study.

Quinidine has prevented sudden death in some patients resuscitated after out-of-hospital cardiac arrest and may be combined with other antiarrhythmic agents for increased efficacy in suppressing ventricular tachyarrhythmias. It is important to stress that no published data from controlled, randomized studies indicate improved survival in quinidine-treated patients after myocardial infarction (see Fig. 23-5). Cardiac arrest can occur despite quinidine therapy.[208] [209] Because it crosses the placenta, quinidine can be used to treat arrhythmias in the fetus.

ADVERSE EFFECTS.

The most common adverse effects of chronic oral quinidine therapy are gastrointestinal and include nausea, vomiting, diarrhea, abdominal pain, and anorexia. Gastrointestinal side effects may be milder with the gluconate form. Central nervous system toxicity includes tinnitus, hearing loss, visual disturbances, confusion, delirium, and psychosis. *Cinchonism* is the term usually applied to these side effects. Allergic reactions may be manifested as rash, fever, immune-mediated thrombocytopenia, hemolytic anemia, and, rarely, anaphylaxis. Thrombocytopenia is due to the presence of antibodies to quinidine-platelet complexes, causing platelets to agglutinate and lyse. In patients receiving oral anticoagulants, quinidine may cause bleeding. Side effects may preclude long-term administration of quinidine in 30 to 40 percent of patients.

Quinidine can slow cardiac conduction, sometimes to the point of block, manifested as prolongation of the QRS duration or sinoatrial (SA) or AV node conduction disturbances. Quinidine-induced cardiac toxicity can be treated with molar sodium lactate. Quinidine can prolong the QT interval and cause torsades de pointes in 1 to 3 percent of patients.[178] [179] [180] [181] [182] [183] [184] [185] [186] [187] [188] [189]

Quinidine can produce syncope in 0.5 to 2.0 percent of patients, most often the result of a self-terminating episode of torsades de pointes (see Chaps. 22 and 25). Torsades de pointes may be due to the development of early afterdepolarizations, as noted earlier. Quinidine prolongs the QT interval in most patients, whether or not ventricular arrhythmias occur, but significant QT prolongation (QT interval of 500 to 600 msec) is often a characteristic of patients with quinidine syncope. Many of these patients are also receiving digitalis or diuretics; women are more susceptible than men.[210] Syncope is unrelated to plasma concentrations of quinidine or duration of therapy, although the majority of episodes occur within the first 2 to 4 days of therapy (often after conversion of atrial fibrillation to sinus rhythm). Hypokalemia often is a prominent feature. Therapy for quinidine syncope requires immediate discontinuation of the drug and avoidance of other drugs that have similar pharmacologic effects, such as disopyramide, because cross-sensitivity exists in some patients. Magnesium given intravenously (2 gm over 1 to 2 minutes, followed by an

infusion of 3 to 20 mg/min) is the initial drug treatment of choice. Atrial or ventricular pacing can be used to suppress the ventricular tachyarrhythmia and may act by suppressing early afterdepolarizations. For some patients, drugs that do not prolong the QT interval, such as lidocaine or phenytoin, can be tried. When pacing is not available, isoproterenol can be given *with caution.*

Drugs that induce hepatic enzyme production, such as phenobarbital and phenytoin, can shorten the duration of quinidine's action by increasing its rate of elimination. Quinidine may elevate serum digoxin and digitoxin concentrations by decreasing total-body clearance of digitoxin and by decreasing the clearance, volume of distribution, and affinity of tissue receptors for digoxin.

Procainamide

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

The cardiac actions of procainamide on automaticity, conduction, excitability, and membrane responsiveness resemble those of quinidine. Procainamide predominantly blocks the inactivated state of I_{Na} . It also blocks I_{Kr} and I_{KATP} .[211] Like quinidine, procainamide usually prolongs the ERP more than it prolongs the APD and thus prevents early responses from occurring, arising from less negative resting potentials that might conduct slowly or block and cause an arrhythmia. Compared with disopyramide and quinidine, procainamide exerts the least severe anticholinergic effects but does produce more local anesthetic effects than quinidine. It does not affect normal sinus node automaticity. In vitro, procainamide decreases abnormal automaticity, with less effect on triggered activity or catecholamine-enhanced normal automaticity.

The electrophysiological effects of NAPA,[212] procainamide's major metabolite, differ

from those of the parent compound. NAPA (10 to 40 mg/liter) does not suppress the rate of phase 4 diastolic depolarization of Purkinje fibers and does not alter resting membrane potential, action potential amplitude, or
max of phase 0 of the action potential of Purkinje fibers or ventricular muscle. However, NAPA, a K^+ channel blocker (I_{Kr}), exerts a Class III action and prolongs the APD of ventricular muscle and Purkinje fibers in a dose-dependent manner. Toxic doses produce early afterdepolarizations, triggered activity, and ventricular tachyarrhythmias, including torsades de pointes. Procainamide appears to exert greater electrophysiological effects than NAPA.

HEMODYNAMIC EFFECTS.

Procainamide can depress myocardial contractility in high doses. It does not produce alpha blockade but can result in peripheral vasodilation, possibly through antisympathetic effects on brain or spinal cord that can impair cardiovascular reflexes.[213]

PHARMACOKINETICS (see Table 23-1).

Oral administration produces peak plasma concentration in about 1 hour. Absorption may be reduced in the first week after myocardial infarction. Approximately 80 percent of oral procainamide is bioavailable, with 20 percent bound to serum proteins. The overall elimination half-life for procainamide is 3 to 5 hours, with 50 to 60 percent of the drug eliminated by the kidney and 10 to 30 percent eliminated by hepatic metabolism. Prolonged-release forms of procainamide given every 6 hours provides steady-state plasma levels of the drug equivalent to an equal total daily dose of short-acting procainamide given every 4 hours.

The drug is acetylated to NAPA, which is excreted almost exclusively by the kidneys. As renal function decreases and in patients with heart failure, procainamide levels--particularly NAPA levels--increase and, because of the risk of serious cardiotoxicity, need to be carefully monitored in such situations. NAPA has an elimination half-life of 7 to 8 hours but exceeds 10 hours if high doses of procainamide are used. Small amounts of NAPA are converted back to procainamide by deacetylation. Increased age, congestive heart failure, and reduced creatinine clearance lower the procainamide clearance and necessitate reduced dosage.

DOSAGE AND ADMINISTRATION (see Table 23-1).

Procainamide can be given by the oral, intravenous, or intramuscular route to achieve plasma concentrations in the range of 4 to 10 mg/ml that produce an antiarrhythmic effect. Occasionally, plasma concentrations exceeding 10 mg/ml have been required, but the probability of adverse effects at these higher plasma concentrations generally precludes long-term administration. Several IV regimens have been used to administer procainamide. Twenty-five to 50 mg can be given over a 1-minute period and then repeated every 5 minutes until the arrhythmia is controlled, hypotension results, or the QRS complex is prolonged more than 50 percent. Doses of 10 to 15 mg/kg at 50

mg/min are commonly used during EPS.[214] [215] Using this method, plasma concentration falls rapidly during the first 15 minutes after the loading dose, with parallel effects on refractoriness and conduction. A constant-rate IV infusion of procainamide can be given at a dose of 2 to 6 mg/min. The upper limits regarding total IV dose are flexible and range between 1000 and 2000 mg, depending on the patient's response.

Oral administration of procainamide requires a 3- to 4-hour dosing interval at a total daily dose of 2 to 6 gm, with a steady state reached within 1 day. When a loading dose is used, it should be twice the maintenance dose. Frequent dosing is required because of the short elimination half-life in normal subjects. For the prolonged-release forms of procainamide, dosing is at 6- to 12-hour intervals.[216] Although a longer half-life may be seen in some cardiac patients, allowing longer intervals between drug administration, this needs to be documented for the individual patient. Procainamide is well absorbed after intramuscular injection, with virtually 100 percent of the dose bioavailable.

INDICATIONS.

Procainamide is used to treat both supraventricular and ventricular arrhythmias in a manner comparable with that of quinidine.[217] Although both drugs have similar electrophysiological actions, either drug can effectively suppress a supraventricular or ventricular arrhythmia that is resistant to the other drug.

Procainamide can be used to convert atrial fibrillation of recent onset to sinus rhythm.[218] As with quinidine, prior treatment with digitalis, propranolol, or verapamil is recommended to prevent acceleration of the ventricular response after procainamide therapy. In patients with paroxysmal SVT, procainamide can inhibit the induction of sustained AVNRT as a result of selective depression of retrograde AV node conduction in the fast pathway. Procainamide can block conduction in the accessory pathway of patients with the Wolff-Parkinson-White syndrome and is particularly useful in patients with atrial fibrillation and a rapid ventricular response due to conduction over the accessory pathway. Whether it can be used intravenously to identify those patients who have a short anterograde ERP is not resolved. It can produce His-Purkinje block (see Fig. 23-5) and is sometimes administered during EPS to "stress" the His-Purkinje system in evaluating the need for a pacemaker. However, it should be used with caution in patients with evidence of His-Purkinje disease (bundle branch block) in whom a ventricular pacemaker is not readily available.

Procainamide is more effective than lidocaine in preventing the induction of VT by programmed stimulation[219] and in acutely terminating sustained VT. The electrophysiological response to procainamide given intravenously appears to predict the response to the drug given orally. Patients with ejection fractions greater than 40 percent whose VT is rendered noninducible by procainamide have a high

likelihood of responding to the drug given orally. High doses, 500 to 1000 mg orally

every 4 hours, resulting in a plasma concentration exceeding 10.0 mg/ml, may be necessary to suppress VT in some patients. Most consistently, procainamide slows the rate of the induced VT, a change correlated with the increase in QRS duration. Adding amiodarone to procainamide slows the VT cycle length further but increases the noninducibility success rate only slightly. Procainamide appears to preferentially affect the reentrant circuit of the VT compared with other areas of myocardium. The antiarrhythmic response to procainamide does not predict the response to NAPA.

ADVERSE EFFECTS.

Multiple adverse noncardiac effects have been reported with procainamide administration and include rashes, myalgias, digital vasculitis, and Raynaud's phenomenon. Fever and agranulocytosis may be due to hypersensitivity reactions, and white blood cell and differential blood cell counts should be performed at regular intervals. Gastrointestinal side effects are less frequent than with quinidine, and adverse central nervous system side effects are less frequent than with lidocaine. Procainamide can cause giddiness, psychosis, hallucinations, and depression. Toxic concentrations of procainamide can diminish myocardial performance and promote hypotension. A variety of conduction disturbances or ventricular tachyarrhythmias[220] can occur similar to those produced by quinidine, including prolonged QT syndrome and polymorphic VT. NAPA also can induce QT prolongation and torsades de pointes. In the absence of sinus node disease, procainamide does not adversely affect sinus node function. In patients with sinus dysfunction, procainamide tends to prolong corrected SNRT and can worsen symptoms in some patients who have the bradycardia-tachycardia syndrome. Procainamide does not increase the serum digoxin concentration.

Arthralgia, fever, pleuropericarditis, hepatomegaly, and hemorrhagic pericardial effusion with tamponade have been described in a systemic lupus erythematosus (SLE)-like syndrome related to procainamide administration. The syndrome can occur more frequently and earlier in patients who are "slow acetylators" of procainamide and is influenced by genetic factors.[170] The aromatic amino group on procainamide appears important for induction of SLE syndrome, because acetylating this amino group to form NAPA appears to block the SLE-inducing effect. Sixty to 70 percent of patients who receive procainamide on a chronic basis develop antinuclear antibodies, with clinical symptoms in 20 to 30 percent, but this is reversible when procainamide is stopped. When symptoms occur, SLE cell preparations are often positive. Positive serological tests are not necessarily a reason to discontinue drug therapy; however, the development of symptoms or a positive anti-DNA antibody is, except for patients whose life-threatening arrhythmia is controlled only by procainamide. Corticosteroid administration in these patients may eliminate the symptoms. In contrast to naturally occurring SLE, the brain and kidney are spared and there is no predilection for females.

Disopyramide

Disopyramide has been approved in the United States for oral but not IV administration to treat patients with ventricular arrhythmias.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Although structurally different from quinidine and procainamide, disopyramide produces similar electrophysiological effects in vitro. It causes use-dependent block of I_{Na} and non-use-dependent block of I_{Kr} .[199] Along with quinidine, low concentrations tend to prolong APD and induce early afterdepolarizations just as do higher concentrations.[190] Disopyramide also inhibits I_{KATP} .[211] It decreases the slope of phase 4 diastolic depolarization in Purkinje fibers, produces a rate-dependent depression of $_{max}$ of phase 0, prolongs the ERP more than it prolongs the APD, lengthens conduction time in normal and depolarized Purkinje fibers, and does not affect calcium-dependent action potentials, except possibly at very high concentrations, or suppress late potentials in the signal-averaged ECG. Disopyramide, like procainamide, reduces the differences in APD between normal and infarcted tissue by lengthening the action potential of normal cells more than it lengthens the action potential of cells from infarcted regions of the heart.

Stereochemical properties influence the effects of disopyramide. Racemic (clinically used) and (+)-disopyramide prolong canine Purkinje fiber action potential, whereas (-)-disopyramide shortens it. The (+) isomer exerts approximately three times more vagolytic effects than does the (-) isomer. Disopyramide, as a muscarinic blocker, can speed the sinus node discharge rate and shorten AV node conduction time and refractoriness when the nodes are restrained by cholinergic influences. Disopyramide also can slow the sinus node discharge rate by a direct action when given in high concentration and can significantly depress sinus node activity in patients with sinus node dysfunction. Disopyramide exerts greater anticholinergic effects than quinidine and does not appear to affect alpha- or beta-adrenoceptors.

Atrial and ventricular refractory periods increase, as do conduction time and refractoriness of the accessory pathway in patients with the Wolff-Parkinson-White syndrome. Disopyramide's effect on AV node conduction and refractoriness in vivo is not consistent. Disopyramide prolongs His-Purkinje conduction time, but infra-His block results infrequently. Disopyramide can be administered safely to patients who have first-degree AV block and narrow QRS complexes.

HEMODYNAMIC EFFECTS.

Disopyramide administered intravenously reduces systemic blood pressure and cardiac and stroke indexes and increases right atrial pressures and total peripheral resistance. Profound hemodynamic deterioration can occur, and patients who have abnormal ventricular function tolerate the negative inotropic effects of IV and oral disopyramide quite poorly. In these patients, the drug should be used with extreme caution or not at all.

PHARMACOKINETICS (see Table 23-1).

Disopyramide is 80 to 90 percent absorbed, with a mean elimination half-life of 8 to 9 hours in healthy volunteers but almost 10 hours in patients with heart failure and sometimes longer in some patients with ventricular arrhythmias. Total-body clearance and volume of distribution decrease in patients, and mean serum concentration is higher than that reported in normal subjects. Renal insufficiency prolongs the elimination time. Thus, in patients who have renal, hepatic, or cardiac insufficiency, loading and maintenance doses need to be reduced. Peak blood levels after oral administration result in 1 to 2 hours, and bioavailability exceeds 80 percent. The fraction of disopyramide bound to serum protein varies inversely with the total plasma concentration of the drug but may be more stable (30 to 40 percent) at clinically relevant concentrations of 3 mg/ml. It is bound to alpha$_1$ -acid glycoprotein and passes through the placenta. About half an oral dose is recovered unchanged in the urine, with about 30 percent as the mono-*N*-dealkylated metabolite. The metabolites appear to exert less effect than the parent compound. Erythromycin inhibits its metabolism.[221]

DOSAGE AND ADMINISTRATION (see Table 23-1).

Doses are generally 100 to 200 mg orally every 6 hours, with a range of 400 to 1200 mg/d. A controlled-release preparation can be given as 200 to 300 mg every 12 hours. The IV (investigational) dose is 1 to 2 mg/kg as an initial bolus given over 5 to 10 minutes, which may be followed by an infusion of 1 mg/kg/hr.

INDICATIONS.

Disopyramide appears comparable to quinidine and procainamide in reducing the frequency of

PVCs and effectively preventing recurrence of VT in selected patients. Disopyramide has been combined with other drugs such as mexiletine to treat patients who do not respond or only partially respond to one drug.

Disopyramide terminates and prevents recurrent episodes of paroxysmal SVT due to AV and AV nodal reentry. It prolongs the anterograde and retrograde refractory periods of the accessory pathway in patients with the Wolff-Parkinson-White syndrome, helps prevent recurrence of atrial fibrillation after successful cardioversion as effectively as quinidine, and may terminate atrial flutter. In treating patients with atrial fibrillation, particularly atrial flutter, the ventricular rate must be controlled before administering disopyramide, or the atrial rate may decrease sufficiently, aided by the vagolytic effects of disopyramide, to create 1:1 conduction during atrial flutter. Disopyramide may be useful in preventing inducible and spontaneous neurally mediated syncope.

ADVERSE EFFECTS.

Three categories of adverse effects follow disopyramide administration. The most common relates to the drug's potent parasympatholytic properties and includes urinary hesitancy or retention, constipation, blurred vision, closed-angle glaucoma, and dry mouth. Symptoms may be minimized by concomitant administration of pyridostigmine. Second, disopyramide can produce ventricular tachyarrhythmias that are commonly associated with QT prolongation and torsades de pointes. Some patients can have "cross-sensitivity" to both quinidine and disopyramide and develop torsades de pointes while receiving either drug. When drug-induced torsades de pointes occurs, agents that prolong the QT interval should be used very cautiously or not at all. Finally, disopyramide can reduce contractility of the normal ventricle, but the depression of ventricular function is much more pronounced in patients with preexisting ventricular failure. Occasionally, cardiovascular collapse can result.

CLASS IB ANTIARRHYTHMIC AGENTS

Lidocaine

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Lidocaine blocks I_{Na} , predominantly in the open or possibly inactivated state.[222] It has rapid onset and offset kinetics and does not affect normal sinus node antomaticity but does depress both normal and abnormal forms of automaticity, as well as early and late afterdepolarizations in Purkinje fibers in vitro. Lidocaine exhibits only a modest depressant effect on
and has no effect on maximal diastolic potential of normal muscle and specialized tissue in concentrations of about 1.5 mg/ml. However, faster rates of stimulation, reduced pH,[223] increased extracellular K^+ concentration, and reduced membrane potential--all changes that can result from ischemia--increase the ability of lidocaine to block I_{Na} . Lidocaine reduces the magnitude of the transient inward current responsible for some forms of afterdepolarization. Intracellular calcium activity may be reduced because of the sodium-calcium exchange mechanism. Lidocaine can convert areas of unidirectional block into bidirectional block during ischemia and prevent development of VF by preventing fragmentation of organized large wavefronts into heterogeneous wavelets. Lidocaine may be arrhythmogenic if it depresses conduction but not to the point of bidirectional block, but this does not appear to be an important clinical problem.

Lidocaine, except in very high concentrations, does *not* affect slow-channel-dependent action potentials despite its moderate suppression of the slow inward current. In fact, its depressant effect on electrical potentials from ischemic myocardium supports the notion that these ischemic potentials are depressed fast responses rather than slow responses. Lidocaine significantly reduces the APD and the ERP of Purkinje fibers and ventricular muscle owing to blocking of tetrodotoxin-sensitive sodium channels and decreasing entry of sodium into the cell. It has little effect on atrial fibers and does not affect conduction in accessory pathways. In some in vitro preparations, lidocaine can

improve conduction by hyperpolarizing tissues depolarized as a result of stretch or low external potassium concentration.

In vivo, lidocaine has a minimal effect on automaticity or conduction except in unusual circumstances. Patients with preexisting sinus node dysfunction, abnormal His-Purkinje conduction, or junctional or ventricular escape rhythms can develop depressed automaticity or conduction. Part of its effects may be to inhibit cardiac sympathetic nerve activity.

HEMODYNAMIC EFFECTS.

Clinically significant adverse hemodynamic effects are rarely noted at usual drug concentrations unless left ventricular function is severely impaired.

PHARMACOKINETICS (see Table 23-1).

Lidocaine is used only parenterally because oral administration results in extensive first-pass hepatic metabolism and unpredictable, low plasma levels with excessive metabolites that can produce toxicity. Hepatic metabolism of lidocaine depends greatly on hepatic blood flow, so clearance of this drug almost equals (and can be approximated by) measurements of this flow. Severe hepatic disease or reduced hepatic blood flow, as in heart failure or shock, can markedly decrease the rate of lidocaine metabolism. Beta-adrenoceptor blockers can decrease hepatic blood flow and increase lidocaine serum concentration. Prolonged infusion can reduce lidocaine clearance. Its elimination half-life averages 1 to 2 hours in normal subjects, more than 4 hours in patients after relatively uncomplicated myocardial infarction, more than 10 hours in patients after myocardial infarction complicated by cardiac failure, and even longer in the presence of cardiogenic shock. Maintenance doses should be reduced by one third to one half for patients with low cardiac output. Lidocaine is 50 to 80 percent protein bound and binds to alpha1-acid glycoprotein, which may increase in heart failure and myocardial infarction. Intravenous infusions should be discontinued as far in advance of EPS as possible to avoid residual lidocaine effects. A two-compartment model accurately predicts serum concentrations.[224]

DOSAGE AND ADMINISTRATION (see Table 23-1).

Although lidocaine can be given intramuscularly, the IV route is most commonly used (Fig. 23-12) . Intramuscular lidocaine is given in doses of 4 to 5 mg/kg (250 to 350 mg), resulting in effective serum levels at about 15 minutes and lasting for about 90 minutes. Intravenously, lidocaine is given as an initial bolus of 1 to 2 mg/kg of body weight at a rate of 20 to 50 mg/min, with a second injection of one half of the initial dose 20 to 40 minutes later. Patients treated with an initial bolus followed by a maintenance infusion may experience transient subtherapeutic plasma concentrations at 30 to 120 minutes after initiation of therapy. A second bolus of about 0.5 mg/kg without increasing the maintenance infusion rate reestablishes therapeutic serum concentrations.

If recurrence of arrhythmia appears after a steady state has been achieved (e.g., 6 to 10

hours after starting therapy), a similar bolus should be given and the maintenance infusion rate increased. Increasing the maintenance infusion rate alone without an additional bolus results in a very slow increase in plasma lidocaine concentrations, reaching a new plateau in over 6 hours (four elimination half-lives), and is therefore not recommended. Another recommended IV dosing is 1.5 mg/kg initially and 0.8 mg/kg at 8-minute intervals for three doses. Doses are reduced by about 50 percent for patients with heart failure.

If the initial bolus of lidocaine is ineffective, up to two more boluses of 1 mg/kg may be administered at 5-minute

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Figure 23-12 *A, top,* Plasma concentrations after a bolus of lidocaine, with the therapeutic range indicated by a dashed line. *Bottom,* The disposition of the drug in the body, with the larger box indicating the total volume of distribution and the smaller box the central compartment. The bolus initially produces therapeutic lidocaine concentrations in the small central compartment. Rapid distribution of the drug to the rest of the body produces subtherapeutic concentrations within 15 minutes. *B,* Lidocaine is administered by an initial bolus as in *A,* with a maintenance infusion begun just after the bolus. The maintenance infusion replaces drug eliminated from the body, but drug is also lost from the central compartment by distribution, which is more rapid than elimination. As a result, plasma concentrations decrease transiently. In this instance, lidocaine concentration is subtherapeutic between 30 and 70 minutes after initiation of therapy. *C,* Subtherapeutic lidocaine concentrations after an initial bolus (as in *B*) can be prevented by giving a second lidocaine bolus 10 minutes after the first. A maintenance infusion should be started after the second bolus rather than after the first, as shown here. This will prevent excessive lidocaine concentrations after the second bolus. *D,* An alternative method to produce therapeutic lidocaine concentrations rapidly. This illustration indicates plasma concentrations after the administration of a loading dose of lidocaine given over 10 minutes. A maintenance infusion is begun after the loading dose has been given. *(From Nattel S, Zipes DP: Clinical pharmacology of old and new antiarrhythmic drugs. Cardiovasc Clin 11:221, 1980.)*

intervals. Patients who require more than one bolus to achieve a therapeutic effect have arrhythmias that respond only to higher lidocaine plasma concentrations, and a greater maintenance dose may be necessary to sustain these higher concentrations. Patients requiring only a single initial bolus of lidocaine should probably receive a maintenance infusion of 30 mu/kg/min, whereas those requiring two or three boluses may need infusions at 40 to 50 mug/kg/min.

Loading doses also may be administered by rapid infusion, and a constant-rate IV infusion may be used to maintain an effective concentration. Maintenance infusion rates in the range of 1 to 4 mg/min produce steady-state plasma levels of 1 to 5 mg/ml in patients with uncomplicated myocardial infarction, but these rates must be reduced during heart failure or shock because of concomitant reduced hepatic blood flow. A loading dose of approximately 75 mg followed by an initial infusion rate of 5.33 mg/min that declines exponentially to 2 mg/min with a half-life of 25 minutes also has been recommended.

INDICATIONS.

Lidocaine demonstrates efficacy against ventricular arrhythmias of diverse etiology, the ability to achieve effective plasma concentrations rapidly, and a fairly wide toxic-to-therapeutic ratio with a low incidence of hemodynamic complications and other side effects. However, its first-pass hepatic effect precludes oral use, and it is generally ineffective against supraventricular arrhythmias. In patients with the Wolff-Parkinson-White syndrome, for whom the ERP of the accessory pathway is relatively short, lidocaine generally has no significant effect and may even accelerate the ventricular response during atrial fibrillation.

Lidocaine is used primarily for patients with acute myocardial infarction[225] [226] or recurrent ventricular tachyarrhythmias. It has been effective in patients resuscitated from out-of-hospital VF[227] and in patients after coronary revascularization.[228] Lidocaine prophylaxis in patients with acute myocardial infarction is controversial. However, most data suggest that the benefits of prophylactic lidocaine therapy in reducing the incidence of VF in hospitalized patients who have had acute myocardial infarction have not been clearly established.[225] [226] Drug-induced side effects and a possible increase in the risk of developing asystole led to the conclusion that prophylaxis is probably not indicated for all patients. Subcutaneous lidocaine given for local anesthesia during EPS can affect inducibility of ventricular arrhythmias by programmed electrical stimulation.[229]

ADVERSE EFFECTS.

The most commonly reported adverse effects of lidocaine are dose-related manifestations of central nervous system toxicity: dizziness, paresthesias, confusion, delirium, stupor, coma, and seizures.[230] Occasional sinus node depression and His-Purkinje block have been reported. In patients with atrial tachyarrhythmias, ventricular rate acceleration has been noted. Rarely, lidocaine can cause malignant hyperthermia.[231] Both lidocaine and procainamide can elevate defibrillation thresholds.[232]

Mexiletine

Mexiletine, a local anesthetic congener of lidocaine with anticonvulsant properties, is used for oral treatment of patients with symptomatic ventricular arrhythmias.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Mexiletine is similar to lidocaine in many of its electrophysiological actions. In vitro, mexiletine

shortens the APD and ERP of Purkinje fibers and, to a lesser extent, of ventricular muscle. It depresses
max of phase 0 by blocking I_{Na} , especially at faster rates, and depresses automaticity of Purkinje fibers but not of the normal sinus node. Its onset and offset kinetics are rapid. Hypoxia or ischemia can increase its effects on
max.

Mexiletine can result in severe bradycardia and abnormal SNRT in patients with sinus node disease but not in patients with a normal sinus node. It does not affect AV nodal conduction and can depress His-Purkinje conduction, but not greatly, unless conduction was abnormal initially. Mexiletine does not appear to affect the ERP of human atrial and ventricular muscle. The duration of the QT interval does not increase. Because of its rate-dependent effects, theoretically, mexiletine might be expected to suppress closely coupled rather than late-coupled ventricular extrasystoles or faster tachycardias.

HEMODYNAMIC EFFECTS.

Mexiletine exerts no major hemodynamic effects. It does not depress myocardial performance when given orally, although IV administration can produce hypotension.

PHARMACOKINETICS (see Table 23-1).

Mexiletine has been reported to be rapidly and almost completely absorbed after oral ingestion by volunteers, with peak plasma concentrations attained in 2 to 4 hours. Elimination half-life in healthy subjects is approximately 10 hours, and in patients after myocardial infarction it is 17 hours. Therapeutic plasma levels of 1 to 2 mg/ml are maintained by oral doses of 200 to 300 mg every 6 to 8 hours. Absorption with less than a 10 percent first-pass hepatic effect occurs in the upper small intestine and is delayed and incomplete in patients who have myocardial infarction and in patients receiving narcotic analgesics, antacids, or atropine-like drugs that retard gastric emptying. Bioavailability of orally administered mexiletine is approximately 90 percent, and about 70 percent of the drug is protein bound. The apparent volume of distribution is large, reflecting extensive tissue uptake. Normally, mexiletine is eliminated metabolically by the liver, with less than 10 percent excreted unchanged in the urine. Doses probably should be reduced in patients with cirrhosis and those with left ventricular failure. Renal clearance of mexiletine decreases as urinary pH increases. Known metabolites exert no electrophysiological effects. Metabolism can be increased by phenytoin, phenobarbital, and rifampin and reduced by cimetidine. It is influenced by the genotype for the CYP206 gene.[159]

DOSAGE AND ADMINISTRATION (see Table 23-1).

The recommended starting dose is 200 mg orally every 8 hours when rapid arrhythmia control is not essential. Doses may be increased or decreased by 50 to 100 mg every 2 to 3 days and are better tolerated when given with food. Total daily dose should not exceed 1200 mg. In some patients, administration every 12 hours can be effective. For

rapid loading, 400 mg followed in 8 hours by a 200-mg dose is suggested.

INDICATIONS.

Mexiletine is an effective antiarrhythmic agent for treating patients with both acute and chronic ventricular tachyarrhythmias but not with SVTs. Success rates vary from 6 to 60 percent and can be increased in some patients if mexiletine is combined with other drugs such as procainamide, beta blockers, quinidine, disopyramide, or amiodarone. Most studies show no clear superiority of mexiletine over other Class I agents. In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) investigation, sotalol was more effective than mexiletine.[11] [20] It may be very useful in children with congenital heart disease and serious ventricular arrhythmias. In treating patients with a long QT interval, mexiletine may be safer than drugs such as quinidine that increase the QT interval further. Limited experience in treating subsets of patients with long QT syndrome (LQT3, which is related to the SCN5A gene for the cardiac sodium channel) suggests a beneficial role. It does not appear to alter the prognosis of patients with inducible ventricular tachyarrhythmias after myocardial infarction. It may be effectively combined with propafenone.[233] [234]

ADVERSE EFFECTS.

Thirty to 40 percent of patients may require a change in dose or discontinuation of mexiletine therapy as a result of adverse effects, including tremor, dysarthria, dizziness, paresthesia, diplopia, nystagmus, mental confusion, anxiety, nausea, vomiting, and dyspepsia. Cardiovascular side effects are seen most often after IV dosing and include hypotension, bradycardia, and exacerbation of arrhythmia. Adverse effects of mexiletine appear to be dose related, and toxic effects occur at plasma concentrations only slightly higher than therapeutic levels. Therefore, effective use of this antiarrhythmic drug requires careful titration of dose and monitoring of plasma concentration. Lidocaine should be avoided, or dose reduced, in patients also receiving lidocaine congeners like mexiletine.[235]

Phenytoin

Phenytoin was employed originally to treat seizure disorders. Its value as an antiarrhythmic agent remains limited.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Therapeutic concentrations of phenytoin do not alter the discharge rate of rabbit sinus node tissue but may depress normal automaticity in cardiac Purkinje fibers in vitro or spontaneous ventricular rate in vivo. Phenytoin effectively abolishes abnormal automaticity caused by digitalis-induced delayed afterdepolarizations in cardiac Purkinje fibers and suppresses certain digitalis-induced arrhythmias in humans. Similar to lidocaine, phenytoin abbreviates Purkinje fiber APD more than it shortens the ERP, thus increasing the ratio of ERP to APD. Phenytoin can cause depolarized cells to repolarize by increasing potassium conductance and, in so doing, may increase the

max of phase 0 in Purkinje fibers, particularly when these are depressed by digitalis.

The rate of rise of action potentials initiated early in the relative refractory period is increased, as is membrane responsiveness, possibly reducing the chance for impaired conduction and block. Phenytoin may slow conduction at high potassium concentrations but minimally affects sinus discharge rate and AV conduction in humans. As with other Class IB agents, phenytoin has little effect on
max in normally polarized fibers at slow rates and shows use-dependence and rapid kinetics for onset and termination of effects.

Some of phenytoin's antiarrhythmic effects may be neurally mediated, because phenytoin may reduce the increase in impulse traffic in cardiac sympathetic nerves caused by ouabain toxicity and protect against some arrhythmias when it is injected into the central nervous system. The drug also may modulate vagal efferent activity centrally. It has no peripheral cholinergic or beta-adrenergic blocking actions. Phenytoin exerts minimal hemodynamic effects.

PHARMACOKINETICS (see Table 23-1).

The pharmacokinetics of phenytoin are less than ideal. Absorption after oral administration is incomplete and varies with the brand of drug. Plasma concentrations peak 8 to 12 hours after an oral dose. Ninety percent of the drug is protein bound. Phenytoin has limited solubility at physiological pH, and intramuscular administration is associated with pain, muscle necrosis, sterile abscesses, and variable absorption. Therapeutic serum concentrations of phenytoin (10 to 20 mg/ml) are similar for treating both cardiac arrhythmias and epilepsy. Lower concentrations can suppress certain digitalis-induced arrhythmias or other arrhythmias when decreased plasma protein binding occurs (as in uremia), because a larger fraction of drug is free and pharmacologically active.

METABOLISM.

Over 90 percent of a dose is hydroxylated in the liver to presumably inactive compounds. Some families have a genetically determined inability to hydroxylate phenytoin, whereas others have a higher than usual capability for hydroxylation. Elimination half-time is about 24 hours and can be slowed in the presence of liver disease or when phenytoin is administered concomitantly with drugs such as phenylbutazone, dicumarol, isoniazid, chloramphenicol, and phenothiazines that compete with phenytoin for hepatic enzymes (see Table 23-3). Because of the large number of medications that can increase or decrease phenytoin levels during chronic therapy, phenytoin plasma concentration should be determined frequently when changes are made in other medications. In some patients, maintenance dose regimens of phenytoin are difficult to predict because the enzyme system that metabolizes phenytoin becomes saturated at plasma concentrations within the therapeutic range. The half-life then increases with increasing phenytoin load. Above the saturation point, phenytoin elimination follows zero-order kinetics, so only a fixed amount of drug is

eliminated per unit of time. These concentration-dependent

kinetics for elimination can cause unexpected toxicity, because disproportionately large changes in plasma concentration can follow dose increases.

DOSAGE AND ADMINISTRATION (see Table 23-1).

To achieve therapeutic plasma concentration rapidly, 100 mg of phenytoin should be administered intravenously every 5 minutes until the arrhythmia is controlled, about 1 gm has been given, or adverse side effects result. Generally, 700 to 1000 mg will control the arrhythmia. A large central vein should be used to avoid pain and development of phlebitis produced by the extremely alkalotic (pH 11.0) vehicle in which phenytoin is dissolved. Orally, phenytoin is given as a loading dose of approximately 1000 mg the first day, 500 mg on the second and third days, and 300 to 400 mg daily thereafter. All maintenance doses can be given once or twice daily, depending on the brand, because of the long half-life of elimination.

INDICATIONS.

Phenytoin has been used successfully to treat atrial and ventricular arrhythmias caused by digitalis toxicity but is much less effective in treating ventricular arrhythmias in patients with ischemic heart disease or with atrial arrhythmias not due to digitalis toxicity. The drug has been somewhat more successful in treating ventricular arrhythmias associated with general anesthesia and cardiac surgery. It can be tried in patients with the long QT syndrome.

ADVERSE EFFECTS.

The most common manifestations of phenytoin toxicity are central nervous system effects of nystagmus, ataxia, drowsiness, stupor, and coma. Progression of such symptoms can be correlated with increases in plasma drug concentration. Neurological signs, such as nystagmus on lateral gaze, develop at plasma drug levels of about 20 mg/ml. Nausea, epigastric pain, and anorexia are also relatively common effects of phenytoin. Long-term administration can result in hyperglycemia, hypocalcemia, rashes, megaloblastic anemia, gingival hypertrophy, lymph node hyperplasia (a syndrome resembling malignant lymphoma), peripheral neuropathy, pneumonitis,[236] and drug-induced systemic lupus erythematosus (SLE). Birth defects also can result.[237] [238]

CLASS IC ANTIARRHYTHMIC AGENTS

Flecainide

Flecainide is approved by the U.S. Food and Drug Administration (FDA) to treat patients

with life-threatening ventricular arrhythmias as well as a variety of supraventricular arrhythmias.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Flecainide exhibits marked use-dependent depressant effects on the rapid sodium channel,[239] decreasing
max with slow onset and offset kinetics. Drug dissociation from the sodium channel is very slow, with time constants of 10 to 30 seconds (compared with 4 to 8 seconds for quinidine and less than 1 second for lidocaine). Thus, marked drug effects can occur at physiological heart rates. Flecainide shortens the duration of Purkinje fiber action potential but prolongs it in ventricular muscle, actions that, depending on the circumstances, could enhance or reduce electrical heterogeneity and create or suppress arrhythmias. Flecainide profoundly slows conduction in all cardiac fibers and, in high concentrations, inhibits the slow Ca^{2+} channel. Conduction time in the atria, ventricles, AV node, and His-Purkinje system is prolonged. It can terminate experimental atrial reentry by causing conduction block in the reentry pathway[240] [241] [242] and eliminate atrial tachycardia by producing exit block from the focus.[243] Flecainide also can promote reentry.[244] Minimal increases in atrial or ventricular refractoriness or in the QT interval result. Anterograde and retrograde refractoriness in accessory pathways can increase significantly in a use-dependent fashion.[245] Normal sinus node function remains unchanged, but abnormal sinus node discharge may be depressed. Pacing thresholds are increased.

HEMODYNAMIC EFFECTS.

Flecainide depresses cardiac performance, particularly in patients with compromised myocardial function. Left ventricular ejection fraction decreases after oral (single dose of 200 to 250 mg) or IV (1 mg) administration. Caution is warranted, particularly in patients with a history of heart failure. Flecainide should be used cautiously, if at all, in patients with severely compromised cardiac function.

PHARMACOKINETICS (see Table 23-1).

Flecainide is at least 90 percent absorbed, with peak plasma concentrations in 3 to 4 hours. Elimination half-life in patients with ventricular arrhythmias is 20 hours, 85 percent of the drug being excreted unchanged or as an inactive metabolite in urine. Two major metabolites exert fewer effects than the parent drug. Rate of elimination is slower in patients with renal disease and heart failure, and doses should be reduced in these situations. Therapeutic plasma concentrations range from 0.2 to 1.0 mg/ml. About 40 percent of the drug is protein bound. Increases in serum concentrations of digoxin (15 to 25 percent) and propranolol (30 percent) result during coadministration with flecainide. Propranolol, quinidine, and amiodarone may increase flecainide serum concentrations. Five to 7 days of dosing may be required to reach steady state in some patients.

DOSAGE AND ADMINISTRATION (see Table 23-1).

The starting dose is 100 mg every 12 hours, increased in increments of 50 mg twice daily, no sooner than every 3 to 4 days, until efficacy is achieved, an adverse effect is noted, or to a maximum of 400 mg/d. Cardiac rhythm and QRS duration should be monitored.

INDICATIONS.

Flecainide is indicated for the treatment of life-threatening ventricular tachyarrhythmias, SVTs, and paroxysmal atrial fibrillation.[246] [247] [248] Therapy should begin in the hospital while the ECG is being monitored because of the high incidence of proarrhythmic events (see later). Serum concentration should not exceed 1.0 mg/ml. Flecainide is particularly effective, more so than quinidine, in almost totally suppressing PVCs and short runs of nonsustained VT, although the importance of such a response on the subsequent outcome of the patient has not been established. As with other Class I antiarrhythmic drugs, there are no data from controlled studies to indicate that the drug favorably affects survival or sudden cardiac death, and data from CAST (see later) indicate an increased mortality in patients with coronary artery disease. Flecainide prevents electrical induction of ventricular tachyarrhythmias in a small percentage of patients (10 to 30 percent) and eliminates recurrence of life-threatening ventricular tachyarrhythmias in about 40 percent. However, it produces a use-dependent prolongation of VT cycle length that improves hemodynamic tolerance.[247]

Flecainide is also very useful in a variety of SVTs[249] [250] [251] [252] such as atrial flutter[253] and atrial fibrillation,[249] [254] [255] [256] in Wolff-Parkinson-White syndrome,[257] and for atrial tachycardia.[258] Isoproterenol can reverse some of these effects. Flecainide may be more effective than procainamide in the acute termination of atrial fibrillation.[249] It is important to slow the ventricular rate before treating with flecainide to avoid 1:1 conduction.[259] Flecainide has been used to treat fetal arrhythmias[260] [261] and arrhythmias in children.[262] It may increase defibrillation thresholds.[263]

ADVERSE EFFECTS.

Proarrhythmic effects are some of the most important adverse effects of flecainide. Its marked slowing of conduction precludes its use in patients with second-degree AV block without a pacemaker and warrants cautious administration in patients with intraventricular conduction disorders. Aggravation of existing ventricular arrhythmias or onset of new ventricular arrhythmias can occur in 5 to 30 percent of patients, the increased percentage in patients with preexisting sustained VT, cardiac decompensation, and higher doses of the drug. Failure of the flecainide-related arrhythmia to respond to therapy, including electrical cardioversion-defibrillation, may result in mortality as high as 10 percent in patients who develop proarrhythmic events. Negative inotropic effects can cause or worsen heart failure. Patients with sinus node dysfunction may experience sinus arrest, and those with pacemakers may develop an increase in pacing threshold. In CAST, patients treated with flecainide had 5.1 percent mortality or nonfatal cardiac arrest compared with 2.3 percent in the

placebo group over 10 months.[18] [193] Mortality was highest in those with non-Q-wave infarction, frequent PVCs, and faster heart rates, raising the possibility of drug interaction with ischemia and electrical instability.[17] [264] [265] Exercise can amplify the conduction slowing in the ventricle produced by flecainide and in some cases can precipitate a proarrhythmic response. Therefore, exercise testing has been recommended to screen for proarrhythmia. Central nervous system complaints, including confusion and irritability, represent the most frequent noncardiac adverse effect. The safety of flecainide during pregnancy has not been determined. It is concentrated in breast milk to levels 2.5- to 4-fold higher than plasma.

Propafenone

Propafenone has been approved by the FDA for treatment of patients with life-threatening ventricular tachyarrhythmias.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Propafenone blocks the fast sodium current in a use-dependent manner, as well as at rest, in Purkinje fibers and to a lesser degree in ventricular muscle. Use-dependent effects contribute to its ability to terminate experimental atrial fibrillation.[266] The dissociation constant is slow, like that of flecainide. Effects are greater in ischemic than normal tissue and at reduced membrane potentials. Propafenone decreases excitability and suppresses spontaneous automaticity and triggered activity. It terminates experimental VT by producing conduction block or by collision of the impulse with an echo wave.[267] Effects on APD are variable in that guinea pig APD is shortened, whereas rabbit APD is prolonged. Propafenone is a weak blocker of I_{Kr} .[268] Although ventricular refractoriness increases, conduction slowing is the major effect. The active metabolites of propafenone exert important actions, reducing
max, action potential amplitude, and duration in canine Purkinje fibers. In contrast to propafenone and the *N*-depropylpropafenone metabolite, the 5-hydroxypropafenone metabolite suppressed VT in the postinfarct canine model. Propafenone depresses sinus node automaticity. In patients, the AH, HV, PR, and QRS intervals increase, as do refractory periods of the atria, ventricles, AV node, and accessory pathways. The corrected QT interval increases only as a function of increased QRS duration.

HEMODYNAMIC EFFECTS.

Propafenone and 5-hydroxypropafenone exhibit negative inotropic properties at high concentrations in vitro, and large doses depress left ventricular function in vivo.[269] In patients with ejection fractions exceeding 40 percent, the negative inotropic effects are well tolerated, but patients with preexisting left ventricular dysfunction and congestive heart failure may have symptomatic worsening of their hemodynamic status.

PHARMACOKINETICS (see Table 23-1).

With more than 95 percent of the drug absorbed, propafenone's maximum plasma concentration occurs in 2 to 3 hours. Systemic bioavailability is dose dependent and ranges from 3 to 40 percent due to variable presystemic clearance. Bioavailability increases as the dose increases, and plasma concentration is therefore nonlinear. A threefold increase in dosage (300 to 900 mg/d) results in a tenfold increase in plasma concentration, presumably due to saturation of hepatic metabolic mechanisms. Propafenone is 97 percent bound to alpha1-acid glycoprotein, with an elimination half-life of 5 to 8 hours. Maximum therapeutic effects occur at serum concentrations of 0.2 to 1.5 mg/ml. Marked interpatient variability of pharmacokinetics and pharmacodynamics may be due to genetically determined differences in metabolism. About 93 percent of the population are extensive metabolizers and exhibit shorter elimination half-lives (5 to 6 hours), lower plasma concentrations of the parent compound, and higher concentrations of metabolites. Poor metabolizers, due to diminished capacity of the microsomal cytochrome P450 enzyme system in the liver (see earlier), exhibit an elimination half-life of 15 to 20 hours for the parent compound and virtually no 5-hydroxypropafenone.[159] Low-dose quinidine may inhibit the metabolism of propafenone, and stereoselectivity may be important with the (+) enantiomer, providing nonspecific beta-adrenergic receptor blockade 2.5 to 5 percent the potency of propranolol. Poor metabolizers have a greater beta-adrenergic receptor blocking effect than extensive metabolizers. Because plasma propafenone concentrations may be 50 times or more propranolol levels, these beta-blocking properties may be relevant.[270] Propafenone also blocks the slow calcium channel to a degree about 100 times less than verapamil.

DOSAGE AND ADMINISTRATION (see Table 23-1).

Most patients respond to oral doses of 150 to 300 mg every 8 hours, not exceeding 1200 mg/d. Doses are similar for patients of both phenotypes. Concomitant food administration increases bioavailability, as does hepatic dysfunction. No good correlation between plasma propafenone concentration and arrhythmia suppression has been shown. Doses should not be increased more often than every 3 to 4 days. Propafenone increases plasma concentrations of warfarin, digoxin, and metoprolol.

INDICATIONS.

Propafenone is indicated for the treatment of SVTs, paroxysmal atrial fibrillation, and life-threatening ventricular tachyarrhythmias and effectively suppresses spontaneous PVCs[271] and nonsustained and sustained VT.[272] Propafenone has also been approved for use in patients with atrial tachycardia,[272] [273] AV node reentry, AV reentry,[274] and atrial flutter[253] or fibrillation.[271] [275] [276] [277] [278] Acute termination of atrial fibrillation episodes was effected with a single 600-mg oral dose of propafenone in 76 percent of patients given the drug, compared with 37 percent of those given placebo.[279] It has been used effectively in the pediatric age group.[280] [281] [282] [283] Propafenone increases the pacing threshold[284] [285] but minimally affects the defibrillation threshold. Spontaneous sinus rate during exercise is reduced. Propafenone use is associated with

a higher mortality in cardiac arrest survivors compared with an implantable defibrillator.[286] Sotalol was more effective than propafenone in the ESVEM trial.[11] Propafenone has been combined effectively with mexiletine.[233] [234]

ADVERSE EFFECTS.

Minor noncardiac effects occur in about 15 percent of patients, with dizziness, disturbances in taste, and blurred vision the most common and gastrointestinal side effects next. Exacerbation of bronchospastic lung disease can occur due to mild beta-blocking effects. Cardiovascular side effects occur in 10 to 15 percent of patients, including conduction abnormalities such as AV block, sinus node depression, and worsening of heart failure. Proarrhythmic responses, which occur more often in patients with a history of sustained VT and decreased ejection fractions, appear less commonly than with flecainide and may be in the range of 5 percent. The applicability of data from CAST about flecainide to propafenone is not clear, but limiting propafenone's application in a manner similar to other Class IC drugs seems prudent at present until more information is available. Its beta-blocking actions may make it different, however.[270] The safety of propafenone administration during pregnancy has not been established.

Moricizine (Ethmozine)

Moricizine is a phenothiazine derivative used for treatment of patients with ventricular tachyarrhythmias. It was formerly discussed as a Class IB antiarrhythmic drug because it shortens Purkinje fiber action potential. However, the intensity of its effect on the Na^+ channel is more like

that of a Class IA antiarrhythmic drug, whereas the time constants for onset and offset resemble those of Class IC agents.

ELECTROPHYSIOLOGICAL ACTIONS.

Moricizine decreases I_{Na} predominantly in the inactivated state, with a resultant decrease in
max of phase 0, action potential amplitude, and APD in canine cardiac Purkinje fibers (see Tables 23-4 , 23-6 , and 23-7).[287] Maximum diastolic potential is not changed. Moricizine blocks $I_{Ca\text{-}L}$ and I_K and prolongs AV node and His-Purkinje conduction times and QRS duration. The JT interval shortens slightly, whereas the QTc is prolonged 5 percent owing to QRS prolongation. Ventricular refractoriness is prolonged slightly, with no consistent atrial change. No alterations in sinus node automaticity result. In vitro, moricizine slows spontaneous automaticity in normal Purkinje fibers and suppresses abnormal automaticity arising from depolarized fibers and delayed afterdepolarizations. It terminates experimental flutter by causing block in the area of slow conduction.[288] Moricizine decreases RR interval variability, which does not predict mortality.[289]

Moricizine minimally raises the defibrillation threshold.[290]

HEMODYNAMIC EFFECTS.

Moricizine exerts minimal effects on cardiac performance in patients with impaired left ventricular function. Exercise tolerance and ejection fraction do not change. A small but consistent increase in blood pressure and heart rate results. An occasional patient with significant left ventricular dysfunction may have worsening of heart failure.

PHARMACOKINETICS (see Table 23-1).

After oral ingestion, moricizine undergoes extensive first-pass metabolism, resulting in absolute bioavailability of 35 to 40 percent. Peak plasma concentrations are reached in 0.5 to 2 hours and later if the drug is taken after meals. Extent of absorption is not changed. Proportionality exists between dose and plasma concentrations in the therapeutic range. Protein binding is 95 percent to alpha1-acid glycoprotein and albumin. Antiarrhythmic and electrophysiological actions do not relate to plasma concentrations or to any identified metabolite, of which there are more than 20. At least two metabolites are pharmacologically active but are in small concentrations. Moricizine induces its own metabolism,[291] and plasma concentrations decrease with multiple dosing. Plasma elimination half-life is 1.5 to 3.5 hours, with slightly more than half the drug excreted in the feces and slightly less than half excreted in the urine.

DOSAGE AND ADMINISTRATION (see Table 23-1).

The usual adult dose is 600 to 900 mg/d, given every 8 hours in three equally divided doses. Increments of 150 mg/d at 3-day intervals can be tried. Some patients may be treated every 12 hours. Dose reductions in patients with hepatic or neural disease, AV conduction disturbances, or sick sinus syndrome without a pacemaker and with significant congestive heart failure should be observed.

INDICATIONS.

Moricizine is indicated for prevention of life-threatening ventricular arrhythmias and exerts an efficacy that is about comparable with those of quinidine and disopyramide.[292] It is less effective in preventing VT initiation at EPS and may have proarrhythmic effects.[293] [294] [295] It caused an increase in mortality compared with placebo during initial treatment of patients who had symptomatic or minimally symptomatic ventricular arrhythmias after myocardial infarction.[17] [194] [195] Risk was greater in patients taking diuretics.[194]

ADVERSE EFFECTS.

Usually the drug is well tolerated. Noncardiac adverse effects primarily involve the nervous system and include tremor, mood changes, headache, vertigo, nystagmus, and dizziness. Gastrointestinal side effects include nausea, vomiting, and diarrhea.

Worsening of congestive heart failure is uncommon but can happen. Proarrhythmic effects have been reported in 3 to 15 percent of patients[296] [297] and appear to be more common in patients with severe ventricular arrhythmias. Advancing age increases the susceptibility to adverse effects.[298] Moricizine appears to be relatively safe to use during pregnancy and is present in small amounts in breast milk.

CLASS II ANTIARRHYTHMIC AGENTS

Beta-Adrenoceptor Blocking Agents

Although many beta-adrenoceptor blocking drugs have been approved for use in the United States (see Table 23-8), acebutolol (PVCs), esmolol (SVT), metoprolol (post-myocardial infarction), atenolol (post-myocardial infarction), propranolol (post-myocardial infarction, SVT, VT), and timolol (post-myocardial infarction) have been approved to treat arrhythmias or to prevent sudden death after myocardial infarction.[163] It is generally considered that no beta blocker offers distinct advantages over the others and that, when titrated to the proper dose, all can be used effectively to treat cardiac arrhythmias, hypertension, or other disorders. However, differences in pharmacokinetic or pharmacodynamic properties that confer safety, reduce adverse effects, or affect dosing intervals or drug interactions influence the choice of agent. Also, some beta blockers such as sotalol exert unique actions.

Beta receptors can be separated into those that affect predominantly the heart ($beta_1$) and those that affect predominantly

TABLE 23-8 -- PHARMACODYNAMIC PROPERTIES OF BETA-ADRENOCEPTOR BLOCKING DRUGS

DRUG	$BETA_2$ BLOCKADE POTENCY RATIO (PROPRANOLOL = 1.0)	RELATIVE $BETA_2$ SELECTIVITY	INTRINSIC SYMPATHOMIMETIC ACTIVITY	CLASS I ACTIVITY
Acebutolol	0.3	+	+	+
Atenolol	1.0	++	0	0
Bevantolol	0.3	++	0	0
Bisoprolol	10.3	++	0	0
Bucindolol*		0	+	0
Carteolol	10.0	0	+	0
Carvedilol	10.0	0	0	++
Celiprolol	9.4	+	+	0
Dilevalol§	1.0	0	+	0

Esmolol	0.02	++	0	0
Labetalol[*]	0.3	0	+	0
Metoprolol	1.0	++	0	0
Nadolol	1.0	0	0	0
Oxprenolol	0.5-1.0	0	+	+
Penbutolol	1.0	0	+	0
Pindolol	6.0	0	++	+
Propranolol	1.0	0	0	++
Sotalol	0.3	0	0	0
Timolol	6.0	0	0	0

Adapted from Duran A, Myerburg RJ: In Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL (eds): Cardiovascular Pharmacology and Therapeutics. New York, Churchill Livingstone, 1994, pp 665-674.

*Bucindolol and labetalol have additional $beta_1$ -adrenergic blocking activity and direct vasodilatory actions ($beta_2$ -agonism).

Carvedilol has additional $beta_1$ -adrenergic blocking activity without peripheral $beta_2$ -agonism.

Celiprolol may have additional peripheral $beta_2$ -adrenergic blocking activity at high doses.
§Dilevalol is an isomer of labetalol with peripheral $beta_2$ -agonism but no $beta_1$ -blocking activity.

Sotalol has an additional type of antiarrhythmic activity.

blood vessels and the bronchi ($beta_2$). In low doses, selective beta blockers can block $beta_1$ receptors more than they block $beta_2$ receptors and might be preferable for treating patients with pulmonary or peripheral vascular diseases. In high doses, the selective $beta_1$ blockers also block $beta_2$ receptors.

Some beta blockers exert intrinsic sympathomimetic activity; that is, they slightly activate the beta receptor. These drugs appear to be as efficacious as beta blockers without intrinsic sympathomimetic actions and may cause less slowing of heart rate at rest and less prolongation of AV nodal conduction time. They have been shown to induce less depression of left ventricular function than beta blockers without intrinsic sympathomimetic activity. Only nonselective beta blockers without intrinsic sympathomimetic activity have been demonstrated to reduce mortality in patients after

myocardial infarction[299] (Fig. 23-13) .

The following discussion will concentrate on the use of propranolol as a prototypical antiarrhythmic agent.

ELECTROPHYSIOLOGICAL ACTIONS.

Beta blockers exert an electrophysiological action by competitively inhibiting catecholamine binding at beta-adrenoceptor sites, an effect almost entirely due to the (-)-levorotatory stereoisomer, or by their quinidine-like or direct membrane-stabilizing action (see Tables 23-4 , 23-6 , and 23-7). The latter is a local anesthetic effect that depresses I_{Na} and membrane responsiveness in cardiac Purkinje fibers, occurs at concentrations generally 10 times that necessary to produce beta blockade, and most likely plays an insignificant antiarrhythmic role. Thus, major effects of beta blockers will take place in cells most actively stimulated by adrenergic actions. At beta-blocking concentrations, propranolol slows spontaneous automaticity in the sinus node or in Purkinje fibers that are being stimulated by adrenergic tone, producing

Figure 23-13 Metaanalytical data from randomized clinical trials of antiarrhythmic drugs in survivors of acute myocardial infarction. The relative risk is compared with placebo therapy (mean and 95 percent confidence interval) for death during therapy with various electrophysiological classes of compounds. Class I agents, particularly IC, and sotalol increase mortality, whereas beta blockers and amiodarone decrease mortality. Numbers under each drug class refer to number of patients involved in the trials. *(Modified from Teo KK, Yusuf S: In Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL [eds]: Cardiovascular Pharmacology and Therapeutics. New York, Churchill Livingstone, 1994, pp 631-643, and Waldo AL, Camm AJ, deRuyter H, et al: Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction: The SWORD Investigators. Survival With Oral d-Sotalol. Lancet 348:7, 1996.)*

block of I_f (see Chap. 22). Beta blockers also block $I_{Ca\text{-}L}$ stimulated by beta agonists. In the absence of adrenergic stimulation, only high concentrations of propranolol slow normal automaticity in Purkinje fibers, probably by a direct membrane action.

Concentrations that cause beta-receptor blockade but no local anesthetic effects do not alter the normal resting membrane potential, maximum diastolic potential amplitude, max, repolarization, or refractoriness of atrial, Purkinje, or ventricular muscle cells when these tissues are not being superfused with catecholamines. However, in the presence of isoproterenol, a pure beta-receptor stimulator, beta blockers reverse isoproterenol's accelerating effects on repolarization; in the presence of norepinephrine, beta blockade permits unopposed alpha-adrenoceptor stimulation to prolong APD in Purkinje fibers. Propranolol (2×10^{-6} M) reduces the amplitude of digitalis-induced delayed afterdepolarizations and suppresses triggered activity in Purkinje fibers.

Propranolol upregulates beta adrenoceptors in part by externalizing receptors from a light vesicle fraction to the sarcolemma. Beta blockers do not blunt heart rate variability

in dogs after myocardial infarction.[44]

Concentrations exceeding 3 mg/ml are required to depress max action potential amplitude, membrane responsiveness, and conduction in normal atrial, ventricular, and Purkinje fibers without altering resting membrane potential. These effects probably result from depression of I_{Na} . Propranolol shortens the APD of Purkinje fibers and, to a lesser extent, of atrial and ventricular muscle fibers. Long-term administration of propranolol may lengthen APD. Similar to the effects of lidocaine, acceleration of repolarization of Purkinje fibers is most marked in areas of the ventricular conduction system in which the APD is greatest. The reduction in refractory period is not as great as the reduction in APD (ERP/APD>1.0). At least one beta blocker, sotalol, markedly increases the time course of repolarization in Purkinje fibers and ventricular muscles. Smaller doses of propranolol are required to prevent sympathetically induced shortening of ventricular refractoriness than are required to prevent sympathetically induced sinus acceleration.

Propranolol slows the sinus discharge rate in humans by 10 to 20 percent, whereas severe bradycardia occasionally results if the heart is particularly dependent on sympathetic tone or if sinus node dysfunction is present. The slowing is probably due to beta blockade because *d*-propranolol does not significantly slow the sinus discharge rate in doses comparable to the racemic mixture. The PR interval lengthens, as do AV node conduction time and effective and functional refractory periods (if the heart rate is maintained constant), but refractoriness and conduction in the normal His-Purkinje system remain unchanged even after high doses of propranolol. Therefore, therapeutic doses of propranolol in humans do not exert a direct depressant or "quinidine-like" action but influence cardiac electrophysiology through a beta-blocking action. Beta blockers do not affect conduction in normal ventricular muscle, as evidenced by their lack of effect on the QRS complex, and they insignificantly prolong the right ventricular ERF and uncorrected QT interval.

Because administration of beta blockers that do not have direct membrane action prevents many arrhythmias resulting from activation of the autonomic nervous system, it is thought that the beta-blocking action is responsible for their antiarrhythmic effects.[300] [301] [302] [303] [304] Nevertheless, the possible importance of the direct membrane effect of some of these drugs cannot be discounted totally because beta blockers with direct membrane actions can affect transmembrane potentials of diseased cardiac fibers at much lower concentrations than are needed to affect normal fibers directly. However, indirect actions on arrhythmogenic effects of ischemia are probably quite important. Beta blockers reduce myocardial injury during experimental cardiopulmonary resuscitation.[305]

HEMODYNAMIC EFFECTS.

Beta blockers exert negative inotropic effects and can precipitate or worsen heart

failure. However, beta blockers clearly improve survival in heart failure patients (see Chap. 18). By blocking beta receptors, these drugs may cause peripheral vasoconstriction and exacerbate coronary artery spasm in some patients.

PHARMACOKINETICS (see Table 23-1).

Although various types of beta blockers exert similar pharmacological effects, their pharmacokinetics differ substantially. Propranolol is almost 100 percent absorbed, but the effects of first-pass hepatic metabolism reduce bioavailability to about 30 percent and produce significant interpatient variability of plasma concentration for a given dose. Reduction in hepatic blood flow, as in patients with heart failure, decreases the hepatic extraction of propranolol; in these patients propranolol may further decrease its own elimination rate by reducing cardiac output and hepatic blood flow. Beta blockers eliminated by the kidney tend to have longer half-lives and exhibit less interpatient variability of drug concentration than do those beta blockers metabolized by the liver.

DOSAGE AND ADMINISTRATION (see Tables 23-1 and 23-8).

The appropriate dose of propranolol is best determined by a measure of the patient's physiological response, such as changes in resting heart rate or in the prevention of exercise-induced tachycardia, because wide individual differences exist between the observed physiological effect and plasma concentration. For example, intravenous dosing is best achieved by titrating the dose to a clinical effect, beginning with doses of 0.25 to 0.50 mg, increasing to 1.0 mg if necessary, and administering doses every 5 minutes until either a desired effect or toxicity is produced or a total of 0.15 to 0.20 mg/kg has been given. In many instances, the short-acting effects of esmolol are preferred. Orally, propranolol is given in four divided doses, usually ranging from 40 to 160 mg/d to more than 1 gm/d. A once-daily long-acting propranolol preparation is available. Generally, if one agent in adequate doses proves to be ineffective, other beta blockers will be ineffective also.

INDICATIONS.

Arrhythmias associated with thyrotoxicosis, pheochromocytoma, and anesthesia with cyclopropane or halothane or arrhythmias largely due to excessive cardiac adrenergic stimulation, such as those initiated by exercise, emotion, or cocaine, often respond to beta-blocker therapy. Beta-blocking drugs usually do not convert chronic atrial flutter or atrial fibrillation to normal sinus rhythm but may do so if the arrhythmia is of recent onset and in patients who have recently undergone cardiac surgery. The atrial rate during flutter/fibrillation is not changed, but the ventricular response decreases because beta blockade prolongs AV node conduction time and refractoriness. Esmolol combined with digoxin has been useful.[306] In the absence of heart failure, beta blockers can be more effective than digoxin to control the rate.[307] For reentrant SVTs using the AV node as one of the reentrant pathways, such as AVNRT[308] [309] and orthodromic reciprocating tachycardias in the Wolff-Parkinson-White syndrome or inappropriate sinus tachycardia,[310] [311] or for SNRT, beta blockers can slow or terminate the tachycardia and be used prophylactically to prevent a recurrence. Combining beta blockers with digitalis, quinidine, or a variety of other agents may be effective when the beta blocker

as a single agent fails. *Metoprolol* and *esmolol* may be useful in patients with multifocal atrial tachycardia.[312] These agents must be used with caution in this arrhythmia, however, because a common setting for it is advanced lung disease, often with a bronchospastic component.

Beta blockers may be effective for digitalis-induced arrhythmias such as atrial tachycardia, nonparoxysmal AV junctional tachycardia, PVCs, or VT. If a significant degree of AV block is present during a digitalis-induced arrhythmia, lidocaine or phenytoin may be preferable to propranolol. Beta blockers also may be useful to treat ventricular arrhythmias associated with the prolonged QT interval syndrome[313] [314] [315] and with mitral valve prolapse. For patients with ischemic heart disease, beta blockers generally do not prevent episodes of chronic recurrent monomorphic ventricular tachycardia that occur in the absence of acute ischemia but may be effective in some patients, usually at a beta-blocking concentration. It is well accepted that propranolol, timolol, and metoprolol reduce the incidence of overall death and sudden cardiac death after myocardial infarction.[316] [317] [318] The mechanism of this reduction in mortality is not entirely clear and may relate to reduction in the extent of ischemic damage, autonomic effects, a direct antiarrhythmic effect, or combinations of these factors. Beta blockers may have been protective against proarrhythmic responses in CAST[319] and may be more effective in some patients than electrophysiologically guided antiarrhythmic drug therapy[135] for ventricular tachyarrhythmias. Labetalol has been used for ventricular arrhythmias in eclampsia.[320]

Labetalol is an alpha$_1$ - and beta-blocking drug. Carvedilol, another alpha- and beta-blocking agent, has been shown to improve survival in moderate to severe heart failure (see Chap. 15).[321] *Esmolol* is an ultra-short-acting (elimination half-life, 9 minutes), cardioselective beta-adrenoceptor blocker that is useful for the rapid control of the ventricular rate in patients with atrial flutter/fibrillation.[322] Its withdrawal has been used in tilt-table testing.[100]

ADVERSE EFFECTS.

Adverse cardiovascular effects from beta blockers include unacceptable hypotension, bradycardia, and congestive heart failure. The bradycardia may be due to sinus bradycardia or AV block. Sudden withdrawal of propranolol in patients with angina pectoris can precipitate or worsen angina and cardiac arrhythmias and cause an acute myocardial infarction, possibly owing to heightened sensitivity to beta agonists caused by previous beta blockade (upregulation). Heightened sensitivity may begin several days after cessation of beta-blocker therapy and may last 5 or 6 days. Other adverse effects of beta blockers include worsening of asthma or chronic obstructive pulmonary disease, intermittent claudication, Raynaud's phenomenon, mental depression, increased risk of hypoglycemia among insulin-dependent diabetic patients, easy fatigability, disturbingly vivid dreams or insomnia, and impaired sexual function. Many of these side effects were noted less frequently when using beta$_1$ -selective agents, but even so-called cardioselective beta blockers can exacerbate asthma or diabetic control in individual patients.

CLASS III ANTIARRHYTHMIC AGENTS

Amiodarone

Amiodarone is a benzofuran derivative approved by the FDA for the treatment of patients with life-threatening ventricular tachyarrhythmias when other drugs are ineffective or are not tolerated.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

When chronically given orally, amiodarone prolongs APD and refractoriness of all cardiac fibers without affecting resting membrane potential. When acute effects are evaluated, amiodarone and its metabolite, desethylamiodarone, prolong the APD of ventricular muscle but shorten the APD of Purkinje fibers. Injected into the sinus and AV node arteries, amiodarone reduces sinus and junctional discharge rates and prolongs AV node conduction time. It decreases the slope of diastolic depolarization of the sinus node and markedly depresses
max in guinea pig papillary muscle in a rate- or use-dependent manner. Such depression of
max is caused by blocking of inactivated sodium channels, an effect that is accentuated by depolarized and reduced by hyperpolarized membrane potentials. Amiodarone also inhibits depolarization-induced automaticity. Amiodarone depresses conduction at fast rates more than at slow rates (use or frequency dependence),[323] [324] [325]

not only by depressing
max but also by increasing resistance to passive current flow. It does not prolong repolarization more at slow than fast rates (i.e., does not demonstrate reverse use or frequency dependence) but does exert time-dependent effects on refractoriness, which may in part explain the low incidence of torsades de pointes and high efficacy.[323] [324]

Desethylamiodarone has relatively greater effects on fast-channel tissue and probably contributes importantly to antiarrhythmic efficacy. The delay to build up adequate concentrations of this metabolite may explain in part the delay in amiodarone's antiarrhythmic action.

In vivo, amiodarone noncompetitively antagonizes alpha and beta receptors and blocks conversion of thyroxine (T_4) to triiodothyronine (T_3), which may account for some of its electrophysiological effects. Amiodarone exhibits slow-channel blocking effects, and chronic oral therapy slows the spontaneous sinus node discharge rate in anesthetized dogs even after pretreatment with propranolol and atropine. With oral administration it prolongs the QT interval, at times changing the contour of the T wave and producing U

waves, and slows the sinus rate by 20 to 30 percent.

ERPs of all cardiac tissues are prolonged. His-Purkinje conduction time increases and QRS duration lengthens, especially at fast rates. Amiodarone given intravenously modestly prolongs the refractory period of atrial and ventricular muscle. The PR interval and AV node conduction time lengthen. The duration of the QRS complex lengthens at increased rates but less than after oral amiodarone. Thus, far less increase in prolongation of conduction time (except for the AV node), duration of repolarization, and refractoriness occurs after IV administration compared with the oral route. Considering these actions, it is clear that amiodarone has Class I (blocks I_{Na}), Class II (antiadrenergic), and Class IV (blocks $I_{Ca\text{-}L}$) actions, in addition to Class III effects (blocks I_K). Amiodarone's actions approximate those of a theoretically ideal drug that exhibits use-dependence of Na^+ channels with fast diastolic recovery from block and use-dependent prolongation of APD. It does not increase[60] and may decrease[326] QT dispersion. Catecholamines can partially reverse some of the effects of amiodarone.[202] [323]

HEMODYNAMIC EFFECTS.

Amiodarone is a peripheral and coronary vasodilator. When administered intravenously in doses of 2.5 to 10 mg/kg, amiodarone decreases heart rate, systemic vascular resistance, left ventricular contractile force, and left ventricular dP/dt (see Chaps. 11 , 14 , and 15). Left ventricular output may increase. Oral doses of amiodarone sufficient to control cardiac arrhythmias do not depress left ventricular ejection fraction, even in patients with reduced ejection fractions measured by radionuclide ventriculography. However, because antiadrenergic actions of amiodarone may block I_{si} to some degree, and because it does exert some negative inotropic action, it should be given cautiously, particularly intravenously, to patients with marginal cardiac compensation.

PHARMACOKINETICS (see Table 23-1).

Amiodarone is slowly, variably, and incompletely absorbed, with systemic bioavailability of 35 to 65 percent. Plasma concentrations peak 3 to 7 hours after a single oral dose. There is minimal first-pass effect, indicating little hepatic extraction. Elimination is by hepatic excretion into bile with some enterohepatic recirculation. Extensive hepatic metabolism occurs with desethylamiodarone as a major metabolite. The plasma concentration ratio of parent to metabolite is 3:2. Both extensively accumulate in the liver, lung, fat, "blue" skin, and other tissues. Myocardium develops a concentration 10 to 50 times that found in the plasma. Plasma clearance of amiodarone is low, and renal excretion is negligible. Doses need not be reduced in patients with renal disease. Amiodarone and desethylamiodarone are not dialyzable. Volume of distribution is large but variable, averaging 60 liters/kg. Amiodarone is highly protein bound (96 percent), crosses the placenta (10 to 50 percent), and is found in breast milk.

The onset of action after IV administration is generally within 1 to 2 hours. After oral administration, the onset of action may require 2 to 3 days, often 1 to 3 weeks, and, on occasion, even longer. Loading doses reduce this time interval. Plasma concentrations

relate well to oral doses during chronic treatment, averaging about 0.5 mg/ml for each 100 mg/d at doses between 100 and 600 mg/d. Elimination half-life is multiphasic with an initial 50 percent reduction in plasma concentration 3 to 10 days after cessation of drug ingestion (probably representing elimination from well-perfused tissues) followed by a terminal half-life of 26 to 107 days (mean 53 days), with most patients in the 40- to 55-day range. To achieve steady state without a loading dose takes about 265 days. Interpatient variability of these pharmacokinetic parameters mandates close monitoring of the patient. Therapeutic serum concentrations range from 1 to 2.5 mg/ml. Greater suppression of arrhythmias may occur up to 3.5 mg/ml, but the risk of side effects increases.

DOSAGE AND ADMINISTRATION (see Table 23-1).

An optimal dosing schedule for all patients has not been achieved.[327] [328] [329] [330] One recommended approach is to treat with 800 to 1600 mg/d for 1 to 3 weeks,[331] reduced to 800 mg/d for the next 2 to 4 weeks, then 600 mg/d for 4 to 8 weeks, and finally, after 2 to 3 months of treatment, a maintenance dose of 300 mg or less per day. Maintenance drug can be given once or twice daily and should be titrated to the *lowest effective dose* to minimize the occurrence of side effects.[332] Doses as low as 100 mg/d can be effective in some patients.[333] Regimens must be individualized for a given patient and clinical situation. Amiodarone may be administered intravenously[334] [335] to achieve more rapid loading and an effect in emergencies at initial doses of 15 mg/min for 10 minutes, followed by 1 mg/min for 6 hours and then 0.5 mg/min for the remaining 18 hours and for the next several days, as necessary. Supplemental infusions of 150 mg over 10 minutes can be used for breakthrough VT or VF. IV infusions can be continued safely for 2 to 3 weeks. IV amiodarone is generally well tolerated even in patients with left ventricular dysfunction.[336] Patients with depressed ejection fractions should receive IV amiodarone with great caution because of hypotension. High-dose oral loading (800 to 2000 mg two or three times a day to maintain trough serum concentrations of 2 to 3 mg/ml) may suppress ventricular arrhythmias in 1 to 2 days.

INDICATIONS.

Amiodarone has been used to suppress a wide spectrum of supraventricular and ventricular tachyarrhythmias in utero,[337] [338] in adults,[332] and in children,[339] [340] including AV node and AV entry, junctional tachycardia,[341] atrial flutter and fibrillation,[342] [343] [344] [345] [346] [347] [347A] VT and VF associated with coronary artery disease,[348] [349] [350] [351] and hypertrophic cardiomyopathy. Success rates vary widely depending on patient population,[352] arrhythmia, underlying heart disease, length of follow-up, definition and determination of success, and other factors. In general, however, amiodarone's efficacy equals or exceeds that of all other antiarrhythmic agents and may be in the range of 60 to 80 percent for most supraventricular tachyarrhythmias (including those associated with the Wolff-Parkinson-White syndrome) and 40 to 60 percent for ventricular tachyarrhythmias. Amiodarone may be useful in improving survival in patients with hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy,[353] asymptomatic ventricular arrhythmias after myocardial infarction, and ventricular tachyarrhythmia after resuscitation. Amiodarone given before open-heart surgery,[354] as well as postoperatively,[355] has been shown to decrease the incidence of

postoperative atrial fibrillation. Amiodarone is superior to Class I antiarrhythmic agents in maintaining sinus rhythm in patients with recurrent atrial fibrillation.[356]

Patients who have an internal cardioverter-defibrillator (ICD) receive fewer shocks if they are treated with amiodarone compared with conventional drugs.[357] Amiodarone

may facilitate defibrillation experimentally[358] but typically increases the electrical defibrillation threshold.[359] [360]

A number of prospective, randomized, controlled trials have demonstrated improved survival with amiodarone therapy compared with placebo[361] [362] [363] [364] [365] or metoprolol[366] in patients after myocardial infarction (Table 23-9) . Amiodarone was found to improve survival in patients resuscitated from VF compared with conventional drugs.[367] [368] In patients with congestive heart failure, amiodarone therapy improved survival in one study,[353] whereas no benefit was observed in another.[369] The Antiarrhythmics Versus Implantable Defibrillator (AVID) trial was designed to compare mortality between patients treated with antiarrhythmic drugs (empirical amiodarone or EPS- or Holter-guided sotalol) versus an ICD, in patients with ejection fraction less than 0.40 who had suffered spontaneous hypotensive VT or cardiac arrest.[370] This study was stopped prematurely when interim analysis showed that ICD-treated patients survived better after 1 year of treatment.[371]

Some controversy exists regarding the ability to predict the effectiveness of amiodarone in patients with ventricular tachyarrhythmias. Clinical assessment, suppression of spontaneous ventricular arrhythmias as documented by 24-hour ECG recordings, and response to EPS have served as endpoints to judge therapy. In the patient with a history of sustained VT or VF and minimal spontaneous ventricular arrhythmias in between symptomatic episodes, an invasive EPS is indicated to judge drug efficacy. The answer to when, after amiodarone therapy is started, such a study should be done is still not entirely resolved but probably should be 1 week or longer. In the 10 to 20 percent of patients whose electrically induced, clinical, ventricular tachyarrhythmias become no longer inducible while they are receiving amiodarone, the chances for a spontaneous recurrence of the arrhythmias are low while the patients are taking amiodarone, probably less than 5 to 10 percent at 1 year. For those patients whose ventricular tachyarrhythmias are still inducible, the recurrence rate is 40 to 50 percent at 1 year. However, in this latter group, greater difficulty in inducing the arrhythmias may predict a less likely possibility of a recurrence.

Patients' hemodynamic responses to the induced arrhythmia also may predict how they tolerate a spontaneous recurrence. Amiodarone slows the VT,[372] [373] but it is important to remember that the supine patient in the electrophysiology laboratory may tolerate the same tachycardia better than when in an erect position. An ejection fraction greater than 0.4 may predict a good response to amiodarone in patients with VT or VF.[374]

Because of the serious nature of the arrhythmias being treated, the unusual pharmacokinetics of the drug, and its adverse effects (see later), amiodarone therapy should be started with the patient hospitalized and monitored for at least several days. Combining other antiarrhythmic agents with amiodarone may improve efficacy in some patients.[375] [376]

ADVERSE EFFECTS.

Adverse effects are reported by about 75 percent of patients treated with amiodarone for 5 years but compel stopping the drug in 18 to 37 percent. The most frequent side effects requiring drug discontinuation involve pulmonary and gastrointestinal complaints.[332] [377] Most adverse effects are reversible with dose reduction or cessation of treatment. Adverse effects become more frequent when therapy is continued long term. Of the noncardiac adverse reactions, pulmonary toxicity is the most serious; in one study it occurred between 6 days and 60 months of treatment in 33 of 573 patients, with three deaths. The mechanism is unclear but may relate to a hypersensitivity reaction and/or widespread phospholipidosis.[378] Dyspnea, nonproductive cough, and fever are common symptoms, with rales, hypoxia, a positive gallium scan, reduced diffusion capacity,[379] [380] and radiographic evidence of pulmonary infiltrates noted. Amiodarone must be discontinued if such pulmonary inflammatory changes occur. Corticosteroids can be tried, but no controlled studies have been done to support their use. A 10 percent mortality results in patients with pulmonary inflammatory changes, often in patients with unrecognized pulmonary involvement that is allowed to progress. Chest radiographs and pulmonary function tests, including diffusion capacity (DL_{CO}), at 3-month intervals for the first year and then twice a year for several years have been recommended. At maintenance doses less than 300 mg/d, pulmonary toxicity is uncommon. Advanced age, high drug maintenance dose, and reduced predrug diffusion capacity are risk factors for developing pulmonary toxicity. An unchanged DL_{CO} may be a negative predictor of pulmonary toxicity.

Although asymptomatic elevations of liver enzymes are

TABLE 23-9 -- CLINICAL TRIALS EVALUATING USE OF AMIODARONE TO PREVENT DEATH

STUDY (NO. OF SUBJECTS)	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
CASCADE (228)	Resuscitated cardiac arrest	Cardiac death	Empirical amiodarone	39% reduction in cardiac death at 2 years, 22% reduction at 6 years

		Resuscitated cardiac arrest	EP- or Holter-guided drug therapy	
		ICD shock after syncope		
GESICA (516)	Heart failure (Classes II-IV)	Sudden death	Amiodarone	27% reduction in sudden death
	Enlarged heart (CXR) or EF<0.35	Total mortality	Standard therapy	28% reduction in total mortality
CHF-STAT (674)	Heart failure (Classes II-IV)	Total mortality	Amiodarone	No difference in total mortality
	EF<0.40		Placebo	
	> 10 VPC/hr			
EMIAT (1486)	Recent MI	Sudden death	Amiodarone	50% reduction in sudden death
	EF<0.40	Total mortality	Placebo	No difference in total mortality
CAMIAT (1202)	Recent MI	Sudden death/resuscitated cardiac arrest	Amiodarone	48% reduction in sudden death
	> 10 VPC/hr or NSVT		Placebo	
AVID (1016)	Cardiac arrest/severely symptomatic sustained VT	Total mortality	Empirical amiodarone or EP/Holter-guided sotalol	
	No acutely reversible cause		ICD	
	EF<0.40			

ICD=implantable cardioverter-defibrillator; EP=electrophysiology; CXR=chest X-ray; EF=ejection fraction; VPC=ventricular premature complex; MI=myocardial infarction; NSVT=nonsustained ventricular tachycardia.

found in most patients, the drug is not stopped unless values exceed two or three times normal in a patient with initially abnormal values. Cirrhosis occurs uncommonly but may be fatal. Neurological dysfunction, photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration, gastroenterological disturbances, and hyperthyroidism[381] [382] (1 to 2 percent) or hypothyroidism (2 to 4 percent) can occur. Amiodarone appears to inhibit the peripheral conversion of T_4 to T_3 so that chemical changes result, which are characterized by a slight increase in T_4 , reverse T_3 and thyroid-stimulating hormone (TSH), and a slight decrease in T_3 . Reverse T_3 concentration has been used as an index of drug efficacy. During hypothyroidism, TSH increases greatly, whereas T_3 increases in hyperthyroidism. Corneal microdeposits occur in almost 100 percent of adults receiving the drug more than 6 months; more serious ocular reactions, including optic neuritis and/or atrophy with visual loss, have been reported[383] but are rare.

Cardiac side effects include symptomatic bradycardias in about 2 percent; aggravation of ventricular tachyarrhythmias (with occasional development of torsades de pointes) in 1 to 2 percent,[384] possibly higher in women[210] ; and worsening of congestive heart failure in 2 percent. Possibly due to interactions with anesthetics, complications after open-heart surgery, including pulmonary dysfunction, hypotension, hepatic dysfunction, and low cardiac output, have been noted by some,[385] but not all,[386] investigators.

In general, the lowest possible maintenance dose of amiodarone that is still effective should be used to avoid significant adverse effects. Many supraventricular arrhythmias can be successfully managed with dally doses of 200 mg or less,[386A] whereas ventricular arrhythmias generally require higher doses. Adverse effects are uncommon at doses of 200 mg/d or less but still occur.[387] Because of potential toxicity in a variety of organ systems, special multidisciplinary amiodarone clinics have been used by some to attempt to prevent adverse outcomes when using the drug.[388]

Important interactions with other drugs occur, and when given concomitantly with amiodarone, the doses of warfarin, digoxin, and other antiarrhythmic drugs should be reduced by one third to one half and the patient watched closely. Drugs with synergistic actions, such as beta blockers or calcium channel blockers, must be given cautiously. Amiodarone's safety during pregnancy has not been established, and it should be used in the pregnant patient only if no alternatives exist.

Bretylium Tosylate

Bretylium is a quaternary ammonium compound that is approved by the FDA for

parenteral use only in patients with life-threatening ventricular tachyarrhythmias.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Bretylium is selectively concentrated in sympathetic ganglia and their postganglionic adrenergic nerve terminals. After initially *causing* norepinephrine release, bretylium *prevents* norepinephrine release by depressing sympathetic nerve terminal excitability without depressing preganglionic or postganglionic sympathetic nerve conduction, impairing conduction across sympathetic ganglia, depleting the adrenergic neuron of norepinephrine, or decreasing the responsiveness of adrenergic receptors. It produces a state resembling chemical sympathectomy. During chronic bretylium treatment, the beta-adrenergic responses to circulating catecholamines are increased. The initial release of catecholamines results in several transient electrophysiological responses, such as an increase in the discharge rates of the isolated, perfused sinus node and of in vitro Purkinje fibers, often making quiescent fibers automatic.

Bretylium initially increases conduction velocity and excitability and decreases refractoriness in the rabbit atrium, and partially depolarized fibers may hyperpolarize. Pretreatment with reserpine or propranolol prevents these early changes. Initial catecholamine release can aggravate some arrhythmias, such as those caused by digitalis excess or myocardial infarction. Prolonged drug administration lengthens the duration of the action potential and refractoriness of atrial and ventricular muscle and Purkinje fibers, possibly by blocking one or more repolarizing potassium currents. The ratio of ERP to APD does not change, nor do membrane responsiveness and conduction velocity. Bretylium exerts little effect on diastolic excitability but increases VF thresholds in some studies[389] [390] but not others.[391] It is not clear whether the chemical sympathectomy-like state alone or together with other actions exerts the antifibrillatory effect. Reduced disparity between APD and ERP in regions of normal and infarcted myocardium may account for some of its antifibrillatory effects. Bretylium has no effect on vagal reflexes and does not alter the responsiveness of cholinergic receptors in the heart.

HEMODYNAMIC EFFECTS.

Bretylium does not depress myocardial contractility. After an initial increase in blood pressure, the drug can cause significant hypotension by blocking the efferent limb of the baroreceptor reflex. Hypotension results most commonly when patients are sitting or standing but also can occur in the supine position in seriously ill patients. Bretylium reduces the extent of the vasoconstriction and tachycardia reflexes during standing. Orthostatic hypotension can persist for several days after the drug has been discontinued.

PHARMACOKINETICS (see Table 23-1).

Bretylium is effective orally as well as parenterally, but it is absorbed poorly and erratically from the gastrointestinal tract. Bioavailability may be less than 50 percent, and elimination is almost exclusively by renal excretion without significant metabolism or

active metabolites being recognized. Elimination half-life is 5 to 10 hours but with fairly wide variability. Doses should be reduced in patients with renal insufficiency. In survivors of VT or VF, bretylium had an elimination half-life of 13.5 hours after single IV dosing, which was similar to previous results in normal subjects. Renal clearance accounted for virtually all elimination. Onset of action after IV administration occurs within several minutes, but full antiarrhythmic effects may not be seen for 30 minutes to 2 hours.

DOSAGE AND ADMINISTRATION (see Table 23-1).

Bretylium can be given intravenously in doses of 5 to 10 mg/kg of body weight diluted in 50 to 100 ml of 5 percent dextrose in water and administered over 10 to 20 minutes or more quickly in a life-threatening state. This dose can be repeated in 1 to 2 hours if the arrhythmia persists. The total daily dose probably should not exceed 30 mg/kg. A similar initial dose, but undiluted, can be given intramuscularly. The maintenance IV dose is 0.5 to 2.0 mg/min. Intramuscular injection during cardiopulmonary resuscitation from cardiac arrest and in shock states should be avoided because of unreliable absorption during reduced tissue perfusion. In this situation, bretylium should be given intravenously.

INDICATIONS.

Bretylium is used in patients who are in an intensive care setting and who have life-threatening, recurrent ventricular tachyarrhythmias that have not responded to other antiarrhythmic drugs. Bretylium has been effective in treating some patients with drug-resistant tachyarrhythmias and in treating victims of out-of-hospital VF.

ADVERSE EFFECTS.

Hypotension, most prominently orthostatic but also supine, appears to be the most significant side effect and can be prevented with tricyclic drugs such as protriptyline. Transient hypertension, increased sinus rate, and worsening of arrhythmias, often those due to digitalis excess or ischemia, may follow initial drug administration and may be due to initial release of catecholamines. Bretylium should be used cautiously or not at all in patients who have a relatively fixed cardiac output, such as those with severe aortic stenosis. Vasodilators or diuretics can enhance these hypotensive effects. Nausea and vomiting can occur after parenteral administration. Parotid pain primarily during meals commonly occurs after 2 to 4 months of oral therapy and is associated with increased salivation without parotid swelling or inflammation.

Sotalol

Sotalol is a nonspecific beta-adrenoceptor blocker without intrinsic sympathomimetic activity that prolongs repolarization. It was approved in 1992 by the FDA to treat patients with life-threatening ventricular tachyarrhythmias.[350] [392] [392A]

ELECTROPHYSIOLOGICAL ACTIONS (Tables 23-4 , 23-6 , and 23-7).

Both *d*- and *l*-isomers have similar effects on prolonging repolarization, whereas the *l*-isomer is responsible for virtually all the beta-blocking activity. Sotalol does not block alpha adrenoceptors and does not block the sodium channel (no membrane-stabilizing effects) but does prolong atrial and ventricular repolarization times[393] by reducing I_{Kr} , thus prolonging the plateau of the action potential. Action potential prolongation is greater at slower rates (reverse use-dependence). Resting membrane potential, action potential amplitude, and
max are not significantly altered. Sotalol prolongs atrial and ventricular refractoriness, AH and QT intervals, and sinus cycle length. It narrows the excitable gap in reentrant VT.[394]

HEMODYNAMICS.

Sotalol exerts a negative inotropic effect only through its beta-blocking action. It can increase the strength of contraction by prolonging repolarization, which will occur maximally at slow heart rates. In patients with reduced cardiac function, sotalol can cause a decrease in cardiac index, an increase in filling pressure, and overt heart failure. Therefore, it must be used cautiously in patients with marginal cardiac compensation but appears to be well tolerated in patients with normal cardiac function.[395] [396] [397] .

PHARMACOKINETICS (see Table 23-1).

Sotalol is completely absorbed and not metabolized, making it 90 to 100 percent bioavailable. It is not bound to plasma proteins, is excreted unchanged primarily by the kidneys, and has an elimination half-life of 10 to 15 hours. Peak plasma concentrations occur 2.5 to 4.0 hours after oral ingestion, with steady state attained after five or six doses. Effective antiarrhythmic plasma concentration is in the range of 2.5 mg/ml. There is very little intersubject variability in plasma levels. Over the dose range of 160 to 640 mg, sotalol displays dose proportionality with plasma concentration. The dose must be reduced in patients with renal disease. The beta-blocking effect is half maximal at 80 mg/d and maximal at 320 mg/d. Significant beta-blocking action occurs at 160 mg/d.

DOSAGE (see Table 23-1).

The typical oral dose is 80 to 160 mg every 12 hours, allowing 2 to 3 days between dose adjustments to attain steady state and monitor the ECG for arrhythmias and QT prolongation. Doses exceeding 320 mg/d can be used in patients when the potential benefits outweigh the risk of proarrhythmia.

INDICATIONS.

Approved by the FDA only to treat patients with ventricular tachyarrhythmias,[398] [399] [400] sotalol is also useful to prevent recurrence of a wide variety of SVTs, including atrial flutter and fibrillation,[266] [401] atrial tachycardia, AV node reentry, and AV reentry. It also shows the ventricular response to atrial tachyarrhythmias.[402] It appears to be more effective than conventional antiarrhythmic drugs and comparable with amiodarone in treating patients with ventricular tachyarrhythmias.[11] Sotalol has been shown to be superior to lidocaine for acute termination of sustained VT[403] and is useful in patients with arrhythmogenic right ventricular dysplasia.[404] It can prolong the duration of late potentials.[405] Sotalol may be effective in pediatric patients.[406] It may decrease the frequency of ICD discharges[407] and reduce the defibrillation threshold.[359]

ADVERSE EFFECTS.

Proarrhythmia is the most serious adverse effect. Overall, new or worsened ventricular tachyarrhythmias occur in about 4 percent, and this response is due to torsades de pointes in about 2.5 percent. The incidence of torsades de pointes increases to 4 percent in patients with a history of sustained VT and is dose related, reportedly only 1.6 percent at 320 mg/d but 4.4 percent at 480 mg/d.[408] This proarrhythmic effect is probably the cause of excess mortality in patients given *d*-sotalol (the enantiomer lacking a beta-blocking effect) after an acute myocardial infarction in the Survival With Oral *d*-Sotalol (SWORD) trial.[409] Other adverse effects commonly seen with other beta blockers also apply to sotalol. Sotalol should be used with caution or not at all in combination with other drugs that prolong the QT interval. However, such combinations have been used successfully.[410]

Ibutilide

Ibutilide is a relatively new agent released for use in acutely terminating episodes of atrial flutter and fibrillation.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Like other Class III agents, ibutilide prolongs repolarization. Although it is like other Class III agents that block outward potassium currents such as I_{Kr} , ibutilide is unique in that it also appears to activate a slow inward sodium current (see Chap. 22).[411] Administered intravenously, ibutilide causes mild slowing of the sinus rate and has minimal effects on AV conduction or QRS duration, but the QT interval is characteristically prolonged. Ibutilide has no significant effect on hemodynamics.

PHARMACOKINETICS (see Table 23-1).

Ibutilide is administered intravenously and has a large volume of distribution. Clearance is predominantly renal, with a drug half-life averaging 6 hours (but with considerable

interpatient variability). Protein binding is approximately 40 percent. One of the drug's metabolites has weak Class III effects.

DOSAGE AND ADMINISTRATION (see Table 23-1).

Ibutilide is given as an IV rapid infusion of 1 mg over 10 minutes. It should not be given in the presence of a QTc interval greater than 440 milliseconds or other drugs that prolong the QT interval or of uncorrected hypokalemia or bradycardia. A second 1-mg dose may be given if the arrhythmia persists. Patients must be on continuous ECG monitoring throughout the dosing period and for 6 to 8 hours thereafter because of the risk of ventricular arrhythmias (see later). Up to 60 percent of patients with atrial fibrillation and 70 percent of those with atrial flutter will convert to sinus rhythm after 2 mg of ibutilide.[412]

INDICATIONS.

Ibutilide is indicated for termination of an established episode of atrial flutter or fibrillation. It should not be used in patients with frequent, short paroxysms of atrial fibrillation because it merely terminates episodes and is not useful for prevention. Patients whose condition is hemodynamically unstable should proceed to direct-current cardioversion (see later). Ibutilide has been administered at the time of transthoracic electrical cardioversion to increase the likelihood of termination of atrial fibrillation. Oral and associates found that all 50 patients given ibutilide before attempted electrical cardioversion achieved sinus rhythm, whereas only 34 of 50 who did not receive the drug converted to sinus rhythm.[413] Of note, all 14 patients who failed electrical cardioversion without ibutilide were successfully electrically cardioverted to sinus rhythm when a second attempt was made after ibutilide pretreatment.

ADVERSE EFFECTS.

The most significant adverse effect of ibutilide is torsades de pointes, which occurs in approximately 2 percent of patients given the drug. This occurs within the first 4 to 6 hours of dosing, after which the risk is negligible. Thus, patients in whom the drug is used must undergo ECG monitoring for up to 8 hours after dosing. This can make ibutilide's use in emergency departments or private offices problematic. Ibutilide's safety during pregnancy is not well studied. Its use should be restricted to cases in which no safer alternative exists.

Dofetilide

Dofetilide is a relatively new agent (approved by the FDA in early 2000) for acute conversion of atrial fibrillation into sinus rhythm as well as chronic suppression of recurrent atrial fibrillation.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

The sole electrophysiological effect of dofetilide appears to be block of the rapid component of the delayed rectifier potassium current (I_{Kr}), which is important in repolarization (see Chap. 22). This effect is more prominent in the atria than in the ventricles (30 percent increase in atrial refractory periods vs. 20 percent in the ventricles).[414] Dofetilide's effect on I_{Kr} prolongs refractoriness without slowing conduction, which is believed to be largely responsible for its antiarrhythmic effect. It is also responsible for the prolongation of the QT interval on the ECG, which averages 11 percent but can be much greater. This effect on the QT interval is dose dependent and linear. No other important ECG changes are observed with the

drug. It has no significant hemodynamic effects.[415] Dofetilide has been shown to be more effective than quinidine at converting atrial fibrillation to sinus rhythm.[416]

PHARMACOKINETICS (see Table 23-1).

Orally administered dofetilide is absorbed well, with over 90 percent bioavailability. Fifty to 60 percent of the drug is excreted unchanged in urine, with a mean elimination half-life of 7 to 13 hours. [417] [418] The remainder of the drug undergoes hepatic metabolism to inert compounds. There have been no significant drug interactions yet reported. Dofetilide appears to exert no adverse effect on hemodynamics.

DOSAGE AND ADMINISTRATION (see Table 23-1).

At the time of this writing, dofetilide is available only as an oral preparation. Dosing is from 0.01 to 0.5 mg twice daily.

INDICATIONS.

Intravenous dofetilide has been used for termination of an established episode of atrial flutter, fibrillations, or other types of SVT.[419] [420] Oral dofetilide is indicated for prevention of episodes of supraventricular tachyarrhythmias, particularly atrial flutter and fibrillation.[420A] Dofetilide's role in therapy for ventricular arrhythmias is less clear. Dofetilide has been shown to have a neutral effect on mortality when given to patients after myocardial infarction.[421]

ADVERSE EFFECTS.

The most significant adverse effect of dofetilide is QT interval prolongation with torsades de pointes, occurring in 2 to 4 percent of patients given the drug.[420] Risk is highest in patients with a baseline prolonged QT interval, those who are hypokalemic, those taking some other agent that prolongs repolarization, and after conversion from atrial fibrillation

to sinus rhythm.[422]

Azimilide

Azimilide is a new agent (not yet approved by the FDA at the time of this writing) for use in the treatment of atrial flutter and fibrillation.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Unlike dofetilide, which blocks the rapid component of the delayed rectifier potassium current, azimilide produces a more balanced blockade of both rapid and slow components of I_K (see Chap. 22).[423] [424] It is presumed that this effect is responsible for the lower rate of proarrhythmia as well as better preservation of drug efficacy at higher heart rates with this agent compared with purer I_{Kr} blockers. Azimilide produces a mild prolongation of the QT interval but no other meaningful ECG changes. Unlike dofetilide and sotalol, which have greater effects on atrial than ventricular refractoriness, azimilide exerts a similar effect on each.

PHARMACOKINETICS (see Table 23-1).

Azimilide's pharmacokinetic profile is relatively simple and predictable.[425] It can be taken orally once a day, and its absorption is nearly complete and unaffected by food intake. Few drug interactions have been reported. Azimilide is cleared by the kidney; some metabolism of the drug to inactive compounds occurs.[426] The drug has no significant adverse hemodynamic effects.

DOSAGE AND ADMINISTRATION (see Table 23-1).

Azimilide can be taken by mouth once a day at a dose of 100 to 200 mg. The drug is well tolerated, and dosing need not be adjusted in the presence of renal or hepatic disease.

INDICATIONS.

Azimilide is indicated for IV administration to terminate an established episode of atrial flutter or fibrillation, as well as orally for long-term prevention of these arrhythmias. Studies are under way to evaluate its efficacy in ventricular arrhythmias.[427]

ADVERSE EFFECTS.

The drug is generally well tolerated. As with other Class III agents, the most significant adverse effect of azimilide is torsades de pointes, although this arrhythmia appears to be less common with this agent than with other Class III medications (occurring in approximately 1 percent of patients given the drug).

CLASS IV ANTIARRHYTHMIC AGENTS

Calcium Channel Antagonists: Verapamil and Diltiazem

Verapamil, a synthetic papaverine derivative, is the prototype of a class of drugs that block the slow calcium channel and reduce $I_{Ca\text{-}L}$ in cardiac muscle. *Diltiazem* has electrophysiological actions similar to those of verapamil.[163] *Nifedipine* (see Chap. 37) exhibits minimal electrophysiological effects at clinically used doses and will not be discussed here. *Felodipine* blocks the T-type calcium current (see Chap. 22), and its clinical application has not been established. Neither of these drugs is discussed here.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

By blocking $I_{Ca\text{-}L}$ in all cardiac fibers, verapamil reduces the plateau height of the action potential, slightly shortens muscle action potential, and slightly prolongs total Purkinje fiber action potential. It does not appreciably affect the action potential amplitude, max of phase 0, or resting membrane voltage in cells that have fast-response characteristics due to I_{Na} (atrial and ventricular muscle, the His-Purkinje system). Verapamil suppresses slow responses elicited by a variety of experimental methods as well as triggered sustained rhythmic activity and early and late afterdepolarizations (see Chap. 22). Verapamil and diltiazem suppress electrical activity in the normal sinus and AV nodes in concentrations that do not suppress action potentials of fast-channel-dependent cells. Verapamil depresses the slope of diastolic depolarization in sinus node cells, max of phase 0, maximum diastolic potential, and action potential amplitude in the sinus and AV node cells and prolongs conduction time and the effective and functional refractory periods of the AV node. The AV node blocking effects of verapamil and diltiazem[428] are more apparent at faster rates of stimulation (use-dependence) and in depolarized fibers (voltage-dependence). Verapamil slows the activation and delays recovery from inactivation of the slow channel. Unbinding of the drug from its receptor occurs more rapidly in tissue that is hyperpolarized.

Verapamil does exert some local anesthetic activity because the dextrorotatory stereoisomer of the clinically used racemic mixture exerts slight blocking effects on I_{Na} . The levorotatory stereoisomer blocks the slow inward current carried by calcium, as well as other ions, traveling through the slow channel. Verapamil does not modify calcium uptake, binding, or exchange by cardiac microsomes, nor does it affect calcium-activated adenosine triphosphatase. Verapamil does not block beta receptors and may block alpha receptors and potentiate vagal effects on the AV node. Verapamil also may cause other effects that indirectly alter cardiac electrophysiology, such as decreasing platelet adhesiveness or reducing the extent of myocardial ischemia.

In vivo, both in experimental animals and in humans, verapamil prolongs conduction time through the AV node (the AH interval) without affecting the P wave onset to atrial (PA), HV, or QRS interval and lengthens the anterograde and retrograde functional refractory periods and ERPs of the AV node. Spontaneous sinus rate may decrease

slightly, an event only partially reversed by atropine. More commonly, the sinus rate does not change significantly in vivo because verapamil causes peripheral vasodilation, transient hypotension, and reflex sympathetic stimulation that mitigates any direct slowing effect verapamil may exert on the sinus node. If verapamil is given to a patient who is also receiving a beta blocker, the sinus node discharge rate

may slow because reflex sympathetic stimulation is blocked. Verapamil does not exert a significant direct effect on atrial or ventricular refractoriness or on anterograde or retrograde properties of accessory pathways. However, reflex sympathetic stimulation may increase the ventricular response over the accessory pathway during atrial fibrillation in patients with the Wolff-Parkinson-White syndrome.

HEMODYNAMIC EFFECTS.

Because verapamil interferes with excitation-contraction coupling, it inhibits vascular smooth muscle contraction and causes marked vasodilation in coronary and other peripheral vascular beds. Propranolol does not block the vasodilation produced by verapamil. Reflex sympathetic effects may reduce in vivo the marked negative inotropic action of verapamil on isolated cardiac muscle, but the direct myocardial depressant effects of verapamil may predominate when the drug is given in high doses. In patients with well-preserved left ventricular function, combined therapy with propranolol and verapamil appears to be well tolerated, but beta blockade can accentuate the hemodynamic depressant effects produced by oral verapamil. Patients who have reduced left ventricular function may not tolerate the combined blockade of beta receptors and of slow channels, and the combined use of verapamil and propranolol in these patients must be undertaken cautiously or not at all. Verapamil decreases myocardial oxygen demand while decreasing coronary vascular resistance and reduces the extent of ischemic damage in experimental preparations. Such changes may be antiarrhythmic. Diltiazem also reduces ventricular arrhythmias during coronary occlusion in the dog, possibly by preventing calcium overload.

Peak alterations in hemodynamic variables occur 3 to 5 minutes after completion of the verapamil injection, the major effects being dissipated within 10 minutes. Mean arterial pressure decreases and left ventricular end-diastolic pressure increases; systemic resistance decreases and left ventricular dP/dt max decreases. Heart rate, cardiac index, left ventricular minute work, and mean pulmonary artery pressure do not change significantly. Thus, afterload reduction produced by verapamil significantly minimizes its negative inotropic action so that the cardiac index may not be reduced. In addition, when verapamil slows the ventricular rate in a patient with a tachycardia, cardiac slowing also may improve hemodynamics. Nevertheless, caution should be exercised when giving verapamil to patients with severe myocardial depression or those receiving beta blockers or disopyramide because hemodynamic deterioration may progress in some patients.

PHARMACOKINETICS (see Table 23-1).

After single oral doses of verapamil, measurable prolongation of AV node conduction time occurs in 30 minutes and lasts 4 to 6 hours. After IV administration, AV node conduction delay occurs within 1 to 2 minutes and AH interval prolongation is still detectable after 6 hours. Effective plasma concentrations necessary to terminate SVT are in the range of 125 ng/ml after doses of 0.075 to 0.150 mg/kg. After oral administration, absorption is almost complete, but an overall bioavailability of 20 to 35 percent suggests substantial first-pass metabolism in the liver, particularly of the *l* isomer. The elimination half-life of verapamil is 3 to 7 hours, with up to 70 percent of the drug excreted by the kidneys. Norverapamil is a major metabolite that may contribute to verapamil's electrophysiological actions. Serum protein binding is approximately 90 percent. With diltiazem, the percentage of heart rate reduction in atrial fibrillation relates to plasma concentration.[429]

DOSAGE AND ADMINISTRATION (see Table 23-1).

The most commonly used IV dose of verapamil is 10 mg infused over 1 to 2 minutes while cardiac rhythm and blood pressure are monitored. A second injection of equal dose may be given 30 minutes later. The initial effect achieved with the first bolus injection, such as slowing of the ventricular response during atrial fibrillation, may be maintained by a continuous infusion of the drug at a rate of 0.005 mg/kg/min. The oral dose is 240 to 480 mg/d in divided doses. Diltiazem is given intravenously at a dose of 0.25 mg/kg as a bolus over 2 minutes, with a second dose in 15 minutes if necessary. Orally, doses must be adjusted to the patient's needs, with a 120- to 360-mg range. Various long-acting preparations exist for verapamil and diltiazem.

INDICATIONS.

After simple vagal maneuvers have been tried and adenosine given, IV verapamil or diltiazem[430] is the next treatment of choice for terminating sustained sinus node reentry, AV node reentry, or orthodromic AV reciprocating tachycardia associated with the Wolff-Parkinson-White syndrome. Verapamil is as effective as adenosine for termination of these arrhythmias.[431] Verapamil should definitely be tried before attempting termination by digitalis administration, pacing, electrical direct-current cardioversion, or acute blood pressure elevation with vasopressors. Verapamil and diltiazem terminate 60 to more than 90 percent of episodes of paroxysmal SVTs within several minutes. Verapamil may be of use in some fetal SVTs as well. Although IV verapamil has been given along with IV propranolol, this combination should be used only with great caution.

Verapamil and diltiazem decrease the ventricular response over the AV node during atrial fibrillation or atrial flutter, possibly converting a small number of episodes to sinus rhythm, particularly if the atrial flutter or fibrillation is of recent onset.[288] Some patients who exhibit atrial flutter may develop atrial fibrillation after verapamil administration. Quinidine, flecainide, and esmolol appear to be more effective than verapamil in establishing and maintaining sinus rhythm in patients with atrial fibrillation. As noted

earlier, in patients with atrial fibrillation associated with the Wolff-Parkinson-White syndrome, intravenous verapamil may *accelerate* the ventricular response; therefore, the intravenous route is contraindicated in this situation. Verapamil can terminate some atrial tachycardias. Even though verapamil terminates a left septal VT,[432] hemodynamic collapse can occur if intravenous verapamil is given to patients with the more common forms of VT. A general rule to avoid complications, however, is to not give intravenous verapamil to any patient with wide QRS tachycardia unless one is absolutely certain of the nature of the tachycardia and its response to verapamil.

Orally, verapamil or diltiazem can prevent the recurrence of AV node reentrant and orthodromic AV reciprocating tachycardias[430] [431] [433] associated with the WolffParkinson-White syndrome as well as help maintain a decreased ventricular response during atrial flutter or atrial fibrillation in patients without an accessory pathway.[434] [435] [436] In this regard, the effectiveness of verapamil appears to be enhanced when given concomitantly with quinidine, and that of diltiazem is enhanced when given with digoxin.[322] Verapamil generally has not been effective in treating patients who have recurrent ventricular tachyarrhythmias, although it may suppress some forms of VT such as a left septal VT,[432] [437] [438] [439] [440] [441] as noted earlier. It may be useful in about two thirds of patients with idiopathic VT that has a left bundle branch block morphology,[437] in patients with hypertrophic cardiomyopathy who have experienced cardiac arrest,[148] in patients with a short-coupled variant of torsades de pointes,[442] in patients with right ventricular dysplasia,[404] and in patients with ventricular arrhythmias due to coronary artery spasm.[443] Whereas data from animal models suggest that verapamil may be useful in reducing or preventing ventricular arrhythmias due to acute myocardial ischemia, calcium antagonists have not been shown to reduce mortality or prevent sudden cardiac death in patients

after acute myocardial infarction, except for diltiazem in patients with non-Q-wave infarctions. Verapamil abolishes the wall motion abnormality found in patients with the long QT syndrome.[77]

ADVERSE EFFECTS.

Verapamil must be used cautiously in patients with significant hemodynamic impairment or in those receiving beta blockers, as previously noted. Hypotension, bradycardia, AV block, and asystole are more likely to occur when the drug is given to patients who are already receiving beta-blocking agents. Hemodynamic collapse has been noted in infants, and verapamil should be used cautiously in patients younger than 1 year old. Verapamil also should be used with caution in patients with sinus node abnormalities, because marked depression of sinus node function or asystole can result in some of these patients. Isoproterenol, calcium, glucagon infusion, dopamine, or atropine (which may be only partially effective) or temporary pacing may be necessary to counteract some of the adverse effects of verapamil. Isoproterenol may be more effective for treating bradyarrhythmias and calcium for treating hemodynamic dysfunction secondary to verapamil. AV node depression is common in overdoses.[444] Contraindications to the

use of verapamil and diltiazem include the presence of advanced heart failure, second- or third-degree AV block without a pacemaker in place, atrial fibrillation and anterograde conduction over an accessory pathway, significant sinus node dysfunction, most VTs, cardiogenic shock, and other hypotensive states. While the drugs probably should not be used in patients with manifest heart failure, if the latter is due to one of the supraventricular tachyarrhythmias noted earlier, verapamil or diltiazem may restore sinus rhythm or significantly decrease the ventricular rate, leading to hemodynamic improvement. Finally, it is important to note that verapamil can decrease the excretion of digoxin by about 30 percent. Hepatotoxicity may occur on occasion. Verapamil crosses the placental barrier; its use in pregnancy has been associated with impaired uterine contraction, fetal bradycardia, and, possibly, fetal digital defects. It should thus be used only if no good alternatives exist.

OTHER ANTIARRHYTHMIC AGENTS

Adenosine

Adenosine is an endogenous nucleoside present throughout the body and has been approved by the FDA to treat patients with SVTs.[445]

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Adenosine interacts with A_1 receptors present on the extracellular surface of cardiac cells, activating K^+ channels ($I_{K\ Ach}$, $I_{K\ Ado}$) in a fashion similar to that produced by acetylcholine. The increase in K^+ conductance shortens atrial APD, hyperpolarizes the membrane potential, and decreases atrial contractility. Similar changes occur in the sinus and AV nodes. In contrast to these direct effects mediated through the guanine nucleotide regulatory proteins G_i and G_o , adenosine antagonizes catecholamine-stimulated adenylate cyclase to decrease cyclic adenosine monophosphate accumulation and to decrease $I_{Ca\text{-}L}$ and the pacemaker current I_f in sinus node cells (see Chap. 22).
max is reduced. Shifts in pacemaker site within the sinus node and sinus exit block may occur. Reflex-mediated sinus tachycardia can follow adenosine administration. In the N region of the AV node, conduction is depressed, along with decreases in action potential amplitude, duration, and
max. Adenosine slows the sinus rate in humans, which is followed by a reflex increase in sinus discharge. Transient prolongation of the AH interval results, often with transient first-, second-, or third-degree AV node block. Delay in AV node conduction is rate dependent.[446] His-Purkinje conduction is generally not directly affected. Adenosine does not affect conduction in normal accessory pathways. Conduction may be blocked in accessory pathways that have long conduction times or decremental conduction properties. Patients with heart transplants exhibit a supersensitive response to adenosine.[446] Adenosine may mediate the phenomenon of ischemic preconditioning.[445]

PHARMACOKINETICS (see Table 23-1).

Adenosine is removed from the extracellular space by washout, enzymatically by degradation to inosine, by phosphorylation to adenosine monophosphate, or by reuptake into cells through a nucleoside transport system. The vascular endothelium and the formed blood elements contain these elimination systems, which result in very rapid clearance of adenosine from the circulation. Elimination half-life is 1 to 6 seconds. Most of adenosine's effects are produced during its first passage through the circulation. Important drug interactions occur. Methyl xanthines are competitive antagonists, and therapeutic concentrations of theophylline totally block the exogeneous adenosine effect. Dipyridamole is a nucleoside transport blocker that blocks reuptake of adenosine, delaying its clearance from the circulation or interstitial space and potentiating its effect. Smaller adenosine doses should be used in patients receiving dipyridamole.

DOSAGE AND ADMINISTRATION (see Table 23-1).

To terminate tachycardia, a bolus of adenosine is rapidly injected intravenously into a central vein (if possible) at doses of 6 to 12 mg. Pediatric dosing should be 0.1 to 0.3 mg/kg.[447] When given into a central vein and in patients after heart transplantation or in patients receiving dipyridamole, the initial dose should be reduced to 3 mg.[448] [449] Transient sinus slowing or AV node block results.

INDICATIONS.

Adenosine has become the drug of first choice to terminate acutely an SVT such as AV node or AV reentry.[450] [451] [452] [453] [454] It is useful in pediatric patients[447] [455] and to judge the effectiveness of ablation of accessory pathways.[456] Adenosine can produce AV block or terminate atrial tachycardias[457] [458] and sinus node reentry. It results in transient AV block during atrial flutter or fibrillation. Adenosine terminates a group of VTs whose maintenance depends on adrenergic drive, which is most often located in the right ventricular outflow tract but found at other sites as well.[438] [439] [459] [460] Adenosine has less potential than verapamil for lowering the blood pressure should tachycardia persist after injection.

Doses as low as 2.5 mg terminate some tachycardias; doses of 12 mg or less terminate 92 percent of SVTs, usually within 30 seconds. Successful termination rates with adenosine are comparable with those achieved with verapamil. Because of its effectiveness and extremely short duration of action, adenosine is preferable to verapamil in most instances, particularly in patients who previously have received intravenous beta-adrenoceptor blockers, in those having poorly compensated heart failure or severe hypotension, and in neonates. Verapamil might be chosen first in patients receiving drugs such as theophylline, which is known to interfere with adenosine's actions or metabolism; in patients with active bronchoconstriction; and in those with inadequate venous access. Adenosine produces transient AV nodal block in patients with atrial flutter, atrial fibrillation, and some types of atrial tachycardia, facilitating the diagnosis by exposing the atrial rhythm.

Adenosine may be useful to help differentiate among causes of wide QRS

tachycardias[460] because it terminates many SVTs with aberrancy or reveals the underlying atrial mechanism, and it does not block conduction over an accessory pathway or terminate most VTs. Adenosine does in

rare cases terminate some VTs (characteristically those of right ventricular outflow tract origin), and therefore tachycardia termination is not completely diagnostic for an SVT.[461] This agent may predispose to the development of atrial fibrillation and possibly can increase the ventricular response in patients with atrial fibrillation conducting over an accessory pathway. Adenosine also may be useful in differentiating conduction over the AV node versus an accessory pathway during ablative procedures designed to interrupt the accessory pathway. However, this distinction is not absolute because adenosine can block conduction in slowly conducting accessory pathways and does not always effect block in the AV node.[462] Endogenously released adenosine may be important in ischemia and hypoxia-induced AV node block and in postdefibrillation bradyarrhythmias.

ADVERSE EFFECTS.

Transient side effects occur in almost 40 percent of patients with SVT given adenosine and are most commonly flushing, dyspnea, and chest pressure. These symptoms are fleeting, lasting less than 1 minute, and are well tolerated. PVCs, transient sinus bradycardia, sinus arrest, and AV block are common when an SVT abruptly terminates. Atrial fibrillation is occasionally observed (12 percent in one study) with adenosine administration,[463] perhaps owing to the drug's effect in shortening atrial refractoriness.[464] Induction of atrial fibrillation can be problematic in patients with the Wolff-Parkinson-White syndrome or rapid AV conduction.[465] [466]

Digoxin

Cardiac actions of digitalis glycosides have been recognized for centuries. Digoxin is used for control of supraventricular arrhythmias, mainly control of ventricular rate during atrial fibrillation. The use of digoxin has decreased in recent years owing to the availability of agents with greater potency and a wider therapeutic-to-toxic drug concentration range.

ELECTROPHYSIOLOGICAL ACTIONS (see Tables 23-4 , 23-6 , and 23-7).

Digoxin acts mainly through the autonomic nervous system, in particular by enhancing both central and peripheral vagal tone. These actions are largely confined to slowing the sinus node discharge rate, shortening atrial refractoriness, and prolonging AV node refractoriness.[445] Electrophysiological effects on the His-Purkinje system and ventricular muscle are minimal except in toxic concentrations. In studies on denervated hearts, digoxin has relatively little effect on the AV node and causes a mild increase in atrial refractoriness. Digoxin has a mild antiadrenergic effect in low doses but may enhance

central sympathetic tone at higher concentrations, which may be important in the development of digitalis-toxic arrhythmias.

The sinus rate and P wave duration are minimally changed in most patients taking digoxin. The sinus rate may decrease in patients with heart failure whose left ventricular performance is improved by the drug; individuals with significant underlying sinus node disease also have slower sinus rates or even sinus arrest. Similarly, the PR interval is generally unchanged except in patients with underlying AV node disease. QRS and QT intervals are unaffected. The characteristic ST and T wave abnormalities seen with digoxin use do not represent toxicity.

PHARMACOKINETICS (see Table 23-1).

Intravenously administered digoxin yields some electrophysiological effect within minutes, with a peak effect occurring after 1.5 to 3 hours. After oral dosing, the peak effect occurs in 4 to 6 hours. The extent of digoxin absorption after oral administration varies depending on the preparation: Tablet forms are 60 to 75 percent absorbed, whereas encapsulated gel forms are almost completely absorbed. Ingestion of cholestyramine or antacid preparation at the same time as digoxin ingestion decreases its absorption. The serum half-life of digoxin is 36 to 48 hours, and the drug is excreted unchanged by the kidneys.[445]

DOSAGE AND ADMINISTRATION (see Table 23-1).

In acute loading doses of 0.5 to 1.0 mg, digoxin may be given intravenously or by mouth. Chronic daily oral dosing should be adjusted based on clinical indications and the extent of renal dysfunction. Most patients require from 0.125 to 0.25 mg/d as a single dose; however, as little as 0.125 mg every other day is needed in some patients on renal dialysis, whereas young patients may require as much as 0.5 mg/d. Serum digoxin levels may be used to monitor compliance with therapy as well as to determine whether digitalis toxicity is the cause of new symptoms compatible with the diagnosis. However, routine monitoring of digoxin levels is not warranted in patients whose ventricular rate is controlled during atrial fibrillation and who have no symptoms of toxicity.

A large number of pharmacokinetic interactions have been described for digoxin, the most important being with quinidine (which increases serum digoxin concentrations by displacing the drug from tissue binding sites and decreasing renal clearance).

INDICATIONS.

Digoxin can be used intravenously to slow the ventricular rate during atrial fibrillation and flutter; it has been used in the past to attempt to convert SVTs to sinus rhythm, but its onset of action is much slower and its success rate less than adenosine, verapamil, or beta blockers; thus it is rarely used in this way at present. Digoxin is more commonly used orally to control the ventricular rate in chronic atrial fibrillation. When the patient with atrial fibrillation is at rest and vagal tone predominates, the ventricular rate can be

maintained between 60 and 100 beats/min in 40 to 60 percent of cases. However, when the patient begins to exercise, the decrease in vagal tone and increase in adrenergic tone combine to diminish digoxin's beneficial effects on AV node conduction.[307] Patients may experience a marked increase in ventricular rate with even mild exertion. Thus, digoxin is rarely used as a single agent to control the ventricular rate in chronic atrial fibrillation. The drug has little capacity to prevent episodes of *paroxysmal* atrial fibrillation or to control ventricular rate during episodes. Finally, digoxin is no more effective than placebo at terminating episodes of acute- or recent-onset atrial fibrillation.[467]

ADVERSE EFFECTS.

One of the main reasons that digoxin use has decreased is the potential for serious adverse effects and the narrow window between therapeutic and toxic concentrations. Digitalis toxicity produces a variety of symptoms and signs, including headache, nausea and vomiting, altered color perception and halo vision, and generalized malaise. More serious than these are digitalis-related arrhythmias. These include bradycardias due to a markedly enhanced vagal effect (sinus bradycardia or arrest, AV node block) and tachyarrhythmias that may be due to delayed afterdepolarization-mediated, triggered activity (atrial, junctional, and fascicular/ventricular tachycardia; see Chap. 22). Worsening renal function, advanced age, hypokalemia, chronic lung disease, hypothyroidism, and amyloidosis increase the patient's sensitivity to digitalis-related arrhythmias. The diagnosis can be confirmed using serum digoxin levels. Therapy for most bradycardias consists of withdrawal of digoxin; atropine or temporary pacing may be needed in symptomatic patients. Phenytoin can be used for control of atrial tachyarrhythmias, whereas lidocaine has been successful in treating infranodal tachycardias. Life-threatening arrhythmias can be treated with digoxin-specific antibody fragments. Electrical direct-current cardioversion should be performed only when absolutely necessary in the digitalis-toxic patient, because life-threatening VT or VF can result that can be very difficult to control.

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Electrotherapy of Cardiac Arrhythmias

Direct-Current Electrical Cardioversion

Electrical cardioversion offers obvious advantages over drug therapy in terminating tachycardia. Under conditions optimal for close supervision and monitoring, a precisely regulated "dose" of electricity can restore sinus rhythm immediately and safely. The distinction between supraventricular and ventricular tachyarrhythmias--crucial to the proper medical management of arrhythmias--becomes less significant, and the time-consuming titration of drugs with potential side effects is obviated.[468]

MECHANISMS.

Electrical cardioversion appears to most effectively terminate those tachycardias due to reentry, such as atrial flutter and atrial fibrillation, AV node reentry, reciprocating tachycardias associated with the WolffParkinson-White syndrome, most forms of VT, ventricular flutter, and VF. The electrical shock, by depolarizing all excitable myocardium and possibly by prolonging refractoriness, interrupts reentrant circuits and establishes electrical homogeneity that terminates reentry. The mechanism by which a shock successfully terminates VF has not been completely explained, although recent evidence suggests that hyperpolarization of cell membranes is an important effect.[469] If the precipitating factors are no longer present, interrupting the tachyarrhythmia for only the brief time produced by the shock may prevent its return for long periods even though the anatomical and electrophysiological substrates required for the tachycardia are still present.

Tachycardias thought to be due to disorders of impulse formation (automaticity) include parasystole, some forms of atrial tachycardia, nonparoxysmal AV junctional tachycardia,

and accelerated idioventricular rhythms. An attempt to cardiovert these tachycardias electrically is not indicated in most instances, because they typically recur within seconds after the shock. It has not been established whether cardioversion can terminate tachycardias due to enhanced automaticity or triggered activity.

TECHNIQUE.

Before elective cardioversion, a careful physical examination, including palpation of all pulses, should be performed. A 12-lead ECG is obtained before and after cardioversion, as well as a rhythm strip during the electroshock. The patient, who should be informed completely about what to expect, is in a fasting state and "metabolically balanced"; that is, blood gases, pH, and electrolytes should be normal with no evidence of drug toxicity. Withholding digitalis for several days before elective cardioversion in patients without clinical evidence of digitalis toxicity is not necessary, although patients in whom digitalis toxicity is suspected should not be electrically cardioverted until this situation is corrected. Maintenance antiarrhythmic drug administration 1 to 2 days before electrical cardioversion of patients with atrial fibrillation can revert some patients to sinus rhythm, help prevent recurrence of atrial fibrillation once sinus rhythm is restored, and help determine patient tolerance to the drug.

Self-adhesive pads applied in the standard apex-anterior or apex-posterior paddle positions have transthoracic impedances similar to paddles and are very useful in elective cardioversions or other situations in which there is time for their application, such as at the start of an EPS.[470] [471] Paddles 12 to 13 cm in diameter can be used to deliver maximum current to the heart, but the benefits of these paddles compared with those of 8 to 9 cm in diameter have not been clearly established. Larger paddles may distribute the intracardiac current over a wider area and may reduce shock-induced myocardial necrosis.

A synchronized shock (i.e., one delivered during the QRS complex) is used for all cardioversions except for very rapid ventricular tachyarrhythmias, such as ventricular flutter or VF (Fig. 23-14) . Data suggest that for internal cardioversion, shocks delivered late in the QRS complex during VT are more effective and have a lower risk of acceleration than those delivered near QRS onset.[472] Because myocardial damage increases directly with increases in applied energy, the minimum effective energy should be used. Therefore, shocks are "titrated" when the clinical situation permits. Except for atrial fibrillation, shocks in the range of 25 to 50 joules successfully terminate most SVTs and should be tried initially. If unsuccessful, a second shock of higher energy can be delivered. The starting level to terminate atrial fibrillation should be no less than 100 joules.[472A] If this fails, up to 360 joules can be used safely. Anteroposterior pads may have a higher efficacy rate by placing more of the atrial mass in the shock vector than is the case for apical-anterior pads. If 360 joules fails to convert the rhythm, repeated shocks at the same energy

Figure 23-14 *Top,* A synchronized shock (note synchronization marks in the apex of the QRS complex [arrow]) during ventricular tachycardia is followed by a single repetitive ventricular response and then

normal sinus rhythm. *Bottom,* A shock synchronized to the terminal portion of the QRS complex (arrow) in a patient with atrial fibrillation and conduction to the ventricle over an accessory pathway (Wolff-Parkinson-White syndrome) results in ventricular fibrillation that was promptly terminated by a 400-joule shock. Recording was lost for 1.5 seconds (arrow) owing to baseline drift after the shock.

may succeed by decreasing chest wall impedance; reversing pad polarity can occasionally help as well.[472B] Administration of ibutilide has been shown to facilitate electrical cardioversion of atrial fibrillation to sinus rhythm.[413] Intracardiac defibrillation can be tried if all attempts at external cardioversion fail.[473] [474] [475] For patients with stable VT, starting levels in the range of 25 to 50 joules can be employed. If there is some urgency to terminate the tachyarrhythmia, one can begin with higher energies. To terminate VF, 200 to 360 joules generally is used, although much lower energies (< 100 joules) terminate VF when the shock is delivered at the *very onset* of the arrhythmia, using adhesive pads in the electrophysiology laboratory, for example.[476] [477] [478] [479]

During elective cardioversion, a short-acting barbiturate such as methohexital, a sedative such as propofol, or an amnesic such as diazepam or midazolam can be used. A physician skilled in airway management should be in attendance, an IV route should be established, and monitoring of pulse oximetry, ECG, and blood pressure should be operating. All equipment necessary for emergency resuscitation should be immediately accessible. Before cardioversion, 100 percent oxygen may be administered for 5 to 15 minutes by nasal cannula or face mask and is continued throughout the procedure. Manual ventilation of the patient may be necessary to avoid hypoxia during periods of deepest sedation. Adequate sedation of the patient undergoing cardioversion is essential; some patients who have needlessly been shocked while awake (due to uneasiness of the physician with the arrhythmia) have declined further medical care for their arrhythmias after this experience out of concern they will again undergo cardioversion without appropriate sedation.

In 2 to 5 percent of patients with atrial fibrillation, sinus rhythm cannot be restored by external countershock, despite all the above measures including ibutilide pretreatment.[413] Very obese patients or those with severe obstructive lung disease are most frequently affected. In such cases, internal cardioversion can be performed using specially configured catheters with multiple large electrodes covering several centimeters of the distal portion of the catheter for distributing shock energy. Using standard percutaneous access, these catheters can be situated in the lateral right atrium and coronary sinus to achieve a shock vector across most of the atrial mass. With such configurations, internal shocks of from 2 to 15 joules are able to terminate atrial fibrillation in more than 90 percent of patients whose arrhythmia was refractory to transthoracic shock.

INDICATIONS.

As a rule, any tachycardia that produces hypotension, congestive heart failure, or angina and does not respond promptly to medical management should be terminated

electrically. Very rapid ventricular rates in patients with atrial fibrillation and the Wolff-Parkinson-White syndrome are often best treated by electrical cardioversion. In almost all instances, the patient's hemodynamic status improves after cardioversion. An occasional patient may develop hypotension, reduced cardiac output, or congestive heart failure after the shock. This may be related to complications of the cardioversion, such as embolic events, myocardial depression resulting from the anesthetic agent or the shock itself,[480] [481] hypoxia, lack of restoration of left atrial contraction despite return of electrical atrial systole,[482] or postshock arrhythmias. Direct-current countershock of digitalis-induced tachyarrhythmias is contraindicated.

Favorable candidates for electrical cardioversion of atrial fibrillation include those patients who (1) have symptomatic atrial fibrillation of less than 12 months' duration and derive significant hemodynamic benefits from sinus rhythm, (2) have embolic episodes, (3) continue to have atrial fibrillation after the precipitating cause has been removed (e.g., after treatment of thyrotoxicosis), and (4) have a rapid ventricular rate that is difficult to slow.[482A]

Unfavorable candidates include patients with (1) digitalis toxicity, (2) no symptoms and a well-controlled ventricular rate without therapy, (3) sinus node dysfunction and various unstable supraventricular tachyarrhythmias or bradyarrhythmias (often the bradycardia-tachycardia syndrome) who finally develop and maintain atrial fibrillation (which in essence represents a "cure" for the sick sinus syndrome), (4) little or no benefit from normal sinus rhythm who promptly revert to atrial fibrillation after cardioversion despite drug therapy, (5) a large left atrium and long-standing atrial fibrillation, (6) infrequent episodes of atrial fibrillation that revert spontaneously to sinus rhythm, (7) no mechanical atrial systole after the return of electrical atrial systole, (8) atrial fibrillation and advanced heart block, (9) cardiac surgery planned in the near future, and (10) antiarrhythmic drug intolerance. Atrial fibrillation is likely to recur after cardioversion in patients who have significant chronic obstructive lung disease, congestive heart failure, mitral valve disease (particularly mitral regurgitation), atrial fibrillation longer than 1 year, and an enlarged left atrium (>4.5 cm by echocardiography).

In patients with atrial flutter, slowing the ventricular rate by administering digitalis or terminating the flutter with an antiarrhythmic agent may be difficult, so electrical cardioversion is often the initial treatment of choice. For the patient with other types of SVT, electrical cardioversion may be employed when (1) vagal maneuvers or simple medical management (e.g., intravenous adenosine and verapamil) has failed to terminate the tachycardia and (2) the clinical setting indicates that fairly prompt restoration of sinus rhythm is desirable because of hemodynamic decompensation or electrophysiological consequences of the tachycardia. Similarly, in patients with VT, the hemodynamic and electrophysiological consequences of the arrhythmias determine the need and urgency for direct-current cardioversion. Electrical countershock is the *initial* treatment of choice for ventricular flutter or VF.[468] [483] [484] Speed is essential.

If, after the first shock, reversion of the arrhythmia to sinus rhythm does not occur, a higher energy level should be tried. When transient ventricular arrhythmias result after an unsuccessful shock, a bolus of lidocaine can be given before delivering a shock at

the next energy level. If sinus rhythm returns only transiently and is promptly supplanted by the tachycardia, a repeat shock can be tried, depending on the tachyarrhythmia being treated and its consequences. Administration of an antiarrhythmic agent intravenously may be useful before delivering the next cardioversion shock (such as ibutilide in resistant atrial fibrillation). After cardioversion, the patient should be monitored at least until full consciousness has been restored and preferably for several hours thereafter.

RESULTS.

Cardioversion restores sinus rhythm in 70 to 95 percent of patients, depending on the type of tachyarrhythmia. However, sinus rhythm remains after 12 months in less than one third to one half of the patients with chronic atrial fibrillation. Thus, maintenance of sinus rhythm, once established, is the difficult problem, not the immediate termination of the tachycardia. The likelihood of maintaining sinus rhythm depends on the particular arrhythmia, the presence of underlying heart disease, and the response to antiarrhythmic drug therapy. Atrial size decreases after termination of atrial fibrillation and restoration of sinus rhythm,[485] [486] and functional capacity improves.[487] [488] [489]

COMPLICATIONS.

Arrhythmias induced by electrical cardioversion generally are caused by inadequate synchronization, with the shock occurring during the ST segment or T wave. Occasionally, a properly synchronized shock can produce VF (see Fig. 23-14). Postshock arrhythmias usually are transient and do not require therapy. Embolic episodes are reported to occur in 1 to 3 percent of the patients converted from atrial fibrillation to sinus rhythm. Prior anticoagulation

for 2 to 3 weeks should be employed for patients who have no contraindication to such therapy and have had atrial fibrillation present for longer than 2 to 3 days or is of indeterminate duration. This is particularly true for those who are at high risk for emboli, such as those with mitral stenosis and atrial fibrillation of recent onset, a history of recent or recurrent emboli, a prosthetic mitral valve, an enlarged heart (including left atrial enlargement), or congestive heart failure. Anticoagulation with warfarin for at least 4 weeks *afterward* is recommended because restoration of mechanical function lags behind that of electrical systolic function, and thrombi can still form in largely akinetic atria, although they are electrocardiographically in sinus rhythm. Importantly, exclusion of left atrial thrombus by transesophageal echocardiography may not always preclude embolism after cardioversion of atrial fibrillation.[490] [491] [492] [493] Atrial thrombi may be present in patients with nonfibrillation atrial tachyarrhythmias such as atrial flutter and congenital heart disease.[494] The same pre-cardioversion and postcardioversion anticoagulation recommendations apply to these patients as well as to those with atrial fibrillation. Although direct-current shock has been demonstrated in animals to cause myocardial injury, studies in humans indicate that elevations of myocardial enzymes

after cardioversion are not common. ST segment elevation can occur immediately after elective direct-current cardioversion, although cardiac enzymes and myocardial scintigraphy may be unremarkable. A decrease in serum K^+ and Mg^{2+} can occur after cardioversion of VT.[495]

Cardioversion of VT also can be achieved by a chest thump. Its mechanism of termination probably relates to a mechanically induced PVC that interrupts a tachycardia. The thump cannot be timed very well and is probably only effective when delivered during a nonrefractory part of the cardiac cycle. The thump can alter a VT and possibly induce ventricular flutter or VF if it occurs during the vulnerable period of the T wave. Because there may be a slightly greater likelihood of converting a stable VT to VF than of terminating VT to sinus rhythm, the thump version should not be attempted unless a defibrillator is simply unavailable.

Implantable Electrical Devices for Treatment of Cardiac Arrhythmias

Implantable devices that monitor the cardiac rhythm and can deliver competing pacing stimuli and low- and high-energy shocks have been used effectively in selected patients and are discussed fully in Chapter 24 .

Ablation Therapy for Cardiac Arrhythmias

The purpose of catheter ablation is to destroy myocardial tissue by delivering electrical energy over electrodes on a catheter placed next to an area of the endocardium integrally related to the onset and/or maintenance of the arrhythmia. The first catheter ablation procedures were performed using direct-current shocks, but this energy source has been almost wholly supplanted by radio frequency (RF) energy, which is delivered from an external generator and destroys tissue by controlled heat production.[496] Lasers, cryothermy, and microwave energy sources have been used, but not commonly. Once a target tissue has been identified, the tip of the ablation catheter is maneuvered into apposition with this tissue. After stable catheter position and recordings have been assured, RF energy is delivered between the catheter tip and an indifferent electrode, usually an electrocautery-type grounding pad on the skin of the

Figure 23-15 Radio frequency lesion in human ventricular myocardium (explanted heart at the time of transplantation). A 30-second application of energy was made at the location denoted by arrows using the tip of the catheter shown. The lesion is 5 mm in diameter and has a clear border. A central depression in the lesion results from partial desiccation of tissue.

patient's thigh. Because energies in the RF portion of the electromagnetic spectrum are not conducted by cardiac tissue, RF energy instead causes resistive heating in the cells in close proximity to the catheter tip (i.e., these cells transduce the electrical energy into thermal energy). Once tissue temperature exceeds 50°C, irreversible cellular damage and tissue death occur. An expanding front of conducted heat emanates from the region of resistive heating while RF delivery continues, resulting in production of a homogenous hemispheric lesion of coagulative necrosis 3 to 5 mm in radius (Fig. 23-15)

. RF-induced heating of tissue that has inherent automaticity (His bundle, foci of automatic tachycardias) results in acceleration of a rhythm, whereas RF delivery during a reentrant arrhythmia typically causes slowing and termination of the arrhythmia. In most cases, RF delivery is painless, although ablation of atrial or RV tissue can be uncomfortable for some patients.

Radio Frequency Catheter Ablation of Accessory Pathways

LOCATION OF PATHWAYS.

The safety, efficacy, and cost-effectiveness of RF catheter ablation of an accessory AV pathway[496] [497] [498] [499] [500] [501] [502] have made ablation the treatment of choice in most adult and many pediatric patients who have AV reentrant tachycardia (AVRT)[503] or atrial flutter/fibrillation associated with a rapid ventricular response over the accessory pathway.[504] [505] [506] [507] However, the fact that the lesion size, when RF energy is delivered to an immature heart, can increase as the heart grows makes the long-term outlook for ablation less certain in the very young.[508] [509] [510] [511] [512] RF energy has replaced direct-current shock as the optimal energy source.[513] [514] [515]

An EPS is performed initially to determine that the accessory pathway is part of the tachycardia circuit or capable of rapid AV conduction during atrial fibrillation and to localize the accessory pathway (the optimal site for ablation). Pathways can exist in the right or left free wall or septum of the heart (Fig. 23-16) . Septal accessory pathways are further classified as anteroseptal, midseptal, and posteroseptal.[516] [517] [518] [519] Rare parahissian pathways can be distinguished from anteroseptal pathways.[517] Midseptal locations are true septal pathways, whereas those classified as anteroseptal generally have no septal connection but are located anteriorly along the central fibrous body or the right fibrous trigone at the right anterior free wall. Pathways classified as

Figure 23-16 Locations of accessory pathways by anatomic region. Tricuspid and mitral valve annuli are depicted in a left anterior oblique view. Locations of coronary sinus, AV node, and bundle of His are shown. Accessory pathways may connect atrial to ventricular myocardium in any of the regions shown.

posteroseptal are located posterior to the central fibrous body within the so-called pyramidal space, which is bounded by the posterior superior process of the left ventricle and the inferomedial aspects of both atria. Anteroseptal pathways are found near the His bundle, and accessory pathway activation potential as well as His bundle potential can be recorded simultaneously from a catheter placed at the His bundle region. Midseptal pathways are classified as right midseptal if an accessory pathway potential is recorded through a catheter located in an area bounded anteriorly by the tip electrode of the His bundle catheter and posteriorly by the coronary sinus ostium. Pathways located in a similar region but which can be ablated only from a left-sided approach are called

left midseptal pathways. Right posteroseptal pathways insert along the tricuspid ring in the immediate vicinity of the coronary sinus ostium, whereas left posteroseptal pathways are close to the terminal portion of the coronary sinus and may be located at a subepicardial site around the proximal coronary sinus, within a middle cardiac vein or coronary sinus diverticulum, or subendocardially along the ventricular aspect of the mitral annulus. Pathways at all locations and in all age groups can be ablated successfully.[520] [521] Multiple pathways are present in about 5 percent of patients.[522] [523] Occasional epicardial locations may be more easily approached from within the coronary sinus.[524] Conduction block after ablation usually occurs between the local atrial electrogram and the accessory pathway potential.[525]

ABLATION SITE.

The optimal ablation site can be found by direct recordings of the accessory pathway (Fig. 23-17) , although deflections that mimic accessory pathway potentials can be recorded at other sites. The ventricular insertion site can be determined by finding the site of the earliest onset of the ventricular electrogram in relation to the onset of the delta wave. Other helpful guidelines are unfiltered unipolar recordings that register a QS wave and the

Figure 23-17 Wolff-Parkinson-White syndrome. *A,* Two beats of atrial pacing are conducted over the accessory pathway (dark arrow in Abl_{bi} recording, from the site of the accessory pathway) resulting in a delta wave on the ECG; a premature atrial stimulus (center) encounters accessory pathway refractoriness (white arrow) instead conducting over the AV node and bundle of His, resulting in a narrow QRS complex and starting an episode of AVRT. After each narrow QRS complex is an atrial deflection, the earliest of which is recorded at the ablation site (gray arrow). *B,* Ablation of this pathway is accomplished by delivery of radio frequency (RF) energy from the ablation catheter tip. Dark arrow denotes onset of RF energy delivery; two QRS complexes later, the delta wave is abruptly lost (gray arrow) owing to elimination of conduction over the accessory pathway. T wave inversion in lead 3 is due to "memory" (see Chap. 22).

shortest AV conduction time during maximal preexcitation. A major ventricular potential synchronous with the onset of the delta wave can be a target site in left-sided preexcitation, whereas earlier ventricular excitation in relation to the delta wave is to be found for right-sided preexcitation. The atrial insertion site of manifest or concealed pathways (i.e., delta wave present or absent, respectively) can be found by locating the site showing the shortest ventriculoatrial interval during retrograde conduction over the pathway. Reproducible mechanical inhibition of accessory pathway conduction during catheter manipulation[526] and subthreshold stimulation [527] also have been used to determine the optimal site. Accidental catheter trauma should be avoided, however, because this can "hide" the target for prolonged periods.[528] Intracardiac echocardiography can be helpful at times in delineating unusual anatomy, guiding transseptal puncture, and determining adequacy of catheter contact at ablation sites.[529] [530]

Accessory pathways often cross the left AV groove obliquely, with the atrial insertion site located closer to the ostium of the coronary sinus.[531] Consequently, the earliest site of retrograde atrial activation and the earliest site of anterograde ventricular activation are not directly across the AV groove from each other. Ablation from the atrial aspect is from a site more proximal along the coronary sinus than is the ablation site from a ventricular approach. Identification of the earliest site of atrial activation is usually performed during orthodromic AVRT or during relatively rapid ventricular pacing, such that retrograde conduction using the AV node does not confuse assessment of location of the earliest atrial activation.

Successful ablation sites should exhibit stable fluoroscopic and electrical characteristics. During orthodromic AVRT, the interval between the onset of ventricular activation in any lead and local atrial activation is usually 70 to 90 milliseconds at the successful ablation site (see Fig. 23-17). When thermocouple- or thermistor-tipped ablation catheters are used, a stable rise in catheter tip temperature is a helpful indicator of catheter stability and adequate contact between the catheter and tissue. In such an instance, the tip temperature generally exceeds 50°C.[532] The retrograde transaortic and transseptal approaches have been used with equal success to ablate accessory pathways located on the left side of the heart.[533] [534] Routine EPS performed weeks after the ablation procedure is generally not indicated but should be considered in patients who have recurrent delta wave or symptoms of tachycardia.[535] [536]

Patients with atriofascicular accessory pathways have connections consisting of a proximal portion responsible for conduction delay and decremental conduction properties and a long distal segment located along the endocardial surface of the right ventricular free wall that has electrophysiological properties similar to the right bundle branch. The distal end of the right atriofascicular accessory pathway can insert into the apical region of the right ventricular free wall close to the distal right bundle branch or can actually fuse with the latter.[537] Right atriofascicular accessory pathways actually may represent a duplication of the AV conduction system and can be localized for ablation by recording potentials from the rapidly conducting distal component crossing the tricuspid annulus (analogous to the His bundle) and extending to the apical region of the right

Figure 23-18 AV node reentry. *A,* Two atrial paced complexes from the coronary sinus (CS) are followed by an atrial premature stimulus at coupling interval 260 msec, resulting in an AH interval of 145 msec. *B,* The same atrial drive train is followed by an atrial extrastimulus 10 msec earlier than before (250 msec). This results in a marked increase in the AH interval to 210 msec, after which AVNRT ensues, because the extrastimulus encounters block in a "fast" AV node pathway, conducts down a "slow" pathway, and then conducts back up the "fast" pathway in a repeating fashion. Dark arrows denote atrial electrograms coincident with QRS complexes, characteristic of the most common type of AV node reentry.

ventricular free wall.[538] Ablation attempts should be performed more proximally to avoid inadvertently ablating the distal right bundle branch, which could actually be proarrhythmic and create incessant tachycardia by lengthening the reentrant circuit.[452] [539] [540]

INDICATIONS.

Ablation of accessory pathways is indicated in patients with symptomatic AVRT that is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy. It is also indicated in patients with atrial fibrillation (or other atrial tachyarrhythmias) and a rapid ventricular response by means of an accessory pathway when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy. Other candidates might include patients with AVRT or atrial fibrillation with rapid ventricular rates identified during EPS of another arrhythmia; asymptomatic patients with ventricular preexcitation whose livelihood, profession, important activities, insurability, mental well-being, or the public safety would be affected by spontaneous tachyarrhythmias or by the presence of the ECG abnormality; patients with atrial fibrillation and a controlled ventricular response by means of the accessory pathway; and patients with a family history of sudden cardiac death.[119] Not all patients with accessory pathways need treatment; however, ablation has such a high success rate and low complication rate that in many centers patients who need any form of therapy are referred for catheter ablation.

RESULTS.

From the results of a survey conducted by the North American Society of Pacing and Electrophysiology (NASPE),[155] successful ablation of left free wall accessory pathways was obtained in 2312 of 2527 (91 percent) patients; for septal accessory pathways, 1115 of 1279 (87 percent); and for right free wall accessory pathways, 585 of 715 (82 percent). Significant complications were reported in 94 of 4521 patients (2.1 percent), and there were 13 procedure-related deaths in 4521 patient studies (0.2 percent). In Europe, the complication rate was 4.4 percent, with three deaths in 2222 patients.[154] A large study of patients using a temperature-controlled ablation system had similar success rates (overall success, 398/465 [93 percent] with an 8 percent recurrence rate).[541]

Radio Frequency Catheter Modification of the AV Node for AVNRTs

Atrioventricular node reentry is a very common cause of SVT episodes. Although controversy still exists as to the exact nature of the tachycardia circuit, abundant evidence indicates that two pathways in the region of the AV node participate, one with relatively fast conduction but long refractoriness and the other with shorter refractoriness but slower conduction. PACs can encounter refractoriness in the fast pathway, conduct down the slow pathway, and reenter the fast pathway retrogradely, initiating AV node reentrant SVT (Fig. 23-18) . Although this is the most common presentation of AV node reentry, some patients have what appears to be propagation in the opposite direction in this circuit (anterograde fast, retrograde slow) as well as a "slow-slow" variant. Two or more of these variants can exist in the same patient (Fig.

23-19) .

FAST-PATHWAY ABLATION.

Ablation can be performed to eliminate conduction in the fast pathway or the slow pathway.[542] [543] [544] [545] [546] [547] [548] [549] [550] [551] [552] [553] [554] [555] For fast-pathway ablation, the electrode tip is positioned along the AV node-His bundle axis in the anterosuperior portion of the tricuspid annulus. The catheter is gradually withdrawn until the atrial electrogram amplitude equals or exceeds that of the ventricular electrogram and the His bundle recording is either absent or extremely small (0.05 mV). During energy delivery, the ECG is monitored for PR prolongation and/or the occurrence of AV block. If accelerated junctional rhythm is noted during delivery of RF energy, the atrium can be paced at a faster rate to ensure integrity of AV conduction. The initial RF pulse is

Figure 23-19 Three variants of AV node reentrant supraventricular tachycardia (SVT) in the same patient. Recordings as in other figures; CL = cycle length. The left panel shows the most common type of AV node SVT (anterograde slow pathway, retrograde fast); atrial activation is coincident with ventricular activation. The center panel shows "atypical" AV node reentry, with anterograde fast pathway conduction and retrograde conduction over a slow pathway. A rare variety is shown in the right panel, with anterograde conduction over a slow pathway and retrograde conduction over a second slow pathway. Note the similar atrial activation sequences in the latter two (coronary sinus before right atrium), as distinct from that of "slow-fast" AV node reentry (coronary sinus and right atrial activation nearly simultaneous). Note also the different P-QRS relationships, from simultaneous activation (left panel, short RP interval) to P in front of the QRS (middle panel, long RP interval) and P midway in the cardiac cycle (right panel).

delivered at 15 to 20 watts for 10 to 15 seconds and gradually increased. Endpoints are PR prolongation, elimination of retrograde fast-pathway conduction, and noninducibility of AVNRT. An alternative approach is to apply RF current at the site of earliest retrograde atrial activation during tachycardia. RF current should be discontinued if the PR interval is prolonged by more than 50 percent or if AV block results.[542] [543] [555]

The major electrophysiological effects of fast-pathway ablation are elimination or marked attenuation of ventriculoatrial conduction, an increase in the AH interval, and elimination of dual AV node physiology. Titrating the energy may reduce the risk of complete AV block, which is the most important complication associated with ablation of the fast pathway. If it is going to occur, complete AV block usually occurs during the ablation procedure, but some episodes have occurred 24 hours or more after the procedure, possibly as a result of the extension of the RF lesion over time. The tachycardia recurrence rate after successful fast-pathway ablation is 10 to 15 percent.[542] [543] [555]

SLOW-PATHWAY ABLATION.

The slow pathway can be located by mapping along the posteromedial tricuspid annulus close to the coronary sinus os. Electrogram recordings are obtained with an atrial-to-ventricular electrogram ratio of less than 0.5 and either a multicomponent atrial electrogram or a recording of possible slow-pathway potential.[547] [548] In the anatomical approach,[542] [549] target sites are selected fluoroscopically. Serial RF lesions are created in each region, starting at the most posterior site (near the coronary sinus os) and progressing to the more anterior locus (closer to the His bundle recording site). Finally, the slow pathway can be localized during ventricular pacing, seeking the site of earliest atrial activation when conducting over the slow pathway. An accelerated junctional rhythm (Fig. 23-20) usually occurs when RF energy is applied at a site that will result in successful elimination of SVT. The success rate with the anatomical or electrogram mapping approach is equivalent, and, most often, combinations of both are used, yielding success rates approaching 100 percent, with less than a 1 percent chance of complete heart block.

Slow-pathway ablation results in an increase in the anterograde AV block cycle length and AV node ERP without a change in the AH interval or retrograde conduction properties of the AV node (see Chap. 25). Approximately 40 percent of patients can have evidence of residual slow-pathway function after successful elimination of sustained AVNRT, usually manifested as persistent dual AV node physiology and single AV node echoes during atrial extrastimulation. The endpoint for slow-pathway ablation is the elimination of sustained AVNRT both with and without an infusion of isoproterenol.[544] [551] [553]

AVNRT recurs in about 5 percent of patients after slow-pathway ablation. In some patients, the ERP of the fast pathway decreases after slow-pathway ablation, possibly due to electrotonic interaction between the two pathways.[308] [556] Atypical forms of reentry can result after ablation,[557] as can apparent parasympathetic denervation, resulting in inappropriate sinus tachycardia.[558]

At present, the fast-pathway approach is appropriate when the slow-pathway approach has been found unsuccessful and perhaps in some patients in whom the induction of AVNRT is not reproducible, because fast-pathway ablation provides a reliable endpoint of PR prolongation, in contrast to slow-pathway ablation, for which the only reliable endpoint is elimination of tachycardia. Ablation of the slow pathway is a safe and effective means for treating atypical AVNRT. In patients with AVNRT undergoing slow-pathway ablation, junctional ectopy during application of RF energy is a sensitive but nonspecific marker of successful ablation,[559] [560] [561] occurring in longer bursts at effective target sites than at ineffective sites. Ventriculoatrial conduction should be expected during the junctional ectopy, and poor ventriculoatrial conduction or actual block is a predictor of AV block in patients undergoing RF ablation of the slow pathway.

INDICATIONS.

RF catheter ablation for AV node reentrant tachycardia can be considered in patients with symptomatic, sustained AVNRT that is drug resistant or when the patient is drug intolerant or does not desire long-term drug treatment. The procedure also can be considered in patients with sustained AVNRT identified during EPS or catheter ablation of another arrhythmia or when finding dual AV node pathway physiology and atrial echoes but without AVNRT during EPS in a patient suspected of having AVNRT clinically.[119]

RESULTS.

Results of the NASPE survey indicate that 3052 patients had slow-pathway ablation with a 96 percent reported success rate, whereas 255 had fast-pathway ablation that was successful in 229 (90 percent). Significant complications occurred in 0.96 percent, but no procedure-related deaths were reported.[155] In Europe, the complication rate was 8.0 percent, mostly due to AV block after fast-pathway ablation, and there were no deaths in 815 patients.[154] [562] Most centers currently employ slow-pathway ablation, resulting in a procedural success rate of 98 percent, recurrence rate of less than 2 percent and incidence of heart block requiring permanent pacing of less than 1 percent.[541]

Radio Frequency Catheter Ablation of Atrial Tachycardia, Sinus Node Reentry/Inappropriate Sinus Tachycardia, and Atrial Flutter

Atrial arrhythmias amenable to catheter ablation include atrial tachycardias that are automatic or reentrant,[457] [563] [564] [565] sinus node reentry,[566] incessant/inappropriate sinus tachycardia, junctional tachycardias,[567] and typical and atypical atrial flutter.[568] [569] [570] In "focal" atrial tachycardias (automatic

Figure 23-20 AV node slow pathway modification for cure of AV node reentrant SVT. Recordings as in prior figures. The ablation recording (gray arrow) shows a slurred deflection between atrial and ventricular electrogram components; this may represent the AV node slow pathway deflection (but it is not the bundle of His deflection, which is instead recorded from a separate catheter 15 mm away). Shortly after the onset of RF delivery (dark arrow), an accelerated junctional rhythm begins and gradually speeds up further. Retrograde conduction is present during the junctional rhythm.

Figure 23-21 Atrial tachycardias. *A,* Automatic atrial tachycardia arising in the left inferior pulmonary vein (LIPV). A sinus beat is shown at left, followed by a fusion beat (F) of sinus and tachycardia activation. The last three beats in the panel are atrial tachycardia. The ablation catheter was within the LIPV and recorded a sharp potential (gray arrow) 40 msec before the P wave onset (dashed line). Ablation at this site terminated the tachycardia. *B,* Intraatrial reentrant tachycardia in a patient who had undergone atrial septal defect repair years earlier. The ablation catheter is in the posterior right atrium (PRA), where a

fragmented signal is recorded. A portion of this electrogram (dark arrow) precedes the P wave onset during tachycardia (dashed line) by 70 msec. Ablation at this site terminated the tachycardia.

or triggered foci), activation mapping is used to determine the site of the atrial tachycardia by recording the earliest onset of local activation. Ten to 15 percent of patients can have multiple atrial foci. Sites tend to cluster near the pulmonary veins in the left atrium and the mouths of the atrial appendages and along the crista terminalis on the right (Fig. 23-21 *A*). Reentrant atrial tachycardia appears to occur more commonly in the setting of structural heart disease, in particular after prior atrial surgery. The region of slow conduction is not in a constant anatomical location but varies from patient to patient depending on the operation performed. Therefore, careful review of operative reports and electrophysiological mapping is essential. The atriotomy scar often plays an important role in the genesis of the tachycardia. The ablation strategy is to identify regions with diastolic atrial activation during tachycardia that can be proven by pacing techniques to be integral to the tachycardia (see Fig. 23-21 *B*). Focal ablation of these sites can then be performed, but in many cases tachycardia can still be initiated (often at a slower rate) or it recurs after the procedure. Because these sites are typically located at the ends of prior scars or surgical incisions, another technique is to make a line of ablation lesions from the end of the scar to the nearest electrical barrier, such as the tricuspid annulus or a caval orifice. Reentry can thus be prevented. This technique is analogous to that used in curing atrial flutter (see later).

SINUS NODE ABLATION.

When the sinus node area is to be ablated, it can be identified anatomically as well as electrophysiologically, and ablation lesions are usually placed between the superior vena cava and crista terminalis. Care must be taken in applying RF energy at the most cephalad sites first; initial ablation performed farther down the crista terminalis does not alter the atrial rate but may damage subsidiary pacemaker regions that may be needed after the sinus node is eventually ablated. Recurrence rates are high after sinus node modification (up to 30 percent), and in other cases pacemaker therapy is required after ablation because of inadequate atrial rates at rest or with exercise.

ATRIAL FLUTTER.

Understanding the reentrant pathway for typical atrial flutter (negative sawtooth waves in leads II, III, and aVF at a rate of about 300 beats/min) has been essential for developing an ablation approach. Reentry in the right atrium, with the left atrium passively activated, constitutes the mechanism of typical atrial flutter, with a caudocranial activation along the right atrial septum and a craniocaudal activation of the right atrial free wall (Fig. 23-22 *A*). In some cases a zone of slow conduction exists in the low right atrium, which is typically bounded by the tricuspid annulus, the inferior vena cava, and the coronary sinus.[571] [572] [573] In other cases, conduction velocity is more uniform throughout the large circuit. Placing an ablative lesion between any two anatomical barriers that transect a portion of the circuit necessary for perpetuation of reentry can be curative. Typically, this is across the isthmus of atrial tissue between the tricuspid annulus and inferior vena caval orifice, a relatively narrow point in the circuit. Successful ablation can be accomplished where the advancing flutter wavefront enters

this zone in the low inferolateral right atrium, near the exit of this zone at the inferomedial right atrium, or in between these sites. Lesions can be guided anatomically or electrophysiologically. Less commonly, the direction of wavefront propagation in this large right atrial circuit is reversed ("clockwise" flutter proceeding cephalad up the right atrial free wall and caudad down the septum, with upright flutter waves in the inferior leads [see Fig. 23-22 *A*]). This arrhythmia, which has been called "atypical atrial flutter," may also be ablated using the same techniques as with more typical atrial flutter. These two arrhythmias constitute "isthmus-dependent" flutter and are distinct from other rapid atrial arrhythmias that may have similar ECG appearance but utilize different (and often multiple) circuits in other parts of the right or left atrium. Ablation can be more difficult in these cases, which often occur in the setting of advanced lung disease or after cardiac surgery.

The endpoint of flutter ablation procedures was initially termination of flutter with RF application and noninducibility of the arrhythmia. However, using these criteria, up to 30 percent of patients had recurrent flutter. In the last several years, the endpoint of ablation has changed to ensuring a line of bidirectional block in the tricuspid-inferior vena caval isthmus by pacing from opposite sides of the isthmus (see Fig. 23-22 *B*). With the use of these criteria, recurrence rates have fallen to less than 5 percent.

INDICATIONS.

Candidates for RF catheter ablation include patients with atrial tachycardia, sinus node reentry, inappropriate sinus tachycardia, or atrial flutter that is drug resistant; those who are drug intolerant; or those who do not desire long-term drug therapy.[119]

Figure 23-22A Two forms of atrial flutter are shown from the same patient (see also Fig. 23-22 *B*). A "halo" catheter with 10 electrode pairs is situated on the atrial side of the tricuspid annulus (TA), with recording sites displayed from the top of the annulus ("12:00") to the inferomedial aspect ("5:00"), as shown in fluoroscopic views in *B.* On the left, the wavefront of atrial activation proceeds in a "clockwise" fashion (arrows) along the annulus, whereas in the right panel the direction of propagation is the reverse.

RESULTS.

From the U.S. NASPE survey, 371 patients underwent ablation for atrial tachycardia and atrial flutter with a success rate of 75 percent with three significant complications (0.8 percent) and no deaths.[155] The complication rate was 5 percent in the European survey, and there were no deaths in 141 patients.[154]

Ablation and Modification of Atrioventricular Conduction for Atrial Tachyarrhythmias

In some patients with atrial tachyarrhythmias who have rapid ventricular rates despite

optimal drug therapy, RF ablation can be used to modify AV conduction to control the ventricular rates. To achieve RF catheter ablation of AV conduction, a catheter is placed across the tricuspid valve and positioned to record the largest His bundle electrogram associated with the largest atrial electrogram. RF energy is applied until complete AV block is achieved and is continued for an additional 30 to 60 seconds. If no change in AV conduction is observed after 15 seconds of RF ablation, the catheter is repositioned and the attempt is repeated. In occasional patients, attempts at RF ablation using this right-sided heart approach fail to achieve heart block. These patients can undergo an attempt from the left ventricle with a catheter positioned along the posterior interventricular septum just beneath the aortic valve to record a large His bundle electrogram. Energy is applied between the catheter electrode and the skin patch or between catheters in the left and right ventricles. Success rates approach 100 percent in most studies today, with recurrence of AV conduction in less than 5 percent.[541] [574] Improved left ventricular function can result from both control of ventricular rate during atrial fibrillation, as well as withdrawal of rate-controlling medications with negative inotropic action.[575]

In some cases, the AV junction can be modified to merely slow the ventricular rate without producing complete AV block by ablation in the region of the slow pathway, as described under AV node modification for AV node reentry. Initial success rates for slowing the ventricular response are quite good; however, long-term results are less consistent.[576] Some patients have a gradual increase in ventricular rate to nearly preablation levels, whereas late complete heart block may occur in others. Nonetheless, this procedure can be tried before producing complete AV block.[577] [578] [579]

INDICATIONS.

Ablation and modification of AV conduction can be considered in (1) patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates unless primary ablation of the atrial tachyarrhythmia is possible; (2) similar patients when drugs are not tolerated or the patient does not wish to take them, even though the ventricular rate can be controlled; (3) patients with symptomatic, nonparoxysmal, junctional tachycardia that is drug resistant or by whom drugs are not tolerated or are not desired; (4) patients resuscitated from sudden cardiac death due to atrial flutter or atrial fibrillation

Figure 23-22B Ablation of the isthmus of atrial tissue between the tricuspid annulus and inferior vena caval orifice for cure of atrial flutter. Recordings are displayed from the multipolar catheter around much of the circumference of the tricuspid annulus (see left anterior oblique fluoroscopy images). Ablation of this isthmus is performed during coronary sinus pacing. In the two beats on the left, atrial conduction proceeds in two directions around the tricuspid annulus, as indicated by arrows and recorded along the halo catheter. In the two beats on the right, ablation has interrupted conduction in the floor of the right atrium, eliminating one path for transmission along the tricuspid annulus. The halo catheter now records conduction proceeding all the way around the annulus. This demonstrates unidirectional block in the

isthmus; block in the other direction may be demonstrated by pacing from one of the halo electrodes and observing a similar lack of isthmus conduction. (The bundle of His recording in the right panel is lost owing to catheter movement.)

with a rapid ventricular response in the absence of an accessory pathway; and (5) patients with a dual-chamber pacemaker and a pacemaker-mediated tachycardia that cannot be treated effectively by drugs or by reprogramming the pacemaker.[119] The last three situations are rarely encountered.

RESULTS.

Results from the U.S. survey indicated that the procedure was successful in producing complete AV block in 95 percent of 1600 patients, with significant complications occurring in 21 (1.3 percent) and two procedure-related deaths (0.1 percent).[155] In Europe, the complication rate was 3.2 percent, and there was 1 death in 900 patients.[154] In early studies, up to 4 percent of patients had an episode of sudden death after AV junction ablation despite adequate pacemaker function, presumably due to relative bradycardia after long periods of rapid ventricular rates.[541] In one study, 6 of 100 patients died suddenly when the initial pacing rate was set to 60 beats/min, but none of 135 died suddenly when the rate was set to 90 beats/min for 1 to 3 months after ablation.[580]

Radio Frequency Catheter Ablation of Atrial Fibrillation

In recent years, considerable progress has been made in understanding the pathophysiology of atrial fibrillation. The

use of this information has translated directly into therapeutic advances. For example, it is now recognized that a significant proportion of patients with paroxysmal atrial fibrillation in the absence of structural heart disease have a focal origin of the arrhythmia; that is, very rapid discharges from a focal source (often in a pulmonary vein or on the crista terminalis) drive the atrium more rapidly than it can uniformly conduct, leading to the ECG appearance of atrial fibrillation.[581] [582] [583] [584] If this focus can be located and successfully ablated, recurrences of atrial fibrillation are prevented. Patients in this group typically have frequent isolated PACs that can be detected with ambulatory ECG monitoring. In some, the onset of spontaneous atrial fibrillation can be observed after one or more PACs. A significant problem with focal atrial fibrillation ablation is that some patients do not have a sufficient amount of PACs to allow mapping. In some cases, burst pacing, isoproterenol infusion, and removal of sedation during the procedure may allow expression of PACs and atrial fibrillation.

The surgical Maze procedure (see later) has become established as a successful technique for permanently restoring sinus rhythm. In 1994, the first human reports appeared of replicating the surgically induced lines of block in the atria using catheter

ablation.[585] The intent of the procedure is to compartmentalize the atrial muscle into segments too small to support fibrillation wavefronts yet have the segments connected enough to participate in contraction. Several techniques have been used, including creation of long, linear RF lesions limited to either the right or left atrium or both. It appears that the procedure is capable of restoring sinus rhythm, but many patients have recurrences of atrial fibrillation, atrial flutter, or rapid, regular tachycardias arising in the left atrium ("left atrial flutter") and require subsequent left atrial procedures to eliminate these arrhythmias.[586] Procedure durations can exceed 8 hours, and fluoroscopy times more than 90 minutes are not uncommon. Because of the length of time spent in the left atrium and the large areas of endocardial damage produced to successfully make the lines of block, patients must be vigorously anticoagulated during the procedures. This increases the risk of bleeding complications and still has not entirely prevented thromboemboli related to the procedure. In addition, there have been reports of pulmonary vein stenosis with consequent pulmonary venous hypertension after extensive ablations within the pulmonary veins.[586A]

INDICATIONS.

Candidates for focal atrial fibrillation ablation have paroxysmal atrial fibrillation in the absence of structural heart disease, and frequent PACs on monitoring, and include those whose atrial fibrillation is either refractory to medications or who prefer not to take medications. Patients in whom linear ablation for atrial fibrillation might be considered are those with some degree of structural heart disease and persistent or chronic atrial fibrillation for whom maintenance of sinus rhythm is important and in whom atrial fibrillation recurs despite standard antiarrhythmic drugs or in whom drug therapy is not tolerated or preferred.

RESULTS.

Success rates of ablation for focal atrial fibrillation range from 40 to 85 percent. As noted earlier, the inability to observe and map PACs is a major limitation of this procedure. Procedures for making linear ablations in the left or right atrium are still undergoing refinement. Preliminary data suggest a success rate of about 30 percent in preventing recurrences of atrial fibrillation for right atrial-only procedures and up to 80 percent success for primarily left atrial procedures (often including a "flutter lesion" in the floor of the right atrium, because many patients undergoing a purely left atrial procedure have subsequent episodes of flutter). The risk of stroke related to extensive left atrial ablation is approximately 5 percent even with rigorous anticoagulation regimens. Although surgical procedures involving incision and isolation of atrial myocardium have been devised to eliminate atrial fibrillation and their feasibility has been demonstrated, catheter techniques for

Figure 23-23 Ventricular tachycardia and pacemapping. All 12 surface ECG leads are shown along with intracardiac recordings during VT. The Abl_{1-2} recording shows a small deflection occurring early in electrical diastole (arrow) 110 msec before the onset of the QRS (dashed line). In the right panel, pacing is performed from this site. This produces an identical QRS complex in each lead, with a stimulus-QRS

onset interval similar to the electrogram-QRS onset interval during VT. Ablation at this site eliminated VT in 2 seconds. RVOT = right ventricular outflow tract.

eliminating atrial fibrillation are in the relatively early stage of development, but preliminary success has been reported.[585] [587] [588] [589] [590] [591] [591A] [592] [593] [593A]

Other nonpharmacological modalities for the treatment of atrial fibrillation, such as preventive pacing[594] and implantable atrial defibrillators/atrial rhythm management devices,[595] are discussed in Chapter 24 .

Radio Frequency Catheter Ablation of Ventricular Tachycardia

In general, the success rate for ablation of VTs is lower than for AV node or AV reentry.[439] [440] [596] [597] [598] [599] [600] [601] [602] [603] [604] [605] [606] [607] [608] [609] This may be related to the fact that this procedure is often a last resort in patients with drug-resistant VTs but also relates to more difficult mapping in the ventricles. Furthermore, the VT induction must be reproducible, uniform in QRS morphology from beat to beat, sustained, and hemodynamically stable so that the patient can tolerate the VT long enough during the procedure to undergo the extensive mapping necessary to localize optimal ablation target sites. (Patients with several electrocardiographically distinct, uniform morphologies of VT can still be candidates for ablation, because in many instances a common reentrant pathway is shared by two or more VT morphologies.[610]) Also, the origin of the VT must be fairly circumscribed and endocardially situated (rare cases of successful ablation only from the epicardial aspect have been reported[611]). Very rapid VT, polymorphic VT, and infrequent, nonsustained episodes are not amenable to this form of therapy at this time.[596] [609]

RF catheter ablation of VT can be divided into idiopathic VT that occurs in patients with essentially normal hearts,[439] [440] [596] [599] [600] [603] [605] [609] VT that occurs in a variety of disease settings but without coronary artery disease, and VT in patients with coronary artery disease and prior myocardial infarction.[597] [601] [602] [604] [605] [606] [609] In the first group, the VTs arise most commonly in the right ventricular outflow tract and less often in the inflow tract. Initiation of tachycardia can be facilitated by catecholamines. The majority of left VTs are septal in origin and have a characteristic QRS configuration (right bundle branch block, superior axis); other VTs occur less commonly and arise from other areas of the left ventricle, including the left ventricular outflow tract, that have similar ECG appearance and clinical behavior to those arising in the right ventricular outflow tract (see Fig. 23-8). Abnormal patterns of sympathetic innervation may be present in some.[612] VTs in abnormal hearts without coronary artery disease can be due to bundle branch reentry, a characteristic of dilated cardiomyopathies. In these patients, ablation of the right bundle branch eliminates the tachycardia.[613] VT can occur in right ventricular dysplasia, sarcoidosis, Chagas' disease, hypertrophic cardiomyopathy, and a host of other noncoronary disease problems (see Chap. 25).

Activation mapping[598] [602] and pace mapping are effective in patients with idiopathic VTs to locate the site of origin of the VT. In activation mapping, the timing of sampled endocardial electrograms from the mapping catheter is compared with the onset of the surface QRS complex. Sites that are activated before the surface QRS onset are near the origin of the VT (see Figs. 23-8 and 23-23). In idiopathic VT, ablation at a site at which the unipolar electrogram shows a "QS" complex may yield greater success than if an "rS" potential is observed (Fig. 23-24) . Pace mapping involves stimulation of various ventricular sites to initiate a QRS contour that duplicates the QRS contour of the spontaneous VT, thus establishing the apparent site of origin of the arrhythmia (see Fig. 23-23). This technique is limited by several methodological problems but may be useful when the tachycardia cannot be initiated and when a 12-lead ECG has been obtained during the spontaneous VT. Purkinje potentials can be recorded during VT from sites at which ablation will cure VT in most patients with left VTs that have right bundle branch block/superior axis.[440] [596] [609] Localization of optimal ablation sites for VT in patients with coronary artery disease and prior infarction is more difficult than in patients with structurally normal hearts because of the altered anatomy and electrophysiology. [614] Pace mapping has lower sensitivity and specificity than it does for idiopathic VT. Furthermore, reentry circuits can sometimes be large and resistant to the relatively small lesions produced by RF catheter ablation in scarred endocardium. Finding a protected region of diastolic activation used as a critical part of the reentrant circuit is desirable, because ablation at this site has a good chance of eliminating the tachycardia (Fig. 23-25) . Because of the extensive derangement in electrophysiology caused

Figure 23-24 Recordings from unsuccessful and successful ablation sites in a patient with idiopathic ventricular tachycardia arising in the inferior right ventricular wall. In the recordings from the unsuccessful ablation site, the unipolar signal (arrow) has a small "r" wave, indicating that a portion of the wavefront from the focus of tachycardia was approaching the site from elsewhere. At the successful site, the unipolar recording has a "QS" configuration, indicating all depolarization was emanating from this site. In each site, the bipolar recording (Abl_{1-2}) occurs an identical 43 msec before QRS onset (dashed lines).

Figure 23-25 Radio frequency ablation of postinfarct ventricular tachycardia (VT). Recordings are as in previous figures. The electrogram in the ablation recording (vertical arrow) precedes the QRS onset (dashed line) by 131 msec. Ablation here (RF on at diagonal arrow) results in slight deceleration of VT before termination in 1.3 seconds. Temperature monitored from the catheter tip had just peaked (approximately 70°C) at the time VT terminated.

by the infarction, many areas of the ventricle may have diastolic activation but not be relevant to the perpetuation of the VT. These "bystander sites" make activation mapping more difficult.

In patients without structural heart disease, only a single VT is usually present, and

catheter ablation of that VT is curative. In patients with extensive structural heart disease, especially those with prior myocardial infarction, multiple VTs are usually present. Catheter ablation of a single VT in such patients may only be palliative and may not eliminate the need for further antiarrhythmic therapy. The genesis of multiple tachycardia morphologies is not clear, although in some cases they are merely different manifestations of one circuit (e.g., different directions of wavefront propagation or exit to the ventricle as a whole), and ablation of one may prevent recurrence of others. The presence of multiple VT morphologies contributes to the difficulties in mapping and ablation of VT in these patients, because pacing techniques employed to validate recordings at potential sites of ablation may result in a change in morphology to another VT that does not arise in the same region.

After ablation of VT, repeat ventricular stimulation is performed to assess efficacy. In some cases, rapid polymorphic VT or fibrillation is initiated. The clinical significance of these arrhythmias is unclear, but some evidence suggests that they have a low likelihood of spontaneous occurrence during follow-up.

INDICATIONS.

Patients considered for RF catheter ablation of VT are those with symptomatic, sustained, monomorphic VT when the tachycardia is drug resistant, when the patient is drug intolerant, or when the patient does not desire long-term drug therapy; patients with bundle branch reentrant VT; and patients with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by reprogramming or concomitant drug therapy.[607] Occasionally, nonsustained VT or even severely symptomatic PVCs require RF catheter ablation.[119]

RESULTS.

In the U.S. NASPE survey, 429 patients underwent ablation, with an overall success rate of 71 percent. In 224 patients with structurally normal hearts, the success rate was 85 percent. The success rate was 54 percent in 115 patients with VT due to ischemic heart disease and 61 percent in 90 patients with idiopathic cardiomyopathy. There were 13 significant complications (3.0 percent) and, interestingly, considering the nature of the disease, no procedure-related deaths.[155] The complication rate was 7.5 percent in the European survey, and there was 1 death in 320 patients.[154] More recent series suggest a 30 percent "cure" rate for patients (no inducible ventricular arrhythmia of any type, no recurrences), whereas over 70 percent of patients no longer have recurrences of VT after the procedure, despite inducibility of rapid VT or VF.[606] [607] [615]

New Mapping and Ablation Technologies

MULTIELECTRODE MAPPING SYSTEMS.

As noted earlier, many of the limitations of ablation are related to inadequate mapping. These problems include only isolated premature complexes during the EPS as opposed to sustained tachycardias (in idiopathic atrial and ventricular tachycardias),

nonsustained episodes of VT, poor hemodynamic tolerance of VT, and multiple VT morphologies. Standard mapping techniques sample single sites sequentially and are poorly suited to these situations listed earlier. New mapping systems are available that enable sampling of many sites simultaneously and incorporate sophisticated computer algorithms for analysis and display of global maps. These mapping systems use a variety of technologies, ranging from multiple electrodes situated on each of several splines of a "basket" catheter,[616] to use of low-intensity magnetic fields to localize the catheter tip in the heart and record and plot activation times on a contour map of the chamber,[617] to use of complex mathematics to compute "virtual" electrograms recorded from a mesh electrode situated in the middle of a chamber cavity.[618] [619] Some of these systems are capable of generating activation maps of an entire chamber using only one complex, an obvious advantage in patients with only premature complexes, nonsustained arrhythmias, or poor hemodynamic tolerance. Although these mapping systems offer great promise in selected cases, they are complex and expensive to use.

COOLED-TIP RF ABLATION.

There are situations in which the catheter can be delivered to the correct location but conventional RF energy delivery is unable to eliminate the tachycardia. In some such cases, the amount of damage (either depth or breadth) caused by standard RF is inadequate. Using standard RF, power delivery is usually regulated to maintain a preset catheter tip temperature (typically 70°C). Tip temperatures greater than 90°C are associated with coagulation of blood elements on the electrode that preclude further energy delivery and could also become detached and embolize. Cooling the catheter tip, either by an internal circulation of liquid or continuous fluid infusion through the tip electrode, can prevent excessive heating of the tip and allow greater power delivery, thus effecting larger lesion size and potentially enhancing efficacy. Preliminary studies have shown the safety of this technology, but efficacy has yet to be demonstrated.[156]

CHEMICAL ABLATION.

Chemical ablation with alcohol or phenol of an area of myocardium involved in a tachycardia has been used to create AV block in patients not responding to catheter ablation and to eliminate atrial and ventricular tachycardias.[620] [621] Recurrences of tachycardia several days after apparently successful ablation are common. Excessive myocardial necrosis is the major complication, and alcohol ablation should be considered only when other ablative approaches fail or cannot be done.

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Surgical Therapy for Tachyarrhythmias

The objectives of a surgical approach to treating a tachycardia are to excise, isolate, or interrupt tissue in the heart critical for the initiation, maintenance, or propagation of the tachycardia while preserving or even improving myocardial function. In addition to a direct surgical approach to the arrhythmia, indirect approaches such as aneurysmectomy, coronary artery bypass grafting, and relief of valvular regurgitation or stenosis can be useful in selected patients by improving cardiac hemodynamics and myocardial blood flow. Cardiac sympathectomy alters adrenergic influences on the heart and has been effective in some patients, particularly those who have recurrent VT with the long QT syndrome.

Supraventricular Tachycardias

Surgical procedures[622] [623] [624] [625] [626] [627] exist for patients (adults and children) with atrial tachycardias,[625] atrial flutter, AV node reentry,[623] and AV reentry,[624] [628] [629] (Fig. 23-26) . RF catheter ablation adequately treats the majority of these patients except for those with atrial fibrillation. Therefore, RF catheter ablation has replaced direct surgical intervention except for the occasional patient in whom RF catheter ablation fails or who is having concomitant cardiovascular surgery. In some instances, a prior attempt at RF catheter ablation complicates surgery by obliterating the normal tissue planes that exist in the AV groove of the heart or by rendering tissues too friable. Occasionally, patients with atrial tachycardias have multiple foci that require surgical intervention.[625]

The Maze procedure,[626] [630] [631] [631A] developed to treat patients with atrial fibrillation (see Chap. 25), eliminates the arrhythmia by reducing atrial tissue mass to a size at any instant in time too small to perpetuate the reentrant circuits responsible for atrial fibrillation. It forces atrial activation to proceed along a surgically determined pathway,

thus maintaining sinus rhythm with AV node conduction. The Maze procedure permits organized electrical depolarization of the atria, restores atrial transport function, and in so doing decreases the risk of thromboembolism. Maintenance of sinus rhythm more than 3 months after the procedure approaches 100 percent, although up to 10 percent of patients require pacemakers because of chronotropic incompetence of the sinus node (either due to the surgery or the preexisting atrial pathology). The advent of minimally invasive endoscopic and endovascular techniques may make it possible to perform an equivalent of the Maze procedure without thoracotomy in the future. The Maze procedure is currently most commonly performed concomitantly with mitral valve surgery rather than as a primary indication. In some centers, intraoperative RF ablation has replaced surgical incisions for performing the Maze procedure.[632]

Ventricular Tachycardia

In contrast to patients with supraventricular arrhythmias, candidates for surgical therapy for ventricular arrhythmias often have severe left ventricular dysfunction, which is generally caused by coronary artery disease. The cause of the underlying heart disease influences the type of surgery performed. Candidates are patients with drug-resistant, symptomatic, recurrent ventricular tachyarrhythmias who ideally have a segmental wall motion abnormality (scar or aneurysm) with preserved residual left ventricular function. Poorer surgical results are obtained in patients with a history of congestive heart failure and left ventricular dysfunction.

Ischemic Heart Disease

In almost all patients who have VT associated with ischemic heart disease, the arrhythmia, regardless of its configuration on the surface ECG, arises in the left ventricle or on the left ventricular side of the interventricular septum. The ECG contour of the VT can change from a right bundle branch block to a left bundle branch block pattern without

Figure 23-26 Schematic diagram showing the two approaches for surgical interruption of an accessory pathway. The left panel depicts the left atrioventricular groove and its vascular contents, the coronary sinus (C.S.) and circumflex coronary artery (C.A.). Multiple accessory pathways (AP) course through the fat pad. The middle panel shows the epicardial dissection approach, whereas the right panel exhibits the endocardial dissection. Both approaches clear out the fat pad and interrupt any accessory pathways. *(From Zipes DP: Cardiac electrophysiology: Promises and contributions. J Am Coll Cardiol 13:1329, 1989. Reprinted by permission of the American College of Cardiology.)*

a change in the site of earliest diastolic activation, suggesting that the left ventricular site of origin remains the same, often near the septum, but its exit pathway is altered.

Indirect surgical approaches, including cardiothoracic sympathectomy, coronary artery

bypass grafting, and ventricular aneurysm or infarct resection with or without coronary artery bypass grafting, have been successful in 20 to 30 percent of reported cases. Coronary artery bypass grafting as a primary therapeutic approach generally has only been successful in rare patients who experience VT during ischemia as well as patients with ischemia-related VF but can sometimes be useful in patients with coronary disease resuscitated from sudden death who have no inducible arrhythmias at EPS. Patients with sustained monomorphic VT or only polymorphic VT rarely have their arrhythmias affected by coronary bypass surgery, although the latter can reduce the frequency of the arrhythmic episodes in some patients and prevent new ischemic events.

SURGICAL TECHNIQUES.

Generally, two types of direct surgical procedures are used: resection and ablation (Fig. 23-27) . The first direct surgical approach to VT was *encircling endocardial ventriculotomy,* using a transmural ventriculotomy to isolate areas of endocardial fibrosis that were recognized visually; this procedure is rarely employed now. The rationale for *subendocardial resection* is based on animal and clinical data indicating that arrhythmias after myocardial infarction arise mostly at the subendocardial borders between normal and infarcted tissue. Subendocardial resection involves peeling off a 1- to 3-mm-thick layer of endocardium, often near the rim of an aneurysm, that has been demonstrated by means of mapping procedures to be the site of earliest activation recorded during the VT. Some VTs can arise from the epicardium. Tachycardias arising from near the base of the papillary muscles are cryoablated using a 1.5-cm flat probe cooled to -70°C. Cryoablation also can be used to isolate areas of the ventricle that cannot be resected and is often combined with resection. The neodymium:yttrium-aluminum-garnet laser approaches have been used as well with good success, but the equipment is very expensive and difficult to work with.

RESULTS.

For ventricular tachyarrhythmias, operative mortality ranges from 6 to 23 percent, with success rates defined as absence of recurrence of spontaneous ventricular arrhythmias ranging from 59 to 98 percent. In experienced centers, operative mortality may be as low as 5 percent in stable patients undergoing elective procedures, with 85 to 95 percent of survivors free of inducible or spontaneous ventricular tachyarrhythmias. Long-term recurrence rates range from 2 to 38 percent and correlate with results of the patient's postoperative electrophysiological stimulation

Figure 23-27 Schematic diagram showing surgical procedures for treatment of postinfarct ventricular tachycardia with left ventricular aneurysm. A damaged left ventricle is depicted as opened along the lateral wall and viewing the septum and papillary muscles. The tachycardia circuit (arrow) takes a meandering course near where the aneurysm meets normal myocardium and at times is superficial, other times coursing deeper (dashed line). Simple aneurysmectomy that leaves a portion of the aneurysm for suturing often misses the circuit and thus does not cure the arrhythmia. Using subendocardial resection, a layer of endocardium and subjacent tissue is removed, including at least some of the tachycardia circuit. This results in elimination of tachycardia. Encircling endocardial ventriculotomy attempts to electrically isolate the circuit without removing tissue, but it probably actually works by incising portions of

the circuit. Cryoablation can be used either to encircle the infarct zone or in combination with resection to damaged tissue too deep in the wall to safely resect.

study. Operative survival is strongly influenced by the degree of left ventricular dysfunction. Patients with less favorable anatomy who are poor surgical candidates and who fail drug treatment are generally considered for an ICD. By no longer having to operate on these sicker patients, surgeons have improved the overall operative mortality.[627] [633] [634]

Operative mortality for nonthoracotomy ICD implantation is less than 1 percent, with an annual sudden cardiac death mortality rate of less than 1 percent.[635] Because of the difference in operative survival and shorter hospital stay with ICD therapy compared with direct surgery for VT, relatively few curative surgical procedures are now performed. Nevertheless, ICD patients are relegated to a form of therapy that, naturally, does not prevent the arrhythmia but only terminates it after its onset. Some experts recommend surgery for patients with VT who have discrete aneurysms that are amenable to intraoperative mapping and resection because such patients have a very high probability for cure of their arrhythmias.[636]

Electrophysiological Studies

PREOPERATIVE ELECTROPHYSIOLOGICAL STUDY.

In patients for whom direct surgical therapy for VT is planned, a preoperative EPS is usually warranted. This involves initiation of the VT and electrophysiological mapping to localize the area to be resected, as is done with catheter ablation. A resolution of 4 to 8 cm^2 of ventricular endocardium is thereby achieved, although more accurate anatomical localization of the mapping electrode tip in the ventricle may be possible. Tachycardias that are too rapid, short in duration, or polymorphic cannot be mapped accurately unless multiple catheters or a multielectrode array is used. Administering a drug such as procainamide may slow the VT and transform a nonsustained polymorphic VT into a sustained VT of uniform contour that can be mapped.

INTRAOPERATIVE VENTRICULAR MAPPING.

Electrophysiological mapping is also performed at the time of surgery, with the surgeon using a hand-held probe or an electrode array coupled with on-line computer techniques that instantaneously provide an overall activation map cycle by cycle. The sequence of activation during VT can be plotted and the area of earliest activation determined.

During VT, the origin of the arrhythmia is generally ascribed to electrical activity recorded more than 50 milliseconds before the onset of the QRS complex (ideally, isolated mid-diastolic potentials). Generally, potentials recorded before the onset of the surface QRS complex suggest that the origin of the tachycardia is nearby. Resection or

cryoablation of tissue from which these recordings are made usually cures the VT, indicating that they represent a critical portion of the reentrant circuit. However, it is quite clear that such electrical activity can be late following the preceding cycle or early in advance of the next cycle. When the earliest recordable endocardial electrical activity occurs less than 30 milliseconds before the onset of the QRS complex, the critical portions of the circuit may be in the interventricular septum or near the epicardium of the free wall.

The area of earliest recorded electrical activity during VT may not actually represent a critical portion of the tachycardia circuit, because the latter may be several centimeters away (e.g., in a small, scarred area). The impulse may then conduct very slowly until it reaches more normally excitable tissue, where it exits and spreads rapidly to the rest of the endocardium to generate a QRS complex. However, this area of early activation is probably closely related to the origin of the tachycardia that, based on the present state of knowledge and results from surgery, warrants surgical intervention at that site. Finding an area from which "continuous electrical activity" is recorded rarely if ever indicates that the entire circuit is being recorded. However, it is likely that a critical portion of the tachycardia circuit is close to the area of continuous electrical activity. In some patients, intramural mapping using a plunge needle electrode can be useful, particularly if the origin of the tachycardia is not located in the subendocardium. Most centers now employ a strategy of "sequential" subendocardial resection, in which VT is initiated, mapped, and ablated (resected or cryoablated) and stimulation is immediately repeated. If VT can still be initiated, mapping and resection are also repeated until VT can no longer be initiated.

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GUIDELINES
AMBULATORY MONITORING AND ELECTROPHYSIOLOGICAL TESTING

Thomas H. Lee

This appendix summarizes guidelines from American College of Cardiology/American Heart Association (ACC/AHA) task forces on ambulatory monitoring published in 1999[1] and electrophysiological testing and cardiac ablation procedures published in 1995. Information on guidelines for implantable cardioverter-defibrillators (ICDs) is included in the Guidelines in Chapter 24 .

AMBULATORY MONITORING

Guidelines for the use of ambulatory electrocardiography (ECG) continue to evolve with advances in technology of the monitoring devices, as well as other medical devices and clinical research. An ACC/AHA task force issued updated guidelines for the use of this technology in 1999,[1] a decade after its first guidelines in this area.[2] Particularly important progress was made during this period in several areas, including

- Understanding of the limited usefulness of suppression of ventricular ectopy with drug therapy as a predictor of prognosis[3]
- Solid-state digital technology that facilitates transtelephonic transmission of ECG data
- Technical advances in long-term event recorders

Improved signal quality and interpretation

Improved computer arrhythmia interpretation

Increasingly sophisticated monitoring capacity of pacemakers and implantable defibrillators

As result of progress in these areas, ambulatory ECG is now considered to be of uncertain appropriateness for many indications for which it was an accepted strategy in prior guidelines.

ACC/AHA guidelines on the appropriateness of ambulatory ECG for various clinical settings are summarized in Table 23-G-1 . As is the case for other ACC/AHA guidelines, the indications are divided into classes.

Class I
: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class II
: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa
: Weight of evidence/opinion in favor of usefulness/efficacy

Class IIb
: Usefulness/efficacy less well established by evidence/opinion

Class III
: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

DIAGNOSIS.

In the assessment of symptoms that may be related to arrhythmias, ambulatory ECG is most clearly established for evaluation of syncope. The ability of 24-hour ambulatory ECG to capture rare events such as syncope is low; however, the rhythm during asymptomatic periods may be useful. When continuous ambulatory ECG is not diagnostic, intermittent recorders may be useful. The guidelines note that data on the use of ambulatory ECG for near syncope or dizziness are insufficient to describe the diagnostic performance of this technology for those indications.

A second Class I indication is the use of ambulatory ECG in patients with recurrent palpitations. This test is considered useful in this setting because the frequency of recurrence of palpitations makes it more likely that ECG data will be captured during episodes of palpitations than during syncope.

Other indications for ambulatory ECG for diagnostic purposes are of uncertain appropriateness at best. The ACC/AHA guidelines explicitly discourage use of this technology for patients with syncope, near syncope, dizziness, or palpitations in whom

another cause has been identified. Also considered inappropriate was ambulatory ECG for patients with cerebrovascular accidents and no other evidence of arrhythmia. Thus, these guidelines discourage performance of ambulatory ECG for "completeness" of an evaluation in such patients.

ASSESSMENT OF RISK.

The ACC/AHA guidelines are not generally encouraging of the use of ambulatory ECG for either arrhythmia detection or analysis of heart rhythm variability if the goal is risk assessment among patients without symptoms of arrhythmia (see Table 23-G-1). No clinical indications were considered Class I or Class IIa. In certain patients at high risk for arrhythmias, the ACC/AHA guidelines considered ambulatory ECG Class IIb (i.e., controversial, without the weight of evidence or opinion in support of appropriateness). Such "marginal" indications include patients with left ventricular dysfunction after myocardial infarction, congestive heart failure, or idiopathic hypertrophic cardiomyopathy. However, data from Multicenter Automatic Defibrillator Implantation Trial (MADIT) and Multicenter Unsustained Tachycardia Trial (MUSTT) suggest that documenting nonsustained ventricular tachycardia in patients after myocardial infarction who have reduced ejection fractions identifies a high-risk group who may benefit from ICD implantation. Ambulatory ECG may be indicated in this population.

EFFICACY OF ANTIARRHYTHMIC THERAPY.

Ambulatory ECG is considered appropriate for assessment of the efficacy of antiarrhythmic therapy in some patients with frequent, reproducible arrhythmia (see Table 23-G-1) but the ACC/AHA guidelines recognize the lack of correlation between arrhythmia suppression after an intervention and subsequent clinical outcome. In the absence of clinical trial data demonstrating that antiarrhythmic agents that suppress arrhythmia

TABLE 23--G-1 -- ACC/AHA GUIDELINES FOR AMBULATORY ELECTROCARDIOGRAPHY

Indication	Class I	Class IIa	Class IIb	Class III

To assess symptoms possibly related to rhythm disturbances	Patients with unexplained syncope, near syncope, or episodic dizziness in whom the cause is not obvious Patients with unexplained recurrent palpitations		Patients with episodic shortness of breath, chest pain, or fatigue that is not otherwise explained Patients with neurological events when transient atrial fibrillation or flutter is suspected Patients with symptoms such as syncope, near syncope, episodic dizziness, or palpitations in whom a probable cause other than arrhythmia has been identified but in whom symptoms persist despite treatment of this other cause	Patients with symptoms such as syncope, near syncope, episodic dizziness, or palpitations in whom other causes have been identified by history, physical examination, or laboratory tests Patients with recurrent cerebrovascular accidents, without other evidence of arrhythmia

Use of ambulatory electrocardiography for arrhythmia detection to assess risk for future cardiac events in patients without symptoms from arrhythmia	None		Post-MI patients with LV dysfunction Patients with CHF Patients with idiopathic hypertrophic cardiomyopathy	Patients who have sustained myocardial contusion Systemic hypertensive patients with LV hypertrophy Post-MI patients with normal LV function Preoperative arrhythmia evaluation of patients for noncardiac surger Patients with sleep apnea Patients with valvular heart disease
Use of HRV to assess risk for future cardiac events in patients without symptoms from arrhythmia	None		Post-MI patients with LV dysfunction Patients with CHF Patients with idiopathic hypertrophic cardiomyopathy	Post-MI patients with normal LV function Diabetic subjects to evaluate for diabetic neuropathy Patients with rhythm disturbances that preclude HRV analysis (i.e., atrial fibrillation)

To assess antiarrhythmic therapy	To assess antiarrhythmic drug response in individuals in whom baseline frequency of arrhythmia has been well characterized as reproducible and of sufficient frequency to permit analysis	To detect proarrhythmic responses to antiarrhythmic therapy in high-risk patients	To assess rate control during atrial fibrillation To document recurrent symptomatic or asymptomatic nonsustained arrhythmias during therapy in the outpatient setting	None
For ischemia monitoring	None	Patients with suspected variant angina	Evaluation of patients with chest pain who cannot exercise Preoperative evaluation for vascular surgery in patients who cannot exercise Patients with known CAD and atypical chest pain syndrome	Initial evaluation of patients with chest pain who are able to exercise Routine screening of asymptomatic patients

Implantable loop recorders are just being evaluated and may cause modifications of the above recommendations.

ACC/AHA = American College of Cardiology/American Heart Association; CAD = coronary artery disease; CHF = congestive heart failure; HRV = heart rate variability; LV = left ventricular; MI = myocardial infarction.

From Crawford MH, Bernstein SJ, Deedwania PC, et al: ACC/AHA guidelines for ambulatory electrocardiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography. J Am Coll Cardiol 34:913, 1999. Reprinted with permission from the American College of Cardiology.

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also improve survival, the usefulness of a test that documents arrhythmia suppression is moot at best. ICDs offer an alternative strategy for treatment of life-threatening arrhythmias, and ambulatory ECG is rarely needed to assess the function of these

devices.

Although the role of antiarrhythmic drugs for the treatment of supraventricular tachycardia is more clear, the role of ambulatory ECG in such patients is limited by the fact that most patients do not have episodes of sustained arrhythmia every day. However, event recorders

can be useful for documenting the relationship between recurrent arrhythmia and the interval between episodes, which is a useful measure of drug efficacy.

The ACC/AHA guidelines reflect some support for the use of ambulatory ECG for detection of proarrhythmic responses to drug therapy in patients at high risk for such complications. However, patients at high risk for proarrhythmia frequently undergo initiation of therapy as inpatients with continuous ECG monitoring.

ASSESSMENT OF PACEMAKER AND ICD FUNCTION.

The role of ambulatory ECG for assessment of the function of pacemakers and ICDs is being eroded by the increasingly sophisticated diagnostic and monitoring functions of these devices themselves. However, ambulatory ECG can provide useful information by correlating symptoms with device activity and by detecting abnormalities in sensing and capture during chronic follow-up. For example, ambulatory ECG can help prolong the longevity of devices by assessing function after reprogramming of output parameters. Nevertheless, in the long run, ambulatory ECG will probably be used even more rarely for assessment of these devices.

MONITORING FOR MYOCARDIAL ISCHEMIA.

The 1999 ACC/AHA guidelines do not unequivocally support any indications for routine clinical use of ambulatory ECG monitoring for myocardial ischemia. The only indication that was rated as high as Class IIa was detection of ischemia in patients with suspected variant angina. The guidelines gave particular emphasis to the multiple causes of false-positive test results, as well as the marked day-to-day variability in the frequency and duration of ST depression and ischemic episodes. Because of complex technical requirements and diagnostic criteria, the guidelines recommend that ambulatory ECG to detect myocardial ischemia be performed only by laboratories and personnel with specific training in this area.

ELECTROPHYSIOLOGICAL PROCEDURES

ACC/AHA guidelines for the use of intracardiac electrophysiological procedures were first published in 1989[4] and, because of rapid evolution in this field, were revised in

1995.[5] The more recent version of these guidelines reflects the emerging importance of catheter ablation as a therapeutic strategy and primary treatment option for most forms of paroxysmal supraventricular tachycardia and preexcitation syndromes and in patients with monomorphic ventricular tachycardia and structurally normal hearts. The new guidelines also reflect progress in understanding the role of electrophysiological studies for risk stratification of patients with tachyarrhythmias and emphasize consideration of whether the test is likely to influence management decisions.

The ACC/AHA task force used a three-category system for assessment of appropriateness (see below).

The ACC/AHA guidelines identified a narrow list of indications for which electrophysiological testing was clearly appropriate for guiding drug therapy: sustained ventricular tachycardia or cardiac arrest, especially among patients with prior myocardial infarction, and supraventricular tachyarrhythmias associated with reentry loops and/or accessory pathways. However, the ACC/AHA guidelines reflect the increasing importance of electrophysiological testing as a prelude to interventions such as implantable electrical devices and catheter ablation.

EVALUATION OF SINUS NODE FUNCTION

Clinical evaluation of sinus node dysfunction is often difficult because of the episodic nature of symptomatic abnormalities and the finding that asymptomatic patients frequently have wide variability in sinus node rates. Invasive tests of sinus node function can test the ability of the sinus node to recover from overdrive suppression (sinus node recovery time) and assess sinoatrial conduction by introducing atrial extrastimuli or by atrial pacing. These tests can be used to complement data from noninvasive testing, including ambulatory ECG, exercise testing, and tilt-table testing to assess chronotropic incompetence.

The ACC/AHA guidelines considered electrophysiological studies of sinus node function most appropriate for patients in whom dysfunction was suspected but not proved despite a noninvasive evaluation; conversely, such studies would be inappropriate (Class III) when bradyarrhythmias had been proved to be the cause of symptoms and electrophysiological studies would not alter treatment. When bradyarrhythmias were recognized as the cause of the patient's symptoms, electrophysiological studies were considered to have possible, but uncertain appropriateness (Class II) when data might refine treatment choices. These procedures were deemed inappropriate for asymptomatic patients who have bradyarrhythmias observed only during sleep.

ACQUIRED ATRIOVENTRICULAR BLOCK

Electrophysiological studies permit evaluation of conduction above, within, and below the His bundle. This information can be useful to clinicians because patients with atrioventricular (AV) block that is lower in the conduction system tend to have a worse prognosis. However, both prognosis and the level at which AV block is occurring can

often be predicted from ECG data.

Therefore, the ACC/AHA guidelines emphasized that electrophysiological studies are inappropriate (Class III) when ECG findings correlate with symptoms and the findings from electrophysiological studies are unlikely to alter therapy. For example, if a patient warrants implantation of a pacemaker because of documented symptomatic advanced AV block, documentation of His bundle conduction will rarely contribute to management. Similarly, electrophysiological studies are not appropriate for asymptomatic patients with mild degrees of AV block who are not likely to warrant pacemaker implantation. According to these guidelines, electrophysiological studies of AV conduction should be performed when a relationship between symptoms and AV block has not been proved; in such patients, another arrhythmia could be the cause of symptoms.

CHRONIC INTRAVENTRICULAR CONDUCTION DELAY

Patients who have prolonged H-V intervals have an increased risk for the development of complete trifascicular block, but the specificity of the H-V interval for predicting the development of complete block among patients with bifascicular block is only about 63%.[5] The use of rapid atrial pacing can improve the specificity of this test, but the annual incidence of progression to complete trifascicular block is low unless patients are exposed to intervening events (e.g., drugs) that adversely affect intracardiac conduction. Therefore, the main role for electrophysiological testing in this population, according to the ACC/AHA guidelines, is not to predict future complications but to determine whether the symptoms of arrhythmia are due to conduction delay versus some other arrhythmia.

The only Class I (clearly appropriate) indication for electrophysiological testing in patients with intraventricular conduction delay according to the ACC/AHA guidelines is determination of the cause of symptoms. These guidelines discouraged the use of electrophysiological testing in asymptomatic patients with conduction system delay. Testing of asymptomatic patients in whom treatment with drugs that could increase conduction delay is being considered was regarded as being of uncertain appropriateness (Class II).

NARROW AND WIDE COMPLEX QRS TACHYCARDIAS.

In narrow QRS tachycardia, the site of abnormal impulse formation or the reentry circuit can be located in the sinus node, in the atria, in the AV node-His bundle axis, or in the accessory pathway. The correct diagnosis can often be made from information from the 12-lead ECG, particularly when the ECG is combined with vagal maneuvers. In contrast, wide QRS tachycardias can be caused by ventricular or supraventricular arrhythmias, and identifying the site of origin of the tachycardia is frequently impossible with ECG tracings alone.

As a result, electrophysiological testing plays different roles in these two types of tachycardias. In patients with wide complex tachycardias, electrophysiological testing permits accurate diagnosis in virtually all patients. Since knowledge of the mechanism of the arrhythmia is essential for selection of the best therapeutic strategy, use of

electrophysiological testing was considered appropriate (Class I) for the diagnosis of wide complex tachycardias by the ACC/AHA task force. However, when the diagnosis is already clear from other data, electrophysiological testing is unlikely to influence therapy, and these procedures are not generally useful.

In patients with narrow QRS tachycardias, electrophysiological testing was considered more appropriate as a guide to therapy than as a tool for diagnosis. Therefore, Class I indications for such testing include patients with recurrent tachycardia in whom data from electrophysiological testing may help clinicians choose among drug therapy, catheter ablation, pacing, or surgery. However, the ACC/AHA task force did not believe that electrophysiological testing was useful for patients who have narrow complex tachycardias that are well controlled with medications and who are not candidates for nonpharmacological therapy.

OTHER CONDITIONS

PROLONGED QT INTERVALS.

The ACC/AHA task force concluded that electrophysiological testing has a limited role in the evaluation of congenital or acquired forms of prolonged QT syndrome. Whether catecholamine infusion during testing can unmask patients who are at high risk for complications or whether electrophysiological testing can be used to evaluate proarrhythmic effects in this population is unclear. Therefore, no indication for electrophysiological testing for this problem was called clearly appropriate.

WOLFF-PARKINSON-WHITE SYNDROME.

Electrophysiological studies can be used in patients with this syndrome to determine the mechanism of arrhythmia, assess the electrophysiological properties of the accessory pathway, and evaluate the location and response of accessory pathways to drugs. Therefore, electrophysiological studies were considered appropriate by the ACC/AHA task force for patients who were candidates for catheter or surgical ablation, for those who had had cardiac arrests or unexplained syncope, or for patients whose management might be altered by knowledge of the electrophysiological properties of the accessory pathway and normal conduction system. For asymptomatic patients, however, electrophysiological testing was deemed inappropriate except in special situations, such as patients with high-risk occupations or those with a family history of sudden cardiac death.

NONSUSTAINED VENTRICULAR TACHYCARDIA.

For patients with ventricular premature complexes, couplets, and nonsustained

ventricular tachycardia, the usefulness of electrophysiological testing is compromised by the lack of therapeutic strategies that have been shown to improve outcome. There were no indications for which the ACC/AHA task force agreed that electrophysiological testing was clearly useful in this patient population, and these tests were considered inappropriate for patients with no or only mild symptoms. (An exception is a patient who fits the MADIT or MUSTT criteria.) For certain patients with other data suggesting an adverse prognosis, electrophysiological testing was believed to have possible but unproven appropriateness (Class II).

UNEXPLAINED SYNCOPE.

Among patients with structural heart disease, arrhythmia is an important cause of syncope and a worrisome prognostic sign. Therefore, electrophysiological testing is highly useful for the evaluation of syncope in this patient population. In contrast, among patients without structural heart disease, an arrhythmic cause of syncope is uncommon, and the yield of electrophysiological testing is low. Therefore, the ACC/AHA guidelines recommend a higher threshold for the use of electrophysiological testing in patients without known heart disease and suggest that head-up tilt testing may provide more useful data in this population.

SURVIVORS OF CARDIAC ARREST.

Electrophysiological testing is frequently used for patients who have survived cardiac arrest to assess prognosis and identify drugs that suppress inducible arrhythmia. The assumption that these data can be used to improve patient outcome has been called into question by data from the Electrophysiologic Study Versus Electrocardiographic Monitoring Trial.[6] Nevertheless, electrophysiological testing was considered appropriate by the ACC/AHA task force for patients who survived cardiac arrest without evidence that the event was directly provoked by ischemia or myocardial infarction. These tests were deemed inappropriate when the cardiac arrest was closely associated with acute ischemic syndromes or other specific causes.

UNEXPLAINED PALPITATIONS.

The procedure of choice to determine the cause of palpitations, according the ACC/AHA guidelines, is ambulatory ECG. Electrophysiological testing should be reserved for patients with associated syncope or those in whom ECGs have failed to capture a cause of the palpitations but who have been noted to have a rapid pulse rate by medical personnel. Electrophysiological testing is of equivocal value in patients whose symptoms are so sporadic that they cannot be documented while ambulatory ECGs are being performed.

APPROPRIATENESS OF CATHETER ABLATION PROCEDURES

Catheter ablation of the AV junction or accessory pathways is a rapidly advancing technology that has been reviewed in guidelines and position papers from several organizations, including the American Medical Association,[7] the ACC,[8] the North American Society of Pacing and Electrophysiology,[9] and an ACC/AHA task force.[5] The ACC/AHA task force identified several conditions for which they considered catheter ablation an appropriate strategy (Table 23-G-2) . The characteristics that are common among appropriate indications include supraventricular arrhythmias that are symptomatic; that cannot be controlled with medications because of either limited effectiveness, side effects, or inconvenience; or that have caused sudden cardiac death. Catheter ablation is also useful for some patients with ventricular tachycardia, although patients with extensive structural heart disease tend to have multiple sites of origin of their arrhythmia and may therefore be poor candidates for this procedure.

TABLE 23--G-2 -- ACC/AHA GUIDELINES FOR CLINICAL INTRACARDIAC ELECTROPHYSIOLOGICAL STUDIES (1995)

Setting	**Class I (Appropriate)**	**Class II (Equivocal)**	**Class III (Inappropriate)**
Evaluation of sinus node function	Symptomatic patients in whom sinus node dysfunction is suspected to be the cause of symptoms but a casual relation between an arrhythmia and the symptoms has not been established after appropriate evaluation	Patients who have documented sinus node dysfunction in whom evaluation of AV or Va conduction or susceptibility to arrhythmias may aid in selection of the most appropriate pacing modality Patients with ECG-documented sinus bradyarrhythmias to determine whether the abnormalities are due to intrinsic disease, autonomic nervous system dysfunction, or the effects of drugs in order to help select therapeutic options Symptomatic patients with known sinus bradyarrhythmias to evaluate the	Symptomatic patients in whom an association between symptoms and a documented bradyarrhythmia has been established and the choice of therapy would not be affected by the results of an EP study Asymptomatic patients with sinus bradyarrhythmias or sinus pauses observed only during sleep, including sleep apnea

		Symptomatic patients with known sinus bradyarrhythmias to evaluate the potential for other arrhythmias as the cause of their symptoms	
Patients with acquired AV block	Symptomatic patients in whom His-Purkinje block, suspected as a cause of symptoms, has not been established Patients with second- or third-degree AV block treated with a pacemaker who remain symptomatic and in whom another arrhythmia is suspected as a cause of symptoms	Patients with second- or third-degree AV block in whom knowledge of the site of block or its mechanism or the response to pharmacological or other temporary intervention may help direct therapy or assess prognosis Patients with premature concealed junctional depolarizations suspected as a cause of the second- or third-degree AV block pattern (i.e., pseudo-AB block)	Symptomatic patients in whom the symptoms and the presence of AV block are correlated by ECG findings Asymptomatic patients with transient AV block associated with sinus slowing (e.g., nocturnal type I second-degree AV block)
Patients with chronic intraventricular conduction delay	Symptomatic patients in whom the cause of the symptoms is not known	Asymptomatic patients with bundle branch block in whom pharmacological therapy is contemplated with a drug that could increase conduction delay or produce a heart attack	Asymptomatic patients with intraventricular conduction delay Symptomatic patients in whom the symptoms can be correlated with or excluded by ECG events

Patients with a narrow QRS tachycardia (QRS complex <0.12 seconds)	Patients with frequent or poorly tolerated episodes of tachycardia not adequately responding to drug therapy in whom information about the site of origin, mechanism, and EP properties of the pathways of the tachycardia is essential for choosing appropriate therapy (drugs, catheter ablation, pacing, or surgery) Patients who prefer ablative therapy to pharmacological management	Patients with frequent episodes of tachycardia requiring drug treatment in whom there is concern about proarrhythmia or the effects of the antiarrhythmic drugs on the sinus node or on AV conduction	Patients whose tachycardias are easily controlled by vagal maneuvers and/or well-tolerated drug therapy and who are not candidates for nonpharmacological forms of therapy
Patients with wide complex tachycardias	Patients with wide QRS tachycardias when the correct diagnosis is unclear after analysis of available ECG tracings and when knowledge of the correct diagnosis is necessary for appropriate patient care	None	Patients with VT or SVT and aberrant conduction or preexcitation syndromes that are diagnosed with certainty by ECG criteria and in whom invasive EP data would not influence therapy. Data obtained at baseline EP study in these patients might be appropriate, however, as a guide to subsequent therapy (see sections on therapy)

Patients with a prolonged QT interval syndrome	None	Identification of a proarrhythmic effect of antiarrhythmics drugs in a patient experiencing sustained VT or cardiac arrest while receiving the drug Patients who have equivocal abnormalities in QT interval duration or TU wave configuration along with syncope or symptomatic arrhythmias and in whom catecholamine effects may unmask a distinct QT abnormality	Patients with clinically manifested congenital QT prolongation with or without symptomatic arrhythmias Patients with acquired prolonged QT syndrome and symptoms closely related to an identifiable cause or mechanism
Patients with the Wolff-Parkinson-White syndrome	Patients being evaluated for catheter ablation or surgical ablation of an accessory pathway Patients with ventricular preexcitation who have survived cardiac arrest or who have unexplained syncope Symptomatic patients in whom determination of the mechanism of arrhythmia or knowledge of the EP properties of the accessory pathway and normal conduction system would help in determining appropriate therapy	Asymptomatic patients with ventricular preexcitation but no spontaneous arrhythmia who engage in high-risk occupations or activities and in whom knowledge of the EP properties of the accessory pathway or inducible tachycardia may help determine the recommendation for further activities or therapy or those who have a family history of sudden cardiac death Patients with ventricular preexcitation who are undergoing cardiac surgery for other reasons	Asymptomatic patients with ventricular preexcitation, except those in Class II

	determining appropriate therapy	Patients with ventricular preexcitation who are undergoing cardiac surgery for other reasons	
Patients with ventricular premature complexes, couplets, and nonsustained VT	None	Patients with other risk factors for further arrhythmic events, such as a low ejection fraction, positive signal-averaged ECG, and nonsustained VT on ambulatory ECG recordings in whom EP studies will be used for further risk assessment and for guidance of therapy in patients with inducible VT Patients with highly symptomatic, uniform-morphology ventricular premature complexes, couplets, and nonsustained VT who are considered potential candidates for catheter ablation	Asymptomatic or mildly symptomatic patients with premature ventricular complexes, couplets, and nonsustained VT without other risk factors for sustained arrhythmias
Patients with unexplained syncope	Patients with syncope that remains unexplained after appropriate evaluation and who are suspected to have structural heart disease	Patients with recurrent unexplained syncope without structural heart disease and a negative head-up tilt test	Patients with known cause of syncope in whom treatment will be guided by EP testing

Survivors of cardiac arrest	Patients surviving an episode of cardiac arrest without evidence of an acute Q wave myocardial infarction Patients surviving an episode of cardiac arrest occurring 48 hr after acute myocardial infarction	Patients surviving cardiac arrest caused by bradyarrhythmia Patients surviving cardiac arrest thought to be associated with a congenital repolarization abnormality (long QT syndrome) in whom the results of noninvasive diagnostic testing are equivocal	Patients surviving a cardiac arrest that occurred during the acute phase (<48 hr) of myocardial infarction Patients with cardiac arrest resulting from clearly definable specific causes such as reversible ischemia, severe valvular aortic stenosis, or noninvasively defined congenital or acquired long QT syndrome
Patients with unexplained palpitations	Patients with palpitations who have a pulse rate that has been documented by medical personnel to be inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations Patients with palpitations preceding a syncopal episode	Patient with clinically significant palpitations suspected to be of cardiac origin and in whom the symptoms are sporadic and cannot be documented. Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis	Patients with palpitations documented to be due to extracardiac causes (e.g., hyperthyroidism)

Guidance of drug therapy	Patients with sustained VT or cardiac arrest, especially those with prior myocardial infarction Patients with AVNRT, AV reentrant tachycardia using an accessory pathway, or atrial fibrillation associated with an accessory pathway in whom chronic drug therapy is involved	Patients with sinus node reentrant tachycardia, atrial tachycardia, atrial fibrillation, or atrial flutter without ventricular preexcitation syndrome in whom chronic drug therapy is planned Patients with arrhythmias not inducible during control EP study in whom drug therapy is planned	Patients with isolated atrial or ventricular premature complexes Patients with ventricular fibrillation with a clearly identified reversible cause
Patients who are candidates for or who have implantable electrical devices	In patients with tachyarrhythmias, prior to and during implantation and final (predischarge) programming of an electrical device to confirm the ability of the system to perform as anticipated Patients in whom an electrical device has been implanted and in whom changes in patient status or therapy may have influenced continued safety and efficacy of the device In patients who have a pacemaker to treat a bradyarrhythmia, and receive a cardioverter-defibrillator to test for device interactions	Patients with previously documented indications for pacemaker implantation to test for the most appropriate chronic pacing mode and sites to optimize symptomatic improvement and hemodynamics	Patients who are not candidates for device therapy

Indications for catheter ablation procedures	Patients with symptomatic atrial tachyarrhythmias who have inadequately controlled ventricular rates *unless* primary ablation of the atrial tachyarrhythmia is possible Patients with symptomatic atrial tachyarrhythmias, such as those above, but when drugs are not tolerated or the patient does not wish to take them even though the ventricular rate can be controlled Patients with symptomatic nonparoxysmal junctional tachycardia that is drug resistant, drugs are not tolerated, or the patient does not with to take them Patients resuscitated from sudden cardiac death caused by atrial flutter or atrial fibrillation with a rapid ventricular response in the absence of an accessory pathway	Patients with a dual-chamber pacemaker and pacemaker-mediated tachycardia that cannot be treated effectively by drugs or by reprogramming the pacemaker	Patients with atrial tachyarrhythmias responsive to drug therapy that is acceptable to the patient

Radiofrequency catheter ablation for AVNRT	Patients with symptomatic sustained AVNRT that is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy	Patients with sustained AVNRT identified during EP study or catheter ablation of another arrhythmia The finding of dual--AV nodal pathway physiology and atrial echos but without AVNRT during EP study in a patient suspected to have AVNRT clinically	Patients with AVNRT that is responsive to drug therapy and the therapy is well tolerated and preferred by the patient to ablation The finding of dual--AV nodal pathway physiology (with or without echo complexes) during EP study in a patient in whom AVNRT is not suspected clinically
Ablation of atrial tachycardia, flutter, and fibrillation: Atrium/atrial sites	Patients with atrial tachycardia that is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy Patients with atrial flutter that is drug resistant or when the patient is drug intolerant or not desire long-term drug therapy	Atrial flutter/atrial tachycardia associated with paroxysmal atrial fibrillation when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy Patients with atrial fibrillation in whom there is evidence of (a) localized site(s) of origin when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy	Patients with atrial arrhythmia responsive to drug therapy and the therapy is well tolerated and preferable to the patient than ablation Patients with multiform atrial tachycardia

Ablation of atrial tachycardia, flutter, and fibrillation: Accessory pathways	Patients with symptomatic AV reentrant tachycardia that is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy Patients with atrial fibrillation (or other atrial tachyarrhythmia) and a rapid ventricular response via the accessory pathway when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy	Patients with AV reentrant tachycardia or atrial fibrillation with rapid ventricular rates identified during EP study of another arrhythmia Asymptomatic patients with ventricular preexcitation whose livelihood, profession, important activities, insurability, or mental well-being or the public safety would be affected by spontaneous tachyarrhythmias of by the presence of the ECG abnormality Patients with atrial fibrillation and a controlled ventricular response via the accessory pathway Patients with a family history of sudden cardiac death	Patients who have accessory pathway-related arrhythmias that are responsive to drug therapy and the therapy is well tolerated and preferable to ablation by the patient

Ablation of VT	Patients with symptomatic sustained monomorphic VT when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy Patient with bundle branch ventricular reentrant tachycardia Patients with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by reprogramming or concomitant drug therapy	Nonsustained VT that is symptomatic when the tachycardia is drug resistant or when the patient is drug intolerant or does not desire long-term drug therapy	Patients with Vt that is responsive to drug, ICD, or surgical therapy and that therapy is well tolerated and preferable to ablation by the patient Unstable, rapid, multiple, or polymorphic VT that cannot be adequately localized by present mapping techniques Asymptomatic and clinically benign nonsustained VT

ACC/AHA = American College of Cardiology/American Heart Association; AV = atrioventricular; AVNRT = AV nodal reentrant tachycardia; ECG = electrocardiographic; EP = electrophysiological; ICD = implantable cardioverter-fibrillator; SVT = supraventricular tachycardia; VA = ventriculoatrial; VT = ventricular tachycardia.

From Zipes DP, DiMarco JP, Gilette PC, et al: Guidelines for clinical intracardiac electrophysiologic and catheter ablation procedures. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Subcommittee on Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures). J Am Clin Cardiol 26:555, 1995. Reprinted with permission from the American College of Cardiology.

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Chapter 24 - Cardiac Pacemakers and Cardioverter-Defibrillators

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Cardiac pacing has evolved rapidly since its inception in the late 1950s. The collective intelligence of creative biomedical engineers and clinicians, coupled with the advent and increasing sophistication of the microprocessor, has made this possible. What began with asynchronous ventricular pacing as a therapy for patients with Stokes-Adams attacks has made momentous strides every decade. Similar to what has happened in other highly technical fields, many times in the past 20 years it was believed that the ultimate pacemaker had been designed and there was little possibility of further improvement. Each time, the "next generation" of devices yielded greater sophistication, more variables, and the ability to better tailor the device to the needs of the patient. Most recently, we have witnessed a number of new indications for pacing that are based not on the need to treat bradycardia but on an attempt to improve hemodynamics. Investigation into the arenas of pacing for hemodynamic improvement is truly in its infancy and, without doubt, will yield even more technological improvements in cardiac pacemakers.

The rapid technological advancements in cardiac pacemakers have, at least to some

degree, served as a catalyst for an even faster evolution in implantable cardioverter-defibrillators (ICDs). Considering that the first human cardioverter-defibrillator implantation occurred in 1979, the evolution of this technology has been staggering. The initial implants were large pulse generators capable of defibrillation, but that required open-chest implantation techniques. Only 20 years later, ICDs are now a fraction of the size, implanted almost exclusively by transvenous techniques in the same manner as permanent pacemakers, and capable of many options, including multiple programmable therapies for ventricular tachycardia and ventricular fibrillation, dual-chamber rate-responsive pacing, and atrial defibrillation.

As the technology for both pacemakers and ICDs has evolved and potential indications have expanded, clinical trials have been crucial to prove efficacy. Clinical trials were uncommon in this field before the 1990s but are now an integral part of the discipline of implantable device therapy and will remain so as we see further innovative improvements in the years to come.

PACEMAKER NOMENCLATURE

Current pacemaker nomenclature established by members of the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) is designated the NBG code for pacing nomenclature (Table 24-1) . [1] The code has five positions, but the fifth position is restricted to antitachycardia functions and is rarely used. It is a generic code and does not describe specific or unique functional characteristics of each device.

The first position reflects the chamber or chambers in which stimulation occurs: A = atrium; V = ventricle; and D = dual chamber, or both A and V.

The second position refers to the chamber or chambers in which sensing occurs. The letters are the same as those for the first position. (Manufacturers also use "S" in both the first and the second positions to indicate that the device is capable of pacing only a single cardiac chamber.)

TABLE 24-1 -- NBG* CODE

I **Chamber(s) Paced**	II **Chamber(s) Sensed**	III **Response to Sensing**	IV **Programmability, Rate Modulation**
O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	P = Simple programmable
V = Ventricle	V = Ventricle	I = Inhibited	M = Multiprogrammable
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)	C = Communicating
			R = Rate modulation

Modified from Bernstein AD, Camm AJ, Fletcher RD, et al: The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive-rate pacing and antitachyarrhythmia devices. Pacing Clin Electrophysiol 10:794, 1987. By permission of Futura Publishing Company.

*The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group.

The third position refers to the mode of sensing, or how the pacemaker responds to a sensed event. An "I" indicates that a sensed event inhibits the output pulse and causes the pacemaker to recycle for one or more timing cycles. "T" means that an output pulse is triggered in response to a sensed event. "D" means that both "T" and "I" responses can occur. This designation is restricted to dual-chamber systems. An event sensed in the atrium inhibits the atrial output but triggers a ventricular output. Unlike a single-chamber triggered mode (VVT or AAT), in which an output pulse is triggered immediately on sensing, a dual-chamber mode has a delay between the sensed atrial event and the triggered ventricular output to mimic the normal PR interval. If a native ventricular signal or R wave is sensed, the ventricular output and possibly even the atrial output are inhibited, depending on where sensing occurs.

The fourth position of the code reflects both programmability and rate modulation. An "R" in the fourth position indicates that the pacemaker incorporates a sensor to modulate the rate independently of intrinsic cardiac activity, such as with activity or respiration. From a practical standpoint, "R" is the only indicator commonly used in the fourth position. Other indicators are described in Table 24-1 .

INDICATIONS FOR CARDIAC PACING

Criteria established by a joint committee of the American College of Cardiology (ACC) and the American Heart Association (AHA) have established indications for pacing into categories of "generally indicated," "may be indicated," and "not indicated."[2] Although some indications for permanent pacing are relatively certain or unambiguous, others require considerable expertise and judgment.[3] The clinician prescribing permanent pacing systems should be aware of the published indications and controversies regarding indications.

The clinical need for pacing and appropriate objective data, such as electrocardiographic (ECG) tracings, must be clearly documented in the patient's medical record to ensure reimbursement by Medicare or third-party payers.

Indications are considered in categories of acquired atrio-ventricular (AV) block, congenital AV block, chronic bifascicular and trifascicular block, sinus node dysfunction,

and neurocardiogenic syndromes. Currently, sinus node dysfunction is the most frequent indication for pacing, followed by AV node dysfunction. Pacing for tachyarrhythmias and miscellaneous indications comprises a relatively small percentage. Potential hemodynamic indications for permanent pacing are discussed separately.

Acquired AV Block

AV block is classified traditionally into first-, second-, and third-degree (or complete) heart block. Alternatively, it can be defined anatomically as supra-, intra-, or infra-Hisian. If the QRS complex is prolonged more than 0.12 second, there is a greater probability that the conduction disturbance is infra-Hisian. Acquired AV block is most commonly idiopathic and related to aging, but there are many potential causes (Table 24-2) (see Chap. 25). Indications for permanent pacing in acquired AV block are listed in Table 24-3 .

Indications for permanent pacing for AV block that occurs with an acute myocardial infarction are more controversial. A pacemaker is generally considered indicated if complete AV block, Mobitz type II block, or bilateral or alternating bundle branch block persists for more than 72 hours after the acute event. Some clinicians consider new and persistent bifascicular block an indication for pacing, and others consider pacing for a new left anterior or left posterior hemiblock alone (see Chap. 35).

TABLE 24-2 -- CAUSES OF ACQUIRED ATRIOVENTRICULAR (AV) BLOCK

Idiopathic (senescent) AV block
Coronary artery disease
Calcific valvular disease
Postoperative or traumatic
AV node ablation
Therapeutic irradiation of the chest
Infectious
Syphilis
Diphtheria
Chagas' disease
Tuberculosis
Toxoplasmosis
Lyme disease*
Viral myocarditis (e.g., Epstein-Barr, varicella)
Infective endocarditis
Collagen vascular

Rheumatoid arthritis
Scleroderma
Dermatomyositis
Ankylosing spondylitis
Polyarteritis nodosa
Systemic lupus erythematosus
Marfan syndrome
Infiltrative
Sarcoidosis
Amyloidosis
Hemochromatosis
Malignancy (lymphomatous or solid tumor)
Neuromuscular
Progressive external ophthalmoplegia (Kearns-Sayre syndrome)
Myotonic muscular dystrophy
Peroneal muscular atrophy (Charcot-Marie-Tooth disease)
Scapuloperoneal syndrome
Limb-girdle dystrophy
Drug effect
Digoxin
Beta blockers
Calcium-blocking agents
Amiodarone
Procainamide
Class 1C agents: propafenone, encainide, flecainide
Taxol
From Hayes DL, Osborn MJ: Pacing: A. Antibradycardia devices. In Giuliani ER, Gersh BJ, McGoon MD, et al (eds): Mayo Clinic Practice of Cardiology, 3rd ed. St. Louis, Mosby, 1996, p 911. By permission of Mayo Foundation.

*Lyme disease may require temporary cardiac pacing. Lyme disease is not usually an indication for permanent pacing.

Congenital Complete Heart Block

Although some controversy remains about when to pace in congenital complete heart block, there is now a tendency to pace in all these patients and to do so earlier, even if they are asymptomatic. This clinical approach has evolved because of recognition of a high incidence of unpredictable syncope with significant mortality from initial attacks, gradual decrease in heart rate, and a high incidence of acquired mitral insufficiency.[4] In pediatric patients with congenital complete heart block, pacemaker implantation is recommended for congestive heart failure, average heart rate of less than 50 beats/min in the awake infant, history of syncope or presyncope, significant ventricular ectopy, or exercise intolerance.[5]

Chronic Bifascicular and Trifascicular Block

If bifascicular or trifascicular block is associated with transient complete heart block, whether symptomatic or not, pacing is indicated. Pacing in the patient with bifascicular or trifascicular block and syncope that cannot be attributed to any other cause is a Class II ACC/AHA indication. If only fascicular block is noted in the asymptomatic patient, pacing is not indicated.

TABLE 24-3 -- INDICATIONS FOR PERMANENT PACING IN ATRIOVENTRICULAR (AV) BLOCK

TYPE OF AV BLOCK	PACEMAKER NECESSARY	PACEMAKER PROBABLY NECESSARY	PACEMAKER NOT NECESSARY
Third	Symptomatic congenital CHB		
	Acquired symptomatic CHB		
	Atrial fibrillation with CHB		
	Acquired asymptomatic CHB		
Second	Symptomatic, type I	Asymptomatic, type II	Asymptomatic, type I, at supra-His (AV nodal)* level

	Symptomatic, type II	Asymptomatic, type I, at intra-His or infra-His level	
		Hemodynamically symptomatic due to loss of AV synchrony	
First		Hemodynamically symptomatic due to effective loss of AV synchrony with markedly prolonged PR interval (e.g., >300 msec)	Asymptomatic
CHB = complete heart block.			

*An exception may be in the elderly with asymptomatic type I AV block.

Sinus Node Dysfunction

Tachycardia-bradycardia syndrome, sick sinus syndrome, symptomatic sinus bradycardia, sinus arrest and sinus pauses, and chronotropic incompetence are all variants of sinus node dysfunction, and often the terms are used synonymously. The definition of bradycardia varies but is generally accepted to be rates of less than 40 beats/min during waking hours. There is disagreement about the absolute cycle length at which pacing should be considered. Although every patient needs to be considered individually, most experts would agree that sinus pauses exceeding 3 seconds during waking hours should be considered abnormal and may warrant pacing. Pauses that occur during sleep are more difficult to categorize. Because of vagal influences, many normal persons display pauses significantly longer than 3 seconds during sleep, and 3-second pauses without symptoms or rhythm disturbances during waking hours should not require treatment. Permanent pacing should be considered for any patient who has symptomatic bradyarrhythmias if the cause of the bradyarrhythmia is not reversible (Table 24-4) .

Permanent pacing for patients with sinus node dysfunction after myocardial infarction is reserved for patients who have symptoms during bradycardia. If drug therapy results in symptomatic bradycardia, criteria for permanent pacing should follow the guidelines given for sinus node dysfunction in Table 24-4 .

Neurocardiogenic Syncope

Permanent pacing may be indicated for some of the several types of neurally mediated syncope.[5A] Neurally mediated syncope includes carotid sinus hypersensitivity and vasovagal syncope (see Chap. 27).

Understanding the physiology involved is crucial to understanding the clinical manifestations.[6] [7] The carotid sinus reflex is the physiological response to pressure

exerted on the carotid sinus. Stimulation results in activation of baroreceptors within the wall of the carotid sinus, and they initiate an afferent response. Discharge from vagal efferents then results in cardiac slowing. Although this reflex is physiological, some persons have an exaggerated or even pathological response. This reflex has two components, cardioinhibitory and vasodepressor. A cardioinhibitory response results from increased parasympathetic tone and may be manifested by sinus bradycardia, PR prolongation, or advanced AV block. The vasodepressor response is due to sympathetic withdrawal and secondary hypotension. Although a pure cardioinhibitory or pure vasodepressor response can occur, a mixed response is most common.

Tilt-table testing can provide the physiological environment to reproduce vasovagal syncope. With head-up tilt, susceptible patients have decreased venous return and subsequent decrease in left ventricular filling. This response triggers stimulation of baroreceptors and adrenergic discharge, which can result in efferent vagal discharge and sympathetic withdrawal. Vasodilatation and hypotension as well as cardiac slowing may result. It is important to document whether the predominant cause of symptoms is cardioinhibitory or vasodepressor, because therapy differs. Tilt-table testing is often helpful in determining the predominant cause.

Drugs such as beta blockers are commonly used as first-line therapy. Although significant controversy persists, vasovagal syncope can be aborted or blunted by dual-chamber pacing; and even if syncope does occur, pacing can prolong consciousness to avoid injury.[8] Conversely, the beneficial effect of pacing was challenged in a series of 22 patients with bradycardia during neurocardiogenic syncope in whom pacing failed to prevent a significant drop in blood pressure during a repeat tilt test.[9] Nonetheless, pacing significantly altered symptoms. Of 21 patients with an abnormal response to the initial tilt test, 18 had syncope and 3 had presyncope. During repeat tilt testing, 5 patients experienced syncope, 15 had presyncope, and 1 had no symptoms. Although presyncope was not prevented in most patients, the shift from syncope in 18 patients to syncope in only 5 patients represented significant clinical improvement.

TABLE 24-4 -- INDICATIONS FOR PERMANENT PACING IN SINUS NODE DYSFUNCTION (SND)

PACEMAKER NECESSARY	PACEMAKER PROBABLY NECESSARY	PACEMAKER NOT NECESSARY
Symptomatic sinus bradycardia	Symptomatic patients with SND who have documented rates of <40 beats/min without a clear-cut association between significant symptoms and bradycardia	Asymptomatic SND
Symptomatic sinus bradycardia due to long-term drug therapy of a type and at a dose for which there is no accepted alternative		

TABLE 24-5 -- TRIALS OF PACING THERAPY IN NEUROCARDIOGENIC SYNCOPE

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
VPS-1[10]	Six lifetime episodes of syncope *and* Positive HUT test with syncope or presyncope Relative bradycardia	Time to recurrent syncope	Standard drug therapy *vs.* Pacemaker	85% risk reduction for recurrent syncope with pacing
VPS-2	History strongly suggests vasovagal syncope Six lifetime episodes of syncope *or* Three in past 2 yr *or* One episode in past 6 mo *and* Positive HUT test with syncope or presyncope	Time to recurrent syncope Efficacy of rate drop response	Randomization to DDD or no pacing for 6 months or until first episode of syncope Rerandomization to DDD pacing with or without rate drop response	In progress

VASIS[12]	Three syncopal episodes in prior 2 yr	Recurrence of syncope	Dual-chamber pacing with hysteresis	In progress
	Duration of symptoms >6 mo	Recurrence of presyncope	*vs.*	
		Need for secondary PM implant or drug therapy	No pacing (no specific therapy)	
SAFE PACE 2[13]	Age 50 yr	Recurrent falls	Pacemaker	In progress
	Two unexplained falls ±1 syncopal episode in prior 12 mo	Time to first fall	*vs.*	
	>3-Sec asystole on CSM	Frequency of dizziness or presyncope	Conventional therapy	
	No other cause of falls	Health care utilization		
		Quality of life		
SYDIT[14]	No cardiac disease	Recurrence of syncope	Atenolol or etilefrine	In progress
	Age >35 yr		*vs.*	
	Three syncopal spells in preceding 2 yr		DDD pacing with rate drop response	
	Positive HUT test with HR			
	30% and bradycardia 50 beats/min			

CSM, carotid sinus massage; HR
, heart rate decrease; HUT, head-up tilt; PM, pacemaker; SAFE PACE, Syncope and Falls in the Elderly--Pacing and Carotid Sinus Evaluation; SYDIT, Syncope: Diagnosis and Treatment Study; VASIS, Vasovagal Syncope International Study; VPS, North American Vasovagal Pacemaker Study.

In the North American Vasovagal Pacemaker Study (VPS-1),[10] 46 patients with recurrent syncope and a positive tilt test were randomized to dual-chamber pacemaker with a special feature known as "rate drop" or to no pacemaker therapy. (The "rate drop" algorithm allows the pacemaker to pace at a faster rate if bradycardia suddenly occurs.) Stopped prematurely because of the benefit observed with pacemaker therapy, the study revealed that only 17 percent of paced patients had recurrent syncope compared with 59 percent of patients without pacing.

Brignole and coworkers[11] randomized 60 patients with carotid sinus hypersensitivity to pacing or no pacing. At a mean follow-up of 36 months, syncope recurred in 9 percent of paced patients compared with 57 percent of patients without pacing.

Additional trials, North American Vasovagal Pacemaker Study-2 (VPS-2), Vasovagal Syncope International Study (VASIS),[12] and Syncope and Falls in the Elderly-Pacing and Carotid Sinus Evaluation 2 (SAFE PACE 2),[13] are under way to assess pacing therapy in both neurocardiogenic syncope and carotid sinus hypersensitivity (Table 24-5) .

SELECTION OF THE APPROPRIATE PACING MODE

When an indication for pacing has been identified, consideration should be given to selecting the most appropriate pacing mode for the patient. Factors to consider when choosing the pacing mode include

- Underlying rhythm disturbance
- Overall physical condition
- Associated medical problems
- Exercise capacity
- Chronotropic response to exercise
- Effect of pacing mode on long-term morbidity and mortality

Before individual pacing modes and how they can restore rate response or AV synchrony are discussed, the larger issue of the effect of pacing mode on morbidity and

mortality should be considered.

An early study by Rosenqvist and associates [15] paved the way for intense clinical interest and subsequent clinical trials on the effect of pacing mode on morbidity and mortality. At 4 years of follow-up, atrial fibrillation had occurred in 47 percent of the patients receiving VVI pacing but in only 7 percent of those receiving AAI pacing (p 0.0005); congestive heart failure occurred in 37 percent of the VVI group and in 15 percent of the AAI group (p 0.005); and mortality was 23 percent in the VVI group and 8 percent in the AAI group (p 0.025).

Many other investigators performed retrospective reviews to assess the effect of pacing mode on mortality. Despite the inherent weaknesses of retrospective analyses, it is difficult to dismiss the similar finding among all the studies of a significantly lower mortality with DDD or AAI pacing than with VVI pacing and significantly lower incidences of atrial fibrillation.[16]

Lamas and associates[17] reported survival in a large population of patients (20,948) with sinus node dysfunction. The population was a random sample of the complete U.S. cohort of Medicare patients paced for sinus node dysfunction in 1988 through 1990. The DDD/DDDR pacing mode was an independent correlate of survival.

A number of prospective trials are now completed or under way.[17A] Results to date are mixed (Table 24-6) . Andersen and colleagues[24] published the first prospective data on pacing mode and survival. In 225 patients (mean age, 76 years) with sinus node dysfunction randomized to AAI or VVI pacing, they demonstrated a higher incidence of atrial fibrillation in the VVI group (14 percent of the AAI group vs. 23 percent of the VVI group; $p = 0.12$) and a higher incidence of thromboembolism in the VVI group than in the AAI group ($p = 0.0083$). Although no difference in mortality could be detected at the initial analysis at 3.3 years, subsequent analysis at 5.5 years showed improved survival and less heart failure in the AAI group.[18] In addition, there was a persistent reduction in the incidences of atrial fibrillation and thromboembolic events.

Lamas and associates[19] subsequently developed a prospective, randomized, single-blind trial, Pacemaker Selection in the Elderly (PASE), to compare DDDR and VVIR pacing modes. There was no statistically significant difference in quality of life between DDDR and VVIR pacing modes, but there was a trend toward improved quality of life in patients with sinus node dysfunction randomized to dual-chamber pacing. Perhaps more significant was a crossover of 26 percent of patients from ventricular pacing to dual-chamber pacing due to pacemaker syndrome.

The PASE study was the template for the subsequent MOST (Mode Selection Trial) study.[21] In this study of 2000 patients with sinus node dysfunction randomized to either

VVI or DDD pacing, primary endpoints are all causes of mortality and cerebrovascular accidents. Results are expected in the year 2000.

The Canadian Trial of Physiologic Pacing (CTOPP)[20] compared VVIR with DDDR or AAIR and had primary endpoints of overall mortality and cerebrovascular accidents and secondary endpoints of atrial fibrillation, hospitalizations for congestive heart failure, and death due to a cardiac cause. CTOPP demonstrated that physiological pacing (DDD/AAI) was associated with a reduced rate in the development of chronic atrial fibrillation, from 3.78 to 2.87 percent per year, at the 3-year analysis. However, no difference in quality of life or mortality was demonstrated.

In a smaller trial by Schrepf and coworkers, [25] paroxysmal atrial fibrillation occurred more frequently with VVI pacing than with DDD pacing. However, the Pac-A-Tach trial[26] found no significant difference in recurrence of atrial tachyarrhythmias by intention to treat at 1 year, 48 percent in DDDR and 43 percent in VVI.

TABLE 24-6 -- TRIALS ASSESSING THE EFFECT OF PACING MODE ON MORBIDITY AND MORTALITY

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
Danish study[18]	Sick sinus syndrome requiring pacing	Mortality	AAI pacing (n = 110)	Cumulative incidence of cardiovascular death, PAF, chronic AF, and TE events lower with AAI pacing
		Cardiovascular death	*vs.*	Less severe heart failure with AAI
		AF	VVI pacing (n = 115)	Multivariate analysis: AAI associated with freedom from TE events, survival from cardiovascular death
		TE events		
		Heart failure		
		AV block		

PASE[19]	Age 65 yr	QOL	Single-blind, randomized, controlled comparison; VVIR pacing	QOL improved significantly, but no difference between pacing modes
	Need for PPM for prevention or treatment of bradycardia	All-cause mortality	*vs.*	26% pt with VVIR crossover to DDDR due to pacemaker syndrome
		First nonfatal CVA or death		Trends of borderline statistical significance in endpoints favoring DDDR in patient with SND
		First hospitalization for congestive heart failure	DDDR pacing	
		AF		
		Pacemaker syndrome		
CTOPP[20]	Initial pacemaker	Cardiovascular mortality or stroke	DDD/R or AAI/R pacing	No difference in QOL, VVI vs. DDD/AAI
	Life expectancy >1 yr	Paroxysmal or chronic AF	*vs.*	No statistically significant difference in mortality or stroke
	Not in chronic AF	Hospitalization for congestive heart failure	VVI/R pacing	No difference in hospitalizations
			QOL	24% incidence of chronic or paroxysmal AF with DDD/AAI
		6-Minute walk		

MOST[21]	SND requiring pacemaker	Stroke	DDDR	In progress
	NSR or atrial standstill at time of implantation	Health status	*vs.*	
		Cost effectiveness	VVIR	
		Total mortality		
		Cardiovascular mortality		
		AF		
		Heart failure score		
		PM syndrome		
UKPACE[22]	Age 70 yr	All-cause mortality	DDDR (50%)	In progress
	High-grade AV block requiring PPM		*vs.*	
			VVIR (25%)	
			vs.	
			VVI (25%)	
DANPACE[23]	Tachycardia-bradycardia syndrome with normal AV conduction	All-cause mortality	AAIR	In progress
		Cardiovascular mortality	*vs.*	
		Incidence of AF and TE events	DDDR	
		QOL		
		Cost-effectiveness		

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; CTOPP = Canadian Trial of Physiologic Pacing; CVA = cardiovascular accident; DANPACE = Danish Pacing Trial; MOST = Mode Selection Trial; NSR = normal sinus rhythm; PAF = paroxysmal atrial fibrillation; PASE = Pacemaker Selection in the Elderly; PPM = permanent pacemaker; QOL = quality of life; SND = sinus node dysfunction; TE = thromboembolic; UKPACE = United Kingdom Pacing and Cardiovascular Events.

Figure 24-1 The VVI timing cycle consists of a defined lower rate limit (LR) and a ventricular refractory

period (VRP, represented by triangle). When the LR timer is complete, a pacing artifact is delivered in the absence of a sensed intrinsic ventricular event. If an intrinsic QRS occurs, the LR timer is started from that point. A VRP begins with any sensed or paced ventricular activity.

A prospective, randomized British trial, U.K. PACE, has been initiated to compare DDD with VVI pacing modes in 2000 patients 70 years of age and older requiring permanent pacing for second- or third-degree AV block.[22]

The prospective data to date are inconsistent. Although later analyses of initially negative trial results could potentially minimize the current inconsistencies, definitive statements are difficult to make on the basis of current information.

MODES AND TIMING CYCLES

The advantages and disadvantages of each pacing mode cannot be completely comprehended unless the timing cycle of each is understood.

Single-Chamber Triggered Pacing

Single-chamber triggered pacing (AAT and VVT) releases an output pulse every time a native event is sensed. This feature increases the current drain on the battery, accelerating its rate of depletion, and deforms the inscription of the intrinsic spontaneous complex on the ECG. However, it can serve as an excellent marker for the site of sensing within an intrinsic complex and can prevent inappropriate inhibition from oversensing when the patient does not have a stable escape rhythm. Triggered pacing is used infrequently.

VENTRICULAR INHIBITED PACING (VVI).

This pacing mode incorporates sensing on the ventricular channel, enabling a sensed ventricular event to inhibit pacemaker output (Fig. 24-1) . VVI pacemakers are refractory for an interval after a paced or sensed ventricular event, the ventricular refractory period (VRP). Any ventricular event occurring within the VRP is not sensed and does not reset the ventricular timer.

VVI pacing remains the most commonly used pacing mode worldwide. Although VVI pacing protects the patient from lethal bradycardias, it is significantly limited because it does not restore or maintain AV synchrony and does not provide rate responsiveness in the chronotropically incompetent patient, that is, the patient in whom the spontaneous sinus heart rate does not increase in response to a physiological demand. In addition, some patients with VVI pacing experience symptomatic hemodynamic deterioration during ventricular pacing.[27] [28] Adverse hemodynamics associated with a normally functioning pacing system that cause overt symptoms or limit the patient's ability to achieve optimal functional status are referred to as "pacemaker syndrome" (Fig. 24-2) . Pacemaker syndrome was initially recognized with ventricular (VVI) pacing but can occur with any pacing mode if there is AV dissociation. The incidence of pacemaker syndrome is difficult to determine and depends on how the syndrome is defined. If the

definition is restricted to patients with clinical limitations during any pacing mode that results in AV dissociation, the incidence is

Figure 24-2 Hemodynamic tracing from a patient with pacemaker syndrome. In the initial portion of the tracing there is sinus rhythm with intrinsic atrioventricular node conduction with a systolic arterial pressure of approximately 125 mm Hg. This is followed by fusion beats and a progressive decrease in systolic pressure. When the ventricle is completely depolarized by the pacemaker, the systolic pressure decreases to approximately 80 mm Hg. This hemodynamic response is compatible with pacemaker syndrome.

Figure 24-3 The AAI timing cycle consists of a defined lower rate limit (LR) and an atrial refractory period (ARP). When the LR cycle is complete, a pacing artifact is delivered in the atrium in the absence of a sensed atrial event. If an intrinsic P wave occurs, the LR timer is started from that point. An ARP begins with any sensed or paced atrial activity. The AAI timing cycle should not be affected by events in the ventricle. In this schematic example, a premature ventricular contraction (PVC) occurs. Appropriately, it is not sensed by the AAI pacemaker, and the atrial pacing artifact occurs in the T wave of the PVC. Even though atrial capture presumably would occur, there is no ventricular event after the paced atrial event because the ventricle is still refractory. However, the timing cycle will be reset by anything that is sensed on the atrial sensing circuit. In this schematic example, a premature ventricular contraction occurs. It is appropriately not sensed, and the pacing artifact is delivered after the PVC. Even though there appears to be atrial depolarization, no intrinsic ventricular depolarization occurs because the ventricle is refractory.

probably in the range of 7 to 10 percent of patients with VVI pacing.[27] In a study of patients with DDD pacemakers who were randomized to DDD or VVI pacing mode, some degree of pacemaker syndrome was thought to be present in 83 percent.[29] The most common symptoms reported were shortness of breath, dizziness, fatigue, pulsations in the neck or abdomen, cough, and apprehension. It can be concluded from this study that if patients with VVI pacing have some basis for comparison, they may be more aware of symptoms with VVI pacing.

ATRIAL INHIBITED PACING (AAI).

This pacing mode incorporates the same timing cycles, with the obvious difference that pacing and sensing occur from the atrium and pacemaker output is inhibited by a sensed atrial event (Fig. 24-3) . An atrial paced or sensed event initiates a refractory period during which no spontaneous event is sensed by the pacemaker. When the atrial timing cycle ends, the atrial pacing artifact is delivered regardless of ventricular events, because an AAI pacemaker should not sense ventricular events. The single exception to this rule is far-field sensing; that is, the ventricular signal is large enough to be inappropriately sensed by the atrial lead. In this situation, the atrial timing cycle is reset by events sensed in the ventricle. Sometimes this abnormality can be corrected by

making the atrial channel less sensitive or by lengthening the refractory period.

AAI pacing is appropriate for patients with sinus node dysfunction and normal AV conduction. The obvious disadvantage of atrial pacing is lack of ventricular support should AV block occur. If the patient with sinus node dysfunction is assessed carefully for AV node disease at the time of pacemaker implantation, the occurrence of clinically significant AV nodal disease is very low, that is, less than 2 percent per year.[30] Assessment before use of an AAI system should include incremental atrial pacing at the time of pacemaker implantation. Although criteria vary among institutions and implanting physicians, the adult patient should be capable of 1-to-1 AV nodal conduction to rates of 120 to 140 beats/min.

Dual-Chamber Pacing

AV sequential, ventricular inhibited pacing (DVI) is rarely used as the preimplantation pacing mode of choice. By definition, DVI provides pacing in both the atrium and the ventricle (D) but sensing only in the ventricle (V). The pacemaker is inhibited and reset by sensed ventricular activity but ignores all intrinsic atrial complexes and therefore prevents atrial tracking. In addition, lack of atrial sensing may lead to competitive atrial pacing and initiation of atrial rhythm disturbances.

AV SEQUENTIAL, NON-P-SYNCHRONOUS PACING.

This pacing mode with dual-chamber sensing (DDI) incorporates atrial sensing, as well as ventricular sensing, which prevents competitive atrial pacing (Fig. 24-4) . The DDI mode of response is inhibition only; that is, no tracking of P waves can occur. Therefore, the programmed rate, which by definition is the lower rate, because only a single rate exists, is the fastest paced rate that can be seen. DDI is rarely the preimplantation mode of choice but remains a programmable option in most dual-chamber pacemakers.[31] The DDI pacing mode could be considered in patients with intermittent atrial tachyarrhythmias, but DDD or DDDR pacing with mode switching is preferable.

ATRIAL SYNCHRONOUS PACING (VDD).

These pacemakers pace only in the ventricle, sense in both chambers, and respond both by inhibition of ventricular output due to intrinsic ventricular activity and by ventricular tracking of P waves. The VDD mode has become increasingly available as a single-lead pacing system. In this system, a single lead is capable of pacing in the ventricle in response to sensing atrial activity by way of a remote electrode situated on the intra-atrial portion of the ventricular pacing lead.[32]

In the VDD mode, sensed atrial events initiate the AV interval (AVI). If an intrinsic ventricular event occurs before the termination of the AVI, ventricular output is inhibited

Figure 24-4 The timing cycle in DDI pacing consists of a lower rate limit, an atrioventricular (AV) interval,

a ventricular refractory period (VRP), and an atrial refractory period (ARP). The VRP is initiated by any sensed or paced ventricular activity, and the ARP is initiated by any sensed or paced atrial activity. The lower rate limit cannot be violated even if the sinus rate is occurring at a faster rate. PVARP = postventricular atrial refractory period; VA = ventriculoatrial.

Figure 24-5 The timing cycle of VDD consists of a lower rate limit (LRL), an atrioventricular interval (AVI), a ventricular refractory period, a postventricular atrial refractory period (PVARP), and an upper rate limit. A sensed P wave initiates the AVI (during the AVI the atrial sensing channel is refractory). At the end of the AVI a ventricular pacing artifact is delivered if no intrinsic ventricular activity has been sensed; this represents P-wave tracking pacing. Ventricular activity, paced or sensed, initiates the PVARP and the ventriculoatrial interval (the LRL interval minus the AVI). If no P-wave activity occurs, the pacemaker escapes with a ventricular pacing artifact at the LRL. PV = interval from intrinsic atrial event to paced ventricular event; TARP = total atrial refractory period.

and the lower rate timing cycle is reset (Fig. 24-5) . If a paced ventricular beat occurs at the end of the AVI, this beat resets the lower rate. If no atrial event occurs, the pacemaker escapes with a paced ventricular event at the lower rate limit; that is, the pacemaker displays VVI activity in the absence of a sensed atrial event. VDD pacing may be appropriate for the patient with normal sinus node function and conduction disease of the AV node.

DUAL-CHAMBER PACING AND SENSING WITH INHIBITION AND TRACKING (DDD).

In this mode the basic timing circuit associated with lower rate pacing is divided into two sections, the VA interval and the AVI. The AVI may be defined by AV sequential pacing initiated by pacing with subsequent intrinsic ventricular conduction or initiated by a native P wave with subsequent ventricular pacing (Fig. 24-6) .

The postventricular atrial refractory period, or PVARP, is the period after a sensed or paced ventricular event during which the atrial sensing circuit is refractory. Any atrial event occurring during the PVARP is not sensed by the atrial sensing circuit. If a P wave occurs after the PVARP and is sensed, no atrial pacing artifact is delivered at the end of the VA interval (Fig. 24-6) . Because the maximum tracking rate of the pacemaker is determined by the total atrial refractory period (TARP), the PVARP is a significant determinant of the upper rate limit. The PVARP is *especially important for the prevention of endless-loop, or pacemaker-mediated, tachycardia*.

Four different rhythms can result in normal DDD function: (1) normal sinus rhythm, (2) atrial pacing, (3) AV sequential pacing, and (4) P-synchronous pacing.

DDD pacing mode is most appropriate for patients with normal sinus node function and AV block. DDD pacing is often considered the mode of choice in neurocardiogenic

syndromes with symptomatic cardioinhibition.

DDD pacing has limitations in the patient with sinus node dysfunction, because P-synchronous pacing is not possible in chronic atrial fibrillation or in patients with a paralyzed or nonexcitable atrium. Also, DDD pacing does not restore rate response in the chronotropically incompetent patient.

Figure 24-6 The timing cycle in DDD consists of a lower rate limit (LR), an atrioventricular interval (AVI), a postventricular atrial refractory period (PVARP), and an upper rate limit. The AVI and PVARP together comprise the total atrial refractory period (TARP). If intrinsic atrial and ventricular activity occur before the LR times out, both channels are inhibited and no pacing occurs. If no intrinsic atrial or ventricular activity occurs, there is AV sequential pacing (first sequence). If no atrial activity is sensed before the ventriculoatrial (VA) interval is completed, an atrial pacing artifact is delivered, which initiates the AVI. If intrinsic ventricular activity occurs before the termination of the AVI, the ventricular output from the pacemaker is inhibited, that is, atrial pacing (second sequence). If a P wave is sensed before the VA interval is completed, output from the atrial channel is inhibited. The AVI is initiated; and if no ventricular activity is sensed before the AVI terminates, a ventricular pacing artifact is delivered, that is, P-synchronous pacing (third sequence). ID = intrinsic deflection.

Figure 24-7 Electrocardiographic (ECG) example of pacemaker-mediated tachycardia (PMT) in a patient whose device is programmed to the DDD pacing mode. The ECG tracing demonstrates atrial pacing with a long AR interval. The second QRS complex is followed by a paced ventricular beat that is followed by continuous ventricular pacing at a rate of approximately 100 beats/min. This appearance is consistent with PMT, or endless-loop tachycardia. It is unclear what initiates the PMT, although the most likely explanation is a retrograde P wave after the intrinsic QRS.

In any pacemaker capable of P-synchronous pacing, endless-loop tachycardia, also called "pacemaker reentrant tachycardia" or "pacemaker-mediated tachycardia," can result.[33] If AV synchrony is dissociated by any event, most commonly a premature ventricular complex (PVC), retrograde ventriculoatrial (VA) conduction can result in a retrograde P wave (Fig. 24-7) . If the retrograde P wave is sensed by the atrial sensing circuit of the pacemaker, the AVI is initiated, resulting in a paced ventricular complex at a cycle length approximately equal to the maximum tracking rate. The paced ventricular event may again result in retrograde VA conduction, perpetuating this rapid reentrant circuit. Endless-loop tachycardia can be prevented by a PVARP that is long enough to prevent sensing of the retrograde P wave. Most pacemakers also have specific algorithms that attempt to recognize and abort endless-loop tachycardia.

INDICATIONS FOR RATE-ADAPTIVE PACING

Rate-adaptive pacemakers have the ability to increase the pacing rate through sensors that monitor physiological processes such as activity and minute ventilation.

Single-chamber rate-adaptive pacing (AAIR, VVIR) has timing cycles that are not significantly different from those of its non-rate-adaptive counterparts. The difference lies in the potential variability of the paced rate (Fig. 24-8) . Depending on the sensor incorporated and the level of exertion of the patient, the basic interval shortens from the programmed lower rate limit to an upper rate limit programmed to define the absolute shortest cycle length allowable.

VVIR pacing, like VVI, is generally contraindicated if ventricular pacing results in retrograde (VA) conduction or a decrease in blood pressure. Also, if the sinus node is normal, P-synchronous pacing should be considered the optimal rate-adaptive mode and used when possible.

AAIR pacing can be considered in the patient with sinus node dysfunction and normal AV node function, because this mode restores rate responsiveness and maintains AV synchrony. If AAIR pacing is contemplated, normal AV node conduction must first be determined, as previously discussed for AAI pacing.

Dual-chamber rate-adaptive (DDDR) pacemakers are capable of all the variations described for DDD pacemakers. In addition to using P-synchronous pacing as a method for increasing the heart rate, the sensor incorporated in the pacemaker may also drive the increase in heart rate. The resulting rhythm may be sinus driven (alternatively called "atrial-driven" or "P-synchronous") or sensor driven. The ideal patient for DDDR pacing is one with combined sinus node and AV node dysfunction, because this mode allows restoration of rate responsiveness and AV synchrony.

Algorithms for determining the appropriate pacing mode for patients with sinus node disease and AV node disease are shown in Figure 24-8 . In Figure 24-8 *A*, a more complex algorithm, most of the available pacing modes are considered. The second algorithm is simpler and assumes that a pacemaker capable of rate adaptation is used (Fig. 24-8 *B*).

Selecting the Appropriate Sensor for Rate-Adaptive Pacing

In an effort to classify sensors on the basis of their response to physiological variables, Rossi[34] divided sensors into five orders (Table 24-7) . A variety of sensors appropriate for

Figure 24-8 Algorithms for pacemaker mode selection. *A*, Choice of VVI, VVIR, AAI, AAIR, DDD, or DDDR is allowed. *B*, Only VVIR or DDDR is selected.

rate-adaptive pacing have been developed and are displayed in Figure 24-9 as endpoints of some physiological response.[34A]

ACTIVITY SENSORS.

Activity sensing with vibration detection (piezoelectric crystal or accelerometer) has been the most widely used form of rate adaptation because it is simple, easy to apply clinically, and rapid in onset of rate response.[35] [36] The main difference between the piezoelectric crystal sensor and the accelerometer is that the former senses vibration from "up and down" motion and the latter in addition senses anterior and posterior motion. Accelerometers have been shown to have a slightly more physiological response than piezoelectric crystal sensors and specifically to have a more appropriate rate response to stair walking.[37]

Subsequent variations include a gravitational sensor able to discriminate changes in vertical gravitational acceleration[38] and a moving magnetic ball that measures electrical signals.[39]

MINUTE-VENTILATION SENSORS.

The minute volume (respiratory rate times tidal volume) sensor has an excellent correlation with metabolic demand. In a rate-adaptive pacing system, minute volume is determined by emission of a small charge of known current (1 mA every 15 msec) from the pacemaker and measurement of the resulting voltage at the lead tip.[40] When both current and voltage are known, transthoracic impedance can be measured between the ring electrode and the pacemaker. Because transthoracic impedance varies with respiration and its amplitude varies with tidal volume, the impedance measurement can be used to determine respiratory rate and tidal volume. A pacing algorithm uses the minute volume measurements to alter pacing rate.[41] Long-term reliability of the minute volume sensor has been excellent.

TABLE 24-7 -- CLASSIFICATION OF SENSORS BY RESPONSE TO PHYSIOLOGIC VARIABLES

ORDER	DESCRIPTION	PHYSIOLOGIC VARIABLE
First	A sensor that directly measures oxygen consumption or energy expenditure	Oxygen uptake
Second	A sensor with a linear relationship to sensors of the first order	Cardiac output, minute ventilation,* atrio-ventricular oxygen difference
Third	A sensor with a linear relationship to sensors of the second order	Heart rate,* stroke volume, mixed oxygen saturation, respiratory rate,* tidal volume

Fourth	A sensor that relies on changes in sympathetic activity and circulating catecholamines	QT interval,* right ventricular dP/dt, preejection interval, ventricular depolarization gradient
Fifth	A sensor that responds to physiological feedback mechanisms in terms of metabolic activity or receptor reflexes	Central venous pH, central venous temperature,* right atrial pressure, mixed venous lactate and bicarbonate levels

Data from Rossi P: Rate-responsive pacing: Biosensor reliability and physiological sensitivity. Pacing Clin Electrophysiol 10:454, 1987.

*Available clinically in the United States or Europe.

Under investigation.

Figure 24-9 Physiologic responses that have been investigated or clinically used for rate adaptation of permanent pacemakers. The "boxed" terms are the endpoints used for rate adaptation. ANS = autonomic nervous system; PDI = paced depolarization integral; PEI = preejection interval; SV = stroke volume.

STIMULUS-T OR QT SENSING PACEMAKER.

The interval from the onset of a paced QRS complex to the end of the T wave has been used for rate adaptation for many years.[42] Autonomic activity and heart rate affect the stimulus-T interval, and the relationship allows measurement of the stimulus-T interval to be used for rate adaptation. The QT-sensing rate-adaptive pacing system has been very successful clinically.

OTHER SENSORS.

Several other sensors have been used clinically for rate-adaptive pacing (Table 24-8) . Although some have shown significant clinical potential, none has achieved widespread clinical use.

DUAL-SENSOR COMBINATIONS.

The overall performance of market-approved single-sensor rate-adaptive systems has

been excellent. However, the perfect sensor would mimic the response of the normal sinus node at all levels of activity and during emotional stress.

Clinical problems with available rate-adaptive pacing systems have been minimal. Both activity-sensing and minute-ventilation devices may respond to nonphysiological stimuli. For example, with activity-sensing systems, rate acceleration may occur when the pacemaker is tapped or the patient rolls over on the pacemaker. A paradoxical rate response to stair ascent has been shown with activity-sensing pacemakers that incorporate a piezoelectric crystal, that is, the sensor-driven rate response is often faster during descent of stairs than during ascent.[37] Although response to nonphysiological stimuli represents less-than-perfect specificity of the sensor response, both activity sensing and minute ventilation have served patients well. The perfect sensor would be resistant to these nonphysiological stimuli. A multisensor rate-adaptive pacing system could improve specificity by having one sensor verify or cross-check the other. For example, if one sensor indicated a rate increase and the other did not, a rate increase would not occur. Both sensors would have to indicate a rate increase before it would be allowed.

Potential concerns with dual-sensor pacing systems include more complex programming and greater battery consumption because two or more sensors are monitored and activated.[43] To date, the overall experience with multisensor rate-adaptive pacemakers is positive, and information is emerging to suggest that they may have a hemodynamic benefit over single-sensor devices.[44]

TABLE 24-8 -- OTHER SENSORS FOR RATE-ADAPTIVE PACING

SENSOR	SPEED OF RESPONSE	SPECIFICITY	COMMENTS
Temperature	Slow onset	Relatively specific	Special lead required
Preejective interval, stroke volume	Relatively rapid	Relatively specific	Special lead required; partially closed-loop system
dP/dt	Relatively rapid	High specificity	Special lead required; partially closed-loop system
Mixed V_{O_2}	Rapid	High specificity	Special lead required; some concern about long-term performance
Paced depolarization interval	Relatively rapid	Relatively specific	Standard lead; closed-loop characteristics

Figure 24-10 Hemodynamic tracing demonstrating left ventricular outflow gradient reduction during a temporary pacing study. During normal sinus rhythm (NSR), the patient exhibits marked left ventricular outflow obstruction with gradient of 70 to 90 mm Hg. With initiation of P-synchronous pacing at an atrioventricular interval of 120 milliseconds, the gradient is reduced to 10 to 25 mm Hg. *(From Symanski JD, Nishimura RA: The use of pacemakers in the treatment of cardiomyopathies. Curr Prob Cardiol 21:385, 1996. By permission of CV Mosby.)*

PACING FOR HEMODYNAMIC IMPROVEMENT

Whenever a patient receives a pacemaker for bradycardia-related symptoms for any of the pacemaker indications already discussed, resolution of the bradyarrhythmia results in hemodynamic improvement. In the past decade, however, several nonbradyarrhythmic indications for permanent pacing for hemodynamic improvement have emerged.

Hypertrophic Obstructive Cardiomyopathy (See Chap. 48.)

Dual-chamber pacing is useful as a therapeutic modality for some patients with severe, symptomatic hypertrophic obstructive cardiomyopathy (HCM).[45] [45A] [45B] Multiple investigators have reported a significant reduction in the left ventricular outflow tract gradient and symptomatic improvement in patients with HCM in whom dual-chamber pacemakers have been implanted (Fig. 24-10) .

Fananapazir and colleagues[45] reported on 84 patients with HCM and drug-resistant symptoms who were treated with dual-chamber pacemakers programmed to the DDD mode with AV intervals short enough to fully activate the ventricle from the pacing site at the right ventricular apex (according to ECG criteria). After a mean of 2.3 years, symptoms resolved (28 patients) or decreased (47 patients) in 89 percent of cases. These results were associated with a significant improvement in mean New York Heart Association (NYHA) functional class from 3.2 to 1.6 and a reduction in the left ventricular outflow tract gradient from 96 to 27 mm Hg in patients with significant outflow obstruction. These benefits persisted after cessation of pacing during normal sinus rhythm, as did some changes on the surface ECG (T wave morphology) and the signal-averaged ECG.

MECHANISMS OF BENEFIT.

The most widely accepted hypothesis to explain the improvement in hemodynamics that may occur with pacing in patients who have HCM is that the altered septal activation caused by right ventricular apical pacing may result in less narrowing of the left ventricular outflow tract and a subsequent decrease in the Venturi effect, responsible for systolic anterior motion of the mitral valve.[46] However, the persistence of improvement after cessation of pacing in some series and the observation that subjective and

objective improvement may also be seen in some patients with left bundle branch block suggest that the effect of long-term pacing cannot be attributed solely to alteration of the septal activation sequence by ventricular pacing. There are hypotheses that permanent pacing in patients with hypertrophic cardiomyopathy may result in long-term remodeling of the left ventricle.[47]

CLINICAL TRIALS.

Pacing in HCM has been the subject of several randomized single-center and multicenter trials (Table 24-9) . A single-center randomized crossover trial demonstrated symptomatic improvement in 63 percent of patients with pacing in the DDD mode.[48] However, 42 percent of patients had improvement when the pacemaker was programmed to a low pacing rate in the AAI mode, that is, effectively no pacing, suggesting a significant placebo effect.

In the Pacing in Cardiomyopathy (PIC) study, a multicenter randomized crossover study,[49] dual-chamber pacing resulted in a 50 percent reduction of the left ventricular outflow tract gradient, a 21 percent increase in exercise duration, and improvement in NYHA functional class compared with baseline status. When clinical parameters, including chest pain, dyspnea, and subjective health status, were compared between DDD and backup AAI pacing, there was no significant difference, again suggesting a significant placebo effect.

In another randomized, double-blind crossover study, the Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy (M-PATHY) trial, no significant differences were evident with randomization between pacing and no pacing, either subjectively or objectively, when exercise capacity, quality of life score, treadmill exercise time, and peak oxygen consumption were compared.[50] The investigators

TABLE 24-9 -- CLINICAL TRIALS IN PACING FOR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HCM)

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
Mayo: Pacing in HCM[48]	Symptomatic HCM despite maximal medical regimen	LVOT gradient	Blinded crossover of DDD pacing	Subjective improvement in ~60% of patients
		Quality of life	*vs.*	Significant placebo effect from pacing
		Exercise duration	No pacing (AAI)	LVOT gradient of ~40%

		Oxygen consumption		
Pacing in Cardiomyopathy (PIC)[49]	Refractory symptoms from HCM despite stable drug regimen	Exercise tolerance	Blinded crossover of DDD pacing	50% reduction in LVOT gradient
		Dyspnea-angina symptom score	*vs.*	21% in exercise duration
	NYHA Class II or III	NYHA Class	No pacing (AAI)	0.7 in NYHA Class
	Angina or dyspnea	Quality of life		
	LVOT >30 mm Hg			
Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy (M-PATHY)[50]	Symptomatic HCM despite maximal medical regimen	Quality of life	Blinded crossover of DDD pacing	No significant subjective or objective improvement with randomization
	LVOT 50 mm Hg	Treadmill exercise duration	*vs.*	Significant placebo effect
		Peak O_2 consumption	No pacing (AAI at 30 beats/min)	LVOT gradient of 40%
		Delta LVOT gradient		
		Delta LV wall thickness		

LV = left ventricular; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

Data from Maron BJ, Nishimura RA, McKenna WJ, et al: Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy: A randomized, double-blind, crossover study (M-PATHY). Circulation 99:2927, 1999.

Figure 24-11 Pressure tracings at different atrioventricular (AV) intervals in a patient with hypertrophic obstructive cardiomyopathy. In this example, the outflow gradient was minimized at an AV interval of 120 milliseconds.

concluded that pacing should not be regarded as a primary treatment for HCM and that subjective benefit without objective evidence of improvement should be interpreted cautiously.

Pacing for the treatment of medically refractory HCM is currently a Class IIb indication for pacing by the ACC/AHA guidelines.[2]

When pacing is applied in the patient with HCM, AVI programming is crucial to achieve optimal hemodynamic improvement. Ventricular depolarization must occur as a result of pacing. Therefore, the AVI must be short enough to result in depolarization by the paced event (Fig. 24-11) . However, the shortest AVI is not necessarily the best.[48] Some experts have advocated AV nodal ablation to ensure paced ventricular depolarization if rapid intrinsic AV nodal conduction prevents total ventricular depolarization by means of the pacing stimulus.[46]

Dilated Cardiomyopathy (See Chap. 48.)

Treatment of idiopathic dilated cardiomyopathy with short AVI DDD pacing was first reported by Hochleitner and coworkers.[51] They treated 16 critically ill patients with idiopathic dilated cardiomyopathy refractory to pharmacological therapy who were in NYHA functional Class III or IV (see Chap. 18). They reported dramatic improvement in NYHA functional class and a reduction in mortality from that expected at 1 year. (Hochleitner and coworkers[52] subsequently published 5-year follow-up results for their original patient cohort. No deaths occurred from continued deterioration in ventricular function, and no patient needed rehospitalization because of worsening heart failure after pacemaker implantation.)

Subsequent investigators have shown markedly discrepant responses to standard dual-chamber pacing, with great interindividual variability and no consistent benefit from dual-chamber pacing.[53] [54] [55] [56] Although the finding is not consistent, some patients receive hemodynamic benefit from standard dual-chamber pacing by optimization of AV timing.[57] Pacing for the treatment of medically refractory dilated cardiomyopathy has been designated a Class IIb indication for pacing by the ACC/AHA guidelines.[2]

It was subsequently hypothesized that in addition to the need for optimization of AV synchrony, correction of intraventricular conduction disturbances might result in clinical improvement. Although estimates from limited studies vary on the proportion of patients with heart failure who also have ventricular dyssynchrony--usually left bundle branch--it appears to be fairly significant and certainly is in excess of the rate in the general population.[58] [59] Ventricular dyssynchrony has been associated with paradoxical septal wall motion, reduced left ventricular pressure, prolonged duration of mitral regurgitation,

and reduced diastolic filling times in patients with left bundle branch block.

BIVENTRICULAR PACING.

Biventricular or left ventricular pacing may counter the decreased septal contribution to stroke volume caused by late left ventricular activation occurring as the septum has begun repolarizing and help to increase ejection fraction[59A] (Fig. 24-12) .

One of the earliest studies of biventricular pacing prospectively assessed six patients with end-stage congestive heart failure, dilated cardiomyopathy, sinus rhythm, and left bundle branch block (LBBB).[60] In this study, biventricular pacing was accomplished with a transvenous right ventricular lead and an epicardial left ventricular lead. After 3 months of biventricular pacing, median NYHA class had significantly improved from 4.0 to 2.5 (p = 0.03).

In a study of 47 patients with advanced heart failure (32 percent Class III, 68 percent Class IV), biventricular pacing resulted in improved quality of life, increased exercise tolerance, and improvement in NYHA functional class.[61]

Auricchio and associates[62] studied pacing with transvenous right atrial and right ventricular leads and a left ventricular epicardial lead in 27 patients with severe left ventricular systolic dysfunction. Overall, they found that biventricular and left ventricular pacing increased maximum left ventricular pressure derivative and aortic pulse pressure more than right ventricular pacing. They concluded that patients with congestive heart failure who have sufficiently wide QRS on surface ECGs derive maximum short-term benefit from left ventricular stimulation at an optimized AVI.

Although the data to date are promising, randomized prospective trials are necessary to prove the efficacy and safety of cardiac resynchronization. Trials currently under way are Multicenter InSync Randomized Clinical Evaluation (MIRACLE), Multisite Stimulation in Cardiomyopathy (MUSTIC), [63] Pacing Therapy in Congestive Heart Failure (PATH-CHF),[64] Right Ventricular Outflow Versus Apical Pacing (ROVA), and Vigor-Congestive Heart Failure (Vigor-CHF)[65] (Table 24-10) .

Pacing to Prevent Atrial Fibrillation (See Chaps. 23 and 25.)

Dual-site atrial pacing has been used to prevent recurrent atrial tachyarrhythmias, presumably by decreasing the dispersion of refractoriness in the atrium.[65A] Daubert and colleagues[66] used biatrial synchronous pacing with leads in the right atrial appendage and coronary sinus. Sensing from the lead in the right atrial appendage led to immediate pacing at the coronary sinus site. In a trial of biatrial synchronous pacing (SYNBIAPACE),[67] there was a trend toward a decreased incidence of atrial arrhythmias but no real benefit was shown. Saksena and associates[68] used one lead in a standard right atrial position and the other lead in the coronary sinus or near the coronary sinus ostium (Fig. 24-13) . Both leads were connected to the same port, resulting in simultaneous pacing at both sites. Dual-site pacing has been shown to reduce the number of episodes of paroxysmal atrial fibrillation and flutter and to increase the

interval to recurrent atrial arrhythmias.[68] [69] When "no pacing" was compared with dual-site or single-site atrial pacing,

Figure 24-12 Posteroanterior *(A)* and lateral *(B)* chest radiographs demonstrating a ventricular lead that courses posteriorly in the coronary sinus and into a cardiac vein, probably a tributary of the posterior cardiac vein. From the posteroanterior view alone, this determination cannot be made.

TABLE 24-10 -- CLINICAL TRIALS IN PACING FOR CONGESTIVE HEART FAILURE (CHF)

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
InSync[61]	NYHA Class III or IV on stable drug regimen	Quality of life	Nonrandomized	In a nonrandomized trial, biventricular pacing resulted in sustained improvement in all three endpoints
	LVEDD >60 mm, LVEF 0.35	NYHA Class		
	QRS width 150 msec	6-minute hall walk		
MIRACLE	NYHA Class III or IV on stable drug regimen	Quality of life	Randomized to pacing or no pacing for 6 mo and then to pacing	In progress
	LVEDD 55 mm, LVEF 0.35	NYHA Class		
	QRS width 130 msec	6-minute hall walk		

Vigor-CHF[65]	Symptomatic CHF on stable drugs	Oxygen consumption	One arm, VDD pacing	In progress
	QRS <120 msec	Peak exercise capacity	Other arm, no pacing for 6 wk and then reprogrammed to VDD	
	PR >160 msec	Quality of life		
	No bradycardia indication for pacing	Cost-effectiveness		
		NYHA Class		
PATH-CHF[64]	DCM of any cause	Maximum LV pressure derivative	Acute hemodynamic assessment of RV pacing	Biventricular and LV: LV pressure derivative and aortic pulse pressure more than RV pacing
	NYHA Class III or IV on stable drug regimen	Aortic pulse pressure	*vs.*	LV pacing: LV pressure derivative more than biventricular pacing
	QRS 120 msec		LV pacing	
	PR 150 msec		*vs.*	
			Biventricular pacing	
ROVA	Standard indication for PPM	Quality of life	Blinded crossover from RV apical to RV outflow tract pacing	In progress
	Chronic AF	VVIR pacing from RV apex vs. RV outflow tract		
	NYHA Class II or III			

	LVEF 0.40			
MUSTIC[63]	NYHA Class III	Functional capacity	Biventricular pacing	In progress
	Refractory symptoms on stable drug therapy	Quality of life	*vs.*	
	LVEF <0.35	Metabolic exercise performance	No pacing with crossover	
	LVEDD >60 mm	Mortality or need for transplant or LVAD		
	<450 m in 6-minute walk	Hospital admission for CHF		
	NSR with QRS >150 msec or AF with paced QRS >200 msec			

AF = atrial fibrillation; DCM = dilated cardiomyopathy; LV = left ventricular; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MUSTIC = Multisite Stimulation in Cardiomyopathy; NSR = normal sinus rhythm; NYHA = New York Heart Association; PATH-CHF = Pacing Therapy in Congestive Heart Failure; PPM = permanent pacemaker; ROVA = Right Ventricular Outflow Versus Apical Pacing; RV = right ventricular; Vigor-CHF = Vigor-Congestive Heart Failure.

dual-site pacing was better, but single-site atrial pacing also resulted in a significant improvement over "no pacing." Single-site atrial septal pacing[70] and Bachmann's bundle pacing[71] have also been tested. In the Atrial Pacing Periablation for Prevention of Paroxysmal Atrial Fibrillation (PA3) study, atrial rate-adaptive pacing did not prevent paroxysmal atrial fibrillation during short-term follow-up in patients with drug-resistant paroxysmal atrial fibrillation.[72] The best pacing approach will be determined by multiple trials already under way, including Dual-Site Atrial Pacing to Prevent Atrial Fibrillation (DPPAF),[73] Systematic Trial of Pacing for Atrial Fibrillation (STOP-AF),[74] Pacing in Prevention of Atrial Fibrillation (PIPAF), and Atrial Fibrillation Therapeutics Trial (AFT)[75] (Table 24-11) .

Pacing in Long QT Syndrome (See Chaps. 23 and 25.)

The long QT syndrome is characterized by abnormally prolonged ventricular repolarization and a risk of development of life-threatening ventricular tachyarrhythmias. Therapy must be individualized depending on the clinical situation. Therapeutic options include beta-blocker therapy, permanent pacing, and the ICD (see later and Chap. 25).[76]

PULSE GENERATOR IMPLANTATION

Only qualified physicians should undertake pacemaker or cardioverter-defibrillator implantation. The recommended training requirements for pacemaker implantation[77] [78] are as follows: a base of core knowledge for pacemaker follow-up, participation in at least 100 pacemaker follow-up visits, participation in at least 50 initial transvenous pacemaker implantations as the primary operator (recommended that at least one half of these be dual-chamber), participation in at least 20 revisions of pacing systems, exposure to lead extraction techniques (suggested), and thorough knowledge of recognition and treatment of pacemaker and surgical complications and emergencies. A detailed description of pacemaker and cardioverter-defibrillator implantation technique can be found in texts devoted to these disciplines.[79] However, certain information related to the implantation technique is important for the referring physician to know.

Almost all pacemakers and defibrillators are now implanted transvenously, with the pulse generator placed in the upper anterior portion of the chest, just anterior to the pectoralis major muscle. Epicardial pacing is considered only in persons without reasonable venous access, that is, no access to the right ventricle because of an associated

TABLE 24-11 -- CLINICAL TRIALS IN PACING FOR THE PREVENTION OF ATRIAL FIBRILLATION (AF)

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
SYNBIAPACE[67]	1 yr history of recurrent and drug-refractory AA P wave duration 120 msec and IACT 100 msec	Time to first AA recurrence	BASP at 70 beats/min *vs.* Single-site HRA at 70 beats/min	Trend to a in incidence of AA with BASP, but no real benefit of BASP

			or	
			Single-site HRA at 40 beats/min	
DAPPAF[73]	Bradycardia requiring pacing	Time to first recurrence of symptoms of AF	Dual-site right atrial pacing	Results pending
	Two documented episodes of AF in prior 3 mo	Quality of life	*or*	
		Safety of DAP	Single-site atrial pacing	
			vs.	
			Support pacing mode (control arm)	
STOP-AF[74]		Time to recurrence of PAF	Physiological pacing	In progress
			vs.	
			VVI pacing	
PA3[72]	History of PAF with three episodes within year before	Time to recurrence of PAF 5 min occurring 2 wk after entry	DDDR pacemaker implanted and randomized to atrial pacing or no pacing	Atrial RAP did not prevent PAF over short term in patients with drug-resistant PAF
	Most recent PAF within 3 mo of entry	Intervals between successive episodes of PAF		
	At least one episode of PAF documented by ECG	Frequency of PAF		
		Proportion of patients who chose to defer ablation		

PIPAF	Indication for pacing	Time to first recurrence of AA	Comparison of six different lead and algorithm combinations	In progress
	Documented paroxysmal AAs for at least 1 yr, three episodes	Cumulative arrhythmia duration		
	Stable drug therapy			
	< Two cardioversions in past year			
AFT[75]	Paroxysmal AF	Frequency of AF recurrences	DDD pacing at 40 beats/min (backup pacing)	In progress
			vs.	
			DDD pacing at 70 beats/min with specific AF prevention algorithm	

AA = atrial arrhythmia; AFT = Atrial Fibrillation Trial; BASP = biatrial synchronous pacing; DAP = dual-site atrial pacing; DAPPAF = Dual-Site Atrial Pacing to Prevent Atrial Fibrillation; ECG = electrocardiography; HRA = high right atrium; IACT = interatrial conduction time; PA3 = Atrial Pacing Periablation for Prevention of Paroxysmal Atrial Fibrillation; PAF = paroxysmal atrial fibrillation; PIPAF = Pacing in Prevention of Atrial Fibrillation; RAP = rate-adaptive pacing; STOP-AF = Systematic Trial of Pacing for Atrial Fibrillation; SYNBIAPACE = Synchronous Biatrial Pacing.

Figure 24-13 Posteroanterior *(A)* and lateral *(B)* chest radiographs in a patient with a dual-site atrial pacing system for the prevention of paroxysmal atrial fibrillation. Leads are positioned in the right atrium, near the coronary sinus ostium, and in the right ventricular apex.

congenital anomaly, a prosthetic tricuspid valve, or an intracardiac right-to-left shunt.

Although multiple venous routes have been used for lead placement, the subclavian and cephalic veins are most commonly used. The subclavian approach involves a

subclavian puncture and the use of one or more peel-away introducers. A lateral approach to the subclavian vein, often lateral enough to be the axillary vein, is preferred to minimize the risk of pneumothorax and to avoid subclavian crush injury to the lead, which is more common when a medial approach is used. The cephalic vein is often large enough to accept one or two pacing leads, and this approach avoids the risks associated with blind subclavian puncture. Potential complications of subclavian puncture include pneumothorax, hemopneumothorax, subclavian artery puncture, brachial nerve plexus injury, and thoracic duct injury.

Specific measurements must be accomplished at the time of pacemaker or cardioverter-defibrillator implantation (Table 24-12) .

After placement of the pulse generator, posteroanterior and lateral chest radiographs must be obtained to exclude pneumothorax and also to ensure adequate lead positioning. Before hospital dismissal, the pulse generator should be programmed to determine pacing and sensing thresholds for final programming with adequate safety margins. If the pulse generator is being programmed to a rate-adaptive pacing mode, adequate rate response should be assessed by formal or informal stress testing.

TABLE 24-12 -- MEASUREMENTS DURING IMPLANTATION OF PACEMAKER OR CARDIOVERTER-DEFIBRILLATOR

Threshold of stimulation
Atrium*
Ventricle
Sensing threshold
Atrium
Ventricle
Measurement of electrogram
Atrium*
Ventricle
Measurement of antegrade conduction§
Wenckebach-block point
Defibrillation threshold

*Necessary only when an atrial lead is being placed.

Necessary only when an atrial lead or a single-pass VDD lead is used.

Considered optional by many, and these measurements may be accomplished noninvasively with many devices.
§Necessary only when an AAI/R implant is considered.

For ICD implantation only.

PACEMAKER PROGRAMMING

Almost all pacemakers are capable of programming rate, pulse width, voltage amplitude, sensitivity, refractory period, and polarity (Table 24-13) . Many clinicians fail to take advantage of optimizing pacemaker function with programmable options, with estimates that up to 50 percent of all pacemakers implanted are never changed from nominal parameters. A few features deserve additional discussion.

Programming Pulse Width and Voltage Amplitude

Output programming is probably the most important aspect of programming that should be performed routinely. The output must be high enough to allow an adequate pacing margin of safety but should also be programmed with the intent of maximizing pacemaker longevity. A strength-duration curve plots voltage and pulse width thresholds and

Figure 24-14 Programmer-generated strength-duration threshold curve. "X" notes the output parameter settings calculated by the programmer that would allow an adequate safety margin and maximize pacemaker longevity.

TABLE 24-13 -- PROGRAMMABLE OPTIONS FOR PACEMAKERS

PARAMETER	DESCRIPTION	TYPICAL VARIABLES
Mode	Preset or programmed response from a pacemaker with or without intrinsic cardiac events	VOO, AOO, VVI, AAI, VDD, DVI, DDD, DDI, DOO, VVT, AAT (all but AAT, VVT could also have "R," or rate-adaptive, capability)
Lower rate limit	Preset or programmed rate at which a pacemaker emits an output pulse without intrinsic cardiac activity	30 to 150 beats/min (options faster than 150 beats/min available in some pulse generators)

Ventricular refractory period	An interval of the pacemaker timing cycle following a sensed or paced ventricular event during which the ventricular sensing channel is totally or partially unresponsive to incoming signals	150 to 500 msec
Pulse width	Duration, in milliseconds, over which the output is delivered	0.05 to 1.9 msec
Pulse amplitude	Magnitude of the voltage level reached during a pacemaker output pulse, usually expressed in volts	0.5 to 8.1 V
Sensitivity	Ability to sense an intrinsic electrical signal, which depends on the amplitude, slew rate, and frequency of the signal	Atrial: 0.18 to 8 mV Ventricular: 1.0 to 14 mV
Polarity	Stimulating electrode typically is the cathode, which has negative polarity relative to the indifferent electrode (anode)	Device may be programmable to only bipolar or unipolar; others may have more control by programming unipolar-bipolar pace-sense on either lead
Hysteresis	Extension of the escape interval after a sensed intrinsic event	In single-chamber modes, commonly 40, 50, or 60 beats/min or off
Circadian lower rate limit	Reduces the lower rate limit during sleeping hours	Lower rates during sleep, programmable from 30 beats/min as the slowest rate usually offered
Mode switch	Capability of a dual-chamber pacemaker to automatically switch from an atrial tracking (P-synchronous) mode to a non-atrial-tracking mode when an atrial rhythm occurs that the pacemaker determines to be pathologic. When the atrial rhythm meets the criteria for a physiologic rhythm, the mode switches back to an atrial-tracking mode.	On or off; if on, the detection rates are often programmable for rates 120 to 190 beats/min

Fallback	An upper rate response in which the ventricular paced rate decelerates to, and is maintained at, a programmable fallback rate that is lower than the original programmed maximum tracking rate. Fallback mechanisms vary among pacemakers.	May be programmable on or off; if on, the rate to which the fallback occurs may be fixed or programmable (i.e., 50 to 80 beats/min)
Rate smoothing	Prevents atrial or ventricular paced rate from changing by more than a programmed percentage from one cardiac cycle to the next. This prevents large cycle-to-cycle intervals that can be seen at the upper rate limit or during rapid acceleration of atrial rate.	On or off; may then have options of % smoothing (i.e., 9% to 25% change per cycle length allowed); may also have option of being on or off for rate increments or decrements, or both
Atrioventricular interval (AVI)	Period between the initiation of the paced or sensed atrial event and the delivery of a consecutive ventricular output pulse.	30 to 350 msec
Differential AVI	Feature that permits a longer AVI after a paced atrial event than after a sensed AVI. In some pacemakers, this differential is fixed; in others, it is programmable.	Offset from 0 to 200 msec
Rate-adaptive AVI	Shortens the AVI as the heart rate increases	On or off only in some devices; in others, able to set the minimum atrioventricular delay to as short as 30 msec
Postventricular atrial refractory period (PVARP)	Period after a paced or sensed ventricular event during which the atrial channel is refractory	150 to 500 msec; in some devices, auto-PVARP adjusts with cycle length
PVARP extension	Lengthening of the PVARP after a sensed premature ventricular contraction to prevent sensing of a retrograde P wave	On or off in some; others may program length of extension to as long as ~500 msec
Pacemaker-mediated tachycardia (PMT) algorithms	Manufacturer-specific algorithms to terminate PMT	On or off; in others, can choose how long the maximum tracking rate must persist before detection criteria are met

Blanking period	Temporary disabling of pacemaker-sensing amplifiers after an output pulse	Ventricular blanking: 20 to 50 msec Postventricular atrial blanking: 100 to 350 msec
Ventricular safety pacing	Delivery of a ventricular output pulse after atrial pacing if a signal is sensed by the ventricular channel during the crosstalk sensing portion of the AVI	On or off
Maximum tracking rate	The sum of the AVI and the PVARP	80 to 180 beats/min

Figure 24-15 *A*, The paced atrioventricular interval (AVI) corresponds to the programmed value, that is, the interval allowed after a paced atrial beat before a ventricular pacing artifact is delivered. *B*, The initial portion of the AVI in most dual-chamber pacemakers is designated the blanking period, during which sensing is suspended. The blanking period is intended to prevent ventricular sensing of the atrial pacing artifact. Any event that occurs during the blanking period, even if it is an intrinsic ventricular event, as shown in this illustration, is not sensed and is followed by a ventricular pacing artifact delivered at the programmed AVI. *C*, If the ventricular sensing circuit senses activity during the crosstalk sensing window, a ventricular pacing artifact is delivered early, usually at 100 to 110 milliseconds after the atrial event, that is, "ventricular safety pacing." PVC = premature ventricular contraction. *(From Hayes DL, Levine PA: Pacemaker timing cycles. In Ellenbogen KA [ed]: Cardiac Pacing, Boston, Blackwell Scientific Publications, 1992, p 263.)*

allows determination of appropriate values to ensure an adequate safety margin. There is no consensus of the best way to program output parameters, but options[80] include doubling the voltage amplitude at threshold; tripling the pulse width at threshold; determining the threshold, obtaining a telemetered reading of threshold energy in microjoules, and programming output parameters to achieve a triple microjoule threshold; basing programmer-determined output parameters on autothreshold testing; and applying autocapture technology.

At least one manufacturer has pacemakers capable of calculating and graphically displaying a strength-duration curve as well as suggesting optimal output parameters (Fig. 24-14) . Automatic programming of output functions, "autocapture," has been actively investigated for over a decade, but only recently have manufacturers developed this as a reliable option. It is too early to determine how widely this feature will be embraced by clinicians.[80A]

Atrioventricular Interval

Several components of the AVI must be understood to optimally program the pacemaker (Fig. 24-15 *A*). The initial portion of the AVI is the blanking period, during which all sensing is suspended. This period is necessary to prevent sensing of the atrial output pulse on the ventricular sensing circuit, that is, crosstalk. This interval is commonly in the range of 12 to 50 msec, depending on the pacemaker, and is programmable in many pacemakers. If the blanking period is too long, a spontaneous R wave, occurring soon after the atrial stimulus, is not sensed and a competitive ventricular stimulus is emitted (see Fig. 24-15 *B*). The period after the blanking period is the crosstalk-sensing window. After the relatively short blanking period, if an event is sensed on the ventricular sensing circuit, the pacemaker is unable to distinguish with certainty the source of the sensed event. Given the possibility of sensing the decay of the atrial pacing output, sensing in the crosstalk-sensing window forces ventricular safety pacing or the "nonphysiological AV delay" (see Fig. 24-15 *C*). Because the "safety" stimulus occurs at a fixed delay after the beginning of the "safety pacing" interval, the total AVI is likely to be abbreviated. Because several early pacemakers had a ventricular safety pacing interval of 110 milliseconds, the designation "110-msec phenomenon" has also been used.

DIFFERENTIAL AVI.

Because the interatrial contraction after a sensed atrial event is shorter than that after a paced atrial event, an option exists for a differential AVI in an attempt to provide a PR interval of equal duration whether the atrial contraction is paced or sensed[81] (Fig. 24-16) . In some pacemakers, the differential is programmable, and in others, a preset differential is used when this feature is programmed "on."

RATE-VARIABLE OR RATE-ADAPTIVE AVI.

DDDR pacemakers can shorten the AVI during AV sequential sensor-driven pacing. Rate-adaptive or rate-variable AVI is intended to optimize cardiac output by mimicking the normal physiological decrease in the PR interval that occurs in the normal heart as the atrial rate increases during exercise.[82]

Mode Switching

Mode switching is the ability of the pacemaker to automatically change from one mode to another in response to an inappropriately rapid atrial rhythm[83] [83A] (Fig. 24-17) . Mode switching is particularly useful for patients with paroxysmal supraventricular rhythm disturbances.[83B] In the DDD or

Figure 24-16 Differential atrioventricular interval (AVI) is demonstrated by a paced atrial event initiating an AVI of approximately 150 milliseconds and a sensed atrial event initiating an AVI of approximately 125 milliseconds. The measured AVI is numerically noted between the A and V markers. The numbers following the V marker reflect the measured VA interval (top) and VV interval (bottom).

DDDR pacing modes, if a supraventricular rhythm disturbance occurs and the pacemaker senses the pathological atrial rhythm, rapid ventricular pacing can occur. Any pacing mode that eliminates tracking of the pathological rhythm, that is, DDI, DDIR, DVI, or DVIR, also eliminates the ability to track normal sinus rhythm, which is usually the predominant rhythm. Mode switching avoids this limitation by switching from DDD or DDDR during sinus rhythm to a nontracking mode, such as DDIR, during the pathological atrial rhythm.

Rate-Adaptive Parameters

The goal of programming rate-adaptive pacemakers is to optimize the patient's chronotropic response.[83C] It is inappropriate to implant a rate-modulating pacemaker and program the sensor "on" without assessing rate response. Pacemakers capable of rate modulation are packaged with the sensor "off"; and to effect rate modulation, the sensor must be programmed "on." Although the manufacturer usually states "nominal" values for rate response parameters, the nominal values are not appropriate for all patients. Some form of exercise is necessary to optimize rate-adaptive parameters. For patients who are limited to "activities of daily living," informal exercise testing, such as walking at casual and brisk paces in the hospital corridor or in the outpatient facility, is often adequate. In determining the appropriate heart rate response, the patient's age and "usual activities" must be taken into consideration.[84]

If formal exercise testing is performed, the chronotropic exercise assessment protocol[85] or a low-intensity exercise protocol may be preferable to a standard Bruce protocol. The chronotropic exercise assessment protocol allows for a gradual increase in speed and grade and thus mimics levels of exercise that are likely to occur during activities of daily living.

Alternatively, rate adaptation can be assessed and enhanced

Figure 24-17 Electrocardiographic tracing from a patient with a DDD pacemaker. In the initial portion of the tracing, the pacing is in sinus rhythm. This is followed by the onset of an atrial tachyarrhythmia with initial tracking, but mode switching causes reversion to a VVIR pacing mode. (The top tracing is the surface electrocardiogram, the middle tracing represents the atrial electrogram, and the lower tracing represents the ventricular electrogram.)

by diagnostic tools incorporated within the pacemaker. There are many variations, including histograms of rate response and ambulatory monitoring capabilities. If the

pacemaker is capable of automatically optimizing rate response parameters, the patient must still be assessed to see if the automatically programmed parameters result in the appropriate rate response.

PACEMAKER COMPLICATIONS

Complications can be divided into those related to implantation and those related to failure of a component of the pacing system.[86] There are also problems encountered during follow-up that are actually pseudoabnormalities, that is, a normal response that appears abnormal because of unusual timing or because of idiosyncrasies of the device. Many complications are directly related to the experience of the implanter. One study demonstrated a significantly higher incidence of complications when implanters performed fewer than 12 implantations per year.[87]

Implant-Related Complications

Most patients undergoing pacemaker implantation have some discomfort at the site of the incision in the early postoperative period. Mild analgesics may be required. Mild ecchymoses around the incision are not uncommon. As previously noted, if subclavian puncture is used for lead placement, several potential complications of this "blind" technique can occur, including the possibility of traumatic pneumothorax and hemopneumothorax, inadvertent arterial puncture, air embolism, arteriovenous fistula, thoracic duct injury, subcutaneous emphysema, and brachial plexus injury.[88]

Hematoma formation at the pulse generator site most commonly occurs when anticoagulant therapy is initiated or reinstituted prematurely. A hematoma must be dealt with on the basis of its secondary consequences. Evacuation of the hematoma should be considered only if there is continued bleeding, potential compromise of the suture line or skin integrity, or pain from the hematoma that cannot be managed with analgesics. Aspiration is generally not advised.

Introduction of the lead or leads into the subclavian artery, the aorta, and the left ventricle usually is readily recognized because of the pulsatile flow of saturated blood. A pacing lead may also be placed in the left ventricle by passing it across an unsuspected atrial or ventricular septal defect (Fig. 24-18) . Once the lead is within the subclavian artery, passage into the left ventricle is as easy as passage into the right ventricle via the venous system. Left ventricular lead placement should be recognized if lateral fluoroscopy is used or a lateral chest radiograph is obtained, because the lead is in the posterior aspect of the heart. The ECG during right ventricular pacing usually has an LBBB pattern and during left ventricular pacing most commonly an RBBB pattern.

Although thresholds may be adequate, lead placement in the arterial circulation is associated with thrombus formation, embolization, and, consequently, stroke. Reports of long-term uncomplicated left ventricular endocardial pacing exist, but the risk of embolization continues. Removal of the left ventricular lead should be undertaken if this position is recognized early after implantation. If it is recognized years after uncomplicated pacing, the best approach may be to administer anticoagulants and

leave the lead in place. Management must be individualized.

Patients undergoing device implantation should be made aware of the potential for lead perforation. Although cardiac tamponade is the most dramatic outcome from perforation, lack of symptoms after ventricular perforation by a lead is not uncommon. The only sign may be a rising stimulation threshold. In other patients, the signs may include RBBB pattern from a lead placed in the right ventricle, intercostal muscle, or diaphragmatic contraction; friction rub after implantation; and pericarditis, pericardial effusion, or cardiac tamponade. (Depending on lead position, an RBBB pattern is also possible when the lead is within the right ventricular cavity.)

Ventricular perforation may be suggested by radiography, electrocardiography, and echocardiography. Once perforation is identified, lead withdrawal and repositioning are usually uncomplicated, although pericardial bleeding or tamponade results rarely.

Partial or silent inconsequential venous thrombosis of the subclavian vein is not uncommon after transvenous lead placement and is usually clinically insignificant. Such partial or silent thrombosis may limit venous access at the time of pacing system revision.[89] Symptomatic thrombosis can be the result of occlusion of the superior vena cava, with superior vena cava syndrome; thrombosis of the superior vena cava, right atrium, or right ventricle, with hemodynamic compromise or pulmonary embolism; or symptomatic thrombosis of the subclavian vein, with an edematous, painful upper extremity.

Lead-Related Complications

Several lead-related complications deserve attention, including lead dislodgment (Fig. 24-19) , loose connector pin

Figure 24-18 Posteroanterior chest radiographs of a dual-chamber pacemaker. *A*, Ventricular lead is passing through an atrial septal defect into the left ventricle. *B*, Lead is repositioned in the right ventricular apex.

Figure 24-19 Posteroanterior chest radiographs of a dual-chamber pacemaker. *A*, Underpenetrated film makes it difficult to identify lead position. *B*, Lateral view demonstrates definite dislodgment of the atrial lead into the superior vena cava.

(Fig. 24-20) , conductor coil fracture, insulation break, and exit block.

Active and passive fixation mechanisms common to current pacing leads have

significantly reduced the incidence of lead dislodgment. Acceptable dislodgment rates should probably be less than 1 percent for ventricular leads and no more than 2 to 3 percent for atrial leads. Dislodgment has been classified as "macrodislodgment" and "micro-dislodgment." Macrodislodgment is radiographically evident (see Fig. 24-19), microdislodgment is not. Adequate lead position is assessed by posteroanterior and lateral chest radiographs and comparison with any previous chest radiographs.

Intermittent or complete failure of output can occur because of a loose connection at the interface of the lead and connector block (see Fig. 24-20), usually because the lead was inadequately secured at

Figure 24-20 *A*, Posteroanterior chest radiograph in a patient with a VVI pacemaker and a bifurcated bipolar ventricular lead. The patient presented with recurrent near-syncope and intermittent failure to output. (Arrowhead notes inadequate atrial lead positioning; that is, the J portion of the lead is too shallow.) *B*, Close-up of the pacemaker reveals that the lower connector pin is not securely in the connector block (arrow). (For comparison, the arrowhead notes an appropriately engaged connector pin.) *(From Hayes DL: Pacemaker radiography. In Furman S, Hayes DL, Holmes DR Jr [eds]: A Practice of Cardiac Pacing. 3rd ed. Mount Kisco, NY, Futura Publishing Company, 1993, p 361. By permission of Mayo Foundation.)*

Figure 24-21 Posteroanterior chest radiographs in a patient with a dual-chamber pacemaker. *A*, Fracture of one lead (upper arrow) has occurred where the lead passes below the clavicle. Positioning of the atrial lead is shallow and suboptimal (lower arrow). *B*, Enlarged view of fracture (arrow). *(From Hayes DL: Pacemaker complications. In Furman S, Hayes DL, Holmes DR Jr [eds]: A Practice of Cardiac Pacing. 3rd ed. Mount Kisco, NY, Futura Publishing Company, 1993, p 537. By permission of Mayo Foundation.)*

the time of pacemaker implantation. When a connection is loose, manipulating the pulse generator or pocket may reproduce the problem. The poor connection may be evident radiographically.

Lead fractures most often occur adjacent to the pacemaker or near the site of venous access, that is, at a stress point (Fig. 24-21) . Although uncommon, direct trauma may result in damage to the pacing lead. If a fracture of a bipolar lead occurs and the pacemaker is polarity programmable, it may be possible to restore pacing by reprogramming to the unipolar configuration. This is a short-term solution and should not be a substitute for replacing the lead.

Loss of integrity of the insulating material has occurred because of flaws in the design or manufacturing process of the lead, "wear and tear," and crush injury. Insulation defects and conductor fractures may both be caused by crush injury, specifically at the

costoclavicular space when placement is by the subclavian puncture technique.[90]

Thresholds, lead impedance, and electrograms are helpful in differentiating an insulation defect from a conductor fracture. This information may be obtained by measurements made during implantation or by telemetric capabilities of many pacemakers (Table 24-14) .

Failure to capture due to exit block is uncommon. Exit block appears to be an abnormality at the myocardial tissue-electrode interface, resulting in a progressive rise in thresholds with normal radiographic appearance. Steroid-eluting leads are often effective in preventing exit block.

Supraventricular and ventricular arrhythmias, often encountered during pacemaker implantation, are usually inconsequential.

"Tip extrasystoles" can be seen in the early postimplantation period. These are ventricular complexes morphologically similar to the paced beats because they originate at the same site as the paced beats, but they are not preceded by a pacemaker stimulus. Tip extrasystoles most often occur during the first 24 to 48 hours after implantation and usually resolve spontaneously. Pharmacological suppression of tip extrasystoles is rarely necessary.

"Runaway pacemaker" describes a sudden increase in pacing rate caused by circuit malfunction. This phenomenon is rare with current pacemakers. In recent years, the rare reports of runaway have usually described a complication of pacemaker exposure to therapeutic radiation, with subsequent damage to the circuit.[91]

Endless-loop tachycardia, already described, is another well-recognized pacemaker-related rhythm disturbance.

Extracardiac stimulation usually involves the diaphragm or pectoral muscle. Diaphragmatic stimulation may be due to direct stimulation of the diaphragm (usually stimulation of the left hemidiaphragm) or stimulation of the phrenic nerve (usually stimulation of the right hemidiaphragm). Diaphragmatic stimulation occurring during the early postimplantation period may be due to either microdislodgment or macrodislodgment of the pacing lead. Stimulation can be minimized or alleviated by decreasing the voltage output or pulse width (or both), but an adequate pacing margin of safety must be maintained after the output parameters are decreased.

Local muscle stimulation occurs much more commonly with unipolar than with bipolar pacemakers and is usually noted in the early postimplantation period. Pectoral muscle stimulation can also be due to an insulation defect of the pacing lead, current leakage from the connector or sealing plugs, or erosion of the pacemaker's protective coating. If the problem is due to an insulation defect on either a unipolar pacemaker or the pacemaker lead, decreasing the voltage output or the pulse width (or both) may minimize the stimulation, but the defective portion of the system may have to be replaced. If pectoral muscle stimulation occurs in a polarity-programmable pacemaker that is programmed unipolar, reprogramming to the bipolar configuration may alleviate

the problem.

Pacemaker System Infection

Erosion is an uncommon complication that most commonly occurs because of an indolent infection, although it may also be the result of a pacemaker pocket that is too "tight."

If the patient seeks medical attention before the pacemaker has eroded through the skin, it may be possible to revise the pocket and reimplant the pacemaker. Impending erosion should be dealt with as an emergency, because once any portion of the pacemaker has eroded through the skin, the only choice is removal of the pacemaker system and placement of a new system in another site.

Infection may be present even without purulent material; therefore, a specimen for culture should be obtained and proven negative before pocket revision. Adherence of the

TABLE 24-14 -- INTRAOPERATIVE EVALUATION OF PACING SYSTEM

DEFECT	VOLTAGE THRESHOLD	CURRENT THRESHOLD	LEAD IMPEDANCE
Wire fracture	High	High, normal, or low	High
Insulation break	Low	High	Low
Lead dislodgment	High	High	Normal
Exit block	High	High	Normal

Modified from Hayes DL, Osborn MJ: Pacing: A. Antibradycardia devices. In Giuliani ER, Gersh BJ, McGoon MD, et al (eds): Mayo Clinic Practice of Cardiology, 3rd ed. St. Louis, CV Mosby, 1996, p 961. By permission of Mayo Foundation.

pacemaker to the skin strongly suggests an infection, and salvage of the site may not be possible.

The incidence of infection after pacemaker implantation should certainly be less than 2 percent and in most series has been less than 1 percent.[92] Careful attention to surgical details and sterile procedures is of paramount importance in avoiding pacemaker site infection. Prophylactic use of antibiotics before implantation and in the immediate postoperative period remains controversial.[93] Most studies do not show any significant difference in the rate of infection between patients who have had prophylactic administration of antibiotics and those who have not. Irrigation of the pacemaker pocket with an antibiotic solution at the time of pacemaker implantation is probably more

important in the prevention of infection.

Pacemaker infection may appear as local inflammation or abscess formation in the pacemaker pocket, erosion of part of the pacing system with secondary infection, or sepsis with positive blood culture findings with or without a focus of infection elsewhere.

The most common clinical presentation is localized pocket infection; septicemia is uncommon. Many infectious agents can be responsible, but early infections are most commonly caused by *Staphylococcus aureus*, are aggressive, and are often associated with fever and systemic symptoms. Late infections commonly are caused by *Staphylococcus epidermidis* and are more indolent--usually without fever or systemic manifestation. Treatment for both organisms requires removal of the entire infected pacing system, pacemaker, and leads.

A detailed description of lead extraction techniques is beyond the scope of this text.[94] [94A] The various approaches include simple traction, locking stylet and telescoping sheaths with countertraction,[95] laser-assisted extraction,[96] and open surgical techniques.

Laser-assisted lead extraction has been the subject of a multicenter study, the Pacing Lead Extraction with Excimer Laser System (PLEXES) trial. Randomization of patients to laser-assisted extraction technique or to standard extraction techniques demonstrated efficacy of laser-assisted lead extraction.[96]

When to extract leads is at times controversial. A question that arises frequently is how many noninfected leads can be abandoned and left in place. Multiple leads can usually safely be left in place as long as no one of them has been part of an infected system.[97]

TROUBLESHOOTING ELECTROCARDIOGRAPHIC ABNORMALITIES

Electrocardiographic (ECG) abnormalities in the paced patient can be broadly grouped into failure to capture, failure to output, sensing abnormalities (undersensing or oversensing), and inappropriate rate change.[98] [99]

FAILURE TO CAPTURE.

Failure to capture indicates that a pacing artifact is present without subsequent cardiac depolarization (Fig. 24-22) . The possible causes of failure to capture are high thresholds with an inadequately programmed output, partial conductor coil fracture, insulation defect, lead dislodgment or perforation, impending total battery depletion, functional noncapture, poor or incompatible connection at the connector block, circuit failure, air in the pulse generator pocket (unipolar pacemaker), and elevated thresholds due to drugs or metabolic abnormality.

FAILURE TO PACE.

Failure to pace, or failure to output, that is, failure to deliver an appropriate pacing stimulus, is often due to oversensing and inhibition of output but could also be due to true failure to output from the pacemaker or circuit interruption that prevents the electrical signal from reaching the heart (Fig. 24-23) . The reasons for failure to output are circuit failure, complete or intermittent conductor coil fracture, intermittent or permanently loose set screw, incompatible lead or header, total battery depletion, internal insulation failure (bipolar lead), oversensing of any noncardiac activity, crosstalk, and lack of anodal connector contact (e.g., unipolar lead in bipolar generator, bipolar lead in pacemaker programmed in unipolar mode, air in the pocket of a unipolar device, and unipolar pacemaker not in the pocket).

The differential diagnoses of failure to capture and failure to pace obviously overlap somewhat. For example, ECG manifestations of a conductor coil fracture may include failure to capture due to significant leakage of current at the incomplete fracture site, with not enough current remaining to result in stimulation. Nonetheless, the pacemaker stimuli can appear. Alternatively, escaping current can be sensed by the pacemaker and inhibit pacemaker output. If the conductor coil is completely fractured, rendering the circuit incomplete, no pacemaker output will be detected on the ECG. Insulation defects can also be signaled by oversensing and failure to pace or by failure to capture, although the most common consequences of insulation failure are sensing abnormalities.

As the pacemaker battery reaches end stages of depletion, either failure to capture due to decreasing voltage output or failure to pace due to total battery depletion can occur. This degree of battery depletion should be avoided by appropriate pacemaker follow-up.

Apparent failure to capture is noted if a pacemaker stimulus occurs during the refractory period of a spontaneous beat. This is referred to as "functional noncapture."

FAILURE TO SENSE.

Sensing abnormalities can be divided into true abnormalities, including undersensing, a failure to recognize normal intrinsic cardiac activity (Fig. 24-24) , and oversensing (see Fig. 24-23), unexpected sensing of an intrinsic or extrinsic electrical signal, and functional sensing abnormalities. The possible causes of sensing abnormalities are lead dislodgment or poor lead positioning, lead insulation failure, circuit failure, magnet application, malfunction of reed switch, electromagnetic interference, and battery depletion. The morphology of the intrinsic event is different from that measured at implantation.

True undersensing is most commonly due to lead dislodgment or inadequate initial lead placement. Sensing abnormalities commonly can be seen secondary to insulation defects and to intermittent, "make or break" conductor fracture. A normally functioning pacing system at times fails to detect atrial or ventricular extrasystoles. The intrinsic events measured at the time of implantation generate an electrogram at the electrode tip. If an extrasystole is occurring elsewhere in the heart, the sensing vector is different from that of the normal intrinsic beat, and the resulting voltage generated may not be

great enough to be sensed by the pacemaker. This anomaly cannot be anticipated unless extrasystoles of the same morphology occur during implantation and can be measured. It is reasonable to attempt reprogramming the sensitivity to allow the extrasystoles to be sensed, but if this is unsuccessful, it is rarely, if ever, necessary to reposition the lead for this abnormality.

Functional undersensing is present when an intrinsic cardiac event is not sensed because it falls within a programmed refractory period.[100] For example, if an intrinsic atrial event occurs within the PVARP, the event is not, and should not be, sensed. However, without a thorough understanding of the timing cycle, it may appear as though there is true undersensing.

Fusion and pseudofusion beats occur as a result of superimposition of an ineffective pacemaker stimulus on a spontaneously occurring P wave or QRS complex (Fig. 24-25) . (Fusion is present when the

Figure 24-22 Electrocardiographic tracing from a patient with a VVIR pacemaker programmed to a lower rate of 60 beats/min (1000 milliseconds). The second ventricular pacing artifact fails to result in ventricular depolarization, failure to capture. This is followed by a pause longer than the programmed lower rate of 1000 milliseconds. This pause most likely is explained by oversensing of some event on the ventricular sensing circuit. Ventricular pacing then resumes at the programmed rate of 60 beats/min.

Figure 24-23 Electrocardiographic tracings. *A*, Patient with a VVIR pacemaker with a lower rate of 70 beats/min. After an initial paced ventricular beat, there is a pause of approximately 2.8 seconds with significant baseline artifact. After two additional paced beats, another pause of approximately 2.8 seconds occurs. This patient had a pacemaker programmed to a unipolar sensing configuration. Sensing of myopotentials led to symptomatic pauses, and reprogramming the pacemaker to a bipolar sensing configuration prevented subsequent myopotential oversensing. *B*, Patient with a DDD pacemaker. After the third atrial pacing artifact, there is evidence of atrial depolarization, but there is no ventricular pacing output. Failure to deliver the ventricular pacing artifact is due to crosstalk; that is, the atrial pacing output is sensed by the ventricular sensing circuit, with subsequent inhibition.

morphology of the cardiac event is a hybrid of the intrinsic morphology and the paced morphology. Pseudofusion is present when the pacemaker artifact occurs late enough that the intrinsic morphology is not deformed, but it may appear so because of distortion on the ECG by the superimposed pacing artifact.) Pseudofusion is usually the consequence of pacemaker discharge during the refractory period of intrinsic P or QRS before sufficient intracardiac voltage is generated to activate the sensing circuit. This is most likely to occur when the pacing rate and the intrinsic rate are similar. Pseudofusion beats also can be the result of a delayed activation due to intraventricular conduction abnormalities.

INAPPROPRIATE PACING MODE.

Every pacing mode has a defined lower rate, and dual-chamber pacemakers and rate-adaptive pacemakers also require a defined upper rate. It is necessary to be familiar with the timing cycle of a particular pacing mode and any idiosyncrasies of the specific pacemaker to be able to determine whether the paced rate is appropriate. The possible causes of a paced rate that appears to be different from that programmed are circuit failure, battery failure, magnet application, hysteresis (Fig. 24-26) , crosstalk, undocumented reprogramming of the pacemaker, oversensing, runaway pacemaker, and malfunction of the ECG recording equipment, such as alteration in the paper speed.

Drugs can affect sensing thresholds, pacing thresholds, and defibrillation thresholds and result in ECG abnormalities.[98] [101] Although many drugs have been reported to affect pacing thresholds, the Class 1C agents are the only drugs that commonly cause a problem. Encainide, flecainide, propafenone, and moricizine have the potential to increase pacing thresholds and sensing thresholds. If these drugs are administered to the patient with a pacemaker, especially a pacemaker-dependent patient, thresholds should be monitored for change.

Electrolyte and metabolic abnormalities can also affect pacing and sensing thresholds. Hyperkalemia is the most common electrolyte abnormality to cause clinically significant problems, but severe acidosis or alkalosis, hypercapnia, severe hyperglycemia, hypoxemia, and myxedema may also result in threshold alteration.[98]

ELECTROMAGNETIC INTERFERENCE

Electromagnetic interference (EMI) is defined as any signal, biological or nonbiological, that is within a frequency spectrum that can be detected by the sensing circuitry of the pacemaker or ICD. EMI can result in rate alteration, sensing abnormalities, asynchronous pacing, noise reversion (Fig. 24-27) , or reprogramming. [101A] EMI can also result in failure to deliver antibradycardia pacing, inappropriate delivery of antitachycardia therapy, resetting of programmed parameters, and damage to the pulse generator or myocardial interface.

Other cardiac and extracardiac signals that may be falsely interpreted as a P or QRS and result in oversensing include T waves (Fig. 24-28) , myopotential interference, afterpotential delay, and P waves.

Nonbiological sources of EMI are best divided into sources of EMI within the hospital and outside the hospital. Although multiple sources of EMI in the nonhospital environment can potentially result in single-beat inhibition, few, if any, of these are clinically significant and truly represent a threat to the paced patient.

Several potential sources of EMI require specific mention either because of their real potential for causing significant EMI or because of confusion or controversy that exists in or out of the medical community. Industrial-strength welding equipment, that is, more

than 500 A, certain degaussing equipment, and induction ovens are identified sources of EMI that can cause significant pacemaker or ICD interference.[101] Most welding equipment used for "hobby" welding should

Figure 24-24 Electrocardiographic tracing from a patient with a VVI pacemaker with a programmed rate of 70 beats/min. After two paced ventricular complexes, a premature ventricular complex occurs. In approximately 260 milliseconds, a ventricular pacing artifact occurs. This is followed by a P wave with intrinsic atrioventricular nodal conduction and native QRS complex. A pacemaker artifact follows in approximately 220 milliseconds. This represents ventricular undersensing. In this patient, the abnormality occurred because of an insulation failure of the ventricular pacing lead.

Figure 24-25 Electrocardiographic tracing from a patient with a VVI pacemaker. The first two complexes represent fully paced ventricular depolarizations. The third ventricular event is an intrinsic QRS complex, and the fourth event represents a fusion beat. This is followed by two paced ventricular complexes.

Figure 24-26 Electrocardiographic tracing from a patient with a VVI pacemaker programmed to a lower rate of 60 beats/min and a hysteresis rate of 40 beats/min. The longer cycle follows an intrinsic ventricular beat.

Figure 24-27 Electrocardiographic tracing from a patient with a DDD pacemaker during exposure to electromagnetic interference. This pacemaker responds with asynchronous pacing as the noise reversion mode.

not cause any significant problems. In the pacemaker-dependent patient who does hobby welding or any other activity that raises the clinician's concerns about EMI, attempts should be made to be certain that the environment is safe for the patient.

Currently, there is much interest in the potential EMI that may emanate from cellular telephones[102] [103] and antitheft devices.[104] [105] [106] Available information suggests that analog cellular phones are safe for the paced patient. Digital cellular phones have greater potential for EMI, and some caution remains for the pacemaker-dependent patient using a telephone with digital technology. If the patient avoids having the cellular phone over the pacemaker, either from random motion of the phone or by carrying the activated phone in a breast pocket over the pacemaker, any adverse clinical event is

unlikely.

Antitheft devices also have potential for pacemaker interference.[104] [105] [106] Practical suggestions are for patients with pacemakers or ICDs to be aware of electronic equipment for surveillance of articles and to avoid leaning on or lingering near such devices. If the patient passes through the equipment at a normal pace, adverse effects are unlikely. Any patient who feels unusual in any way when near electronic surveillance equipment should move away.

Hospital sources of potentially significant EMI are electrocautery, cardioversion, defibrillation, magnetic resonance imaging, lithotripsy, radiofrequency ablation, electroshock therapy, and diathermy. The most important aspect of pacemaker or ICD care after exposure to any of these sources of EMI is to reassess the device to be certain that programmed parameters have not been changed.

One of the most frequent questions asked is how to manage the patient with a pacemaker or ICD during an operative procedure, given the potential effects of electrocautery and guidelines for cardioversion and defibrillation. Routine interrogation of the device and deactivation of ICD therapy should be accomplished before the operation. After the procedure, the device should be reinterrogated and ICD therapy reinitiated. (During the time ICD therapy is "off," the patient must be monitored.) For pacemaker-dependent patients, it is reasonable to program the pacemaker to an asynchronous pacing mode, VOO or DOO, or to achieve the same effect by placing a magnet over the pacemaker throughout the procedure. The potential effects of electrocautery are reprogramming; permanent damage to the pulse generator; pacemaker inhibition; reversion to a fall-back mode, noise reversion mode, or electrical reset; and myocardial thermal damage. The guidelines for cardioversion and defibrillation in the patient with a pacemaker or ICD are as follows: Ideally, place paddles in the anterior-posterior position, try to keep the paddles at least 4 inches from the pulse generator, have the appropriate pacemaker programmer available, and interrogate the pacemaker after the procedure.

DEVICE FOLLOW-UP

Pacemakers and ICDs must be followed up on a regular schedule. There are different follow-up methods depending on clinician preference. Pacemaker and ICD follow-up schedules should be discussed separately because of the significant effect that transtelephonic monitoring has on pacemaker follow-up as opposed to essentially no use in ICD follow-up at this time. For pacemaker follow-up, some prefer regular office assessment, others predominantly transtelephonic follow-up, and still others a combination of the two techniques. Table 24-15 details the Medicare-approved follow-up schedule for reimbursement for transtelephonic monitoring.[106]

Figure 24-28 Electrocardiographic tracing from a patient with a VVI pacemaker programmed to a rate of 70 beats/min (857 milliseconds). The third and fourth VV cycles are longer than the programmed lower rate. Measuring 857 milliseconds backward from the ventricular pacing artifact at the end of the longer

cycles locates the point at which there was oversensing. In this case, probably the T wave is sensed. Definite retrograde P waves can be recognized by deformation of the T wave. Although it is possible that the retrograde P wave is being oversensed, the relationship of the P waves does not appear to consistently coincide with the point of oversensing.

TABLE 24-15 -- FOLLOW-UP SCHEDULE FOR TRANSTELEPHONIC MONITORING OF PACEMAKERS*

Single-chamber pacemakers	
1st month	Every 2 weeks
2nd through 36th month	Every 8 weeks
37th month to battery depletion	Every 4 weeks
Dual-chamber pacemakers	
1st month	Every 2 weeks
2nd through 6th month	Every 4 weeks
7th through 72nd month	Every 8 weeks
73rd month to battery depletion	Every 4 weeks

*This guideline is in effect for most pacemakers currently in use. A separate set of guidelines is available for specific pacing systems with sufficient long-term clinical information to meet certain standards for longevity and battery depletion characteristics.

Transtelephonic assessment should include collection of a nonmagnet ECG strip, an ECG strip with magnet applied to the pacemaker, and measurement of magnet rate and pulse duration (pulse duration on both atrial and ventricular channels should be measured for a dual-chamber pacemaker). During an office visit, the same information should be collected. In addition, on some periodic basis, for example, once a year, patients programmed to a rate-adaptive pacing mode should be assessed to determine whether rate-response is appropriate.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY

Indications

The ACC/AHA Joint Committee has established indications for implantation of an ICD and for pacing.[2] The indications for ICD therapy continue to evolve on the basis of results of clinical trials.

Clinical trials have been designed to determine the effect of ICD therapy in secondary prevention of sudden cardiac death (Table 24-16) , that is, in patients who have already experienced a life-threatening ventricular rhythm disturbance, or in primary prevention (Table 24-17) , that is, in patients who are at high risk for sudden cardiac death.[119] The Antiarrhythmics Versus Implantable Defibrillators (AVID)[107] trial (secondary prevention), Multicenter Automatic Defibrillator Implantation Trial (MADIT)[111] [112] (primary prevention), Cardiac Arrest Study-Hamburg (CASH)[108] (secondary prevention), and Multicenter Unsustained Tachycardia Trial (MUSTT)[114] (primary prevention) have all demonstrated significant improvement in overall survival with ICD therapy compared with conventional or drug treatment. No significant difference in overall survival was seen with ICD therapy in the Canadian Implantable Defibrillator Study (CIDS) trial (secondary prevention, probably underpowered) or the Coronary Artery Bypass Graft-Implantable Cardioverter-Defibrillator (CABG-PATCH)[113] study

TABLE 24-16 -- CLINICAL TRIALS OF PACING FOR THE SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
AVID[107]	Survivor of cardiac arrest	Total mortality	Amiodarone or sotalol	Significant improvement in overall survival with ICD
	VT with syncope	Mode of death		
	Symptomatic sustained VT with LVEF 0.40	Quality of life		
		Cost benefit		
CASH[108]	Survivor of cardiac arrest	Total mortality	ICD	Significant improvement in overall survival with ICD
		Recurrences of arrhythmias requiring CPR	Amiodarone, propafenone, or metoprolol	
		Recurrence of unstable VT		

CIDS	Survivor of cardiac arrest	Total mortality	Amiodarone	No significant improvement in survival with ICD
	Syncope with symptomatic sustained VT with LVEF 0.35 or syncope with inducible VT			
MAVERIC[109]	Resuscitated VT/VF, SCD	All-cause mortality	Empirical amiodarone	In progress
	Sustained nonsyncopal VT	Event-free survival	EP-guided therapy (drug or nondrug)	
	Dilated nonischemic cardiomyopathy with EF 0.35, syncope, and NSVT or positive SAECG	Costs		Immediate ICD implantation
		Quality of life		
		Cost-effectiveness		
ASTRID[110]	Patients with Ventak AV1810 implanted for current indication	Time to first occurrence of inappropriate therapy	Standard-features programming	Completed; results not published
	DFT <600 V and minimum 1 mV atrial, 5 mV ventricular EGM amplitudes at implantation	Health care utilization	Enhanced-features programming	
		Quality of life		
VT-MASS	ICD indication	Combined endpoint of symptomatic arrhythmia, appropriate ICD therapy, or death	ICD and metoprolol	In progress
	EF >20%		ICD and sotalol	

			ICD without AAD or BB	

AAD = antiarrhythmia drugs; ASTRID = Atrial Sensing to Reduce Inappropriate Defibrillation; AVID = Antiarrhythmics Versus Implantable Defibrillators; BB = beta blockers; CASH = Cardiac Arrest Study-Hamburg; CIDS = Canadian Implantable Defibrillator Study; CPR = cardiopulmonary resuscitation; DFT = defibrillation threshold; EF = ejection fraction; EGM = electrogram; EP = electrophysiologic; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MAVERIC = Midlands Trial of Empirical Amiodarone Versus Electrophysiologically Guided Intervention and Cardioverter Implant in Ventricular Arrhythmias; NSVT = nonsustained ventricular tachycardia; SAECG = signal-averaged electrocardiography; SCD = sudden cardiac death; VT = ventricular tachycardia; VT-MASS = Metoprolol and Sotalol for Sustained Ventricular Tachycardia.

TABLE 24-17 -- CLINICAL TRIALS OF PACING FOR THE PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
MADIT[111] [112]	Q wave MI 3 weeks	Overall mortality	ICD (n = 95)	ICDs reduced overall mortality by 54%
	Asymptomatic NSVT	Costs and cost-effectiveness	Conventional therapy (n = 101)	ICDs cost $16,900 per life-year saved
	LVEF 0.35			*vs.*
	Inducible and nonsuppressible VT on EPS with procainamide			Conventional therapy
	NYHA Class I-III			

CABG-PATCH[113]	Scheduled for elective CABG surgery	Overall mortality	ICD (n = 446)Standard treatment (n = 454)	Survival not improved by prophylactic implantation of ICD at time of elective CABG
	LVEF <0.36			
	Abnormal SAECG			
MUSTT[114]	CAD	Sudden arrhythmic death or spontaneous sustained VT	ICD in nonsuppressible group	In progress
	EF 0.40		Antiarrhythmic drug therapy in suppressible group	
	NSVT		No therapy	
	Inducible VT or VF			
CardioMyopathy study[115]	Nonischemic DCM	Total mortality	ICD	In progress
	LVEF 0.30	Sudden death	Standard treatment	
	NYHA Class II or III	Serious arrhythmia		
Defibrillat	Patient with CHF awaiting heart transplant	Total mortality	ICD	In progress
		Serious arrhythmias	Standard treatment	
BEST[116]	Acute MI	All-cause mortality	Conventional + beta-blocker therapy	In progress
	EF 0.40	Cost-effectiveness	EPS: if inducible, ICD and beta blocker; if noninducible, beta blocker	

	SDRR <70 msec or 109 VPCs/hr or abnormal SAECG			
DINAMIT	Acute MI (6-21 days)	All-cause mortality	Conventional therapy	In progress
	LVEF 0.35	Quality of life	ICD	
	HR 80 beats/min or SDRR <70 msec	Cost-effectiveness		
MADIT-II[117]	Prior MI	All-cause mortality	Conventional therapy	In progress
	EF 0.30	Cost-effectiveness	ICD	
SCD-HeFT*[118]	Ischemic or nonischemic cardiomyopathy	All-cause mortality	Placebo and standard therapy	
	EF 0.35	Quality of life	*vs.*	
	NYHA Class II or III	Cost-effectiveness	Amiodarone and standard therapy	
	Appropriate ACE inhibitor	Morbidity	*vs.*	
	No history of sustained VT/VF	Incidence of arrhythmias	ICD and standard therapy	
DEFINITE*	Symptomatic nonischemic cardiomyopathy	All-cause mortality	ICD, standard drug therapy	In progress
	NSVT	Quality of life		
	Low EF (35%)	Cost-effectiveness	*vs.*	
			Standard drug therapy and beta blocker only	

DEBUT (SUDS)	Survivor of sudden cardiac arrest from resuscitated VT/VF	All-cause mortality	ICD	In progress
	Probable sudden cardiac arrest with RBBB and ST segment elevation	Rhythms from stored EGMs that triggered ICD shocks	*vs.*	
			Beta blocker	
VENTAK-CHF/CONTAK CD[65]	Indication for ICD	Functional capacity	Biventricular pacing or no pacing and then crossover	In progress
	Symptomatic CHF on stable drugs, including ACE	Quality of life		
	EF 0.35	NYHA Class		
	QRS >120 msec			
PRIDE	VT, VF, or cardiomyopathy with syncope, NSVT	All-cause mortality	ICD	In progress
		Cost-effectiveness	*vs.*	
			EPS and randomization to ICD	
			vs.	
			amiodarone or sotalol	
			Negative EPS: therapy at MD discretion	

ACE = angiotensin-converting enzyme; BEST-ICD = Beta-Blocker Strategy Plus Implantable Cardioverter-Defibrillator; CABG = coronary artery bypass graft; CABG-PATCH = Coronary Artery Bypass Graft Patch Trial; CAD = coronary artery disease; CHF = congestive heart failure; DCM = dilated cardiomyopathy; DEBUT (SUDS) = Defibrillator Versus Beta-Blockers for Unexplained Death in Thailand (Sudden Unexplained Death Syndrome); Defibrillat = Defibrillator Implantation as a Bridge to Transplantation; DEFINITE = Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; EF = ejection fraction; EGM = electrogram; EPS = electrophysiologic study; HR = heart rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter Unsustained Tachycardia Trial; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PRIDE = Primary Implantation of Cardioverter-Defibrillator in High-Risk Ventricular Arrhythmias; RBBB = right bundle branch block; SAECG = signal-averaged electrocardiography; SCD-HeFT = Sudden Cardiac Death-Heart Failure Trial; SDRR = standard deviation of RR interval; Ventak-CHF/Contak CD = Ventak-Congestive Heart Failure/Contak Cardioverter-Defibrillator; VF = ventricular fibrillation; VPC = ventricular premature contraction; VT = ventricular tachycardia.

*Primary prevention in patients with heart failure.

(primary prevention). CABG-PATCH should probably be considered separately, because this study randomized patients who were to undergo coronary artery bypass grafting to either ICD implantation at the time of bypass surgery or postoperative antiarrhythmic treatment. The study was terminated prematurely when the interim analysis failed to show a survival difference between the two study groups. The deaths in both groups were perioperative and therefore could not have been prevented by antiarrhythmic therapy. Analysis of subgroups showed the benefits of the ICD in patients at risk of life-threatening ventricular tachyarrhythmia.[120] The role of ICD therapy for patients with asymptomatic sustained monomorphic ventricular tachycardia and structural heart disease but with an ejection fraction greater than 40 percent is less clear.[121] [122]

The underlying disease state may affect the decision to implant an ICD. In patients with coronary artery disease, active ischemia is the cause of significant ventricular tachyarrhythmias and should be assessed and treated before implantation. Patients with coronary artery disease and reduced left ventricular dysfunction appear to experience greater benefit with ICD therapy than with drug therapy.[112] [123] In the AVID trial, patients with an ejection fraction greater than 35 percent who received an ICD did not have a significant mortality benefit over those who received amiodarone. Clinical trials are under way to more specifically assess the benefit of primary prevention of sudden cardiac death after myocardial infarction (Table 24-18) .

In patients with idiopathic dilated cardiomyopathy (see Chap. 48), the combination of poor left ventricular function and nonsustained ventricular tachycardia is associated with an increased risk of sudden death[107] (see Chap. 26). Trials of primary prevention in

patients with dilated cardiomyopathy are under way.

ICD therapy is recommended in patients with congenital long-QT syndrome who experience recurrent syncope, sustained ventricular arrhythmias, or sudden cardiac arrest despite drug therapy[124] (see Chaps. 23 and 25).

Patients with HCM who have experienced sudden cardiac arrest should receive an ICD[125] [125A] (see Chap. 48). Medications may still be necessary to control other symptoms secondary to HCM as well as for antiarrhythmic therapy, but ICD therapy affords better protection for the prevention of recurrent syncope. The asymptomatic patient with HCM and a family history of sudden death, syncope, or nonsustained ventricular tachycardia should also be considered for ICD implantation[126] (see Chap. 48).

The patient with idiopathic ventricular fibrillation should receive an ICD.[127] However, patients with idiopathic ventricular tachycardia and no structural heart disease should probably be considered for catheter ablation before consideration of ICD therapy.[128] Although several treatment

TABLE 24-18 -- CLINICAL TRIALS OF PACING FOR PRIMARY PREVENTION AFTER MYOCARDIAL INFARCTION

STUDY	PATIENT INCLUSION CRITERIA	ENDPOINT(S)	TREATMENT ARMS	KEY RESULTS
SEDET	Acute MI (1 to 3 weeks)	All-cause mortality	ICD	In progress
	Ineligible for thrombolysis	Quality of life	*vs.*	
	EF 0.15 to 0.40	Incidence of VT	Conventional therapy	
	Nonsustained VT or 10 PVCs/hr between 6 and 21 days after MI	Sudden and nonsudden death		
		Cardiac death		
		Predictive value of BRS and HRV		
IRIS	Acute MI	All-cause mortality	ICD	In progress
	Fast NSVT >150 beats/min	Resource utilization	*vs.*	

	HR >100 beats/min at admission	Quality of life	Conventional therapy	

BRS = baroreceptor sensitivity; EF = ejection fraction; HR = heart rate; HRV = heart rate variability; ICD = implantable cardioverter-defibrillator; IRIS = Immediate Risk Stratification Improves Survival; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; SEDET = South European Defibrillator Trial; VT = ventricular tachycardia.

strategies may be necessary for the patient with arrhythmogenic right ventricular dysplasia, ICD therapy should be considered for prophylaxis against syncope due to hemodynamically unstable ventricular tachycardia and sudden cardiac death (see Chap. 25).

Basics of Design and Selection

The basic components of the ICD are electronic circuitry, power source, and memory, with a microprocessor coordinating the various parts of the system.[119] [129] High-voltage capacitors transform the battery-provided voltage into discharges ranging from less than 1 V for pacing to 750 V for defibrillation. ICDs incorporate a different sensing circuit

TABLE 24-19 -- IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY

ZONE	TACHYCARDIA RATE (beats/min)	THERAPY DELIVERED
1	126-160	ATP-1, ATP-2, 1 J, 5 J, 34 J
2	161-200	ATP, 10 J, 34 J
3	>200	34 J

ATP = antitachycardia pacing therapy; ATP-1 = first ATP; ATP-2 = second (and different) ATP.

Figure 24-29 Posteroanterior *(A)* and lateral *(B)* chest radiographs of an implantable cardioverter-defibrillator (ICD) system in the left prepectoral position. The ICD is connected to a single-coil ventricular lead and a lead positioned in the superior vena cava (SVC). In this patient, adequate defibrillation thresholds (DFTs) could not be obtained with the single-coil ventricular lead. With the additional lead positioned high in the SVC, excellent DFTs were achieved.

than most pacemakers. Because of the need to reliably sense low-amplitude signals during ventricular fibrillation and to avoid sensing extracardiac noise and cardiac signals other than ventricular tachycardia or fibrillation, the sensing circuit is designed to automatically adjust either the gain or the sensing threshold.[119] [130]

ICD systems have evolved rapidly from thoracotomy to nonthoracotomy, that is, transvenous pectorally placed systems, and from ventricular bradycardia pacing to dual-chamber pacing with rate-adaptive options.[130A] In addition, atrial defibrillation capabilities are available in some devices. Longevity of ICDs depends on the frequency of shock

Figure 24-30 Posteroanterior *(A)* and lateral *(B)* chest radiographs from a patient with an implantable cardioverter-defibrillator. Unacceptable defibrillation thresholds necessitated placement of a subcutaneous array.

delivery, the degree of pacemaker dependency, and other programmable options, but most are expected to last from 5 to 9 years.

It is important to have an understanding of "shock waveforms." Biphasic waveforms are more efficient, that is, require lower energies, than monophasic shocks. All currently available ICDs use biphasic shock waveforms, but the specifics of the waveform differ among various manufacturers.

The ICD functions by continuously monitoring the patient's cardiac rate and delivering therapy when the rate exceeds the programmed rate "cutoff." For example, if the ICD is programmed to deliver shocks for the treatment of tachyarrhythmias at a rate cutoff of 175 beats/min, once the patient's heart rate exceeds 175 beats/min and this event is detected by the ICD, the device delivers antitachycardia pacing (ATP) or charges and delivers a shock, depending on the programmed therapy.

ATP has the advantage of terminating a rhythm disturbance without delivery of a shock. ICDs capable of ATP have significant programming flexibility to adjust many aspects of tachycardia detection and therapy and thereby customize therapy for the individual patient. Different "zones" or "tiers" of therapy can be programmed to detect ventricular tachyarrhythmias to allow slower arrhythmias to be treated with ATP before a shock is delivered but to still allow faster tachycardias to be treated more aggressively. Table 24-19 outlines programming for a hypothetical patient. In this patient, slower ventricular tachycardia in the range of 126 to 190 beats/min is treated with ATP therapies in zone 1. If initial ATP therapy (ATP-1) is unsuccessful, a second and different ATP therapy (ATP-2) is automatically delivered. If this is unsuccessful, lower energy shocks are attempted before high-energy (34 J) shocks are delivered. Shocks are synchronized during ventricular tachycardia (cardioversion) or are asynchronous

Figure 24-31 *A* and *B,* Printouts from an implantable cardioverterdefibrillator (ICD) programmer of a

specific episode detected by the ICD. The text includes 29 VV interval lengths before therapy for ventricular fibrillation and 20 VV cycle lengths after therapy, documenting return to a nonpathologic ventricular rhythm. FD = fibrillation detected; FS = fibrillation sensed; TS = tachycardia sensed; VS = ventricular sensed event.

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during ventricular fibrillation (defibrillation). A second zone of therapy is determined for a faster ventricular tachycardia, and still faster ventricular tachycardia or ventricular fibrillation is treated aggressively with a high-energy shock. In addition, current ICDs provide bradycardia support, as single- or dual-chamber devices.

The zones, detection rates of the different zones, specifics of the different therapies, and bradycardia pacing options are all programmable, and programming flexibility varies significantly from device to device.

Implant Procedure

When the ICD is placed transvenously with the pulse generator in the prepectoral position, the implantation technique and related complications are the same as those for pacemaker implantation, with the exception that complications can arise as a result of determining the defibrillation threshold (DFT). (DFT can be defined as the minimal energy that terminates ventricular fibrillation.[119]) Risks associated with both procedures include lead dislodgment, pneumothorax and other potential complications of subclavian puncture if this venous approach is used, infection, and perforation.

Most ICD implantations are now performed with conscious sedation and local anesthesia. During DFT testing, the patient is placed under deep anesthesia with mask-supported ventilation. When DFT determination is completed, the patient can be allowed to recover from deeper anesthesia as the pocket is closed.

An acceptable DFT is a value that ensures an adequate safety margin for defibrillation, usually at least 10 J less than the maximum output of the ICD. The maximum output of current ICDs is in the range of 26 to 38 J. It is difficult to state an "ideal" DFT because it is ideally the lowest achievable DFT with an adequate safety margin.

It is generally best to implant the ICD in the left pectoral region because of a more favorable vector for delivery of the shock. Although successful defibrillation can usually be accomplished with a right-sided implant, the shocking vector is less optimal and may have an effect on achievable DFT.[131] Regardless of whether the ICD is placed on the right or the left, in a small percentage of patients adequate DFT cannot be achieved with standard lead placement. In this situation, options include

1. Repositioning the ventricular lead. If the lead was not initially placed in a right ventricular apical position, such a position should be sought. If the right ventricular apical position resulted in unacceptable DFT, repositioning the lead slightly

superior to the apex or in a septal position may be successful.
2. Adding a second lead in the superior vena cava (Fig. 24-29) .
3. Adding a subcutaneous array (Fig. 24-30) .

Follow-Up

Follow-up of the patient with an ICD must include periodic visits at which specific information is collected and assessed. In addition, patients may require interim assessment if there are concerns about the appropriateness of delivered therapy or other changes in the patient's medical status or drug regimen that could affect ICD therapy.

The electrophysiologist or an allied professional with ICD expertise and immediate access to the electrophysiologist should perform follow-up procedures. Aspects of follow-up are history with specific emphasis on awareness of delivered therapy and any tachyarrhythmic events, device interrogation, assessment of battery status and charge time, retrieval and assessment of stored diagnostic data, periodic radiographic assessment, and periodic arrhythmic induction in the electrophysiology laboratory to assess defibrillation thresholds and efficacy.

Diagnostic information that can be retrieved varies with different ICDs. All ICDs provide information about the cycle length, or rate, of the detected tachyarrhythmias (Fig. 24-31) , and most current devices provide stored electrograms of detected arrhythmias (Fig. 24-32) .

Follow-up protocols for patients with ICDs vary. Some manufacturers have recommended follow-up every 3 months, but some institutions are comfortable with follow-up every 6 months for the first 3 to 4 years, after which the follow-up frequency increases.

Complications

Exposure of the patient with an ICD to sources of EMI can result in the concerns expressed for pacemaker recipients.[119] EMI can interfere with bradycardia support and with detection of or response to tachyarrhythmias. Possible adverse effects of EMI are inappropriate delivery of anti-tachycardia therapy, reprogramming of the ICD parameters, and failure to deliver antibradycardia pacing. After any known or potential EMI exposure, the ICD, like a permanent pacemaker, should be reinterrogated, and programmed parameters should be compared with records obtained before the EMI exposure to be certain that EMI has not inappropriately reprogrammed the device.

Figure 24-32 Stored electrogram from a patient with an episode of ventricular fibrillation and a dual-chamber pacemaker and implantable cardioverter-defibrillator. The upper tracing is the atrial electrogram, the middle tracing is the ventricular electrogram, and the bottom tracing is the surface

electrocardiogram.

TABLE 24-20 -- DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF MULTIPLE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD) SHOCKS

CLINICAL FINDING	MANAGEMENT
Frequent ventricular tachycardia or ventricular fibrillation (electrical storm)	Reassess antiarrhythmic therapy and programmed ICD therapy
Unsuccessful ICD therapy due to inappropriately low output shock or elevation of defibrillation threshold	Reprogram ICD
	Assess potential causes of defibrillation threshold increase (e.g., drugs)
Lead fracture	Replace fractured lead
Lead dislodgement	Reposition lead
Sensing supraventricular rhythms	Reassess antiarrhythmic therapy
	Reprogram ICD parameters
	Ablate supraventricular arrhythmic focus
Oversensing separate pacing system	Reprogram pacemaker or ICD (or both)
	Reposition pacemaker or ICD leads (or both)
	Remove pacemaker and replace ICD with another ICD with more sophisticated bradycardia support
Oversensing electromagnetic interference	Avoid source
	Reprogram ICD
Oversensing intracardiac signals	Reprogram ICD
	Reposition sensing lead

Modified from Pinsky SL, Fahy GJ: Implantable cardioverter-defibrillators. Am J Med 106:446, 1999. By permission of Excerpta Medica.

Specific EMI sources and their potential effect on ICDs should be mentioned. In the hospital, magnetic resonance imaging is still considered contraindicated in the patient with an ICD, although there are scattered case reports of it being successfully done. Lithotripsy is contraindicated if the ICD is in the lithotripsy field.[132] Concerns have also been raised about transcutaneous nerve stimulation when an ICD is present.[133] Outside

the hospital, welding has generally been considered a contraindication. However, some data suggest that some patients can be allowed to carry out this activity if they are evaluated in their work environment.

It appears that cellular phones can be used safely by the patient with an ICD so long as the same guidelines noted for pacemaker patients are followed.[134] When using a cellular phone, the patient should avoid having the phone in close contact with the ICD and should not carry an activated phone in a pocket that is near the device. Theft detector devices are not a problem unless there is prolonged exposure.[135]

Changes in drug therapy must be monitored closely in the patient with an ICD.[136] Certain drugs have the potential for interaction by altering the detection of ventricular tachycardia, altering the pacing threshold (as previously discussed), increasing defibrillation thresholds, and producing proarrhythmic effects.

Drug alteration of the rate of ventricular tachycardia may result in inadequate detection of the arrhythmia. Elevation of the DFT may occur as the result of amiodarone administration.[137] Other drugs can theoretically increase the DFT or have been reported to do so in single-case reports, but a clinically significant change does not often result.[136]

Frequent ICD discharges may represent a clinical emergency. These discharges may be appropriate or inappropriate (Table 24-20) . Appropriate discharges represent frequently occurring ventricular tachycardia or fibrillation or electrical storm. If the device is discharging frequently because the defibrillation is unsuccessful, the device may be programmed to an inappropriately low shock output or an alteration in the DFT may have occurred that resulted in inadequate programmed therapy.

Inappropriate discharges are usually the result of inappropriate detection of a supraventricular tachyarrhythmia, most commonly atrial fibrillation (see Table 24-20). Inappropriate discharge can also be the result of device failure, for example, lead fracture.

Before the incorporation of sophisticated bradycardia support within the ICD, many patients had separate pacing and ICD systems. Numerous types of interactions between pacemakers and ICDs have been described.[138] Pacemaker output preventing proper detection of ventricular tachycardia or ventricular fibrillation by the ICD is one of the more serious. Asynchronous pacemaker activity during ventricular arrhythmias may be caused by either undersensing of the arrhythmia or noise reversion. Conditions favoring noise reversion are specific pacemaker models, arrhythmia cycle lengths in the range causing noise reversion of the individual pacemaker model, long noise sampling periods, and the VVI pacing mode. Noise reversion can be diagnosed by telemetering the pacemaker marker channel during ventricular arrhythmias as a part of routine evaluation of pacemaker-ICD interaction.

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GUIDELINES USE OF CARDIAC PACEMAKERS AND ANTIARRHYTHMIA DEVICES

Thomas H. Lee

An American College of Cardiology/American Heart Association (ACC/AHA) task force updated guidelines for the implantation of cardiac pacemakers and antiarrhythmia devices in 1998.[1] These guidelines evaluate potential indications for the implantation of pacemakers and antiarrhythmic devices. The guidelines use the same system as other guidelines from these organizations; i.e., they divide them into classes according to their appropriateness. Class I signifies general agreement that the device or therapy is indicated. Class II indicates a divergence of opinion with respect to their usefulness, with Class IIa favoring and Class IIb not favoring usefulness. The level of evidence to support each position is rated on a scale from A to C (see Guidelines to Chap. 5), in which "A" indicates that data were derived from multiple randomized trials involving a large number of individuals, "B" indicates that data were derived from a limited number of trials involving a relatively small number of patients or from well-designed observational studies, and "C" indicates that expert consensus was the primary source of the recommendation.

Indications for Permanent Pacing (Table 24-G-1)

ACQUIRED ATRIOVENTRICULAR BLOCK.

For patients with acquired atrioventricular (AV) block, bifascicular or trifascicular block, or sinus node dysfunction, permanent pacing was considered appropriate when the abnormality caused complications and was not precipitated by a drug that could be discontinued. Examples of complications include symptomatic bradycardia, congestive

heart failure, and confusional states. Permanent pacing was also deemed appropriate for asymptomatic patients with a high risk for the subsequent development of complications, such as patients with complete heart block and periods of asystole of 3 seconds or more or a slow escape rate or patients with bifascicular or trifascicular block with intermittent third-degree AV block.

For patients with first-degree AV block who have symptoms suggestive of pacemaker syndrome, these guidelines include a new indication for permanent pacing that is considered equivocal but supported by some data (Class IIa). Patients with pacemaker syndrome need a dual-chamber pacemaker to restore normal AV synchrony. A Class IIb indication for permanent pacing was described for patients with a prolonged PR interval and drug-refractory dilated cardiomyopathy if acute hemodynamic studies demonstrate the benefit of pacing.

Indications for permanent pacing for patients who do not have symptoms or complications are less certain. In asymptomatic patients, complete heart block with a ventricular escape rate of 40 or more beats/min or type II second-degree AV block was considered an equivocal (Class IIa) indication for permanent pacing. Bifascicular or trifascicular block in patients with syncope was also not a clear indication for permanent pacing but was regarded as acceptable if other possible causes of syncope cannot be identified. Pacemakers were explicitly discouraged for patients with mild asymptomatic conduction abnormalities, such as type I second-degree AV block at the supra-His level, fascicular block with no or only a first-degree AV block, and sinus node dysfunction.

Symptoms do not play as important a role in determination of the appropriateness of permanent pacing in patients with acute myocardial infarction because of the poor prognosis and high incidence of sudden death in postinfarction patients with conduction system disturbances. The ACC/AHA task force emphasized that the requirement for temporary pacing after acute myocardial infarction is not in itself an indication for permanent pacing (see Guidelines to Chap. 35 for guidelines on temporary pacing in acute myocardial infarction). However, permanent pacemakers were considered appropriate for patients with persistent advanced-degree AV block or transient infranodal AV block and associated bundle branch block. The usefulness of electrophysiology study to determine the site of block was acknowledged. The usefulness of permanent pacemakers for patients with advanced

TABLE 24--G-1 -- ACC/AHA GUIDELINES FOR PERMANENT PACING*

Issue	Class	Recommendation	Level of Evidence

Permanent pacing in acquired AV block	I	Third-degree AV block at any anatomical level associated with any one of the following conditions:	
		Bradycardia with symptoms presumed to be due to AV block	C
		Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia	C
		Documented periods of asystole of 3.0 sec or any escape rate of < 40 beats/min in awake, symptom-free patients	B, C
		After catheter ablation of the AV junction	B, C
		Postoperative AV block that is not expected to resolve	C
		Neuromuscular diseases with AV block such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb's dystrophy (limb-girdle), and peroneal muscular atrophy	B
		Second-degree AV block, regardless of the type or site of block, with associated symptomatic bradycardia	B
	IIa	Asymptomatic third-degree AV block at any anatomical site with average awake ventricular rates of 40 beats/min or faster	B, C
		Asymptomatic type II second-degree AV block	B
		Asymptomatic type I second-degree AV block at the intra- or infra-His levels found incidentally at electrophysiological study performed for other indications	B
		First-degree AV block with symptoms suggestive of pacemaker syndrome and documented alleviation of symptoms with temporary AV pacing	B
	IIb	Marked first-degree AV block (> 0.30 sec) in patients with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval results in hemodynamic improvement, presumably by decreasing left atrial filling pressure	C
	III	Asymptomatic first-degree AV block	B
		Asymptomatic type 1 second-degree AV block at the supra-His (AV node) level or not known to be intra- or infra-Hisian	B, C

	III		
		Asymptomatic type 1 second-degree AV block at the supra-His (AV node) level or not known to be intra- or infra-Hisian	B, C
		AV block expected to resolve and unlikely to recur (e.g., drug toxicity, Lyme disease)	B
Permanent pacing in chronic bifascicular and trifascicular block	I	Intermittent third-degree AV block	B
		Type II second-degree AV block	B
	IIa	Syncope not proved to be due to AV block when other likely causes have been excluded, specifically VT	B
		Incidental finding at electrophysiological study of markedly prolonged H-V interval (> 100 msec) in asymptomatic patients	B
		Incidental finding at electrophysiological study of a pacing-induced infra-His block that is not physiological	B
	III	Fascicular block without AV block or symptoms	B
		Fascicular block with first-degree AV block without symptoms	B
Permanent pacing after the acute phase of myocardial infarction	I	Persistent second-degree AV block in the His-Purkinje system with a bilateral bundle branch block or third-degree AV block within or below the His-Purkinje system after acute MI	B
		Transient advanced (second- or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary	B
		Persistent and symptomatic second- or third-degree AV block	C
	IIb	Persistent second- or third-degree AV block at the AV node level	B
	III	Transient AV block in the absence of intraventricular conduction defects	B
		Transient AV block in the presence of isolated left anterior fascicular block	B
		Acquired left anterior block in the absence of AV block	B
		Persistent first-degree AV block in the presence of a bundle branch block that is old or age indeterminate	B

Permanent pacing in sinus node dysfunction	I	Sinus node dysfunction with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms	C
		Symptomatic chronotropic incompetence	C
	IIa	Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy, with a heart rate of <40 beats/min when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented	C
	IIb	In minimally symptomatic patients, chronic heart rate of less than 30 beats/min while awake	C
	III	Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate of <40 beats/min) is a consequence of long-term drug treatment	
		Sinus node dysfunction in patients with symptoms suggestive of bradycardia that are clearly documented as not associated with a slow heart rate	
		Sinus node dysfunction with symptomatic bradycardia from nonessential drug therapy	
Permanent pacemakers that automatically detect and pace to terminate tachycardias	I	Symptomatic recurrent supraventricular tachycardia that is reproducibly terminated by pacing after drugs and catheter ablation fail to control the arrhythmia or produce intolerable side effects	C
		Symptomatic recurrent sustained VT as part of an automatic defibrillator system	B
	IIb	Recurrent supraventricular tachycardia or atrial flutter that is reproducibly terminated by pacing as an alternative to drug therapy or ablation	C
	III	Tachycardias frequently accelerated or converted to fibrillation by pacing	
		The presence of accessory pathways with the capacity for rapid anterograde conduction regardless of whether the pathways participate in the mechanism of the tachycardia	

Pacing indications to prevent tachycardia	I	Sustained pause-dependent VT, with or without a prolonged QT, in which the efficacy of pacing is thoroughly documented	C
	IIa	High-risk patients with congenital long QT syndrome	C
	IIb	AV reentrant or AV node reentrant supraventricular tachycardia not responsive to medical or ablative therapy	C
		Prevention of symptomatic, drug-refractory, recurrent atrial fibrillation	C
	III	Frequent or complex ventricular ectopic activity without sustained VT in the absence of long QT syndrome	
		Long QT syndrome from reversible causes	
Permanent pacing in hypersensitive carotid sinus syndrome and neurally mediated syncope	I	Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3-sec duration in the absence of any medication that depresses the sinus node or AV conduction	C
	IIa	Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response	C
		Syncope of unexplained origin when major abnormalities of sinus node function or AV conduction are discovered or provoked in electrophysiological studies	C
	IIb	Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt with or without isoproterenol or other provocative maneuvers	B
	III	A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms	
		A hyperactive cardioinhibitory response to carotid sinus stimulation in the presence of vague symptoms such as dizziness, lightheadedness, or both	
		Recurrent syncope, lightheadedness, or dizziness in the absence of a hyperactive cardioinhibitory response	
		Situational vasovagal syncope in which avoidance behavior is effective	

Hypertrophic cardiomyopathy	I	Class I indications for sinus node dysfunction or AV block as previously described	C
	IIb	Medically refractory, symptomatic hypertrophic cardiomyopathy with significant resting or provoked LV outflow obstruction	C
	III	Patients who are asymptomatic or medically controlled	
		Symptomatic patients without evidence of LV outflow obstruction	
Dilated cardiomyopathy	I	Class I indications for sinus node dysfunction or AV block as previously described	C
	IIb	Symptomatic, drug-refractory dilated cardiomyopathy with a prolonged PR interval when acute hemodynamic studies have demonstrated a hemodynamic benefit of pacing	C
	III	Asymptomatic dilated cardiomyopathy	
		Symptomatic dilated cardiomyopathy when patients are rendered asymptomatic by drug therapy	
		Symptomatic ischemic cardiomyopathy	
Cardiac transplantation	I	Symptomatic bradyarrhythmias/chronotropic incompetence not expected to resolve and other Class I indications for permanent pacing	C

AV = atrioventricular; LV = left ventricular; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

From Gregoratos G, Cheitlin M, Conill A, et al: ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). J Am Coll Cardiol 31:1175-1209, 1998. Reprinted with permission from the American College of Cardiology.

*For definition of classes and levels of evidence, see guidelines AHA/ACC guidelines for Electrocardiography.

block at the AV node was less clear (Class II), but permanent pacing was discouraged if the sole indication was transient AV conduction disturbances or left anterior hemiblock.

The ACC/AHA guidelines also defined explicit criteria for the appropriateness of permanent pacing in patients with hypersensitive carotid sinus and neurovascular syndromes. The only Class I indication was recurrent syncope[2] associated with clear,

spontaneous events provoked by carotid sinus stimulation. In such patients, minimal carotid sinus pressure should induce asystole of 3 seconds or more in the absence of medications that depress the sinus node.

Recommendations were also included for the use of permanent pacemakers for termination of tachyarrhythmias. Antitachycardia devices include permanent pacemakers that can be programmed to interrupt reentrant arrhythmias or prevent their occurrence, as well as automatic defibrillator devices. The ACC/AHA guidelines stressed that these devices should be implanted only after careful evaluation by experienced electrophysiologists.

Permanent pacemakers were considered appropriate for use for recurrent supraventricular tachycardias in patients who were symptomatic and whose arrhythmias could not be controlled with drug therapy or catheter ablation. For patients with symptomatic ventricular tachycardia, permanent pacemakers were considered appropriate as part of an automatic defibrillator system.

For patients with hypertrophic cardiomyopathy or dilated cardiomyopathy, clearly appropriate indications for permanent pacemakers were similar to those for patients without these conditions. The task force thought there was some evidence to support the use of dual-chamber or right ventricular pacemakers in some patients with medically refractory, symptomatic hypertrophic cardiomyopathy and significant resting or provoked left ventricular outflow obstruction (Class IIb). Similarly, permanent pacemakers for patients with symptomatic, drug-refractory dilated cardiomyopathy with a prolonged PR interval were considered to be possibly appropriate when acute hemodynamic studies demonstrated hemodynamic benefit from pacing. For patients who have undergone cardiac transplantation, permanent pacemakers were considered appropriate when the patients had symptomatic bradyarrhythmias that were not expected to resolve.

The guidelines offer general recommendations on the type of permanent pacemaker most appropriate for specific patient subsets but noted that technologies are evolving quickly and prospective randomized data are few.

Implantable Cardioverter-Defibrillator Therapy

The enthusiasm for implanting cardioverter-defibrillator devices has been increasing because of disappointing data on the lack of impact of antiarrhythmic medications on survival and data showing low rates of sudden cardiac death and improved quality of life after device implantation. Implantable cardioverter-defibrillators (ICDs) can be combined with drug therapy or ablation techniques applied at surgery or percutaneously via catheter techniques. Ablation techniques are in particularly rapid evolution, which hinders the ability to develop formal guidelines for their appropriateness and relative merits in comparison to alternative strategies.

ICDs are now regarded as clearly appropriate therapy for patients who have had cardiac arrest as a result of ventricular fibrillation or ventricular tachycardia without a transient or reversible cause, as well as for patients with spontaneous sustained ventricular

tachycardia (Table 24-G-2) . The ACC/AHA guidelines consider ICDs appropriate for patients who have electrophysiological studies that suggest arrhythmia as a likely cause of syncope and other patients with high-risk electrophysiology tests.

ICDs are not recommended by the ACC/AHA task force for several groups, including the following:

Patients for whom a reversible triggering factor for arrhythmia can be identified, such as evolving myocardial infarction or electrolyte abnormalities.

Patients with coronary disease without inducible or spontaneous ventricular tachycardia who are undergoing routine coronary artery bypass graft surgery.

Patients with Wolff-Parkinson-White syndrome and ventricular fibrillation secondary to atrial fibrillation. (These patients should undergo catheter or surgical ablation if their accessory pathways are amenable to such treatment.)

Patients with frequent tachyarrhythmias that may trigger shock therapy.

TABLE 24--G-2 -- ACC/AHA GUIDELINES FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY*

Class	Recommendation	Level of Evidence
I	Cardiac arrest due to VF or VT not due to a transient or reversible cause	A
	Spontaneous sustained VT	B
	Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study when drug therapy is ineffective, not tolerated, or not preferred	B
	Nonsustained VT with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at electrophysiological study that is not suppressible by a class I antiarrhythmic drug	B

IIb	Cardiac arrest presumed to be due to VF when electrophysiological testing is precluded by other medical conditions	C
	Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation	C
	Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy	B
	Nonsustained VT with coronary artery disease, prior MI, and LV dysfunction and inducible sustained VT or VF at electrophysiological study	B
	Recurrent syncope of undetermined etiology in the presence of ventricular dysfunction and inducible ventricular arrhythmias at electrophysiological study when other causes of syncope have been excluded	C
III	Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias	C
	Incessant VT or VF	C

LV = left ventricular; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

From Gregoratos G, Cheitlin M, Conill A, et al: ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). J Am Coll Cardiol 31:1175-1209, 1998. Reprinted with permission from the American College of Cardiology.

*For definition of classes and levels of evidence, see guidelines AHA/ACC guidelines for Electrocardiography.

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Chapter 25 - Specific Arrhythmias: Diagnosis and Treatment

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DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

History

The initial evaluation of a patient suspected of having a cardiac arrhythmia begins with a careful history addressing specific questions regarding the presence of palpitations, syncope, spells of lightheadedness, chest pain, or symptoms of congestive heart failure. Palpitations,[1] an awareness of one's heartbeat (see Chap. 3), may result from irregularities in cardiac rate or rhythm or a change in contractility of the heart. Some patients are able to reproduce this sensation by tapping their hand on their chest, knee, or a table top in a fashion similar to the perceived palpitation or may recognize a cadence tapped out by a physician. Such a maneuver can help establish the rate and rhythm of the arrhythmia by narrowing it to a particular rate range, a regular or irregular arrhythmia, or one in which a regular rhythm is interrupted by premature beats. The latter are often perceived only upon the contraction that ends the pause following the

premature beat. The patient may feel as though the heart has stopped for a moment. Rapid, irregular tapping can suggest the ventricular response to atrial fibrillation, whereas rapid, regular tapping can suggest an atrioventricular (AV) nodal reentrant supraventricular tachycardia, particularly in a young person, or ventricular tachycardia (VT) in an older person. Information regarding the nature of the onset and termination of the rhythm disturbance is particularly important. Knowing the rate of the arrhythmia is crucial, and a brief demonstration by the physician of how to determine the heart rate can yield important dividends. The patient, and sometimes a close relative, should be instructed in how to count the pulse.

Answers by the patient to key questions can provide clues to the type of rhythm disturbance, particularly if the physician has additional information, such as physical findings and a 12-lead electrocardiogram (ECG). For example, a young adult with presyncope, normal physical findings, and ECG changes indicating Wolff-Parkinson-White (WPW) syndrome should be asked whether the palpitations are regular or irregular, how fast they are, and how they start and stop. If the tachycardia is regular, with a rate of approximately 200 beats/min, and of sudden onset and termination, it is likely that the patient is experiencing an AV reciprocating tachycardia; on the other hand, if the rhythm is irregular, the patient may have atrial fibrillation, a potentially more serious arrhythmia in the presence of WPW syndrome. In an older patient with presyncope, especially with a history of myocardial infarction, the physician should suspect VT if the ventricular rate is rapid and suspect AV heart block or sinus nodal disease if the rate is slow. The ventricular rhythm can be regular or irregular. Premature atrial or ventricular beats, perceived as dropped or skipped beats by the patient, are probably the most common cause of palpitations.

The physician should inquire about circumstances that can trigger the arrhythmia, such as emotionally upsetting events, ingestion of caffeine-containing beverages, cigarette smoking, exercise, excessive alcohol intake, or gastrointestinal problems (Fig. 25-1) . A careful diet and drug history can be useful, for example, in revealing that palpitations develop only after the use of a nasal decongestant that contains a sympathomimetic vasoconstrictor or in revealing that the patient has been exposed to "street" drugs such as cocaine. States conducive to the genesis of arrhythmias should be considered, such as thyrotoxicosis, pericarditis, mitral valve prolapse, hypokalemia secondary to diuretics, and so forth. The family history can be helpful. In addition to the congenital long QT syndrome, a variety of other familial disorders can result in arrhythmias, including myotonic dystrophy, Duchenne muscular dystrophy (see Chap. 71), and dilated cardiomyopathy (see Chap. 48). Congenital conduction system disorders can result in sudden death.

Physical Examination

In addition to recording the cardiac rate and rhythm, a number of physical findings can be helpful. For example, findings accompanying AV dissociation include variable peak systolic blood pressure as the atria alter their contribution

TABLE 25-1 -- ARRHYTHMIA CHARACTERISTI

TYPE OF ARRHYTHMIA	P WAVES			QRS COMPLEXES			VENTRICULA RESPONSE TO CAROTI SINUS MASSAGE
	Rate (bpm)	*Rhythm*	*Contour*	*Rate*	*Rhythm*	*Contour*	
Sinus rhythm	60-100	Regular	Normal	60-100	Regular	Normal	Gradual slowi and return to former rate
Sinus bradycardia	<60	Regular	Normal	<60	Regular	Normal	Gradual slowi and return to former rate
Sinus tachycardia	100-180	Regular	May be peaked	100-180	Regular	Normal	Gradual slowi and return to former rate
AV nodal reentry	150-250	Very regular except at onset and termination	Retrograde; difficult to see; lost in QRS complex	150-250	Very regular except at onset and termination	Normal	Abrupt slowin caused by termination of tachycardia, o no effect
Atrial flutter	250-350	Regular	Sawtooth	75-175	Generally regular in absence of drugs or disease	Normal	Abrupt slowin and return to former rate; flutter remains
Atrial fibrillation	400-600	Grossly irregular	Baseline undulation, no P waves	100-160	Grossly irregular	Normal	Slowing; gros irregularity remains

Atrial tachycardia with block	150-250	Regular; may be irregular	Abnormal	75-200	Generally regular in absence of drugs or disease	Normal	Abrupt slowin and return to normal rate; tachycardia remains
AV junctional rhythm	40-100[§]	Regular	Normal	40-60	Fairly regular	Normal	None; may be slight slowing
Reciprocating tachycardias using an accessory (WPW) pathway	150-250	Very regular except at onset and termination	Retrograde; difficult to see; monitor the QRS complex	150-250	Very regular except at onset and termination	Normal	Abrupt slowin caused by termination of tachycardia, o no effect
Nonparoxysmal AV junctional tachycardia	60-100[¶]	Regular	Normal	70-130	Fairly regular	Normal	None, may be slight slowing
Ventricular tachycardia	60-100[¶]	Regular	Normal	110-250	Fairly regular; may be irregular	Abnormal, >0.12 sec	None
Accelerated idioventricular rhythm	60-100[¶]	Regular	Normal	50-110	Fairly regular; may be irregular	Abnormal, >0.12 sec	None
Ventricular flutter	60-100[¶]	Regular	Normal; difficult to see	150-300	Regular	Sine wave	None
Ventricular fibrillation	60-100[¶]	Regular	Normal; difficult to see	400-600	Grossly irregular	Baseline undulations; no QRS complexes	None
First-degree AV block	60-100[*]	Regular	Normal	60-100	Regular	Normal	Gradual slowi caused by sin
Type I second-degree AV block	60-100[*]	Regular	Normal	30-100	Irregular	Normal	Slowing caus by sinus slowing and a increase in AV block

Type II second-degree AV block	60-100[*,**]	Regular	Normal	30-100	Irregular	Abnormal, >0.12 sec	Gradual slowi caused by sin slowing
Complete AV block	60-100[¶]	Regular	Normal	<40	Fairly regular	Abnormal, 0.12 sec	None
Right bundle branch block	60-100	Regular	Normal	60-100	Regular	Abnormal, 0.12 sec	Gradual slowi and return to former rate
Left bundle branch block	60-100	Regular	Normal	60-100	Regular	Abnormal, >0.12 sec	Gradual slowi and return to former rate

AV = atrioventricular; WPW = Wolff-Parkinson-White.

Modified from Zipes DP: Arrhythmias. In Andreoli K, Zipes DP, Wallace AG, et al (eds): Comprehensiv

*In an effort to summarize these arrhythmias in tabular form, generalizations have to be made. For example, the response to carotid sinus massage may be slightly different from what is listed. Acute therapy to terminate a tachycardia may be different from chronic therapy to prevent recurrence. Some of the exceptions are indicated in the footnotes; the reader is referred to the text for a complete discussion.

P waves initiated by sinus node discharge may not be precisely regular because of sinus arrhythmia.

Often, carotid sinus massage fails to slow a sinus tachycardia.
§Any independent atrial arrhythmia may exist or the atria may be captured retrogradely.
¶Constant if the atria are captured retrogradely.
**Atrial rhythm and rate may vary, depending on whether sinus bradycardia, sinus tachycardia, or another abnormality is the atrial mechanism.

Regular or constant if block is unchanging.

Figure 25-1 Transient atrioventricular (AV) block. This monitor lead recording demonstrates a transient AV block during a period of nausea and vomiting that was most probably caused by excessive vagal stimulation.

to ventricular filling, variable intensity of the first heart sound as the PR interval changes despite a regular ventricular rhythm, intermittent cannon *a* waves in the jugular venous

pulse as atrial contraction occurs against closed AV valves, and apparent "intermittent" gallop sounds when atrial systole occurs at various times of the cardiac cycle. The *venous pulse* provides a window through which to judge atrial and ventricular rates and relative timing relationships. It is of interest that Wenckebach first noted the two types of second-degree AV block that bear his name by recording the jugular phlebogram before the ECG was available.

Examining the *second heart sound* can be helpful (see Chap. 4). A paradoxically split second heart sound can occur during a QRS complex with a left bundle branch block contour that results from VT or supraventricular tachycardia with aberration. A widely split second heart sound that does not become single during expiration can accompany a right bundle branch block. Unfortunately, similar physical findings occur with different cardiac arrhythmias. For example, progressive diminution of the intensity of the first heart sound results as the PR interval lengthens, which can occur during AV dissociation when the atrial rate exceeds the ventricular rate or during a Wenckebach second-degree AV block. Similarly, constant cannon *a* waves can occur with 1:1 AV relationships during ventricular or supraventricular tachycardia. Since AV dissociation can occur (uncommonly) during supraventricular tachycardia and VA association can occur during VT, the clues provided by physical findings can be only suggestive.

Carotid Sinus Massage

The response to carotid sinus massage or the Valsalva maneuver provides important diagnostic information by increasing vagal tone and primarily slowing the rate of sinus nodal discharge and prolonging AV nodal conduction time and refractoriness. Sinus tachycardia slows gradually during carotid massage and then returns to the previous rate when the massage is discontinued; AV nodal reentry and AV reciprocating tachycardias that involve the AV node in one of its pathways can slow slightly, terminate abruptly, or not change, and the ventricular response to atrial flutter, atrial fibrillation, and some atrial tachycardias usually decreases (Table 25-1) . Rarely, carotid sinus massage terminates a VT.

To perform carotid massage, the patient is placed in a supine position with the neck hyperextended and the head turned away from the side being tested, the sternocleidomastoid muscles relaxed or gently pushed out of the way, and the carotid impulse felt at the angle of the jaw. The carotid bifurcation is touched gently initially with the palmar portion of the fingertips to detect hypersensitive responses. Then, if no change in cardiac rhythm occurs, pressure is applied more firmly for approximately 5 seconds, first on one side and then on the other (*never* on both sides simultaneously) with a gentle rotating massaging motion. External pressure stimulates baroreceptors in the carotid sinus to trigger a reflex increase in vagal activity and sympathetic withdrawal. Responses can occur with right-sided massage and not left, or vice versa, so each side should be tested separately. Generally, the maximal response occurs with the first massage if repeated attempts are performed at short intervals. Some risk is associated with carotid sinus massage, particularly in older patients, and cerebral emboli can occur.[2] Before massage, the carotid artery should be auscultated so that massage is not performed in patients who have carotid bruits indicative of carotid arterial disease.

Electrocardiography

The ECG remains the most important and definitive single noninvasive diagnostic test. Figure 25-2 depicts an algorithm for diagnosing specific tachyarrhythmias from the 12-lead ECG. Initially, a 12-lead ECG is recorded, and a long recording using the lead that shows distinct P waves is obtained for proper analysis. If P waves are not clearly visible, atrial activity can be recorded by placing the right and left arm leads in various chest positions to discern P waves (so-called Lewis leads) and applying esophageal electrodes or by using intracavitary right atrial leads. An echocardiogram showing atrial contraction can be helpful.

Each arrhythmia must be approached in a systematic manner to answer the following questions: Are P waves present? What are the atrial and ventricular rates? Are they identical? Are the P-P and R-R intervals regular or irregular? If irregular, is it a consistent, repeating irregularity? Is there a P wave related to each ventricular complex? Does the P wave precede or follow the QRS complex? Is the resultant PR or RP interval constant? Is the RP interval long and the PR interval short, or vice versa? Are all P waves and QRS complexes identical and normal in contour? To determine the significance of changes in P wave or QRS contour or amplitude, one must know the lead being recorded. Are P, PR, QRS, and QT durations normal? In view of the clinical setting, what is the significance of the arrhythmia? Should it be treated and, if so, how? For supraventricular tachycardias with a normal QRS complex, a branching decision tree may be useful.

The Ladder Diagram

The ladder diagram is used to depict depolarization and conduction schematically. Straight or slightly slanting lines drawn on a tiered framework beneath an ECG trace represent electrical events occurring in the various cardiac structures (Fig. 25-3 *A* and *B*). Since the ECG and therefore the ladder diagram represent electrical activity against a time base, conduction is indicated by the lines of the ladder diagram sloping in a left-to-right direction. A less steep line depicts slower conduction. A short bar drawn perpendicular to a sloping line represents blocked conduction (Fig. 25-3 *C*). Activity originating in an ectopic site such as the ventricle is indicated in another tier drawn beneath the ventricular tier. In general, atrial, AV junctional, or ventricular activity is diagrammed to begin in that particular tier. It is important to remember that sinus nodal discharge and conduction and, under certain circumstances, AV junctional discharge and conduction can only be assumed; their activity is not recorded on scalar ECG.

Figure 25-2 Stepwise approach to diagnose tachycardias from the 12-lead electrocardiogram (ECG). The first step is to determine whether the tachycardia is a narrow- or wide-complex tachycardia. For

wide-complex tachycardias, refer to Table 25-4 . The remainder of the algorithm is useful in diagnosing types of supraventricular tachycardias from the 12-lead ECG.

Electrophysiological Study

When an electrophysiological study is indicated, it is performed by introducing multipolar catheter electrodes into the vascular system and positioning them in various parts of the heart. The catheters are used to record local electrical activity and to stimulate the heart. Multiple leads are recorded simultaneously, usually at a paper speed of 50 to 200 mm/sec. (Standard ECGs are generally recorded at a paper speed of 25 mm/sec.) Because of the rapid recording speed, intervals or complexes of normal duration may appear prolonged. An electrode positioned across the septal leaflet of the tricuspid valve records His bundle activity, as well as low right atrial activity and high ventricular septal depolarization. Occasionally, a right bundle branch deflection

Figure 25-3 *A,* Ladder diagram. Straight or slightly sloping lines beginning with the P wave and QRS complex indicate atrial and ventricular depolarization. The instants at which the sinus node discharges and the duration of sinoatrial conduction cannot be measured in the surface electrocardiogram and are therefore assumed. The sloping line connecting A and V, delimited by the interrupted lines, represents atrioventricular (AV) conduction. *B,* Normal and ectopic beats; a = normal sinus rhythm; b = ectopic atrial beat; c = AV junctional beat; d = ventricular ectopic beats. All are drawn with appropriate ladder diagrams beneath (T waves omitted). Retrograde atrial conduction is inscribed for the latter two beats. As with the sinus node, the exact discharge time of the AV junctional focus and the conduction time from that point to the ventricles and atria are assumed. *C,* Second-degree Wenckebach type I AV block. The PR interval lengthens progressively until finally the fourth P wave fails to reach the ventricles. As the PR interval is prolonged, note the decreasing slope of the line representing AV conduction and the small line perpendicular to the fourth sloping line indicating that the P wave is blocked. *(A to C from Zipes DP, Fisch C: ECG analysis: 1. Introduction. Premature ventricular complexes. Arch Intern Med 128:140, Copyright 1971, American Medical Association.) D,* A single cardiac cycle showing the intervals measured during an electrophysiological study. In this and in similar subsequent figures, A-H = interval representing AV nodal conduction time; BAE = bipolar atrial electrogram recording high right atrial activity; BHE = bipolar His electrogram recording low right atrial activity (A), His bundle activity (H), and ventricular septal activity (V); CS = bipolar electrogram recording of left atrial activity in the coronary sinus lead; H-V = interval representing His-Purkinje conduction time; I = lead I; II = lead II; III = lead III; PA = interval representing intraatrial conduction time; RV = right ventricular electrogram recording right ventricular activity; V_1 = lead V_1 . All values are in milliseconds. Normal values for the PA, A-H, and H-V intervals are given at the upper right. Paper speed = 100 mm/sec unless otherwise stated. Interrupted lines demarcate the various intervals. Note the normal sequence of atrial activation recorded with this technique: High right atrial activity (BAE) precedes low right atrial activity recorded in the BHE lead, which precedes left atrial activity recorded in the CS lead. Large time lines = 50 milliseconds. Small time lines = 10 milliseconds.

can also be recorded. Three basic measurements are made by using the ECG and the

His bundle catheter recording: the PA, A-H, and H-V intervals (Fig. 25-3 *D*). The PA interval is the time between the onset of the P wave in the surface tracing (which generally slightly precedes the onset of the high right atrial recording) and the low right atrial deflection and is recorded in the His lead. This interval reflects intraatrial conduction and has not proved to be of much clinical value.

THE A-H INTERVAL.

The A-H interval is timed from the onset of the first rapid deflection recorded in the atrial electrogram (A) in the His bundle lead to the beginning of the His (H) deflection. Since the low right part of the atrium and the His bundle anatomically delineate the boundaries of the AV node, the A-H interval closely approximates AV nodal conduction time. The A-H interval is affected by various interventions: Atropine and isoproterenol shorten the A-H interval, whereas vagal maneuvers, digitalis, propranolol, verapamil, adenosine, and rapid or premature atrial pacing lengthen it. The normal range for the A-H interval is 55 to 130 milliseconds, depending on the heart rate, autonomic tone, and other factors.

THE H-V INTERVAL.

The H-V interval is the time from the beginning of the H deflection to the earliest onset of ventricular depolarization recorded in *any* lead. This interval represents conduction from the His bundle through the bundle branch-Purkinje system to the point of ventricular muscle activation and is usually constant--between 30 and 55 milliseconds--regardless of the heart rate or autonomic tone. Other intervals are discussed under the individual tachycardias.

Consequences of Arrhythmias

The ventricular rate and duration of an arrhythmia, its site of origin, and the cardiovascular status of the patient primarily determine the electrophysiological and hemodynamic consequences of a particular rhythm disturbance. Electrophysiological consequences, often influenced by the presence of underlying heart disease such as acute myocardial infarction, include the development of serious arrhythmias as a result of rapid or slow rates, initiation of sustained arrhythmias by premature systoles, or the progression of rhythms such as VT to ventricular fibrillation. Extremes of heart rate or loss of the atrial contribution to ventricular filling can alter circulatory dynamics. Rapid rates greatly shorten the diastolic filling time, and particularly in diseased hearts, the increased heart rate can fail to compensate for the reduced stroke output; as a consequence, arterial pressure, cardiac output, and coronary blood flow decline. Arrhythmias that prevent sequential AV contraction mitigate the hemodynamic benefits of the atrial booster pump, whereas atrial fibrillation causes complete loss of atrial contraction and can reduce cardiac output. Chronic tachycardias can cause cardiac dilation and heart failure from tachycardia-induced cardiomyopathy.[3]

Management

The therapeutic approach to a patient with a cardiac arrhythmia begins with an accurate

ECG *interpretation* of the arrhythmia and continues with determination of the *cause* of the arrhythmia (if possible), the nature of the underlying *heart disease* (if any), and the *consequences* of the arrhythmias in the individual patient. Thus, one does not treat arrhythmias as isolated events without having knowledge of the entire clinical situation. *Patients* who have arrhythmias are treated rather than the arrhythmias themselves.

When a tachyarrhythmia develops, slowing the ventricular rate is the initial and often the most important therapeutic maneuver. Therapy can differ radically for the same arrhythmia in two different patients because the consequences of tachycardia in individual patients differ. For example, a supraventricular tachycardia at a rate of 200 beats/min can produce few or no symptoms in a healthy young adult and therefore requires little or no therapy because it is usually self-limited. The same arrhythmia can precipitate pulmonary edema in a patient with mitral stenosis, syncope in a patient with aortic stenosis, shock in a patient with acute myocardial infarction, or hemiparesis in a patient with cerebrovascular disease. In these situations, the tachycardia requires prompt electrical conversion.

The *cause* of the arrhythmia can influence therapy greatly. Electrolyte imbalance (potassium, magnesium, calcium), acidosis or alkalosis, hypoxemia, and many drugs can produce rhythm disturbances, and their identification and treatment can abolish or prevent these arrhythmias. Because heart failure can cause arrhythmias, treatment of this condition with digitalis, diuretics, or vasodilators can suppress some of the arrhythmias that accompany cardiac decompensation. Similarly, arrhythmias secondary to hypotension may respond to leg elevation or vasopressor therapy. Mild sedation or reassurance can be successful in treating some arrhythmias related to emotional stress. Precipitating or contributing disease states such as myocarditis, infection, hypokalemia, anemia, and thyroid disorders should be sought and treated when possible. Since therapy always involves some risk, one must be sure--particularly as the therapeutic regimen escalates--that the risks of *not* treating the arrhythmia continue to outweigh the risks of therapy with potentially hazardous antiarrhythmic measures.

Individual Cardiac Arrhythmias

SINUS NODAL DISTURBANCES

Normal Sinus Rhythm

Normal sinus rhythm is arbitrarily limited to impulse formation beginning in the sinus node at frequencies between 60 and 100 beats/min. A range of 50 to 90 beats/min has been suggested.[4] Infants and children generally have faster heart rates than adults do, both at rest and during exercise. The P wave is upright in leads I, II, and aV_f and negative in lead aV_r , with a vector in the frontal plane between 0 and +90 degrees. In the horizontal plane, the P vector is directed anteriorly and slightly leftward and can therefore be negative in leads V_1 and V_2 but positive in V_3 to V_6 . The PR interval exceeds 120 milliseconds and can vary slightly with the rate. If the pacemaker site

shifts, a change in morphology of the P wave can occur. The rate of sinus rhythm varies significantly and depends on many factors, including age, sex, and physical activity.

The sinus nodal discharge rate responds readily to autonomic stimuli and depends on the effect of the two opposing autonomic influences. Steady vagal stimulation decreases the spontaneous sinus nodal discharge rate and predominates over steady sympathetic stimulation, which increases the spontaneous sinus nodal discharge rate. Single or brief bursts of vagal stimulation can speed, slow, or entrain sinus nodal discharge. A given vagal stimulus produces a greater absolute reduction in heart rate when the basal heart rate has been increased by sympathetic stimulation, a phenomenon known as *accentuated antagonism.*

Sinus Tachycardia

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-4 *A*).

Tachycardia in an adult is defined as a rate exceeding 100 beats/min. During sinus tachycardia, the sinus node exhibits a discharge frequency between 100 and 180 beats/min, but it may be higher with extreme exertion. The maximum heart rate achieved during strenuous physical activity decreases with age from near 200 beats/min to less than 140 beats/min. Sinus tachycardia generally has a gradual onset and termination. The P-P interval can vary slightly from cycle to cycle. P waves have a normal contour, but a larger amplitude can develop and the wave can

Figure 25-4 *A,* Sinus tachycardia (150 beats/min) in a patient during acute myocardial ischemia; note the ST segment depression. P waves are indicated by arrows. *B,* Sinus bradycardia at a rate of 40 to 48 beats/min. The second and third QRS complexes (arrows) represent junctional escape beats. Note the P waves at the onset of the QRS complex. *C,* Nonrespiratory sinus arrhythmia occurring as a consequence of digitalis toxicity. Monitor leads.

become peaked. They appear before each QRS complex with a stable PR interval unless concomitant AV block ensues.

Accelerated phase 4 diastolic depolarization of sinus nodal cells is generally responsible for sinus tachycardia. Rate changes can result from a shift in pacemaker cells to a different locus within the sinus node. Carotid sinus massage and the Valsalva or other vagal maneuvers gradually slow a sinus tachycardia, which then accelerates to its previous rate upon cessation of enhanced vagal tone. More rapid sinus rates can fail to slow in response to a vagal maneuver.

CLINICAL FEATURES.

Sinus tachycardia is common in infancy and early childhood and is the normal reaction to a variety of physiological or pathophysiological stresses such as fever, hypotension, thyrotoxicosis, anemia, anxiety, exertion, hypovolemia, pulmonary emboli, myocardial ischemia, congestive heart failure, or shock. It can occur during rapid eye movement sleep[5] and can be an adverse prognostic sign after heart transplantation.[6] Drugs such as atropine, catecholamines,[7] and thyroid medications, [8] as well as alcohol, nicotine, caffeine, and inflammation, can produce sinus tachycardia. Persistent sinus tachycardia can be a manifestation of heart failure.

In patients with mitral stenosis or severe ischemic heart disease, sinus tachycardia can result in reduced cardiac output or angina or can precipitate another arrhythmia, in part related to the abbreviated ventricular filling time and compromised coronary blood flow. Sinus tachycardia can be a cause of inappropriate defibrillator discharge in patients with an implantable automatic defibrillator.[9] *Chronic inappropriate sinus tachycardia* has been described in otherwise healthy persons, possibly secondary to increased automaticity of the sinus node or an automatic atrial focus located near the sinus node.[10] [11] [12] The abnormality can result from a defect in either sympathetic or vagal nerve control of sinoatrial (SA) automaticity, or an abnormality of the intrinsic heart rate can be present.[13] It has been noted after radiofrequency catheter ablation of AV nodal tachycardia.[14] [15] [16]

MANAGEMENT.

Management should focus on the *cause* of the sinus tachycardia. Elimination of tobacco, alcohol, coffee, tea, or other stimulants, such as the sympathomimetic agents in nose drops, may be helpful. Drugs such as propranolol or verapamil or fluid replacement in a hypovolemic patient or fever reduction in a febrile patient can be used to help slow the sinus nodal discharge rate. Treatment of inappropriate sinus tachycardia requires beta blockers, calcium channel blockers, or digitalis, alone or in combination. In severe cases, sinus node radiofrequency[11] [17] or surgical[18] ablation may be indicated.

Sinus Bradycardia

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-4 *B*).

Sinus bradycardia exists in an adult when the sinus node discharges at a rate less than 60 beats/min. P waves have a normal contour and occur before each QRS complex with a constant PR interval exceeding 120 milliseconds unless a concomitant AV block is present. Sinus arrhythmia often coexists.

CLINICAL FEATURES.

Sinus bradycardia can result from excessive vagal or decreased sympathetic tone, as an effect of medications, or from anatomical changes in the sinus node. Sinus bradycardia frequently occurs in healthy young adults, particularly well-trained athletes

(who can also have tachyarrhythmias), and decreases in prevalence with advancing age. It may be present in patients with anorexia nervosa[19] and following cardiac transplantation.[20] During sleep, the normal heart rate can fall to 35 to 40 beats/min, especially in adolescents and young adults, with marked sinus arrhythmia sometimes producing pauses of 2 seconds or longer. Eye surgery, coronary arteriography, meningitis, intracranial tumors, increased intracranial pressure, cervical and mediastinal tumors, and certain disease states such as severe hypoxia, Chagas disease,[21] myxedema, hypothermia, fibrodegenerative changes, convalescence from some infections, gram-negative sepsis, and mental depression can produce sinus bradycardia. Obstructive jaundice is thought to cause sinus bradycardia, but the evidence is not clear. Sinus bradycardia also occurs during vomiting or vasovagal syncope (see Chap. 27) and can be produced by carotid sinus stimulation or by the administration of parasympathomimetic drugs, lithium, amiodarone, beta-adrenoceptor blocking drugs, clonidine, propafenone, or calcium antagonists. Conjunctival instillation of beta blockers for glaucoma can produce sinus or AV nodal abnormalities, especially in the elderly.

In most instances, sinus bradycardia is a benign arrhythmia and can actually be beneficial by producing a longer period of diastole and increasing the ventricular filling time. It can be associated with syncope caused by an abnormal reflex.[22] Sinus bradycardia occurs in 10 to 15 percent of patients with acute myocardial infarction and may be even more prevalent when patients are seen in the early hours of infarction. Unless accompanied by hemodynamic decompensation or arrhythmias, sinus bradycardia is generally associated with a more favorable outcome following myocardial infarction than is the presence of sinus tachycardia. It is usually transient and occurs more commonly during inferior than anterior myocardial infarction; it has also been noted during reperfusion with thrombolytic agents. Bradycardia following resuscitation from cardiac arrest is associated with a poor prognosis.

MANAGEMENT.

Treatment of sinus bradycardia per se is not usually necessary. For example, if a patient with acute myocardial infarction is asymptomatic, it is probably best to not speed up the sinus rate. If cardiac output is inadequate or if arrhythmias are associated with the slow rate, atropine (0.5 mg intravenously [IV] as an initial dose, repeated if necessary) is usually effective. Lower doses of atropine, particularly when given subcutaneously or intramuscularly, can exert an initial parasympathomimetic effect, possibly via a central action. Ephedrine, hydralazine, or theophylline can be useful in managing some patients with symptomatic sinus bradycardia. These drugs should be given with caution so as to not "overshoot" and produce too rapid a rate. In some patients who experience congestive heart failure or symptoms of low cardiac output as a result of chronic sinus bradycardia, electrical pacing may be needed. Atrial pacing is usually preferable to ventricular pacing to preserve sequential AV contraction and is preferable to drug therapy for long-term management of sinus bradycardia. As a general rule, no available drugs increase the heart rate reliably and safely over long periods without important side effects.

Sinus Arrhythmia

Sinus arrhythmia (see Fig. 25-4 *C*) is characterized by a phasic variation in sinus cycle length during which the maximum sinus cycle length minus the minimum sinus cycle length exceeds 120 milliseconds or the maximum sinus cycle length minus the minimum sinus cycle length divided by the minimum sinus cycle length exceeds 10 percent. It is the most frequent form of arrhythmia and is considered to be a normal event. P wave morphology does not usually vary, and the PR interval exceeds 120 milliseconds and remains unchanged since the focus of discharge remains relatively fixed within the sinus node. Occasionally, the pacemaker focus can wander within the sinus node, or its exit to the atrium may change and produce P waves of slightly different contour (but not retrograde) and a slightly changing PR interval that exceeds 120 milliseconds.

Sinus arrhythmia commonly occurs in the young, especially those with slower heart rates or following enhanced vagal tone, such as after the administration of digitalis or morphine, and decreases with age or with autonomic dysfunction, such as diabetic neuropathy. Sinus arrhythmia appears in two basic forms. In the *respiratory* form, the P-P interval cyclically shortens during inspiration, primarily as a result of reflex inhibition of vagal tone, and slows during expiration; breath-holding eliminates the cycle length variation. Efferent vagal effects alone have been suggested as being responsible for respiratory sinus arrhythmias. *Nonrespiratory* sinus arrhythmia is characterized by a phasic variation in the P-P interval unrelated to the respiratory cycle and may be the result of digitalis intoxication. Loss of sinus rhythm variability is a risk factor for sudden cardiac death (see Chap. 26). Loss of sinus arrhythmia can occur in patients with acute intracranial lesions.[23]

Symptoms produced by sinus arrhythmia are uncommon, but on occasion, if the pauses between beats are excessively long, palpitations or dizziness may result. Marked sinus arrhythmia can produce a sinus pause sufficiently long to produce syncope if not accompanied by an escape rhythm.

Treatment is usually unnecessary. Increasing the heart rate by exercise or drugs generally abolishes sinus arrhythmia. Symptomatic individuals may experience relief from palpitations with sedatives, tranquilizers, atropine, ephedrine, or isoproterenol administration, as in the treatment of sinus bradycardia.

VENTRICULOPHASIC SINUS ARRHYTHMIA.

This arrhythmia occurs when the ventricular rate is slow. The most common example occurs during complete AV block, when P-P cycles that contain a QRS complex are shorter than P-P cycles without a QRS complex. Similar lengthening can be present in the P-P cycle that follows a premature ventricular complex with a compensatory pause. Alterations in the P-P interval are probably due to the influence of the autonomic

nervous system responding to changes in ventricular stroke volume.

Sinus Pause or Sinus Arrest

Sinus pause or sinus arrest (Fig. 25-5) is recognized by a pause in the sinus rhythm. The P-P interval delimiting the pause does not equal a multiple of the basic P-P interval. Differentiation of sinus arrest, which is thought to be due to slowing or cessation of spontaneous sinus nodal automaticity and therefore a disorder of impulse formation, from sinoatrial (SA) exit block (see below) in patients with sinus arrhythmia can be quite difficult without direct recordings of sinus node discharge.[24] [25]

Failure of sinus nodal discharge results in the absence of atrial depolarization and in periods of ventricular asystole if escape beats initiated by latent pacemakers do not occur (see Fig. 25-5). Involvement of the sinus node by acute myocardial infarction,[26] degenerative fibrotic changes, effects of digitalis toxicity, stroke, or excessive vagal tone can all produce sinus arrest. Transient sinus arrest may have no clinical significance by itself if latent pacemakers promptly escape to prevent ventricular asystole or the genesis of other arrhythmias precipitated by the slow rates. Sinus arrest and AV block have been demonstrated in as many as 30 percent of patients with sleep apnea.[27]

Treatment is as outlined above for sinus bradycardia. In patients who have a chronic form of sinus node disease characterized by marked sinus bradycardia or sinus arrest, permanent pacing is often necessary. However, as a general rule, chronic pacing for sinus bradycardia is indicated only in symptomatic patients or those with a sinus pause exceeding 3 seconds.[28]

Sinoatrial Exit Block

This arrhythmia is recognized electrocardiographically by a pause resulting from absence of the normally expected P wave[25] [29] (Fig. 25-6) . The duration of the pause is a multiple of the basic P-P interval. SA exit block is due to a conduction disturbance during which an impulse formed within the sinus node fails to depolarize the atria or does so with delay[30] (Fig. 25-7) . An interval without P waves that equals approximately two, three, or four times the normal P-P cycle characterizes type II second-degree SA exit block. During type I (Wenckebach) second-degree SA exit block, the P-P interval progressively shortens prior to the pause, and the duration of the pause is less than two P-P cycles. (See Chap. 23 for further discussion of Wenckebach intervals.) First-degree SA exit block cannot be recognized by ECG because SA nodal discharge is not recorded. Third-degree SA exit block can be manifested as a complete absence of P waves and is difficult to diagnose with certainty without sinus node electrograms.

Excessive vagal stimulation, acute myocarditis, infarction, or fibrosis involving the atrium, as well as drugs such as quinidine, procainamide, or digitalis, can produce SA exit block. SA exit block is usually transient. It may be of no clinical importance except to prompt a

Figure 25-5 Sinus arrest. The patient had a long-term electrocardiographic (ECG) recorder connected when he died suddenly of cardiac standstill. The rhythms demonstrate progressive sinus bradycardia and sinus arrest at 8:41 A.M. The rhythm then becomes a ventricular escape rhythm, which progressively slows and finally ceases at 8:47 A.M. Monitor lead. The double ECG strips are continuous recordings.

Figure 25-6 Sinus nodal exit block. *A,* A type I sinoatrial (SA) nodal exit block has the following features: The P-P interval shortens from the first to the second cycle in each grouping, followed by a pause. The duration of the pause is less than twice the shortest cycle length, and the cycle after the pause exceeds the cycle before the pause. The PR interval is normal and constant. Lead V_1 . *B,* The P-P interval varies slightly because of sinus arrhythmia. The two pauses in sinus nodal activity equal twice the basic P-P interval and are consistent with a type II 2:1 SA nodal exit block. The PR interval is normal and constant. Lead III.

search for the underlying cause. Occasionally, syncope can result if the SA block is prolonged and unaccompanied by an escape rhythm. SA exit block can occur in well-trained athletes[31] and can be a factor in sick sinus syndrome.[30]

Therapy for patients who have symptomatic SA exit block is as outlined for sinus bradycardia.

Wandering Pacemaker

This variant of sinus arrhythmia involves passive transfer of the dominant pacemaker focus from the sinus node to latent pacemakers that have the next highest degree of automaticity located in other atrial sites (usually lower in the crista terminalis) or in AV junctional tissue. Thus, only one pacemaker at a time controls the rhythm, in sharp contrast to AV dissociation. As with other forms of sinus arrhythmia, the change occurs in a gradual fashion over the duration of several beats. The ECG (Fig. 25-8) displays a cyclical increase in the R-R interval, a PR interval that gradually shortens and can become less than 120 milliseconds, and a change in the P wave contour, which becomes negative in lead I or II (depending on the site of discharge) or is lost within the QRS complex. Generally, these changes occur in reverse as the pacemaker shifts back to the sinus node. Rarely, the rate may remain unchanged during these P wave transitions.

Wandering pacemaker is a normal phenomenon that often occurs in the very young and particularly in athletes, presumably because of augmented vagal tone. Persistence of an AV junctional rhythm for long periods, however, may indicate underlying heart disease. *Treatment* is not usually indicated but, if necessary, is the same as that for sinus bradycardia (see above).

Figure 25-7 Sinus node exit block. After a period of atrial pacing (only the last paced cycle is shown), sinus node exit block developed. The tracing demonstrates sinus node potentials (arrowheads), recorded with a catheter electrode, not conducting to the atrium until the last complex. Recordings are leads I, II, III, and V_1 , right atrial recording, sinus node recording, and right ventricular apical recording. The bottom tracing is femoral artery blood pressure.

Hypersensitive Carotid Sinus Syndrome (see also Chap. 27)

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-9) .

Hypersensitive carotid sinus syndrome is characterized most frequently by ventricular asystole caused by cessation of atrial activity from sinus arrest or SA exit block. AV block is observed less frequently, probably in part because the absence of atrial activity from sinus arrest precludes the manifestations of AV block. However, if an atrial pacemaker maintained an atrial rhythm during the episodes, a higher prevalence of AV block would probably be noted. In symptomatic patients, AV junctional or ventricular escapes generally do not occur or are present at very slow rates, thus suggesting that heightened vagal tone and sympathetic withdrawal can suppress subsidiary pacemakers located in the ventricles, as well as supraventricular structures.

CLINICAL FEATURES.

Two types of hypersensitive carotid sinus responses are noted. *Cardioinhibitory* carotid sinus hypersensitivity is generally defined as ventricular asystole exceeding 3 seconds during carotid sinus stimulation, although normal limits have not been carefully established. In fact, asystole exceeding 3 seconds during carotid sinus massage is not common but can occur in asymptomatic subjects (see Fig. 25-9). *Vasodepressor* carotid sinus hypersensitivity is generally defined as a decrease in systolic blood pressure of 50 mm Hg or more without associated cardiac slowing or a decrease in systolic blood pressure exceeding 30 mm Hg when the patient's symptoms are reproduced.

Even if a hyperactive carotid sinus reflex is elicited in patients, particularly in older patients who complain of syncope or presyncope, the hyperactive reflex elicited with carotid sinus massage may not necessarily be responsible for these symptoms. Direct pressure or extension on the carotid sinus from head turning, neck tension, and tight collars can also be a source of syncope by reducing blood flow through the cerebral arteries.

Hypersensitive carotid sinus reflex is most commonly associated with coronary artery disease. The mechanism responsible for hypersensitive carotid sinus reflex is not known, but possibilities include a high level of resting vagal tone, hyperresponsiveness to acetylcholine, excessive release of acetylcholine, baroreflex hypersensitivity, inadequate cholinesterase activity to metabolize the acetylcholine released, and concomitant sympathetic abnormality. Carotid sinus receptors, autonomic centers of the brain stem, and the afferent limb of the reflex have all been incriminated.

Figure 25-8 Wandering atrial pacemaker. As the heart rate slows, the P waves become inverted and then gradually revert toward normal when the heart rate speeds up again. The PR interval shortens to 0.14 second with the inverted P wave and is 0.16 second with the upright P wave. This phasic variation in cycle length with varying P wave contour suggests a shift in pacemaker site and is characteristic of wandering atrial pacemaker.

MANAGEMENT.

Atropine abolishes cardioinhibitory carotid sinus hypersensitivity. However, most symptomatic patients require pacemaker implantation. It must be stressed that because AV block can occur during periods of hypersensitive carotid reflex, some form of *ventricular* pacing, with or without atrial pacing, is generally required. Atropine and pacing do not prevent the decrease in systemic blood pressure in the vasodepressor form of carotid sinus hypersensitivity,[32] which may result from inhibition of sympathetic vasoconstrictor nerves and possibly from activation of cholinergic sympathetic vasodilator fibers. Combinations of vasodepressor and cardioinhibitory types can occur, and vasodepression can account for continued syncope after pacemaker implantation in some patients. Patients who have a hyperactive carotid sinus reflex that does not cause symptoms require no treatment. Drugs such as digitalis, alpha-methyldopa, clonidine, and propranolol can enhance the response to carotid sinus massage and be responsible for symptoms in some patients. Severe vasodepressor or mixed vasodepressor and cardioinhibitory responses may require treatment with either radiation therapy or surgical denervation of the carotid sinus. Elastic support hose and sodium-retaining drugs may be helpful in patients with vasodepressor responses.

Figure 25-9 *A,* Right carotid sinus massage (RCSM, arrow) results in sinus arrest and a ventricular escape beat (probably fascicular) 5.4 seconds later. Sinus discharge then resumes. *B,* Carotid sinus massage (CSM, see arrow; monitor lead) results in slight sinus slowing but, more importantly, advanced atrioventricular block. Obviously, an atrial pacemaker without ventricular pacing would be inappropriate for this patient.

Figure 25-10 Sick sinus syndrome with bradycardia-tachycardia. Intermittent sinus arrest is apparent with junctional escape beats at irregular intervals (filled circles, top). In the *bottom* panel of this continuous monitor lead recording, a short episode of atrial flutter is followed by almost 5 seconds of asystole before a junctional escape rhythm resumes. The patient became presyncopal at this point.

Sick Sinus Syndrome

This term is applied to a syndrome encompassing a number of sinus nodal abnormalities[25] that include (1) persistent spontaneous sinus bradycardia not caused by drugs and inappropriate for the physiological circumstance, (2) sinus arrest or exit block,[29] [30] [33] (3) combinations of SA and AV conduction disturbances, or (4) alternation of paroxysms of rapid regular or irregular atrial tachyarrhythmias and periods of slow atrial and ventricular rates (bradycardia-tachycardia syndrome, Fig. 25-10). More than one of these conditions can be recorded in the same patient on different occasions, and often their mechanisms can be shown to be causally interrelated and combined with an abnormal state of AV conduction or automaticity. Animal data suggest that rapid atrial rates can "remodel" the sinus node and depress its automaticity, so the sinus tachycardia may be functional and, in part, reversible.[34]

More than one pathophysiological mechanism can produce the clinical manifestations of sick sinus syndrome. The spontaneous clinical arrhythmia and the response to electrophysiological testing (see Chap. 23) depend on the underlying mechanism of sinus nodal dysfunction. Patients who have sinus node disease can be categorized as having intrinsic sinus node disease unrelated to autonomic abnormalities or combinations of intrinsic and autonomic abnormalities. Symptomatic patients with sinus pauses and/or SA exit block frequently show abnormal responses on electrophysiological testing and can have a relatively high incidence of atrial fibrillation[35] and/or embolic episodes.[36] In children, sinus node dysfunction most commonly occurs in those with congenital or acquired heart disease, particularly following corrective cardiac surgery.[37] [38] [39] A familial disorder has also been suggested. Sick sinus syndrome can, however, occur in the absence of other cardiac abnormalities. The course of the disease is frequently intermittent and unpredictable because it is influenced by the severity of the underlying heart disease. Excessive physical training can heighten vagal tone and produce syncope related to sinus bradycardia or AV conduction abnormalities in otherwise normal individuals.

The anatomical basis of sick sinus syndrome can involve total or subtotal destruction of the sinus node, areas of nodal-atrial discontinuity, inflammatory or degenerative changes in the nerves and ganglia surrounding the node, and pathological changes in the atrial wall. Fibrosis and fatty infiltration occur, and the sclerodegenerative processes generally involve the sinus node and the AV node or the bundle of His and its branches or distal subdivisions.[40] Occlusion of the sinus node artery may be important.[41]

MANAGEMENT.

For patients with sick sinus syndrome, treatment depends on the basic rhythm problem but generally involves permanent pacemaker implantation when symptoms are manifested[42] (see Chap. 24). DDD pacing may be preferable. [43] Although medical therapy is usually ineffective in the long term, theophylline has been used.[44] Pacing for the bradycardia combined with drug therapy to treat the tachycardia is required in those with the bradycardia-tachycardia syndrome. In these patients, drug therapy without pacing can aggravate the bradycardia. Digitalis and other drugs that can affect sinus

discharge should be used cautiously in patients with sick sinus syndrome without a pacemaker. Beta blockers with intrinsic sympathetic activity may help prevent bradycardia.[45] A prolonged SA conduction time or sinus nodal recovery time at electrophysiological study in the absence of symptoms is not an indication for prophylactic pacing since therapy is directed toward control of symptoms. Adenosine has been suggested as a noninvasive test of sinus node function.[46] [47]

Figure 25-11 Sinus node reentry. After three spontaneous sinus-initiated beats, premature stimulation of the high right atrium (S_2 , S_3) initiates a sustained tachycardia at a cycle length of 450 milliseconds that has the identical high-low atrial activation sequence characteristic of sinus node discharge. This is sinus node reentry. Leads I, II, III, and V_1 are scalar leads. A = atrial electrogram; H = His electrogram; HBE = His bundle electrogram; HRA = high right atrial electrogram; RV = right ventricular electrogram; V = ventricular electrogram. Numbers are milliseconds.

Figure 25-12 Diagrammatic representation of various tachycardias. In the top portion of each example, a schematic of the presumed anatomical pathways is drawn; in the bottom half, the electrocardiographic appearance and the explanatory ladder diagram are depicted. *A,* Atrioventricular (AV) nodal reentry. In the left example, reentrant excitation is drawn with retrograde atrial activity occurring simultaneously with ventricular activity as a result of anterograde conduction over the slow AV nodal pathway (SP) and retrograde conduction over the fast AV nodal pathway (FP). In the right example, atrial activity occurs slightly later than ventricular activity because of retrograde conduction delay. *B,* Atypical AV nodal reentry caused by anterograde conduction over a fast AV nodal pathway and retrograde conduction over a slow AV nodal pathway. *C,* Concealed accessory pathway. Reciprocating tachycardia is due to anterograde conduction over the AV node and retrograde conduction over the accessory pathway. Retrograde P waves occur after the QRS complex. *D,* Sinus nodal reentry. The tachycardia is due to reentry within the sinus node, which then conducts the impulse to the rest of the heart. *E,* Atrial reentry. Tachycardia is due to reentry within the atrium, which then conducts the impulse to the rest of the heart. *F,* Automatic atrial tachycardia. Tachycardia is due to automatic discharge in the atrium, which then conducts the impulse to the rest of the heart; it is difficult to distinguish from atrial reentry. *G,* Nonparoxysmal AV junctional tachycardia. Various manifestations of this tachycardia are depicted with retrograde atrial capture, AV dissociation with the sinus node in control of the atria, and AV dissociation with atrial fibrillation.

SINUS NODAL REENTRY TACHYCARDIA

The rate of sinus nodal reentrant tachycardia varies from 80 to 200 beats/min but is generally slower than the other forms of supraventricular tachycardia, with an average rate of 130 to 140 beats/min[48] (Fig. 25-11) . Electrocardiographically, P waves are identical or very similar to the sinus P wave morphologically; the PR interval is related to the tachycardia rate, but generally the RP interval is long, with a shorter PR interval (Fig. 25-12 *D*). AV block can occur without affecting the tachycardia, and vagal maneuvers can slow and then abruptly terminate the tachycardia. Electrophysiologically, the tachycardia can be initiated and terminated by premature atrial and, uncommonly, premature ventricular stimulation (see Fig. 25-11). Initiation of sinus nodal reentry does

not depend on a critical degree of intraatrial or AV nodal conduction delay, and the atrial activation sequence is the same as during sinus rhythm. An AV nodal Wenckebach block during the tachycardia is common. The development of a bundle branch block does not affect the cycle length or PR interval during tachycardia. Prolongation of AV nodal conduction time or development of an AV nodal block can occur prior to termination of the tachycardia but does not affect sinus nodal reentry.

Sinus nodal reentry may account for 5 to 10 percent of cases of supraventricular tachycardia. It occurs in all age groups without sex predilection. Patients may be slightly older and have a higher incidence of heart disease than do patients with supraventricular tachycardia resulting from other mechanisms. Many may not seek medical attention because the relatively slow rate of the tachycardia does not result in serious symptoms. On the other hand, sinus nodal reentry may be responsible for apparent "anxiety-related sinus tachycardia" in some patients. Drugs such as beta blockers, calcium channel blockers, and digitalis may be effective in terminating and preventing recurrences of sinus node reentrant tachycardia. Catheter ablation is very effective in treating this arrhythmia when drugs fail or are not tolerated.

DISTURBANCES OF ATRIAL RHYTHM

Premature Atrial Complexes

Premature complexes are among the most common causes of an irregular pulse. They can originate from any area in the heart--most frequently from the ventricles, less often from the atria and the AV junctional area, and rarely from the sinus node. Although premature complexes arise commonly in normal hearts, they are more often associated with structural heart disease and increase in frequency with age.

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-13) .

The diagnosis of premature atrial complexes is indicated on

Figure 25-13 *A,* Premature atrial complexes (PACs) that block conduction entirely or conduct with a functional right or functional left bundle branch block. Depending on the preceding cycle length and coupling interval of the PAC, the latter blocks conduction entirely in the atrioventricular (AV) node (
) or conducts with a functional left bundle branch block (
) or functional right bundle branch block (
). *B,* A PAC on the left (arrow) initiates AV nodal reentry that is due to reentry anterogradely and retrogradely over two slow AV nodal pathways, with a retrograde P wave produced midway in the cardiac cycle. On the right, a PAC (arrow) initiates AV nodal reentry as a result of anterograde conduction over the slow pathway and retrograde conduction over the fast pathway (see Fig. 25-12 *A*), which produces a retrograde P wave in the terminal portion of the QRS complex that simulates an r wave. *C* and *D,* A PAC (

) initiating a short run of atrial flutter *(C)* and a PAC (
) depressing return of the next sinus nodal discharge *(D)*. A slightly later PAC (
) in *D* does not depress sinus nodal automaticity. *B* to *D*, Monitor leads. *E,* Diagrammatic example of the effects of a PAC. The sinus interval (A_1 -A_1) equals X. The third P wave represents a PAC (A_2) that reaches and discharges the sinoatrial (SA) node, which causes the next sinus cycle to begin at that time. Therefore, the P-P (A_2 -A_3) interval equals X+2Y milliseconds, assuming no depression of SA nodal automaticity. *(Modified from Zipes DP, Fisch C: Premature atrial contraction. Arch Intern Med 128:453, 1971.) F,* Diagram of interactions of a PAC (QRS complexes omitted) with the sinus node depending on the degree of prematurity. The top represents spontaneous sinus rhythm. The bottom is a late coupled PAC that collides with the exiting sinus impulse and therefore does not affect (or reset) the sinus pacemaker. The next sinus impulse (S3) occurs at exactly twice the sinus interval. An early coupled PAC in the next diagram is able to penetrate the sinus node and thus resets the pacemaker, thereby resulting in resetting of the sinus node (as depicted in *E*). An even earlier coupled PAC in the lower figure reaches refractory tissue around the sinus node and is thus unable to penetrate the sinus node (SN entrance block); therefore, it does not affect sinus node discharge. The next spontaneous sinus beat (S3) arrives exactly at the sinus interval.

the ECG by a premature P wave with a PR interval exceeding 120 milliseconds (except in WPW syndrome, in which case the PR interval is usually less than 120 milliseconds). Although the contour of a premature P wave can resemble that of a normal sinus P wave, it generally differs. While variations in the basic sinus rate can at times make the diagnosis of prematurity difficult, differences in the contour of the P waves are usually apparent and indicate a different focus of origin. When a premature atrial complex occurs early in diastole, conduction may not be completely normal. The AV junction may still be refractory from the preceding beat and prevent propagation of the impulse (blocked or nonconducted premature atrial complex, Fig. 25-13 *A*) or cause conduction to be slowed (premature atrial complex with a prolonged PR interval). As a general rule, the RP interval is inversely related to the PR interval; thus, a short RP interval produced by an early premature atrial complex occurring close to the preceding QRS complex is followed by a long PR interval. When premature atrial complexes occur early in the cardiac cycle, the premature P waves can be difficult to discern because they are superimposed on T waves. Careful examination of tracings from several leads may be necessary before the premature atrial complex is recognized as a slight deformity of the T wave. Often, such premature atrial complexes are blocked before reaching the ventricle and can be misinterpreted as a sinus pause or sinus exit block (Fig. 25-13 *A*).

The length of the pause following any premature complex or series of premature complexes is determined by the interaction of several factors. If the premature atrial complex occurs when the sinus node and perinodal tissue are not refractory, the impulse can be conducted into the sinus node, discharge it prematurely, and cause the next sinus cycle to begin from that time. The interval between the two normal P waves flanking a premature atrial complex that has reset the timing of the basic sinus rhythm is less than twice the normal P-P interval, and the pause after the premature atrial complex is said to be "noncompensatory." Referring to Figure 25-13 *E* and *F,* reset (noncompensatory pause) occurs when the A_1 -A_2 interval plus the A_2 -A_3 interval is less than two times the A_1 -A_1 interval and the A_2 -A_3 interval is greater than the A_1 -A_1

interval. The interval between the premature atrial complex (A_2) and the following sinus-initiated P wave (A_3) exceeds one sinus cycle but is less than "fully compensatory" (see below) because the A_2-A_3 interval is lengthened by the time that it takes the ectopic atrial impulse to conduct to the sinus node and depolarize it and then for the sinus impulse to return to the atrium. These factors lengthen the return cycle, i.e., the interval between the premature atrial complex (A_2) and the following sinus-initiated P wave (A_3) (Fig. 25-13 *E* and *F*). Premature discharge of the sinus node by an early premature atrial complex can temporarily depress sinus nodal automatic activity and cause the sinus node to beat more slowly initially (Fig. 25-13 *D*). Often when this happens, the interval between the A_3 and the next sinus-initiated P wave exceeds the A_1-A_1 interval.

Less commonly, the premature atrial complex encounters a refractory sinus node or perinodal tissue (Fig. 25-13F), in which case the timing of the basic sinus rhythm is not altered since the sinus node is not reset by the premature atrial complex, and the interval between the two normal, sinus-initiated P waves flanking the premature atrial complex is twice the normal P-P interval. The interval following this premature atrial discharge is said to be a "full compensatory pause," i.e., of sufficient duration so that the P-P interval bounding the premature atrial complex is twice the normal P-P interval. However, sinus arrhythmia can lengthen or shorten this pause. Rarely, an *interpolated premature atrial* complex may occur. In this case, the pause after the premature atrial complex is very short, and the interval bounded by the normal sinus-initiated P waves on each side of the premature atrial complex is only slightly longer than or equals one normal P-P cycle length. The interpolated premature atrial complex fails to affect the sinus nodal pacemaker, and the sinus impulse following the premature atrial complex is conducted to the ventricles, often with a slightly lengthened PR interval. An interpolated premature complex of any type represents the only type of premature systole that does not actually replace the normally conducted beat. Premature atrial complexes can originate in the sinus node and are identified by premature P waves that have a contour identical to that of the normal sinus P wave. The cycle after the premature sinus complex equals or is slightly shorter than the basic sinus cycle. Premature sinus complexes are not commonly recognized.

On occasion, when the AV node has had sufficient time to repolarize and conduct without delay, the supraventricular QRS complex initiated by the premature atrial complex can be aberrant in configuration because the His-Purkinje system or ventricular muscle has *not* completely repolarized and conducts with a functional delay or block (Fig. 25-13 *A*). It is important to remember that the refractory period of cardiac fibers is directly related to cycle length. (In an adult, the AV nodal effective refractory period is prolonged at shorter cycle lengths.) A slow heart rate (long cycle length) produces a longer His-Purkinje refractory period than does a faster heart rate. As a consequence, a premature atrial complex that follows a long R-R interval (long refractory period) can result in a functional bundle branch block (aberrant ventricular conduction). Since the right bundle branch at long cycles has a longer refractory period than the left bundle branch does, aberration with a right bundle branch block pattern at slow rates occurs more commonly than aberration with a left bundle branch block pattern. At shorter cycles, the refractory period of the left bundle branch exceeds that of the right bundle

branch, and a left bundle branch block pattern may be more likely to occur.

CLINICAL FEATURES.

Premature atrial complexes can occur in a variety of situations, e.g., during infection, inflammation, or myocardial ischemia, or they can be provoked by a variety of medications, by tension states, or by tobacco, alcohol, or caffeine. Premature atrial complexes can precipitate or presage the occurrence of sustained supraventricular (see Fig. 25-13 *B* and *C*) and, rarely, ventricular tachyarrhythmias.

MANAGEMENT.

Premature atrial complexes generally do not require therapy.[49] In symptomatic patients or when the premature atrial complexes precipitate tachycardias, treatment with digitalis, a beta blocker, or a calcium antagonist can be tried.

Atrial Flutter (see also Chap. 23)

Atrial flutter is now recognized as a macro-reentrant atrial rhythm. Typical atrial flutter (sometimes called *type I*) is a reentrant rhythm in the right atrium constrained anteriorly by the tricuspid annulus[50] and posteriorly by the crista terminalis and eustachian ridge.[51] The flutter can circulate in a counterclockwise direction around the tricuspid annulus in the frontal plane (typical flutter, counterclockwise flutter) or in a clockwise direction (atypical, clockwise, or reverse flutter).[52] [53] Since both of these forms of atrial flutter are constrained by anatomical structures, their rates and flutter wave morphology on surface ECG are consistent and predictable (see below).[52] Other forms of atrial flutter are now

Figure 25-14 Various manifestations of atrial flutter. *A,* Atrial flutter at a rate of 300 beats/min conducting impulses to ventricles with a 2:1 block. In the midportion of the tracing, carotid sinus massage converts the block to 4:1, and the ventricular rate slows to 75 beats/min. *B,* Carotid sinus massage produces a transient period of atrioventricular (AV) block clearly revealing the flutter waves. *C,* Quinidine has slowed the atrial flutter rate to approximately 188 beats/min. The block is variable. *D,* Wide QRS complexes with an rSR' configuration in V_1 begin after a short cycle that follows a long cycle in the midportion of the electrocardiogram strip. This pattern represents a functional right bundle branch block. Arrows indicate flutter waves. *E,* The QRS complexes are 0.12 second in duration and have a regular interval at a rate of 200 beats/min. Atrial activity is also regular at a rate of 300 beats/min and independent of ventricular activity (arrows). Thus, atrial flutter is present with a probable ventricular tachycardia, an example of complete AV dissociation. *F*, Adenosine injection given to a patient with an supraventricular tachycardia (SVT) at a rate of 150 beats/min reveals underlying atrial flutter, thus diagnosing the SVT as atrial flutter with 2:1 AV conduction and the flutter waves obscured within the T waves. Monitor leads in *A, B, C, E*, and *F*.

recognized as distinct types and include atrial macro-reentry caused by incisional scars from prior atrial surgery,[54] idiopathic fibrosis in areas of the atrium, or other anatomical or functional conduction barriers in the atria.[52] [53] [55] [56] Because the barriers that constrain these atrial flutters are variable, the ECG pattern of these so-called atypical atrial flutters can be varied. Oftentimes, flutter wave morphology changes during the same episode of flutter, which indicates multiple circuits and/or nonfixed conduction barriers.

ELECTROCARDIOGRAPHIC RECOGNITION.

The atrial rate during typical atrial flutter is usually 250 to 350 beats/min, although it is occasionally slower, particularly when the patient is treated with antiarrhythmic drugs, which can reduce the rate to the range of 200 beats/min. If such slowing occurs, the ventricles can respond in a 1:1 fashion to the slower atrial rate. Ordinarily, the atrial rate is about 300 beats/min, and in untreated patients the ventricular rate is half the atrial rate, i.e., 150 beats/min (Fig. 25-14 *A* and *F*). A significantly slower ventricular rate (in the absence of drugs) suggests abnormal AV conduction. In children, in patients with the preexcitation syndrome (see also Chap. 23), occasionally in patients with hyperthyroidism, and in those whose AV nodes conduct rapidly, atrial flutter can conduct to the ventricle in a 1:1 fashion and produce a ventricular rate of 300 beats/min.

In typical atrial flutter, the ECG reveals identically recurring regular sawtooth flutter waves (see Figs. 25-13 *C* and 25-14 *B* and *F*) and evidence of continual electrical activity (lack of an isoelectric interval between flutter waves), often best visualized in leads II, III, aV_f , or V_1 (Fig. 25-15) . In some instances, transient slowing of the ventricular response, either with carotid sinus massage (see Fig. 25-14 *B*) or with adenosine (see Fig. 25-14 *F*), is necessary to visualize the flutter waves. The flutter waves for (type I) typical atrial flutter are inverted (negative) in these leads because of a counterclockwise reentrant pathway, and sometimes they are upright (positive) when the reentrant loop is clockwise (see Fig 25-15). When the flutter waves are upright from clockwise rotation, they are often notched. If the AV conduction ratio remains constant, the ventricular rhythm will be regular; if the ratio of conducted beats varies (usually the result of a Wenckebach AV block), the ventricular rhythm will be irregular. Alternation between 2:1 and 4:1 AV conduction often occurs and may be due to two levels of block--2:1 high in the AV node and 3:2 lower down. The irregular ventricular response is frequently due to Wenckebach periodicity. Recurrent alternation of short and long ventricular intervals can be due to concealed conduction. Various degrees of penetration into the AV junction by flutter impulses can also influence AV conduction. The ratio of flutter waves to conducted ventricular complexes is most often an even number (e.g., 2:1, 4:1, and so on).

CLINICAL FEATURES.

Atrial flutter is less common than atrial fibrillation. Paroxysmal atrial flutter can occur in

patients without structural heart disease, whereas chronic (persistent) atrial flutter is usually associated with underlying heart disease such as rheumatic or ischemic heart disease or cardiomyopathy. It can occur as a result of atrial dilation from septal defects, pulmonary emboli, mitral or tricuspid valve stenosis or regurgitation, or chronic ventricular failure. Toxic and metabolic conditions that affect the heart, such as thyrotoxicosis, alcoholism, and pericarditis, can cause atrial flutter. Occasionally, it can be congenital, follow surgery for congenital heart disease,[57] or even occur in utero.[58] [59] In children, continued episodes of atrial flutter are associated with an increased possibility of sudden death.

Figure 25-15 Twelve-lead electrocardiogram of counterclockwise and clockwise atrial flutter. In counterclockwise atrial flutter, the flutter waves are negative in leads II, III, aV_f , and V_6 and upright in V_1 . In counterclockwise atrial flutter, the flutter waves are upright in leads II, III, and aV_f and often notched.

Atrial flutter usually responds to carotid sinus massage with a decrease in the ventricular rate in stepwise multiples and returns in reverse manner to the former ventricular rate at the termination of carotid massage (see Fig. 25-14 *A*). Very rarely, sinus rhythm follows carotid sinus massage. Exercise, by enhancing sympathetic or lessening parasympathetic tone, can reduce the AV conduction delay and produce a doubling of the ventricular rate.

Physical examination may reveal rapid flutter waves in the jugular venous pulse. If the relationship of flutter waves to conducted QRS complexes remains constant, the first heart sound will have a constant intensity. Occasionally, sounds caused by atrial contraction can be auscultated.

MANAGEMENT.

Cardioversion (see Chap. 23) is commonly the initial treatment of choice for atrial flutter since it promptly and effectively restores sinus rhythm. Cardioversion can be accomplished with synchronous direct current (DC), which often requires relatively low energies (<50 J). If the electrical shock results in atrial fibrillation, a second shock at a higher energy level is used to restore sinus rhythm, or depending on clinical circumstances, the atrial fibrillation can be left untreated. The latter can revert to atrial flutter or sinus rhythm. The short-acting antiarrhythmic medication ibutilide can also be given IV to convert atrial flutter. Ibutilide appears to successfully cardiovert about 60 to 90 percent of episodes of atrial flutter.[60] [61] [62] [63] However, because this medication prolongs the QT interval, torsades de pointes is a potential complication during and shortly after the infusion. Other medications such as procainamide can be given to chemically convert atrial flutter. *Rapid atrial pacing* with a catheter in the esophagus[64] or the right atrium can effectively terminate type I (counterclockwise and clockwise) and some forms of atypical atrial flutter in most patients and produce sinus rhythm or atrial

fibrillation with a slowing of the ventricular rate and concomitant clinical improvement.[65] [66] [67] Although the risk of thromboembolism is lower than that for atrial fibrillation, patients with atrial flutter do appear to have a risk of thromboembolism immediately after conversion to sinus rhythm.[68] [69] [70]

Verapamil (see Chap. 23) given as an initial bolus of 5 to 10 mg IV, followed by a constant infusion at a rate of 5 mg/kg/min, or *diltiazem* 0.25 mg/kg to slow the ventricular response can be tried. *Adenosine* produces a transient AV block and can be used to reveal flutter waves if diagnosis of the arrhythmias is in doubt. It will not generally terminate the atrial flutter and can provoke atrial fibrillation.[71] Esmolol, a beta-adrenergic blocker with a 9-minute elimination half-life, can be used in doses of 200 mg/kg/min to slow the ventricular rate.[72]

If the flutter cannot be electrically cardioverted, terminated by pacing, or slowed by the aforementioned drugs, a *short-acting digitalis preparation* (such as digoxin or deslanoside) can be tried alone or with a calcium antagonist or beta blocker. The dose of digitalis necessary to slow the ventricular response varies and at times can result in toxic levels because it is often difficult to slow the ventricular rate during atrial flutter. Frequently, atrial fibrillation develops after digitalis administration and can revert to normal sinus rhythm upon withdrawal of digitalis treatment; occasionally, normal sinus rhythm may occur without intervening atrial fibrillation. IV amiodarone has been shown to slow the ventricular rate as effectively as digoxin.[73]

If the atrial flutter persists, class IA or IC drugs (see Chap. 23) can be tried in an attempt to restore sinus rhythm and prevent recurrence of atrial flutter.[74] Amiodarone, especially in low doses of 200 mg/day, can also prevent recurrences. Side effects of these drugs, especially proarrhythmic responses, must be carefully considered and are dealt with at length in Chapter 23 . Sometimes, treatment of the underlying disorder, such as thyrotoxicosis, is

Figure 25-16 Atrial flutter with 1:1 conduction caused by flecainide. *Top,* Atrial flutter occurs with 2:1 conduction. *Middle,* 2:1 conduction alternates with 3:2 conduction. *Bottom*, Flecainide administration has been started, and the atrial flutter rate slows, with subsequent 1:1 conduction.

necessary to effect conversion to sinus rhythm. In certain instances, atrial flutter can continue, and if the ventricular rate can be controlled with drugs, conversion to sinus rhythm may not be indicated. Therapy with class I and III drugs should be discontinued if flutter remains.

It is important to reemphasize that class I or III drugs should *not* be used unless the ventricular rate during atrial flutter has been *slowed* with digitalis or with a calcium antagonist or beta-blocking drug.[75] Because of the vagolytic action of quinidine, procainamide, and disopyramide (see Chap. 23) , but primarily because of the ability of class I drugs to slow the flutter rate, AV conduction can be *facilitated* sufficiently to result in a 1:1 ventricular response to the atrial flutter (Fig. 25-16) .

Prevention of recurrent atrial flutter is often difficult to achieve medically but should be approached as outlined for the prevention of paroxysmal supraventricular tachycardia resulting from AV nodal reentry (see also Chap. 23). If recurrences cannot be prevented, therapy is directed toward controlling the ventricular rate when the flutter does recur with digitalis alone or combined with beta blockers or calcium antagonists. Mounting evidence indicates that the risk of emboli in atrial flutter may be more significant[68] [69] [70] than once thought.[76] Since many patients with atrial flutter also have atrial fibrillation, anticoagulation is usually warranted. However, carefully controlled studies to determine the degree of embolic risk in patients with only atrial flutter are lacking. Long-term anticoagulation, as in atrial fibrillation, should probably be considered until more definitive data are available. Radiofrequency catheter ablation of typical flutter (counterclockwise and clockwise) is highly effective at curing atrial fibrillation and has a long-term success rate of 90 to 100 percent.[77] [78] [79] Because ablation of atrial flutter is highly effective with little risk, it can be offered as an alternative to drug therapy. Ablation of other forms of atrial flutter is also effective, although success rates are somewhat lower and more variable.[54] [56] [80]

Atrial Fibrillation (see also Chap. 22)

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-17) .

This arrhythmia is characterized by wavelets propagating in different directions[81] and causing disorganized atrial depolarizations without effective atrial contraction.[82] [83] [84] Electrical activity of the atrium can be detected on ECG as small irregular baseline undulations of variable amplitude and morphology, called f waves, at a rate of 350 to 600 beats/min. At times, small, fine, rapid f waves can occur and are detectable only by right atrial leads or by intracavitary or esophageal electrodes. The ventricular response is grossly irregular ("irregularly irregular") and, in an untreated patient with normal AV conduction, is usually between 100 and 160 beats/min. In patients with WPW syndrome, the ventricular rate during atrial fibrillation can at times exceed 300 beats/min and lead to ventricular fibrillation. Atrial fibrillation should be suspected when the ECG shows supraventricular complexes at an irregular rhythm and no obvious P waves. The recognizable f waves probably do not represent total atrial activity but depict only the larger vectors generated by the multiple wavelets of depolarization that occur at any given moment.

Each recorded f wave is not conducted through the AV junction, so a rapid ventricular response comparable to the atrial rate does not occur. Many atrial impulses are concealed because of a collision of wavefronts, or they are blocked in the AV junction without reaching the ventricles (i.e., concealed conduction, which accounts for the irregular ventricular rhythm). The refractory period and conductivity of the AV node are determinants of the ventricular rate. When the ventricular rate is very rapid or very slow, it may appear to be more regular. Even though conversion of atrial fibrillation to atrial

flutter is accompanied by slowing of the atrial rate, an increase in the ventricular response can result since more atrial impulses are transmitted to the ventricle because of less concealed conduction. Also, it is easier to slow the ventricular rate during atrial fibrillation than during atrial flutter with drugs such as digitalis, calcium antagonists, and beta blockers because the increased concealed conduction makes it easier to produce an AV block.

CLINICAL FEATURES.

Atrial fibrillation is a common arrhythmia that is found in 1 percent of persons older than 60 years to more than 5 percent of patients older than 69 years.[85] The overall chance of atrial fibrillation developing over a period of two decades in patients older than 30 years, according to Framingham data, is 2 percent. Estimates are that 1 to 2 million Americans have atrial fibrillation, which occurs more commonly in men than in women.[86] In one study of men and women 65 years or older, atrial fibrillation had a prevalence of 9.1 percent in those with clinical cardiovascular disease, 4.6 percent in those with subclinical cardiovascular disease, and 1.6 percent in those without cardiovascular disease.[87] A history of congestive heart failure, valvular heart disease and stroke, left atrial enlargement, abnormal mitral or aortic valve function, treated systemic hypertension, and advanced age was independently associated with the prevalence of atrial fibrillation. Four important aspects of atrial fibrillation are etiology, control of the ventricular rate, prevention of recurrences, and prevention of thromboembolic episodes. Occult or manifested thyrotoxicosis should be considered in patients with recent-onset atrial fibrillation.[88] [89] Atrial fibrillation can be intermittent or chronic and may be influenced by autonomic activity.[90] Atrial fibrillation, whether it is persistent or intermittent, is a predictor of stroke. Symptoms as a result of atrial fibrillation are determined by multiple factors, including the underlying cardiac status, the rapid ventricular rate, and loss of atrial contraction.

Physical findings include a slight variation in intensity of the first heart sound, absence of *a* waves in the jugular venous pulse, and an irregularly irregular ventricular rhythm. Often, with fast ventricular rates a significant pulse deficit appears, during which the auscultated or palpated apical rate is faster than the rate palpated at the wrist (pulse deficit) because each contraction is not sufficiently strong to open the aortic valve or transmit an arterial pressure

Figure 25-17 Atrial fibrillation produced by "focal" mechanisms. *A*, A rapid, regular atrial tachycardia (left side of figure) at a cycle length of 200 milliseconds degenerates into atrial fibrillation (right side of figure) characterized by rapid, irregular atrial depolarizations. *B*, A premature atrial complex (marked by the asterisk) induces atrial fibrillation (right side of figure). Elimination of these focal triggers for atrial fibrillation can eliminate the atrial fibrillation.

wave through the peripheral artery. If the ventricular rhythm becomes regular in patients

with atrial fibrillation, conversion to sinus rhythm, atrial tachycardia, or atrial flutter with a constant ratio of conducted beats or the development of junctional tachycardia or VT should be suspected.

EMBOLIZATION AND ANTICOAGULATION(see alsoChap. 62) .

In addition to hemodynamic alterations, the risk of systemic emboli, probably arising in the left atrial cavity or appendage as a result of circulatory stasis, is an important consideration. Nonvalvular atrial fibrillation is the most common cardiac disease associated with cerebral embolism. In fact, almost half of cardiogenic emboli in the United States occur in patients with nonvalvular atrial fibrillation. The risk of stroke in patients with nonvalvular atrial fibrillation is five to seven times greater than that in controls without atrial fibrillation. Overall, 20 to 25 percent of ischemic strokes are due to cardiogenic emboli.

Many studies have evaluated the risk of stroke in patients with nonvalvular atrial fibrillation and the benefits of anticoagulation and antiplatelet therapy.[91] [92] [93] [94] [95] [96] [97] [98] [99] [100] Certain patients with atrial fibrillation appear to have a higher risk of emboli.[101] For example, patients with mitral stenosis and atrial fibrillation have a 4 to 6 percent incidence of embolism per year. Risk factors that predict stroke in patients with nonvalvular atrial fibrillation include a history of previous stroke or transient ischemic attack (relative risk 22.5), diabetes (relative risk 1.7), history of hypertension (relative risk 1.6), and increasing age (relative risk 1.4 for each decade). Patients with any of these risk factors have an annual stroke risk of at least 4 percent if untreated. Patients whose only stroke risk factor is congestive heart failure or coronary artery disease have stroke rates approximately three times higher than do patients without any risk factors.[102] Left ventricular (LV) dysfunction and a left atrial size greater than 2.5 cm/m^2 on echocardiographic examination are associated with thromboembolism.

Patients younger than 60 to 65 years who have a normal echocardiogram and no risk factors have an extremely low risk for stroke (1 percent per year).[103] Therefore, the risk of stroke in patients with *lone atrial fibrillation,* i.e., idiopathic atrial fibrillation in the absence of any structural heart disease or any of the above risk factors, is quite low.

The annual rate of stroke for the unanticoagulated control group in five large anticoagulation trials[104] was 4.5 percent but was reduced to 1.4 percent (68 percent risk reduction) for the warfarin-treated group (60 percent risk reduction in men; 84 percent risk reduction in women). Aspirin 325 mg/d produced a risk reduction of 44 percent. The annual rate of major hemorrhage was 1 percent for the control group, 1 percent for the aspirin group, and 1.3 percent for the warfarin group. No difference was noted in stroke risk when patients with paroxysmal (intermittent) atrial fibrillation were compared with those with constant (chronic) atrial fibrillation. Anticoagulation therapy was approximately 50 percent more effective than aspirin therapy for the prevention of ischemic stroke in patients with atrial fibrillation. Risk factors for anticoagulant-associated intracranial hemorrhage included excessive anticoagulation and poorly controlled hypertension. Elderly individuals were at increased risk for anticoagulant-associated brain hemorrhage, especially if overanticoagulated.[104]

From these and other data, it appears that individuals younger than 60 years without any clinical risk factors or structural heart disease (lone atrial fibrillation) do not require antithrombotic therapy for stroke prevention because of their low risk. The stroke rate is also low (about 2 percent per year) in patients between the ages of 60 and 75 years with lone atrial fibrillation. These patients may be adequately protected from stroke by aspirin therapy. In very elderly (older than 75 years) patients with atrial fibrillation, anticoagulation should be used with caution and carefully monitored because of the potential increased risk of intracranial hemorrhage. Nevertheless, elderly patients with atrial fibrillation are still likely to benefit from anticoagulation because they are at particularly high stroke risk.[105] Food[106] and drugs such as antibiotics and antiarrhythmics (e.g., amiodarone) can influence the effects of warfarin (see Chap. 62).

The following recommendations for antithrombotic therapy can be made[102] [105] : Any patient with atrial fibrillation who has risk factors for stroke (prior stroke or transient ischemic attack, significant valvular heart disease, hypertension, diabetes, age older than 65 years, left atrial enlargement, coronary artery disease, or congestive heart failure) should be treated with warfarin anticoagulation to achieve an international normalized ratio (INR) of 2.0 to 3.0 for stroke prevention if the individual is a good candidate for oral anticoagulation. Patients with contraindications to anticoagulation and unreliable individuals should be considered for aspirin treatment. Patients with atrial fibrillation who do not have any of the preceding risk factors have a low stroke risk (2 percent per year or less) and can be protected from stroke with aspirin. In patients older than 75 years, anticoagulation should be used with caution and monitored carefully to keep the INR less than 3.0 because of the risk of intracranial hemorrhage.[107] [108] [109] [110] [111] [112]

The risk of embolism following cardioversion to sinus rhythm in patients with atrial fibrillation varies from 0 to 7 percent, depending on the underlying risk factors. Importantly, this risk is independent of the mode of cardioversion, either by chemical (drug) or DC shock. Patients at high risk are those with prior embolism, a mechanical valve prosthesis, or mitral stenosis. Low-risk patients are those younger than 60 years without underlying heart disease. The high-risk group should receive chronic anticoagulation (see below), regardless of whether they will undergo cardioversion, and anticoagulation may not be necessary in the low-risk group. Patients not in the low-risk group who have atrial fibrillation longer in duration than 2 days should receive warfarin to achieve an INR of 2.0 to 3.0 for 3 weeks before elective cardioversion and for 3 to 4 weeks after reversion to sinus rhythm.[113] [114] An alternative strategy is to obtain a transesophageal echocardiogram to exclude the presence of an atrial thrombus. It appears that this technique predicts a group at low risk for the development of thromboembolism following cardioversion, provided that the patients are immediately treated with heparin followed by therapeutic doses of warfarin.[115] [116] [117] [118] Anticoagulation with heparin has been recommended for emergency cardioversion when 3 weeks of anticoagulation or a transesophageal echocardiogram cannot be obtained. It is important to emphasize that no matter which strategy is used, anticoagulation should be continued for at least 4 weeks following cardioversion since atrial contractile function may not fully return until then.[119] [120] [121] [122] [123]

It is important to emphasize that these suggestions must be individualized for a given patient. For example, patients at risk of trauma by virtue of occupation, participation in sports, and episodes of dizziness or syncope are at increased risk of bleeding if given anticoagulants and should probably not receive warfarin. Patients should be warned about taking any new drugs, e.g., nonsteroidal antiinflammatory agents, if they are receiving warfarin.

For patients with intermittent atrial fibrillation, guidelines are unclear. A reasonable approach would be to treat them according to the recommendations noted above, particularly if recurrences are frequent.

MANAGEMENT.

The atria are often abnormal in patients with atrial fibrillation in that they show an increased conduction time or enlargement. Maintenance of sinus rhythm after cardioversion is influenced by the duration of atrial fibrillation and, in some adults, atrial dilatation. Animal studies[83] [124] [125] [126] [127] indicate that atrial fibrillation begets atrial fibrillation; the longer the patient has atrial fibrillation, the

greater the likelihood that it will remain because of a process called electrophysiological remodeling. While similar electrophysiological abnormalities can be demonstrated in patients following short episodes of atrial fibrillation, the mechanism(s) and clinical significance are currently unknown.[128] [129] [130] [131] Nonetheless, the overall management strategies in patients with atrial fibrillation are to prevent thromboembolism (see above) and reduce symptoms. The latter is accomplished by controlling the ventricular rate during atrial fibrillation and/or restoring and maintaining sinus rhythm. Currently, no clear benefit has been ascribed to one treatment strategy over the other (rate control vs. rhythm control), particularly since antiarrhythmic drugs are not 100 percent effective and carry risks of proarrhythmia (see below). Data from large clinical studies (such as Atrial Fibrillation Follow Up Investigation of Rhythm Management [AFFIRM], Pharmacologic Intervention in Atrial Fibrillation [PIAF], and Rate Control versus Electrical Cardioversion [RACE]) will address this issue, at least in part.[132] The overall treatment strategy (i.e., ventricular rate control or restoration and maintenance of sinus rhythm) should be individualized for each patient and based on symptomatology and risk for side effects from drugs.

A patient with atrial fibrillation discovered for the first time should be evaluated for a precipitating cause, such as thyrotoxicosis, mitral stenosis, pulmonary emboli, or pericarditis. The patient's clinical status determines initial therapy, the objectives being to slow the ventricular rate and restore atrial systole. If sudden onset of atrial fibrillation with a rapid ventricular rate results in acute cardiovascular decompensation, electrical cardioversion is the initial treatment of choice. For other patients, the decision to cardiovert is largely based on the individual clinical situation. The need for restoration of

sinus rhythm must be weighed against the likelihood of successful cardioversion and long-term maintenance of sinus rhythm. While parameters such as atrial size and duration of atrial fibrillation predict the success of cardioversion in population studies, enlarged atria and atrial fibrillation of long duration are not absolute contraindications to attempted cardioversion. Internal cardioversion via intracavitary catheters can be effective when transthoracic shocks fail, particularly in obese patients or those with significant pulmonary disease.[133] [134] Alternatively, antiarrhythmic drugs that lower defibrillation thresholds such as ibutilide can be used to pretreat the patient and increase the success of DC cardioversion.[135] Recently, a biphasic waveform has been adapted to external cardioversion, which in early studies appears to require less energy than traditional external cardioversion (damped sine wave waveform) and may be more efficacious in the difficult-to-cardiovert patient.[135A] Atrial contraction may not return immediately after restoration of electrical systole, and clinical improvement may be delayed.[119] [120] DC cardioversion establishes normal sinus rhythm in over 90 percent of patients, but sinus rhythm remains for 12 months in only 30 to 50 percent. Patients with atrial fibrillation of less than 12 months' duration have a greater chance of maintaining sinus rhythm after cardioversion. For patients who do not require emergent cardioversion, chemical cardioversion with IV antiarrhythmics is effective in 35 to 75 percent of patients, depending on the population studied.[60] [61] [62] [136] Although procainamide has been used extensively for years, no well-controlled studies have been performed to determine its efficacy. Outside the United States, IV flecainide has been used with good results.[136] IV amiodarone appears to be less effective, with no difference in conversion rates from placebo. IV ibulitide is also effective in about 35 to 75 percent of patients, depending on the population studied.[60] [62] [63] [137] In the absence of decompensation, the patient can be treated with drugs such as digitalis, beta blockers, or calcium antagonists to maintain a resting apical rate of 60 to 80 beats/min that does not exceed 100 beats/min after slight exercise.[138] The combined use of digitalis and a beta blocker[72] or calcium antagonist can be helpful in slowing the ventricular rate. Digitalis may be more effective if associated LV dysfunction is present; without such dysfunction, a beta blocker may be preferable to control the ventricular rate.[139] Clonidine has been used to slow the rate.[140]

Class IA, IC,[141] and III (amiodarone, sotalol[142]) agents can be used to terminate acute-onset atrial fibrillation and prevent recurrences of atrial fibrillation.[74] No one drug, with the possible exception of amiodarone,[108] appears clearly superior, and selection is often based on the side effect profile and risk of proarrhythmia.[136] [143] [144] [145] [146] This appears to be true for newer drugs, such as azimilide and dofetilide, as well, although comparative trials have not yet been done.[146A] [146B] Most antiarrhythmic drugs increase the likelihood of maintaining sinus rhythm from about 30 to 50 percent to 50 to 70 percent of patients per year after cardioversion. However, whether it is preferable to allow atrial fibrillation to continue with just rate control is being evaluated by a multicenter trial (AFFIRM). Before electrical cardioversion, an antiarrhythmic agent is often administered for a few days to help prevent relapse of atrial fibrillation, as well as to convert some patients to sinus rhythm.[147] Rapid atrial pacing will not terminate atrial fibrillation.[124] [148] In some patients with frequent recurrence and rapid ventricular rates not controlled by drugs, AV node modification[149] or interruption by radiofrequency catheter ablation and implantation of a rate-adaptive VVI (VVIR) pacemaker can be acceptable therapy[150] [151] (see Chap. 24). Whenever possible, atrial or dual-chamber pacing is preferable since the incidence of atrial fibrillation and stroke appears to be

reduced in comparison to VVI pacing. Surgical application of the Maze procedure,[152] the atrial compartment operation,[153] and new catheter ablation approaches have been used to eliminate atrial fibrillation.[154] [155] [156] Identification of triggers (either premature atrial complexes or atrial tachycardias, see Fig. 25-17) for atrial fibrillation at electrophysiology study and ablation of these foci have been demonstrated to prevent recurrence of atrial fibrillation in some patients[157] [158] [159] (see Chap. 23). Although most of these patients have had paroxysmal atrial fibrillation and frequent premature atrial complexes without structural heart disease, the role of these triggers and the efficacy of ablation in patients with significant structural heart disease remain to be determined. There are, however, some data to suggest that even chronic atrial fibrillation is initiated by these triggers, which can potentially be ablated.[159A] An atrial defibrillator has also been designed and implanted in patients in several early studies[160] [161] [161A] (see Chap. 24). Further studies will be needed to determine its tolerability and which patients are most appropriate for this form of therapy. Atrial or dual-chamber pacing may reduce recurrences of atrial fibrillation in some patients who have intermittent episodes.[162] [163] [164] [165]

Many elderly patients tolerate atrial fibrillation well without therapy because the ventricular rate is slow as a result of concomitant AV nodal disease. These patients often have associated sick sinus syndrome, and the development of atrial fibrillation represents a cure of sorts. Such patients may demonstrate serious supraventricular and ventricular arrhythmias or asystole after cardioversion, so the likelihood of establishing and maintaining sinus rhythm should be weighed against the risks of cardioversion or other forms of therapy.

Atrial Tachycardias

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-18) .

Atrial tachycardia has an atrial rate of generally 150 to 200 beats/min with a P wave contour different from that of the sinus P wave. P waves are usually found in the second half of the tachycardia cycle[48] (long RP/short PR tachycardia).

Figure 25-18 Atrial tachycardia. This 12-lead electrocardiogram and rhythm strip (bottom) demonstrate an atrial tachycardia at a cycle length of approximately 520 milliseconds. Conduction varies between 3:2 and 2:1. Note the negative P waves in leads II, III, and aV_f and, when consecutive P waves are conducted, that the RP interval exceeds the PR interval. Note also that the tachycardia persists despite the development of atrioventricular (AV) block, an important finding that excludes the participation of an AV accessory pathway and sharply differentiates this tachycardia from the one shown in Figure 25-36 .

When the tachycardia is due to digitalis excess, the atrial rate can increase gradually as digitalis therapy is continued (a similar response can occur in nonparoxysmal AV junctional tachycardia); this increase may be associated with gradual prolongation of the

PR interval. If the atrial rate is not excessive and AV conduction is not significantly depressed by the digitalis, each P wave may conduct to the ventricles. As the atrial rate increases and AV conduction becomes impaired, a Wenckebach (Mobitz type I) second-degree AV block can ensue. This aberration is sometimes called *atrial tachycardia with block.* Frequently, other manifestations of digitalis excess are present, such as premature ventricular complexes. In nearly half the cases of atrial tachycardia with block, the atrial rate is irregular. Characteristic isoelectric intervals between P waves, in contrast to atrial flutter, are usually present in all leads. However, at rapid atrial rates, the distinction between atrial tachycardia with block and atrial flutter can be difficult. Analysis of P wave configuration during tachycardia indicates that a positive or biphasic P wave in aV_l predicts a right atrial focus whereas a positive P wave in V_1 predicts a left atrial focus.

CLINICAL FEATURES.

While atrial tachycardia occurs most commonly in patients with significant structural heart disease such as coronary artery disease, with or without myocardial infarction, cor pulmonale, or digitalis intoxication, it is also seen in patients without structural heart disease. Potassium depletion can precipitate the arrhythmia in patients taking digitalis. The signs, symptoms, and prognosis are usually related to the underlying cardiovascular status and the rate of the tachycardia.

Physical findings include a variable rhythm and intensity of the first heart sound as a result of the varying AV block and PR interval. An excessive number of *a* waves may be seen in the jugular venous pulse. Carotid sinus massage increases the degree of AV block by slowing the ventricular rate in stepwise fashion without terminating the tachycardia, as in atrial flutter. It should be performed cautiously in patients with digitalis toxicity because serious ventricular arrhythmias can result.

MANAGEMENT.

Atrial tachycardia with block in a patient not receiving digitalis is treated in a manner similar to the treatment of other atrial tachyarrhythmias. Depending on the clinical situation, digitalis, a beta blocker, or a calcium channel blocker can be administered to slow the ventricular rate, and then if atrial tachycardia remains, class IA, IC, or III drugs can be added. Catheter ablation procedures are usually effective at eliminating the atrial tachycardia, depending on the mechanism and underlying heart disease[54] [80] [166] [167] [168] (see Chap. 23). However, tachycardias can occasionally recur at a different site following a successful ablation attempt. If atrial tachycardia appears in a patient receiving digitalis, the drug should initially be assumed to be responsible for the arrthythmia. Therapy includes cessation of digitalis and administration of potassium chloride orally or IV if serum $[K^+]$ is not abnormally elevated or administration of a drug such as lidocaine, propranolol, and phenytoin while cardiac rhythm is monitored. Often, the ventricular response is not excessively fast, and simply withholding digitalis is all that is necessary.

Mechanisms: Automatic Atrial Tachycardia

Three types of atrial tachycardia have been distinguished experimentally: automatic, triggered, and reentrant atrial tachycardia. The characteristics of automatic and reentrant tachycardias will be discussed separately. Entrainment,[169] [170] resetting of curve patterns in response to overdrive pacing,[171] the patient's response to adenosine,[172] and recording of monophasic action potentials can be used to help distinguish one mechanism from the other.[173] [174] However, no clear clinical distinctions can be made between tachycardias with different mechanisms.

ELECTROCARDIOGRAPHIC FEATURES(see Fig. 25-12 *F*).

Automatic atrial tachycardia is characterized electrocardiographically by a supraventricular tachycardia that generally accelerates after its initiation, with heart rates less than 200 beats/min. The P wave contour differs from the sinus P wave, the PR interval is influenced directly by the tachycardia rate, and AV block can exist without affecting the tachycardia; i.e., it continues uninterrupted. Vagal maneuvers do not generally terminate the tachycardia, even though they can produce AV nodal block. Thus, pharmacological or physiological maneuvers that selectively result in AV block do not affect the automatic focus, nor does the development of bundle branch block alter the PR or RP interval unless it is associated with prolongation of the H-V interval.

Initiation of tachycardia with premature atrial stimulation is not generally possible but is independent of intraatrial or AV nodal conduction delay when it occurs. The atrial activation sequence usually differs from a sinus-initiated P wave, and the A-H interval is related to the tachycardia rate. The first P wave of the tachycardia is the same as the subsequent P waves of the tachycardia, in contrast to most forms of reentrant supraventricular tachycardia, in which the initial and subsequent P waves differ.[175] Usually,

Figure 25-19 Macro-reentrant atrial tachycardia in a patient who underwent atrial septal defect repair 10 years earlier. This tachycardia uses a reentrant circuit established by the atriotomy on the lateral atrial wall. Ablation to extend the scar to the tricuspid annulus eliminated this tachycardia.

the tachycardia cannot be terminated by pacing, although it can exhibit overdrive suppression. The introduction of premature atrial complexes during tachycardia merely resets the timing of the tachycardia. It is very difficult to differentiate this mechanism from micro-reentry by the leading-circle concept (see Chap. 22).

CLINICAL FEATURES.

Many supraventricular tachycardias associated with AV block are probably due to automatic atrial tachycardia,[175] including atrial tachycardia from digitalis intoxication (see Fig. 25-18). Automatic atrial tachycardia occurs in all age groups and is seen in settings of myocardial infarction, chronic lung disease (especially with acute infection), acute alcohol ingestion, and a variety of metabolic derangements. Abnormal histology can be present.[175] Differentiation from other tachycardias such as sinus nodal reentry (if the P waves of the automatic atrial tachycardia resemble the sinus-initiated P waves), atrial reentry (particularly if caused by micro-reentry), and some other mechanisms can be difficult.

Management is as discussed under atrial tachycardia from digitalis.

Mechanisms: Atrial Tachycardia Caused by Reentry

ELECTROCARDIOGRAPHIC RECOGNITION(Figs. 25-12 *E* and 25-19).

This arrhythmia is electrocardiographically manifested by a P wave that has a contour different from that of the sinus P wave, a PR interval directly influenced by the tachycardia rate, and the capability of development of an AV block without interrupting the tachycardia. Reentry can exist around a surgical scar, anatomical structure, or atriotomy incision.[54] [166] Electrophysiologically, initiation of the tachycardia occurs with premature stimulation during the atrial relative refractory period, which results in a critical degree of intraatrial conduction delay, an atrial activation sequence different from what occurs during sinus rhythm, and an AV nodal conduction time related to the tachycardia rate. Vagal maneuvers generally do not terminate the tachycardia and can produce AV block.

CLINICAL FEATURES.

Forms of atrial reentry producing atrial tachycardias include those that occur with atrial fibrosis (with pulmonary disease) or surgical atriotomy scars (see Fig. 25-19). The tachycardia can be started and stopped by an atrial extrastimulus. Spontaneous termination can be either sudden, with progressive slowing, or with alternating long-short cycle lengths.

Chaotic Atrial Tachycardia

Chaotic (sometimes called *multifocal*) atrial tachycardia is characterized by atrial rates between 100 and 130 beats/min, with marked variation in P wave morphology and totally irregular P-P intervals (Fig. 25-20) . Generally, at least three P wave contours are noted, with most P waves conducted to the ventricles. This tachycardia occurs commonly in older patients with chronic obstructive pulmonary disease and congestive heart failure and may eventually develop into atrial fibrillation. Digitalis appears to be an unusual cause, and theophylline administration has been implicated. Chaotic atrial

tachycardia can occur in childhood.

Figure 25-20 Chaotic (multifocal) atrial tachycardia. Premature atrial complexes occur at varying cycle lengths and with differing contours.

MANAGEMENT.

Management is primarily directed toward the underlying disease. Antiarrhythmic agents are often ineffective in slowing either the rate of the atrial tachycardia or the ventricular response. Beta-adrenoreceptor blockers should be avoided in patients with bronchospastic pulmonary disease but can be effective if tolerated. Verapamil and amiodarone have been useful. Potassium and magnesium replacement may suppress the tachycardia.

AV JUNCTIONAL RHYTHM DISTURBANCES

AV Junctional Escape Beats

MECHANISM.

Automatic fibers that are prevented from initiating depolarization by a pacemaker such as the sinus node, which possesses a more rapid rate of firing, are called *latent pacemakers.* Such latent pacemakers are found in some parts of the atrium, in the AV node-His bundle area, in the right and left bundle branches, and in the Purkinje system. Under usual conditions, automatic fibers are *not* found in atrial or ventricular myocardium. It is possible that the N region of the AV node is automatic, at least in some species, but is kept suppressed by neighboring atrial tissue. A latent pacemaker can become the dominant pacemaker by default or usurpation, i.e., by passive or active mechanisms. A decrease in the number of impulses arriving at a latent pacemaker site, the result of slowing of the sinus node or interruption of propagation of the normal impulse anywhere along its course, allows the latent pacemaker to escape and initiate depolarization passively, by default. An increase in the discharge rate of a latent pacemaker can capture pacemaker control actively, by usurpation. As will be seen, the implication of the two different mechanisms of ectopic impulse formation is important therapeutically.

ELECTROCARDIOGRAPHIC RECOGNITION.

An AV junctional escape beat occurs when the rate of impulse formation of the primary pacemaker, generally the sinus node, becomes less than that of the AV junctional region or when impulses from the primary pacemaker do not penetrate to the region of

the escape focus and allow the AV junctional focus to reach threshold and discharge. The interval from the last normally conducted beat to the AV junctional escape beat is a measure of the initial discharge rate of the AV junctional focus and generally corresponds to a rate of 35 to 60 beats/min (see Fig. 25-4 *B*). Although an AV junctional escape rhythm is usually fairly regular, intervals between subsequent escape beats after the initial escape beat can gradually shorten as the rate of discharge of the escape focus increases, the so-called *rhythm of development* or *warm-up phenomenon.*

The ECG displays pauses longer than the normal P-P interval, interrupted by a QRS complex of supraventricular configuration with absent, retrograde, fusion, or sinus P waves that do not conduct to the ventricle. If P waves precede the QRS, they have a PR interval generally less than 0.12 second. The exact site of impulse formation (i.e., AN, N, or NH regions; low atrium; or His bundle) is not known and may differ from patient to patient and be influenced by the cause of the arrhythmia.

Treatment, if any, lies in increasing the discharge rate of the higher pacemakers and improving AV conduction and can require pacing. Frequently, no treatment is necessary.

Premature AV Junctional Complexes

Premature AV junctional complexes are characterized by an impulse that arises prematurely in the AV junction (the exact site--i.e., AN, N, or NH regions; low atrium; or His bundle--is not known and may vary from patient to patient) and that attempts conduction in anterograde and retrograde directions. If unimpeded in its course, the impulse discharges the atrium to produce a premature retrograde P wave and a premature QRS complex with a supraventricular contour. The retrograde P wave can occur before, during, or after the QRS complex. Alterations in conduction time can influence the PR or RP relationships without a change in the site of origin of the impulse. Premature AV junctional complexes that conduct aberrantly are difficult to distinguish from premature ventricular complexes observed on scalar ECG.

Treatment of premature AV junctional complexes is not generally necessary. However, since they may arise distal to the AV node, they can occur early in the cardiac cycle and can initiate a ventricular tachyarrhythmia in some instances. Under these circumstances, therapy is approached as for premature ventricular complexes (see Chap. 23).

AV Junctional Rhythm

If the AV junctional escape beats continue for a period of time, the rhythm is called an *AV junctional rhythm* (Fig. 25-21) . Since the inherent rate of the AV junctional tissue is 35 to 60 beats/min, the AV junctional tissue can assume the role of the dominant pacemaker at this rate only by passive default of the sinus pacemaker. The ECG displays a normally conducted QRS complex, which can conduct retrogradely to the atrium or can occur independently of atrial discharge and produce AV dissociation.

An AV junctional escape rhythm can be a normal phenomenon in response to the effects of vagal tone, or it can occur during pathological sinus bradycardia or heart block. The escape beat or rhythm serves as a safety mechanism to prevent the occurrence of ventricular asystole. *Physical findings* vary depending on the P-QRS relationship. Large *a* waves in the jugular venous pulse and a loud, soft, or changing intensity of the first heart sound may be present if atrial contraction occurs when the tricuspid valve is shut.

Therapy is discussed under AV junctional escape beats (see above).

Nonparoxysmal AV Junctional Tachycardia

ELECTROCARDIOGRAPHIC RECOGNITION (Figs. 25-22 and 25-23) .

To usurp dominant pacemaker status, AV junctional tissue must exhibit an enhanced discharge rate such as during nonparoxysmal AV junctional tachycardia. The tachycardia is usually of gradual onset and termination,

Figure 25-21 Atrioventricular (AV) junctional rhythm. *Top,* AV junctional discharge occurs fairly regularly at a rate of approximately 50 beats/min. Retrograde atrial activity follows each junctional discharge. *Bottom,* Recording made on a different day in the same patient. The AV junctional rate is slightly more variable, and retrograde P waves precede onset of the QRS complex. The positive terminal portion of the P wave gives the appearance of AV dissociation, which was not present.

Figure 25-22 Nonparoxysmal atrioventricular (AV) junctional tachycardia. *A,* Control; *B,* response to carotid sinus massage; *C,* response to atropine 1 mg intravenously. Note that His bundle depolarization is the earliest recordable electrical activity in each cycle. The atria are depolarized retrogradely (low right atrial activity recorded in the BHE precedes high right atrial activity recorded in the BAE). Note also that carotid sinus massage slows the junctional discharge rate while atropine speeds it up. From these tracings alone one could not distinguish the rhythm from some other types of supraventricular tachycardia. However, the onset and termination of this tachycardia were typical of nonparoxysmal AV junctional tachycardia.

hence the modifier *nonparoxysmal.* On occasion, nonparoxysmal AV junctional tachycardia can become manifested abruptly because slowing of the dominant pacemaker may then allow sudden capture and control of the rhythm by the AV junctional focus.

Nonparoxysmal AV junctional tachycardia is recognized by a QRS of supraventricular configuration at a fairly regular rate of 70 to 130 beats/min, but it can be faster.

Accepted terminology assigns the label of tachycardia to rates exceeding 100 beats/min. The term *nonparoxysmal AV junctional tachycardia,* although not entirely correct when the rate is 70 to 100 beats/min, has generally been accepted since rates exceeding 60 beats/min in effect represent tachycardia for the AV junctional tissue. Enhanced vagal tone can slow while vagolytic agents can speed up the discharge rate. Although retrograde activation of the atria can occur, the atria are commonly controlled by an independent sinus, atrial, or on occasion, a second AV junctional focus resulting in AV dissociation (see Fig. 25-12 *G*). The ECG diagnosis can be complicated by the presence of entrance and exit blocks at the AV junctional tissue level and incomplete forms of AV dissociation.

The cause of this arrhythmia is probably *accelerated automatic discharge* in or near the His bundle. It is possible that nonparoxysmal AV junctional tachycardia originates in atrial fibers without recognition of the latter's role from analysis of the scalar ECG or on intracardiac electrograms unless a careful search is made. Wenckebach periods can occur, but the presence of exit block has not yet been demonstrated by His bundle recording in humans, and the block can be in the AV node with the origin of the nonparoxysmal AV junctional tachycardia proximal to the site of the His bundle recording.

CLINICAL FEATURES.

Nonparoxysmal AV junctional tachycardia occurs most commonly in patients with underlying heart disease, such as inferior infarction or myocarditis (often the result of acute rheumatic fever), or after open-heart surgery.[176] [177] [178] An important cause is excessive digitalis, which can also produce the ECG manifestations of varying degrees of exit block (usually the Wenckebach type) from the accelerated AV junctional focus. Junctional tachycardia occurs commonly during radiofrequency catheter ablation of the slow pathway[179] (see Chap. 23). Nonparoxysmal AV junctional tachycardia can occur in otherwise healthy individuals without symptoms (Fig. 25-23) or can be a serious and difficult-to-control tachycardia, occasionally chronic, rapid, and long lasting. It can occur congenitally in infants or children and is associated with relatively high mortality.[173] [180]

The clinical features vary depending on the rate of the arrhythmia and the underlying etiology and severity of heart disease. As in most arrhythmias, the physical signs are determined by the relationship of the P wave to the QRS complex and the rate of atrial and ventricular discharge. The first heart sound can therefore be constant or varying, and cannon *a* waves may or may not occur in the jugular venous pulse.

The ventricular rhythm can be regular or irregular, often in a constant fashion. It is especially important to recognize slowing and regularization of the ventricular rhythm in a patient with atrial fibrillation as being caused by nonparoxysmal AV junctional tachycardia and as a possible early sign of *digitalis intoxication* (see Chap. 23). Initially, during atrial fibrillation the regular ventricular rhythm can result from an AV junctional escape rhythm because the depressed AV conduction caused by digitalis blocks the passage of impulses from the fibrillating atria (see Fig. 25-12 *G*). As digitalis administration is continued, the ventricular rate can then accelerate because of increased discharge of the AV junctional pacemaker but can still be regular. Further

digitalis administration can produce a rate that is slow and irregular because of varying degrees of AV junctional exit block. The rhythm can be misdiagnosed as resumption of conduction from the fibrillating atria. The rate can then increase further because of development of VT.

MANAGEMENT.

Therapy is directed toward the underlying etiological factor and functional support of the cardiovascular system. If the rhythm is regular, cardiovascular status is not compromised, and the patient is not taking digitalis, digitalis administration could be considered. Electrical cardioversion can be tried if necessary and if digitalis toxicity is excluded; theoretically, however, if the nonparoxysmal AV junctional tachycardia is due to enhanced automaticity, cardioversion may be ineffective. If the patient tolerates the arrhythmia well, careful monitoring and attention to the underlying heart disease are usually all that are required in an adult. The arrhythmia will generally abate spontaneously. If digitalis toxicity is the cause, treatment with the drug must be stopped and potassium, lidocaine, phenytoin, or propranolol administered. Drug therapy includes agents from classes IA, IC, and III.[173] [176] [180] [181] Catheter ablation of the junctional site can be effective.[182] [183] [184] [185]

Figure 25-23 Nonparoxysmal atrioventricular junctional tachycardia in a healthy young adult. This tachycardia occurs at a fairly regular interval ("W-shaped" complexes) and is interrupted intermittently with sinus captures that produce functional right and left bundle branch blocks. Two P waves are indicated by arrows. The junctional discharge rate is approximately 120 beats/min (cycle length = 500 milliseconds) and the rhythm irregular, sometimes shortened by sinus captures or delayed by concealed conduction that resets and displaces the junctional focus. In the bottom panel, carotid sinus massage slows the junctional as well as the sinus discharge rate.

TACHYCARDIAS INVOLVING THE AV JUNCTION

Much confusion exists regarding the nomenclature of tachycardias characterized by a supraventricular QRS complex, a regular R-R interval, and no evidence of ventricular preexcitation. Because it is now apparent that a variety of electrophysiological mechanisms can account for these tachycardias (see Fig. 25-12), the nonspecific term *paroxysmal supraventricular tachycardia* has been proposed to encompass the entire group. This term may be inappropriate because some tachycardias in patients with accessory pathways (see below) are no more supraventricular than they are ventricular in origin in that they may require participation of both the atria and the ventricles in the reentrant pathway and they exhibit a QRS complex of normal contour and duration only because anterograde conduction occurs over the normal AV node-His bundle pathways (see Fig. 25-12 *C*). If conduction over the reentrant pathway reverses direction and travels in an "antidromic" direction--i.e., to the ventricles over the accessory pathway and to the atria over the AV node-His bundle--the QRS complex exhibits a prolonged

duration, although the tachycardia is basically the same. The term *reciprocating tachycardia* has been offered as a substitute for paroxysmal supraventricular tachycardia, but use of such a term presumes the mechanism of the tachycardia to be reentrant (which is probably the case for many supraventricular tachycardias). Reciprocating tachycardia is probably the mechanism of many VTs as well. Thus, no universally acceptable nomenclature exists for these tachycardias. In this chapter, descriptive titles, although cumbersome, will be used for the sake of clarity. In addition, the mechanism of reentry will be assumed to be operative when the weight of evidence supports its presence even though unequivocal proof is not always available.

AV Nodal Reentrant Tachycardia

ELECTROCARDIOGRAPHIC RECOGNITION.

Reentrant tachycardia in the AV node is characterized by a tachycardia with a QRS complex of supraventricular origin, with sudden onset and termination generally at rates between 150 and 250 beats/min (commonly 180 to 200 beats/min in adults) and with a regular rhythm. Uncommonly, the rate may be as low as 110 beats/min and occasionally, especially in children, may exceed 250. Unless functional aberrant ventricular conduction or a previous conduction defect exists, the QRS complex is normal in contour and duration. P waves are generally buried in the QRS complex. Often, the P wave is seen just prior to or just after the end of the QRS and causes a subtle alteration in the QRS complex that results in a pseudo-S or pseudo-r , which may be recognized only on comparison to the QRS complex in normal sinus rhythm (Fig. 25-24) . AV nodal reentry recorded at the onset begins abruptly, usually following a premature atrial complex that conducts with a prolonged PR interval (see Figs. 25-12 *A* and 25-13 *B*). The abrupt termination, usually with a retrograde P wave, is sometimes followed by a brief period of asystole or bradycardia. The R-R interval can shorten over the course of the first few beats at the onset or lengthen during the last few beats preceding termination of the tachycardia. Variation in cycle length is usually caused by variation in anterograde AV nodal conduction time. Cycle length and/or QRS alternans can occur, usually when the rate is very fast. Carotid sinus massage can slow the tachycardia slightly prior to its termination or, if termination does not occur, can produce only slight slowing of the tachycardia.

ELECTROPHYSIOLOGICAL FEATURES.

An atrial complex that conducts with a critical prolongation of AV nodal conduction time generally precipitates AV nodal reentry (Figs. 25-25 , 25-26 , and 25-27) . Premature ventricular stimulation can also induce AV nodal reentry in about one third of patients. Data from radiofrequency catheter ablation results[186] [187] and mapping[188] [189] [190] [191] support the presence of separate atrial inputs into the AV node, the fast and slow pathways,[192] [193] to explain this tachycardia (see Chap. 22). In Figure 22-31 , and Figure 25-12 *A* and *B*, the atria are shown as a necessary link between the fast and slow pathways. In most examples, the retrograde P wave occurs at the onset of the QRS complex, clearly excluding the possibility of an accessory pathway. If an accessory pathway in the ventricle were part of the tachycardia circuit, the ventricles would have to be activated anterogradely before the accessory pathway could be activated

retrogradely

Figure 25-24 Twelve-lead electrocardiogram of atrioventricular nodal reentrant tachycardia. *A*, During tachycardia a pseudo-r
is seen in lead V_1 (arrow) and pseudo-S waves (arrow) are seen in leads II, III, and aV_f . These waves become more obvious when compared with the QRS complexes during sinus rhythm *(B)*.

Figure 25-25 *A,* Initiation of atrioventricular (AV) nodal reentrant tachycardia in a patient with dual AV nodal pathways. *Upper* and *lower* panels show the last two paced beats of a train of stimuli delivered to the coronary sinus at a pacing cycle length of 500 milliseconds. The results of premature atrial stimulation at an S_1 -S_2 interval of 250 milliseconds on two occasions are shown. In the *upper* panel, S_2 was conducted to the ventricle with an A-H interval of 170 milliseconds and was then followed by a sinus beat. In the *lower* panel, S_2 was conducted with an A-H interval of 300 milliseconds and initiated AV nodal reentry. Note that the retrograde atrial activity occurs (arrow) prior to the onset of ventricular septal depolarization and is superimposed on the QRS complex. Retrograde atrial activity begins first in the low right atrium (HBE lead) and then progresses to the high right atrium (RA) and coronary sinus (CS) recordings. *B,* Two QRS complexes in response to a single atrial premature complex. After a basic train of S_1 stimuli at 600 milliseconds, an S_2 at 440 milliseconds is introduced. The first QRS complex in response to S_2 occurs after a short (95 milliseconds) A-H interval caused by anterograde conduction over the fast AV nodal pathway. The first QRS complex is labeled number 1 (in lead V_1). The second QRS complex in response to the S_2 stimulus (labeled number 2) follows a long A-H interval (430 milliseconds) caused by anterograde conduction over the slow AV nodal pathway.

Figure 25-26 H_1 -H_2 intervals *(left)* and A_2 -H_2 intervals *(right)* at various A_1 -A_2 intervals with a discontinuous atrioventricular (AV) nodal curve. At a critical A_1 -A_2 interval the H_1 -H_2 and the A_1 -H_2 intervals increase markedly. At the break in the curves, AV nodal reentrant tachycardia is initiated.

and depolarize the atria, thus placing the retrograde P wave no earlier than during the ST segment (see Preexcitation Syndrome, Chap. 23).

In approximately 30 percent of instances, atrial activation begins at the end of or just after the QRS complex and gives rise to a discrete P wave on the surface ECG (often appearing as a nubbin of an R in V_1) (see Fig. 25-12 *A*), whereas in the majority of patients, P waves are not seen since they are buried within the inscription of the QRS complex. In the most common variety of AV nodal reentrant tachycardia, the VA interval

(i.e., the interval between the onset of QRS and the onset of atrial activity) is less than 50 percent of the R-R interval, and the ratio of the AV to the VA interval exceeds 1.0. Most

Figure 25-27 Atrial preexcitation during atrioventricular (AV) reciprocating tachycardia in a patient with a concealed accessory pathway. No evidence of accessory pathway conduction is present in the two sinus-initiated beats shown in *A*. A premature stimulus in the coronary sinus (S) precipitates a supraventricular tachycardia at a cycle length of approximately 330 milliseconds. The retrograde atrial activation sequence begins first in the distal coronary sinus (A
, DCS), followed by activation recorded in the proximal coronary sinus (PCS), low right atrium (HBE), and then the high right atrium (not shown). The QRS complex is normal and identical to the sinus-initiated QRS complex. (The terminal portion is slightly deformed by superimposition of the retrograde atrial recording.) Note that the RP interval is short and the PR interval is long. The shortest VA interval exceeds 65 milliseconds, consistent with conduction over a retrogradely conducting AV pathway. *B,* Premature ventricular stimulation at a time when the His bundle is still refractory from anterograde activation during tachycardia shortens the A-A interval from 330 to 305 milliseconds without a change in the retrograde atrial activation sequence. (Note that no change occurs in the H-H interval when the right ventricular stimulus, S, is delivered. H-H intervals are in milliseconds in the HBE lead.) Thus the ventricular stimulus, despite His bundle refractoriness, still reaches the atrium and produces an identical retrograde atrial activation sequence. The only way that this finding can be explained is via conduction over a retrogradely conducting accessory pathway. Therefore, the patient has a concealed accessory pathway with the Wolff-Parkinson-White syndrome.

of these patients during tachycardia have a VA minimum value of 61 milliseconds measured to the earliest recorded atrial activity and 95 milliseconds measured to atrial activity recorded in the high right atrial electrogram. These VA intervals are longer in patients with tachycardia related to accessory pathways, as well as in atypical forms of AV nodal reentry (see Fig. 25-12 *B*).

SLOW AND FAST PATHWAYS.

In the majority of patients, anterograde conduction to the ventricle occurs over the slow (alpha) pathway and retrograde conduction occurs over the fast (beta) pathway (see Chap. 22 and Fig. 25-12 *A* and *B*). To initiate tachycardia, an atrial complex blocks conduction in the fast pathway anterogradely, travels to the ventricle over the slow pathway, and returns to the atrium over the previously blocked fast pathway. The proximal and distal final pathways for this circus movement appear to be located within the AV node, so as currently conceived, the circus movement occurs over the two atrial approaches and the AV node (see Fig. 25-12 *A* and *B*). The reentrant loop for typical AV nodal reentry is the anterograde slow AV nodal pathway to the final distal common pathway (probably the distal AV node), to the retrograde fast AV nodal pathway, and then to atrial myocardium. In atypical AV node reentry, the reentry occurs in the opposite direction.[194] In some patients, the His bundle may be incorporated in the reentrant circuit. Less commonly, the reentry pathway can be over two slow pathways, so-called slow-slow AV node reentry (see Fig. 25-13 *B*). Some data are consistent with

intranodal activity.[195]

The cycle length of the tachycardia generally depends on how well the slow pathway conducts because the fast pathway usually exhibits excellent capability for retrograde conduction and has the shorter refractory period in the retrograde direction. Therefore, conduction time in the anterograde slow pathway is a major determinant of the cycle length of the tachycardia.

THE DUAL-PATHWAY CONCEPT.

Evidence supporting the dual-pathway concept derives from several observations, the most compelling of which is that radiofrequency catheter ablation of *either* the slow pathway or the fast pathway eliminates AV nodal reentry without eliminating AV nodal conduction. Other observations provide supporting proof. For example, in these patients a plot of the A_1 -A_2 versus the A_2 -H_2 or the A_1 -A_2 versus the H_1 -H_2 interval shows a discontinuous curve (see Fig. 25-26). The explanation is that at a crucial A_1 -A_2 interval the impulse is suddenly blocked in the fast pathway and is conducted with delay over the slow pathway, with sudden prolongation of the A_2 -H_2 (or H_1 -H_2) interval. Generally, the A-H interval increases at least 50 milliseconds, with only a 10- to 20-millisecond decrease in the coupling interval of the premature atrial complex. Less commonly, dual pathways may be manifested by different PR or A-H intervals during sinus rhythm or at identical paced rates or by a sudden jump in the A-H interval during atrial pacing at a constant cycle length. Two QRS complexes in response to one P wave provide additional evidence[196] (see Fig. 25-25 *B*).

Some patients with AV nodal reentry may not have discontinuous refractory period curves, and some patients who do not have AV nodal reentry can exhibit discontinuous refractory curves. In the latter patients, dual AV nodal pathways can be a benign finding. Many of these patients also exhibit discontinuous curves retrogradely. Similar mechanisms of tachycardia can occur in children. Triple AV nodal pathways can be demonstrated in occasional patients. Virtually irrefutable proof of dual AV nodal pathways is the simultaneous propagation in opposite directions of two AV nodal wavefronts without collision (see Chap. 22) or the production of two QRS complexes from one P wave (Fig. 25-25 *B*) or two P waves from one QRS complex.[197]

In less than 5 to 10 percent of patients with AV nodal reentry, anterograde conduction proceeds over the fast pathway and retrograde conduction over the slow pathway (termed the *unusual form* of AV nodal reentry or atypical AV node reentry), with production of a long VA interval and a relatively short AV interval[186] [187] [188] [189] [190] [191] [193] [194] (generally AV/VA<0.75; see Fig. 25-12 *B*). Finally, it is possible to have tachycardias that use either the anterograde slow or fast pathways and conduct retrogradely over an accessory pathway (see below).

The ventricles are not needed to maintain AV nodal reentry in humans, and spontaneous AV block has been noted on occasion, particularly at the onset of the arrhythmia. Such block can take place in the AV node distal to the reentry circuit, between the AV node and bundle of His, within the bundle of His, or distal to it[198] (see

Chap. 22). Rarely, the block can be located between the reentry circuit in the AV node and the atrium. Most commonly, when block appears, it is below the bundle of His. Termination of the tachycardia generally results from a block in the anterogradely conducting slow pathway ("weak link"), so a retrograde atrial response is not followed by a His or ventricular response.

RETROGRADE ATRIAL ACTIVATION.

The sequence of retrograde atrial activation is normal during AV nodal reentrant supraventricular tachycardia, which means that the earliest site of atrial activation during retrograde conduction over the fast pathway is recorded in the His bundle electrogram, followed by electrograms recorded from the os of the coronary sinus and then spreading to depolarize the rest of the right and left atria. During retrograde conduction over the slow pathway in the atypical type of AV nodal reentry, atrial activation recorded in the proximal coronary sinus precedes atrial activation recorded in the low right atrium, which suggests that the slow and fast pathways can enter the atria at slightly different positions. Mapping at the time of surgery confirms this conclusion. Functional bundle branch block during AV nodal reentrant tachycardia does not modify the tachycardia significantly.

CLINICAL FEATURES.

AV nodal reentry commonly occurs in patients who have no structural heart disease. Symptoms frequently accompany the tachycardia and range from feelings of palpitations,[199] nervousness, and anxiety to angina, heart failure, syncope, or shock, depending on the duration and rate of the tachycardia and the presence of structural heart disease. Tachycardia can cause syncope because of the rapid ventricular rate, reduced cardiac output, and cerebral circulation or because of asystole when the tachycardia terminates as a result of tachycardia-induced depression of sinus node automaticity. The prognosis for patients without heart disease is usually good.

The hemodynamic consequences of supraventricular tachyarrhythmias in patients with normal ventricular function are due primarily to a marked decrease in LV end-diastolic and stroke volumes along with an increase in the ejection rate and cardiac output but without a significant change in the ejection fraction (EF) as the heart rate is increased and the atrial contribution to ventricular filling is lost. Heart disease or tachycardia can reduce the EF. Initial hypotension during tachycardia can evoke a sympathetic response that increases blood pressure and in turn causes a rise in vagal tone that can terminate the tachycardia.

MANAGEMENT

The Acute Attack (Table 25-2) .

Management depends on the underlying heart disease, how well the tachycardia is tolerated, and the natural history of previous attacks in the individual patient. For some patients, rest, reassurance, and sedation may be all that are required to abort an attack.

Vagal maneuvers, including carotid sinus massage, the Valsalva and Mueller maneuvers, gagging, and occasionally exposure of the face to ice water, serve as the first line of therapy. These maneuvers may slightly slow the tachycardia rate, which may then speed up to the original rate following cessation of the attempt or may terminate it. Vagal maneuvers should be tried *again* after each pharmacological approach. Digitalis, calcium antagonists, beta-adrenoceptor blockers, and adenosine normally depress conduction in the anterogradely conducting slow AV nodal pathway, whereas class IA and IC drugs depress conduction in the retrogradely conducting fast pathway.

Adenosine(see Chap. 23).

Adenosine 6 to 12 mg given rapidly IV is the initial drug of choice.[200] *Verapamil* (Chap. 23) 5 to 10 mg IV or diltiazem 0.25 to 0.35 mg/kg IV terminates AV nodal reentry successfully in about 2 minutes in approximately 90 percent of instances and is given when simple vagal manuevers and adenosine fail.

Cholinergic Drugs.

Cholinergic drugs such as *edrophonium chloride* (Tensilon), a short-acting cholinesterase inhibitor, can terminate AV nodal reentry when administered initially at a trial dose of 3 to 5 mg IV. If unsuccessful, a dose of 10 mg IV may be given. Edrophonium is infrequently needed. Similarly, *intravenous digitalis* administration is not usually necessary to terminate AV nodal reentry. If digitalis is used, digoxin can be given, 0.5 to 1.0 mg IV over a period of 10 to 15 minutes, followed by 0.25 mg every 2 to 4 hours, with a total dose less than 1.5 mg within any 24-hour period. *Oral digitalis* administration to terminate an acute attack is not generally indicated. Vagal

TABLE 25-2 -- DRUGS THAT SLOW CONDUCTION IN AND PROLONG REFRACTORINESS OF THE ACCESSORY PATHWAY AND AV NODE

AFFECTED TISSUE	DRUGS
Accessory pathway	Class IA
AV node	Class II
	Class IV
	Adenosine
	Digitalis
Both	Class IC
	Class III (amiodarone)

maneuvers that were previously ineffective can terminate the tachycardia following digitalis administration and should therefore be repeated.

Beta-adrenoceptor blockers must be used cautiously, if at all in patients with heart failure, chronic lung disease, or a history of asthma because its beta-adrenoceptor blocking action depresses myocardial contractility and can produce bronchospasm. Digitalis, calcium antagonists, beta blockers, and adenosine normally depress conduction in the anterogradely conducting slow pathway, whereas class IA and IC drugs depress conduction in the retrogradely conducting fast pathway.

DC Cardioversion.

Before digitalis or a beta blocker is administered, it is advisable to reassess the clinical status of the patient and consider whether DC cardioversion may be advisable. DC shock administered to patients who have received excessive amounts of digitalis can be dangerous and result in serious postshock ventricular arrhythmias (see Chap. 23). Particularly if signs or symptoms of cardiac decompensation occur, DC electrical shock should be considered early. DC shock, synchronized to the QRS complex to avoid precipitating ventricular fibrillation, successfully terminates AV nodal reentry with energies in the range of 10 to 50 J; higher energies may be required in some instances.

In the event that digitalis has been given in large doses and DC shock is contraindicated, competitive *atrial* or *ventricular pacing* can restore sinus rhythm. In some instances, esophageal pacing can be useful (see Chap. 24).

Class IA, IC, and III drugs are not usually required to terminate AV nodal reentry. Unless contraindicated, DC cardioversion should generally be attempted before using these agents, which are more often administered to prevent recurrence.

Pressor drugs can terminate AV nodal reentry by inducing reflex vagal stimulation mediated by baroreceptors in the carotid sinus and aorta when systolic blood pressure is acutely elevated to levels of about 180 mm Hg. One of the following drugs, diluted in 5 to 10 ml of 5 percent dextrose and water, can be given over a 1- to 3-minute period: phenylephrine (Neo-Synephrine) 0.5 to 1.0 mg, methoxamine (Vasoxyl) 3 to 5 mg, or metaraminol (Aramine) 0.5 to 2.0 mg. Pressor drugs should be used cautiously or not at all in the elderly and in patients who have structural heart disease, significant hypertension, hyperthyroidism, or acute myocardial infarction. This potentially dangerous and almost always uncomfortable mode of therapy is rarely needed unless the patient is also hypotensive.

Prevention of Recurrences.

Initially, one must decide whether the frequency and severity of the attacks warrant long-term therapy. If the attacks of paroxsymal tachycardia are infrequent, well tolerated, and short lasting and either terminate spontaneously or are easily terminated by the patient, no prophylactic therapy may be necessary. If the attacks are sufficiently frequent and/or long lasting to necessitate therapy, the patient can be treated with drugs empirically or on the basis of serial electrophysiological testing. If empirical testing is desirable, digitalis, a long-acting calcium antagonist, or a long-acting beta-adrenoceptor

blocker is a reasonable initial choice. The clinical situation and potential contraindications, e.g., beta blockers in an asthmatic, usually dictate the selection. If digitalis is used, rapid oral digitalization can be accomplished in 24 to 36 hours with digoxin at an initial dose of 1.0 to 1.5 mg, followed by 0.25 to 0.5 mg every 6 hours for a total dose of 2.0 to 3.0 mg. A less rapid oral regimen induces digitalization in 2 to 3 days with an initial dose of 0.75 to 1.0 mg, followed by 0.25 to 0.5 mg every 12 hours for a total dose of 2.0 to 3.0 mg. Alternatively, digoxin administered as a maintenance dose of 0.125 to 0.500 mg achieves digitalization in about 1 week. If any of these drugs are ineffective when taken singly, combinations can be tested.

Because it is preferable to *cure* the patient of the tachycardia rather than use potentially toxic drugs to suppress it or to implant an antitachycardia device that terminates the tachycardia only after its onset (see Chap. 23), radiofrequency catheter ablation should be considered early in the management of patients with symptomatic recurrent episodes of AV node reentry. For patients who do not wish to take drugs, patients who are drug intolerant, or those in whom drugs are ineffective, radiofrequency catheter ablation is the treatment of choice.[201] [202] It should be considered before long-term therapy with class IA, IC, or III antiarrhythmic drugs. Ablation has replaced surgery[191] [203] [204] in virtually all instances and may be considered the initial treatment of choice in many symptomatic patients.[205] [206] [207] [208] [209] [210] [211] [212] [213] [214] [215]

Reentry over a Concealed (Retrograde Only) Accessory Pathway

ELECTROCARDIOGRAPHIC RECOGNITION(see Fig. 25-27).

The presence of an accessory pathway that conducts unidirectionally from the ventricle to the atrium but not in the reverse direction is not apparent by analysis of the scalar ECG during sinus rhythm because the ventricle is not preexcited.[216] [217] Therefore, ECG manifestations of WPW syndrome are absent, and the accessory pathway is said to be "concealed." Since the mechanism responsible for most tachycardias in patients who have WPW syndrome is macro-reentry caused by anterograde conduction over the AV node-His bundle pathway and retrograde conduction over an accessory pathway, the latter, even if it only conducts retrogradely, can still participate in the reentrant circuit to cause an *AV reciprocating* tachycardia. Electrocardiographically, a tachycardia resulting from this mechanism can be *suspected* when the QRS complex is normal and the retrograde P wave occurs *after* completion of the QRS complex, in the ST segment, or early in the T wave (see Fig. 25-12 *C*).

MECHANISMS.

The cause of unidirectional propagation is not clear and can relate to multiple factors. During sinus rhythm, the atrial impulse probably enters the accessory pathway but is blocked near the ventricular insertion site with both right- and left-sided concealed accessory pathways. During functional block in patients with anterograde conduction over accessory pathways, block occurs near the ventricular insertion site most commonly with left-sided pathways but more often near the atrial insertion site with

right-sided accessory pathways.

The P wave follows the QRS complex during tachycardia because the ventricle must be activated before the propagating impulse can enter the accessory pathway and excite the atria retrogradely. Therefore, the retrograde P wave must occur after ventricular excitation, in contrast to AV nodal reentry, in which the atria are usually excited during ventricular activation (see Fig. 25-12 *A*). Also, the contour of the retrograde P wave can differ from that of the usual retrograde P wave since the atria may be activated eccentrically, i.e., in a manner other than the normal retrograde activation sequence, which starts at the low right atrial septum as in AV nodal reentry. This eccentric activation occurs because the concealed accessory pathway in most instances is left sided, i.e., inserts into the left atrium, which makes the left atrium the first site of retrograde atrial activation and causes the retrograde P wave to be negative in lead I (see Fig. 25-27).

Finally, since the tachycardia circuit involves the ventricles, if a functional bundle branch block occurs in the same ventricle in which the accessory pathway is located, the VA interval and cycle length of the tachycardia can become longer (see Fig. 25-32). This important change ensues because the bundle branch block lengthens the reentrant circuit (see Preexcitation Syndrome). For example, the normal activation sequence for a reciprocating tachycardia circuit with a left-sided accessory pathway but without a functional bundle branch block progresses from the atrium to the AV node-His bundle, to the right and left ventricles, to the accessory pathway, and then to the atrium. However, during a functional left bundle branch block, for example, the tachycardia circuit travels from the atrium to the AV node-His bundle, to the right ventricle, to the septum, to the left ventricle, to the accessory pathway, and then back to the atrium. This increase in the VA interval provides definitive proof that the ventricle and accessory pathway are part of the reentry circuit. The additional time required for the impulse to travel across the septum from the right to the left ventricle before reaching the accessory pathway and atrium lengthens the VA interval, which lengthens the cycle length of the tachycardia by an equal amount, assuming that no other changes

in conduction times occur within the circuit. Thus, lengthening of the tachycardia cycle length by more than 35 milliseconds during an ipsilateral functional bundle branch block is diagnostic of a free wall accessory pathway if the lengthening can be shown to be due to VA prolongation only and not to prolongation of the H-V interval (which can develop with the appearance of a bundle branch block). In an occasional patient, the increase in cycle length because of prolongation of VA conduction can be nullified by a simultaneous decrease in the PR (A-H) interval.

The presence of an ipsilateral bundle branch block can facilitate reentry and cause an incessant AV reentrant tachycardia.[218] A functional bundle branch block in the ventricle contralateral to the accessory pathway does not lengthen the tachycardia cycle if the

H-V interval does not lengthen.

Septal Accessory Pathway.

An exception to these observations occurs in a patient with a concealed septal accessory pathway. First, retrograde atrial activation is normal because it occurs retrogradely up the septum. Second, the VA interval and the cycle length of the tachycardia increase 25 milliseconds or less with the development of an ipsilateral functional bundle branch block.

Vagal maneuvers, by acting predominantly on the AV node, produce a response on AV reentry similar to AV nodal reentry, and the tachycardia can transiently slow and sometimes terminate. Generally, termination occurs in the anterograde direction, so the last retrograde P wave fails to conduct to the ventricle.

ELECTROPHYSIOLOGICAL FEATURES.

Electrophysiological criteria supporting the diagnosis of tachycardia involving reentry over a concealed accessory pathway include the fact that initiation of tachycardia depends on a critical degree of atrioventricular delay (necessary to allow time for the accessory pathway to recover excitability so that it can conduct retrogradely), but the delay can be in the AV node or His-Purkinje system; i.e., a critical degree of A-H delay is not necessary. Occasionally, a tachycardia can start with little or no measurable lengthening of AV nodal or His-Purkinje conduction time. The AV nodal refractory period curve is smooth, in contrast to the discontinuous curve found in many patients with AV nodal reentry. Dual AV nodal pathways can occasionally be noted as a concomitant, but unrelated finding.

Diagnosis of Accessory Pathways.

Diagnosis can be accomplished by demonstrating that during ventricular pacing, premature ventricular stimulation activates the atria before retrograde depolarization of the His bundle, thus indicating that the impulse reached the atria before it depolarized the His bundle and must have traveled a different pathway to do so. Also, if the ventricles can be stimulated prematurely during tachycardia at a time when the His bundle is refractory and the impulse still conducts to the atrium, retrograde propagation traveled to the atrium over a pathway other than the bundle of His (see Fig. 25-27 *B*). If the premature ventricular complex depolarizes the atria without lengthening of the VA interval and with the same retrograde atrial activation sequence, one assumes that the stimulation site (i.e., ventricle) is within the reentrant circuit without intervening His-Purkinje or AV nodal tissue that might increase the VA interval and therefore the A-A interval. In addition, if a premature ventricular complex delivered at a time when the His bundle is refractory terminates the tachycardia without activating the atria retrogradely, it most likely invaded and blocked conduction in an accessory pathway.

The VA interval (a measurement of conduction over the accessory pathway) is generally constant over a wide range of ventricular paced rates and coupling intervals of

premature ventricular complexes, as well as during the tachycardia in the absence of aberration. Similar short VA intervals can be observed in some patients during AV nodal reentry, but if the VA conduction time or RP interval is the same during tachycardia *and* ventricular pacing at comparable rates, an accessory pathway is almost certainly present. The VA interval is usually less than 50 percent of the R-R interval. The tachycardia can be easily initiated following premature ventricular stimulation that conducts retrogradely in the accessory pathway but blocks conduction in the AV node or His bundle. Atria and ventricles are required components of the macro-reentrant circuit, and therefore, continuation of the tachycardia in the presence of AV or VA block excludes an accessory AV pathway as part of the reentrant circuit.

CLINICAL FEATURES.

The presence of concealed accessory pathways is estimated to account for about 30 percent of patients with apparent supraventricular tachycardia referred for electrophysiological evaluation. The great majority of these accessory pathways are located between the left ventricle and left atrium and in the posteroseptal area, less commonly between the right ventricle and right atrium. It is important to be aware of a concealed accessory pathway as a possible cause of apparently "routine" supraventricular tachycardia since the therapeutic response may at times not follow the usual guidelines. Tachycardia rates tend to be somewhat faster than those occurring in AV nodal reentry (200 beats/min), but a great deal of overlap exists between the two groups.

Syncope can occur because the rapid ventricular rate fails to provide adequate cerebral circulation or because the tachyarrhythmia depresses the sinus pacemaker and causes a period of asystole when the tachyarrhythmia terminates. Physical examination reveals an unvarying, regular ventricular rhythm with constant intensity of the first heart sound. Jugular venous pressure can be elevated, but the waveform generally remains constant.

MANAGEMENT.

The therapeutic approach to terminate this form of tachycardia acutely is as outlined for AV nodal reentry. It is necessary to achieve block of a single impulse from atrium to ventricle or ventricle to atrium. Generally, the most successful method is to produce a transient AV nodal block; therefore, vagal maneuvers, IV adenosine, verapamil or diltiazem, digitalis, and beta blockers are acceptable choices. Radiofrequency catheter ablation and conventional antiarrhythmic agents that prolong the activation time or refractory period in the accessory pathway need to be considered for chronic prophylactic therapy, similar to that discussed for reciprocating tachycardias associated with the preexcitation syndrome. Radiofrequency catheter ablation is curative, has low risk, and should be considered early for symptomatic patients[215] [216] [217] [219] [220] [221] (see Chap. 23). The presence of atrial fibrillation in patients with a *concealed accessory pathway* should not be a greater therapeutic challenge than in patients who do not have such a pathway because anterograde AV conduction occurs only over the AV node and not over an accessory pathway. Intravenous verapamil and digitalis are not contraindicated. However, it must be remembered that under some circumstances, such as catecholamine stimulation, anterograde conduction can occur in the apparently

concealed accessory pathway.

Preexcitation Syndrome

ELECTROCARDIOGRAPHIC RECOGNITION (Fig. 25-28) .

Preexcitation, or the WPW ECG abnormality, occurs when the atrial impulse activates the whole or some part of the ventricle or the ventricular impulse activates the whole or some part of the atrium earlier than would be expected if the impulse traveled by way of the normal specialized conduction system only.[216] [217] This premature activation is caused by muscular connections composed of working myocardial fibers that exist outside the specialized conducting tissue and connect the atrium and ventricle while bypassing AV nodal conduction delay. They are named *accessory AV pathways* or connections and are responsible for the most common variety of preexcitation (incidentally noted in other species such as monkeys, dogs, and cats). The term *syndrome* is attached to this disorder when tachyarrhythmias occur as a result of the accessory pathway. Three basic features typify the ECG abnormalities of patients with the usual form of WPW conduction caused by an AV connection: (1) PR interval less than 120 milliseconds during sinus rhythm; (2) QRS complex duration exceeding 120 milliseconds with a slurred, slowly rising onset of the QRS in some leads (delta wave) and usually a normal terminal QRS portion; and (3) secondary ST-T wave changes that are generally directed in an opposite direction to the major delta and QRS vectors. Analysis of the scalar ECG can be used to localize the accessory pathway[222] [223] [224] [225] (Fig. 25-28 *D*). Body surface mapping can be useful.[226]

In the *WPW syndrome,* the most common tachycardia is characterized by a normal QRS, a regular rhythm, ventricular rates of 150 to 250 beats/min (generally faster than AV nodal reentry), and sudden onset and termination, in most respects behaving like the tachycardia described for conduction over a concealed pathway (see Chap. 22). The major difference between the two is the capacity for anterograde conduction over the accessory pathway during atrial flutter or atrial fibrillation (see below).

Figure 25-28 *A,* Right anteroseptal accessory pathway. The 12-lead electrocardiogram characteristically exhibits a normal to inferior axis. The delta wave is negative in V_1 and V_2 , upright in leads I, II, aVL, and aVF, isoelectric in lead III, and negative in aVR. Location was verified at surgery. The arrow indicates a delta wave (lead I). *B,* Right posteroseptal accessory pathway. Negative delta waves in leads II, III, and aVF, upright in I and aVL, localize this pathway to the posteroseptal region. The negative delta wave in V_1 with sharp transition to an upright delta wave in V_2 pinpoints it to the right posteroseptal area. Atrial fibrillation is present. Location was verified at surgery. *C,* Left lateral accessory pathway. A positive delta

wave in the anterior precordial leads and in leads II, III, and aVF, positive or isoelectric in leads I and aVL, and isoelectric or negative in V_5 and V_6 is typical of a left lateral accessory pathway. Rapid coronary sinus pacing (450-millisecond cycle length) was used to enhance preexcitation (negative P wave in leads I, II, III, aVF, and V_3 through V_6). Location was verified at surgery. *D,* Right free wall accessory pathway. The predominantly negative delta wave in V_1 and the axis more leftward than in *A* indicate the presence of a right free wall accessory pathway. *E,* Logic diagram to determine the location of accessory pathways. Begin with analysis of V_1 to determine whether the delta wave and the QRS complex are negative or positive. That establishes the ventricle in which the accessory pathway is located. Next, determine whether the delta wave and QRS complex are negative in leads II, III, and aVF. If so, the accessory pathway is located in a posteroseptal position. If the accessory pathway is located in the right ventricle, an inferior axis indicates an anteroseptal location whereas a left axis indicates a right free wall location. If the accessory pathway is located in the left ventricle, an isoelectric or negative delta wave and QRS complex in leads I, aVL, V_5 , and V_6 indicate a left lateral (free wall) location.

VARIANTS

A variety of other anatomical substrates exist and provide the basis for different ECG manifestations of several variations of the preexcitation syndrome[216] (Fig. 25-29) . Fibers from the atrium to the His bundle bypassing the physiological delay of the AV node are called *atriohisian tracts* (Fig. 25-29 *B*) and are associated with a short PR interval and a normal QRS complex. Although demonstrated anatomically (see below), the electrophysiological significance of these tracts in the genesis of tachycardias with a short PR interval and a normal QRS complex (Lown-Ganong-Levine [LGL] syndrome) remains to be established. Indeed, evidence does *not* support the presence of a specific LGL syndrome consisting of a short PR interval, normal QRS complex, and tachycardias related to an atriohisian bypass tract.

Another variant of accessory pathway conduction is that due to *atriofascicular or nodofascicular* accessory pathways. These fibers result in a unique AV conduction pattern (sometimes referred to as Mahaim conduction) characterized by the development of ventricular

preexcitation (widened QRS and short H-V interval) with a progressive increase in the AV interval in response to atrial overdrive pacing, as opposed to the behavior of the usual accessory pathway in which preexcitation occurs with short AV intervals (Fig. 25-30) . Because the accessory pathways responsible for this conduction pattern usually insert into the right bundle branch, preexcitation generally results in a left bunch branch block pattern. This phenomenon can be due to fibers passing from the AV node to the ventricle, called *nodoventricular fibers* (or nodofascicular if the insertion is into the right bundle branch rather than ventricular muscle) (see Fig. 25-29 *C*). For nodoventricular connections, the PR interval may be normal or short, and the QRS complex is a fusion beat. This pattern of preexcitation can also result from *atriofascicular* accessory pathways. These fibers almost always represent a duplication of the AV node and the distal conducting system and are located in the right ventricular free wall. The apical end lies close to the lateral tricuspid annulus and conducts slowly,

with AV node-like properties. After a long course, the distal portion of these fibers, which conducts rapidly, inserts into the distal right bundle branch or the apical region of the right ventricle.[216] [227] [228] [229] No preexcitation is generally apparent during sinus rhythm but can be exposed by premature right atrial stimulation. The absence of retrograde conduction in these pathways produces only an antidromic AV reentry tachycardia ("preexcited" tachycardia) characterized by anterograde conduction over the accessory pathway and retrograde conduction over the right bundle branch-His bundle-AV node, thus making the atrium a necessary part of the circuit. The preexcited tachycardia has a left bundle branch block pattern, long AV interval (because of the long conduction time over the accessory pathway), and short VA interval. A right bundle branch block can be proarrhythmic by increasing the length of the tachycardia circuit (the VA interval is prolonged because of a delay in retrograde activation of the His bundle), and the tachycardia can become incessant.[216] [227]

In patients who have an atriohisian tract, theoretically, the QRS complex would remain normal and the short A-H interval fixed or show very little increase during atrial pacing at more rapid rates. This response is very uncommon. Rapid atrial pacing in patients who have

nodoventricular or nodofascicular connections shortens the H-V interval and widens the QRS complex, with production of a left bundle branch block contour, but in contrast to the situation in patients who have an AV connection (Fig. 25-31) , the AV interval also lengthens. In patients who have fasciculoventricular connections, the H-V interval remains short and the QRS complex unchanged and anomalous during rapid atrial pacing.

ELECTROPHYSIOLOGICAL FEATURES OF PREEXCITATION(see Figs. 25-29 to 25-38).

If the accessory pathway is capable of anterograde conduction, two parallel routes of AV conduction are possible, one subject to physiological delay over the AV node and the other passing directly without delay from the atrium to the ventricle. This direct route of conduction produces the typical QRS complex that is a fusion beat as a result of depolarization of the ventricle in part by the wavefront traveling over the accessory pathway and in part by the wavefront traveling over the normal AV node-His bundle route. The delta wave represents ventricular activation from input over the accessory pathway. The extent of the contribution to ventricular deplorization by the wavefront over each route depends on their relative activation times. If AV nodal conduction delay occurs because of a rapid atrial pacing rate or premature atrial complex, e.g., more of the ventricle becomes activated over the accessory pathway, and the QRS complex becomes more anomalous in contour. Total activation of the ventricle over the accessory pathway can occur if the AV nodal conduction delay is sufficiently long. In contrast, if the accessory pathway is relatively far from the sinus node, e.g., a left lateral accessory pathway, or if the AV nodal conduction time is relatively short, more of the ventricle may be activated by conduction over the normal pathway (see Fig. 25-31). The normal fusion beat during sinus rhythm has a short H-V interval, or His bundle

activation actually begins after the onset of ventricular depolarization because part of the atrial impulse bypasses the AV node and activates the ventricle

Figure 25-29 Schematic representation of accessory pathways. *A,* The "usual" atrioventricular (AV) accessory pathway giving rise to most clinical manifestations of tachycardia associated with Wolff-Parkinson-White (WPW) syndrome. *B,* The very uncommon atriohisian accessory pathway. If the Lown-Ganong-Levine syndrome exists, it would have this type of anatomy, which has been demonstrated on occasion histopathologically. *C,* Nodoventricular pathways, original concept, in which anterograde conduction travels down the accessory pathway with retrograde conduction in the bundle branch-His bundle-AV node (see below). *D,* Fasciculoventricular connections, which are not thought to play an important role in the genesis of tachycardias. *E,* The current concept of nodofascicular accessory pathway in which the accessory pathway is an AV communication with AV nodal-like properties. Sinus rhythm results in a fusion QRS complex, as in the usual form of WPW syndrome shown in *A*. Maximum preexcitation results in ventricular activation over the accessory pathway, and the His bundle is activated retrogradely. During reciprocating tachycardia, anterograde conduction occurs over the accessory pathway with retrograde conduction over the normal pathway. (*E* from Benditt DG, Milstein S: Nodoventricular accessory connection: A misnomer or a structural/functional spectrum. J Cardiovasc Electrophysiol 1:231, 1990.)

Figure 25-30 Development of preexcitation over an atriofascicular accessory pathway. During atrial pacing (S), on the left side of the figure, conduction occurs down the atrioventricular node as evidenced by a normal-appearing QRS complex and a normal H-V interval. The stimulus marked by the arrow conducts the impulse down an atriofascicular fiber, which results in a preexcited QRS, as evidenced by a widened QRS and short H-V interval.

Figure 25-31 Atrial pacing at different atrial sites illustrating different conduction over the accessory pathway. *A,* High right atrial pacing at a cycle length of 500 milliseconds produces anomalous activation of the ventricle (note the upright QRS complex in V_1) and a stimulus-delta interval of 155 milliseconds. This interval indicates that the time from the onset of the stimulus to the beginning of the QRS complex is relatively long because the stimulus is delivered at a fairly large distance from the accessory pathway. Note that His bundle activation (H) occurs at about the onset of the QRS complex. *B,* Atrial pacing occurs through the distal coronary sinus electrode (DCS). At the same pacing cycle length, DCS pacing results in more anomalous ventricular activation and a shorter stimulus-delta interval (80 milliseconds). His bundle activation is now buried within the inscription of the ventricular electrogram in the HBE lead. *C,* Pacing from the proximal coronary sinus electrode (PCS) results in the shortest stimulus-delta interval (45 milliseconds); such an interval indicates that the pacing stimulus is being delivered very close to the atrial insertion of the accessory pathway, which is located in the left posteroseptal region of the atrioventricular groove.

Figure 25-32 *A,* Recording of depolarization of an accessory pathway (AP) with a catheter electrode. The first QRS complex illustrates conduction over the AP. In the scalar ECG, a short P-R interval and delta wave (best seen in leads I and V_1) are apparent. His bundle activation is buried within the ventricular complex. In the following complex, conduction has blocked over the AP and a normal QRS complex results. His bundle activation clearly precedes the onset of ventricular depolarization by 45 milliseconds. The A-H interval for this complex is 90 milliseconds. *(From Prystowsky EN, Browne KF, Zipes DP: Intracardiac recording by catheter electrode of accessory pathway depolarization. J Am Coll Cardiol 1:468, 1983. Reprinted with permission from the American College of Cardiology.) B,* Influence of functional ipsilateral bundle branch block on the VA interval during an atrioventricular reciprocating tachycardia. Partial preexcitation can be noted in the sinus-initiated complex (first complex). Two premature ventricular stimuli (S_1 , S_2) initiate a sustained supraventricular tachycardia that persists with a left bundle branch block for several complexes before finally reverting to normal. The retrograde atrial activation sequence is recorded first in the proximal coronary sinus lead (arrow, PCS), then in the distal coronary sinus lead (DCS) and low right atrium (HBE), and then high in the right atrium (HRA). During the functional bundle branch block, the VA interval in the PCS lead is 140 milliseconds, which shortens to 110 milliseconds when the QRS complex reverts to normal. Such behavior is characteristic of a left-sided accessory pathway with prolongation of the reentrant pathway by the functional left bundle branch block.

early, at a time when the atrial impulse traveling the normal route just reaches the His bundle. This finding of a short or negative H-V interval occurs *only* during conduction over an accessory pathway or from retrograde His activation during a complex originating in the ventricle, such as a VT.

Pacing the atrium at rapid rates, at premature intervals, or from a site close to the atrial insertion of the accessory pathway accentuates the anomalous activation of the ventricles and shortens the H-V interval even more (His activation may become buried in the ventricular electrogram, as in Fig. 25-31 *B*). The position of the accessory pathway can be determined by careful analysis of the spatial direction of the delta wave in the 12-lead ECG in maximally preexcited beats[222] [223] [224] [225] (see Fig. 25-28). T wave abnormalities can occur after the disappearance of preexcitation with orientation of the T wave according to the site of preexcitation (T wave memory). A variety of electrical, radionuclide, and echocardiographic techniques can be used to localize the insertion site of the accessory pathway (see Chap. 23).

ACCESSORY PATHWAY CONDUCTION.

Even though the accessory pathway conducts more rapidly than the AV node (conduction velocity is faster in the accessory pathway), the accessory pathway usually has a longer refractory period during long cycle lengths (e.g., sinus rhythm)--i.e., it takes longer for the accessory pathway to recover excitability than it does for the AV node. Consequently, a premature atrial complex can occur sufficiently early to block conduction anterogradely in the accessory pathway and conduct to the ventricle only over the normal AV node-His bundle (Fig. 25-33 *A* and *B*). The resultant H-V interval and the QRS complex become normal. Such an event can initiate the most common type of reciprocating tachycardia, one characterized by anterograde conduction over the normal pathway and retrograde conduction over the accessory pathway *(orthodromic AV reciprocating tachycardia*) (Fig. 25-33) . The accessory pathway, which blocks

conduction in an anterograde direction, recovers excitability in time to be activated after the QRS complex in a retrograde direction, thereby completing the reentrant loop.

Much less commonly, patients can have tachycardias called *antidromic* tachycardias during which anterograde conduction occurs over the accessory pathway and retrograde conduction over the AV node. The resultant QRS complex is abnormal because of total ventricular activation over the accessory pathway (Figs. 25-33 *C* and 25-34). In both tachycardias, the accessory pathway is an obligatory part of the reentrant circuit. In patients with bidirectional conduction over the accessory pathway, different fibers can be used anterogradely and retrogradely.

A small percentage of patients have multiple accessory pathways often suggested by various ECG clues, and on occasion, tachycardia can be due to a reentrant loop conducting anterogradely over one accessory pathway and retrogradely over the other. Interestingly, 15 to 20 percent of patients may exhibit AV nodal echoes or AV nodal reentry after interruption of the accessory pathway.

Figure 25-33 Schematic diagram of tachycardias associated with accessory pathways. *A,* Orthodromic tachycardia with anterograde conduction over the atrioventricular (AV) node-His bundle route and retrograde conduction over the accessory pathway (left sided for this example as depicted by left atrial activation preceding right atrial activation). *B,* Orthodromic tachycardia and ipsilateral functional bundle branch block. *C,* Antidromic tachycardia with anterograde conduction over the accessory pathway and retrograde conduction over the AV node-His bundle. *D,* Orthodromic tachycardia with a slowly conducting accessory pathway. *E,* Atrial fibrillation with the accessory pathway as a bystander. *F,* Anterograde conduction over a portion of the AV node and a nodoventricular pathway and retrograde conduction over the AV node.

Figure 25-34 Antidromic atrioventricular (AV) reciprocating tachycardia. Tachycardia in this example is due to anterograde conduction over the accessory pathway (note the abnormal QRS complex of a left posterior accessory pathway) and a normal retrograde atrial activation sequence (beginning first in the HBED lead), which is due to retrograde conduction over the AV node. Tachycardia cycle length is 390 milliseconds, with a VA interval of 300 milliseconds measured in the high right atrial lead, 260 milliseconds in the distal His lead, and 280 milliseconds in the proximal coronary sinus lead. I, II, III, and V_1 are scalar leads. DCS = distal coronary sinus lead; HBEP and HBED leads = His bundle electrogram, proximal and distal; HRA = high right atrial electrogram; MCS1-3 = midcoronary sinus leads; PCS = proximal coronary sinus; RV = right ventricular electrogram.

PERMANENT FORM OF AV JUNCTIONAL RECIPROCATING TACHYCARDIA.

An incessant form of supraventricular tachycardia has been recognized that generally occurs with a long RP interval that exceeds the PR interval (Figs. 25-35 and 25-36). Usually, a posteroseptal accessory pathway (most often the right ventricular but other

locations as well[230]) that conducts very slowly, possibly because of a long and tortuous route, appears responsible. Tachycardia is maintained by anterograde AV nodal conduction and retrograde conduction over the accessory pathway (see Fig. 25-33 *D*). While anterograde conduction over this pathway has been demonstrated, the long anterograde conduction time over the accessory pathway ordinarily prevents ECG manifestations of accessory pathway conduction during sinus rhythm. Therefore, during sinus rhythm, the QRS is prolonged from conduction over this accessory pathway only when conduction times through the AV node-His bundle exceed those in the accessory pathway.[216] [217]

RECOGNITION OF ACCESSORY PATHWAYS.

When retrograde atrial activation during tachycardia occurs over an accessory pathway that connects the left atrium to the left ventricle, the earliest retrograde activity is recorded from a left atrial electrode usually positioned in the coronary sinus (see Fig. 25-27). When retrograde atrial activation during tachycardia occurs over an accessory pathway that connects the right ventricle to the right atrium, the earliest retrograde atrial activity is generally recorded from a lateral right atrial electrode. Participation of a septal accessory pathway creates the earliest retrograde atrial activation in the low right portion of the atrium situated near the septum, anterior or posterior, depending on the insertion site. These mapping techniques with catheter electrodes and at the time of surgery (see Chap. 23) provide an accurate assessment of the position of the accessory pathway, which can be anywhere in the AV groove except in the intervalvular trigone between the mitral valve and the aortic valve annuli. Recording electrical activity directly from the accessory pathway obviously provides precise localization.

It may be difficult to distinguish AV nodal reentry from participation of a septal accessory connection using the retrograde sequence of atrial activation because activation sequences during both tachycardias are similar. Other approaches to demonstrate retrograde atrial activation over the accessory pathway must be tried and can be accomplished by inducing premature ventricular complexes during tachycardia to determine whether retrograde atrial excitation can occur from the ventricle at a time when the His bundle is refractory (see Fig. 25-27 *B*). Since VA conduction cannot occur over the normal conduction system because the His bundle is refractory, an accessory pathway must be present for the atria to become excited. No patient with a reciprocating tachycardia from an accessory AV pathway has a VA interval of less than 70 milliseconds measured from the onset of ventricular depolarization to the onset of the earliest atrial activity recorded on an esophageal lead or a VA interval of less than 95 milliseconds when measured to the high right part of the atrium. In contrast, in the majority of patients with reentry in the AV node, intervals from the onset of ventricular activity to the earliest onset of atrial activity recorded in the esophageal lead are less than 70 milliseconds.

Other Forms of Tachycardia in Patients with Wolff-Parkinson-White Syndrome

Patients can have other types of tachycardia during which the accessory pathway is a "bystander," i.e., uninvolved in the mechanism responsible for the tachycardia, such as AV nodal reentry or an atrial tachycardia that conducts to the ventricle over the

accessory pathway. In patients with atrial flutter or atrial fibrillation, the accessory pathway is not a requisite part of the mechanism responsible for tachycardia, and the flutter or fibrillation occurs in the atrium unrelated to the accessory pathway (see Fig. 25-33 *E*). Propagation to the ventricle during atrial flutter or atrial fibrillation can therefore occur over the normal AV node-His bundle or accessory pathway. Patients with WPW syndrome who have atrial fibrillation almost always have inducible reciprocating tachycardias as well, which can develop into atrial fibrillation (Fig. 25-37) . In fact, interruption of the accessory pathway and elimination of AV reciprocating tachycardia usually prevent recurrence of the atrial fibrillation. Atrial fibrillation presents a potentially serious risk because of the possibility for very rapid conduction over the accessory pathway. At more rapid rates, the refractory period of the accessory pathway can shorten significantly and

Figure 25-35 Termination of the permanent form of atrioventricular (AV) junctional reciprocating tachycardia (PJRT). In the left portion of this example, PJRT is present. The atrial activation sequence is indistinguishable from atypical AV nodal reentry and atrial tachycardia originating in the low right atrium. The response to premature stimulation(s) identifies the tachycardia as PJRT. Premature ventricular stimulation (arrowhead) occurs at a time when the His bundle is refractory from depolarization during the tachycardia (second labeled H). Therefore, premature ventricular stimulation cannot enter the AV node. Furthermore, premature ventricular stimulation does not reach the atrium. Yet premature ventricular stimulation terminates the tachycardia. This detail can only be explained by the premature ventricular complex invading and blocking in a retrogradely conducting accessory pathway. I, II, III, and V_1 are scalar electrocardiographic leads. DCS = distal coronary sinus electrograms; HBEP, HBED = His bundle electrogram, proximal and distal; HRA = high right atrial electrogram; MCS1, MCS2 = midcoronary sinus electrograms; PCS = proximal coronary sinus electrogram; RV = right ventricular electrogram.

permit an extremely rapid ventricular response during atrial flutter or atrial fibrillation (see Fig. 25-28 *B*). The rapid ventricular response can exceed the ability of the ventricle to follow in an organized manner; it can result in fragmented, disorganized ventricular activation and hypotension and lead to ventricular fibrillation (Fig. 25-38) . Alternatively, a supraventricular discharge bypassing AV nodal delay can activate the ventricle during the vulnerable period of the antecedent T wave and precipitate ventricular fibrillation. Patients who have had ventricular fibrillation have ventricular cycle lengths during atrial fibrillation in the range of 200 milliseconds or less.

Patients with preexcitation syndrome can have other causes of tachycardia such as AV nodal reentry, sometimes with dual AV nodal curves, sinus nodal reentry, or even VT unrelated to the accessory pathway. Some accessory pathways can conduct anterogradely only; more commonly, pathways conduct retrogradely only. If the pathway conducts only anterogradely, it cannot participate in the usual form of reciprocating tachycardia (see Fig. 25-33 *A*). It can, however, participate in antidromic tachycardia (Fig. 25-33 *C*), as well as conduct to the ventricle during atrial flutter or atrial fibrillation (Fig. 25-33 *E*). Some data suggest that the accessory pathway demonstrates automatic

activity, which could conceivably be responsible for some instances of tachycardia.

"WIDE QRS TACHYCARDIAS."

In patients with the preexcitation syndrome, so-called wide QRS tachycardias can be due to multiple mechanisms, including sinus or atrial tachycardias, AV nodal reentry, and atrial flutter or fibrillation with anterograde conduction over the accessory pathway; orthodromic reciprocating tachycardia with functional or preexisting bundle branch block; antidromic reciprocating tachycardia; reciprocating tachycardia with anterograde conduction over one accessory pathway and retrograde conduction over a second one; tachycardias using nodofascicular or atriofascicular fibers; or VT.[231]

CLINICAL FEATURES.

The reported incidence of preexcitation syndrome depends in large measure on the population studied and varies from 0.1 to 3.0 per thousand in apparently healthy subjects, with an average of about 1.5 per thousand. The incidence of the ECG pattern of WPW conduction in 22,500 healthy aviation personnel was 0.25 percent with a prevalence of documented tachyarrhythmias of 1.8 percent. Left free wall accessory pathways are most common, followed in frequency by posteroseptal, right free wall, and anteroseptal locations. WPW syndrome is found in all age groups from the fetal and neonatal periods to the elderly, as well as in identical twins. The prevalence is higher in males and decreases with age, apparently because of loss of preexcitation. The majority of adults with preexcitation syndrome have normal hearts, although a variety of acquired and congenital cardiac defects have been reported, including Ebstein anomaly,[232] mitral valve prolapse,[233] and cardiomyopathies. Patients with Ebstein anomaly (see Chaps. 43 and 44) often have multiple accessory pathways, right sided either in the posterior septum or in the posterolateral wall, with preexcitation localized to the atrialized ventricle. They often have reciprocating tachycardia with a long VA interval and a right bundle branch block morphology.

The frequency of paroxysmal tachycardia apparently increases with age, from 10 per 100 patients with WPW syndrome in a 20- to 39-year-old age group to 36 per 100 in

Figure 25-36 Permanent form of junctional reciprocating tachycardia (PJRT) in a patient with a left-sided accessory pathway. The 12-lead electrocardiogram demonstrates a long RP interval-short PR interval tachycardia, which in contrast to the usual form of PJRT, exhibits negative P waves in leads I and aV_L . The rhythm strips below (lead I) indicate that whenever a nonconducted P wave occurs, the tachycardia always terminates, only to begin again after several sinus beats. This pattern is in marked contrast to that in Figure 25-14 , in which the tachycardia continues despite nonconducted P waves.

patients older than 60 years. Approximately 80 percent of patients with tachycardia have

a reciprocating tachycardia, 15 to 30 percent have atrial fibrillation, and 5 percent have atrial flutter. VT occurs uncommonly. The anomalous complexes can mask or mimic myocardial infarction (see Chap. 35), bundle branch block, or ventricular hypertrophy, and the presence of the preexcitation syndrome can call attention to an associated cardiac defect. The prognosis is excellent in patients without tachycardia or an associated cardiac anomaly. For most patients with recurrent tachycardia the prognosis is good, but sudden death occurs rarely,[234] with an estimated frequency of 0.1 percent.[235]

Figure 25-37 Atrioventricular (AV) reciprocating tachycardia disorganizing into atrial fibrillation. During sustained AV reciprocating tachycardia at a cycle length of approximately 265 milliseconds, the retrograde atrial activation sequence began first in the right paraseptal region (not shown in this example; location proved at surgery) and was then recorded in the proximal coronary sinus electrogram, followed by atrial activity in the distal coronary sinus, in the low right atrium recorded in the His bundle lead, and then in the high right atrium. Spontaneously, the atrial activation sequence becomes irregular (after the last A
) and atrial fibrillation begins. Note that the last QRS complex reflects conduction over the accessory pathway. Such a transformation occurred repeatedly in this patient and was associated with quickening of the ventricular rate. Atrial fibrillation did not recur following surgical interruption of the accessory pathway.

Figure 25-38 Atrial fibrillation (AF) becoming ventricular fibrillation (VF). In the left portion of this panel, the electrocardiogram (ECG) demonstrates AF with conduction over an accessory pathway producing a rapid ventricular response, at times in excess of 350 beats/min. In the midportion of the tracing VF can be seen to develop. I, II, III, and V_1 are scalar ECG leads. HRA = high right atrial electrogram; RVA = right ventricular apex electrogram.

It is very likely that an accessory pathway is congenital, although its manifestations can be detected in later years and appear to be "acquired." Relatives of patients with preexcitation, particularly those with multiple pathways, have an increased prevalence of preexcitation, thus suggesting a hereditary mode of acquisition. Some children and adults can lose their tendency for the development of tachyarrhythmias as they grow older, possibly as a result of fibrotic or other changes at the site of the accessory pathway insertion. Pathways can lose their ability to conduct anterogradely. Tachycardia beginning in infancy can disappear but frequently recurs. Tachycardia still present after 5 years of age persists in 75 percent of patients regardless of accessory pathway location. Intermittent preexcitation during sinus rhythm and abrupt loss of conduction over the accessory pathway after intravenous ajmaline or procainamide and with exercise suggest that the refractory period of the accessory pathway is long and that the patient is not at risk for a rapid ventricular rate should atrial flutter or fibrillation develop. These approaches are relatively specific, but not very sensitive, with a low positive predictive accuracy. Exceptions to these safeguards can occur.

TREATMENT.

Patients with ventricular preexcitation who have only the ECG abnormality, without tachyarrhythmias, do not require electrophysiological evaluation or therapy. However, for patients with frequent episodes of symptomatic tachyarrhythmia, therapy should be initiated.

Three therapeutic options exist: electrical or surgical (see Chap. 23) ablation and pharmacological therapy. Drugs are chosen to prolong conduction time and/or refractoriness in the AV node, the accessory pathway, or both to prevent rapid rates from occurring. If successful, this therapy prevents maintenance of an AV reciprocating tachycardia or a rapid ventricular response to atrial flutter or atrial fibrillation. Some drugs can suppress premature complexes that precipitate the arrhythmias.

Adenosine, verapamil, propranolol, and digitalis all prolong conduction time and refractoriness in the AV node. Verapamil and propranolol do not directly affect conduction in the accessory pathway, and digitalis has had variable effects. Because digitalis has been reported to shorten refractoriness in the accessory pathway and speed the ventricular response in some patients with atrial fibrillation, it is advisable to *not* use digitalis as a single drug in patients with WPW syndrome who have or may undergo atrial flutter or atrial fibrillation. Since atrial fibrillation can develop *during* the reciprocating tachycardia in many patients (see Fig. 25-37) , this caveat probably applies to *all* patients who have tachycardia and WPW syndrome. Rather, drugs that prolong the refractory period in the accessory pathway should be used, such as class IA and IC drugs (see Chap. 23).

Class IC drugs,[236] [237] amiodarone,[238] and sotalol can affect both the AV node and the accessory pathway. Lidocaine does not generally prolong refractoriness of the accessory pathway. Verapamil and IV lidocaine can *increase* the ventricular rate during atrial fibrillation in patients with WPW syndrome. IV verapamil can precipitate *ventricular fibrillation* when given to a patient with WPW syndrome who has a rapid ventricular rate during atrial fibrillation. This effect does not appear to happen with *oral* verapamil. Catecholamines can expose WPW syndromes, shorten the refractory period of the accessory pathway, and reverse the effects of some antiarrhythmic drugs.[239]

Termination of an Acute Episode.

Termination of an acute episode of reciprocating tachycardia, suspected electrocardiographically from a normal QRS complex, regular R-R intervals, a rate of about 200 beats/min, and a retrograde P wave in the ST segment, should be approached similar to AV nodal reentry. After vagal maneuvers, adenosine followed by IV verapamil or diltiazem is the initial treatment of choice. It is important to note that atrial fibrillation can occur after drug administration, particularly adenosine, with a rapid ventricular response. An external cardioverter-defibrillator should be immediately available if necessary. For atrial flutter or fibrillation, the latter suspected from an anomalous QRS complex and grossly irregular R-R intervals (see Figs. 25-28 *B* and

25-37), drugs must be used that prolong refractoriness in the accessory pathway, often coupled with drugs that prolong AV nodal

refractoriness (e.g., procainamide and propranolol). In many patients, particularly those with a very rapid ventricular response and any signs of hemodynamic impairment, electrical cardioversion is the *initial* treatment of choice.

Prevention.

For long-term therapy to prevent recurrence, it is not always possible to predict which drugs may be most effective for an individual patient. Some drugs can actually increase the frequency of episodes of reciprocating tachycardia by prolonging the duration of anterograde and not retrograde refractory periods of the accessory pathway, thereby making it easier for a premature atrial complex to block conduction anterogradely in the accessory pathway and initiate tachycardia. Oral administration of two drugs, such as quinidine and propranolol or procainamide and verapamil, to decrease conduction capability in both limbs of the reentrant circuit can be beneficial. Class IC drugs, amiodarone, or sotalol, which prolong refractoriness in both the accessory pathway and the AV node, can be effective.[240] [241] Depending on the clinical situation, empirical drug trials or serial electrophysiological drug testing can be used to determine optimal drug therapy for patients with reciprocating tachycardia. For patients who have atrial fibrillation with a rapid ventricular response, induction of atrial fibrillation while the patient is receiving therapy is essential to be certain that the ventricular rate is controlled. Patients who have accessory pathways with very short refractory periods may be poor candidates for drug therapy since the refractory periods may be insignificantly prolonged in response to the standard agents.

Electrical or Surgical Ablation(see Chap. 23).

Radiofrequency catheter ablation of the accessory pathway is advisable for patients with frequent symptomatic arrhythmias that are not fully controlled by drugs, in patients who are drug intolerant, or in those who do not wish to take drugs. This option should be considered early in the course of treatment of a symptomatic patient because of its high success rate, low frequency of complications, and potential cost-effectiveness.[215] [242] [243] [244] [245] [246] [247] [248] Rarely, surgical interruption of the accessory pathway may be necessary.[249] [250]

Summary of Electrocardiographic Diagnosis of Supraventricular Tachycardias

ECG clues that permit differentiation among the various supraventricular tachycardias are often present. P waves during tachycardia that are identical to sinus P waves and occur with a long RP interval and a short PR interval are most likely due to sinus nodal reentry. Retrograde (inverted in leads II, III, and aV_f) P waves generally represent

reentry involving the AV junction, either AV nodal reentry or reciprocating tachycardia using a paraseptal accessory pathway. Tachycardia without manifested P waves is probably due to AV nodal reentry (P waves buried in QRS), while a tachycardia with an RP interval exceeding 90 milliseconds may be due to an accessory pathway. AV dissociation or AV block during tachycardia excludes the participation of an AV accessory pathway and makes AV nodal reentry less likely. Multiple tachycardias can occur at different times in the same patient. QRS alternans, thought to be a feature of AV reciprocating tachycardia, is more likely a rapid rate-related

TABLE 25-3 -- SUPRAVENTRICULAR TACHYCARDIAS

SHORT RP/LONG PR	LONG RP/SHORT PR
AV node reentry	Atrial tachycardia
AV reentry	Sinus node reentry
	Atypical AV node reentry
	AVRT with a slowly conducting accessory pathway (e.g., PJRT)

AVRT = atrioventricular reciprocating tachycardia; PJRT = paroxysmal junctional reciprocating tachycardia.

phenomenon independent of the tachycardia mechanism. RP-PR relationships (Table 25-3) help differentiate supraventricular tachycardias.

VENTRICULAR RHYTHM DISTURBANCES

Premature Ventricular Complexes

ELECTROCARDIOGRAPHIC RECOGNITION.

A premature ventricular complex is characterized by the premature occurrence of a QRS complex that is abnormal in shape and has a duration usually exceeding the dominant QRS complex, generally greater than 120 milliseconds. The T wave is commonly large and opposite in direction to the major deflection of the QRS. The QRS complex is not preceded by a premature P wave but can be preceded by a nonconducted sinus P wave occurring at its expected time. The diagnosis of a premature ventricular complex can never be made with unequivocal certainty from the scalar ECG since a supraventricular beat or rhythm can mimic the manifestations of ventricular arrhythmia (Fig. 25-39) . Retrograde transmission to the atria from the premature ventricular complex occurs fairly frequently but is often obscured by the distorted QRS complex and T wave. If the retrograde impulse discharges and resets the sinus node prematurely, it produces a pause that is not fully compensatory. More commonly, the sinus node and atria are not discharged prematurely by the retrograde impulse since interference of impulses frequently occurs at the AV junction in the form of collision between the anterograde impulse conducted from the sinus node and the retrograde impulse conducted from the premature ventricular complex. Therefore, a fully compensatory pause usually follows a premature ventricular complex: The R-R interval

produced by the two sinus-initiated QRS complexes on either side of the premature complex equals twice the normally conducted R-R interval. The premature ventricular complex may not produce any pause and may therefore be interpolated (Fig. 25-39 *E*), or it may produce a postponed compensatory pause when an interpolated premature complex causes PR prolongation of the first postextrasystolic beat to such a degree that the P wave of the second postextrasystolic beat occurs at a very short RP interval and is therefore blocked.[251]

Interference within the ventricle can result in *ventricular fusion beats* caused by simultaneous activation of the ventricle by two foci, one from the supraventricular impulse and the other from the premature ventricular complex. On occasion, a fusion beat can be narrower than the dominant sinus beat. This abnormality occurs when a right bundle branch block pattern of a premature ventricular complex arising in the left ventricle fuses with the sinus-initiated complex conducting through the AV junction or when a ventricle with a left bundle branch block pattern is paced artificially and a narrow ventricular fusion beat is produced between the paced and the sinus-conducted beats. Narrow premature ventricular complexes have also been explained as originating at a point equidistant from each ventricle in the ventricular septum and by arising high in the fascicular system. Whether a compensatory or noncompensatory pause, retrograde atrial excitation, or an interpolated complex, fusion complex, or echo beat occurs (see Fig. 25-39), it is merely a function of how the AV junction conducts and the timing of the events taking place.

The term *bigeminy* refers to pairs of complexes and indicates a normal and premature complex, *trigeminy* indicates a premature complex following two normal beats, a premature complex following three normal beats is called *quadrigeminy,* and so on. Two successive premature ventricular complexes are termed a *pair* or a *couplet,* while three successive premature ventricular complexes are termed a *triplet.*

Figure 25-39 Premature ventricular complexes. *A* to *D* were recorded in the same patient. *A,* A late premature ventricular complex results in a compensatory pause. *B,* A slower sinus rate and a slightly earlier premature complex result in retrograde atrial excitation (P). The sinus node is reset, followed by a noncompensatory pause. Before the sinus-initiated P wave that follows the retrograde P wave can conduct the impulse to the ventricle, ventricular escape (E) occurs. *C,* Events are similar to those in *B* except that a ventricular fusion beat (F) results after the premature ventricular complex because of a slightly faster sinus rate. *D,* The impulse propagating retrogradely to the atrium reverses its direction after a delay and returns to reexcite the ventricles (R) to produce a ventricular echo. *E,* An interpolated premature ventricular complex is followed by a slightly prolonged PR interval of the sinus-initiated beat. Lead II.

Arbitrarily, three or more successive premature ventricular complexes are termed *ventricular tachycardia.* Premature ventricular complexes can have different contours and are often called *multifocal* (Fig. 25-40) . More properly they should be called "multiform," "polymorphic," or "pleomorphic" since it is not known whether multiple foci

are discharging or whether conduction of the impulse originating from one site is merely changing.

Premature ventricular complexes can exhibit fixed or variable coupling; i.e., the interval between the normal QRS complex and the premature ventricular complex can be relatively stable or variable. Fixed coupling can be due to reentry, triggered activity (see Chap. 22), or other mechanisms. Variable coupling can be due to parasystole, [252] to changing conduction in a reentrant circuit, or to changing discharge rates of triggered activity. Usually, it is difficult to determine the precise mechanism responsible for the premature ventricular complex based on either constant or variable coupling intervals. Focal mechanism can be important, without macro-reentry.[253]

CLINICAL FEATURES.

The prevalence of premature complexes increases with age, and they are associated with male sex and a reduced serum potassium concentration.[254] Premature ventricular complexes are more frequent in the morning in patients after myocardial infarction, but this circadian variation is absent in patients with severe LV

Figure 25-40 Multiform premature ventricular complexes. The normally conducted QRS complexes exhibit a left bundle branch block contour (arrow) and are followed by premature ventricular complexes with three different morphologies.

dysfunction. [255] Symptoms of palpitations or discomfort in the neck or chest can result because of the greater than normal contractile force of the postextrasystolic beat or the feeling that the heart has stopped during the long pause after the premature complex. Long runs of frequent premature ventricular complexes in patients with heart disease can produce angina, hypotension, or heart failure. Frequent interpolated premature ventricular complexes actually represent a doubling of the heart rate and can compromise the patient's hemodynamic status. Activity that increases the heart rate can decrease the patient's awareness of the premature systole or reduce their number. Exercise can increase the number of premature complexes in some patients. Premature systoles can be quite uncomfortable in patients who have aortic regurgitation because of the large stroke volume. Sleep is usually associated with a decrease in the frequency of ventricular arrhythmias, but some patients can experience an increase.

Premature ventricular complexes occur in association with a variety of stimuli and can be produced by direct mechanical, electrical, and chemical stimulation of the myocardium. Often they are noted in patients with LV false tendons, during infection, in ischemic or inflamed myocardium, and during hypoxia, anesthesia, or surgery. They can be provoked by a variety of medications, by electrolyte imbalance, by tension states, by myocardial stretch,[256] [257] and by excessive use of tobacco, caffeine, or alcohol. Both

central and peripheral autonomic stimulation has profound effects on the heart rate and can produce or suppress premature complexes. Almost 20 percent of patients treated by fibrinolytic drugs who are recovering from acute myocardial infarction have more than 10 premature ventricular complexes per hour.[258] Increased premature ventricular complexes during antiarrhythmic drug titration in the Cardiac Arrhythmia Suppression Trial predicted patients at increased risk of arrhythmic death despite antiarrhythmic drug treatment.[259]

Physical examination reveals the presence of a premature beat followed by a pause that is longer than normal. A fully compensatory pause can be distinguished from one that is not fully compensatory in that the former does not change the timing of the basic rhythm. The premature beat is often accompanied by a decrease in intensity of the heart sounds, often with auscultation of just the first heart sound, which can be sharp and snapping, and a decreased or absent peripheral (e.g., radial) pulse. The relationship of atrial to ventricular systole determines the presence of normal *a* waves or giant *a* waves in the jugular venous pulse, and the length of the PR interval determines the intensity of the first heart sound. The second heart sound can be abnormally split, depending on the origin of the ventricular complex.

The importance of premature ventricular complexes depends on the clinical setting. In the absence of underlying heart disease, the presence of premature ventricular complexes usually has no impact on longevity or limitation of activity; antiarrhythmic drugs are not indicated.[260] [261] Patient should be reassured if they are symptomatic (see Chap. 23 , Exercise Testing and Long-Term ECG Recording). In men without apparent coronary disease, the incidental detection of ventricular arrhythmias is associated with a twofold increased risk for all-cause mortality and myocardial infarction or death from coronary disease.[262] However, it has not been demonstrated that premature ventricular systoles or complex ventricular arrhythmias play a *precipitating* role in the genesis of sudden death in these patients, and the arrhythmias may simply be a marker of heart disease. Results from electrophysiological testing suggest that patients with premature ventricular complexes who do not have VT induced at electrophysiological study have a low incidence of subsequent sudden death. Antiarrhythmic therapy given to suppress the premature ventricular systoles or complex ventricular arrhythmias has not been shown to reduce the incidence of sudden death in such apparently healthy men.

In patients suffering from acute myocardial infarction, premature ventricular complexes once considered to presage the onset of ventricular fibrillation, such as those occurring close to the preceding T wave, more than five or six per minute, bigeminal or multiform complexes, or those occurring in salvoes of two, three, or more, do not occur in about half the patients in whom ventricular fibrillation develops, and ventricular fibrillation does not develop in about half of the patients who have these premature ventricular complexes. Thus these premature ventricular complexes are not particularly helpful prognostically. The presence of 1 to more than 10 ventricular extrasystoles per hour[263] [264] can identify patients at increased risk for VT or sudden cardiac death after myocardial infarction.[265]

MANAGEMENT.

Both fast and slow heart rates can provoke the development of premature ventricular complexes. Premature ventricular complexes accompanying slow ventricular rates can be abolished by increasing the basic rate with atropine or isoproterenol or by pacing, whereas slowing the heart rate in some patients with sinus tachycardia can eradicate premature ventricular complexes. In hospitalized patients, IV lidocaine (see Chap. 23) is generally the initial treatment of choice to suppress premature ventricular complexes. If maximum dosages of lidocaine are unsuccessful, procainamide given IV can be tried. Quinidine can be given IV slowly and cautiously. Propranolol can be tried if the other drugs have been unsuccessful. IV magnesium can be useful.[266] For long-term oral maintenance, a variety of class I,[241] II,[267] and III[238] [268] drugs can be useful to prevent VT. Class IC drugs seem particularly successful in suppressing premature ventricular complexes, but flecainide and moricizine have been shown to increase mortality in patients treated after myocardial infarction.[269] Amiodarone can be quite effective. [238] [270] [271] [272] [273] [274] Athletes with structural heart disease and ventricular extrasystoles who are in high-risk groups can participate in low-intensity sports only.[49] Thrombolysis therapy does not influence the frequency of ventricular extrasystoles,[275] which are related to residual LV pump performance after myocardial infarction.[276] Low levels of serum potassium and magnesium are associated with higher prevalence rates of ventricular arrhythmias.[277] Metroprolol and diltiazem but not enalapril or hydrochlorothiazide reduce premature ventricular complexes in patients with hypertension.[278]

Ventricular Tachycardia

ELECTROCARDIOGRAPHIC RECOGNITION.

VT arises distal to the bifurcation of the His bundle in the specialized

Figure 25-41 Fusion and capture beats during ventricular tachycardia. The QRS complex is prolonged, and the R-R interval is regular except for occasional capture beats (C) that have a normal contour and are slightly premature. Complexes intermediate in contour represent fusion beats (F). Thus, even though atrial activity is not clearly apparent, atrioventricular dissociation is present during ventricular tachycardia and produces intermittent capture and fusion beats.

conduction system, in ventricular muscle, or in combinations of both tissue types.[279] Mechanisms include disorders of impulse formation and conduction considered earlier (see Chap. 22). Autonomic modulation can be important. The ECG diagnosis of VT is suggested by the occurrence of a series of three or more consecutive, abnormally shaped premature ventricular complexes whose duration exceeds 120 milliseconds, with the ST-T vector pointing opposite the major QRS deflection. The R-R interval can be exceedingly regular or can vary. Patients can have VTs with multiple morphologies originating at the same or closely adjacent sites, probably with different exit paths.

Others have multiple sites of origin. Atrial activity can be independent of ventricular activity, or the atria can be depolarized by the ventricles retrogradely (VA association). Depending on the particular type of VT, rates range from 70 to 250 beats/min, and the onset can be paroxysmal (sudden) or nonparoxysmal. QRS contours during the VT can be unchanging (uniform, monomorphic), can vary randomly (multiform, polymorphic, or pleomorphic), can vary in a more or less repetitive manner (torsades de pointes), can vary in alternate complexes (bidirectional ventricular tachycardia), or can vary in a stable but changing contour (i.e., right bundle branch contour changing to a left bundle branch contour). VT can be sustained, defined arbitrarily as lasting longer than 30 seconds or requiring termination because of hemodynamic collapse, or nonsustained, when it stops spontaneously in less than 30 seconds. Most commonly, very premature stimulation is required to initiate VT electrically, whereas late coupled ventricular complexes usually initiate its spontaneous onset[279] (Fig. 25-41) .

Making the ECG distinction between supraventricular tachycardia with aberration and VT can be difficult at times since features of both arrhythmias overlap and under certain circumstances a supraventricular tachycardia can mimic the criteria established for VT.[280] [281] [282] Ventricular complexes with an abnormal and prolonged configuration indicate only that conduction through the ventricle is abnormal, and such complexes can occur in supraventricular rhythms as a result of preexisting bundle branch block, aberrant conduction during incomplete recovery of repolarization, conduction over accessory pathways, and several other conditions. These complexes do not necessarily indicate the origin of impulse formation or the reason for the abnormal conduction. Conversely, ectopic beats originating in the ventricle can uncommonly have a fairly normal duration and shape. However, it is important to emphasize that VT is the most common cause of tachycardia with a wide QRS complex. A past history of myocardial infarction makes the diagnosis even more likely.

During the course of a tachycardia characterized by widespread, abnormal QRS complexes, the presence of fusion beats and capture beats provides maximum support for the diagnosis of VT (Table 25-4) . *Fusion beats* indicate activation of the ventricle from two different foci, with the implication that one of the foci had a ventricular origin. *Capture* of the ventricle by the supraventricular rhythm with a normal configuration of the captured QRS complex at an interval shorter than the tachycardia in question indicates that the impulse has a supraventricular origin (see Fig. 25-41). AV dissociation has long been considered a hallmark of VT. However, retrograde VA conduction to the atria from ventricular beats occurs in at least 25 percent of patients, and therefore, VT may not exhibit AV dissociation. AV dissociation can occur uncommonly during supraventricular tachycardias. Even if a P wave appears to be related to each QRS complex, it is at times difficult to determine whether the P wave is conducted anterogradely to the next QRS complex (i.e., supraventricular tachycardia with aberrancy and a long PR interval) or retrogradely from the preceding QRS complex (i.e., a VT). As a general rule, however, AV dissociation during tachycardia with a wide QRS is strong presumptive evidence that the tachycardia is of ventricular origin.

TABLE 25-4 -- MAJOR FEATURES IN THE DIFFERENTIAL DIAGNOSIS OF WIDE QRS BEATS VERSUS TACHYCARDIA

SUPPORTS SVT	SUPPORTS VT
Slowing or termination by vagal tone	Fusion beats
Onset with premature P wave	Capture beats
RP interval 100 msec	AV dissociation
P and QRS rate and rhythm linked to suggest that ventricular activation depends on atrial discharge, e.g., 2:1 AV block	P and QRS rate and rhythm linked to suggest that atrial activation depends on ventricular discharge, e.g., 2:1 VA block
rSR V_1	
Long-short cycle sequence	"Compensatory" pause
	Left axis deviation; QRS duration >140 msec
	Specific QRS contours (see text)

SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Differentiation Between Ventricular and Supraventricular Tachycardia.

While fusion and capture beats and AV dissociation provide the strongest ECG evidence for differentiating VT from supraventricular tachycardia with aberrant conduction, these features are not always present. Therefore, other clues from the ECG may be required to help with this differentiation. Some ECG features characterizing supraventricular arrhythmia with aberrancy are (1) consistent onset of the tachycardia with a premature P wave, (2) a very short RP interval (0.1 second) often requiring an esophageal recording to visualize the P waves, (3) a QRS configuration the same as that occurring from known supraventricular conduction at similar rates, (4) P wave and QRS rate and rhythm linked to suggest that ventricular activation depends on atrial discharge (e.g., an AV Wenckebach block), and (5) slowing or termination of the tachycardia by vagal maneuvers.

Analysis of specific QRS contours can also be helpful in diagnosing VT and localizing its site of origin. For example, QRS contours suggesting VT include left-axis deviation in the frontal plane and a QRS duration exceeding 140 milliseconds with a QRS of normal duration during sinus rhythm. During VT with a right bundle branch block appearance, (1) the QRS complex is monophasic or biphasic in V_1 with an initial deflection different from that of the sinus-initiated QRS complex, (2) the amplitude of the R wave in V_1 exceeds the R
, and (3) a small R and large S wave or a QS pattern in V_6 may be present. With a VT

having a left bundle branch block contour, (1) the axis can be rightward with negative deflections deeper in V_1 than in V_6 , (2) a broad prolonged (>40 milliseconds) R wave can be noted in V_1 , and (3) a small Q-large R wave or QS pattern in V_6 can exist. A QRS complex that is similar in V_1 through V_6 , either all negative or all positive, favors a ventricular origin, as does the presence of a 2:1 VA block. (An upright QRS complex in V_1 through V_6 can also occur from conduction over a left-sided accessory pathway.) Supraventricular beats with aberration often have a triphasic pattern in V_1 , an initial vector of the abnormal complex similar to that of the normally conducted beats, and a wide QRS complex that terminates a short cycle length following a long cycle (long-short cycle sequence). During atrial fibrillation, fixed coupling, short coupling intervals, a long pause after the abnormal beat, and runs of bigeminy rather than a consecutive series of abnormal complexes all favor a ventricular origin of the premature complex rather than a supraventricular origin with aberration. A grossly irregular, wide QRS tachycardia with ventricular rates exceeding 200 beats/min should raise the question of atrial fibrillation with conduction over an accessory pathway (see Fig. 25-7 *B*). In the presence of a preexisting bundle branch block, a wide QRS tachycardia with a contour different from the contour during sinus rhythm is most likely a VT. Several algorithms, based on the above criteria, for distinguishing VT from supraventricular tachycardia with aberrancy have been suggested.[283] [284] [285] Exceptions exist to all the aforementioned criteria, especially in patients who have preexisting conduction disturbances or preexcitation syndrome; when in doubt, one must rely on sound clinical judgment and consider the ECG only one of several helpful ancillary tests.

Termination of a tachycardia by triggering vagal reflexes is considered diagnostic of supraventricular tachycardias. However, VT can rarely be stopped in a similar manner.

ELECTROPHYSIOLOGICAL FEATURES.

Electrophysiologically, VT can be distinguished by a short or negative H-V interval (i.e., H begins after the onset of ventricular depolarization) because of retrograde activation from the ventricles (see Chap. 23). His bundle deflections are not usually apparent during VT because they are obscured by simultaneous ventricular septal depolarization or inadequate catheter position. The latter must be determined during supraventricular rhythm before the onset or after the termination of VT (Fig. 25-42) . His bundle deflections dissociated from ventricular activation are diagnostic, with rare exception. VT can produce QRS complexes of narrow duration and short H-V interval, most likely when the site of origin is close to the His bundle in the fascicles.

Successful electrical induction of VT by premature stimulation of the ventricle (see Fig. 25-42) depends on the characteristics of the VT and the anatomical substrate. Patients with sustained, hemodynamically stable VT and VT secondary to chronic coronary artery disease have monomorphic VT induced (90 percent) more frequently than do patients with nonsustained VT, VT from non-coronary-related causes or acute ischemia, and cardiac arrest (40 to 75 percent).[286] In general, it is more difficult to induce VT with late premature ventricular stimuli than with early premature stimuli, during sinus rhythm than during ventricular pacing, and with one premature stimulus than with two or three.[287] The specificity of VT induction using more than two premature ventricular

stimuli begins to decrease (while the sensitivity increases), and nonsustained polymorphic VT or ventricular fibrillation can be induced in patients who have no history of VT. Of patients with stable VT who have inducible sustained monomorphic VT, the latter is induced in about 25 percent with single extrastimuli, in 50 percent with double extrastimuli, and in 25 percent with triple extrastimuli.[288] A recent study suggests that using a single basic cycle length of 400 milliseconds and up to four extrastimuli can be an adequate induction technique.[289] Occasionally, VT can be initiated only from the left ventricle or from specific sites in the right ventricle. Multiple premature stimuli reduce the need for LV stimulation. Drugs such as isoproterenol, various antiarrhythmic agents, and alcohol can facilitate the induction of VT. Coughing during VT that causes hypotension can help maintain blood pressure.

Termination by pacing depends significantly on the rate

Figure 25-42 Initiation and termination of ventricular tachycardia by means of programmed ventricular stimulation. The last two ventricular-paced beats at a cycle length of 600 milliseconds are shown in *A*. A premature stimulus (S_2) at an S_1 -S_2 interval of 260 milliseconds and another premature stimulus (S_3) at a cycle length of 210 milliseconds initiate a sustained monomorphic ventricular tachycardia at a cycle length of 300 milliseconds. Two premature ventricular stimuli (S_1 -S_2) in *B* create an unstable ventricular tachycardia that persists for several beats at a shorter cycle length (230 milliseconds) and then terminates, followed by sinus rhythm.

TABLE 25-5 -- CLINICAL TRIALS IN THE TREATMENT OF VENTRICULAR TACHYCARDIA AND PREVENTION OF CARDIAC ARREST

STUDY	PATIENT INCLUSION	ENDPOINTS	TREATMENT ARMS	KEY RESULTS
Primary prevention studies				
BHAT[311]	*Post-MI*	Total mortality	Propranolol	Total mortality and sudden cardiac death reduced in treatment arm
		Sudden cardiac death	Placebo	
CAST[269] [312]	*Post-MI*	Arrhythmic death	Flecainide	Arrhythmic death increased with all treatment arms

	6 PVCs/hr		Encainide	
	LVEF 40%		Moricizine	
			Placebo	
SWORD[313]	*Post-MI*	Total mortality	*d*-Sotalol	Increased mortality in treatment arm
	LVEF <40% or Remote MI NYHA II-III		Placebo	
EMIAT[314]	*Post-MI*	Total mortality	Amiodarone	Amiodarone reduced arrhythmic death but not total mortality
	LVEF <40%	Arrhythmic death	Placebo	
CAMIAT[315]	*Post-MI*	Arrhythmic death	Amiodarone	Amiodarone reduced arrhythmic death but not total mortality
	10 PVCs/hr or NSVT	Total mortality	Placebo	
GESICA[316]	*CHF*	Total mortality	Amiodarone	Amiodarone reduced mortality. Patients with NSVT had higher mortality
	LVEF 35%		Best therapy	
CHF-STAT[317]	*CHF*	Total mortality	Amiodarone	No effect in ischemic cardiomyopathy but trend toward reduced mortality in nonischemic cardiomyopathy

	LVEF 40% 10 PVCs/hr (asymptomatic)		Placebo	
SCD-HeFT[318]	*CHF*	Total mortality	ICD	Ongoing
	LVEF 35%	Arrhythmic mortality	Amiodarone	
	NYHA II-III	Cost	Placebo	
		Quality of life		
CABG Patch[319]	*CAD undergoing CABG*	Total mortality	CABG	No difference in total mortality
			CABG+ICD	
	LVEF <36%			
	Positive SAECG			
MADIT[320]	*Post-MI*	Total mortality	ICD	ICD reduced mortality
	NSVT sustained		Antiarrhythmic drug (80% amiodarone)	
	LVEF 35%			
	NYHA I-III			
	Inducible VT not suppressed by procainamide			
MADIT II[318]	*Post-MI*	Total mortality	ICD	Ongoing
	EF 30%		No ICD	
	>10 PVCs/hr or couplets			
MUSTT*	*Post-MI*	Arrhythmic death or cardiac arrest	ICD in nonsuppressible group	Ongoing

	LVEF <40% NSVT sustained		Antiarrhytmic drug in suppressible group No therapy	
Secondary prevention studies				
ESVEM[321] [322]	*Cardiac arrest, sustained VT or syncope*	Recurrence of arrhythmia	EP guided antiarrhythmics (imipramine, mexiletine, procainamide, quinidine, sotalol, pirmenol, propafenone)	No difference between Holter- and EP-guided groups. Sotalol group had lowest recurrence rate of VT, arrhythmic death, and total death
	10 PVCs/hr Inducible VT		Holter-guided antiarrhythmics	
CASCADE[323]	Cardiac arrest	Cardiac mortality	EP- or Holter-guided conventional drug therapy	Amiodarone survival better than conventional guided drug therapy
	Not associated with acute MI	Aborted cardiac arrest	Empirical amiodarone	
CASH[324]	*Cardiac arrest*	Total mortality	Empirical amiodarone	Sudden cardiac death mortality lowest in ICD arm. Increased mortality in propafenone arm
	Not associated with acute MI		Metoprolol Propafenone	

			ICD	
AVID[325]	*Cardiac arrest or sustained VT*	Total mortality	ICD	Survival better in ICD group, with most of benefit occurring in the first 9 months. Benefit most pronounced in patients with EF <35%
		Cost	Drug therapy (empirical amiodarone or EP/Holter-guided sotalol)	
			Quality of life	
CIDS[326] [327]	*Cardiac arrest or sustained VT*	Total mortality	ICD	Survival trended better in ICD group
			Amiodarone	

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; EP = electrophysiology; ICD = implanted cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular contraction; SAECG = signal-averaged electrocardiogram; VT = ventricular tachycardia.

*Buxton AE, Lee KL, Fisher JD, et al: A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 341:1882-1890, 1999.

of the VT and the site of pacing. [290] Slower VTs are terminated more easily and with fewer stimuli than are more rapid ones. An increasing number of stimuli are required to terminate more rapid VTs, which increases the risks of pacing-induced acceleration of the VT. Subthreshold stimulation and transthoracic stimulation can terminate VT. Atrial pacing, at times, can also induce and terminate VT (see Chap. 23).

CLINICAL FEATURES.

Symptoms occurring during VT depend on the ventricular rate, duration of tachycardia, and the presence and extent of the underlying heart disease and peripheral vascular disease. VT can be in the form of short, asymptomatic, nonsustained episodes[291] ; sustained, hemodynamically stable events, generally occurring at slower rates or in otherwise normal hearts; or unstable runs, often degenerating into ventricular fibrillation.

In some patients who have nonsustained VTs initially, sustained episodes or ventricular fibrillation later develops.[288] The location of impulse formation and therefore the way in which the depolarization wave spreads across the myocardium can also be important. Physical findings depend in part on the P-to-QRS relationship. If atrial activity is dissociated from the ventricular contractions, the findings of AV dissociation are present. If the atria are captured retrogradely, regularly occurring cannon *a* waves appear when atrial and ventricular contractions occur simultaneously and signs of AV dissociation are absent.

More than half the patients treated for symptomatic recurrent VT have ischemic heart disease. The next biggest group has cardiomyopathy (both congestive[292] [293] [294] and hypertrophic[295] [296] [297]), with lesser percentages divided among those with primary electrical disease,[298] mitral valve prolapse,[299] valvular heart disease, congenital heart disease,[300] and miscellaneous causes. LV hypertrophy can lead to ventricular arrhythmias.[301] [302] Coronary artery spasm can cause transient myocardial ischemia with severe ventricular arrhythmias in some patients (during ischemia as well as during the apparent reperfusion period).[286] Complex ventricular arrhythmias can occur *after* coronary artery bypass grafting. In patients resuscitated from sudden cardiac death (see Chap. 26), the majority (75 percent) have severe coronary artery disease, and ventricular tachyarrhythmias can be induced by premature ventricular stimulation in approximately 75 percent. When VT occurs in an ambulatory patient, it is uncommonly induced by R-on-T premature ventricular complexes. Patients who have sustained VT are more likely to have a reduced EF, slowed ventricular conduction and electrogram abnormalities, LV aneurysm, abnormal signal-averaged ECGs, and previous myocardial infarction than are patients who have ventricular fibrillation,

thus indicating different electrophysiological and anatomical substances. When sustained VT can be induced electrically, patients in cardiac arrest have faster rates than do patients with VT. The cycle length of induced VT correlates with whether the patient is in cardiac arrest or has sustained VT.[288] Young patients can also suffer cardiac arrest from VT or ventricular fibrillation, and persistent electrical inducibility of arrhythmias in these patients connotes a poor prognosis. In patients with coronary artery disease, sustained VT displays a circadian variation, with peak frequency in the morning.[303]

Many approaches have been used to assess prognosis in patients with ventricular arrhythmias. Reduced baroreceptor sensitivity and heart period variability apparently caused by reduced vagal activity may indicate an increased risk of VT or sudden cardiac death.[304] [305] The presence of nonsustained VT after myocardial infarction often presages sudden cardiac death. Findings of reduced LV function, spontaneous ventricular arrhythmias, late potentials on signal-averaged ECG,[306] QT interval dispersion,[307] [308] T wave alternans,[309] [310] and inducible sustained VTs at electrophysiological study all carry increased risk, further exaggerated when two or more of these features are present in the same patient. However, currently, no noninvasive technique reliably predicts outcome better than does assessment of LV

function. LV function and inducibility of VT during electrophysiological study are the two strongest predictors of poor outcome. Also, clinical occurrence of cardiac arrest during the first spontaneous episode of ventricular arrhythmia identifies patients at increased risk. Ventricular fibrillation is more likely to occur earlier than sustained VT in patients after myocardial infarction. Electrophysiological testing can be used to stratify patients according to risk and to help guide therapy in cardiac arrest survivors and patients with sustained or nonsustained VT, unexplained syncope after myocardial infarction, and cardiomyopathy. In general, the prognosis for patients with idiopathic VT (see below), in the absence of structural heart disease or a prolonged QT interval, is good and warrants less aggressive treatment than in patients with structural heart disease.

MANAGEMENT.

The dramatic changes in the management of VT and aborted sudden death over the past several years have been fueled by several large clinical trials (Table 25-5) and development of the implantable cardioverter-defibrillator. Management decisions can be stratified into those involved in the acute management (or termination)

and those involved in long-term therapy (or prevention of recurrence or sudden death) (see Chap. 26).

Acute Management of Sustained Ventricular Tachycardia.

VT that does not cause hemodynamic decompensation can be treated medically to achieve acute termination by administering IV lidocaine or procainamide, followed by an infusion of the successful drug. Lidocaine is often ineffective[272] ; sotalol [328] [329] and procainamide appear to be superior. Although quinidine can be used IV, great caution is needed because of hypotension. In patients in whom procainamide is ineffective or in whom procainamide may be problematic (severe heart failure, renal failure), IV amiodarone is often effective.[330] [331] [332] [333] [334] [335] In general, an initial loading dose of 15 mg/min is given over a 10-minute period. This dose is followed by an infusion of 1 mg/min for 6 hours and then a maintenance dose of 0.5 mg/min for the remaining 18 hours and for the next several days, as necessary. If VT does not terminate or if it recurs, a repeat loading dose can be given. Rarely, sinus bradycardia or AV block can be seen with IV amiodarone. The hypotension associated with IV amiodarone, caused largely by the diluent used in earlier formulations, does not seem to be as frequent a problem and is usually related to the rate of infusion. Bretylium is rarely used in this setting because of the frequently associated hypotension and because amiodarone appears to be more effective.

If the arrhythmia does not respond to medical therapy, electrical DC cardioversion can be used. VT that precipitates hypotension, shock, angina, congestive heart failure, or symptoms of cerebral hypoperfusion should be treated *promptly* with DC cardioversion (see Chaps. 23 and 26). Very low energies can terminate VT, beginning with a

synchronized shock of 10 to 50 J. Digitalis-induced VT is best treated pharmacologically. After conversion of the arrhythmia to a normal rhythm, it is essential to institute measures to prevent recurrence.

Striking the patient's chest, sometimes called "thumpversion," can terminate VT by mechanically inducing a premature ventricular complex that presumably interrupts the reentrant pathway necessary to support it. Chest stimulation at the time of the vulnerable period during the arrhythmia can accelerate the VT or possibly provoke ventricular fibrillation.

In some instances, such as VT associated with a remote myocardial infarction (which is due to reentry), ventricular pacing via a pacing catheter inserted into the right ventricle or transcutaneously at rates faster than the tachycardia can terminate the tachycardia. This procedure incurs the risk of accelerating the VT to ventricular flutter or ventricular fibrillation. In patients with recurrent VT, competitive ventricular pacing can be used to prevent recurrence. Intermittent VT, interrupted by several supraventricular beats, is generally best treated pharmacologically.

A search for reversible conditions contributing to the initiation and maintenance of VT should be made and the conditions corrected if possible. For example, VT related to ischemia, hypotension, or hypokalemia can at times be terminated by antianginal treatment, vasopressors, or potassium, respectively. Correction of heart failure can reduce the frequency of ventricular arrhythmias.[294] Slow ventricular rates that are caused by sinus bradycardia or AV block can permit the occurrence of premature ventricular complexes and ventricular tachyarrhythmias, which can be corrected by administering atropine, by temporary isoproterenol administration, or by transvenous pacing. Supraventricular tachycardia can initiate ventricular tachyarrhythmias and should be prevented if possible.

Long-Term Therapy for Prevention of Recurrences.

Long-term therapy for patients with VT or those who have been resucitated from cardiac arrest is based on the high risk of recurrent sudden cardiac death and ventricular arrhythmias in patients with structural heart disease. After myocardial infarction, the risk of death is 5 to 10 percent, with a large portion of these patients dying of an arrhythmia and the largest risk being in patients with poor LV function and spontaneous or induced ventricular arrhythmias. Patients with a prior myocardial infarction and nonsustained VT have a 2-year mortality of 30 percent.[336] Patients with inducible VT have a 50 percent 2-year mortality.[327] In patients with heart failure, up to 50 percent may die suddenly.[338] [339] In patients who survive a cardiac arrest, the mortality is 20 percent at 1 year.[340] [341] These data have spurred several clinical trials (see Table 25-5) that have had an impact on the long-term management of patients with VT or survivors of cardiac arrest.

Since the prognosis is related to whether the patient has structural heart disease, evaluation of LV function and determination of whether the patient has had a prior myocardial infarction are critical in determining whether to treat. In addition, the existence of symptoms and/or hemodynamic compromise during VT is useful clinical information to guide long-term therapy. The following discussion applies to patients with

structural heart disease. Management of specific types of VT and clinical entities is discussed in the following sections.

The goal of long-term therapy is to prevent sudden cardiac death and recurrence of symptomatic VT. Asymptomatic nonsustained ventricular arrhythmias in low-risk populations (i.e., preserved LV function) most often need not be treated. In patients with symptomatic nonsustained tachycardia, beta blockers are frequently effective in preventing recurrences. In patients refractory to beta blockers, class IC agents, sotalol, or amiodarone is usually effective. However, class IC agents should be avoided in patients with structural heart disease, especially those with coronary artery disease because of the increased mortality associated with these drugs because of proarrhythmia. Sotalol should be used cautiously because of its potential for prolonging the QT interval and producing torsades des pointes. Patients with nonsustained VT after myocardial infarction and with poor LV function are at significant risk for sudden death. These patients should generally undergo electrophysiological study and, if they have inducible VT (that is, not suppressed with procainamide), should have an implanted defibrillator.[320]

For secondary prevention of sustained VT or cardiac arrest (see Table 25-5 , Chap. 26) in patients with structural heart disease, it is now clear from several clinical trials that (1) class I antiarrhythmic drugs produce a worse outcome than do class III antiarrhythmic drugs,[321] [322] [324] (2) empirical amiodarone results in better survival than does electrophysiology-guided antiarrhythmic drugs,[323] and (3) implantable defibrillators provide better survival than amiodarone does, particularly in patients with a left ventricular ejection fraction (LVEF) less than 35 percent.[324] [325] [326] Therefore, in patients who have survived a cardiac arrest or who have sustained VT resulting in hemodynamic compromise and poor LV function (EF<35%), an implantable cardioverter-defibrillator is the treatment of choice.[325] For those with higher EFs, amiodarone may produce outcomes similar to those of implanted defibrillators. In patients who refuse a cardioverter-defibrillator, empirical amiodarone is the next best therapy.[323] [324] The optimal therapy for patients with coronary disease who have preserved LV function with sustained VT is not currently known. Empirical amiodarone appears to be the safest therapy,[314] [315] [316] although Holter-guided sotalol has been advocated.[321] [322] Some patients who receive implanted cardioverter-defibrillators have frequent shocks because of recurrent VT. In these patients, concomitant therapy with amiodarone may be required to reduce the frequency of VT or slow the rate of the VT to allow it to be pace-terminated. Other drugs such as sotalol, procainamide, mexiletine, or flecainide may be required if amiodarone is not effective. Occasionally, a combination of drugs may be effective when a single drug is not. While radiofrequency ablation of certain types of idiopathic VT (see below)

is very effective, ablation for postinfarct VT or that associated with dilated cardiomyopathy is somewhat less effective. In addition, because of the significant mortality associated with these arrhythmias in patients with structural heart disease and depressed LV function, ablation is generally used as an adjunct to implanted

cardioverter-defibrillator placement to reduce the frequency of VT and cardioverter-defibrillator shocks.[342] [343] [344] [345] However, in patients with well-tolerated postinfarct VT and well-preserved LV function or in patients refractory to drugs, it may be used as first-line therapy.[342] [343] [345]

Because of the marked increase in sudden death after myocardial infarction and in patients with depressed LV function, numerous clinical trials have been performed to determine whether primary prevention of sudden death is achievable (see Table 25-5). Several conclusions can be drawn from the clinial trials to date: (1) Patient survival after myocardial infarction is dramatically improved with long-term beta blocker therapy.[311] (2) In the post-myocardial infarction population, class IC drugs result in increased mortality (especially in patients with a left ventricular ejection fraction [LVEF]<40%), presumably from proarrhythmia.[269] [312] (3) Amiodarone does not appear to increase mortality in patients after myocardial infarction and/or those with poor LV function. Amiodarone appears to reduce arrhythmic death, but not total mortality in patients after myocardial infarction who have poor LV function.[314] [315] Amiodarone may reduce mortality in patients with nonischemic cardiomyopathy and an EF less than 35 to 40 percent.[316] [317] [317A] Therefore, amiodarone may have a role in primary prevention in patients with nonischemic cardiomyopathy and nonsustained VT. (4) Implantable cardioverter-defibrillators reduce mortality in patients with poor LV function after myocardial infarction who have nonsustained VT that is inducible at electrophysiological study (and not suppressible with procainamide).[320] [320A]

It is still not entirely clear in what population primary prevention is effective and whether amiodarone or implantable cardioverter-defibrillators reduce overall mortality in this setting. Several ongoing studies (Multicenter Automatic Defibrillator Implantation Trial [MADIT] II, Sudden Cardiac Death Heart Failure Trial [SCD-HeFT]) will, it is hoped, refine the populations in which such therapy is effective and determine which of these therapies is more appropriate (see Chap. 26).

Specific Types of Ventricular Tachycardia

A number of fairly specific types of VT have been identified, and distinction is based on either a constellation of distinctive ECG and electrophysiological features or a specific set of clinical events. While our understanding of the electrophysiological mechanisms responsible for clinically occurring VTs is still naive, being able to identify different kinds of VTs is the first step toward understanding their mechanisms. These different kinds of VT often carry different prognoses and responses to different therapy. They are distinct from VTs associated with remote myocardial infarction or dilated cardiomyopathies.

Arrhythmogenic Right Ventricular Dysplasia

Patients with arrhythmogenic right ventricular dysplasia have VT that generally has a left bundle branch block contour (since the tachycardia arises in the right ventricle), often with right-axis deviation and T waves inverted over the right precordial leads[346] (Fig. 25-43 *A*). The VT may be due to reentry.[347] Supraventricular arrhythmias can also occur, and exercise can induce the VT in some patients.

Arrhythmogenic right ventricular dysplasia is due to a type of cardiomyopathy,[348] possibly familial in some patients,[349] with hypokinetic areas involving the wall of the right ventricle. In the familial form, the genetic abnormality has been mapped to chromosomes 1 and 14q23-q24[350] [351] and, most recently, chromosome 10.[351A] It can be an important cause of ventricular arrhythmia in children and young adults with apparently normal hearts, as well as in older patients. Initial findings can be subtle and often mimic those of out-flow tract VT (see below), i.e., manifested only by tachycardia and no symptoms of right-sided heart failure.[352] Right-sided heart failure or asymptomatic right ventricular enlargement can be present with normal pulmonary vasculature. Males predominate, and most patients usually show an abnormal right ventricle by echocardiography,[353] computed tomography,[354] right ventricular angiography, or magnetic resonance imaging,[355] [356] although this abnormality may not be apparent on initial evaluation.[355] [357] Two pathological patterns have been identified, fatty and fibrofatty infiltration. In the latter, myocardial atrophy appears to be the result of injury and myocyte death (perhaps from apoptosis) and culminates in fibrofatty replacement mediated by patchy myocarditis. The fatty degeneration preferentially occurs in the right ventricular in-flow and out-flow tracts and the apex. The left ventricle can be involved in advanced forms of the disease in up to 60 percent of patients.[350] Sympathetic innervation appears to be abnormal.[358] The ECG during sinus rhythm can exhibit complete or incomplete right bundle branch block and T wave inversions in V_1 to V_3 .[359] A terminal notch in the QRS (called an epsilon wave) may be present as a result of slowed intraventricular conduction.[350] The signal-averaged ECG can be abnormal.[360] [361] Although conventional pharmacological approaches to therapy may be appropriate, surgical manipulations have been successful in some of these patients,[362] [363] as has been implantable defibrillator therapy.[364] Radiofrequency catheter ablation can be tried but is often not successful because of the multiple morphologies of VT and the progressive nature of the disease.

Tetralogy of Fallot (see also Chap. 43)

Chronic serious ventricular arrhythmias can occur in patients some years after repair of the *tetralogy of Fallot.* [300] Sustained VT after repair can be caused by reentry at the site of previous surgery in the right ventricular out-flow tract and can be cured by resection[365] or catheter ablation[366] [367] of this area. The signal-averaged ECG can be abnormal.[368] Decreased cardiac output can occur during VT and residual right ventricular out-flow obstruction and lead to ventricular fibrillation.[369]

Cardiomyopathies (see also Chap. 48)

DILATED CARDIOMYOPATHY.

Both dilated and hypertrophic cardiomyopathies (see discussion above under management of VT) can be associated with VTs and an increased risk of sudden cardiac death. Use of the signal-averaged ECG in identifying patients with dilated cardiomyopathy at risk for sudden death is controversial, with positive[370] and negative [371] [372] results. Induction of VT by programed stimulation[373] does not appear to identify

high-risk patients,[292] [374] whereas QT dispersion may.[307] Because it is difficult to predict patients at risk of sudden death or those who might respond favorably to an antiarrhythmic drug, implantable cardioverter-defibrillators have been advocated for patients with life-threatening ventricular arrhythmias and dilated cardiomyopathy.[375] [376] This recommendation has been supported by a large multicenter randomized trial (see Table 25-5) comparing amiodarone with implantable defibrillators in patients with poor ventricular function and symptomatic sustained VT; the study found improved survival in patients who received a defibrillator.[325] Bundle branch reentry may be the basis of some VTs in this population and can be treated by ablating the right bundle branch.[377] [378] [379] Asymptomatic ventricular arrhythmias are common.[380] The role of antiarrhythmic drugs and implantable

Figure 25-43 *A,* Normal sinus rhythm in a patient with arrhythmogenic right ventricular dysplasia. The arrowheads point to late right ventricular activation called an epsilon wave. *B,* Ventricular tachycardia in the same patient with right ventricular dysplasia.

defibrillators in the primary prevention of sudden cardiac death in patients with dilated cardiomyopathy may be warranted in certain high-risk patients, as discussed above. However, ongoing clinical trials will further clarify which patient population will benefit the most and which modality is most effective.

HYPERTROPHIC CARDIOMYOPATHY(see also Chap. 48).

The risk of sudden death in patients with hypertrophic cardiomyopathy is increased by the presence of syncope, a family history of sudden death in first-degree relatives, or the presence of nonsustained VT on 24-hour ECG recordings.[297] [381] Asymptomatic or mildly symptomatic patients with brief and infrequent episodes of nonsustained VT have a low mortality.[295] Results of electrophysiological testing can help identify patients at increased risk of ventricular arrhythmias and sudden death,[382] [383] although its use is controversial. A negative electrophysiological study may not necessarily indicate a good prognosis. Triggering events

such as supraventricular tachycardia and atrial fibrillation[384] and ischemia[296] may be important. Amiodarone has been useful in some patients with mildly symptomatic, nonsustained VT,[381] [385] but not in patients with nonarrhythmic problems. [386] QT dispersion is increased in those with ventricular arrhythmias and sudden death.[387] DDD pacing has been useful in reducing the out-flow gradient, and its role in affecting ventricular arrhythmia is being evaluated. Currently, no totally acceptable way to risk-stratify patients with hypertrophic cardiomyopathy in terms of ventricular tachycardia

has been identified. In patients believed to be at high risk of sudden death, those with sustained VT or frequent nonsustained VT, an implantable defibrillator may be indicated.[388] Since DDD pacing may also be useful in reducing out-flow gradients and since these patients are also at risk for atrial fibrillation, a dual-chamber defibrillator (a ventricular defibrillator with an integrated DDD pacemaker) is often the best choice of devices. Alcohol ablation of the septum via direct injection into the septal branches of the coronary circulation has been used to improve out-flow gradients.

Mitral Valve Prolapse (see also Chap. 46)

Patients with mitral valve prolapse[299] frequently have ventricular arrhythmias, although a causal relationship has not been clearly established between the arrhythmia and the mitral valve prolapse. The prognosis for most patients appears good, although sudden death can occur.[389]

Idiopathic Ventricular Tachyarrhythmias

Idiopathic ventricular fibrillation may occur in about 1 percent of cases of out-of-hospital ventricular fibrillation and affects mostly men and those in middle age.[390] Cardiovascular evaluation is normal except for the arrhythmia. Monomorphic VT is rarely induced at electrophysiological study. The natural history is incompletely known, but recurrences are not uncommon.[391] [392] It is important in this entity, as well as in patients with idiopathic VTs (see below), to remember that the arrhythmia may at times be an early manifestation of a developing cardiomyopathy, at least in some patients. Antiarrhythmic drugs and implantable defibrillators[393] are useful therapeutic choices.

Brugada syndrome is a distinct form of idiopathic ventricular fibrillation in which patients have right bundle branch block and ST segment elevation in the anterior precordial leads without evidence of structural heart disease[394] [395] [396] [397] [398] [399] (Fig. 25-44) . This syndrome[395] probably accounts for approximately 40 to 60 percent of all cases of idiopathic ventricular fibrillation.[400] Sudden unexplained nocturnal death syndrome occurring in apparently healthy young Southeast Asians, sometimes associated with nightmares, is thought to be due to Brugada syndrome. The precise mechanism of the ECG changes and the development of ventricular fibrillation is not known. It is thought that loss of the action potential dome in the right ventricular epicardium, but not in the endocardium, results in the persistent ST segment elevation.[396] Ventricular fibrillation is thought to result from the electrophysiological heterogeneity in the right ventricle that also produces ST elevation and can produce reentry.[396] Among several agents that can reproduce this ECG phenomenon are sodium channel blockers. They can expose latent ECG forms of the syndrome. Recently, mutations in a gene responsible for the sodium channel (*SCN5A*) has been identified in some families with Brugada syndrome.[400] While the mutations are on the same gene as that responsible for one form of the long QT syndrome (LQT3) (see below), the site of mutation is different and does not result in a prolonged QT interval.[400A] Mutations in the Brugada syndrome result either in acceleration of sodium channel recovery or in nonfunctional sodium channels. Mutations on other genes are likely to be found in

Figure 25-44 Twelve-lead electrocardiogram (ECG) of a patient with Brugada syndrome. The ECG is characterized by a right bundle branch block pattern and persistent ST elevation in V_1 through V_3 . *(From Brugada J, Brugada R, Brugada P: Right bundle-branch block and ST-segment elevation in leads V1 through V3: A marker for sudden death in patients without demonstrable structural heart disease. Circulation 97:457-60, 1998. By permission of the American Heart Association, Inc.)*

some patients with Brugada syndrome. Candidate genes include those affecting I_{to} , I_{Ca} , $I_{K\text{-}ATP}$, and autonomic receptors. Currently, no pharmacological treatment can reliably prevent ventricular fibrillation in these patients. Implanted cardioverter-defibrillators are the only effective treatment for preventing sudden death.

Idiopathic VTs with monomorphic contours can be divided into at least three types. Two types, paroxysmal VT and repetitive monomorphic VT,[401] appear to originate from the region of the right ventricular out-flow tract (Figs. 25-45 and 25-46). Right ventricular out-flow tract VTs have a characteristic ECG appearance of a left bundle branch block contour in V_1 and an inferior axis in the frontal plane. Vagal maneuvers, including adenosine,[402] terminate the VT, whereas exercise, stress, isoproterenol infusion, and rapid or premature stimulation can initiate or perpetuate the tachycardia. Beta blockers and verapamil[403] can suppress this tachycardia as well. The mechanism responsible may be cyclic adenosine monophosphate-triggered activity[404] [405] resulting from early[406] or delayed[407] afterdepolarizations. The paroxysmal form is exercise or stress induced, whereas the repetitive monomorphic type occurs at rest with sinus beats interposed between runs of nonsustained VT that may be precipitated by transient increases in sympathetic activity unrelated to exertion.[407] The prognosis for most patients is quite good. Radiofrequency catheter ablation effectively eliminates this focal tachycardia in symptomatic patients.[408] In others, antiarrhythmic drugs can be effective.[409] An anatomical abnormality in the out-flow tract of the right ventricle has been recognized in some patients.[404] [410] [411] In a small number of patients, the tachycardia seems to arise in the in-flow tract or apex of the right ventricle.[408] A similar

Figure 25-45 Ventricular tachycardia originating from the right ventricular out-flow tract. This tachycardia is characterized by a left bundle branch block contour in V_1 and an inferior axis.

tachycardia has been identified in the left ventricle and may mimic that of right ventricular out-flow tract tachycardia.[412]

A *left septal VT* has been described as arising in the left posterior septum, often preceded by a fascicular potential,[413] and is sometimes called a *fascicular tachycardia* (Fig. 25-47) . Entrainment has been demonstrated, which suggests reentry as a cause of some of the tachycardias.[414] Verapamil [415] [416] or dilitiazem[417] suppresses this tachycardia, while adenosine does so only rarely.[418] [419] [420] The response to verapamil

suggests that the slow inward current may be important, possibly in a reentrant circuit or via delayed afterdepolarizations. Several mechanisms may be operative, and the group may not be homogeneous.[182] Oral verapamil is not as effective as IV verapamil. Once initiated, the tachycardia is paroxysmal and sustained. It can be started by rapid atrial or ventricular pacing and sometimes by exercise or isoproterenol. Generally, the prognosis is good.[415] [416] Radiofrequency catheter ablation is effective in symptomatic patients.[408] [413] [421] Late potentials have been reported in one third of patients.[422]

Sudden infant death syndrome is a syndrome of unexplained death that occurs in infancy. The precise cause is not known and is probably due to a variety of etiologies, both cardiac and noncardiac. It is not known what percentage, if any, are due to arrhythmias. Some have suggested that the long QT syndrome (see below) and Brugada syndrome may be responsible in some cases[423] [423A] (see also Chaps. 26 and 43).

Accelerated Idioventricular Rhythm

ELECTROCARDIOGRAPHIC RECOGNITION.

The ventricular rate, commonly between 60 and 110 beats/min, usually hovers within 10 beats of the sinus rate, so control of the cardiac rhythm shifts between these two competing pacemaker sites.[424] Consequently, fusion beats often occur at the onset and termination of the arrhythmia as the pacemakers vie for control of ventricular depolarization (Fig. 25-48) . Because of the slow rate, capture beats are common. The onset of this arrhythmia is generally gradual (nonparoxysmal) and occurs when the rate of the VT exceeds the sinus

Figure 25-46 *A,* Repetitive monomorphic ventricular tachycardia. Short episodes of a monomorphic ventricular tachycardia at a rate of 160 beats/min repeatedly interrupt the normal sinus rhythm. Retrograde atrial capture probably occurs (the arrow points to the deflection in the ST segment), and the retrograde P wave of the last complex of the repetitive monomorphic ventricular tachycardia conducts over the normal pathway to produce a QRS complex with a normal contour. *B,* Short runs of a very rapid (260 beats/min) ventricular tachycardia of uniform contour. They probably provoke a compensatory sympathetic response because each is followed by a brief period of sinus tachycardia. The sinus pacemaker appears unstable as changes in P wave morphology result.

Figure 25-47 Left septal ventricular tachycardia. This tachycardia is characterized by a right bundle branch block contour. In this instance, the axis was rightward. The site of the ventricular tachycardia was established to be in the left posterior septum by electrophysiological mapping and ablation.

rate because of sinus slowing or SA or AV block. The ectopic mechanism can also

begin after a premature ventricular complex, or the ectopic ventricular focus can simply accelerate sufficiently to overtake the sinus rhythm. The slow rate and nonparoxysmal onset avoid the problems initiated by excitation during the vulnerable period, and consequently, precipitation of more rapid ventricular arrhythmias is rarely seen. Termination of the rhythm generally occurs gradually as the dominant sinus rhythm accelerates or as the ectopic ventricular rhythm decelerates. The ventricular rhythm can be regular or irregular and can occasionally show sudden doubling, which suggests the presence of exit block. Many characteristics incriminate enhanced automaticity as the responsible mechanism.

The arrhythmia occurs as a rule in patients who have heart disease, e.g., those with acute myocardial infarction or with digitalis toxicity. It is transient and intermittent, with episodes lasting a few seconds to a minute, and does not appear to seriously affect the patient's clinical course or the prognosis. It commonly occurs at the moment of reperfusion of a previously occluded coronary artery,[425] and it can be found during resuscitation.[426]

MANAGEMENT.

Suppressive therapy is rarely necessary because the ventricular rate is generally less than 100 beats/min, but such therapy may be considered when AV dissociation results in loss of sequential AV contraction, when an accelerated idioventricular rhythm occurs together with a more rapid VT, when an accelerated idioventricular rhythm begins with a premature ventricular complex and causes discharges in the vulnerable period of the preceding T wave, when the ventricular rate is too rapid and produces symptoms, and if ventricular fibrillation develops as a result of the accelerated idioventricular rhythm. This last event appears to be fairly rare. Therapy, when indicated, should be as already noted for VT. Often, simply increasing the sinus rate with atropine or atrial pacing suppresses the accelerated idioventricular rhythm.

Torsades de Pointes

ELECTROCARDIOGRAPHIC RECOGNITION.

The term *torsades de pointes* refers to a VT characterized by QRS complexes of changing amplitude that appear to twist around the isoelectric line and occur at rates of 200 to 250/min[427] [428] [429]

Figure 25-48 Accelerated idioventricular rhythm. In this continuous monitor lead recording, an accelerated idioventricular rhythm competes with the sinus rhythm. Wide QRS complexes at a rate of 90 beats/min fuse (F) with the sinus rhythm, which takes control briefly, generates the narrow QRS complexes, and then yields once again to the accelerated idioventricular rhythm as the P waves move "in and out" of the QRS complex. This example of isorhythmic atrioventricular dissociation may be due to hemodynamic modulation of the sinus rate via the autonomic nervous system.

Figure 25-49 Torsades de pointes. *A,* Continuous monitor lead recording. A demand ventricular pacemaker (VVI) had been implanted because of type II second-degree atrioventricular block. After treatment with amiodarone for recurrent ventricular tachycardia, the QT interval became prolonged (about 640 milliseconds during paced beats), and episodes of torsades de pointes developed. In this recording, the tachycardia spontaneously terminates and a paced ventricular rhythm is restored. Motion artifact is noted at the end of the recording as the patient lost consciousness. *B,* Tracing from a young boy with congenital long QT syndrome. The QTU interval in the sinus beats is at least 600 milliseconds. Note TU wave alternans in the first and second complexes. A late premature complex occurring in the downslope of the TU wave initiates an episode of ventricular tachycardia.

(Fig. 25-49 *A*). Originally described in the setting of bradycardia caused by complete heart block,[430] the term *torsades de pointes* is usually used to connote a *syndrome,* not simply an ECG description of the QRS complex of the tachycardia, characterized by prolonged ventricular repolarization with QT intervals generally exceeding 500 milliseconds. The U wave can also become prominent and merge with the T wave, but its role in this syndrome and in the long QT syndrome is not clear. The abnormal repolarization need not be present or at least prominent on all beats but may be apparent only on the beat prior to the onset of torsades de pointes (i.e., following a premature ventricular contraction).[431] Long-short R-R cycle sequences commonly precede the onset of torsades de pointes from acquired causes.[432] Relatively late premature ventricular complexes can discharge during termination of the long T wave and precipitate successive bursts of VT during which the peaks of the QRS complexes appear successively on one side and then on the other side of the isoelectric baseline and give the typical twisting appearance with continuous and progressive changes in QRS contour and amplitude.[433] Torsades de pointes can terminate with progressive prolongation in cycle length and larger and more distinctly formed QRS complexes and culminate in a return to the basal rhythm, a period of ventricular standstill, and a new attack of torsades de pointes or ventricular fibrillation.

VT that is similar morphologically to torsades de pointes and occurs in patients *without* QT prolongation, whether spontaneous or electrically induced, should generally be classified as polymorphic VT, not as torsades de pointes. The distinction has important therapeutic implications (see below).

ELECTROPHYSIOLOGICAL FEATURES.

The electrophysiological mechanisms responsible for torsades de pointes are not completely understood.[434] [435] Most data suggest that early afterdepolarizations (see Chap. 22) are responsible for both the long QT and the torsades de pointes, or at least its initiation.[436] [437] [438] Perpetuation may be due to triggered activity, reentry resulting from dispersion of repolarization[439] produced by the early afterdepolarizations, or abnormal automaticity. Two out-of-phase discharging foci have been experimentally shown to produce a tachycardia similar to torsades de pointes, as have drifting rotors[440] (see Chap. 22). Dispersion of repolarization from endocardium to epicardium may also

play a role. A distinct group of cells, called M cells, located in the subepicardium have prolonged repolarization and may play a role in the genesis of torsades de pointes.[441] [442] [443]

CLINICAL FEATURES.

While many predisposing factors have been cited, the most common causes are congenital severe bradycardia, potassium depletion, and use of class IA and some class IC drugs. Clinical features depend on whether the torsades de pointes is due to the acquired or congenital (idiopathic) long QT syndrome (see below). Symptoms from the tachycardia depend on its rate and duration, as with other VTs, and range from palpitations to syncope and death. Females, perhaps because of a longer QT interval, are at greater risk for torsades de pointes than are males.[444]

MANAGEMENT.

The approach to VT with a polymorphic pattern depends on whether it occurs in the setting of a prolonged QT interval. For this practical reason and because the mechanism of the tachycardia can differ depending on whether a long QT interval is present, it is important to restrict the definition of torsades de pointes to the typical polymorphic VT in the setting of a long QT and/or U wave in the basal complexes. In all patients with torsades de pointes, administration of class IA, possibly some class IC, and class III antiarrhythmic agents (amiodarone and sotalol) can increase the abnormal QT interval and worsen the arrhythmia. IV magnesium is the initial treatment of choice for torsades de pointes from an acquired cause,[445] [446] followed

by temporary ventricular or atrial pacing. Isoproterenol, given cautiously because it can exacerbate the arrhythmia, can be used to increase the rate until pacing is instituted. Lidocaine, mexiletine, or phenytoin can be tried. Potassium channel openers may be useful.[447] [448] [449] The cause of the long QT should be determined and corrected if possible. When the QT interval is normal, polymorphic VT *resembling* torsades de pointes is diagnosed, and standard antiarrhythmic drugs can be given. In borderline cases, the clinical context may help determine whether treatment should be initiated with antiarrhythmic drugs. Torsades de pointes resulting from congenital long QT syndrome is treated with beta blockade, surgical sympathetic interruption, pacing, and implantable defibrillators (see below). ECGs taken on close relatives can help secure the diagnosis of long QT syndrome in borderline cases.

Long QT Syndrome

ELECTROCARDIOGRAPHIC RECOGNITION(see Fig. 25-49 *B*).

The upper limit for duration of the normal QT interval *corrected* for heart rate (QTc) is

often given as 0.44 seconds. However, the normal corrected QT interval may actually be longer, 0.46 for men and 0.47 for women, with a normal range of plus or minus 15 percent of the mean value.[450] The nature of the U wave abnormality and its relationship to the long QT syndrome are not clear. M cells may be responsible for the U wave[442] (see Chap. 22). The probable risk of life-threatening ventricular arrhythmias developing in patients with idiopathic long QT syndrome is exponentially related to the length of the QTc interval.[450] T wave "humps" in the ECG suggest the presence of long QT syndrome[451] and may be caused by early afterdepolarizations.[452] A point score system has been suggested to aid in the diagnosis.[453] Two-to-one AV block (because of the long repolarization time) and T wave alternans can occur.[454] [455] [456]

CLINICAL FEATURES.

Long QT syndrome can be divided into idiopathic (congenital) and acquired forms.[429] The idiopathic form is a familial disorder that can be associated with sensorineural deafness (Jervell and Lange-Nielsen syndromes, autosomal recessive) or normal hearing (Romano-Ward syndrome, autosomal dominant). A nonfamilial form with normal hearing has been called the sporadic form.

The hypothesis that the idiopathic long QT syndrome results from a preponderance of left sympathetic tone has been replaced by genetic information linking the disorder in different families to sites in several different chromosomes[457] [458] [459] [460] [461] [462] [463] (Table 25-6) . The gene products from several of these mutations have been identified as potassium and sodium channels[464] [465] [466] [467] [468] [469] [470] [471] (see Table 25-5). Clear evidence for genetic heterogeneity exists, and this heterogeneity can be responsible for different-shaped T waves.[471] The chromosome 3 abnormality (LQT3-SCN5A) is associated with the longest QTc durations and delay in onset of the T wave, while the chromosome 7 abnormality (LQT2-HERG) results in T waves of low amplitude and the chromosome 11 mutation (LQT1-KVLQT1) results in the broadest T waves.[471] [472] [473] Thus, the intrinsic cardiac repolarization abnormality probably gives rise to early afterdepolarizations that prolong the QT interval and produce torsades de pointes.

The acquired form has a long QT interval caused by various drugs such as quinidine, procainamide, *N*-acetylprocainamide, sotalol,[474] amiodarone, disopyramide,[475] phenothiazines, or tricyclic antidepressants; cisapride;[476] nonsedating antihistamines such as astemizole and terfenedine,[477] [478] [479] whose actions can be exacerbated by drugs affecting their metabolism such as ketoconazoles; drugs such as erythromycin,[480] [481] [482] pentamidine,[483] [484] and some antimalarials; electrolyte abnormalities such as hypokalemia and hypomagnesemia; the results of a liquid protein diet and starvation; central nervous system lesions; significant bradyarrhythmias; cardiac ganglionitis; mitral valve prolapse; and probucol.[485] The acquired long QT syndrome may be a *forme fruste* of the inherited form.[486]

Patients with congenital long QT syndrome can initially have syncope, at times misdiagnosed as epilepsy,[487] [488] [489] from VTs that are often caused by torsades de pointes. Sudden death can occur in this group of patients, and it occurs in about 10 percent of pediatric patients without preceding symptoms.[488] [490] It is obvious that in some patients the ventricular arrhythmia becomes sustained and probably results in

ventricular fibrillation. Patients with idiopathic long QT syndrome who are at increased risk for sudden death include those with family members who died suddenly at an early age and those who have experienced syncope. It also appears that the specific mutations carry different risks, with LQT1 and LQT2 carrying the highest risk for arrhythmias. Although patients with the LQT3 mutation tend to have fewer cardiac events, they tend to be more lethal ones. Thus, the cumulutive mortality appears to be the same for LQT1, LQT2, and LQT3.[491] Ventricular tachyarrhythmias commonly develop during periods of adrenergic stimulation, such as fright or exertion. However, some phenotypic variation is noted, such that patients with LQT1 and LQT2 mutations tend be more sympathetically driven whereas LQT3 patients tend to have more events during sleep.[491] Syndactyly has recently been described in some patients with the idiopathic form.[492]

Stress testing can prolong the QT interval and produce T wave alternans, the latter indicative of electrical instability.[493] ECGs should be obtained for all family members when the propositus has symptoms. Patients should undergo prolonged ECG recording with various stresses designed to evoke ventricular arrhythmias, such as auditory stimuli, psychological stress, cold pressor stimulation, and exercise.[494] [495] The Valsalva maneuver can lengthen the QT interval and cause T wave alternans and VT in patients who have prolonged QT syndromes. Catecholamines can be infused in some patients,[496] [497] [498] but this challenge must be performed cautiously, with resuscitative equipment along with alpha and beta antagonists close at hand. Stellate ganglion stimulation and blockade have been useful to provoke or abolish arrhythmias. Premature ventricular stimulation electrically does not generally induce arrhythmias in this syndrome. Torsades de pointes commonly develops in patients with the acquired form during periods of bradycardia or after a long pause in the R-R interval, whereas those with the idiopathic form can have a sinus tachycardia preceding the ventricular arrhythmia. Competitive sports are contraindicated for patients with the congenital long QT syndrome.[49] An interesting contractile abnormality that is

TABLE 25-6 -- GENETIC BASIS OF THE LONG QT SYNDROME

CHROMOSOME	GENE	CHANNEL	EFFECT OF MUTATION	AUTOSOMAL DOMINANT	AUTOSOMAL RECESSIVE
11p15.5	*KVLQT1*	I_{Ks}	Function	LQT1	JLN1
7q35-36	*HERG*	I_{Kr}	Function	LQT2	--
3q21-24	*SCN5A*	I_{Na}	Function	LQT3	--
4q25-27	?	?	?	LQT4	--
21q22	*MinK*	I_{Ks}	Function	LQT5	JLN2

abolished by verapamil has been described in patients with the idiopathic long QT syndrome.[499] Cardiac sympathetic innervation appears to be normal,[500] although this point is not completely resolved.[501]

MANAGEMENT.

For patients who have idiopathic long QT syndrome but do not have syncope, complex ventricular arrhythmias, or a family history of sudden cardiac death, generally no therapy is recommended. In asymptomatic patients with complex ventricular arrhythmias or a family history of early sudden cardiac death, beta-adrenoceptor blockers at maximally tolerated doses are recommended initially. Implantation of a permanent pacemaker to prevent the bradycardia and/or pauses that may predispose to the development of torsades de pointes may be indicated.[28] [502] [503] In patients with syncope, beta blockers at maximally tolerated doses, perhaps combined with a class IB antiarrhythmic drug, are suggested. For patients who continue to have syncope despite maximum drug therapy, left-sided cervicothoracic sympathetic ganglionectomy that interrupts the stellate ganglion and the first three or four thoracic ganglia may be helpful, and permanent pacing[504] has also been used. Implantation of a cardioverter-defibrillator seems advisable in patients who have syncope despite sympathetic interruption or in patients in whom aborted sudden death is the initial manifestation of long QT syndrome[28] [429] [505] (see Chap 24). For patients with the acquired form and torsades de pointes, IV magnesium and atrial or ventricular pacing are initial choices. Class IB antiarrhythmic drugs or isoproterenol (cautiously) to increase the heart rate can be tried. Avoidance of precipitating drugs is mandatory. Potassium channel-activating drugs such as pinacidil and cromakalim may be useful[447] [448] [449] in both forms of long QT syndrome. Interventions that reduce QT dispersion may be beneficial.[504]

Bidirectional Ventricular Tachycardia

This uncommon type of VT is characterized by QRS complexes with a right bundle branch block pattern, alternating polarity in the frontal plane from -60 to -90 degrees to +120 to +130 degrees, and a regular rhythm. The ventricular rate is between 140 and 200 beats/min. Although the mechanism and site of origin of this tachycardia have remained somewhat controversial, most evidence supports a ventricular origin.

Bidirectional VT is usually, but not exclusively a manifestation of digitalis excess, typically in older patients and in those with severe myocardial disease. When the tachycardia is due to digitalis, the extent of toxicity is often advanced, with a poor prognosis.

In addition to digoxin-binding antibodies (Digibind), drugs useful to treat digitalis toxicity such as lidocaine, potassium, phenytoin, and propranolol should be considered if excessive digitalis administration is suspected. Otherwise, the usual therapeutic

approach to VT is recommended.

Bundle Branch Reentrant Ventricular Tachycardia

VT secondary to bundle branch reentry is characterized by a QRS morphology determined by the circuit established over the bundle branches or fascicles. Retrograde conduction over the left bundle branch system and anterograde conduction over the right bundle branch create a QRS complex with a left bundle branch block contour and constitute the most common form. The frontal plane axis may be about +30 degrees. Conduction in the opposite direction produces a right bundle branch block contour. Reentry can also occur over the anterior and posterior fascicles. Electrophysiologically, bundle branch reentrant complexes are started after a critical S_2 -H_2 or S_3 -H_3 delay. The H-V interval of the bundle branch reentrant complex equals or exceeds the H-V interval of the spontaneous normally conducted QRS complex.

Bundle branch reentry is a form of monomorphic sustained VT that is usually seen in patients with structural heart disease such as dilated cardiomyopathy. During follow-up, congestive heart failure is the most common cause of death in this population.[506] [507] Myocardial VTs can also be present. Uncommonly, bundle branch reentry can occur in the absence of myocardial disease.[506] [507]

The therapeutic approach is as for other types of VT, except that creation of a bundle branch block by catheter ablation interrupts the reentry circuit and can eliminate the tachycardia.[508]

Ventricular Flutter and Fibrillation (See also Chap. 26)

ELECTROCARDIOGRAPHIC RECOGNITION.

These arrhythmias represent severe derangements of the heartbeat that usually terminate fatally within 3 to 5 minutes unless corrective measures are undertaken promptly. Ventricular flutter is manifested as a sine wave in appearance: regular large oscillations occurring at a rate of 150 to 300/min (usually about 200) (Fig. 25-50 *A*). The distinction between rapid VT and ventricular flutter can be difficult and is usually of academic interest only. Hemodynamic collapse is present with both. Ventricular fibrillation is recognized by the presence of irregular undulations of varying contour and amplitude (Fig. 25-50 *B*). Distinct QRS complexes, ST segments, and T waves are absent. Fine-amplitude fibrillatory waves (0.2 mV) are present with prolonged ventricular fibrillation. These fine waves identify patients with worse survival rates and are sometimes confused with asystole.[509]

MECHANISMS.

Ventricular fibrillation occurs in a variety of clinical situations but is most commonly associated with coronary artery disease and as a terminal event.[510] Intracellular calcium accumulation,[511] the action of free radicals, metabolic alterations, and autonomic modulation are some important influences on the development of ventricular fibrillation

during ischemia. Thrombolytic agents reduce the incidence of ventricular arrhythmias[512] and inducible VT after myocardial infarction. Cardiovascular events, including sudden cardiac death from ventricular fibrillation, but not asystole,[513] occur most frequently in the morning and may be related to increased platelet aggregability. Aspirin reduces this mortality. An excess in sudden deaths appears to occur during the winter months.[514] Ventricular fibrillation can occur during antiarrhythmic drug administration, hypoxia, ischemia, atrial fibrillation, and very rapid ventricular rates in the preexcitation syndrome; after electrical shock administered during cardioversion (see Chaps. 23 and 24) or accidentally by improperly grounded equipment; and during competitive ventricular pacing to terminate VT.

Figure 25-50 Ventricular flutter and ventricular fibrillation. *A,* The sine wave appearance of the complexes occurring at a rate of 300 beats/min is characteristic of ventricular flutter. *B,* The irregular undulating baseline typifies ventricular fibrillation.

CLINICAL FEATURES.

Ventricular flutter or ventricular fibrillation results in faintness, followed by loss of consciousness, seizures, apnea, and eventually, if the rhythm continues untreated, death. The blood pressure is unobtainable, and heart sounds are usually absent. The atria can continue to beat at an independent rhythm for a time or in response to impulses from the fibrillating ventricles. Eventually, electrical activity of the heart ceases.

In patients resuscitated from out-of-hospital cardiac arrest, 75 percent have ventricular fibrillation. Bradycardia or asystole, which can occur in 15 to 25 percent of these patients, is associated with a worse prognosis than is ventricular fibrillation and is usually associated with more advanced LV dysfunction. VT commonly precedes the onset of ventricular fibrillation, although frequently no consistent premonitory patterns emerge. Heart rate variability may be decreased.[515] [516]

While 75 percent of resuscitated patients exhibit significant coronary artery disease, acute transmural myocardial infarction develops in only 20 to 30 percent. In one study, 73 percent had recent coronary artery thrombosis.[517] Those in whom myocardial infarction does *not* develop have an increased recurrence rate for sudden cardiac death or ventricular fibrillation. Patients who have ventricular fibrillation and acute myocardial infarction have a recurrence rate at 1 year of 2 percent. In the past 20 years, there appears to have been an overall decrease in the incidence of sudden cardiac death, parallel to the decrease in death from coronary heart disease. In some studies, patients at risk for sudden cardiac death have ischemia, reduced LV function, 10 or more premature ventricular complexes per hour, spontaneous and induced VT, hypertension and LV hypertrophy, obesity, and elevated cholesterol levels; smoking, male sex, increased age, and excess alcohol consumption also predispose to sudden cardiac

death (see Chap. 26).

Predictors of death for resuscitated patients include a reduced EF,[518] [519] abnormal wall motion, history of congestive heart failure, history of myocardial infarction but no acute event, and the presence of ventricular arrhythmias. Patients discharged after an anterior myocardial infarction complicated by ventricular fibrillation appear to represent a subgroup at high risk of sudden death. Ventricular fibrillation can occur in infants, young people, athletes, and persons without known structural heart disease[520] [521] and in unexplained syndromes. Severe bradycardia or asystole bodes a reduced survival rate for most patients. Transcutaneous pacing for severe bradyarrhythmias does not seem to be helpful.[522] Persons in lower socioeconomic strata are at greater risk for cardiac mortality and are less likely to survive an episode of out-of-hospital cardiac arrest.[523]

MANAGEMENT(see Chap. 26).

Immediate nonsynchronized DC electrical shock using 200 to 400 J is mandatory therapy for ventricular fibrillation and for ventricular flutter that has caused loss of consciousness. Cardiopulmonary resuscitation is used only until the defibrillation equipment is readied. Time should not be wasted with cardiopulmonary resuscitation maneuvers if electrical defibrillation can be done promptly. Defibrillation requires fewer joules if done early. If the circulation is markedly inadequate despite return to sinus rhythm, closed-chest massage with artificial ventilation as needed should be instituted. The use of anesthesia during electrical shock is obviously dictated by the patient's condition and is not generally required. After conversion of the arrhythmia to a normal rhythm, it is essential to monitor the rhythm continuously and institute measures to prevent recurrence.

Metabolic acidosis quickly follows cardiovascular collapse. If the arrhythmia is terminated within 30 to 60 seconds, significant acidosis does not occur. Judicious use of sodium bicarbonate to reverse the acidosis may be necessary (see Chap 26). Intravenous calcium is generally recommended only for situations characterized by hypocalcemia, hyperkalemia, calcium antagonist overdose, and possibly electromechanical dissociation.

If the resuscitation time is short, artificial ventilation by means of a tightly fitting rubber face mask and an AMBU bag is quite satisfactory and eliminates the delay attending intubation by inexperienced personnel. If such a mask and bag are not available, mouth-to-mouth or mouth-to-nose resuscitation is indicated. It is important to reemphasize that there should be *no delay in instituting electrical shock.* If the patient is not monitored and it cannot be established whether asystole or ventricular fibrillation caused the cardiovascular collapse, the electrical shock should be administered *without* wasting precious seconds attempting to obtain an ECG. The DC shock may cause the asystolic heart to begin discharging and also terminate ventricular fibrillation, if the latter is present.

A search for conditions contributing to the initiation of ventricular flutter or fibrillation should be made and the conditions corrected, if possible. Initial medical approaches to prevent recurrence of ventricular fibrillation include IV administration of lidocaine,

bretylium, procainamide, or amiodarone. Ventricular fibrillation rarely terminates spontaneously, and death results unless countermeasures are instituted immediately. Subsequent therapy is necessary to prevent recurrence. Antiischemic approaches are useful in selected patients.[524] Catheter ablation techniques are useful in only well-tolerated monomorphic ventricular arrhythmias.[525] Implantable defibrillators have become the mainstay of chronic therapy in patients at continued risk for ventricular fibrillation or VT from nonreversible causes (see discussion above).

HEART BLOCK

Heart block is a disturbance of impulse conduction that can be permanent or transient depending on the anatomical or functional impairment. It must be distinguished from *interference,* a normal phenomenon that is a disturbance of impulse conduction caused by physiological refractoriness resulting from inexcitability from a preceding impulse. Either interference or block can occur at any site where impulses are conducted, but they are recognized most commonly between the sinus node and atrium (SA block), between the atria and ventricles (AV block), within the atria (intraatrial block), or within the ventricles (intraventricular block). During AV block, the block can occur in the AV node, His bundle, or bundle branches. In some instances of bundle branch block the impulse may only be delayed and not completely blocked in the bundle branch, yet the resulting QRS complex may be indistinguishable from a QRS complex generated by a complete bundle branch block.

The conduction disturbance is classified by severity into three categories. During *first-degree heart block,* conduction time is prolonged but all impulses are conducted. *Second-degree heart block* occurs in two forms: Mobitz type I (Wenckebach) and type II. Type I heart block is characterized by a progressive lengthening of the conduction time until an impulse is not conducted. Type II heart block denotes occasional or repetitive sudden block of conduction of an impulse without prior measurable lengthening of conduction time. When no impulses are conducted, *complete* or *third-degree block* is present. The degree of block may depend in part on the direction of impulse propagation. For unknown reasons, normal retrograde conduction can occur in the presence of advanced anterograde AV block. The reverse can also occur. Some electrocardiographers use the term *advanced heart block* to indicate blockage of two or more consecutive impulses.[526]

Certain features of type I second-degree block deserve special emphasis because when actual conduction times are

Figure 25-51 Typical 4:3 Wenckebach cycle. P waves ("A" tier) occur at a cycle length of 1000 milliseconds. The PR interval ("AV" tier) is 200 milliseconds for the first beat and generates a ventricular response ("V" tier). The PR interval increases by 100 milliseconds in the next complex, which results in an R-R interval of 1100 milliseconds (1000+100). The increment in the PR interval is only 50 milliseconds

for the third cycle, and the PR interval becomes 350 milliseconds. The R-R interval shortens to 1050 milliseconds (1000+50). The next P wave is blocked, and an R-R interval is created that is less than twice the P-P interval by an amount equal to the increments in the PR interval. Thus, the Wenckebach features explained in the text can be found in this diagram. If the increment in the PR interval of the last conducted complex increased rather than decreased (e.g., 150 milliseconds rather than 50 milliseconds), the last R-R interval before the block would increase (1150 milliseconds) rather than decrease and thus become an example of an atypical Wenckebach cycle (see Fig. 25-45). If this were a Wenckebach exit block from the sinus node to the atrium, the sinus node cycle length (S) would be 1000 milliseconds, and the sinoatrial interval would increase from 200 to 300 to 350 milliseconds and culminate in a block. These events would be inapparent in the scalar electrocardiogram (ECG). However, the P-P interval in the ECG would shorten from 1100 to 1050 milliseconds, and finally, there would be a pause of 1850 milliseconds (A) (see Fig. 22-4). If this rhythm were a junctional rhythm arising from the His bundle and conducting to the ventricle, the junctional rhythm cycle length would be 1000 milliseconds (H), and the H-V interval would progressively lengthen from 200 to 300 to 350 milliseconds, whereas the R-R interval would decrease from 1100 to 1050 milliseconds and then increase to 1850 milliseconds (V). The only clue to the Wenckebach exit block would be the cycle length changes in the ventricular rhythm.

not apparent in the ECG, e.g., during SA, junctional, or ventricular exit block (Fig. 25-51) , a type I conduction disturbance can be difficult to recognize. During a typical type I block, the increment in conduction time is greatest in the second beat of the Wenckebach group, and the absolute *increase* in conduction time *decreases* progressively over subsequent beats. These two features serve to establish the characteristics of classic Wenckebach group beating: (1) The interval between successive beats progressively decreases, although the conduction time increases (but by a decreasing function); (2) the duration of the pause produced by the nonconducted impulse is less than twice the interval preceding the blocked impulse (which is usually the shortest interval); and (3) the cycle following the nonconducted beat (beginning the Wenckebach group) is longer than the cycle preceding the blocked impulse. Although much emphasis has been placed on this characteristic grouping of cycles, primarily to be able to diagnose a Wenckebach exit block, this typical grouping occurs in fewer than 50 percent of patients who have a type I Wenckebach AV nodal block.

Differences in these cycle length patterns can result from changes in pacemaker rate (e.g., sinus arrhythmia), in neurogenic control of conduction, and in the increment of conduction delay. For example, if the PR increment in the last cycle *increases,* the R-R cycle of the last conducted beat can lengthen rather than shorten. In addition, since the last conducted beat is often at a critical state of conduction, it can become blocked and produce a 5:3 or 3:1 conduction ratio instead of a 5:4 or 3:2 ratio. During a 3:2 Wenckebach structure, the duration of the cycle following the nonconducted beat will be the same as the duration of the cycle preceding the nonconducted beat.

AV Block

An AV block exists when the atrial impulse is conducted with delay or is not conducted at all to the ventricle at a time when the AV junction is not physiologically refractory.

FIRST-DEGREE AV BLOCK.

During first-degree AV block, every atrial impulse conducts to the ventricles and a regular ventricular rate is produced, but the PR interval exceeds 0.20 second in adults.

PR intervals as long as 1.0 second have been noted and can at times exceed the P-P interval, a phenomenon known as "skipped" P waves. Clinically important PR interval prolongation can result from a conduction delay in the AV node (A-H interval), in the His-Purkinje system (H-V interval), or at both sites. Equally delayed conduction over both bundle branches can uncommonly produce PR prolongation without significant QRS complex aberration. Occasionally, an intraatrial conduction delay can result in PR prolongation. If the QRS complex in the scalar ECG is normal in contour and duration, the AV delay almost always resides in the AV node, rarely within the His bundle itself. If the QRS complex shows a bundle branch block pattern, the conduction delay may be within the AV node and/or His-Purkinje system (Fig. 25-52) . In this latter instance, His bundle ECG is necessary to localize the site of conduction delay. Acceleration of the atrial rate or enhancement of vagal tone by carotid massage can cause first-degree AV nodal block to progress to type I second-degree AV block. Conversely, type I second-degree AV nodal block can revert to first-degree block with deceleration of the sinus rate.

SECOND-DEGREE AV BLOCK (Figs. 25-51 , 25-53 , and 25-54).

Blocking of some atrial impulses conducted to the ventricle at a time when physiological interference is not

Figure 25-52 First-degree atrioventricular (AV) block. One complex during sinus rhythm is shown. The PR interval in the *left* panel measured 370 milliseconds (PA = 25 milliseconds; A-H = 310 milliseconds; H-V = 35 milliseconds) during a right bundle branch block. Conduction delay in the AV node causes the first-degree AV block. In the panel on the *right*, the PR interval is 230 milliseconds (PA = 35 milliseconds; A-H = 100 milliseconds; H-V = 95 milliseconds) during a left bundle branch block. The conduction delay in the His-Purkinje system causes the first-degree AV block.

Figure 25-53 Unidirectional block. *Top*, During spontaneous sinus rhythm at a rate of 68 beats/min, 2:1 anterograde atrioventricular conduction occurs. In the *bottom* electrocardiogram, 1:1 retrograde conduction is seen during ventricular pacing at a rate of 70 beats/min. P waves are indicated by arrows.

involved constitutes second-degree AV block. The nonconducted P wave can be intermittent or frequent, at regular or irregular intervals, and can be preceded by fixed or lengthening PR intervals. A distinguishing feature is that conducted P waves relate to the QRS complex with recurring PR intervals; i.e., the association of P with QRS is not random. Wenckebach and Hay, by analyzing the *a-c* and *v* waves in the jugular venous pulse, described two types of second-degree AV block. After introduction of the ECG, Mobitz classified them as type I and type II. Electrocardiographically, typical type I second-degree AV block is characterized by progressive PR prolongation culminating in a nonconducted P wave (see Fig. 25-53), whereas in type II second-degree AV block,

the PR interval remains constant prior to the blocked P wave (Fig. 25-55 *A*). In both instances the AV block is intermittent and generally repetitive and can block several P waves in a row. Often, the eponyms *Mobitz type I* and *Mobitz type II* are applied to the two types of block, whereas the term *Wenckebach block* refers to type I block only. A Wenckebach block in the His-Purkinje system in a patient with a bundle branch block can resemble an AV nodal Wenckebach block very closely (Fig. 25-55 *B*).

Although it has been suggested that type I and type II AV blocks are different manifestations of the same electrophysiological mechanism that differ only quantitatively in the size of the increments, clinically separating second-degree AV block into type I and type II serves a useful function, and in most instances, the differentiation can be made easily and reliably from the surface ECG. Type II AV block often antedates the development of Adams-Stokes syncope and complete AV block, while type I AV block with a normal QRS complex is generally more benign and does not progress to more advanced forms of AV conduction disturbance. In older people, type I AV block with or without bundle branch block has been associated with a clinical picture similar to that in type II AV block.

In a patient with an acute myocardial infarction, type I AV block usually accompanies inferior infarction (perhaps more often if a right ventricular infarction also occurs), is transient, and does not require temporary pacing, whereas type II AV block occurs in the setting of an acute anterior myocardial infarction, can require temporary or permanent pacing, and is associated with a high rate of mortality, generally from pump failure.[527] A high degree of AV block can occur in patients with acute inferior myocardial infarction and is associated with more myocardial damage and a higher mortality rate than in those without AV block.

While type I conduction disturbance is ubiquitous and can occur in any cardiac tissue in vivo, as well as in vitro, the site of block for the usual forms of second-degree AV block can be judged from the surface ECG with sufficient reliability to permit clinical decisions without requiring invasive electrophysiological studies in most instances. Type I AV block with a normal QRS complex almost always takes place at the level of the AV node, proximal to the His bundle. An exception is the uncommon patient with type I intrahisian block. Type II AV block, particularly in association with a bundle branch block, is localized to the His-Purkinje system. Type I AV block in a patient with a bundle branch block can be due to block in the AV node or in the His-Purkinje system. Type II AV block in a patient with a normal QRS complex can be due to an intrahisian AV block, but the block is likely to be a type I AV nodal block, which exhibits small increments in AV conduction time.

Figure 25-54 Type I (Wenckebach) atrioventricular (AV) nodal block *(A)*. During spontaneous sinus rhythm, progressive PR prolongation occurs and culminates in a nonconducted P wave. From the His bundle recording (HBE) it is apparent that the conduction delay and subsequent block occur within the AV node. Since the increment in conduction delay does not consistently decrease, the R-R intervals do not reflect the classic Wenckebach structure. Panel *B* was recorded 5 minutes after the administration of 0.6 mg atropine intravenously. Atropine has had its predominant effect on sinus and junctional automaticity by this time, with little improvement in AV conduction. Consequently, more P waves are blocked and AV dissociation, caused by a combination of AV block and an enhanced junctional discharge rate, is present.

At 8 minutes (not shown), when atropine finally improved AV conduction, 1:1 AV conduction occurred.

Figure 25-55 Type II atrioventricular (AV) block. *A,* The sudden development of a His-Purkinje block is apparent. The A-H and H-V intervals remain constant, as does the PR interval. Left bundle branch block is present. *B,* Wenckebach AV block in the His-Purkinje system. The QRS complex exhibits a right bundle branch block morphology. However, note that the second QRS complex in the 3:2 conduction exhibits a slightly different contour from the first QRS complex, particularly in V_1 . This finding is the clue that the Wenckebach AV block might be in the His-Purkinje system. The H-V interval increases from 70 milliseconds to 280 milliseconds, and then block distal to the His bundle results.

DIFFERENTIATING TYPE I FROM TYPE II AV BLOCK.

The preceding generalizations encompass the vast majority of patients with second-degree AV block. However, certain caveats must be heeded to avoid misdiagnosis because of subtle ECG changes or exceptions:

1. The 2:1 AV block can be a form of type I or type II AV block (Fig. 25-56) . If the QRS complex is normal, the block is more likely to be type I and located in the AV node, and one should search for transition of the 2:1 block to a 3:2 block, during which the PR interval lengthens in the second cardiac cycle. If a bundle branch block is present, the block can be located either in the AV node or in the His-Purkinje system.
2. AV block can occur simultaneously at two or more levels and can cause difficulty in distinguishing between types I and II.[528]
3. If the atrial rate varies, it can alter conduction times and cause a type I AV block to stimulate a type II block or change a type II AV block into type I.[529] For example, if the shortest atrial cycle length that just achieved 1:1 AV nodal conduction at a constant PR interval is decreased by as little as 10 or 20 milliseconds, the P wave of the shortened cycle can block conduction at the level of the AV node without an apparent increase in the antecedent PR interval. An apparent type II AV block in the His-Purkinje system can be converted to type I in the His-Purkinje system in some patients by increasing the atrial rate.
4. Concealed premature His depolarizations can create ECG patterns that simulate type I or type II AV block.
5. Abrupt, transient alterations in autonomic tone can cause sudden block of one or more P waves without altering the PR interval of the conducted P wave before or after the block. Thus, an apparent type II AV block would be produced at the AV node. Clinically, a burst of vagal tone usually lengthens the P-P interval, as well as producing an AV block.
6. The response of the AV block to autonomic changes either spontaneous or induced to distinguish type I from type II AV block can be misleading. Although vagal stimulation generally increases and vagolytic agents decrease the extent of type I AV block, such conclusions are based on the assumption that the

intervention acts primarily on the AV node and fail to consider rate changes. For example, atropine can minimally improve conduction in the AV node and markedly increase the sinus rate, which results in an *increase* in AV nodal conduction time and the degree of AV block as a result of the faster atrial rate (see Fig. 25-54 *B*). Conversely, if an increase in vagal tone minimally prolongs AV conduction time but greatly slows the heart rate, the net effect on type I AV block may be to improve conduction. In general, however, carotid sinus massage improves and atropine worsens AV conduction in patients with His-Purkinje block, while the opposite results are to be expected in patients who have AV nodal block. These two interventions can help differentiate the site of block without invasive study, although damaged His-Purkinje tissue may be influenced by changes in autonomic tone.

7. During type I AV block with high ratios of conducted beats, the increment in PR interval can be quite small and suggest a type II AV block if only the last few PR intervals before the blocked P wave are measured. By comparing the PR interval of the first beat in the long Wenckebach cycle with that of the beats immediately preceding the blocked P wave, the increment in AV conduction becomes readily apparent.
8. The classic AV Wenckebach structure depends on a stable atrial rate and a maximal increment in AV conduction time for the second PR interval of the Wenckebach cycle, with a progressive decrease in subsequent beats. Unstable or unusual alterations in the increment of AV conduction time or in the atrial rate, often seen with long Wenckebach cycles, result in atypical forms of type I AV block in which the last R-R interval can lengthen because the PR increment *increases;* these alterations are common.
9. Finally, it is important to remember that the PR interval in the scalar ECG is made up of conduction through the atrium, the AV node, and the His-Purkinje system. An increment in H-V conduction, for example, can be masked in the scalar ECG by a reduction in the A-H interval, and the resulting PR interval will not reflect the entire increment in His-Purkinje conduction time. Very long PR intervals (200 milliseconds) are more likely to result from AV nodal conduction delay (and block), with or without concomitant His-Purkinje conduction delay, although an H-V interval of 350 milliseconds is quite possible.

Figure 25-56 A 2:1 atrioventricular (AV) block proximal and distal to the His bundle deflection in two different patients. *Top,* A 2:1 AV block seen in the scalar electrocardiogram occurs distal to the His bundle recording site in a patient with right bundle branch block and anterior hemiblock. The A-H interval (150 milliseconds) and H-V interval (80 milliseconds) are both prolonged. *Bottom,* A 2:1 AV block proximal to the bundle of His in a patient with a normal QRS complex. The A-H interval (75 milliseconds) and the H-V interval (30 milliseconds) remain constant and normal.

First-degree and type I second-degree AV block can occur in normal healthy children, and a Wenckebach AV block can be a normal phenomenon in well-trained athletes, probably related to an increase in resting vagal tone. Occasionally, progressive

worsening of the Wenckebach AV conduction disorder can result and the athlete becomes symptomatic and has to decondition. In patients who have chronic second-degree AV nodal block (proximal to the His bundle) without structural heart disease, the course is relatively benign (except in older age groups), whereas in those who have structural heart disease the prognosis is poor and related to the underlying heart disease. *Advanced AV block* indicates a block of two or more consecutive P waves.

Complete AV Block

ELECTROCARDIOGRAPHIC RECOGNITION.

Complete AV block occurs when no atrial activity is conducted to the ventricles and, therefore, the atria and ventricles are controlled by independent pacemakers. Thus, complete AV block is one type of complete AV dissociation. The atrial pacemaker can be sinus or ectopic (tachycardia, flutter, or fibrillation) or can result from an AV junctional focus occurring above the block with retrograde atrial conduction. The ventricular focus is usually located just below the region of the block, which can be above or below the His bundle bifurcation. Sites of ventricular pacemaker activity that are in or closer to the His bundle appear to be more stable and can produce a faster escape rate than can those located more distally in the ventricular conduction system. The ventricular rate in acquired complete heart block is less than 40 beats/min but can be faster in congenital complete AV block. The ventricular rhythm, usually regular, can vary in response to premature ventricular complexes, a shift in the pacemaker site, an irregularly discharging pacemaker focus, or autonomic influences.

MECHANISMS.

Complete AV block can result from block at the level of the AV node (usually congenital) (Fig. 25-57) , within the bundle of His, or distal to it in the Purkinje system (usually acquired) (Fig. 25-58) . Block proximal to the His bundle generally exhibits normal QRS complexes and rates of 40 to 60 beats/min because the escape focus that controls the ventricle arises in or near the His bundle. In complete AV nodal block, the P wave is not followed by a His deflection, but each ventricular complex is preceded by a His deflection (see Fig. 25-57). His bundle ECG can be useful to differentiate AV nodal from intrahisian block since the latter may carry a more serious prognosis than the former. Intrahisian block is recognized infrequently without invasive studies. In patients with AV nodal block, atropine usually speeds both the atrial and the ventricular rates. Exercise can reduce the extent of AV nodal block. Acquired complete AV block occurs most commonly distal to the bundle of His because of trifascicular conduction disturbance. Each P wave is followed by a His deflection, and the ventricular escape complexes are not preceded by a His deflection (see Fig. 25-58). The QRS complex is abnormal, and the ventricular rate is usually less than 40 beats/min.

Unusual forms such as paroxysmal AV block or AV block following a period of rapid ventricular rates can occur. Paroxysmal AV block in some instances can be due to hyperresponsiveness of the AV node to vagotonic reflexes. Surgery, electrolyte disturbances, myoendocarditis,[530] tumors, Chagas disease, rheumatoid nodules, calcific

aortic stenosis, myxedema, polymyositis, infiltrative processes (such as amyloid, sarcoid, or scleroderma), and an almost endless assortment of common and unusual conditions can produce AV block. In adults, drug toxicity, coronary disease,

Figure 25-57 Congenital third-degree atrioventricular (AV) block. *A,* Complete AV nodal block is apparent. No P wave is followed by a His bundle potential, whereas each ventricular depolarization is preceded by a His bundle potential. *B,* Atrial pacing (cycle length of 500 milliseconds) fails to alter the cycle length of the functional rhythm. Still, no P wave is followed by a His bundle potential. *C,* After 30 seconds of ventricular pacing (cycle length of 700 milliseconds), suppression of the junctional focus results for almost 7 seconds (overdrive suppression of automaticity; see Chapter 22).

Figure 25-58 Complete anterograde atrioventricular (AV) block with retrograde ventriculoatrial conduction. All the sinus P waves are blocked distal to the His bundle, consistent with acquired complete AV block. The ventricles escape at a cycle length of approximately 1800 milliseconds (33 beats/min) and are not preceded by His bundle activation. The ventricular escape rhythm produces a QRS contour with left-axis deviation and right bundle branch block, possibly caused by impulse origin in the posterior fascicle of the left bundle branch. Of interest is the fact that the second ventricular escape beat conducts retrogradely through His (H) and to the atrium (note the low-high atrial activation sequence and the negative P wave in leads II and III). The first ventricular complex does not conduct retrogradely, probably because the His bundle is still refractory from the immediately preceding atrial impulse.

and degenerative processes appear to be the most common causes of AV heart block. The degenerative process produces partial or complete anatomical or electrical disruption within the AV nodal region, the AV bundle, or both bundle branches. Rapid rates can sometimes be followed by block, an event known as *overdrive suppression* of conduction. This form of block may be important as a cause of paroxysmal AV block after cessation of a tachycardia.

Atrioventricular Block in Children.

In children, the most common cause of AV block is congenital (see Chap. 43). Under such circumstances, the AV block can be an isolated finding or be associated with other lesions. Connective tissue disease and the presence of anti-Rh_0 -negative antibodies in the maternal sera of patients with congenital complete AV block raise the possibility that placentally transmitted antibodies play a role in some instances.[531] [532] [533] Anatomical disruption between the atrial musculature and peripheral parts of the conduction system and nodoventricular discontinuity are two common histological findings. Children are most often asymptomatic; however, in some children symptoms develop that require pacemaker implantation. Mortality from congenital AV block is highest in the neonatal period, is much lower during childhood and adolescence, and increases slowly later in life. Adams-Stokes attacks can occur in patients with congenital heart block at any age. It is difficult to predict the prognosis in an individual patient. A persistent heart rate at

rest of 50 beats/min or less correlates with the incidence of syncope, and extreme bradycardia can contribute to the frequency of Adams-Stokes attacks in children with congenital complete AV block. The site of block may not distinguish symptomatic children who have congenital or surgically induced complete heart block from those without symptoms. Prolonged recovery times of escape foci following rapid pacing (see Fig. 25-57 *C*) (see discussion of sinus node recovery time, Chap. 23) slow heart rates on 24-hour ECG recordings, and the occurrence of paroxysmal tachycardias may be predisposing factors to the development of symptoms.

CLINICAL FEATURES.

Many of the signs of AV block are evidenced at the bedside. First-degree AV block can be recognized by a long *a-c* wave interval in the jugular venous pulse and by diminished intensity of the first heart sound as the PR interval lengthens. In type I second-degree AV block, the heart rate may increase imperceptibly with gradually diminishing intensity of the first heart sound, widening of the *a-c* interval, terminated by a pause, and an *a* wave not followed by a *v* wave. Intermittent ventricular pauses and *a* waves in the neck not followed by *v* waves characterize type II AV block. The first heart sound maintains a constant intensity. In complete AV block, the findings are the same as those in AV dissociation (see below).

Significant clinical manifestations of first- and second-degree AV block usually consist of palpitations or subjective feelings of the heart "missing a beat." Persistent 2:1 AV block can produce symptoms of chronic bradycardia. Complete AV block can be accompanied by signs and symptoms of reduced cardiac output, syncope or presyncope, angina, or palpitations from ventricular tachyarrhythmias. It can occur in twins.[534]

MANAGEMENT.

As discussed in Chapter 23 , drugs cannot be relied on to increase the heart rate for more than several hours to several days in patients with symptomatic heart block without producing significant side effects. Therefore, temporary or permanent pacemaker insertion is indicated in patients with symptomatic bradyarrhythmias.[535] Long-term pacing can alter cardiac function.[536] For short-term therapy when the block is likely to be evanescent but still requires treatment or until adequate pacing therapy can be established, vagolytic agents such as atropine are useful for patients who have AV nodal disturbances, whereas catecholamines such as isoproterenol can be used transiently to treat patients who have heart block at any site (see treatment for Sinus Bradycardia, above). Isoproterenol should be used with extreme caution or not at all in patients who have acute myocardial infarction. The use of transcutaneous pacing is preferable.

AV Dissociation

CLASSIFICATION.

As the term indicates, dissociated or independent beating of the atria and ventricles

defines AV dissociation. AV dissociation is never a *primary* disturbance of rhythm but is a "symptom" of an underlying rhythm disturbance produced by one of three causes or a combination of causes (Fig. 25-59) that prevent the normal transmission of impulses from atrium to ventricle, as follows:

1. Slowing of the dominant pacemaker of the heart (usually the sinus node), which allows escape of a subsidiary or latent pacemaker. AV dissociation by *default* of the primary pacemaker to a subsidiary one in this manner is often a normal phenomenon. It may occur during sinus arrhythmia or sinus bradycardia and permit an independent AV junction rhythm to arise (see Fig. 25-4 *B*).
2. Acceleration of a latent pacemaker that *usurps* control of the ventricles. An abnormally enhanced discharge rate of a usually slower subsidiary pacemaker is pathological and commonly occurs during nonparoxysmal AV junctional tachycardia or VT without retrograde atrial capture (see Figs. 25-23 and 25-41).
3. Block, generally at the AV junction, that prevents impulses formed at a normal rate in a dominant pacemaker from reaching the ventricles and allows the ventricles to beat under the control of a subsidiary pacemaker. Junctional or ventricular escape rhythm during AV block, without retrograde atrial capture, is a common example in which block gives rise to AV dissociation. It is important to remember that complete AV block is *not* synonymous with complete AV dissociation; patients who have complete AV block have complete AV dissociation, but patients who have complete AV dissociation may or may not have complete AV block (see Figs. 25-57 and 25-58).
4. A combination of causes, for example, when digitalis excess results in the production of nonparoxysmal AV junctional tachycardia associated with SA or AV block.

Figure 25-59 Diagrammatic illustration of the causes of atrioventricular (AV) dissociation. A sinus bradycardia allowing escape of an AV junctional rhythm that does not capture the atria retrogradely illustrates cause I (*top panel*). Intermittent sinus captures occur (third P wave) and produce incomplete AV dissociation (see Fig. 22-3 *B*). For cause II, ventricular tachycardia without retrograde atrial capture produces complete AV dissociation (see Figs. 25-23 and 25-41). As the third cause, complete AV block with a ventricular escape rhythm is diagrammed (see Figs. 25-57 and 25-58). The combination of causes II and III is shown in panel IV, which represents a nonparoxysmal AV junctional tachycardia and some degree of AV block.

MECHANISMS.

With this classification in mind, it is important to emphasize that the term *AV dissociation* is *not* a diagnosis and is analogous to the term *jaundice* or *fever.* One must state that "AV dissociation is present *due to*..." and then give the cause. An accelerated rate of a slower, normally subsidiary pacemaker or a slower rate of a faster, normally dominant pacemaker that prevents conduction because of physiological collision and mutual extinction of opposing wavefronts (interference) or the manifestations of AV block are

the basic disturbances producing AV dissociation. The atria in all these cases beat independently from the ventricles, under control of the sinus node or ectopic atrial or AV junctional pacemakers, and can exhibit any type of supraventricular rhythm. If a single pacemaker establishes control of both atria and ventricles for one beat (capture) or a series of beats (sinus rhythm, AV junctional rhythm with retrograde atrial capture, VT with retrograde atrial capture, and so forth), AV dissociation is abolished for that period. Conversely, as stated above, whenever the atria and ventricles fail to respond to a single impulse for one beat (premature ventricular complex without retrograde capture of the atrium) or a series of beats (VT without retrograde atrial capture), AV dissociation exists for that period. The interruption of AV dissociation by one or a series of beats under the control of one pacemaker, either anterogradely or retrogradely, indicates that the AV dissociation is incomplete. Complete or incomplete dissociation can also occur in association with all forms of AV block. Commonly, when AV dissociation occurs as a result of AV block, the atrial rate exceeds the ventricular rate. For example, a subsidiary pacemaker with a rate of 40 beats/min can escape in the presence of a 2:1 AV block when the atrial rate is 78. If the AV block is bidirectional, AV dissociation results.

ELECTROCARDIOGRAPHIC AND CLINICAL FEATURES.

The ECG demonstrates the independence of P waves and QRS complexes. The P wave morphology depends on the rhythm controlling the atria (sinus, atrial tachycardia, junctional, flutter, or fibrillation). During complete AV dissociation, both the QRS complex and the P waves appear regularly spaced without a fixed temporal relationship to each other. When the dissociation is incomplete, a QRS complex of supraventricular contour occurs early and is preceded by a P wave at a PR interval exceeding 0.12 second and within a conductable range. This combination indicates ventricular capture by the supraventricular focus. Similarly, a premature P wave with retrograde morphology and a conductable RP interval may indicate retrograde atrial capture by the subsidiary focus.

Physical findings include a variable intensity of the first heart sound as the PR interval changes, atrial sounds, and *a* waves in the jugular venous pulse lacking a consistent relationship to ventricular contraction. Intermittent large (cannon) *a* waves may be seen in the jugular venous pulse when atrial and ventricular contractions occur simultaneously. The second heart sound can split normally or paradoxically, depending on the manner of ventricular activation. A premature beat representing ventricular capture can interrupt a regular heart rhythm. When the ventricular rate exceeds the atrial rate, a cyclical increase in intensity of the first heart sound is produced as the PR interval shortens, climaxed by a very loud sound (bruit de canon). This intense sound is followed by a sudden reduction in intensity of the first heart sound and the appearance of giant *a* waves as the PR interval shortens and P waves "march through" the cardiac cycle.

MANAGEMENT.

Management is directed toward the underlying heart disease and precipitating cause. The individual components *producing the AV dissociation*--not the AV dissociation per se--determine the specific type of antiarrhythmic approach. Therapy ranges from

pacemaker insertion in a patient who has AV dissociation resulting from complete AV block to antiarrhythmic drug administration in a patient who has AV dissociation caused by VT.

Figure 25-60 Supernormal conduction. *A,* Atrial fibrillation with long-short R-R cycle sequences giving rise to QRS complexes conducted with a functional left bundle branch block. In each example, however, a shorter R-R cycle length is terminated by a normal QRS complex (arrow), an example of supernormal conduction. *B,* Graph of the intervals and illustrative recordings during an electrophysiological study of the patient whose electrocardiogram is shown in *A*. The H-V interval of the complexes conducted with a left bundle branch block morphology is 45 milliseconds, whereas the H-V interval of those conducted with normal morphology is 35 milliseconds. The graph indicates the premature interval (H_1 -H_2 , ordinate) plotted against the preceding cycle length (H_1 -H_1 , abscissa). All H_1 -H_1 intervals were taken from complexes with a left bundle branch block morphology. Normal complexes are represented by filled circles and left bundle branch block contours by filled triangles. Four zones of conduction are identified and illustrated by the four examples to the right. The longest H_1 -H_2 intervals are followed by normal intraventricular conduction (zone a), whereas at shorter intervals, left bundle branch block occurs (zone b). When the H_1 -H_2 interval shortens further, normal intraventricular conduction returns and the H-V intervals shorten to 35 milliseconds (zone c, supernormal conduction). At the shortest H_1 -H_2 interval, left bundle branch block again appears (zone d). *(From Miles WM, Prystowsky EN, Heger JJ, Zipes DP: Evaluation of the patient with wide QRS tachycardia. Med Clin North Am 68:1015, 1984.)*

Figure 25-61 Supernormal excitation. *A* and *B,* Noncontiguous portions of a continuous electrocardiogram recording with a middle segment removed (dotted line). The patient had a bipolar pacemaker that had exceeded end-of-life status and was no longer consistently producing ventricular depolarization (small negative deflections indicated by the upright arrow). A temporary pacemaker was implanted and set at a fixed rate (asynchronous, V00). These large deflections are indicated by the inverted arrow. The numbers in milliseconds indicate the interval between the onset of the QRS complex and the following subthreshold pacemaker stimulus. At intervals of 370 milliseconds (beginning, panel *A*) and 490 milliseconds (end, panel *B*), the subthreshold stimulus fails to produce a propagated ventricular response. However, at intervals between 380 and 480 milliseconds, ventricular depolarizations result (filled circles). Thus, the period of supernormal excitation is 100 milliseconds in duration, from 380 to 480 milliseconds after the onset of the QRS complex.

Figure 25-62 Concealed conduction. Following the first normally conducted sinus-initiated complex, a premature ventricular complex is stimulated (S). The next spontaneous sinus-initiated P wave is blocked and a fully compensatory pause is produced. The third sinus-initiated P wave is conducted normally. From the His bundle recording it is obvious that the nonconducted sinus beat is blocked distal to the His bundle recording site. Note that the A-H interval of the nonconducted sinus P wave beat is prolonged, which suggests that the premature ventricular complex retrogradely activated His and invaded the AV

node, thereby making it partially refractory to the next sinus beat. Since retrograde conduction into the atrioventricular (AV) node is not recorded and can be surmised only on the basis of the increase in the following A-H interval, it is an example of concealed conduction. Furthermore, since retrograde His and AV node activation by the premature ventricular complex would not be apparent in the scalar electrocardiogram but is responsible for the compensatory pause, the blocked P wave is an example of concealed conduction.

OTHER ELECTROPHYSIOLOGICAL ABNORMALITIES LEADING TO CARDIAC ARRHYTHMIAS

Supernormal Conduction and Excitation

SUPERNORMAL CONDUCTION.

Supernormal conduction is the term applied to situations characterized by conduction that is better than expected but generally not as good as normal.[537] [538] [539] [540] The phenomenon almost always occurs when conduction is depressed but can be present in normal cardiac tissues as well. It generally occurs when conduction takes place during the relative refractory period of the preceding complex (Fig. 25-60) . The electrophysiological basis can relate, in some examples, to supernormal excitability (see below), but probably to other mechanisms as well. Supernormal conduction has commonly been invoked to explain AV (most probably His-Purkinje rather than AV nodal) conduction that is more rapid than expected or AV conduction that results when AV block is expected.

SUPERNORMAL EXCITATION.

This phenomenon results when a stimulus, normally subthreshold, occurs during the supernormal period of recovery of the preceding complex and produces a propagated response. Stimuli occurring earlier or later fail to produce a propagated response. Demonstrated in vitro in Purkinje fibers but not ventricular muscle, supernormal excitation occurs during phase 3 of the cardiac action potential, when the membrane potential, closer to threshold at the end of repolarization, requires less current to produce a propagated response. A similar phenomenon occurs during phase 4 diastolic depolarization or during afterdepolarizations that reduce the membrane potential closer to threshold. The phenomenon is most easily recognized when a nonsensing pacemaker, failing because of battery exhaustion and reduced output, produces a propagated response only when discharge falls during a specific period in a cardiac cycle (Fig. 25-61) . Similar phenomena probably occur spontaneously with "weak" automatic foci, but recognition of these events clinically is difficult and often speculative.

Concealed Conduction

Concealed conduction describes the phenomenon during which impulses penetrate an area of the conduction tissue, the AV node commonly but other areas as well, without emerging.[541] Since transmission of the impulse is concealed, i.e., electrically silent in the standard ECG, concealed conduction becomes manifested only by its *effects* on the

conduction and/or formation of subsequent impulses.[542] The most common example follows a premature ventricular complex. Partial retrograde penetration of the AV node by the premature ventricular complex is *deduced* because the following sinus-initiated P wave blocks conduction to produce a compensatory pause (Fig. 25-62) or conducts with a longer PR interval if the premature ventricular complex is interpolated. The slower ventricular response when the atrial rate increases from atrial flutter to atrial fibrillation is due to a greater number of atrial impulses being blocked (conducting into, without emerging) in the AV node and is a manifestation of concealed conduction.[543] Concealed conduction occurs in WPW syndrome and can be manifested by unidirectional block anterogradely or retrogradely in an accessory pathway.[544] Concealed junctional extrasystoles can create ECG manifestations of apparent AV block. Strict confirmation of concealed conduction should be the demonstration of conduction, such as in the form of conducted junctional extrasystoles.

Parasystole (Fig. 25-63)

Parasystole refers to a cardiac arrhythmia characterized electrocardiographically by (1) a varying coupling interval between the ectopic (parasystolic) complex and the dominant (generally, sinus-initiated) complex; (2) a common minimal time interval between interectopic intervals, with the longer interectopic intervals being multiples of this minimal interval; (3) fusion complexes; and (4) presence of the parasystolic impulse whenever the cardiac chamber is excitable. Parasystole with exit block is suspected when the parasystolic discharge focus fails to appear even though cardiac tissue is excitable. The analogy commonly invoked to represent parasystole is the behavior of a fixed-rate nonsensing (VOO) pacemaker (see Chap. 24). Parasystole can occur in the sinus and AV nodes, atrium and ventricle, and AV junction. The parasystolic mechanism presumably results from the regular discharge of an automatic focus that is independent of and protected from discharge by the dominant cardiac rhythm. A number of mechanisms have been postulated to explain the apparent protection enjoyed by the parasystolic rhythm.[545]

These "classic" definitions of parasystole now need to be modified because it has been well established that the dominant sinus beats can modulate the discharge rate of the parasystolic rhythm despite entrance block. Thus, wide variations in the modulated parasystolic cycle may occur. The "true" or unmodulated parasystolic cycle length can be determined by finding two consecutive parasystolic complexes without intervening beats. Phase response curves can be generated. Fixed coupling between the dominant and parasystolic rhythms can occur through a variety of mechanisms, including entrainment. It is possible that modulated parasystole in the presence of supernormal excitability can trigger ventricular fibrillation.

Figure 25-63 Atrial parasystole. *Top,* Atrial parasystolic impulses (filled circles under the negative P waves) are present at a fixed coupling interval to the dominant sinus rhythm. The reason for the fixed coupling is as follows: Each time that the parasystolic impulse depolarizes the atrium, it also discharges the sinus node. Diastolic depolarization in the sinus node begins at that point (reset) and results in the following sinus P wave (positive P wave). Thus, the constant parasystolic discharge rate (interectopic interval approximately 960 milliseconds), resetting of the sinus node, and constant phase 4 diastolic

depolarization in the sinus node combine to result in fixed coupling. *Middle* and *bottom*, The sinus discharge rate is slightly faster. It is no longer discharged by the parasystolic impulse, which is still occurring at approximately 960 milliseconds (slightly longer interval in the *bottom* tracing). Variable coupling, the usual manifestation of parasystole, results. Lead II.

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Chapter 26 - Cardiac Arrest and Sudden Cardiac Death

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Definition

Sudden cardiac death (SCD) is natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms. Preexisting heart disease may or may not have been known to be present, but the time and mode of death are unexpected. This definition incorporates the key elements of "natural," "rapid," and "unexpected." It consolidates previous definitions that have conflicted,[1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] largely because the most useful operational definition of SCD in the past differed for the clinician, the cardiovascular epidemiologist, the pathologist, and the scientist attempting to define pathophysiological mechanisms. As causes and mechanisms began to be understood, these differences disappeared.

Four elements must be considered in the construction of a definition of SCD to satisfy medical, scientific, legal, and social considerations: (1) prodromes, (2) onset, (3) cardiac arrest, and (4) biological death (Fig. 26-1) . Because the proximate cause of SCD is a disturbance of cardiovascular function, which is incompatible with maintaining consciousness because of abrupt loss of cerebral blood flow, any definition must

recognize the brief time interval between the onset of the mechanism directly responsible for cardiac arrest and the consequent loss of consciousness (Fig. 26-1 *C*). The 1-hour definition, however, refers to the duration of the "terminal event" (Fig. 26-1 *B*), which defines the interval between the onset of symptoms signaling the pathophysiological disturbance leading to cardiac arrest and the onset of the cardiac arrest itself (Fig. 26-1 *B* and *C*).

Figure 26-1 Sudden cardiac death is viewed from four temporal perspectives: (*A*) prodromes, (*B*) onset of the terminal event, (*C*) cardiac arrest, and (*D*) progression to biological death. Individual variability of the components influence clinical expression: some victims experience no prodromes, with onset leading almost instantaneously to cardiac arrest; others may have an onset that lasts up to 1 hour before clinical arrest; some patients may live weeks after the cardiac arrest before progression to biological death if there has been irreversible brain damage and life-support systems are used. These modifying factors influence interpretation of the 1-hour definition. From the perspective of the clinician, the two most relevant factors are the onset of the terminal event (*B*) and the clinical cardiac arrest itself (*C*). In contrast, legal and social considerations focus on the time of biological death (*D*).

TABLE 26-1 -- DEFINITION OF TERMS RELATED TO SUDDEN CARDIAC DEATH

TERM	DEFINITION	QUALIFIERS OR EXCEPTIONS
Death	Irreversible cessation of all biological functions	None
Cardiac arrest	Abrupt cessation of cardiac pump function, which may be reversible but will lead to death in the absence of prompt intervention	Rare spontaneous reversions; likelihood of successful intervention relates to mechanism of arrest, clinical setting, and time to intervention
Cardiovascular collapse	A (sudden) loss of effective blood flow due to cardiac and/or peripheral vascular factors that may revert spontaneously (e.g., vasodepressor or cardioinhibitory syncope) or only with interventions (e.g., cardiac arrest)	Nonspecific term that includes cardiac arrest and its consequences and also events that characteristically revert spontaneously

Premonitory signs and symptoms, which may occur during the days or weeks before a cardiac arrest,[13] tend to be nonspecific for the impending event.[8] Prodromes (Fig. 26-1 *A*), which may be more specific for an imminent cardiac arrest, are relatively abrupt changes that begin during an arbitrarily defined period of up to 24 hours before the

onset of cardiac arrest.[4] [16] The fourth element, *biological death* (Fig. 26-1 *D*), was an immediate consequence of the clinical cardiac arrest in the past, usually occurring within minutes. However, since the development of community-based intervention systems, and life support systems, patients may now remain biologically alive for a long period of time after the onset of a pathophysiological process that has caused irreversible damage and will ultimately lead to death.[15] [17] [18] [19] In this circumstance, the causative pathophysiological and clinical event is the cardiac arrest itself, rather than the factors responsible for the delayed biological death. However, for legal, forensic, and certain social considerations, biological death must continue to be used as the absolute definition of death. Finally, the forensic pathologist studying *unwitnessed deaths* may use the definition of sudden death for a person known to be alive and functioning normally 24 hours before,[4] and this remains appropriate within obvious limits.[20] The generally accepted clinical-pathophysiological definition of up to 1 hour between onset of the terminal event and biological death requires qualifications for specific circumstances.

The development of community-based intervention systems also has led to inconsistencies in the use of terms considered absolute. *Death* is defined biologically, legally, and literally as an absolute and irreversible event. Thus SCD may be aborted, or a patient may survive cardiac arrest or cardiovascular collapse; however, survival after (sudden) death is a contradiction in terms. Table 26-1 provides definitions for events and terms related to the concept of SCD--death, cardiac arrest, and cardiovascular collapse.

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Epidemiology and Causes of Sudden Death

EPIDEMIOLOGY

The worldwide incidence of SCD is difficult to estimate because it varies largely as a function of coronary heart disease prevalence in different countries.[21] Estimates for the United States range from 250,000 to nearly 400,000 SCDs annually,[22] [23] [24] the variation based in part on the definition of sudden death used in individual studies.[13] The most widely used estimate is 300,000 SCDs annually,[25] a figure that represents 50 percent or more of all cardiovascular deaths in the United States.

The influence of the temporal definition of SCD on epidemiological data is demonstrated by a retrospective death certificate study in a large metropolitan area in the United States reported by Kuller and colleagues. When the temporal definition was restricted to death less than 2 hours after the onset of symptoms, 12 percent of all natural deaths were sudden and 88 percent of the sudden natural deaths were due to cardiac causes. This estimate is similar to observations in a large prospective cohort study--the Framingham Study--in which 13 percent of all deaths observed during a 26-year period were "sudden," defined as death within 1 hour of the onset of symptoms.[28] [29] In contrast to deaths occurring less than 2 hours after the onset of symptoms, the application of the 24-hour definition of sudden death to the data from Kuller and colleagues increased the fraction of all natural deaths falling into the "sudden" category to 32 percent but reduced the proportion of all sudden natural deaths that were cardiac deaths to 75 percent.

Prospective studies demonstrate that about 50 percent of all coronary heart disease deaths are sudden and unexpected, occurring shortly (instantaneous to 1 hour) after the onset of symptoms. In the prospective combined Albany-Framingham Study of 4120

males, sudden deaths within 1 hour of an observed collapse were analyzed for a population of men dying between 45 and 74 years of age.[9] During a 16-year follow-up, there were 234 total coronary deaths/1000 population observed, of which 109 (47 percent) were sudden and unexpected. Because coronary heart disease is the dominant cause of both sudden and nonsudden cardiac deaths in the United States, the fraction of total cardiac deaths that are sudden is similar to the fraction of coronary heart disease deaths that are sudden, although there does appear to be a geographical variation in the fraction of coronary deaths that are sudden.[30] This 50 percent fraction may not apply to other nations or to subcultures that have a lower prevalence of coronary heart disease. It also is of interest that the recent decline in coronary heart disease mortality in the United States[31] has not changed the fraction of coronary deaths that are sudden and unexpected,[32] even though there may be a decline in out-of-hospital deaths compared with emergency department death,[26] and the number of sudden deaths from coronary heart disease that occur in victims' homes may be lower than previously thought.[23]

POPULATION POOLS AND TIME-DEPENDENCE OF RISK

Two factors are of primary importance for identifying populations at risk and when considering strategies for primary prevention of SCD: (1) the size of denominators of population subgroups (Fig. 26-2 *A*), and (2) time-dependence of risk (Fig. 26-2 *B*).

POPULATION SUBGROUPS AND SCD.

The more than 300,000 adult SCDs that occur annually in the United States can be expressed as the global incidence in an unselected adult population. Viewed this way, the overall incidence is 1 to 2/1000 population (0.1-0.2 percent) per year. This large population base includes those victims whose SCDs occur as a first cardiac event, as well as those whose SCDs can be predicted with greater accuracy because they are included in higher-risk subgroups. Any intervention designed for the general population must, therefore, be applied to the 999/1000 who will not have an event, in order

Figure 26-2 Impact of population pools and time-from-events on the clinical epidemiology of sudden cardiac death. The top panel (*A*) compares incidence and total numbers of sudden cardiac deaths in different subgroups; the lower panel (*B*) demonstrates time-dependence of risk for sudden death after major cardiovascular events. In the top panel (*A*), estimates of incidence figures (percent/year) and the total number of events/year are shown for the overall adult population in the United States, and for increasingly higher-risk subgroups. The overall adult population has an estimated sudden death incidence of 0.1 to 0.2 percent/year, accounting for a total number of events of more than 300,000/year. With the identification of increasingly powerful risk factors, the incidence *increases* progressively, but it is accomplished by a progressive *decrease* in the total number of patients identified. The inverse relation between incidence and total number of events occurs because of the progressively smaller denominator pool in the highest subgroup categories. Successful interventions among larger population subgroups will require identification of specific markers to increase the ability to identify specific patients who will be at

particularly high risk for a future event. (*Note:* The horizontal axis for the incidence figures is not linear and should be interpreted accordingly.) In the lower panel (*B*), idealized curves of survival from sudden death are shown for a population of patients with known cardiovascular disease but at low risk because of freedom from major cardiovascular (CV) events (top curve) and for populations of patients who have survived a major cardiovascular event (bottom curve). Attrition over time is accelerated in both absolute and relative terms for the initial 6 to 18 months after the major cardiovascular event. After the initial attrition, the slopes of the curves for the high-risk and low-risk populations parallel each other, highlighting both the early attrition and the attenuation of risk after 18 to 24 months. These relations have been observed in diverse high-risk subgroups (cardiac arrest survivors, post-myocardial infarction patients with high-risk markers, recent onset of heart failure), and highlight the changing risk pattern as a function of time and the importance of the time dimension for recognition and intervention in strategies designed to alter outcome. (Modified from Myerburg RJ, et al: Sudden cardiac death: Structure, function and time-dependence of risk. Circulation 85[Suppl 1]:1-2, 1992. Copyright 1992 American Heart Association.)

to reach and possibly influence the 1/1000 who will. The cost and risk-to-benefit uncertainties limit the nature of such broad-based interventions and demand a higher resolution of risk identification. Figure 26-2 *A* highlights this problem by expressing the incidence (percent/year) of SCD among various subgroups and comparing the incidence figures to the total number of events that occur annually in each subgroup. By moving from the total adult population to a subgroup with high risk because of the presence of selected coronary risk factors, there may be a 10-fold or greater increase in the incidence of events annually, with the magnitude of increase dependent on the number of risk factors operating in the subgroup. The size of the denominator pool, however, remains very large, and implementation of interventions remains problematic, even at this heightened level of risk. Higher resolution is desirable and can be achieved by identification of more specific subgroups. However, the corresponding absolute number of deaths becomes progressively smaller as the subgroups become more focused (Fig. 26-2 *A*), limiting the potential benefit of interventions to a much smaller fraction of the total number of patients at risk.

TIME-DEPENDENCE OF RISK.

Risk of SCD is not linear as a function of time after a change in cardiovascular status.[25] [32] [33] Survival curves after major cardiovascular events, which identify populations at high risk for both sudden and total cardiac death, usually demonstrate that the most rapid rate of attrition occurs during the first 6 to 18 months (Fig. 26-2 *B*). Thus there is a time-dependence of risk that focuses the opportunity for maximum efficacy of an intervention during the early period after a conditioning event. Curves that have these characteristics have been generated from among survivors of out-of-hospital cardiac arrest, new onset of heart failure, and unstable angina, and from high-risk subgroups of patients having recent myocardial infarction. Even though attrition rates decrease over time, an effective intervention can still cause late diversion of treated versus control risk curves, indicating continuing benefit. *The addition of time as a dimension for measuring risk may increase the resolution within subgroups.*

AGE, HEREDITY, GENDER, AND RACE

AGE.

There are two ages of peak incidence of sudden death: between birth and 6 months of

age (the sudden infant death syndrome) and between 45 and 75 years of age.[3] In the adult population the *incidence* of sudden death due to coronary heart disease increases as a function of advancing age,[31] [34] [35] [36] [346A] in parallel with the age-related increase in incidence of total coronary heart disease deaths. The incidence is 100-fold less in adolescents and adults younger than the age of 30 years (1 in 100,000 per year) than in adults older than age of 35 years (1 in 1,000 per year)[37] [38] [39] (Fig. 26-3) . However, in contrast to incidence, the *proportion* of deaths caused by coronary heart diseases that are sudden and unexpected decreases with advancing age.[31] [34] [35] [36] [346A] Kuller and colleagues[40] reported that 76 percent of coronary heart disease deaths in the 20- to 39 year age group were sudden and unexpected, and the Framingham study data demonstrated that 62 percent of all coronary heart disease deaths were sudden in the 45 to 54-year age group in men. The proportion fell progressively to 58 percent in the 55- to 64-year age group and to 42 percent in the 65- to 74-year age group.[35] [36] Age also influences the proportion of cardiovascular causes among all causes of natural sudden death in that the proportion of coronary deaths and of all cardiac causes of death that are sudden is highest in the younger age groups, whereas the fraction of total sudden natural deaths that are due to any cardiovascular cause is higher in the older age groups. In their study of sudden death in children and young adults, Neuspiel and Kuller[41] reported that only 19 percent of sudden natural deaths in children between 1 and 13 years of age were cardiac deaths; the proportion increased to 30 percent in the 14- to 21-year age group. All of these studies of age factors used a 24-hour definition of sudden death.

HEREDITY.

To the extent that SCD is an expression of underlying coronary heart disease, hereditary factors that contribute to coronary heart disease risk have been thought to operate nonspecifically for the SCD syndrome.[42] In addition, however, two population studies suggest that SCD, as an expression of coronary heart disease, clusters in specific families.[43] [44] Whether this familial pattern is genetically or environmentally determined, or both, awaits clarifications.

Among the less common causes of SCD, hereditary patterns have been reported for specific syndromes[45] such as the congenital long QT interval syndromes,[46] [47] [48] [49] [50] [51] [52] [52A] [53] [54] [55] [56] [57] [58] hypertrophic cardiomyopathy,[54] [55] [56] right ventricular dysplasia,[57] [58] the Brugada syndrome,[59] [60] [61] [62] and yet-to-be-defined

Figure 26-3 Age-specific risk of sudden cardiac death (SCD). For the general population age 35 years and older, the risk of SCD is 0.1 to 0.2 percent per year (1 per 500 to 1,000 population). Among the general population of adolescents and adults younger than the age of 30 years, the overall risk of SCD is 1 per 100,000 population, or 0.001 percent per year. The risk of SCD increases dramatically beyond the age of 35 years and continues to increase past the age of 70 years (curve A). The greatest rate of increase is between 40 and 65 years (note that the vertical axis is discontinuous). Among patients older

than 30 years of age, with advanced structural heart disease and markers of high risk for cardiac arrest, the event rate may exceed 25 percent per year (curve B). This magnitude of the risk is determined to a greater extent by the nature of the established disease, rather than by age. Among adolescents and young adults at risk for SCD because of specific identified causes, it is difficult to ascertain risk for individual patient because of variable expression of the disease state and the influences of interventions. However, for many of these conditions (e.g., long QT interval syndromes, Brugada syndrome, right ventricular dysplasia, idiopathic ventricular fibrillation [VF]), the major risk is electrical; and the competing risk of mechanical dysfunction of the heart as in advanced ischemic heart disease or dilated cardiomyopathy does not contribute significantly to risk. Therefore, effective electrical interventions are expected to have a better total mortality benefit than in the latter case (see text for details).

patterns of familial SCD in children and young adults.[63] [63A] Although stable congenital conducting system abnormalities have a good prognosis,[64] progressive familial conducting system disease, which appears to have a hereditary pattern, carry an increased risk of SCD.[65] Familial sudden death associated with cardiac ganglionitis has been reported,[66] but an inheritance pattern has not been demonstrated in the reports to date. Identification of multiple specific gene abnormalities in loci on at least four chromosomes (chromosomes 3, 7, 11, and 21), and linkage analysis suggesting a locus on chromosome 4, in families with long QT interval syndromes have provided a major advance in the understanding of a genetic basis for this cause of sudden death (see Chaps. 23 and 25) . This observation may provide a screening tool for individuals at risk, as well as the potential for specific therapeutic strategies.

GENDER.

The SCD syndrome has a huge preponderance in males compared with females because of the protection females enjoy from coronary atherosclerosis before menopause.[28] [29] [35] During the first 14 years of follow-up in the Framingham Study, 59 of 66 (89 percent) sudden unexpected coronary deaths (<1 hour) occurred in men.[8] The Framingham Study at 20 years of follow-up demonstrated a 3.8-fold excess incidence of sudden coronary death in men compared with women.[35] This male/female ratio is similar to data recorded in three prospective studies of prehospital cardiac arrest in which the percentages of males observed were 75 percent (mean age 63 years),[17] 85 percent (mean age 60 years),[18] and 89 percent (mean age 58 years),[67] respectively. In the study by Kuller and colleagues,[4] 75 percent of all SCDs (using the 24-hour definition) in a 40- to 64-year-old population were in men. When the data in another study by Kuller and colleagues[68] were analyzed for survival of less than 2 hours, the proportion of men increased to 80 percent. In the Framingham Study[35] the excess risk in men peaked at 6.75:1 in the 55- to 64-year age group and then fell to 2.17:1 in the 65- to 74-year age group. Even though the overall risk is much lower in women, the classic coronary risk factors are expressed in them.[28] [29] [69] [70] Cigarette smoking, diabetes, use of oral contraceptives,[71] and reduced vital capacity[29] are particularly strong factors.

RACE.

A number of studies comparing racial differences and relative risk of SCD in whites and blacks with coronary heart disease in the United States have yielded conflicting and inconclusive data.[4] [72] [73] [74] However, a recent large study from an urban area

demonstrated excess risk of cardiac arrest and SCD in blacks compared with whites.[73] An excess was observed across all age groups, but the magnitude of excess among older adults decreased with increasing age.

Data on the prevalence of coronary heart disease in Japanese men living in the United States have demonstrated that the low rates reported in those living in Japan tend to increase toward, but do not reach, levels observed in white men in the United States.[75] Thus, an interplay between race and environmental factors may be operative.

BIOLOGICAL RISK FACTORS AND SUDDEN DEATH

The known coronary risk factors cannot be used to distinguish the patients at risk for SCD from those at risk for other manifestations of coronary heart disease.[9] Using a multivariate analysis of selected risk factors (i.e., age, systolic blood pressure, heart rate, electrocardiographic abnormalities, vital capacity, relative weight, cigarette consumption, and serum cholesterol from the population in the Framingham Study data, Kannel and Schatzkin[31] determined that 53 percent of the SCDs in men and 42 percent of those in women occurred among the 10 percent of the population in the highest risk decile (Fig. 26-4) . The comparison of risk factors in the victims of SCD with those in people who developed any manifestations of coronary artery disease did not provide useful patterns, by either univariate or multivariate analysis, to distinguish victims of SCD from the overall pool.[9] In addition, data from 19,946 patients in the Coronary Artery Surgery Study identified no angiographic or hemodynamic patterns that discriminated sudden from nonsudden cardiac deaths.[36] Familial clustering of SCD as a specific manifestation, however, may lead to identification of specific genetic abnormalities that predispose to SCD.[48] [49]

Figure 26-4 Risk of sudden death by decile of multivariant risk: 26-year follow-up, the Framingham Study. ECG = electrocardiographic; I-V = intraventricular; LVH = left ventricular hypertrophy; non-spec abn = nonspecific abnormality. (From Kannel WB, Shatzkin A: Sudden death: Lessons from subsets in population studies. Reprinted by permission of the American College of Cardiology. J Am Coll Cardiol 5[Suppl 6]:141B, 1985.)

Hypertension is a clearly established risk factor for coronary heart disease and also emerges as a highly significant risk factor for incidence of SCD.?? However, there is no influence of increasing systolic blood pressure levels on the ratio of sudden deaths to total coronary heart disease deaths.[34] No relationship has been observed between cholesterol concentration and the proportion of coronary deaths that were sudden.[37] Neither the electrocardiographic pattern of left ventricular hypertrophy nor nonspecific ST-T wave abnormalities influence the proportion of total coronary deaths that are sudden and unexpected [34] ; *only intraventricular conduction abnormalities are suggestive of a disproportionate number of SCDs.*[35] A low vital capacity also suggests a disproportionate risk for sudden versus total coronary deaths.[35] This is of interest

because such a relation was particularly striking in the analysis of data on women in the Framingham Study who had died suddenly.[28] [29] A high hematocrit also was predictive in women.[30]

The conventional risk factors used in most studies of SCD are the risk factors for coronary artery disease. The rationale is based on two facts: (1) coronary disease is the structural basis for 80 percent of SCDs in the United States, and (2) the coronary risk factors are easy to identify because they tend to be present continuously over time (Fig. 26-5) . However, risk factors specific for fatal arrhythmias are dynamic pathophysiological events and occur transiently.[76] [76A] Transient pathophysiological events are being modeled epidemiologically,[77] in an attempt to express and use them as clinical risk factors[78] for both profiling and intervention.[79]

LIFE STYLE AND PSYCHOSOCIAL FACTORS

LIFE STYLE.

There is a strong association between *cigarette smoking* and all manifestations of coronary heart disease. The Framingham Study demonstrates that cigarette smokers have a twofold to threefold increase in sudden death risk in each decade of life at entry between 30 and 59 years, and that this is one of the few risk factors in which the proportion of coronary heart disease deaths that are sudden increases in association with the risk factor.[35] In addition, in a study of 310 survivors of out-of-hospital cardiac arrest, Hallstrom and associates[80] observed a 27 percent incidence of recurrent cardiac arrest at 3 years in those who continued to smoke after their index event, compared with 19 percent in those who stopped ($P<0.04$). Obesity is a second factor that appears to influence the proportion of coronary deaths that occur suddenly.[29] [35] With increasing relative weight, the percentage of coronary heart disease deaths that were sudden in the Framingham Study increased linearly from a low of 39 percent to a high of 70 percent. Total coronary heart disease deaths increased with increasing relative weight as well.

Epidemiological observations suggest a relationship between *low levels of physical activity* and increased coronary heart disease death risk.[81] The Framingham Study, however, showed an *insignificant* relationship between low levels of physical activity and incidence of sudden death but a high proportion of sudden to total cardiac deaths at higher levels of physical activity.[35] An association between acute physical exertion (especially in physically inactive individuals) and the onset of myocardial infarction has been suggested,[79] but it is not yet known if this also applies to SCD.

PSYCHOSOCIAL FACTORS.

The magnitude of recent life changes in the realms of health, work, home and family, and personal and social factors have been related to myocardial infarction and SCD.[72] There was an association between significant elevations of life-change scores during the 6 months before a coronary event, and the association was particularly striking in victims of SCD. In a study of sudden death in women,[83] those who died suddenly were less often married, had fewer children, and had greater educational discrepancies with

their spouses than did age-related controls living in the same neighborhood as the sudden death victims. A history of psychiatric treatment, cigarette smoking, and greater quantities of alcohol consumption than the controls also characterized the sudden death group.[83] Ruberman and coworkers reported on the influences of psychosocial factors on sudden and total death after myocardial infarction in 2320 male survivors of myocardial infarction[84] Controlling for other major prognostic factors, including frequency of premature ventricular contractions, a greater than fourfold increase in risk of sudden and total deaths was predicted by *social isolation* and a *high level of life stress.* These psychosocial factors were inversely related to levels of education. In an earlier study, a more than threefold increase of sudden death risk during follow-up after myocardial infarction had been reported in men who had complex ventricular ectopy and low levels of education compared with better-educated men with the same arrhythmias.[85] Interestingly, there was no relation between educational level and recurrent myocardial infarction. In a survey of life style, it was found that people with lower educational levels smoked more cigarettes, drank more alcohol, exercised less, and were more overweight.[86] Alteration of modifiable lifestyle factors has been proposed as a strategy for reducing risk of SCD in patients with coronary heart disease.[86A]

Figure 26-5 Epidemiology of SCD: conventional (conditioning) risk factors versus transient (triggering) risk factors. Conventional risk factors predict risk of the disease underlying SCD; transient risk factors predict risk of the pathophysiological event that initiates the fatal event. (Modified from Myerburg RJ, Kessler KM, Kimura S, et al: Life-threatening ventricular arrhythmias: The link between epidemiology and pathophysiology. *In* Zipes DP, Jalife J [eds]: Cardiac Electrophysiology, 2nd ed. Philadelphia, WB Saunders, 1995.)

FUNCTIONAL CLASSIFICATION AND SUDDEN DEATH.

The Framingham Study demonstrated a striking relation between functional classification and death during a 2-year follow-up period. However, the proportion of deaths that were sudden did not vary with functional classification, ranging from 50 to 57 percent in all groups and from those free of clinical heart disease to those in functional Class IV.[35] Another study suggested that heart failure patients with better functional capacity are at lower risk of dying, as expected, but a higher proportion of those deaths are sudden.[87]

Sudden Death and Previous Coronary Heart Disease

Although SCD is the first clinical manifestation of coronary heart disease in 20 to 25 percent or more of all coronary heart disease patients,[9] [12] [20] [25] a previous myocardial infarction can be identified in as many as 75 percent of patients who die suddenly. The high incidence of both recognized and unrecognized prior myocardial infarction in victims of SCD has led to a search for predictors of SCD in survivors of myocardial

infarction, as well as in patients with other clinical manifestations of coronary heart disease.

LEFT VENTRICULAR EJECTION FRACTION IN CHRONIC ISCHEMIC HEART DISEASE.

A marked depression of the left ventricular ejection fraction is the most powerful predictor of SCD in patients with chronic ischemic heart disease, as well as those whose SCD results from other causes (see later). Increased risk, independent of other risk factors, is measurable at ejection fractions greater than 40 percent, but the greatest rate of change of risk is between 30 and 40 percent.[88] An ejection fraction equal to or less than 30 percent is the single most powerful independent predictor for SCD, but it has a low specificity.

VENTRICULAR ECTOPY IN CHRONIC ISCHEMIC HEART DISEASE.

Most forms of ventricular ectopic activity (premature ventricular complexes [PVCs] in the absence of heart disease[89] are prognostically benign. When present in people older than the age of 30, however, PVCs select a subgroup with a higher probability of coronary artery disease and of SCD.[90] In addition, the occurrence of PVCs in survivors of myocardial infarction,[91] particularly if frequent and of complex forms such as multiform or repetitive PVCs,[88] [92] predicts an increased risk of SCD on long-term follow-up. Most of these studies have identified both *frequency* and *forms* of ventricular ectopic activity as indicators of risk, but uniformity for such classifications is lacking.[93] Although most studies cite a frequency cutoff of 10 PVCs/hr as a threshold level for increased risk, some have identified frequency cutoffs in the range of 1 to 9 PVCs/hr, 10 PVCs/1000 sinus beats, and more than 20 PVCs/hr. Forms suggestive of high risk include multiform PVCs, bigeminy, short coupling intervals (R-on-T phenomenon), and salvos of three or more ectopic beats.[93] Several investigators have emphasized that the most powerful predictors among the various forms of PVCs are salvos of three or more complexes,[88] [92] [94] although this relationship is now questioned.

Many of the reported studies have been based on a single ambulatory monitor sample recorded 1 week to several months after the onset of acute myocardial infarction, and the duration of the samples has ranged from 1 hour to 48 hours. Ruberman and coworkers[94] reported that repeated short-term (1-hour) ambulatory recordings at 6-month intervals beginning 1 month after myocardial infarction reestablished the increased risk imparted by complex forms of PVCs for the ensuing 3 1/2-year interval, as long as complex forms remained on the interval recordings. Recent data indicate that ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of death.[94A]

The results of the Cardiac Arrhythmia Suppression Trial (CAST) (see Chap. 25) , designed to test the hypothesis that PVC suppression by antiarrhythmic drugs alters risk of SCD

Figure 26-6 Survival during 3 years of follow-up after acute myocardial infarction as a function of left ventricular dysfunction (ejection fraction, EF) and ventricular arrhythmias (VPDs/hr as measured by Holter monitoring). The survival curves were calculated as Kaplan-Meier estimates. With higher PVC frequencies and lower ejection fractions, the mortality rates increase. The number of patients in groups A, B, C, and D were 536, 136, 80, and 37, respectively. (From Bigger JT: Relation between left ventricular dysfunction and ventricular arrhythmias after myocardial infarction. Am J Cardiol 57:8B, 1986.)

after myocardial infarction, were surprising for two reasons.[95] First, the death rate in the randomized placebo group was lower than expected, and second, the death rate among patients in the encainide and flecainide arms exceeded control rates by more than three times. Thus, for these two Class IC drugs, treatment had an adverse effect for a population dominated by frequent single PVCs, and with a mean ejection fraction of about 40 percent. Subgroup analysis demonstrated increased risk in the placebo group for patients with nonsustained ventricular tachycardia (VT) and with ejection fraction of 30 percent or less, but excess risk in the treated group was still observed. The Survival with Oral*d*-Sotalol (SWORD) study, a comparison of*d*-sotalol to placebo in a postmyocardial infarction population with a low death rate, also demonstrated excess risk in the drug-treated group.[96] In the continuation of CAST (CAST II), comparing moricizine with placebo and altering enrollment to favor patients with more advanced disease, no adverse effect (other than short-term proarrhythmic risk at initiation of therapy) was observed, but no long-term benefit emerged either.[97] Whether the conclusions from CAST, CAST II, and SWORD, extend beyond the drugs studied or to other diseases remains to be learned.[98]

Left ventricular dysfunction is the major modulator of risk implied by chronic PVCs after myocardial infarction.[88] The risk of death predicted by postmyocardial infarction PVCs is enhanced by the presence of left ventricular dysfunction (Fig. 26-6) ; the latter appears to exert its influence most strongly in the first 6 months after infarction.[88] Finally, there are data suggesting that the risk associated with postinfarction ventricular arrhythmias is higher in patients who have non-Q-wave infarctions than in those with transmural infarctions.[99]

Causes of Sudden Cardiac Death

Coronary heart disease and its consequences account for at least 80 percent of SCDs in Western cultures, and the cardiomyopathies, dilated and hypertrophic, cause another 10 to 15 percent of SCDs (Table 26-2) . Coronary heart disease also is the most common cause in many areas of the world in which its prevalence is lower. Despite the established relation between coronary heart disease and SCD,[15] [17] [18] [32]

TABLE 26-2 -- CAUSES AND CONTRIBUTING FACTORS IN SUDDEN CARDIAC DEATH

I. CORONARY ARTERY ABNORMALITIES
- A. Coronary atherosclerosis
  - 1. Chronic ischemic heart disease with transient supply-demand imbalance--thrombosis, spasm, physical stress
  - 2. Acute myocardial infarction
  - 3. Chronic atherosclerosis with change in myocardial substrate
- B. Congenital abnormalities of coronary arteries
  - 1. Anomalous origin from pulmonary artery
  - 2. Other coronary arteriovenous fistula
  - 3. Origin of left coronary artery from right sinus of Valsalva
  - 4. Origin of right coronary artery from left sinus of Valsalva
  - 5. Hypoplastic or aplastic coronary arteries
  - 6. Coronary-intracardiac shunt
- C. Coronary artery embolism
  - 1. Aortic or mitral endocarditis
  - 2. Prosthetic aortic or mitral valves
  - 3. Abnormal native valves or left ventricular mural thrombus
  - 4. Platelet embolism
- D. Coronary arteritis
  - 1. Polyarteritis nodosa, progressive systemic sclerosis, giant cell arteritis
  - 2. Mucocutaneous lymph node syndrome (Kawasaki disease)
  - 3. Syphilitic coronary ostial stenosis
- E. Miscellaneous mechanical obstruction of coronary arteries
  - 1. Coronary artery dissection in Marfan's syndrome
  - 2. Coronary artery dissection in pregnancy
  - 3. Prolapse of aortic valve myxomatous polyps into coronary ostia
  - 4. Dissection or rupture of sinus of Valsalva
- F. Functional obstruction of coronary arteries
  - 1. Coronary artery spasm with or without atherosclerosis
  - 2. Myocardial bridges

II. HYPERTROPHY OF VENTRICULAR MYOCARDIUM
- A. Left ventricular hypertrophy associated with coronary heart disease
- B. Hypertensive heart disease without significant coronary atherosclerosis
- C. Hypertrophic myocardium secondary to valvular heart disease
- D. Hypertrophic cardiomyopathy
  - 1. Obstructive
  - 2. Nonobstructive
- E. Primary or secondary pulmonary hypertension
  - 1. Advanced chronic right ventricular overload
  - 2. Pulmonary hypertension in pregnancy (highest risk peripartum)

III. MYOCARDIAL DISEASES AND HEART FAILURE
A. Chronic congestive heart failure
1. Ischemic cardiomyopathy
2. Idiopathic congestive cardiomyopathy
3. Alcoholic cardiomyopathy
4. Hypertensive cardiomyopathy
5. Post-myocarditis cardiomyopathy
6. Postpartum cardiomyopathy
B. Acute cardiac failure
1. Massive acute myocardial infarction
2. Acute myocarditis
3. Acute alcoholic cardiac dysfunction
4. Ball-valve embolism in aortic stenosis or prosthesis
5. Mechanical disruptions of cardiac structures
(a) Rupture of ventricular free wall
(b) Disruption of mitral apparatus
(1) Papillary muscle
(2) Chordae tendineae
(3) Leaflet
(c) Rupture of interventricular septum
6. Acute pulmonary edema in noncompliant ventricles

IV. INFLAMMATORY, INFILTRATIVE, NEOPLASTIC, AND DEGENERATIVE PROCESSES
A. Viral myocarditis, with or without ventricular dysfunction
1. Acute phase
2. Postmyocarditis interstitial fibrosis
B. Myocarditis associated with the vasculitides
C. Sarcoidosis
D. Progressive systemic sclerosis
E. Amyloidosis
F. Hemochromatosis
G. Idiopathic giant cell myocarditis
H. Chagas' disease
I. Cardiac ganglionitis
J. Arrhythmogenic right ventricular dysplasia; right ventricular cardiomyopathy
K. Neuromuscular diseases (e.g., muscular dystrophy, Friedreich's ataxia, myotonic dystrophy)

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a complete understanding of SCD requires recognition of other causes that, although less common and often quite rare (see Table 26-2) , may be recognizable before death, have therapeutic implications, and provide broad insight into the sudden death problem. Many of these entities emerge as common causes of SCD in adolescents and young adults; among whom the prevalences coronary arteriolosclerosis much lower (see Fig. 26-3) .

CORONARY ARTERY ABNORMALITIES.

Although structural abnormalities of coronary arteries other than coronary

atherosclerosis are infrequent causes of SCD, the relative risk of SCD may be quite high for specific abnormalities. Nonatherosclerotic coronary artery abnormalities include congenital lesions, coronary artery embolism, coronary arteritis, and mechanical abnormalities of the coronary arteries. Among the congenital lesions, *anomalous origin of a left coronary artery from the pulmonary artery* (see Chap. 43) is relatively common[100] and has a high death rate in infancy and early childhood if not surgically treated.[101] The early risk for SCD is not excessively high,[100] but patients who survive to adulthood without surgical intervention are at risk.[101] Other forms of coronary arterial-kenous fistulas are much less frequent and have a low incidence of SCD. *Anomalous origin of a left coronary artery from the right or noncoronary aortic sinus of Valsalva* (see Chap. 12) appears to have increased risk of SCD,[102] [103] [104] particularly during exercise. When the anomalous artery passes between the aortic and the pulmonary artery root, the takeoff angle of the anomalous ostium creates a slitlike opening of the vessel, reducing the effective cross-sectional area for blood flow.[102] *Anomalous origin of the right coronary artery from the left sinus of Valsalva* also has been reported in association with SCD[102] [103] [104] but may not have the same risk as origin of the left coronary from the right sinus of Valsalva. Congenitally hypoplastic, stenotic, or atretic left coronary arteries are uncommon abnormalities that have a high risk of myocardial infarction but not of SCD.[100]

Embolism to the coronary arteries occurs most commonly in aortic valve endocarditis and from thrombotic material on diseased or prosthetic aortic or mitral valves.[105] Emboli also may originate from left ventricular mural thrombi or as a consequence of surgery or cardiac catheterization. Symptoms and signs of myocardial ischemia or infarction are the most common manifestations. In each of these categories SCD is a risk resulting from the electrophysiological consequences of the embolic ischemic event. Although embolism of platelet aggregates is a pathophysiological mechanism that has not clearly been demonstrated to be associated with SCD in clinical settings, some observations have focused attention on the feasibility of such a mechanism.

The *mucocutaneous lymph node syndrome* (Kawasaki disease)[106] (see Chap. 45) carries a risk of SCD in association with coronary arteritis. Polyarteritis nodosa and related vesiculitis syndromes (see Chap. 67) can cause SCD presumably because of coronary arteritis,[107] as can coronary ostial stenosis in syphilitic aortitis[64] (see Chap. 48) . The latter has become a very rare manifestation of syphilis.[108]

Several types of mechanical obstruction to coronary arteries must be listed among causes of SCD. Coronary dissection, with or without dissection of the aorta, occurs in Marfan's syndrome[109] (see Chap. 56) and has also been reported

TABLE 26-2 -- CAUSES AND CONTRIBUTING FACTORS IN SUDDEN CARDIAC DEATH--***Continued***

L. Intramural tumors
1. Primary
2. Metastatic
M. Obstructive intracavitary tumors
1. Neoplastic
2. Thrombotic

V. DISEASES OF THE CARDIAC VALVES
A. Valvular aortic stenosis/insufficiency
B. Mitral valve disruption
C. Mitral valve prolapse
D. Endocarditis
E. Prosthetic valve dysfunction

VI. CONGENITAL HEART DISEASE
A. Congenital aortic or pulmonic valve stenosis
B. Right-to-left shunts with Eisenmenger's physiology
1. Advanced disease
2. During labor and delivery
C. After surgical repair of congenital lesions (e.g., tetralogy of Fallot)

VII. ELECTROPHYSIOLOGICAL ABNORMALITIES
A. Abnormalities of the conducting system
1. Fibrosis of the His-Purkinje system
(a) Primary degeneration (Lenegre's disease)
(b) Secondary to fibrosis and calcification of the "cardiac skeleton" (Lev's disease)
(c) Postviral conducting system fibrosis
(d) Hereditary conducting system disease
2. Anomalous pathways of conduction
B. Abnormalities of repolarization
1. Congenital long QT interval syndromes
(a) Romano-Ward syndrome (without deafness)
(b) Jervell and Lange-Nielsen syndrome (with deafness)
2. Acquired long QT interval syndromes
(a) Drug effect
(1) Cardiac, antiarrhythmic
(2) Noncardiac
(3) Drug interactions
(b) Electrolyte abnormality
(c) Toxic substances
(d) Hypothermia
(e) Central nervous system injury
3. Right bundle branch block and ST segment elevations in the absence of ischemia (the Brugada syndrome)
C. Ventricular fibrillation of unknown or uncertain cause
1. Absence of identifiable structural or functional causes
(a) "Idiopathic" ventricular fibrillation
(b) Short-coupled torsades de pointes, polymorphic VT
(c) Nonspecific fibrofatty infiltration in previously healthy victim (variation of RV dysplasia [?])
2. Sleep-death in Southeast Asians (see VII.B.3)
(a) Bangungut

1. Absence of identifiable structural or functional causes
(a) "Idiopathic" ventricular fibrillation
(b) Short-coupled torsades de pointes, polymorphic VT
(c) Nonspecific fibrofatty infiltration in previously healthy victim (variation of RV dysplasia [?])
2. Sleep-death in Southeast Asians (see VII.B.3)
(a) Bangungut
(b) Pokkuri
(c) Nonlaitai

VIII. ELECTRICAL INSTABILITY RELATED TO NEUROHUMORAL AND CENTRAL NERVOUS SYSTEM INFLUENCES
A. Catecholamine-dependent lethal arrhythmias
B. Central nervous system-related
1. Psychic stress, emotional extremes
2. Auditory-related
3. "Voodoo" death in primitive cultures
4. Diseases of the cardiac nerves
5. Congenital QT interval prolongation

IX. SUDDEN INFANT DEATH SYNDROME AND SUDDEN DEATH IN CHILDREN
A. Sudden infant death syndrome
1. Immature respiratory control functions
2. Susceptibility to lethal arrhythmias (e.g., long QT syndrome)
3. Congenital heart disease
4. Myocarditis
B. Sudden death in children
1. Eisenmenger's syndrome, aortic stenosis, hypertrophic cardiomyopathy, pulmonary atresia
2. After corrective surgery for congenital heart disease
3. Myocarditis
4. Genetic disorders of electrical function (e.g., long QT syndrome)
5. No identified structural or functional cause

X. MISCELLANEOUS
A. Sudden death during extreme physical activity
B. Commotio cordis--blunt chest trauma
C. Mechanical interference with venous return
1. Acute cardiac tamponade
2. Massive pulmonary embolism
3. Acute intracardiac thrombosis
D. Dissecting aneurysm of the aorta
E. Toxic/metabolic disturbances
1. Electrolyte disturbances
2. Metabolic disturbances
3. Proarrhythmic effects of antiarrhythmic drugs
4. Proarrhythmic effects of noncardiac drugs
F. Mimics sudden cardiac death
1. "Cafe coronary"
2. Acute alcoholic states ("holiday heart")
3. Acute asthmatic attacks
4. Air or amniotic fluid embolism

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in the peripartum period of pregnancy.[110] Among the rare mechanical causes of SCD is prolapse of myxomatous polyps from the aortic valve into coronary ostia,[111] as well as dissection or rupture of a sinus of Valsalva aneurysm, with involvement of the coronary ostia and proximal coronary arteries.[112] Finally, deep myocardial bridges over coronary

arteries (see Chap. 12) have been reported in association with SCD occurring during strenuous exercise,[113] possibly due to dynamic mechanical obstruction. However, most myocardial bridges are inconsequential and SCD associated with this anatomy is uncommon.

Coronary artery spasm (see Chap. 37) may cause serious arrhythmias and SCD[114] [115] [116] with or without concomitant coronary atherosclerotic lesions.[115] Painless myocardial ischemia, associated with either spasm or fixed lesions, may be a cause of heretofore unexplained sudden death.[116] [117] [118] Different patterns of silent ischemia (e.g., totally asymptomatic, post-myocardial infarction, and mixed silent/anginal pattern) may have different prognostic implications.[119]

VENTRICULAR HYPERTROPHY.

Left ventricular hypertrophy is an independent risk factor for SCD, accompanies many causes of SCD,[120] and may be a physiological contributor to mechanisms of potentially lethal arrhythmias.[120] [121] The underlying states resulting in hypertrophy include hypertensive heart disease with or without atherosclerosis, valvular heart disease, obstructive and nonobstructive hypertrophic cardiomyopathy, primary pulmonary hypertension with right ventricular hypertrophy, and advanced right ventricular overload secondary to congenital heart disease. Each of these conditions is associated with risk of SCD, and it has been suggested that patients with severely hypertrophic ventricles are particularly susceptible to arrhythmic death.[120]

HYPERTROPHIC CARDIOMYOPATHY

(see Chap. 48) . Risk of SCD in obstructive and nonobstructive hypertrophic cardiomyopathy was identified in the early clinical and hemodynamic studies of this entity.[122] Two large series of the obstructive form yielded similar data on the magnitude of this risk. Goodwin[123] observed 48 deaths, of which 36 (67 percent) were sudden, among a cohort of 254 patients followed for a mean of 6 years, while Shah and associates[124] reported that 26 of 49 deaths (55 percent) among 190 patients were sudden. However, cardiac arrest survivors in this group may have better long-term outcome than do survivors with other causes. In one report

only 11/33 (33 percent) had recurrent cardiac arrest or death during a mean follow-up of 7 years.[125] More recent reports have suggested that the risk of *primary* cardiac arrest and SCD in hypertrophic cardiomyopathy is lower than previously thought.[126] [127]

A substantial proportion of patients with obstructive and nonobstructive cardiomyopathy have a family history of affected relatives or SCDs of unknown cause. Genetic studies have confirmed autosomal dominant inheritance patterns, with a great deal of allele heterogeneity. Seven gene loci on chromosomes 1, 3, 11, 12, 14, 15, and 19, encoding over 80 different mutations, and an additional undefined gene on chromosome 7, have

been identified.[45] [55] Most of the defects encode proteins in the contractile protein complex, the most common being beta-myosin heavy chain and cardiac troponin T, which together account for more than half of identified abnormalities.[55] [56] Risk of SCD appears to be defect-specific, even within specific gene loci.[55] Thus, the specific defect, rather than the locus, is more relevant, and may be independent of the severity of structural hypertrophy.

Specific clinical markers have not been especially predictive of SCD in individual patients, although young age at onset,[123] [128] strong family history,[54] [128] and worsening symptoms[123] appear to indicate higher risk. In one study, however, 54 percent of the sudden deaths occurred in patients without any functional limitations.[128] The mechanism of SCD in patients with hypertrophic obstructive cardiomyopathy was initially thought to involve outflow tract obstruction, possibly as a consequence of catecholamine stimulation, but more recent data have focused on lethal arrhythmias as the common mechanism of sudden death in this disease.[120] [128] [129] [130] [131] [132] These studies have demonstrated a high prevalence of PVCs and nonsustained VT on ambulatory recording or the inducibility[130] of potentially lethal arrhythmias during programed electrical stimulation.[131] [132] However, stable and asymptomatic nonsustained VT has limited predictive power for SCD in these patients. Rapid and/or polymorphic symptomatic nonsustained tachycardias have better predictive power.

The question of whether the pathogenesis of the arrhythmias represents an interaction between electrophysiological and hemodynamic abnormalities, or is a consequence of electrophysiological derangement of hypertrophied muscle,[120] [121] is unanswered. The observation that patients with nonobstructive hypertrophic cardiomyopathy have high-risk arrhythmias and are at increased risk for SCD[130] suggests that an electrophysiological mechanism secondary to the hypertrophied muscle itself plays some role. Stafford and colleagues[133] reported exercise-related cardiac arrest in nonobstructive hypertrophic cardiomyopathy. Ventricular fibrillation (VF) was reproduced during electrophysiological testing after induction of atrial fibrillation with a rapid ventricular response. In athletes younger than 35 years of age, hypertrophic cardiomyopathy is the most common cause of SCD, in contrast to athletes over the age of 35, among whom ischemic heart disease is the most common cause.[103] [104] [134] [135]

SUDDEN DEATH IN DILATED CARDIOMYOPATHY AND HEART FAILURE.

The advent of therapeutic interventions that provide better long-term control of congestive heart failure has begun to improve long-term survival of such patients (see Chap. 18) . However, the proportion of heart failure patients with stable hemodynamics who die suddenly appears to be increasing.[136] In reports to date, as many as 47 percent of deaths in heart failure patients are categorized as SCD. The mechanism of SCD (VT/VF versus bradyarrhythmia/asystole) appears to relate to cause (i.e., ischemic versus nonischemic)[137] The absolute risk of SCD increases with deteriorating left ventricular function, but the ratio of sudden to nonsudden deaths relates inversely to the extent of impairment.[87] Among patients with cardiomyopathy who have good functional capacity (Class I and II), total mortality risk is considerably better than for those with poor functional capacity (Class III and IV). (Fig. 26-7) . Unexplained syncope has been observed to be a powerful predictor of SCD in patients who have functional Class III or

IV disease due to any cause of cardiomyopathy, although ambulatory ventricular arrhythmias do not appear to indicate specific SCD risk in such patients.[94A] [138] [139] The actuarial 1-year probability of SCD was 45 percent in this study.

The interaction between post-myocardial infarction ventricular arrhythmia and depressed ejection fraction in determining risk for SCD has been described.[88] The majority of studies addressing the relation between chronic congestive heart failure and SCD focused on patients with ischemic, idiopathic, and alcoholic congestive cardiomyopathy.[87] [136] [140] [141] [142] A chronic myopathic syndrome after myocarditis has been cited as an infrequent but welldocumented cause of SCD.[143] Peripartum cardiomyopathy (see Chap. 65) also may cause SCD.

Figure 26-7 Risk of sudden cardiac death related to functional classification in heart failure. The relative probability of death being sudden is higher in the patients with better functional capacity who are at lower total mortality risk. (Modified from Kjekshus J: Arrhythmia and mortality in congestive heart failure. Am J Cardiol 65:42-1, 1990.)

Acute Heart Failure.

All causes of acute cardiac failure, in the absence of prompt interventions, can result in SCD caused by either the circulatory failure itself or secondary arrhythmias. The electrophysiological mechanisms involved have been proposed to be related to acute stretching of myocardial fibers and/or the His-Purkinje system, with its experimentally demonstrated arrhythmogenic effect,[144] but the roles of neurohumoral mechanisms and acute electrolyte shifts have not been fully evaluated.[136] Among the causes of acute cardiac failure that are associated with SCD are massive acute myocardial infarction, acute myocarditis, acute alcoholic cardiac dysfunction, and a number of mechanical causes of heart failure, such as massive pulmonary embolism, mechanical disruption of intracardiac structures secondary to infarction or infection, and ball-valve embolism in aortic or mitral stenosis (see Table 26-2) .

INFLAMMATORY, INFILTRATIVE, NEOPLASTIC, AND DEGENERATIVE DISEASES OF THE HEART.

Almost all diseases in this category have been associated with SCD, with or without concomitant cardiac failure. Acute viral myocarditis with left ventricular dysfunction (see Chap. 48) is commonly associated with cardiac arrhythmias, including potentially lethal arrhythmias. It is now recognized that serious ventricular arrhythmias or SCD can occur in myocarditis in the absence of clinical evidence of left ventricular dysfunction.[64] [143] [145] In a report of 19 SCDs among 1,606,167 previously screened US Air Force recruits, 8 of the 19 (42 percent) had evidence of myocarditis (5 nonrheumatic, 3 rheumatic) at postmortem examination, and 15 (79 percent) suffered their cardiac arrests during strenuous exertion.[146] Viral carditis also can cause damage isolated to the specialized conducting system and result in a propensity to arrhythmias; the rare association of this process with SCD has been reported.[147] The risk of potentially lethal arrhythmias is not limited to the acute phase of the disease.[143]

Myocardial involvement in collagen-vascular disorders, tumors, chronic granulomatous diseases, infiltrative disorders, and protozoan infestations varies widely, but in all instances SCD may be the initial or terminal manifestation of the disease process. Among the granulomatous diseases, *sarcoidosis* (see Chap. 48) stands out because of the frequency of SCD associated with it. Roberts and coworkers[148] reported that SCD was the terminal event in 67 percent of sarcoid heart disease deaths; the occurrence of SCD has been related to the extent of cardiac involvement.[149] In a report on the pathological findings in nine patients who died of *progressive systemic sclerosis* (see Chap. 48) , eight who died suddenly had evidence of transient ischemia and reperfusion histologically, suggesting that this might represent Raynaud-like involvement of coronary vessels.[150] *Amyloidosis* of the heart (see Chap. 48) may also cause sudden death. An incidence of 30 percent has been reported,[151] and diffuse involvement of ventricular muscle or of the specialized conducting system may be associated with SCD.[152]

Arrhythmogenic Right Ventricular Dysplasia Cardiomyopathy

(see Chaps. 23 and 25) . This condition is associated with a high incidence of ventricular arrhythmias, particularly recurrent VT.[153] [153A] Although

symptomatic VT has been well recognized in the syndrome for many years, the risk of SCD was unclear[154] and thought to be relatively low. However, the features of the disease, and risks associated with it, have been clarified by a number of studies.[153] [153A] [154] [155] [156] [157] In a high proportion of victims, perhaps as many as 80 percent, the first manifestation of the disease is "unexplained" syncope or SCD.[155] SCD is often exercise related and in some areas of the world where screening for hypertrophic cardiomyopathy has excluded those athletes from competition, right ventricular dysplasia is the most common cause of sport-related SCD.[158]

A genetic basis for right ventricular dysplasia is also being explored. A large proportion of the cases (up to an estimated 30 to 50 percent currently) appear to have a familial distribution.[45] [156] [157] The inheritance pattern is autosomal dominant except in one geographically isolated cluster that is autosomal recessive.[45] To date, no specific gene abnormalities have been characterized, but a heterogeneous distribution of loci (2 on chromosome 14, and one each on chromosomes 1 and 2) have been identified.[57] [58]

VALVULAR HEART DISEASE

(see Chap. 46) . Before the advent of surgery for valvular heart disease, *aortic stenosis* was a relatively common noncoronary cause of SCD. Campbell reported, in 1968, that 44 of 70 (73 percent) deaths in patients with aortic stenosis were sudden.[159] The advent of safe and effective procedures for aortic valve replacement has reduced the incidence of this cause of sudden death,[160] but patients with prosthetic or heterograft aortic valve

replacements remain at some risk for SCD caused by arrhythmias, prosthetic valve dysfunction, or coexistent coronary heart disease.[161] SCD has been reported to be the second most common mode of death after valve replacement surgery, accounting for 62 of 298 deaths (21 percent).[162] The incidence peaked 3 weeks after operation and then plateaued after 8 months. Nonetheless, the risk is still appreciably lower than the historical risk among patients before the advent of valve surgery. In another report analyzing outcome in patients receiving prosthetic valves for isolated severe aortic stenosis, SCD occurred at a rate of only 0.3 percent per year and was responsible for only 18 percent of late deaths.[163] A high incidence of ventricular arrhythmia has been observed during follow-up of patients with valve replacement,[163] [164] especially in those who had aortic stenosis, multiple valve surgery, or cardiomegaly.[164] Sudden death during follow-up was associated with ventricular arrhythmias and thromboembolism. Hemodynamic variables were less predictive. Stenotic lesions of other valves imply much lower risk of SCD. Regurgitant lesions, particularly chronic aortic regurgitation and acute mitral regurgitation, may cause SCD, but the risk is also lower than with aortic stenosis.

Mitral valve prolapse (see Chap. 46) is prevalent, but probably less than previously thought,[164A] and associated with a high incidence of annoying cardiac arrhythmias. However, a risk of SCD, although apparent, is quite low.[165] This uncommon complication appears to correlate with nonspecific ST-T wave changes in the inferior leads on the ECG.[166] In data reviewed from 17 reported instances of SCD in mitral valve prolapse patients, these nonspecific ST-T wave changes were present in six of eight patients who had had prior electrocardiograms.[167] An association with redundancy of mitral leaflets on echocardiogram also has been suggested.[168] Reported associations between QT interval prolongation or preexcitation and SCD in mitral prolapse syndrome are less consistent.[165]

Endocarditis of the aortic and mitral valves (see Chap. 47) may be associated with rapid death resulting from acute disruption of the valvular apparatus, coronary embolism, or abscesses of valvular rings or the septum; however, such deaths are rarely true sudden deaths as conventionally defined. Coronary embolism from valvular vegetations can trigger fatal ischemic arrhythmia on very rare occasions.

CONGENITAL HEART DISEASE.

The congenital lesions most commonly associated with SCD are aortic stenosis (see Chaps. 45 and 46) [145] [169] [170] and communications between the left and right sides of the heart with the Eisenmenger physiology (see Chap. 53) .[171] In the latter the risk of SCD is a function of pulmonary vascular disease severity; also, there is an extraordinarily high risk of maternal mortality during labor and delivery in the pregnant patient with Eisenmenger's syndrome (see Chap. 43) .[172] Potentially lethal arrhythmias and SCD have been described as late complications after surgical repair of complex congenital lesions, particularly tetralogy of Fallot (see Chap. 43) , transposition of the great arteries, and atrioventricular canal.[173] [174] These patients should be followed closely and treated aggressively when cardiac arrhythmias are identified, although the late risk of SCD may not be as high as previously thought.[175]

ELECTROPHYSIOLOGICAL ABNORMALITIES.

Acquired disease of the atrioventricular (AV) node and His-Purkinje system and the presence of accessory pathways of conduction (see Chap. 25) are two groups of structural abnormalities of specialized conduction that may be associated with SCD. Epidemiological studies have suggested that intraventricular conduction disturbances in coronary heart disease are one of the few factors that may increase the proportion of SCD in coronary heart disease.[35] A specific clinical example is the risk of VF during the first 30 days after myocardial infarction in patients with anterior infarctions and bundle branch block. Lie and associates[176] reported that 47 percent of patients who had late hospital VF had had anteroseptal infarcts with bundle branch block and that these 14 were from a total pool of only 40 patients with the combination of bundle branch block and anterior myocardial infarction. Thus there was a 35 percent incidence of VF in this subgroup, which represented only 4.1 percent of a total of 966 myocardial infarctions. This risk persists for 6 weeks after the infarction and then abates.[177] AV block or intraventricular conduction abnormalities were found in 9 of 10 patients who had recurrent VF during hospitalization after resuscitation from prehospital cardiac arrest.[15]

Primary fibrosis (Lenegre's disease)[178] or secondary mechanical injury (Lev's disease)[179] of the His-Purkinje system is commonly associated with intraventricular conduction abnormalities and symptomatic AV block and less commonly with SCD. The identification of people at risk and the efficacy of pacemakers for preventing SCD, rather than only ameliorating symptoms, had been the subjects of debate.[180] [181] However, survival appears to depend more on the nature and extent of the underlying-disease than on the conduction disturbance itself.[182]

Patients with congenital AV block (see Chap. 25) or non-progressive congenital intraventricular block usually have a low risk of SCD.[183] Progressive congenital intraventricular blocks predict a high risk,[183] as does the coexistence of structural congenital defects. A hereditary form has been reported in association with a familial propensity to SCD.[65]

The anomalous pathways of conduction, bundles of Kent in the Wolff-Parkinson-White syndrome, and Mahaim fibers, are commonly associated with nonlethal arrhythmias. However, when the anomalous pathways of conduction have short refractory periods, the occurrence of atrial fibrillation may allow the induction of VF during very rapid conduction across the bypass tract.[184] The incidence of SCD in patients with short refractory period bypass tracts is not yet known. Patients who have multiple pathways appear to be at higher risk of SCD,[184] as do patients with a familial pattern of anomalous pathways and premature SCD.[185] It is important to recognize atrial fibrillation and other markers of risk of SCD in patients with Wolff-Parkinson-White syndrome, such as family history, because catheter ablation procedures are now curative in the vast majority of affected individuals (see Chaps. 23 and 25) .

The Long QT Interval Syndromes

(see also Chaps. 22 , 23 , and 25) . The *congenital* long QT interval syndrome is a functional abnormality caused by hereditary defects of molecular structure in ion channel proteins and apparently is associated with neurogenic triggers that can cause lethal

arrhythmias. [186] [187] [188] [189] [190] [191] [191A] Two hereditary patterns have been described: the much more common autosomal dominant pattern known as the Romano-Ward syndrome[186] [191] and the rare autosomal recessive inheritance pattern, which is associated with deafness, the Jervell and Lange-Neilsen syndrome.[187] Some patients have prolonged QT intervals throughout life without any manifest arrhythmias, whereas others are highly susceptible to symptomatic and potentially fatal ventricular arrhythmias, particularly the torsades de pointes form of VT.[189] [190] [191] [191A] Moreover, genetic studies have demonstrated that penetrance may be low in some families,[45] making electrocardiographic identification of affected members difficult. The relationship between low penetrance and risk of SCD remains undefined, but susceptibility to QT-lengthening effects of drugs might be important in these patients.

Patients at higher risk are characterized by female gender, syncope, and documented torsades de pointes or prior VF, and they require aggressive medical intervention or implantable defibrillators.[191] [192] Moreover, making an effort to identify relatives at risk is an important preventive measure, given the familial pattern of the entity. A recent major advance has been the identification of specific gene defects for the Romano-Ward syndrome at loci on chromosomes 3, 7, 11 and 21.[45] [46] [47] [48] [49] [50] [51] [52] The locus on chromosome 3 encodes the cardiac Na^+ channel; the others encode K^+ channels. A locus mapped to a site on chromosome 4 appears to encode a yet-to-be-identified gene for the Romano-Ward variety of long QT syndrome.[53] The Jervell and Lange-Nielsen form, autosomal recessive with deafness, is caused by inherited abnormalities of *KvLQT1* (chromosome 11) and *minK* (chromosome 21), or homozygous *KvLQT1* mutations. [50] [51] [52] [52A] Multiple specific gene defects have been identified, attesting to the heterogeneity observed in other genetically determined electrophysiological abnormalities.

The *acquired form* of prolonged QT interval may be due to drug effects or individual patient idiosyncrasies (particularly Class IA or Class III antiarrhythmics and psychotropic drugs), electrolyte abnormalities, hypothermia, toxic substances, and central nervous system injury.[193] It also has been reported both in intensive weight reduction programs that involve the use of liquid protein diets[194] and in anorexia nervosa.[195] Lithium carbonate may prolong the QT interval and has been reported to be associated with an increased incidence of SCD in cancer patients with preexisting heart disease.[196] Drug interactions recently have been recognized as a mechanism of prolongation of the QT interval and torsades de pointes.[197] In acquired prolonged QT syndrome, as in the congenital form, the torsades de pointes form of VT is commonly the specific arrhythmia

that triggers or degenerates into lethal VF.

ELECTRICAL INSTABILITY RESULTING FROM NEUROHUMORAL AND CENTRAL NERVOUS SYSTEM INFLUENCES.

Catecholamine-dependent lethal arrhythmias in the absence of QT interval prolongation, with control by beta-adrenoceptor blocking agents, have been described.[198] Several central nervous system-related interactions with cardiac electrical stability have been suggested (see Chap. 71) . Lown and coworkers identified psychic stress as a mediating factor for advanced cardiac arrhythmias and perhaps SCD.[199] Epidemiological data also suggest an association between behavioral abnormalities and the risk of SCD, particularly in women,[83] [84] emotional extremes have been suggested as a triggering mechanism for SCD.[3] [200] Associations between auditory stimulation [145] and auditory auras[201] and SCD have been reported.[145] The auditory abnormalities in some forms of congenital QT prolongation have already been cited.[187]

A variant of torsades de pointes, characterized by short coupling intervals between a normal impulse and the initiating impulse, has been described[202] (Fig. 26-8) . It appears to have familial trends and to be related to alterations in autonomic nervous system activity. The 12-lead ECG demonstrates normal QT intervals, but VF and sudden death are common.

The syndrome of "voodoo death" in developing countries has been studied extensively.[203] [204] There appears to be an association between isolation from the tribe, a sense of hopelessness, severe bradyarrhythmias, and sudden death. With cultural changes in many of these areas, the syndrome has become less amenable to observation and study; however, there do remain pockets of cultural isolation in which the syndrome no doubt still exists.

SUDDEN INFANT DEATH SYNDROME AND SCD IN CHILDREN

The sudden infant death syndrome (SIDS) occurs between birth and 6 months of age, is more common in males, and has an incidence of 0.1 to 0.3 percent of live births.[205] Because of its abrupt nature, a cardiac mechanism has been suspected for many years,[206] but a variety of causes, with central respiratory dysfunction playing a major role, are considered likely.[207] Many cases of SIDS are believed to represent a

Figure 26-8 Short-coupled variant of torsades de pointes. This variant has been observed in people without structural heart disease and normal QT intervals. They are subject to spontaneous episodes of polymorphic ventricular tachycardia (torsades de pointes), which may degenerate into ventricular fibrillation. There is a high risk of sudden death in this uncommon syndrome.

form of "sleep apnea" that, if prolonged, may lead to hypoxia, cyanosis, and cardiac

arrhythmias. Experience with "near misses" and the results of respiratory monitoring, in conjunction with the propensity of the syndrome to occur in premature infants, all suggest impaired central nervous system respiratory control reflexes, possibly owing to immaturity.[205] [207] [208] There has recently been interest, however, in the possibility of obstructive apnea as another mechanism.[207] Identification of individual infants at risk is difficult, but the risk does not persist beyond the first 6 months of life. Having infants sleep on their backs has reduced the incidence of SIDS.[208A]

A primary cardiac cause is still considered the basis of this syndrome in some victims.[206] [209] Marino and Kane[210] observed either accessory pathways (two cases) or dispersed or immature AV nodal or bundle branch cells in the annulus fibrosus (four cases) among a group of seven SIDS victims studied by detailed histopathology. A large study of electrocardiograms in infants suggests an association of risk of SIDS with prolonged QT interval.[211] A near-miss survivor was shown to have a de novo mutation of the Na^+ channel gene (SCN5A; chromosome 3), validating the concept that LQT may be one of the mechanisms of SIDS.[211A]

Sudden death in children beyond the age group at risk for SIDS often is associated with identifiable heart disease[144] [212] although one study identified cardiac causes in only 25 percent of sudden natural death victims between the ages of 1 and 21 years.[41] About 25 percent of SCDs in children occur in those who have undergone previous surgery for congenital cardiac disease. Of the remaining 75 percent, more than one half occur in children who have one of four lesions: congenital aortic stenosis, Eisenmenger's syndrome, pulmonary stenosis or atresia, or obstructive hypertrophic cardiomyopathy.[212] Neuspiel and Kuller[41] observed 14 cases of myocarditis among 51 SCDs in children (27 percent).

OTHER CAUSES OF SUDDEN DEATH

SCD in athletes during or after extreme physical activity is infrequent.[213] The majority of such individuals have a previously unrecognized cardiac abnormality, with hypertrophic cardiomyopathy with or without obstruction, valvular aortic stenosis, and occult congenital or acquired coronary artery disease as the most common causes identified after death.[104] [134] [135] [214] [215] A surprisingly large fraction of people who died suddenly during exertion had unsuspected myocarditis, according to a report of a large cohort of US Air Force recruits.[146] A small group of such victims, however, have neither previously determined functional abnormality nor structural abnormalities at postmortem examination.[19] [103] [104] [143] [144] Cardiac trauma (commotio cordis [see Chap. 59]) may be the cause in some.

When no structural or functional basis for cardiac arrest or SCD can be identified, such VF events or deaths are classified as idiopathic.[216] Although long-term survival after an idiopathic potentially fatal event is still unclear, some degree of risk appears to remain.[217] Limited data suggest that higher risk persists primarily in patients with subtle cardiac abnormalities, in contrast to patients who are truly normal.[218] [219] In addition, these events tend to occur in young, otherwise healthy people.

A specific variation of SCD has been observed in southeast Asians. Many years ago

syndromes referred to as *bangungut* in young Filipino males,[220] *pokkuri* in young Japanese males,[221] and *nonlaltal* in young Laotian males[222] were reported. In each there was a tendency for sudden death to occur during sleep, and at one time a toxic cause was suspected.[220] [221] Documented cases have now been reported in Laotians who came to the United States after the Vietnam war. The mechanism was identified to be VF in some of these cases; in at least one instance electrophysiological study demonstrated inducible ventricular arrhythmia by programmed electrical stimulation.[223] Pathological examinations have revealed a high incidence of mild to significant cardiomegaly (14 of 18) and a variety of structural abnormalities of specialized conducting tissue.[224] The fact that these cases continue to occur in a new cultural setting suggests that there may be a hereditary predisposition.[244] It has now been suggested that these syndromes are variants of the syndrome of right bundle branch block and anterior ST segment elevation, associated with SCD, reported by Brugada and Brugada.[225]

There also are a number of noncardiac conditions that *mimic* SCD. These include the so-called *cafe coronary,*[226] [227] in which food, usually an unchewed piece of meat, lodges in the oropharynx and causes an abrupt obstruction at the glottis. The classic description of a cafe coronary is sudden cyanosis and collapse in a restaurant, during a meal accompanied by lively conversation. The *holiday heart syndrome* is characterized by cardiac arrhythmias, most commonly atrial, and other cardiac abnormalities associated with acute alcoholic states.[228] It has not been determined whether potentially lethal arrhythmias occurring in such settings account for reported sudden deaths associated with acute alcoholic states.[3] *Massive pulmonary embolism* (see Chap. 52) may cause acute cardiovascular collapse and sudden death; sudden death in severe acute asthmatic attacks, without prolonged deterioration of the patient's condition, is well recognized.[229] Air or amniotic fluid embolism at the time of labor and delivery may cause sudden death on rare occasions, with the clinical picture mimicking SCD.[230] Peripartum air embolism caused by an unusual sexual practice has been reported as a cause of such sudden deaths.[231]

Finally, a number of abnormalities that do not directly involve the heart may cause SCD or mimic it. These include aortic dissection (see Chap. 40) , acute cardiac tamponade (see Chap. 50) , and rapid exsanguination (see Chap. 40) .

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Pathology and Pathophysiology

Pathological observations in SCD victims reflect the epidemiological and clinical preponderance of coronary heart disease as the major structural predisposing factor.[232] Liberthson and coworkers[233] reported that 81 percent of 220 autopsied victims of SCD had significant coronary heart disease, defined as more than one coronary vessel with greater than 75 percent stenosis as the primary pathological feature. At least one vessel with more than 75 percent stenosis was found in 94 percent of victims, acute coronary occlusion in 58 percent, healed myocardial infarction in 44 percent, and acute myocardial infarction in 27 percent. These observations are consistent with many other studies of the frequency of coronary disease in sudden death victims. All of the other causes of SCD (see Table 26-2) collectively account for no more than 15 to 20 percent of cases, but they have provided a large base of enlightening pathological data.[64] [143] [234]

THE PATHOLOGY OF SUDDEN DEATH CAUSED BY CORONARY HEART DISEASE

THE CORONARY ARTERIES.

Extensive atherosclerosis is the most common pathological finding in the coronary arteries of victims of SCD (Table 26-3) . In postmortem examinations of 169 hearts, sites of 75 percent or more stenosis were present in three or four major vessels in 61 percent of the hearts studied; two vessels with at least 75 percent stenosis were found in 15 percent; and 24 percent of the hearts had either single-vessel disease or no vessels having lesions producing 75 percent stenosis.[235] A distinctly higher proportion of hearts having three or four vessels with 75 percent stenotic lesions was observed in white men (70 percent) compared with white women (34 percent). In contrast, 58

percent of the hearts of both black men and black women had three or four vessels with 75 percent or more stenoses. Consistent with clinical findings in survivors of out-of-hospital cardiac arrest,[15] there was no special predilection of disease distribution for any specific coronary artery, and there was no quantitative difference between proximal and distal distribution of disease.

TABLE 26-3 -- PATHOLOGICAL FINDINGS IN SUDDEN DEATH DUE TO CORONARY HEART DISEASE

THE CORONARY ARTERIES	VENTRICULAR MYOCARDIUM
Chronic atherosclerosis	Healed myocardial infarction
Acute lesions	Left ventricular hypertrophy
Plaque fissuring/erosion	Ventricular aneurysm
Platelet aggregates	Acute myocardial infarction
Organizing thrombus	
Coronary artery spasm	

Kuller and coworkers[68] pointed out that 90 percent or greater narrowing of at least one coronary artery was found in 77 percent of autopsied victims of sudden *coronary death,* compared with 8 percent of victims of other causes of sudden death. Davies[64] reported that 61 percent of patients dying suddenly because of coronary heart disease had three vessels with 75 percent or more stenosis at any one point; an additional 18 (23 percent) had two vessels with 75 percent or more stenosis. Among 100 age- and sex-matched controls who died of trauma or cerebral tumors, only 27 percent had two- or three-vessel disease, and 52 percent had no vessels with lesions of 75 percent or more. In the same study the majority of sudden deaths caused by coronary heart disease were associated with at least one point of more than 85 percent stenosis, and Davies suggested that this parameter provided the best discrimination between hearts of SCD victims and controls.

Several studies have demonstrated no specific pattern of distribution of coronary artery lesions that preselect for SCD. In a quantitative analysis comparing coronary artery narrowing at postmortem examination in SCD victims and controls, 36 percent of the 5-mm segments of the coronary arteries from the SCD group had 76 to 100 percent cross-sectional area reductions compared with 3 percent in the controls.[236] An additional 34 percent of the sections from the SCD group had 51 to 75 percent reductions in cross-sectional areas. Only 7 percent of the sections from the SCD patients had 0 to 25 percent reductions in cross-sectional areas.

The role of *active coronary artery* lesions, such as plaque fissuring, platelet aggregation, and thrombosis, in the onset of cardiac arrest leading to SCD is becoming clarified, [237]

[239] and there appears to be a poor association between risk factor for CAD, coronary artery calcification, and development of plaque fissuring or acute thrombosis.[76A] In one study of 100 consecutive sudden coronary death victims, 44 percent had major (more than 50 percent luminal occlusion) recent coronary thrombi, 30 percent had minor occlusive thrombi, and 21 percent had plaque fissuring.[236] Only 5 percent had no acute coronary artery changes; 65 percent of the thrombi occurred at sites of preexisting high-grade stenoses, and an additional 19 percent were found at sites of more than 50 percent stenosis. In a subsequent study by the same investigators, 50/168 victims (30 percent) had occlusive intraluminal coronary thrombi, and 73 (44 percent) had mural intraluminal thrombi.[238] Singlevessel disease, acute infarction at postmortem examination, and prodromal symptoms were associated with the presence of thrombi.

An overview of the major studies on the incidence of acute thrombotic occlusions, in which the definition of sudden death ranges from 15 minutes to 24 hours, reveals wide variation in the reported frequency of recant coronary thrombosis in sudden death. It ranges from 15 to 64 percent, but the majority of studies that used 6 hours or less as the definition of "sudden" had frequencies of less than 40 percent.[233] [237] [238] [239] [240] Factors that confound the analysis of such data include relations between platelet aggregates and thrombus formation and the spontaneous lysis of clots.

Baba and colleagues[241] reported the presence of *organizing* thrombus in about 31 percent of 121 sudden coronary heart disease deaths. They were commonly associated with sites of more than 75 percent chronic obstruction and with concomitant acute lesions at the same sites, leading to the speculation that clinical events 5 to 7 days before death might create a substrate for fatal acute coronal events. *Coronary artery spasm,* an established cause of acute ischemia, also may cause SCD and is recognizable in rare instances at postmortem examination.[242]

THE MYOCARDIUM.

Myocardial pathology in SCD caused by coronary heart disease reflects the extensive atherosclerosis that usually is present. Studies in victims of both out-of-hospital SCD and from epidemiological sources indicate that healed myocardial infarction is a common finding in SCD victims, with most investigators reporting, frequencies ranging from 40 to more than 70 percent.[8] [232] [242] [244] For example, Newman and coworkers[243] [244] reported that 72 percent of men in a 25- to 44-year age group who died suddenly (24 or fewer hours) with no previous clinical history of coronary heart disease had scars of large (63 percent) or small (less than 1 cm cross-sectional area, 9 percent) areas of healed myocardial necrosis. The incidence of acute myocardial infarction is considerably less, with cytopathological evidence of recent myocardial infarction averaging about 20 percent. This estimate corresponds well with studies in out-of-hospital cardiac arrest survivors, who have an incidence of new myocardial infarction in the range of 20 to 30 percent.

VENTRICULAR HYPERTROPHY.

Myocardial hypertrophy can coexist and interact with acute or chronic ischemia but appears to confer an independent mortality risk.[245] There is not a close correlation

between increased heart weight and severity of coronary heart disease in SCD victims[214] ; heart weights are higher in SCD victims than in those whose death is not sudden despite similar prevalence of history of hypertension before death.[8] Hypertrophy-associated mortality risk is also independent of left ventricular function and extent of coronary artery disease.[245] Anderson[120] suggests that left ventricular hypertrophy itself may be a predisposing factor to SCD. Experimental data also suggest increased susceptibility to potentially lethal ventricular arrhythmias in left ventricular hypertrophy with ischemia and reperfusion.[246] A study of massively enlarged hearts (i.e., weighing more than 1000 gm), however, did not indicate an excess incidence of SCD,[247] but the underlying pathology in that study was dominated by lesions that produce volume overload.

SPECIALIZED CONDUCTING SYSTEM IN SCD

Pathological data on the specialized conducting system of victims of SCD are relatively sparse. Lie[248] studied the specialized conducting system of 49 of 120 SCD patients with no previous history of coronary heart disease who died within 6 hours of onset of symptoms. Thirty-nine patients had acute myocardial infarction and 10 did not. Two patients with acute anteroseptal infarctions had hemorrhage and/or infarction involving the AV node and peripheral bundle branches. Luminal narrowing of the artery to the AV node was present in 50 percent, but there were no thromboses of vessels to the specialized conducting system. Evidence of ischemic injury was present with an equal frequency in SCD[248] and myocardial infarction patients.

Fibrosis of the specialized conducting system is a common but nonspecific endpoint of multiple causes. Although this process is associated with AV block or intraventricular conduction abnormalities, its role in SCD is uncertain. Lev's and Lenegre's diseases, ischemic injury caused by small-vessel disease, and numerous infiltrative or inflammatory processes all may result in such changes. In addition, active inflammatory processes such as myocarditis and infiltrative processes such as amyloidosis, scleroderma, hemochromatosis, and morbid obesity all may damage or destroy the AV node and/or bundle of His and result in AV block.[249]

Focal diseases such as sarcoidosis, Whipple's disease, and rheumatoid arthritis also may involve the conducting system (see Chap. 25) . These various categories of conducting system disease have been considered as possible pathological substrates for SCD that may be overlooked because of the difficulty in doing careful postmortem examinations of the conducting system routinely.[249] Focal involvement of conducting tissue by tumors (especially mesothelioma of the AV node but also lymphoma, carcinoma, rhabdomyoma, and fibroma) also has been reported,[249] and rare cases of SCD have been associated with these lesions. It has been suggested that abnormal postnatal morphogenesis of the specialized conducting system may be a significant factor in some SCDs in infants and children.

CARDIAC NERVES AND SCD

Diseases of cardiac nerves have been postulated to have a role in SCD.[250] [251] Neural involvement may be the result of random damage to neural elements within the

myocardium (i.e., "secondary" cardioneuropathy), or may be "primary," as in a selective cardiac viral neuropathy.[251] Secondary involvement may be a consequence of ischemic neural injury in coronary heart disease and has been postulated to result in autonomic destabilization, enhancing the propensity to arrhythmias. Some experimental data support this hypothesis, and a

clinical technique for imaging cardiac neural fibers suggests a changing pattern over time after myocardial infarction.[252] [253] [254] Involvement of neural plexuses, with or without conducting system involvement, has been observed at necropsy in 54 percent of patients who died within 24 hours of onset of myocardial infarction.[250] Specific causes for primary cardioneuropathies are less obvious. Viral, neurotoxic, and hereditary causes (e.g., progressive muscular dystrophy and Friedreich's ataxia) have been emphasized.

Disordered extrinsic neural involvement of the heart usually is considered to be functional. Nonetheless, stellate ganglion inflammation has been observed in some tissues removed surgically for symptomatic QT prolongation in hereditary QT syndrome[255] or after myocardial infarction.[256] The possible significance of such extrinsic cardiac neural involvement is not yet clear.

MECHANISMS AND PATHOPHYSIOLOGY

The occurrence of potentially lethal tachyarrhythmias, or of severe bradyarrhythmia or asystole, is the end of a cascade of pathophysiological abnormalities that result from complex interactions between coronary vascular events, myocardial injury, variations in autonomic tone, and/or the metabolic and electrolyte state of the myocardium. There is no uniform hypothesis regarding mechanisms by which these elements interact to lead to the final pathway of lethal arrhythmias. However, Figure 26-9 shows a model of the pathophysiology of SCD, in which the central event is the initiation of a potentially fatal arrhythmia. The risk of this event is conditioned by the presence of *structural abnormalities* and modulated by *functional variations*.[257]

Pathophysiological Mechanisms of Lethal Tachyarrhythmias

CORONARY ARTERY STRUCTURE AND FUNCTION.

Among the 80 percent of SCDs associated with coronary atherosclerosis, the distribution of chronic arterial narrowing has been well defined by pathological studies.[64] [233] [235] However, the specific mechanisms by which these lesions lead to potentially lethal disturbances of electrical stability are poorly understood. Steady-state reductions in regional myocardial blood flow, in the absence of superimposed acute lesions, creates a setting in which alterations in the metabolic or electrolyte state of the myocardium or neural fluctuations may result in loss of electrical stability.[136] Increased myocardial oxygen demand with a fixed supply may be a mechanism of

exercise-induced arrhythmias and sudden death during intense physical activity in athletes or others whose heart disease had not previously become clinically manifested.[103] [104] [134] [135] [146] [214] [215] [258] Vasoactive events leading to acute reduction in regional myocardial blood flow in the presence of a normal or previously compromised circulation constitute a common cause of transient ischemia, angina pectoris, arrhythmias, and perhaps SCD.[116] [117] [118] [119] Coronary artery spasm or modulation of coronary collateral flow exposes the myocardium to the double hazard of transient ischemia and reperfusion (Fig. 26-10) .[116] [245] [259] Sites of endothelial disease appear to predispose. [260] Neurogenic influences may play a role, but do not appear to be a sine qua non for the production of spasm. Vessel susceptibility and humoral factors, particularly those related to platelet activation and aggregation,[261] also appear to be important mechanisms.

Transition of stable atherosclerotic plaques to an "active" state because of endothelial damage, with plaque fissuring leading to platelet activation and aggregation followed by thrombosis, is among the more important mechanisms for SCD.[262] In addition to initiating the thrombus, platelet activation produces a series of biochemical alterations that may enhance or retard susceptibility to VF by means of vasomotor modulation. Hammon and Oates studied the effects of thromboxane synthetase inhibitors[263] and demonstrated protection against the induction of experimental VF, presumably by blocking conversion of prostaglandin H_2 (PGH_2) to thromboxane A_2 , which theoretically shunts accumulated PGH_2 to metabolic pathways that favor conversion to prostacyclin. Inhibition of cyclooxygenase by concurrent indomethacin administration gave further support to the hypothesis that PGH_2 shunting to other prostaglandin pathways might protect against VF by prostacyclin production. The possibility that inhibition of prostacyclin production might enhance the risk of VF[263] is supported by the finding from the Aspirin-Myocardial Infarction Study that the incidence of recurrent myocardial infarction was reduced by aspirin but the relative and perhaps absolute numbers of SCD tended to increase.[264]

A number of pieces of indirect evidence support the possibility that more than the mechanical consequences to flow is involved in platelet-activated thrombosis of coronary arteries in SCD. Davies and Thomas[237] pointed out that 95 of 100 subjects who died suddenly (fewer than 6 hours after the onset of symptoms) had acute coronary thrombi, plaque fissuring, or both. This incidence was considerably higher than in many previous reports, but it is noteworthy that only 44 percent of the patients had the largest thrombus occluding 51 percent or more of the cross-sectional area of the involved vessel, and only 18 percent of the patients had more than 75 percent occlusion. This raises questions whether mechanical obstruction to flow was dominant or whether the high incidence of nonoccluding thrombi simply reflected the state of activation of the platelets. The discrepancy between the relatively high incidence of acute thrombi in postmortem studies and the low incidence of evolution of new myocardial infarction among survivors of out-of-hospital VF[19] [265] highlights this question. Spontaneous thrombolysis, a dominant role of spasm induced by platelet products, or a combination may explain this discrepancy.

ACUTE ISCHEMIA AND INITIATION OF LETHAL ARRHYTHMIAS.

The onset of acute ischemia produces immediate electrical, mechanical, and biochemical dysfunction

Figure 26-9 Biological model of sudden cardiac death. Structural cardiac abnormalities are commonly defined as the causative basis for SCD. However, functional alterations of the abnormal anatomic substrate usually are required to alter stability of the myocardium, permitting a potentially fatal arrhythmia to be initiated. In this conceptual model, short- or long-term structural abnormalities interact with functional modulations to influence the probability that premature ventricular contractions (PVCs) initiate ventricular tachycardia or fibrillation (VT/VF). (From Myerburg RJ, et al: A biological approach to sudden cardiac death: Structure, function, and cause. Am J Cardiol 63:1512, 1989.)

Figure 26-10 Life-threatening ventricular arrhythmias associated with acute myocardial ischemia due to coronary artery spasm and with reperfusion. *A,* Continuous lead II electrocardiographic monitor recording during ischemia [time 0 to 55 sec] due to spasm of the right coronary artery (*B*). There is an abrupt transition [time 56 sec to 72 sec] from repetitive ventricular ectopy to a rapid polymorphic, prefibrillatory tachyarrhythmia [time 80 sec to 130 sec] associated with nitroglycerin-induced reversal of the spasm (*C*).

of cardiac muscle (Figs. 26-9 and 26-10) . The specialized conducting tissue is more resistant to acute ischemia than is working myocardium, and therefore the electrophysiological consequences are less intense and delayed in onset in specialized conduction tissue.[266] Experimental studies also have provided data on the long-term consequences of left ventricular hypertrophy and healed experimental myocardial infarction. Tissue exposed to chronic stress produced by long-term left ventricular pressure overload[267] and tissue that has healed after ischemic injury[249] [268] both show lasting cellular electrophysiological abnormalities, including regional changes in transmembrane action potentials and refractory periods. Moreover, acute ischemic injury or acute myocardial infarction in the presence of healed myocardial infarction is more arrhythmogenic than is the same extent of acute ischemia in previously normal tissue.[269] In addition to the direct effect of ischemia on normal or previously abnormal tissue, reperfusion after transient ischemia may cause lethal arrhythmias[116] [270] [271] (Fig. 26-10) . Reperfusion of ischemic areas may occur by three mechanisms: (1) spontaneous thrombolysis, (2) collateral flow from other coronary vascular beds to the ischemic bed, and (3) reversal of vasospasm. Some mechanisms of reperfusion-induced arrhythmogenesis appear to be related to the duration of ischemia before reperfusion.[271] [272] Experimentally, there is a window of vulnerability beginning 5 to 10 minutes after the onset of ischemia and lasting up to 20 to 30 minutes.

ELECTROPHYSIOLOGICAL EFFECTS OF ACUTE ISCHEMIA.

Within the first minutes after experimental coronary ligation there is a propensity to ventricular arrhythmias that abates after 30 minutes and reappears after several

hours.[273] The initial 30 minutes of arrhythmias is divided into two periods, the first of which lasts for about 10 minutes and is presumably directly related to the initial ischemic injury. The second period (20 to 30 minutes) may be related either to reperfusion of ischemic areas or to the evolution of differing injury patterns in the epicardial and endocardial muscle. Multiple mechanisms of reperfusion arrhythmias have been observed experimentally.[245] [274] [275]

At the level of the myocyte, the immediate consequences of ischemia, which include loss of integrity of cell membranes with efflux of K^+ , influx of Ca^{2+} , acidosis, reduction of transmembrane resting potentials, and enhanced automaticity in some tissues, are followed by a separate series of changes during reperfusion. Those of particular interest are the possible continued influx of Ca^{2+} which may produce electrical instability[270] [276] ; responses to alpha- and/or beta-adrenoceptor stimulation[252] [253] [277] [278] [279] ; and neurophysiologically induced afterdepolarization as triggering responses for Ca^{2+} -dependent arrhythmias.[275] [278] Other possible mechanisms studied experimentally include formation of superoxide radicals in reperfusion arrhythmias[280] [281] and differential responses of endocardial and epicardial muscle activation times and refractory periods during ischemia or reperfusion.[274] [282]

The importance of the myocardial response to the onset of ischemia has been emphasized, on the basis of the demonstration of dramatic cellular electrophysiological changes during the early period after coronary occlusion.[273] [274] [283] However, the state of the myocardium at the time of onset of ischemia is a critical additional factor. Tissue healed after previous injury appears to be more susceptible to the electrical destabilizing effects of acute ischemia, as is chronically hypertrophied muscle. There are data suggesting that remodeling-induced local stretch, regional hypertrophy, or intrinsic cellular alteration may contribute to this vulnerability. Of more direct clinical relevance is the suggestion that K^+ depletion by diuretics and clinical hypokalemia may make ventricular myocardium more susceptible to potentially lethal arrhythmias.[284] [285]

The association of metabolic and electrolyte abnormalities, as well as neurophysiological and neurohumoral changes,[286] [287] [288] with SCD emphasizes the importance of changes in the myocardial substrate in

the propensity to lethal arrhythmias. Most direct among myocardial metabolic changes in response to ischemia are local acute increase in interstitial K^+ levels to values exceeding 15 mM, a fall in tissue pH to below 6.0, changes in adrenoceptor activity, and alterations in autonomic nerve traffic,[144] all of which tend to create and maintain electrical instability, especially if regional in distribution. Other metabolic changes such as cyclic adenosine monophosphate elevation, accumulation of free fatty acids and their metabolites, formation of lysophosphoglycerides, and impaired myocardial glycolysis also have been suggested as myocardial destabilizing influences.[289]

Local myocardial and systemic influences integrate to establish operational

mechanisms. Associations between systemic patterns of autonomic fluctuation are expressed as patterns of heart rate variability,[290] [291] identifying subsets of patients at higher risk for SCD.

TRANSITION FROM MYOCARDIAL INSTABILITY TO LETHAL ARRHYTHMIAS.

The combination of a triggering event and a susceptible myocardium is evolving as a fundamental electrophysiological concept for the mechanism of initiation of potentially lethal arrhythmias (see Figs. 26-5 and 26-9) . The endpoint of their interaction is disorganization of patterns of myocardial activation, often by premature impulses (i.e., the "trigger"), into multiple uncoordinated reentrant pathways (i.e., VF). Clinical,[93] [292] experimental,[268] [293] and pharmacological[292] data all suggest that triggering events in the absence of myocardial instability do not permit the evolution of lethal arrhythmias. Therefore, in the absence of myocardial vulnerability, many triggering events, such as frequent and complex PVCs, may be innocuous.[257]

The onset of ischemia is accompanied by abrupt reduction in transmembrane resting potential and amplitude, and in duration of the action potentials in the affected area,[283] [293a] with little change in remote areas. When ischemic cells depolarize to resting potentials less than -60 mV, they may become inexcitable and of little electrophysiological importance. As they are depolarizing to that range, however, or repolarizing as a consequence of reperfusion, the membranes pass through ranges of reduced excitability, upstroke velocity, and time courses of repolarization. These characteristics result in slow conduction and electrophysiological heterogeneity. These events that occur regionally in ischemic myocardium, adjacent to nonischemic tissue, create a setting for the key elements of reentry--slow conduction and unidirectional block--which makes them vulnerable to reentrant arrhythmias. When premature impulses are generated in this environment, they may further alter the dispersion of recovery between ischemic tissue, chronically abnormal tissue, and normal cells,[269] ultimately leading to complete disorganization and VF. VF is probably not a consequence only of reentry.[144] Rapid-enhanced automaticity caused by ischemic injury to the specialized conducting tissue, or Ca^{2+} channel-triggered activity in partially depolarized tissue, may result in rapid bursts of automatic activity that also could lead to failure of coordinated conduction and VF.

The dispersion of refractory periods produced by acute ischemia, which provides the substrate for reentrant tachycardias and VF, may be further enhanced by a healed ischemic injury. The time course of repolarization is lengthened after healing of ischemic injury[269] and shortened by acute ischemia.[269] [271] [283] The coexistence of the two appears to make the ventricle more susceptible to sustained arrhythmias in some experimental models.[269]

Bradyarrhythmias and Asystolic Arrest

The basic electrophysiological mechanism in this form of arrest is failure of normal subordinate automatic activity to assume pacemaking function of the heart in the absence of normal function of the sinus node and/or AV junction. Bradyarrhythmic and asystolic arrests are more common in severely diseased hearts and probably represent

diffuse involvement of subendocardial Purkinje fibers. Systemic influences that increase extracellular K+ concentration, such as anoxia, acidosis, shock, renal failure, trauma, and hypothermia, may result in partial depolarization of normal or already diseased pacemaker cells in the His-Purkinje system, with a decrease in the slope of spontaneous phase 4 depolarization and ultimate loss of automaticity.[294] These processes may produce global dysfunction of automatic cell activity, in contrast to the regional dysfunction more common in acute ischemia. Functionally depressed automatic cells (e.g., owing to increased extracellular K+ concentration) are more susceptible to overdrive suppression. Under these conditions, brief bursts of tachycardia may be followed by prolonged asystolic periods, with further depression of automaticity by the consequent acidosis and increased local K+ concentration, or by changes in adrenergic tone. The ultimate consequence may be degeneration into VF or persistent asystole.

Pulseless Electrical Activity

Pulseless electrical activity, formerly called electromechanical dissociation (EMD), is separated into *primary* and *secondary forms*. The common denominator in both is continued electrical rhythmicity of the heart in the absence of effective mechanical function. The secondary form includes those causes that result from an abrupt cessation of cardiac venous return, such as massive pulmonary embolism, acute malfunction of prosthetic valves, exsanguination, and cardiac tamponade from hemopericardium. The primary form is the more familiar; in it none of these obvious mechanical factors are present, but ventricular muscle fails to produce an effective contraction despite continued electrical activity (i.e., *failure of electromechanical coupling*).[295] It usually occurs as an end-stage event in advanced heart disease, but it can occur in patients with acute ischemic events or, more commonly, after electrical resuscitation from a prolonged cardiac arrest. Although not thoroughly understood, it appears that diffuse disease, metabolic abnormalities, or global ischemia provides the pathophysiological substrate. The proximate mechanism for failure of electromechanical coupling may be abnormal intracellular Ca^{2+} metabolism, intracellular acidosis, or perhaps adenosine triphosphate depletion.

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Clinical Characteristics of the Patient with Cardiac Arrest

The advent of community-based emergency rescue systems, such as those in Seattle[18] and Miami, [265] have demonstrated that only a minority of survivors of out-of-hospital VF had clinical evidence indicating that a new transmural myocardial infarction was associated with the cardiac arrest. In the Seattle study, only one of five survivors had new transmural infarctions.[18] Thus, in the majority of such patients, transient pathophysiological events are responsible for cardiac arrest. The recurrence rate in survivors of out-of-hospital cardiac arrest is low in the subgroup of patients who had documentation of a new transmural myocardial infarction. In contrast, it was found to be 30 percent at 1 year and 45 percent at 2 years in those survivors who did not have a new transmural myocardial infarction.[17] [18] Recurrence rates decreased subsequently,[67] possibly owing in part to long-term interventions. However, it is not known whether this results from a change in the natural history,[296] [297] [298] changes in preventive strategies for underlying disease, or long-term interventions for controlling arrhythmic risk.[25]

Clinical cardiac arrest and SCD are best described in the framework of the same four phases of the event used to

establish definitions (see Fig. 26-1) : prodromes, onset of the terminal event, the cardiac arrest, and progression to biological death or survival.

Prodromal Symptoms

Patients at risk for SCD may have prodromes such as chest pain, dyspnea, weakness or fatigue, palpitations, syncope, and a number of nonspecific complaints. Several epidemiological and clinical studies demonstrated that such symptoms can presage coronary events, particularly myocardial infarction and SCD,[8] [68] [98] and result in contact with the medical system weeks to months before SCD.

In a prospective study in Edinburgh, Scotland, however, only 12 percent of victims of SCD had consulted a physician because of new or worsening angina pectoris during periods of up to 6 months before death.[299] In contrast, 33 percent of myocardial infarction patients had consulted their physicians for this complaint. Nonetheless, 46 percent of victims of SCD had seen a physician within 4 weeks before death, but three fourths of them had sought medical help for complaints that appeared to be unrelated to the heart. Liberthson and associates, associates,[17] in a study of patients successfully resuscitated after out-of-hospital cardiac arrest, noted that 28 percent reported retrospectively that they had had new or changing angina pectoris or dyspnea in the 4 weeks before arrest and that 31 percent had seen a physician during this time but only 12 percent because of these symptoms.

Patients who have chest pain as a prodrome to SCD appear to have a higher probability of intraluminal coronary thrombosis at postmortem examination.[238] Attempts to identify early prodromal symptoms that are more specific for the patient at risk for SCD have not yet been successful. Fatigue has been a particularly common symptom in the days or weeks before SCD in a number of studies,[298] but this symptom is nonspecific. The symptoms that occur within the last hours or minutes before cardiac arrest are more specific for heart disease and may include symptoms of arrhythmias, ischemia, or heart failure.[16] [300] Liberthson and associates[233] reported specific cardiac symptoms at a mean interval of about 3.8 hours before collapse in 24 percent of victims of SCD. However, most studies have reported such symptoms even less commonly, particularly when victims whose deaths were instantaneous are included.[8]

Onset of the Terminal Event

The period of 1 hour or less between acute changes in cardiovascular status and the cardiac arrest itself, which has been defined as the "onset of the terminal event," is a subject about which there is limited information. Reports from ambulatory recordings fortuitously obtained at the time of unexpected cardiac arrest indicate dynamic change in cardiac electrical activity during the minutes or hours before the onset of cardiac arrest.[301] [302] [303] These reports suggest that increasing heart rate and advancing grades of ventricular ectopy are common antecedents of VF. Although these recordings suggest transient electrophysiological destabilization of the myocardium, the extent to which these objective observations are paralleled by clinical symptoms is less well documented. SCDs caused by either arrhythmias or acute circulatory failure mechanisms involve a high incidence of acute myocardial disorders at the onset of the terminal event; such disorders are more likely to be ischemic when the death is due to arrhythmias and to be associated with low-output states or myocardial anoxia when the

deaths are due to circulatory failure.[16] [304]

Abrupt, unexpected loss of effective circulation may be caused by cardiac arrhythmias or mechanical disturbances, but the majority of such events that terminate in SCD are arrhythmic. Hinkle and Thaler[304] classified cardiac deaths among 142 subjects who died during a follow-up of 5 to 10 years. Class I was labeled arrhythmic death and Class II was death caused by circulatory failure. The distinction between the two classes was based on whether circulatory failure preceded (Class II) or followed (Class I) the disappearance of the pulse. Among deaths that occurred less than 1 hour after the onset of the terminal illness, 93 percent were due to arrhythmias; in addition, 90 percent of deaths caused by heart disease were initiated by arrhythmic events rather than circulatory failure. Table 26-4 demonstrates

TABLE 26-4 -- DIFFERENCES IN CLINICAL STATUS IMMEDIATELY BEFORE DEATH IN PATIENTS DYING OF ARRHYTHMIA AND CIRCULATORY FAILURE

CLINICAL STATUS IMMEDIATELY BEFORE DEATH	ARRHYTHMIC DEATHS (N=82) (CLASS I)	CIRCULATORY FAILURE DEATHS (N=59) (CLASS II)
Comatose	0/82 (0%)	56/59 (95%)
Standing or actively moving	39/82 (48%)	0/59 (0%)
Terminal arrhythmia		
Ventricular fibrillation	15/18 (83%)	3/9 (33%)
Asystole	3/18 (17%)	6/9 (67%)
Duration of terminal illness		
<1 hour	53/82 (65%)	4/59 (7%)
>24 hours	17/82 (21%)	48/59 (81%)
Nature of terminal illness		
Acute cardiac events	80/82 (98%)	8/59 (14%)
Noncardiac events	1/82 (1%)	51/59 (86%)

Data from Hinkle LE, Thaler HT: Clinical classification of cardiac deaths. Circulation 65:457, 1982. Copyright 1982, American Heart Association.

Hypotension (systolic BP <100 mm Hg)

that deaths caused by circulatory failure occurred predominantly among patients who could be identified as having terminal illnesses (95 percent were comatose), were associated more frequently with bradyarrhythmias than with VF as the terminal arrhythmias, and were dominated by noncardiac events as the terminal illness. In contrast, 98 percent of the arrhythmic deaths were associated primarily with cardiac disorders.

Clinical Features of Cardiac Arrest

The cardiac arrest itself is characterized by abrupt loss of consciousness from lack of adequate cerebral blood flow. It is an event that uniformly leads to death in the absence of an active intervention, although spontaneous reversions occur rarely. The most common cardiac mechanism is VF, followed by bradyarrhythmias or asystole, and sustained VT.[15] Other, less frequent mechanisms include electromechanical dissociation, rupture of the ventricle,[305] cardiac tamponade, acute mechanical obstruction to flow, and acute disruption of a major blood vessel.[3] [64] [143]

The potential for successful resuscitation is a function of the setting in which cardiac arrest occurs, the mechanism of the arrest, and the underlying clinical status of the victim.[306] Closely related to the potential for successful resuscitation is the decision of whether to attempt to resuscitate.[307]

At present there are fewer low-risk patients with otherwise uncomplicated myocardial infarctions weighting in-hospital cardiac arrest statistics than previously.[306] Bedell and coworkers[308] reported that only 14 percent of in-hospital cardiopulmonary resuscitation (CPR) patients were discharged from the hospital alive, and that 20 percent of these died within the ensuing 6 months. Although 41 percent of the patients had suffered an acute myocardial infarction, 73 percent had a history of congestive heart failure and 20 percent had had prior cardiac arrests. The mean age of 70 years (10 years older than the populations in several major prehospital cardiac arrest studies[17] [18] [67]) may have influenced the outcome statistics, but the patient population at risk for in-hospital cardiac arrest was heavily influenced by patients with high-risk complicated myocardial infarction or patients with other high-risk markers. Noncardiac clinical diagnoses were dominated by renal failure, pneumonia, sepsis, diabetes, and a history of cancer. The strong male preponderance consistently reported in out-of-hospital cardiac arrest studies is not present in in-hospital patients, but the better prognosis of VT or VF mechanisms, compared with bradyarrhythmic or asystolic mechanisms, persists (27 percent survival versus 8 percent survival). However, the proportion of arrests that are due to in-hospital VT or VF is considerably less (33 percent), with the combination of respiratory arrest, asystole, and electromechanical dissociation dominating the statistics (61 percent). In a more recent report, de Vos and colleagues[309] observed a 22 percent survival to hospital discharge. Adverse risks were age older than 70 years, prior stroke or renal failure, or heart failure on admission. Better

outcomes were predicted by prior angina pectoris or admission because of ventricular arrhythmias.

The important risk factors for death after CPR are listed in Table 26-5 . The facts that the fraction of out-of-hospital cardiac arrest survivors who are discharged from the hospital alive may now equal or exceed the fraction of in-hospital cardiac arrest victims

who are discharged alive[310] and that the postdischarge mortality rate for in-hospital cardiac arrest survivors is higher than that for out-of-hospital cardiac arrest survivors[67] [308] [311] are telling clinical statistics. Not only do they emphasize the success of preventive measures for cardiac arrest in low-risk in-hospital patients, causing those statistics to be dominated by higher-risk patients, but they also emphasize the improvement in pre-hospital and in-hospital care of out-of-hospital cardiac arrest victims.[312]

Cardiac arrest associated with coronary heart disease in the hospitalized elderly patient has a similar outcome. Gulati and colleagues[313] reported that 14 of 52 (27 percent) elderly patients (mean age, 76 years) were successfully resuscitated, although only 9 (17 percent) remained alive after 1 week. Similar outcome was observed in another report comparing patients younger and older than 70 years.[314] Coronary heart disease was the cause in 48 patients (92 percent); 5 of 22 patients (23 percent) with VF arrests survived and only 1 of 19 (5 percent) with asystole survived.[313] Among those patients 70 years of age or older, survival to discharge from hospital after out-of-hospital cardiac arrest was lower (29 percent) than among younger patients (47 percent).[315] However, long-term neurological status, survival, and length of hospitalization were similar among older and younger patients.

Progression to Biological Death

The time course for progression from cardiac arrest to biological death relates to the mechanism of the cardiac arrest, the nature of the underlying disease process, and the delay between onset and resuscitative efforts. Unattended VF characteristically leads to the onset of irreversible brain damage within 4 to 6 minutes, and biological death follows within a matter of minutes. In large series, however, it has been demonstrated that a limited number of victims may remain biologically alive for longer periods and may be resuscitated after delays in excess of 8 minutes before beginning basic life support and in excess of 16 minutes before advanced life support.[316] Despite these exceptions, it is clear that the probability for a favorable outcome deteriorates rapidly as a function of time after unattended cardiac arrest. Younger patients with less severe cardiac disease and the absence of coexistent multisystem disease appear to have a higher probability of a favorable outcome after such delays. Irreversible injury of the central nervous system usually occurs before biological death, and the interval may extend to a period of weeks in those patients who are resuscitated during the temporal gap between brain damage

TABLE 26-5 -- PREDICTORS OF MORTALITY AFTER IN-HOSPITAL CARDIOPULMONARY RESUSCITATION

BEFORE ARREST
Hypotension (systolic BP <100 mm Hg)
Pneumonia
Renal failure (BUN >50 mg/dl)
Cancer
Homebound life style

Modified from Bedell SE, et al: Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569, 1983. Copyright Massachusetts Medical Society.

DURING ARREST

Arrest duration >15 minutes
Intubation
Hypotension (systolic BP <100 mm Hg)
Pneumonia
Homebound life style

Modified from Bedell SE, et al: Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569, 1983. Copyright Massachusetts Medical Society.

AFTER RESUSCITATION

Coma
Need for pressors
Arrest duration >15 minutes

Modified from Bedell SE, et al: Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569, 1983. Copyright Massachusetts Medical Society.

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and biological death (see Definition, p. 890). In-hospital cardiac arrest caused by VF is less likely to have a protracted course between the arrest and biological death, with patients either surviving after a prompt intervention or succumbing rapidly because of inability to stabilize cardiac rhythm or hemodynamics.[308]

Those patients whose cardiac arrest is due to sustained VT with cardiac output inadequate to maintain consciousness can remain in VT for considerably longer periods, with flow that is marginally sufficient to maintain viability. This allows a longer interval between the onset of cardiac arrest and the end of the period that will allow successful resuscitation. The lives of such patients usually end in VF or an asystolic arrest if the VT is not actively or spontaneously reverted. Once the transition from VT to VF or to a bradyarrhythmia occurs, the subsequent course to biological death is similar to that in patients in whom VF or bradyarrhythmias are the initiating event.

The progression in patients with asystole or bradyarrhythmias as the initiating event is more rapid. Such patients, whether in an in-hospital[308] or out-of-hospital[15] [317] environment, have a very poor prognosis because of advanced heart disease or coexistant multisystem disease. They tend to respond poorly to interventions, even if the heart is successfully paced.[318] Although a small subgroup of patients with bradyarrhythmias associated with electrolyte or pharmacological abnormalities may respond well to interventions, the majority progress rapidly to biological death.[317] The infrequent cardiac arrests caused by mechanical factors such as tamponade, structural disruption, and impedance to flow by major thromboembolic obstructions to right or left ventricular outflow are reversible only in those instances in which the mechanism is recognized and an intervention is feasible. The vast majority of these events lead to

rapid biological death, although prompt relief of tamponade may save some lives.

Hospital Course of Survivors of Cardiac Arrest

The conditions of patients who are resuscitated immediately from *primary* VF associated with acute myocardial infarction usually stabilize promptly, and they require no special management after the early phase of the infarction (see Chap. 35) . The management after *secondary cardiac arrest in myocardial infarction* is dominated by the hemodynamic status of the patient. Among survivors of *out-of-hospital cardiac arrest,* the initial 24 to 48 hours of hospitalization are characterized by a tendency to ventricular arrhythmias, which usually respond well to antiarrhythmic therapy. The overall rate of recurrent cardiac arrest is low, 10 to 20 percent, but the mortality rate in patients who have recurrent cardiac arrests is about 50 percent.[15] [265] [300] Only 5 to 10 percent of in-hospital deaths after out-of-hospital resuscitation are due to recurrent cardiac arrhythmias.[15] [17] [18] Patients who have recurrent cardiac arrest have a high incidence of either new or preexisting AV or intraventricular conduction abnormalities.[15]

The most common causes of death in hospitalized survivors of out-of-hospital cardiac arrest are noncardiac events related to central nervous system injury resulting from the cardiac arrest itself. These include anoxic encephalopathy and sepsis related to prolonged intubation and hemodynamic monitoring lines.[15] [19] Fifty-nine percent of deaths during index hospitalization after prehospital resuscitation have been reported to be due to such causes.[15] Thirty-nine percent of 457 consecutive patients in coma never awakened after admission to the hospital and died after a median survival of 3.5 days.[319] Two thirds of the 61 percent who awakened had no gross deficits, and an additional 21

Figure 26-11 Hemodynamic data from prehospital cardiac arrest victims studied during initial post-arrest hospitalization. These data indicate a broad range of cardiac function and a statistically insignificant difference between EF at entry in long-term survivors and in recurrent cardiac arrest victims. However, patients who died suddenly had significantly higher EF than those who died of non-sudden cardiac causes. (From Myerburg RJ et al: Clinical, electrophysiologic, and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. Am J Med 68:568, 1980.)

percent had persisting cognitive deficits only. Of the patients who did awaken, 25 percent had done so by admission, 71 percent by the first hospital day, and 92 percent by the third day. A small number of patients awakened after prolonged hospitalization. Of the 206 hospital deaths (45 percent of the 457 patients), 80 percent had not awakened before death.

Cardiac causes of delayed death during hospitalization after out-of-hospital cardiac arrest are most commonly related to hemodynamic deterioration, which accounts for about one third of deaths in hospitals.[15] [19] Among all deaths, those that occurred within

the first 48 hours of hospitalization usually were due to hemodynamic deterioration or arrhythmias, regardless of the neurological status; later deaths were related to neurological complications. Admission characteristics most predictive of subsequent awakening included motor response, pupillary light response, spontaneous eye movement, and blood glucose level below 300 mg/dl.[320]

Clinical Profile of Survivors of Out-of-Hospital Cardiac Arrest

The clinical features of survivors of out-of-hospital cardiac arrest are heavily influenced by the type and extent of the underlying disease associated with the event. Causation is dominated by coronary heart disease, which accounts for approximately 80 percent of out-of-hospital cardiac arrest in the United States[265] and is commonly extensive. The cardiomyopathies collectively account for another 10 to 15 percent, with all other structural heart diseases, plus functional abnormalities and toxic/environmental causes, accounting for the remainder (see Table 26-2) .[232]

Ambient ventricular arrhythmias have been reported in the majority of survivors of prehospital cardiac arrest who had serial ambulatory monitor recordings.[265] [321] [322] These arrhythmias show trends to higher grades of ventricular ectopy in victims of recurrent cardiac arrest compared with long-term survivors.[67] [322] Repetitive PVCs were strongly associated with a history of congestive heart failure or previous myocardial infarction. The strongest predictors of subsequent mortality were use of digitalis, elevated blood urea nitrogen levels, cerebrovascular accident, previous myocardial infarction, and age; however, the presence of complex PVCs or frequent ectopy (25 PVCs/hr) added strongly to risk.

LEFT VENTRICULAR FUNCTION.

This is abnormal in the majority of survivors of out-of-hospital cardiac arrest, often severely so, but there is a wide variation, ranging from severe dysfunction to normal or near-normal measurements. From data reported in a number of largeseries, the mean ejection fraction has been in the range of 32 to 35 percent (Fig. 26-11) .[67] The ejection fraction of those who died during follow-up was lower than that of the long-term survivors (38 versus 45 percent, respectively).[15] [67] Patients who died of recurrent cardiac arrest had higher ejection fractions than non-SCD victims. Ritchie and coworkers[323] reported on studies of left ventricular function by radionuclide techniques in 154 survivors of out-of-hospital VF, 91 of whom had both rest and exercise studies. The mean ejection fraction at rest was 40 percent, with 20 percent having values greater than 50 percent. Only 3 of 91 patients (3 percent) studied had a normal increase (>5 percent) in ejection fraction during exertion; 18 percent had normal resting wall motion. The ejection fraction at rest was the best predictor of death during follow-up.[305]

CORONARY ANGIOGRAPHY.

Studies in survivors of out-of-hospital cardiac arrest have shown that as a group this population tends to have extensive disease but no specific pattern of abnormalities. Moderate to severe stenosis of the left main coronary artery was present in only 9

percent in one study,[15] a frequency not different from that observed in the overall population of coronary heart disease patients. Significant lesions in two or more vessels were present in 74 percent of the patients who had any coronary lesion.[15] Among patients who had recurrent cardiac arrests, the incidence of triple-vessel disease was higher than among those who did not.

EXERCISE TESTING.

This is commonly used to evaluate the need for and response to antiischemic therapy in survivors of out-of-hospital cardiac arrest. The incidence of positive tests related to ischemia is relatively low, although termination of testing because of fatigue is common.[265] [323] [324] Mortality during follow-up was greater in patients who had angina or failure of a normal rise in systolic blood pressure occurring during exercise.[324]

Figure 26-12 Time-dependence of recurrences among survivors of cardiac arrest. Actuarial analysis of occurrences among a population of 101 cardiac arrest survivors with coronary artery disease is demonstrated. The risk was highest in the first 6 months (11.2 percent) and then fell to 3.3 percent/6 months for the next three 6-month blocks. After 24 months the rate fell to 0.8 percent/6 months. A low ejection fraction (EF) was the most powerful predictor of death during the first 6 months; subsequently, persistent inducibility during programmed stimulation, despite drug therapy or surgery, was the most powerful predictor. (Modified from Furukawa T, et al: Time-dependent risk of and predictors for cardiac arrest recurrence in survivors of out-of-hospital cardiac arrest with chronic coronary artery disease. Circulation 80:599, 1989. The figure is reproduced from Myerburg RJ, et al: Sudden cardiac death: Structure, function and time-dependence of risk. Circulation 85[Suppl I]:1-2, 1992. Copyright 1992 American Heart Association.)

ELECTROCARDIOGRAPHIC OBSERVATIONS.

Among survivors of out-of-hospital cardiac arrest 12-lead electrocardiograms have proved of value only for discriminating risk of recurrence among those whose cardiac arrest was associated with new transmural myocardial infarction. Patients who develop documented new Q waves. In association with a clinical picture suggesting that an acute ischemic event began before the cardiac arrest itself, are at much lower risk for recurrence.[17] [265] A higher incidence of repolarization abnormalities (ST-segment depression, flat T waves, prolonged QT) occurs in out-of-hospital cardiac arrest survivors than in post-myocardial infarction patients, and these might be markers for increased risk.[325]

BLOOD CHEMISTRY.

Lower serum K^+ levels were observed in survivors of cardiac arrest than in patients with acute myocardial infarction or stable coronary heart disease.[326] The investigators concluded that this was a consequence of resuscitation interventions, rather than a

preexisting state owing to chronic diuretic use. Low ionized Ca^{2+} levels, with normal total calcium levels, also were observed during resuscitation from out-of-hospital cardiac arrest.[327] Higher resting lactate levels have been reported in out-of-hospital cardiac arrest survivors than in normal subjects.[328] Lactate levels correlated inversely with ejection fractions and directly with PVC frequency and complexity.

LONG-TERM PROGNOSIS.

Studies from the early 1970s in both Miami [17] and Seattle[18] indicated that the risk of recurrent cardiac arrest in the first year after surviving an initial event was about 30 percent and at 2 years was 45 percent. Total mortality at 2 years was about 60 percent in both studies. In both of these studies, less than half of the patients followed were being treated with long-term antiarrhythmic therapy; beta-adrenoceptor blocker therapy was in its infancy, and Ca^{2+} entry blockers were not yet available. Thus these figures appear to be as close to valid natural history figures as possible. However, they can serve only as historical control figures for current observations, and thus are of limited value, because the risk of recurrent cardiac arrest likely is lower now than it was in the early 1970s.[329] Moreover, the risk of recurrent cardiac arrest/SCD appears to be lower for survivors with hypertrophic cardiomyopathy--about 33 percent during a mean follow-up period of 7 years. [125] The interval risk of recurrent cardiac arrest or SCD is greater during the first 6 to 18 months after the initial event than during later time blocks (i.e., time-dependent risk)[330] (Fig. 26-12) .

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Management of Cardiac Arrest

COMMUNITY-BASED INTERVENTIONS

The initial[331] systems responding to out-of-hospital cardiac arrests as developed in the United States were integrated into fire departments as primary emergency rescue systems. They employ paramedical personnel or emergency medical technicians trained in CPR and the use of CPR monitoring equipment, defibrillators, and specific intravenous drug therapy. Although the initial out-of-hospital intervention experience in Miami and Seattle[17] [18] reported in the early 1970s yielded only 14 and 10 percent survivals to discharge, respectively, later improvements in the systems saved more lives[310] (Fig. 26-13) . By the mid 1970s, both had increased survival rates to about 25 percent,[15] [310] and by the early 1980s to 30 percent or more.[310] Survival rates decreased since then, presumably because of the extension of rescue systems into less densely populated regions.[332] Generally, rural areas have lower success rates,[333] and the national success rate for the United States is likely 5 percent or less.

Recent reports from very densely populated areas (i.e., Chicago and New York City) have also provided disturbing

Figure 26-13 Annual number of emergency rescue responses to out-of-hospital cardiac arrest (vertical bars) and the percent of patients discharged alive (solid line), from 1970 through 1992 in Seattle, Washington. Patients were in cardiac arrest when initially examined by emergency rescue personnel. (Courtesy of Leonard A. Cobb, M.D., Seattle, Washington.)

outcomes data. The Chicago study reported that only 9 percent of out-of-hospital cardiac arrest victims survived to be hospitalized and that only 2 percent were

discharged alive.[73] Moreover, outcomes in blacks were far worse than in whites (0.8 percent vs. 2.6 percent). The fact that a large majority had bradyarrhythmias, asystole, or pulseless electrical activity on initial emergency medical services contact suggests prolonged times between collapse and emergency medical services arrival and/or absent or ineffective bystander interventions. The New York City report indicated a survival-to-hospital discharge rate of only 1.4 percent.[334] Among those who had bystander CPR, the rate increased to 2.9 percent, and bystander CPR plus VF as the initial rhythm yielded a further increase to 5.3 percent. Finally, for those whose arrests occurred after emergency medical services arrival, the success rate increased further to 8.5 percent. These trends suggest that delays and breaks in the "chain of survival"[312] exert a major negative impact on emergency medical services results in densely populated areas.

IMPORTANCE OF ELECTRICAL MECHANISMS.

The electrical mechanism of out-of-hospital cardiac arrest, as defined by the initial rhythm recorded by emergency rescue personnel, has a powerful impact on outcome. The subgroup of patients who are in sustained VT at the time of first contact, although small, has the best outcome (Fig. 26-14) . Eighty-eight percent of patients in cardiac arrest due to VT were successfully resuscitated and admitted to the hospital alive, and 67 percent were ultimately discharged alive.[15] However, this relatively low-risk group represents only 7 to 10 percent of all cardiac arrests. Because of the inherent time lag between collapse and initial recordings, it is likely that many more cardiac arrests begin as rapid sustained VT and degenerate into VF before arrival of rescue personnel.

Patients who have a bradyarrhythmia or asystole at initial contact have the worst prognosis; only 9 percent of such patients in the Miami study were admitted to the hospital alive and none was discharged.[15] In a later experience there was some improvement in outcome, although the improvement was strictly limited to those patients in whom the initial bradyarrhythmia recorded was an idioventricular rhythm that responded promptly to chronotropic agents in the field.[317] Bradyarrhythmias also have adverse prognostic implications after defibrillation from VF in the field. Patients who developed a heart rate less than 60 beats/min after defibrillation regardless of the specific bradyarrhythmic mechanism, had a poor prognosis, with 95 percent of such patients dying either before hospitalization or in the hospital.[17]

Figure 26-14 Survival after out-of-hospital cardiac arrest as function of the intial electrophysiological mechanism recorded by emergency rescue personnel. The mechanisms among 352 out-of-hospital cardiac arrest victims are separated into three categories: ventricular fibrillation (n = 220; 62 percent), ventricular tachycardia (n = 24; 7 percent), and bradycardia/asystole/pulseless electrical activity (PEA) (n = 108; 31 percent). The white bars illustrate the total number of events in each category. The light-colored bars illustrate the number and per cent of patients who were initially resuscitated in the field and reached the hospital alive in each category, and the dark bars illustrate the percentage of total events in which patients were discharged from the hospital alive for each category. The data are derived from the Miami,

Florida, experience.[20]

The outcome in the largest group of patients, those in whom VF is the initial rhythm recorded, is intermediate between sustained VT and bradyarrhythmia and asystole. Figure 26-14 demonstrates that 40 percent of such patients were successfully resuscitated and admitted to the hospital alive and 23 percent were ultimately discharged alive.[15] More recent data indicate improvement in outcome. The proportion of each of the electrophysiological mechanisms responsible for cardiac arrest varied among the earlier reports, with VF ranging from 65 to greater than 90 percent of the study populations, and bradyarrhythmia and asystole ranging from 10 to 30 percent.[15] [300] [310] However, in recent reports from very densely populated metropolitan areas, the ratios of tachyarrhythmic to bradyarrhythmic/pulseless activity events were reversed, and outcomes were far worse.[73] [334]
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Both improved prehospital care and improvements in in-hospital technology and practices can contribute to better outcomes, as described in the "chain of survival" concept.[312] Of these two general factors; the influence of prehospital care has been studied in more detail. Elsenberg and coworkers[316] compared initial resuscitation and ultimate discharge alive in two subgroups of patients, those who had standard CPR continuously from the arrival of emergency rescue personnel through transport to an emergency department where defibrillation took place and another group in whom paramedics or emergency rescue personnel trained to defibrillate were allowed to do so at the scene of the cardiac arrest. The standard CPR technique resulted in only 23 percent of patients arriving at the hospital alive and 7 percent discharged alive, in contrast to the immediate defibrillation group in which 53 percent arrived at the hospital alive and 26 percent were discharged alive. Subsequent data continue to support the concept that early defibrillation is a key element in improving survival rates (Fig. 26-15) .[310] [316] The importance of early defibrillation for improving outcome is supported by a number of studies.[335] [336] [337] [338] [339] [340] In rural communities, earlier defibrillation by ambulance technicians yielded a 19 percent survival, compared with only 3 percent from standard CPR.[332] In another report, an analysis of the relationship between response delay and survival to hospital discharge revealed a 48 percent survival for response times of 2 minutes or less, compared with less than 10 percent survival when responses are longer than 10 minutes[336] (Fig. 26-16 *A*). Mean response time was approximately 13 minutes, and overall survival was 5 percent. It was 9.5 percent for those in VT or VF on first contact. These observations have motivated the search for strategies that shorten response times, such as deploying automatic external defibrillators in public places[340] and in police vehicles.[337] [338] Preliminary data suggest that this strategy may improve outcome by substantial increments.[338] The rationale for this approach is the documentation that police vehicles arrive at cardiac arrest scenes faster[337] (see Fig. 26-16 *B*).

A second element in prehospital care that appears to contribute to outcome is the role of bystander CPR by laypeople awaiting the arrival of emergency rescue personnel. It has been reported that although there was no significant difference in the percentage of patients successfully resuscitated and admitted to the hospital alive with (67 percent) or without (61 percent) bystander intervention, almost twice as many prehospital cardiac arrest victims were ultimately discharged alive when they had had bystander CPR (43

percent) than when such support was not provided (22 percent).[19] Central nervous system protection, expressed as early regaining of consciousness, appears to be the major protective element of bystander CPR.[19] The rationale for bystander intervention is further highlighted by the relation between time to defibrillation and survival, when analyzed as a function of time to initiation of basic CPR. It has been reported that more than 40 percent of victims whose defibrillation and other advanced life support activities were instituted more than 8 minutes after collapse survived if basic CPR had been initiated less than 2 minutes after onset of the arrest.[310] A brief period of CPR before defibrillation may also be helpful.[339]

The time from onset of cardiac arrest to advanced life support influences outcome statistics. Improvement in both early neurological status and survival occurs in the patient defibrillated by first responders, even if they are minimally trained emergency technicians allowed to carry out defibrillation as part of basic life support, compared with outcomes associated with awaiting more highly trained paramedics.[335] Thus the time to defibrillation plays a central role in determining outcome in cardiac arrest caused by VF. The development and deployment of automatic external defibrillators (see Chap. 24) In the community holds promise for progress in the future.[340] This technology is a natural extension of lay bystander CPR.

Figure 26-15 Impact of emergency rescue system design and immediate defibrillation on out-of-hospital cardiac arrest survival. *A,* Percent survival to hospital discharge with rescue activities by standard emergency medical technician (EMT) trained in cardiopulmonary resuscitation (CPR), EMTs allowed to defibrillate immediately (EMT_{dfib}), initial response by paramedics (P-MED), two-tiered system with EMT and P-MED, and two-tiered system with EMTs allowed to defibrillate if they are the first responders plus P-MED. Training of first-responders (EMT_{dfib}) and a two-tiered system have the best outcome. *B,* Comparison of outcomes observed in five geographic areas with EMT providing only CPR (dark color) versus EMT trained to defibrillate as first-responders (light color). In each group, there was a marked improvement in outcome when EMT personnel were trained and permitted to defibrillate. (Modified from Ornato JP, Om A: Community experience in treating out-of-hospital cardiac arrest. *In* Akhtar M, Myerburg RJ, Ruskin J N [eds]: Sudden Cardiac Death: Prevalence, Mechanisms and Approach to Diagnosis and Management. Baltimore, Williams & Wilkins, 1994, p 450, with permission of the publisher.)

Figure 26-16 Influence of response time on survival from out-of-hospital cardiac arrest. *A,* The time from onset of cardiac arrest to initial defibrillation attempt is related to 1-month survival, based on data from the Swedish Cardiac Arrest Registry.[336] The cumulative survival rate was 5 percent, and the survival rate for victims whose initial rhythm was ventricular tachycardia (VT) or ventricular fibrillation (VF) was 9.5 percent. The median response time was nearly 13 minutes. Thirty-day survival ranged from a maximum of 48 percent with responses of less than 2 minutes to less than 5 percent for response time greater than 15 minutes. *B,* The potential for faster response systems, based on the Amsterdam Resuscitation Study, is demonstrated, comparing response times of police vehicles with those of conventional emergency medical systems. At the 50th percentile of response times, polices vehicles provided a nearly 5 minute improvement in arrival time (approximately 6 minutes).[337] Preliminary data suggest that improved

response times of this type translate to improved survival.[338]

MANAGEMENT OF CARDIAC ARREST AND POST-CARDIAC ARREST CARE

Management of the cardiac arrest victim is divided into five elements: (1) initial assessment, (2) basic life support, (3) advanced life support and definitive resuscitative efforts, (4) post-cardiac arrest care, and (5) long-term management. The first of these can be applied by a broad population base, which includes physicians and nurses as well as paramedical personnel, emergency rescue technicians, and laypeople educated in bystander intervention. The requirements for specialized knowledge and skills become progressively more focused as the patient moves through post-cardiac arrest management and into long-term follow-up care.

Initial Assessment and Basic Life Support

This activity includes both diagnostic maneuvers and elementary interventions. The first action of the person(s) in attendance when an individual collapses unexpectedly must be *confirmation that collapse is due to (or suspected to be due to) a cardiac arrest.* A few seconds of evaluation for response to voice, observation for respiratory movements and skin color, and simultaneous palpation of major arteries for the presence or absence of a pulse, yield sufficient information to determine whether a life-threatening incident is in progress. Once suspected or confirmed, contact with an available emergency medical rescue system (911) should be an immediate priority.[306]

The absence of a carotid or femoral pulse, particularly if confirmed by the absence of an audible heartbeat, is the primary diagnostic criterion and can be performed accurately by trained laypeople. Skin color may be pale or intensely cyanotic. Absence of respiratory efforts, or the presence of only agonal respiratory efforts, in conjunction with an absent pulse, is diagnostic of cardiac arrest; however, respiratory efforts can persist for a minute or more after the onset of the arrest. In contrast, absence of respiratory efforts or severe stridor with persistence of a pulse suggests a primary respiratory arrest that will lead to a cardiac arrest in a short time. In the latter circumstance, initial efforts should include exploration of the oropharynx in search of a foreign body and the Heimlich maneuver, particularly if this occurs in a setting in which aspiration is likely (e.g., restaurant death or "cafe coronary").[226] [227]

THUMPVERSION.

Once the diagnosis of a pulseless collapse (presumed cardiac arrest) is established, a blow to the chest (precordial thump, "thumpversion"[344]) may be attempted by a properly trained rescuer. It has been recommended to be reserved as an advanced life support activity.[306] Caldwell and coworkers supported its use on the basis of a prospective study in 5000 patients.[341] Precordial thumps successfully reverted VF in 5 events, VT in 11, asystole in 2, and undefined cardiovascular collapse in 2 others in which the electrical mechanism was unknown. In no instance was conversion of VT to VF observed. Because the latter is the only major concern of the precordial thump technique, and electrical activity can be initiated by mechanical stimulation in the asystolic heart, the technique is considered optional for responding to a *pulseless*

cardiac arrest in the absence of monitoring when a defibrillator is not immediately available. It should not be used unmonitored for the patient with a rapid tachycardia without complete loss of consciousness. For attempted thumpversion in cardiac arrest, one or two blows should be delivered firmly to the junction of the middle and lower thirds of the sternum from a height of 8 to 10 inches, but the effort should be abandoned if the patient does not immediately develop a spontaneous pulse and begin breathing. Another mechanical method, which requires that the patient is still conscious, is "cough-induced cardiac compression"[342] or "cough-version."[341] In the former a conscious act of forceful coughing by the patient in VF may support forward flow by

cyclic increases in intrathoracic pressure[342] ; the same act during sustained VT may cause conversion.[341]

THE ABCs OF CPR.

The goal of this activity is to maintain viability of the central nervous system, heart, and other vital organs until definitive intervention can be achieved. The activities included within basic life support encompass both the initial responses outlined earlier and their natural flow into establishing ventilation and perfusion.[306] This range of activities can be carried out not only by professional and paraprofessional personnel but also by trained emergency technicians and laypeople. Time is the key issue, and there should be minimal delay between the diagnosis and preparatory efforts in the initial response and the institution of basic life support. If only one witness is present, contact of emergency personnel (telephone 911) is the only activity that should precede basic life support.

AIRWAY.

Clearing the airway is a critical step in preparing for successful resuscitation. This includes tilting the head backward and lifting the chin, in addition to exploring the airway for foreign bodies--including dentures--and removing them. The Heimlich maneuver should be performed if there is reason to suspect a foreign body lodged in the oropharynx. This entails wrapping the arms around the victim from the back and delivering a sharp thrust to the upper abdomen with a closed fist.[343] If it is not possible for the person in attendance to carry out the maneuver because of insufficient physical strength, mechanical dislodgment of the foreign body can sometimes be achieved by abdominal thrusts with the unconscious patient in a supine position. The Heimlich maneuver is not entirely benign: Ruptured abdominal viscera in the victim have been reported,[344] as has an instance in which the rescuer disrupted his own aortic root and died.

If there is strong suspicion that respiratory arrest precipitated cardiac arrest, particularly in the presence of a mechanical airway obstruction, a second precordial thump should be delivered after the airway is cleared.

BREATHING.

With the head properly placed and the oropharynx clear, mouth-to-mouth respiration can be initiated if no specific rescue equipment is available. To a large extent, the procedure used for establishing ventilation depends on the site at which the cardiac arrest occurs. A variety of devices are available, including plastic oropharyngeal airways, esophageal obturators, the masked Ambu bag, and endotracheal tubes. Intubation is the preferred procedure, but time should not be sacrificed even in the in-hospital setting while awaiting an endotracheal tube or a person trained to insert it quickly and properly. Thus, in the in-hospital setting, temporary support with Ambu bag ventilation is the usual method until endotracheal intubation can be carried out, and in the out-of-hospital setting mouth-to-mouth resuscitation is used while awaiting emergency rescue personnel. The effect of the acquired immunodeficiency syndrome and hepatitis B transmission on attitudes toward mouth-to-mouth resuscitation by bystanders and even professional personnel in hospitals is an area of concern,[306] but currently available data assessing risk of infection suggest that it is minimal.[345] The impact of this concern on attitudes toward, and outcomes of, resuscitative efforts has not been assessed.

Conventional CPR ventilatory techniques require that the lungs be inflated 10 to 12 times/min whether one or two rescuers are present.[306] For one-rescuer resuscitation, a pause for ventilation (two breaths) is taken after every 15 chest compressions; for two rescuers, one breath is administered after every fifth compression. Techniques of CPR based on the hypothesis that increased intrathoracic pressure is the prime mover of blood, rather than cardiac compression itself,[346] have been evaluated; the cyclic ventilatory techniques are altered in these procedures (see later). However, clinical applicability is still not clarified.[346A]

CIRCULATION

(Fig. 26-17) . This element of basic life support is intended to maintain blood flow (i.e., circulation) until definitive steps can be taken. The rationale is based on the hypothesis that chest compression allows the heart to maintain an externally driven pump function by sequential emptying and filling of its chambers, with competent valves favoring the forward direction of flow. In fact, the application of this technique has proved successful when used as recommended.[306] The palm of one hand is placed over the lower sternum and the heel of the other rests on the dorsum of the lower hand. The sternum is then depressed with the resuscitator's arms straight at the elbows to provide a less tiring and more forceful fulcrum at the junction of the shoulders and back (see Fig. 26-17) . By using this technique, sufficient force is applied to depress the sternum about 3 to 5 cm, with abrupt relaxation, and the cycle is carried out at a rate of about 80 to 100 compressions/min. [306] Despite the fact that this conventional technique produces measurable carotid artery flow and a record of successful resuscitations, the absence of a pressure gradient across the heart in the presence of an extrathoracic arterial-venous pressure gradient has led to a concept that it is not cardiac compression per se but rather a

Figure 26-17 External chest compression. *Left,* Locating the correct hand position on the lower half of the sternum. *Right,* Proper position of the rescuer, with shoulders directly over the victim's sternum and elbows locked. (From Standards and guidelines for cardiopulmonary resuscitation [CPR] and emergency cardiac care [ECC]. JAMA 255:2906, 1986. Copyright 1986, the American Medical Association.)

pumping action produced by pressure changes in the entire thoracic cavity that optimizes systemic blood flow during resuscitation.[346] [347] Experimental work in which the chest is compressed during ventilations rather than between them (simultaneous compression-ventilation [SCV]) demonstrates better extrathoracic arterial flow.[347] [348] However, increased carotid artery flow does not necessarily equate with improved cerebral perfusion,[346] [349] and the reduction in coronary blood flow caused by elevated intrathoracic pressures by certain techniques[346] may be too high a price for the improved peripheral flow. In addition, a high thoracoabdominal gradient has been demonstrated during experimental SCV,[350] which could divert flow from the brain in the absence of concomitant abdominal binding. The comparative hemodynamics of models of conventional cardiac compression and techniques based on chest (thoracic) compression suggest that blood movement is based on both mechanisms in experimental and clinical studies.[351] Based on these observations, new mechanically assisted techniques, including an active decompression phase (i.e., active compression-decompression [ACD]), are being evaluated for improved circulation during CPR.[352] [353] [354] [355] More clinical studies are needed before establishing their general clinical applications.

Advanced Life Support and Definitive Resuscitation

This next step in the resuscitative sequence is designed to achieve definitive stabilization of the patient.[306] The implementation of advanced life support does not indicate abrupt cessation of basic life support activities but rather a transition from one level of activity to the next. In the past, advanced life support required judgments and technical skills that removed it from the realm of activity of lay bystanders and even emergency medical technicians, limiting these activities to specifically trained paramedical personnel, nurses, and physicians. With further education of emergency technicians, most community-based CPR programs now permit them to carry out advanced life support activities.[306] [316] In addition, the development and testing of automatic external defibrillators that have the ability to sense and analyze cardiac electrical activity, and prompt the user to deliver definitive electrical intervention,[356] provides a role for less highly trained rescue personnel (i.e., police, ambulance drivers) and even trained lay bystanders[340] in advanced life support.

The general goals of advanced life support are to revert the cardiac rhythm to one that is hemodynamically effective, optimize ventilation, and maintain and support the restored circulation. Thus, during advanced life support, the patient's cardiac rhythm is

promptly cardioverted or defibrillated as the first priority, if appropriate equipment is immediately available. It has been observed that a few seconds of closed-chest cardiac compression may enhance odds of survival when administered immediately before defibrillation in the field.[339] After the intial attempt to restore a hemodynamically effective rhythm, the patient is intubated and oxygenated, if needed, and the heart is paced if a bradyarrhythmia or asystole occurs. An intravenous line is established to deliver medications. After intubation, the goal of ventilation is to reverse hypoxemia and not merely achieve a high alveolar P_{O_2} . Thus oxygen rather than room air should be used to ventilate the patient; if possible, the arterial P_{O_2} should be monitored. Respirator support in hospital and an Ambu bag by means of an endotracheal tube or face mask in the out-of-hospital setting usually are used.

DEFIBRILLATION-CARDIOVERSION

(Fig. 26-18) . Rapid conversion to an effective cardiac electrical mechanism is a key step for successful resuscitation.[310] Delay should be

Figure 26-18 Advanced life support for ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT). If initial defibrillation fails, the patient should be intubated and intravenous (IV) access immediately established while cardiopulmonary resuscitation (CPR) is continued. Epinephrine, 1 mg intravenously, should be administered, and may be repeated several times with additional attempts to defibrillate with 360-Joule shocks. If the conversion is still unsuccessful, epinephrine may be administered again, although it is unlikely that higher doses would provide any further benefit.[358] Sodium bicarbonate should be administered at this time only if the patient is known to be hyperkalemic, but intravenous antiarrhythmic drugs should be tried (see text). Additional attempts to defibrillate should follow the administration of each drug attempted. (Modified from Emergency Cardiac Care Committee and Subcommittees, American Heart Association: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. JAMA 268:2172, 1992. Copyright 1992 American Medical Association. See original reference for further details.)

minimal, even when conditions for CPR are optimal. When VF or a rapid VT is recognized on a monitor or by telemetry, defibrillation should be carried out immediately with a shock of 200 joules. Up to 90 percent of VF victims weighing up to 90 kg can be successfully resuscitated with a 200-joule shock,[357] and a 300- or 360-joule shock may be used if this is not successful.[306] Failure of the initial shocks to successfully cardiovert to an effective rhythm is a poor prognostic sign.[306] After failure of three shocks up to a maximum of 360 joules of energy, CPR should be continued while the patient is intubated and intravenous access achieved. Epinephrine, 1 mg intravenously, is administered and followed by repeated defibrillation attempts at 360 joules. Epinephrine may be repeated at 3- to 5-minute intervals with defibrillator shocks in between, but high-dose epinephrine does not appear to provide added benefit.[358]

Simultaneously, the rescuer should focus on ventilation to correct the chemistry of the blood, efforts that render the heart more likely to reestablish a stable rhythm (i.e.,

improved oxygenation, reversal of acidosis, and improvement of the underlying electrophysiological condition). Although adequate oxygenation of the blood is crucial in the immediate management of the metabolic acidosis of cardiac arrest, additional correction can be achieved if necessary by intravenous administration of sodium bicarbonate. This is recommended for circumstances of known or suspected preexisting bicarbonate-responsive causes of acidosis, certain drug overdoses, and prolonged resuscitation runs.[306] The more general role for bicarbonate during cardiac arrest has been questioned,[359] [360] but in any circumstance, much less sodium bicarbonate than was previously recommended is adequate for treatment of acidosis in this setting. Excessive quantities can be deleterious.[360] Although some investigators have questioned the use of sodium bicarbonate at all because risks of alkalosis, hypernatremia, and hyperosmolality may outweigh its benefits,[361] the circumstances cited may benefit from administration of 1 mEq/kg of sodium bicarbonate while CPR is being carried out. Up to 50 percent of this dose may be repeated every 10 to 15 minutes during the course of CPR.[362] When possible, arterial pH, P_{O_2} , and P_{CO_2} should be monitored during the resuscitation.

PHARMACOTHERAPY.

For the patient who continues to have VT or VF despite direct-current (DC) cardioversion after epinephrine, electrical stability of the heart may be achieved by intravenous administration of antiarrhythmic agents during continued resuscitation (see Fig. 26-18). As a matter of routine, lidocaine is tried first as an intravenous bolus, at a dose of 1.0 to 1.5 mg/kg (see Chap. 23) , with the dose repeated in 3 to 5 minutes in those in whom resuscitation remains unsuccessful or unstable electrical activity persists. If a total loading dose of 3.0mg/kg has failed to support successful defibrillation, intravenous amiodarone,[363] or bretylium tosylate[364] should be given next. Intravenous amiodarone is administered as an initial dose of 150 mg over 10 minutes (15 mg/min), or 15 mg/kg over 10 minutes, followed by an infusion of 10 mg/kg/day. Another regimen is 1 mg/min over the next 3 hours, followed by a maintenance dose of 0.5 mg/min over the next 18 hours, and for several days as necessary (see Chaps. 23 and 25) . Additional bolus dosing, to a maximum of 500 mg, can be tried if the intial bolus is unsuccessful. Bretylium tosylate is given as an initial bolus of 5 mg/kg IV and repeated 5 minutes later at a dose of 5 to 10 mg/kg if the initial bolus is tolerated hemodynamically but unsuccessful electrophysiologically.

If failure to control the arrhythmia continues, procainamide hydrochloride[365] may be tried as a 30-mg/min intravenous infusion, to a maximum of 17 mg/kg, but it is unlikely to be successful if the other drugs have failed (see also Chap. 23 for other acceptable intravenous dosing regimens of these drugs). In patients in whom acute hyperkalemia is the triggering event for resistant VF, or who have hypocalcemia or are toxic from Ca^{2+} -entry blocking drugs, 10 percent calcium gluconate, 5 to 20 ml infused at a rate of 2 to 4 ml/min, may be helpful.[306] Calcium should not be used routinely during resuscitation,[366] even though ionized Ca^{2+} levels may be low during resuscitation from cardiac arrest. [327] Some resistant forms of polymorphic VT or torsades de pointes, rapid monomorphic VT or ventricular flutter (rate
260/min), or resistant VF may respond to intravenous beta-blocker therapy (propranolol, 1 mg IV boluses to a total dose of up to 15 to 20 mg; metoprolol, 5 mg IV, up to 20 mg)

or intravenous $MgSO_4$ (1 to 2 gm IV given over 1 to 2 minutes).

BRADYARRHYTHMIC AND ASYSTOLIC ARREST; PULSELESS ELECTRICAL ACTIVITY

(Fig. 26-19) . The approach to the patient with bradyarrhythmic or asystolic arrest, or pulseless electrical activity, differs from the approach to patients with tachyarrhythmic events (VT/VF).[306] Once this form of cardiac arrest is recognized, efforts should focus first on establishing control of the cardiorespiratory status (i.e., continue CPR, intubate, and establish intravenous access), then reconfirming the rhythm (in two leads if possible), and finally taking actions that favor the emergence of a stable spontaneous rhythm or attempt to pace the heart. Possible reversible causes, particularly for bradyarrhythmia and asystole, should be considered and excluded (or treated) promptly. These include hypovolemia, hypoxia, cardiac tamponade, tension pneumothorax, preexisting acidosis, drug overdose, hypothermia, and hyperkalemia. Epinephrine (1.0 mg IV every 3 to 5 minutes) and atropine (1.0 to 2.0 mg intravenously) are commonly used in an attempt to elicit spontaneous electrical activity or increase the rate of a bradycardia. These have had only limited success, as have intravenous isoproterenol infusions in doses up to 15 to 20 mug/min. In the absence of an intravenous line, epinephrine (1 mg [i.e., 10 ml of a 1:10,000 solution]) may be given by the intracardiac route, but there is danger of coronary or myocardial laceration. Sodium bicarbonate, 1 mEq/kg, may be tried for known or strongly suspected preexisting hyperkalemia or bicarbonate-responsive acidosis.

Pacing of the bradyarrhythmic or asystolic heart has been limited in the past by the unavailability of personnel capable of carrying out such procedures at the scene of cardiac arrests. With the development of more effective external pacing systems in recent years, the role of pacing and its influence on outcome must now be reevaluated. Unfortunately all data to date suggest that the *asystolic* patient continues to have a very poor prognosis, despite new techniques.[308] [317] [318] [367]

The published standards for CPR and emergency cardiac care[306] included a series of teaching algorithms to be used as guides to appropriate care. Figures 26-18 and 26-19 provide the algorithms for VF and pulseless VT, asystole (or cardiac standstill), and pulseless electrical activity. These general guides are not to be interpreted as inclusive of all possible approaches or contingencies. The special circumstance of CPR in pregnant women requires additional attention to effects of drugs on the gravid uterus and the fetus, mechanical and physiological influences of pregnancy on efficacy of CPR, and risk of complications such as ruptured uterus and lacerated liver.[368]

STABILIZATION.

As soon as electrical resuscitation from VT, VF, bradycardia, asystole, or pulseless electrical activity is achieved, the focus of attention shifts to maintaining a stable electrical and hemodynamic status. For electrical stability, a continuous infusion of an effective drug, based on observation during the cardiac arrest run, is commonly used. This may be lidocaine, 1 to 4 mg/min depending on size and clinical factors; intravenous amiodarone, 10 mg/kg/day (if this drug was required in the initial resuscitation); or

procainamide, 2 to 4 mg/min. Occasionally, a continuous infusion of propranolol or esmolol is used. Catecholamines

Figure 26-19 Advanced cardiac life support for patients with severe bradyarrhythmia, asystole, and pulseless electrical activity. The patient in any of these states should have continued cardiopulmonary resuscitation (CPR) and be intubated, with intravenous (IV) access established, before pharmacological treatment. The initial activity is to confirm persisting asystole or to attempt to assess blood flow in patients thought to have pulseless electrical activity. An immediate attempt should be made to identify and treat reversible or treatable causes of these forms of cardiac arrest. Epinephrine is generally administered first, and atropine and/or bicarbonate may be subsequently administered. An attempt to pace the heart with an external device or an intracardiac pacing catheter is advisable, although usually not successful, except for certain reversible bradyarrhythmias. (Modified from Emergency Cardiac Care Committee and Subcommittees, American Heart Association: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. JAMA 268:2172, 1992. Copyright 1992, American Medical Association. See original reference for further details.)

are used in cardiac arrest not only in an attempt to achieve better electrical stability (e.g., conversion from fine to coarse VF, or increasing the rate of spontaneous contraction during bradyarrhythmias), but also for their inotropic and peripheral vascular effects. Epinephrine is the first choice among the catecholamines for use in cardiac arrest because it increases myocardial contractility, elevates perfusion pressure, may convert electromechanical dissociation to electromechanical coupling, and improves chances for defibrillation. Because of its adverse effects on renal and mesenteric flow, norepinephrine is a less desirable agent despite its inotropic effects. When the chronotropic effect of epinephrine is undesirable, dopamine or dobutamine is preferable to norepinephrine for inotropic effect. Isoproterenol may be used for the treatment of primary or postdefibrillation bradycardia when heart rate control is the primary goal of therapy intended to improve cardiac output. Calcium chloride, 2 to 4 mg/kg, is sometimes used in patients with pulseless electrical activity that persists after administration of catecholamines. The efficacy of this intervention is uncertain. Stimulation of alpha-adrenoceptors may be important during definitive resuscitative efforts.[369] For instance, the alpha-adrenoceptor-stimulating effects of epinephrine and higher dosages of dopamine, producing elevation of aortic diastolic pressures by peripheral vasoconstriction with increased cerebral and myocardial flow,[369] have recently been reemphasized.[346] [369]

Post-Cardiac Arrest Care

For successfully resuscitated cardiac arrest victims, whether the event occurred in or out of hospital, post-cardiac arrest care includes admission to an intensive care unit and continuous monitoring for a minimum of 48 to 72 hours. Some elements of post-arrest management are common to all resuscitated patients, but prognosis and certain details of management are specific for the clinical setting in which the cardiac arrest occurred. The major management categories include (1) primary cardiac arrest in acute

myocardial infarction, (2) secondary cardiac arrest in acute myocardial infarction, (3) cardiac arrest associated with noncardiac disorders, and (4) survival after out-of-hospital cardiac arrest.
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PRIMARY CARDIAC ARREST IN ACUTE MYOCARDIAL INFARCTION

(see also Chap. 35) . VF in the absence of preexisting hemodynamic complications (i.e., primary VF) currently is less common in hospitalized patients than the 15 to 20 percent incidence that existed before availability of cardiac care units (CCUs). Early aggressive treatment--antiarrhythmic, thrombolytic, or both--probably contribute, and those events that do occur are almost always successfully reverted by prompt interventions in properly equipped emergency departments or CCUs.[370] After resuscitation, patients are often maintained on a lidocaine infusion at 2 to 4 mg/min. Antiarrhythmic support is usually discontinued after 24 hours if arrhythmias do not recur (see Chaps. 23 and 25) . The occurrence of VF in the early phase of myocardial infarction is not an indication for subsequent electrophysiological testing or long-term antiarrhythmic or device therapy.[371] Rapid VT producing the clinical picture of cardiac arrest in acute myocardial infarction is treated similarly; its intermediate and long-term implications are the same as those of VF. Cardiac arrest caused by bradyarrhythmias or asystole in acute inferior wall myocardial infarction, in the absence of primary hemodynamic consequences, is uncommon and may respond to either atropine or pacing. The prognosis is good, with no special long-term care required in most instances. Rarely, symptomatic bradyarrhythmias that require permanent pacemakers persist in survivors. In contrast to inferior myocardial infarction, bradyarrhythmic cardiac arrest associated with large anterior wall infarctions (and AV or intraventricular block) has a very poor prognosis (see Chap. 35) .

SECONDARY CARDIAC ARREST IN ACUTE MYOCARDIAL INFARCTION

(see also Chap. 35) . This is defined as cardiac arrest occurring in association with, or as a result of, hemodynamic or mechanical dysfunction. The immediate mortality among patients in this setting ranges from 59 to 89

percent, depending on severity of the hemodynamic abnormalities and size of the myocardial infarction.[372] Resuscitative efforts commonly fail in such patients, and when they are successful, the post-cardiac arrest management often is difficult. When secondary cardiac arrest occurs by the mechanisms of VT or VF, lidocaine in standard dosages is used, although the dose may have to be reduced in the presence of severe heart failure.[373] Other antiarrhythmics may have to be used in addition to or instead of lidocaine if complex arrhythmias persist or cardiac arrest recurs. The success of interventions and prevention of recurrent cardiac arrest relate closely to the outcome of managing the hemodynamic status. The incidence of cardiac arrest caused by bradyarrhythmias or asystole, or by electromechanical dissociation, is higher in the

secondary form of cardiac arrest in acute myocardial infarction.[374] Such patients usually have large myocardial infarctions and major hemodynamic abnormalities and may be acidotic and hypoxemic. Even with aggressive therapy the prognosis after a bradyarrhythmic or asystolic arrest in such patients is very poor, and patients are resuscitated only rarely from electromechanical dissociation. All patients in circulatory failure at the onset of arrest are in a high-risk category, with only a 2 percent survival rate among hypotensive patients in one study.[308]

CARDIAC ARREST AMONG IN-HOSPITAL PATIENTS WITH NONCARDIAC ABNORMALITIES.

These patients fall into two major categories: (1) those with life-limiting diseases such as malignancies, sepsis, organ failure, end-stage pulmonary disease, and advanced central nervous system disease; and (2) those with acute toxic or proarrhythmic states that are potentially reversible. In the former category, the ratio of tachyarrhythmic to bradyarrhythmic cardiac arrest is low,[308] and the prognosis for surviving cardiac arrest is poor. Although the data may be somewhat skewed by the practice of assigning "do not resuscitate" orders to patients with end-stage disease, available data for attempted resuscitations show a poor outcome. Bedell and associates[308] reported that only 7 percent of cancer patients, 3 percent of renal failure patients, and no patients with sepsis or acute central nervous system disease were successfully resuscitated and discharged from the hospital. For the few successfully resuscitated patients in these categories, post-arrest management is dictated by the underlying precipitating factors.

Most antiarrhythmic drugs (see Chap. 23) ,[189] [190] [192] [375] [376] a number of drugs used for noncardiac purposes,[192] [196] [197] and electrolyte disturbances can precipitate potentially lethal arrhythmias and cardiac arrest. Quinidine[377] and the other Class IA antiarrhythmic drugs, and the Class III drugs, are proarrhythmic by the generation of torsades de pointes, the Class IA drugs generally producing a dose-independent idiosyncratic response and the Class III drugs, a dose-dependent adverse effect. The Class IC drugs rarely cause torsades de pointes[378] but cause excess SCD risk in patients with recent myocardial infarction,[95] possibly by interacting with ischemia or other transient risk factors.[379] [380] [381] Among other categories of drugs,[192] [382] the phenothiazines, tricyclic antidepressants, lithium,[196] terfenadine interacting with ketoconazole, or other blockers of enzymes in the hepatic P450 system),[197] pentamidine,[383] cocaine,[384] erythromycin,[385] and cardiovascular drugs that are not antiarrhythmics--such as lidoflazine--are recognized causes. Beyond these, a broad array of pharmacological and pathophysiological/metabolic causes have been reported.[382] Hypokalemia, hypomagnesemia, and perhaps hypocalcemia are the electrolyte disturbances most closely associated with cardiac arrest. Acidosis and hypoxia can potentiate the vulnerability associated with electrolyte disturbances. Proarrhythmic effects may be prewarned by prolongation of the QT interval, although this electrocardiographic change is not always present.[194]

Cardiac arrest caused by *torsades de pointes* is managed by intravenous administration of magnesium, pacing, or treatment with isoproterenol and removal of the offending agent. Class IC drugs may cause a rapid, sinusoidal VT pattern, especially among patients with poor left ventricular function. This VT has a tendency to recur repetitively after cardioversion until the drug has begun to clear; this proarrhythtmic form has been

controlled by propranolol in some patients.[386]

When the patient's condition can be stabilized until the offending factor is removed (e.g., proarrhythmic drugs) or corrected (e.g., electrolyte imbalances, hypothermia), the prognosis is excellent. The recognition of torsades de pointes (see Chap. 25) and the identification of its risk by prolongation of the QT interval in association with the offending agent are helpful in managing these patients. No long-term prophylaxis is required in most patients. In contrast, beta-adrenoceptor blocking drugs are required for long-term management of patients with congenital forms of long QT interval syndromes,[190] [191A] and implantable defibrillators are used for the subgroups who have manifested life-threatening arrhythmias or have strong family histories of SCD[192]

POST-CARDIAC ARREST CARE IN SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST.

The initial management of survivors of out-of-hospital cardiac arrest centers on stabilizing the cardiac electrical status, supporting hemodynamics, and providing supportive care for reversal of organ damage that has occurred as a consequence of the cardiac arrest. The in-hospital risk of recurrent cardiac arrest is relatively low, and arrhythmias account for only 10 percent of in-hospital deaths after successful prehospital resuscitation.[15] [316] However, the mortality rate during the index hospitalization is 50 percent, indicating that nonarrhythmic mortality dominates the mechanisms of early postresuscitation deaths (30 percent hemodynamic; 60 percent central nervous system related).[15] Antiarrhythmic therapy is used in an attempt to prevent recurrent cardiac arrest in patients who demonstrate residual electrophysiological instability and recurrent arrhythmia during the first 48 hours of post-arrest hospitalization. Lidocaine is the drug of choice for initial management, followed by intravenous amiodarone, procainamide, or bretylium if initial drug therapy fails. Patients who have either preexisting or now atrioventricular or intraventricular conduction disturbances are at particularly high risk for recurrent cardiac arrest.[15] The routine use of temporary pacemakers has been evaluated in such patients but was not found to be useful for preventing early recurrent cardiac arrest. Invasive techniques for hemodynamic monitoring are used in a patient whose condition is unstable but not routinely for those whose condition is stable on admission.

Respiratory support by conventional methods is used as necessary. During the convalescent period, attention to central nervous system status, including physical rehabilitation, is of primary importance to an optimal outcome. Bass[387] summarized the neurological sequelae to cardiac arrest, including a review of various interventions. Management of other organ system injury (e.g., renal, hepatic), as well as early recognition and treatment of infectious complications, also contributes to ultimate survival.

LONG-TERM MANAGEMENT OF SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST.

When the survivor of an out-of-hospital cardiac arrest has awakened and achieved electrical and hemodynamic stability, usually between 1 and 7 days after the event, decisions must be made regarding the nature and extent of the work-up required to establish a long-term management strategy. The goals of the work-up are to identify the

specific etiological and triggering cause of the cardiac arrest,[381] clarify the functional status of the patient's cardiovascular system, and establish long-term therapeutic strategies (Fig. 26-20) . The extent of the work up

Figure 26-20 General management algorithm for cardiac arrest survivors. Flow diagram for the diagnostic activities and initial management of survivors of out-of-hospital cardiac arrest. After return of spontaneous circulation and achieving clinical stabilization, attempts are made to establish etiology, mechanism, and initial therapy. Patients who have cardiac arrest associated with new acute transmural myocardial infarction or with reversible nonstructural arrhythmogenic factors are managed by conventional techniques and usually do not require specialized studies. All patients with chronic ischemic heart disease in the absence of a precipitating new transmural myocardial infarction, and many with nonischemic forms of heart disease, enter a diagnostic pathway that includes cardiac catheterization, various imaging studies, and special studies as indicated. Ischemic risk and ventricular dysfunction are managed by conventional techniques. Diagnostic electrophysiologic evaluation and therapy are carried out next (see text for details). In some patients with nonischemic heart disease, definitive medical or surgical management is possible without specialized studies. (Modified from Myerburg RJ, Kessler KM: Management of patients who survived cardiac arrest. Mod Concepts Cardiovasc Dis 55:61, 1996.)

is largely dictated by the degree of central nervous system recovery and the factors already known to have contributed to the cardiac arrest. For instance, patients who have limited return of central nervous system function usually do not undergo extensive work-ups, and patients whose cardiac arrests were triggered by an acute transmural myocardial infarction have work-ups similar to those for other patients with acute myocardial infarction (see Chap. 35) .

Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction who have good return of neurological function undergo extensive diagnostic work-ups to define long-term therapy. The work-up normally includes cardiac catheterization with coronary angiography, an evaluation of functional significance of coronary lesions by stress-imaging techniques, determination of functional and hemodynamic status, and estimation of baseline susceptibility to life-threatening arrhythmias and of the expected response to long-term therapy.

GENERAL CARE.

The general management of survivors of cardiac arrest is determined by the specific cause and the pathophysiology of the underlying process (see Fig. 26-20) . For patients with ischemic heart disease (who constitute approximately 80 percent of cardiac arrest victims), control of episodes of myocardial ischemia, optimization of therapy for left ventricular dysfunction, and attention to general medical status are all addressed. Ischemic risk may be managed by catheter intervention techniques, surgically, or medically, depending on the anatomy and physiology of the disease process. Although there are limited data suggesting that coronary bypass surgery may improve the recurrence rate and total mortality rates after survival from out-of-hospital cardiac

arrest[388] [389] [390] no properly controlled prospective studies have validated this impression for either bypass surgery or angioplasty. Moreover, a randomized trial of prophylactic implantable defibrillators versus usual therapy in patients undergoing coronary bypass surgery in the absence of a history of cardiac arrest or other life-threatening arrhythmia or arrhythmia markers (the Coronary Artery Bypass Graft Patch Trial [CABG-Patch]), revealed no benefit of implantable defibrillators in those patients.[390] Therefore, indications for surgery are limited to two groups of patients: (1) those who have a generally accepted indication for angioplasty or surgery[265] (including a documented ischemic mechanism for the cardiac arrest) and (2) those who meet specific criteria for surgery directed to arrhythmia control.[391]

Medical antiischemic therapy includes nitrates, beta-adrenoceptor blocking agents, and Ca^{2+} entry blockers. Beta-adrenoceptors may have an antianginal effect and also influence the role of sympathetic nervous system activity on the genesis of potentially lethal arrhythmias. Although no placebo-controlled data are available to define a benefit of beta-blockers or other medical antiischemic therapy for long-term survival after out-of-hospital cardiac arrest, Morady and colleagues[114] suggested that medical or surgical antiischemic therapy, rather than antiarrhythmic therapy, should be the primary approach to long-term management of the subgroup of prehospital cardiac arrest survivors in whom transient myocardial ischemia was the inciting factor. Moreover, in an uncontrolled observation comparing cardiac arrest survivors who had ever been on beta-blockers after the index event with those who had not received the drug, a significant improvement in long-term outcome was observed among those who had received beta-blockers.[392]

In a report from the Coronary Artery Surgery Study (CASS), Holmes and associates[393] compared sudden death rates in medically and surgically treated patients in the CASS registry. This study did not directly address the issue of surgery in survivors of out-of-hospital cardiac arrest, but there was a significant difference at 5 years, with a 98 percent sudden death-free survival in the surgical group versus 94 percent in the medical group ($p < 0.0001$). The differences were minimal in the groups with one- or two-vessel disease and no history of heart failure, but expanded to 91 and 69 percent, respectively. In patients with three-vessel disease and a history of heart failure. The question of how to apply these data to indications for surgery for cardiac arrest survivors remains unanswered at this time. The problem is further confounded by the fact that assignment of the 13,476

analyzable patients to medical versus surgical groups was not randomized (i.e., it was based instead on clinical judgment). Further evaluation of the specific role of revascularization procedures after out-of-hospital cardiac arrest is needed.

The long-term management of the consequences of left ventricular dysfunction by conventional means such as digitalis preparations and chronic diuretic use has been evaluated in several studies. Data from the Multiple Risk Factor Intervention Trial (MRFIT) suggested a higher mortality rate in the special intervention group,[394]

presumably related to diuretic use and R+ depletion, and other data regarding the relation between K+ depletion and arrhythmias have focused attention on routine use of such drugs. Although the facts currently are far from conclusive, it is advisable that diuretic use should be accompanied by careful monitoring of electrolytes. The use of digoxin in survivors of out-of-hospital cardiac arrest should be tailored to specific indications for left ventricular dysfunction.[395] [396] [397]
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THERAPY FOR PREVENTION OF CARDIAC ARREST AND SUDDEN CARDIAC DEATH

Therapeutic strategies to prevent SCD can be classified into five categories: (1) prevention of recurrent events in survivors of cardiac arrest or hemodynamically comprising VT (secondary prevention); (2) prevention of an initial event among patients at high risk because of advanced heart disease with ejection fractions less than or equal to 35 percent (primary prevention); (3) primary prevention in patients with less advanced common or uncommon structural heart diseases and ejection fractions more than 35 percent; (4) primary prevention in patients with structurally normal hearts, subtle or minor structural abnormalities, or molecular disorders associated with electrophysiological properties that establish risk for ventricular arrhythmias; and (5) primary prevention among the general population (Table 26-6) .

Four modes of antiarrhythmic therapy, which are not mutually exclusive, may be considered for patients at risk of cardiac arrest: antiarrhythmic drug therapy, surgery, catheter ablation, and implantable defibrillator therapy. The choice of therapy is based on estimation of potential benefit determined by individual patient evaluation and available efficacy and safety data.

Antiarrhythmic Drug Strategies

The earliest approach, historically, to the management of risk of out-of-hospital cardiac arrest and VT with hemodynamic compromise was the use of pharmacological agents. This approach was based initially on the assumption that the high frequency of ambient ventricular arrhythmias constituted a triggering mechanism for potentially lethal arrhythmias and that electrophysiological instability of the myocardium that predisposed to potentially lethal arrhythmias could be modified by antiarrhythmic drugs.[292] [321] The therapeutic strategy for the former was the suppression of ambient ventricular arrhythmias by antiarrhythmic drug, and the strategy for the latter was the suppression of inducibility of VT or VF during programmed electrical stimulation studies. Observational data suggested that suppression of ambient arrhythmias, identified on ambulatory recorders,[398] could be achieved by the empirical use of amiodarone,[399] [400] beta-adrenergic blocking agents,[392] [401] or membrane-active antiarrhythmic drugs.[292] [321] [392] Based on historical expectations, it was suggested, but not proven, that such suppressive techniques would improve mortality risk. For the membrane-active drugs, the observations that post-cardiac arrest survivors who had been treated with Class I antiarrhythmic drugs had a worse outcome than those who were not treated served as a challenge to the concept of benefit,[392] and such skepticism was further supported by the results of CAST,[95] [97] which demonstrated that the Class I antiarrhythmic drugs at

best were neutral (moricizine) and at worst did harm (flecainide, encainide). In contrast, beta-blocker therapy might have some benefit in such patients,[392] [401] and amiodarone might also be effective. [399] [400]

Unfortunately, all of the early data regarding these assumptions and therapeutic approaches were observational or retrospective, and no concurrently controlled data were available. Nonetheless, a *relative* benefit of amiodarone over Class I drugs was suggested by the Cardiac Arrest in Seattle, Conventional versus Amiodarone Drug Evaluation (CASCADE), a post-cardiac arrest survivor study comparing these two therapeutic classes.[400] Another study, the Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) trial, designed to compare the value of ambulatory monitoring to programmed electrical stimulation techniques for predicting therapeutic outcome,[402] suggested that the Class III antiarrhythmic drug sotalol was superior to Class I membrane-active antiarrhythmic agents for patients with life-threatening ventricular tachyarrhythmias but provided no comparison to amiodarone or beta blockers.[403] In summary, ambient arrhythmia suppression as a technique for prediction reduction of risk enjoyed a short period of popularity for such patients but in time yielded to

TABLE 26-6 -- CATEGORIES OF THERAPEUTIC STRATEGIES FOR PREVENTION OF RECURRENT CARDIAC ARREST AND SUDDEN CARDIAC DEATH (SCD)

PREVENTION TARGETS	CLINICAL EXAMPLES	ESTIMATE OF RISK	DATA SOURCES
Secondary*	Survivors of cardiac arrest; VF/VT	High	Observational; RCT: (+) control
Primary			
Advanced structural cardiac disease	CAD/DCM, EF<35%	High	Observational; RCT: (+) control RCT: (-) control
Lower-grade structural disease	CAD/DCM, EF 35% RVD, sarcoidosis, HCM	Variable	Observational; RCT: Subgroup analyses
Functional cardiac disorders	Long QT syndrome, Brugada syndrome	Variable	Observational
SCD as primary event in CAD	Family history of SCD, risk factors for CAD	Low	Epidemiological; genetic (?)

DCM=dilated cardiomyopathy; EF=ejection fraction; HCM=hypertrophic cardiomyopathy; RVD=right ventricular dysplasia; VF=ventricular fibrillation; VT=ventricular tachycardia.

*Much of the data for secondary prevention, identified as a high-risk population because of the occurrence of a prior cardiac arrest, has derived from observational data and, more recently, from randomized controlled trials (RCT), all of which have employed an active-therapy control group [(+) control], comparing outcomes between groups treated with implantable cardioverter-defibrillators (ICDs)

and antiarrhythmic drugs (see Table 26-7) .

RCTs are not feasible for primary prevention in patients with these lower-risk conditions. However, some information can be acquired from subgroup analysis of larger studies. Decisions for ICD implantation in these patients must be judgment-based rather than evidence-based. Recent suggestions of familial clustering of sudden death, as a specific expression of coronary artery disease (CAD), raises the question of primary prevention in patients at risk for SCD using epidemiological and perhaps genetic markers in the future.

the apparent greater benefits of amiodarone, and perhaps beta blockers,[404] prescribed empirically.

Ambulatory Electrocardiographic Recording and Empirical Therapy

The development of reliable methods of analysis of ambulatory recordings led some investigators to study suppressibility of ambient arrhythmias as a specific and individualized means of evaluating drug therapy. Graboys and associates[398] reported outcome in a group of 123 patients with advanced ambient ventricular arrhythmias who had survived one or more cardiac arrests. Suppression of specific forms of complex ventricular ectopy (then defined as three or more consecutive beats and early-cycle PVCs) identified on either ambulatory recording or exercise testing was accompanied by a significantly lower mortality rate compared with those in whom suppression was not achieved. The mortality rate was more than 80 percent at 3 years in patients whose complex forms could not be suppressed, compared with a nearly 90 percent survival among the patients in whom complex PVCs were suppressed.

Other investigators provided data suggesting the possibility that ambient arrhythmia suppression might be equivalent to suppression of inducible arrhythmias by programmed electrical stimulation for predicting outcome.[402] [405] Moreover, analysis of the CAST data base also suggested an association between the ease of suppression of ambient ventricular arrhythmias and survival,[406] supporting the notion of a meaningful relationship between *suppressibility* of ambient arrhythmias and survival. Data from the Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) trial[402] did demonstrate a minor trend favoring outcome prediction by programmed stimulation compared with ambulatory recording techniques in coronary artery disease patients, most evident in the interval of the first 2 years of follow-up. For nonischemic diseases, no benefit was observed. In another randomized trial comparing invasive and noninvasive techniques among patients who had symptomatic tachyarrhythmias, the invasive technique was superior in prevention of recurrences.[407] However, the qualifying arrhythmias were not restricted to cardiac arrests, and therefore the applicability to cardiac arrest survivors remains uncertain.

Although a higher fraction of patients will have successful suppression of the targeted

arrhythmias using ambulatory recording techniques, compared with programmed electrical stimulation, more patients will have electrically inducible arrhythmias to use as targets than ambient ventricular ectopy.[402] [403] [405] Thus, programmed electrical stimulation still maintains preference as the method of choice for estimating antiarrhythmic efficacy against life-threatening arrhythmias. The question of whether *suppressibility* rather than *suppression*[406] is the meaningful marker remains uncertain for both techniques.

Finally, empirical antiarrhythmic therapy, predominantly amiodarone, has been observed to have a relative benefit in several studies.[399] [400] Whether it has an absolute mortality benefit can only be determined by placebo-controlled data, which are not available. Moreover, several controlled trials have now suggested that empirical amiodarone is less effective than implantable defibrillators in reducing risk of death among survivors of life-threatening arrhythmic events (Antiarrhythmics Versus Implantable Defibrillators [AVID], Canadian Implantable Defibrillator Study [CIDS], and the Cardiac Arrest Study of Hamburg [CASH]), particularly when the ejection fraction is less than 35 percent (see Chap. 25) .[408] [409] [410]

Programmed Electrical Stimulation

The second major antiarrhythmic strategy was based on suppression of inducibility of sustained ventricular arrhythmias, considered to be a marker of risk during electrophysiological testing.[411] [412] The use of programmed electrical stimulation to identify benefit on the basis of suppression of inducibility by an antiarrhythmic drug gained popularity for evaluating long-term therapy among survivors of out-of-hospital cardiac arrest.[411] [412] [413] [414] [415] [416] [417] [418] It evolved as the preferred method of management despite concerns about the sensitivity and specificity of the various pacing protocols[419] and the extent to which the myocardial status at the time of the programmed electrical stimulation study reflected that present at the time of the clinical cardiac arrest.[420] Nonetheless, among a series of six early reports,[411] [412] [413] [414] [415] [416] induction of sustained VT or VF at baseline study ranged from 31 to 79 percent and successful suppression of inducibility ranged from 18 to 78 percent. The mortality rate during follow-up of those patients in whom inducibility was suppressed by antiarrhythmic therapy ranged from 0 to 22 percent (mean= 9 percent), compared with the range of 22 to 78 percent (mean= 43 percent) in those patients in whom VT or VF was still inducible on any antiarrhythmic therapy.

The evaluation of these data is significantly influenced by definitions of inducibility and noninducibility and also by the clinical features of the patient population in each of the studies, which varied considerably. In most reports, VF or sustained VT could *not* be induced in 25 to 30 percent of the patients. It is probable that differences are determined in part by the numbers of patients who have anatomically discrete versus ischemic substrates among various populations studied.[313] Careful attention to protocol details, anatomy of the disease processes, and definitions of inducibility may help clarify these discrepancies in the future. For the present, however, 50 to 70 percent of unselected survivors of cardiac arrest caused by VF or sustained VT can be anticipated to have inducible sustained ventricular arrhythmias. For the subgroup with discrete ventricular aneurysms, more than 90 percent may have inducible ventricular arrhythmias.[265] [413]

The clinical significance of induced VF, as opposed to a sustained VT or VF that evolves from an induced VT, is often difficult to interpret. Induced VF is commonly considered nonspecific when the induction protocol is aggressive and the patient has not had a clinical cardiac arrest. However, most accept it as a valid positive endpoint among survivors of out-of-hospital cardiac arrest, especially when the protocol is less aggressive (e.g., double extra stimuli or triple extra stimuli in which coupling intervals are not excessively short), and the induction is reproducible. Most investigators agree that inducibility of a sustained *clinical* arrhythmia provides an indication of risk. Drug-suppression of inducibility was also considered to indicate a beneficial endpoint for therapy, but the results of the Multicenter Unsustained Tachycardia Trial (MUSTT) now provides skepticism about that conclusion[421] (see Primary Prevention of Out-of-Hospital Cardiac Arrest; see also Chaps. 23 and 25) .

The implications of induced nonsustained forms of VT are more controversial. Although it has been suggested that induction of nonsustained ventricular rhythms may indicate risk, it generally is considered nonspecific in the absence of structural heart disease or when an aggressive protocol is used.[419] The use of the suppression of nonsustained arrhythmias as an endpoint of therapy is not considered valid.

The significance of *non*inducibility at baseline electrophysiological stimulation testing in relation to risk and long-term management also is controversial. Opinions have ranged from the conclusion that patients free of inducible ventricular arrhythmias are electrophysiologically stable and require no long-term antiarrhythmic therapy[114] [411] [416] [422] [423] to the other extreme that such patients remain at risk but do not have an objective endpoint of therapy by this method, and therefore must be treated by other techniques.[67] [265] [321] [398] Despite these conflicting opinions, it is generally accepted now that survivors of cardiac arrest with ejection fraction of 35 percent or less remain at high risk

regardless of inducibility status.[418] [423] [424] [425] Some out-ofhospital cardiac arrests can be clearly demonstrated to result from transient ischemia, and this subgroup requires only antiischemic therapy.[114]

In the six early reports cited, 24-month mortality in patients without inducible VT or VF ranged from 3 to 38 percent, which was higher than in patients in whom inducible arrhythmias could be suppressed by antiarrhythmic therapy (average 9 percent) but lower than in those in whom inducibility could not be suppressed (average 43 percent). In one study, left ventricular ejection fraction discriminated high risk from low risk in patients with no inducible ventricular arrhythmias; in another, reversible causes of the index event predicted noninducibility.[418] [423] A later report[426] demonstrated that patients in whom ventricular arrhythmias could not be induced were at risk for recurrent cardiac arrest, although the risk was lower than would be anticipated for patients in whom arrhythmias could be induced. There was a 12 percent event rate at 24 months in the patient population reported. When patients with structural heart disease and low ejection fractions do not have inducible VT or VF after cardiac arrest, it is generally agreed that

high risk of recurrence persists.

Surgical Intervention Strategies

Direct antiarrhythmic surgical techniques (see Chaps. 23 and 25) for control of recurrent sustained VT have included map-guided endocardial resection,[427] encircling endocardial ventriculotomy,[428] and intraoperative map-guided cryoablation techniques.[429] This last approach is limited primarily to those patients who have inducible, hemodynamically stable sustained monomorphic VT during electrophysiological testing and are unresponsive to drug therapy and have suitable ventricular and coronary artery anatomy. Whereas the outcome using this technique has been much better than that of previous techniques,[429] it has very little applicability to survivors of out-of-hospital cardiac arrest because the type of arrhythmia favoring this surgical approach is infrequently observed among cardiac arrest survivors. The less specific antiarrhythmic surgical techniques used previously demonstrate less efficacy and higher mortality. In contrast, coronary revascularization procedures have a clearly defined role for cardiac arrest survivors in whom an ischemic mechanism was responsible for the event and suitable surgical anatomy is present.[114] [430]

Catheter Ablation Therapy

The use of catheter ablation techniques to treat ventricular tachyarrhythmias has been most successful for the benign focal tachycardias that originate in the right ventricle or left side of the interventricular septum (see Chaps. 23 and 25) . Treatment of higher-risk ventricular tachyarrhythmias has been a goal that has met with only limited success. For VT caused by bundle branch reentrant mechanisms, which occur in cardiomyopathies as well as other structural cardiac disorders, ablation of the right bundle branch to interrupt the reentrant cycle has been quite successful.[431] However, this has limited applicability to the large number of patients with structural heart disease at risk for SCD or those who have survived a cardiac risk. For patients with reentrant tachycardias originating in the left ventricle in the presence of coronary artery disease, there had been increasing success as mapping procedures have improved,[432] but the application of this technique as preventive therapy for recurrent cardiac arrest or for primary prevention of cardiac arrest is limited at the present time. The nature of the underlying disease predicts that multiple reentrant pathways may be present, or may emerge over time, limiting the predictability of success of the procedure when it is used for potentially lifesaving strategies. On the other hand, the use of catheter ablation techniques for patients with ICDs who are having multiple tachyarrhythmic events is an appropriate and helpful treatment strategy.[433] Thus, catheter ablation therapy presently must be viewed as largely adjunctive for patients receiving other forms of therapy, rather than as a preferred primary therapy for prevention of SCD.

Implantable Defibrillators

The development of reliable ICDs added a new dimension to the management of patients at high risk of cardiac arrest. Since early reports by Mirowski and coworkers[434] and Echt and colleagues,[435] multiple observational studies have confirmed that ICDs could achieve sudden death rates consistently less than 5 percent at 1 year and total

death rates in the 10 to 20 percent range among populations who have high mortality risks, as predicted by mortality surrogates such as historical controls or time to first appropriate shock.[436] [437] [438] [439] Yet, determination of the value of ICDs in terms of their mortality benefit remained uncertain and debated for many years.[440] [441] [442] Sixteen years elapsed between the first clinical use of an implantable defibrillator[443] and publication of the first major randomized clinical trial comparing implantable defibrillator therapy to antiarrhythmic drug therapy.[444] Through that period of time, reports had documented the ability of implantable devices to successfully revert potentially fatal arrhythmias but could not identify a valid relative or absolute mortality benefit because of confounding factors such as competing risks for sudden and nonsudden death[25] and determination of whether appropriate shocks represented the interruption of an event that would have been fatal.[441] Despite these limitations, ICD therapy continued to increase its relative position among other forms of therapy for survivors of out-of-hospital cardiac arrest and, to a lesser extent, for those considered to be at high risk for a primary cardiac arrest based on specific clinical markers. With publication of the results of the Multicenter Antiarrhythmic Drug Versus Implantable Defibrillator Trial (MADIT),[444] information on the relative benefit of defibrillators over antiarrhythmic drug therapy (largely amiodarone) became available (Table 26-7) . The outcome demonstrated a 59 percent reduction in relative risk of total mortality at 2 years of follow-up (54 percent cumulative) and a 19 percent reduction in absolute risk of dying at 2 years of follow-up. One year later, the first adequately powered secondary prevention trial of ICDs versus antiarrhythmic drugs was published. This study, the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, demonstrated a 27 percent reduction in relative risk of total mortality at 2 years of follow-up, with an absolute risk reduction of 7 percent.[408] The AVID was followed shortly by reports of two other studies--CIDS[409] and CASH[410] --both limited by the power of the enrollment numbers but suggesting trends toward similar benefits (see Table 26-7) . As a consequence of the secondary prevention trials, ICDs have emerged as the preferred therapy for survivors of out-of-hospital cardiac arrest or hemodynamically important VT. A subgroup analysis of AVID suggested that the benefit is limited to patients with ejection fractions of less than 35 percent; above that value the outcome with either amiodarone or an ICD might be equivalent.[425]

Whereas the studies cited documented the ability of implantable devices to successfully revert potentially fatal arrhythmias, and subsequently showed a relative benefit over amiodarone in some patient groups, the absence of placebo-controlled trials still prevents the quantitation of the true magnitude of any mortality benefit, because of the inability of positive-controlled trials to identify the absolute benefit of an intervention.[445] Despite these limitations, implantable

TABLE 26-7 -- SUMMARY OF MAJOR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) TRIALS FOR PREVENTION OF SUDDEN CARDIAC DEATHS

		2-YEAR OUTCOMES

TRIAL	STUDY GROUP	Control	ICDS	Rel RR	Abs RR
Secondary Prevention [*]					
AVID[408] (n=1016)	VF, VT-syncope, VT: EF 40%	25%	18%	-27%	-7%
CIDS[409] (n=659)	VF, VT-syncope, VT: EF 35% and CL<400 ms	21%	15%	-30%	-6%
CASH[410] (n=346)	Cardiac arrest survivors (VF, VT)	20% (Combined)	12%	-37%	-8%
Primary Prevention					
MADIT[444] (n=196)	Prior MI, EF 35%, NS VT, inducible VT, failed IV PA	32%	13%	-59%	-19%
MUSTT[421] (n=704)	Prior MI, EF 40%, NS VT, inducible VT (EP guided therapy/no AAD)	55%	24% (EP guided arm: AAD versus ICD at 60 m)	-56%	-31%
CABG-Patch[390] (n=900)	Coronary bypass surgery, EF<36%, SAECG (+)	18%	18%	0	0
SCD-HeFT (n=2400 est)	Class II-III CHF, EF 35%	20% (Projected)	(?)	(Pending)	(Pending)
MADIT-2 (n=1200 est)	Prior MI (>1 month), EF 30%	19% (Projected)	(?)	(Pending)	(Pending)

Two other large primary prevention trials are in progress (along with a number of smaller trials): the Sudden Cardiac Death in Heart Failure Trail (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial-2 (MADIT-2).

Abs RR=absolute risk reduction; CHF=congestive heart failure; EF=ejection fraction; EP=electrophysiological; MI=myocardial infarction; NS=nonsustained; Rel RR=relative risk reduction; SAECG=signal-averaged electrocardiogram; VF=ventricular fibrillation.

See also Table 24-17 .

*Three major randomized trials for secondary prevention among survivors of out-of-hospital cardiac arrest, or high-risk ventricular tachycardia (VT), have been completed: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study of Hamburg (CASH). Each used an active control, randomized design comparing ICDs to antiarrhythmic drug (AAD) therapy, primarily amiodarone. The cumulative data, as well as the individual data from the larger studies, support the notion that the ICD is preferable to drug therapy for

this high-risk population. However, the large relative benefits translated to more modest absolute benefits, with a large residual risk among the ICD-treated groups in each study.

Three primary prevention trials among patients presumed to be at high risk but who have not had spontaneous life-threatening ventricular arrhythmias have been completed: the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the Multicenter Unsustained Tachycardia Trial (MUSTT), and the coronary artery bypass surgery/implantable defibrillator trial (CABG-Patch). MADIT showed an advantage of ICD therapy over AAD therapy, MUSTT showed a superiority of electrophysiologically (EP) guided evaluation leading to ICD therapy compared with that leading to drug therapy, and CABG-Patch showed no benefit to ICDs for patients undergoing routine coronary bypass surgery.

defibrillator therapy is now the preferred therapy for survivors of cardiac arrest at risk for recurrences. Major questions still unanswered include the relative benefit of amiodarone versus defibrillators among lower risk subgroups of survivors of out-of-hospital cardiac arrest, the role of beta blockers, and the role of antiischemic surgical and medical therapy as definitive approaches.

A much larger issue, and one that has not yet been defined, is the use of implantable defibrillators among patients thought to be at various levels of risk for cardiac arrest but who have not yet had an event. A number of trials are in progress in an attempt to determine whether preventive defibrillator therapy is an effective means of preventing the first cardiac arrest. Many of the trials are studying cost efficacy in addition to medical efficacy. One of the more important strategies being tested is a comparison of defibrillator therapy and empirical amiodarone therapy to placebo in heart failure patients without symptomatic arrhythmias or a history of cardiac arrest (see Chaps. 23 and 25) .

Application of Therapeutic Strategies to Specific Patient Groups

Secondary Prevention After Surviving Cardiac Arrest

Among survivors of out-of-hospital cardiac arrest not associated with acute transmural myocardial infarction, the risk of recurrent cardiac arrest was reported to be 30 percent at 1 year and 45 percent at 2 years in the early 1970s.[17] [18] Total mortality among these patients exceeded 50 percent at 2 years. The value of these data resides in the fact that they represent a reasonable estimate of natural history risk, since most of the interventions now available were not then in use. Moreover, the risk estimates were consistent in two independent large studies. Although no data are available to determine whether this widely quoted natural history risk has remained the same during subsequent decades, it is generally accepted that the risk of recurrence is still substantial, despite general therapies such as reperfusion during acute myocardial infarction, revascularization in patients with chronic coronary artery disease, use of beta-adrenergic blocking agents,[446] and long-term afterload reduction.

As populations of cardiac arrest survivors began to accumulate from community-based emergency rescue activities, long-term therapeutic strategies intended to reduce recurrent cardiac arrest rates and total mortality risks quickly emerged as a mandate for

clinical investigators. The problem that impinges on all long-term strategies, however, is the lack of a reliable current natural history denominator against which to compare the results of interventions. This is a consequence of ethical concerns about withholding therapy in a placebo control study model for patients at such high risk of dying,[445] in conjunction with the likelihood that general therapies used in such patients may also improve total mortality risk. Earlier approaches to long-term therapy centered around the use of antiarrhythmic drug therapy, largely guided by the results of the electrophysiologic testing and the empirical use of antiarrhythmic drugs, particularly amiodarone. During the evolution of therapeutic strategies, various observational and positive-controlled studies suggested first that suppression of inducible ventricular arrhythmias yielded a better outcome than failure of suppression,[411] [412] [413] [414] [415] [416] then that amiodarone was better than Class I antiarrhythmic drugs,[399] [400] and finally that ICDs were better than amiodarone. [408] [409] [410] Therefore, ICD therapy has emerged as preferred therapy, absent absolute benefit data. Electrophysiological testing for secondary prevention--once routine--is now considered of questionable necessity.[408] [421] Unfortunately, none of the large trials over many

Figure 26-21 Relative and absolute benefit of implantable cardioverter-defibrillators (ICDs) in AVID. *A,* ICD-treated subgroup had an 18 percent mortality at 2 years versus 25 percent in drug-treated group, a 27 percent *relative* reduction among the population having events. *B,* When relative reduction is extrapolated to total target population, *absolute* reduction of fatal events among total population is 7 percent. (From Myerburg RJ, Mitrani R, Interian A Jr, Castellanos A: Interpretation of outcomes of antiarrhythmic clinical trials: Design features and population impact. Circulation 97:1514, 1998. Copyright 1998, American Heart Association.)

years have provided a satisfactory and finite answer to this dilemma.

Antiarrhythmic surgery enjoyed a short period of popularity for secondary prevention, limited by the observation that surgical antiarrhythmic procedures appeared to provide benefit to only a small subset of such patients.[447] As the implantable defibrillator came into wider use, it also began to supplant pharmacological antiarrhythmic approaches, with the possible exception of amiodarone, even before the randomized clinical trials demonstrated relative ICD benefit. In the late 1990s, the AVID study report provided the first information from a large randomized clinical trial supporting the use of ICDs as preferred therapy for secondary prevention of cardiac arrest,[408] as noted earlier (Fig. 26-21) . A prior small study from the Netherlands[448] had suggested benefit of ICDs over conventional therapy, but the numbers in that study had been too small to be considered definitive. Two other studies--CIDS[409] and CASH[410] --suggested benefit but were underpowered.

Primary Prevention of Out-of-Hospital Cardiac Arrest with Advanced Heart Disease

Because of the frequency with which SCD is the initial clinical expression of underlying

structural heart disease, there has been a long-standing interest in therapeutic strategies targeted to primary prevention. After the disappointing outcome of CAST[95] [97] and the disturbing suggestions of lack of efficacy or adverse effects of the Class I antiarrhythmic drugs generally when used for primary or secondary prevention,[96] [392] interest shifted to the use of amiodarone and implantable defibrillators. Two major trials of amiodarone in post-myocardial infarction patients,[449] [450] one of which required ejection fractions less than 40 percent, demonstrated no total mortality benefit, even though both trials demonstrated antiarrhythmic benefit, expressed as a reduction in arrhythmic deaths or resuscitated VF. Subgroup analyses suggest that the concomitant use of beta blockers did confirm a mortality benefit.[451]

In parallel with the amiodarone trials, the randomized controlled trial comparing antiarrhythmic therapy (primarily amiodarone) to ICD therapy (MADIT) was carried out[444] (see Table 26-7) . This trial randomized patients with ejection fractions of less than 35 percent, nonsustained VT during ambulatory recording, and inducible VT that was not suppressible by procainamide. This very high risk group demonstrated a 54 percent reduction in total mortality with ICD therapy compared with drug therapy, primarily amiodarone as noted earlier. At the same time, a trial comparing ICD implantation to no specific therapies for arrhythmias among patients with ejection fractions less than 36 percent, who were undergoing coronary bypass surgery (CABG-Patch), demonstrated no benefit of defibrillators for total mortality.[390] The only marker for arrhythmic risk required for entry into the study was a positive signal-averaged ECG. A third trial, the Multicenter Unsustained Tachycardia Trial (MUSTT),[421] was a complex study designed to determine whether electrophysiologically guided therapy provides an improved outcome among patients with nonsustained VT, inducible VT, and a history of prior myocardial infarction. The results demonstrated that while there was a statistically significant benefit on total mortality achieved by guiding therapy according to the results of electrophysiologic testing, compared with patients with inducible tachycardia who did not receive therapy, the subgroup patients who received ICDs because they failed drug therapy did significantly better. There was a 24 percent mortality among ICD-treated patients at 5 years of follow-up, compared with 55 percent among those receiving electrophysiologically guided drug therapy and 48 percent among those randomized to no therapy. Other trials are ongoing. The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) is designed to test the potential benefit of implantable defibrillators versus amiodarone, compared with placebo, among patients with functional Class II or III congestive heart failure and ejection fractions less than 35 percent. MADIT II is studying the potential benefits of ICD therapy compared with conventional therapy among patients with prior myocardial infarction and ejection fractions less than 30 percent. The results of these studies are expected to further refine indications for ICD therapy for primary prevention in high-risk subgroups.

Primary Prevention in Patients with Less Advanced Common Heart Diseases or Uncommon Diseases

Primary prevention trials have focused largely on patient populations with advanced heart disease who were, as a consequence of the severity of the disease, considered to be at very high risk for SCD and total mortality. Most of the clinical trials testing the question of relative efficacy of antiarrhythmic versus ICD therapy have used the ejection fraction as the marker for advanced disease, and a qualifying criteria of less than 35 percent has characterized most of the studies. Moreover, in the secondary prevention

trial, AVID, a subgroup analysis suggested that there was no relative benefit of ICD therapy over amiodarone for patients with ejection fractions between 35 and 40 percent, all of the benefits accruing to those with ejection fraction of 35 percent or less.[425] This observation is important because it establishes a question about appropriate therapy for patients with ejection fractions greater than 35 percent.

Whereas the risk for SCD and total mortality is highest among patients with structural heart disease and ejection fractions of 35 percent or less, there is still considerable risk among patients with coronary heart disease and with the various cardiomyopathies when the ejection fraction is between 35 and 40 percent, and even higher. In addition, among patients with heart failure due to various forms of cardiomyopathy, whereas the total mortality risk is considerably lower among patients who are functional Class I or early Class II, than among those with late Class III or Class IV disease, the probability that a death will be sudden is

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higher in the former group.[87] [452] Despite this observation, there are no data available to guide therapy for primary prevention of cardiac arrest in such patients.[453] [454] In addition, certain other structural entities that are associated with some elevation of risk of sudden death in the absence of a severely reduce ejection fraction, such as right ventricular dysplasia, sarcoidosis, hypertrophic cardiomyopathy, and myocarditis, are managed without the benefit of clinical trials to guide therapeutic approaches (see Table 26-6) . Patients with symptomatic ventricular arrhythmias due to structural disorders such as right ventricular dysplasia, in which most of the risk is an arrhythmic mortality risk, are often advised to have ICDs, even in the absence of a prior cardiac arrest or hemodynamically significant VT. Whether antiarrhythmic therapy would be just as effective remains unknown, but the judgment of using defibrillators in patients with a disorder whose fatal expression is primarily arrhythmic carries the strength of logic. Among those entities in which family history is helpful for defining risk, the clinical judgment is made easier when there is a strong family history of SCD. Specific support for this approach derives from genetic studies in hypertrophic cardiomyopathy, in which a limited number of the known mutations appear to be associated with specific risk of SCD.[55] In addition, clinical observational data support the use of ICDs in high-risk subsets of patients with hypertrophic cardiomyopathy.[454A]

Primary Prevention in Patients with Structurally Normal Hearts or Molecular Disorders of Cardiac Electrical Activity

In recent years, a new category of interest in primary preventive therapy has emerged. Clinically subtle or inapparent structural disorders, or entities with pure electrophysiological expression, such as the congenital long QT interval syndromes, the Brugada syndrome, and idiopathic VF, have received increasing attention. In secondary prevention strategies for entities such as the long QT interval syndrome, the decision-making process is relatively easy. Those individuals who had a cardiac arrest or potentially fatal arrhythmic event, especially when there is a family history of sudden death, are generally treated with ICDs. Beta blockers are still considered useful for affected family members who have not had an event and perhaps for some subgroups

with patients with syncope of undocumented mechanism.[192] [386a] A more difficult decision is the electrocardiographically affected individual without a family history of SCD and/or the absence of symptomatic arrhythmias. In general, such patients are treated with beta blocker therapy at this time, but given the complexity of the pathophysiology of potentially fatal arrhythmias in such patients, the threshold for considering ICD therapy is decreasing.[191A] Specific genetic screening may prove useful for identifying specific risk ultimately, particularly if arrhythmic risk is modified by multiple factors, as opposed to the defect responsible for the long QT interval itself. For the present, if there is a single clinical marker that is useful for the decision-making process for preventive therapy in this general category of patients, it is a family history of sudden death.

Primary Prevention Among the General Population

To have a major impact on the problem of SCD among the general population, we need to move beyond the identification of high-risk patients who have specific clinical entities, advanced or subtle, that predict a high risk of SCD. Rather, it will be necessary to find among the general population small subgroups of patients at specific risk for SCD as a manifestation of underlying heart disease, if and when that disease becomes manifest. As an example, the studies that have recently demonstrated familial clustering of SCD as the first expression of underlying coronary artery disease, suggesting genetic or behavioral predisposition, may provide some help for the future.[43] [44] If highly specific markers can be found, preventive therapy before the first expression of an underlying disease may lead to a major impact on the population problem of SCD. Short of that, successes will be limited to community-based intervention and to those subgroups who are more easy to identify and in whom it is more justifiable to use prophylactic interventional therapy based on population size and magnitude of risk.[232] [454B]

SUDDEN DEATH AND PUBLIC SAFETY

The unexpectedness of SCD has raised questions concerning secondary risk to the public created by people in the throes of a cardiac arrest. There are no controlled data available to guide public policy regarding people at high risk for potentially lethal arrhythmias and for abrupt incapacitation. Myerburg and Davis[455] reported observations on 1348 sudden deaths caused by coronary heart disease in people 65 years of age or younger during a 7-year period in Dade County, Florida. One hundred one (7.5 percent) of these deaths occurred in people who were engaged in activities at the time of death that were potentially hazardous to the public (e.g., 56 were driving private automobiles or taxis, 15 were driving trucks, 10 were working at altitude, 2 were piloting aircraft), and 122 (9.1 percent) of the victims had occupations that could create potential hazards to others if an abrupt loss of consciousness had occurred while at work (e.g., 57 taxi and truck drivers, 8 aircraft pilots, 9 bus drivers, 9 policemen and firemen). There were no catastrophic events as a result of these cardiac arrests, only minor property damage in 19 and minor injuries in 5.

Levy and associates [456] reported a case of a bus driver with a strong history of coronary heart disease who caused the deaths of himself and several others, but they did not conclusively demonstrate that unexpected cardiac arrest was the proximate cause of

the accident. Furthermore, Waller[457] studied an elderly population and demonstrated that cardiac disease alone was not responsible for a significant increase in accident: senility, or senility plus cardiovascular disease, was much more important. Several other studies also have led to the conclusion that risk to the public is small.[458] [459] In specific reference to private automobile drivers, most of the data show that sudden death at the wheel usually involves enough of a prodrome to allow the driver to get to the roadside before losing consciousness.[455] [458] [459] [460] [461] A recent analysis of recurrent VT/VF events among cardiac arrest survivors suggested limitation of driving privileges for the first 8 months after the index event,[33] based on the clustering of recurrent event rates early after the index event.[32] [33] Therefore, although there are likely to be isolated instances in which cardiac arrest causes public hazards in the future, the risk appears to be small; and because it is difficult to identify specific individuals at risk, sweeping restrictions to avoid such risks appear unwarranted. The exceptions are people with multisystem disease, particularly senility, and individual circumstances that require specific consideration, such as high-risk patients who have special responsibilities--school bus drivers, aircraft pilots, trainmen, and truck drivers.[455] [459] [462]

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Chapter 27 - Hypotension and Syncope

HUGH CALKINS
DOUGLAS P. ZIPES

Syncope is a sudden transient loss of consciousness and postural tone with spontaneous recovery. Loss of consciousness results from a reduction of blood flow to the reticular activating system located in the brain stem and does not require electrical or chemical therapy for reversal. The metabolism of the brain, in contrast to that of many other organs, is exquisitely dependent on perfusion. Consequently, cessation of cerebral blood flow leads to loss of consciousness within approximately 10 seconds. Syncope is an important clinical problem because it is common, is costly, is often disabling, may cause injury, and may be the only warning sign before sudden cardiac death.[1] [2] [3] [4] [14A] [21A] [21B] [28A] Patients with syncope account for 1 percent of hospital admissions and 3 percent of emergency department visits.[1] Elderly persons have a 6 percent annual incidence of syncope. Surveys of young adults have revealed that up to 50 percent report a prior episode of loss of consciousness, most of which are isolated events that never come to medical attention. The annual cost of evaluating and treating patients with syncope has been estimated to be $800 million dollars.[2] Patients who experience syncope also report a markedly reduced quality of life, similar to that experienced by patients with chronic diseases such as rheumatoid arthritis and chronic

obstructive pulmonary disease.[3]

CLASSIFICATION OF THE CAUSES OF SYNCOPE

The causes of syncope can be classified into four primary groups: vascular, cardiac, neurologic/cerebrovascular, and metabolic/miscellaneous (Table 27-1) . Vascular causes of syncope can be further subdivided into anatomical, orthostatic, and reflex-mediated causes. A similar approach to subclassification of the causes of syncope can be applied to the other three diagnostic groups. The probable cause of syncope can be identified in approximately 75 percent of patients.[5] [6]

Vascular Causes of Syncope

Vascular causes of syncope, particularly reflex-mediated syncope and orthostatic hypotension, are by far the most common causes of syncope, accounting for at least one third of all syncopal episodes. In contrast, subclavian steal syndrome is an exceedingly uncommon cause of syncope, accounting for less than 0.1 percent of syncopal episodes.

Orthostatic Hypotension

When a person stands, 500 to 800 ml of blood is displaced to the abdomen and lower extremities, resulting in an abrupt drop in venous return to the heart. This leads to a decrease in cardiac output and stimulation of aortic, carotid, and cardiopulmonary baroreceptors that trigger a reflex increase in sympathetic outflow. As a result, heart rate, cardiac contractility, and vascular resistance increase to maintain a stable systemic blood pressure on standing.[7] Orthostatic hypotension, which is defined as a 20-mm Hg drop in systolic blood pressure or a 10-mm Hg drop in diastolic blood pressure within 3 minutes of standing, results from a defect in any portion of this blood pressure control system.[8] Orthostatic hypotension may be asymptomatic or may be associated with symptoms such as lightheadedness, dizziness, blurred vision, weakness, palpitations, tremulousness, and syncope. These symptoms are often worse immediately on arising in the morning and/or after meals or exercise. Syncope that occurs after meals, particularly in the elderly, may result from a redistribution of blood to the gut. A decline in systolic blood pressure of about 20 mm Hg approximately 1 hour after eating has been reported in up to one third of elderly nursing home residents.[9] Although usually asymptomatic, it may result in lightheadedness or syncope.

Drugs that either cause volume depletion or result in vasodilation are the most common cause of orthostatic hypotension (Table 27-2) . Elderly patients are particularly susceptible to the hypotensive effects of drugs because of reduced baroreceptor sensitivity, decreased cerebral blood flow, renal sodium wasting, and an impaired thirst mechanism that develops with aging.[10] Orthostatic hypotension may also result from neurogenic causes, which can be subclassified into primary and secondary autonomic failure.[8] [11] Primary causes are generally idiopathic, whereas secondary causes are associated with a known biochemical or structural anomaly or are seen as part of a particular disease or syndrome. There are three types of primary autonomic failure.

Pure autonomic failure (Bradbury-Eggleston syndrome) is an idiopathic sporadic disorder characterized by orthostatic hypotension, usually in conjunction with evidence of more widespread autonomic failure such as disturbances in bowel, bladder, thermoregulatory, and sexual function. Patients with pure autonomic failure have reduced supine plasma norepinephrine levels. Multiple system atrophy (Shy-Drager syndrome) is a sporadic, progressive, adultonset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination. The third type of primary autonomic failure is Parkinson's disease with autonomic failure. A small subset of patients with Parkinson's disease may also develop autonomic failure, including orthostatic hypotension. In addition to these forms of chronic autonomic failure is a rare acute panautonomic neuropathy.[12] This generally presents in young people and results in a widespread severe sympathetic and parasympathetic failure with orthostatic hypotension, loss of sweating, disruption of bladder and bowel function, fixed heart rate, and fixed dilated pupils.

Postural orthostatic tachycardia syndrome (POTS) is a milder form of chronic autonomic failure and orthostatic intolerance characterized by the presence of symptoms of orthostatic intolerance, a 28-beats/min or greater increase in heart rate, and the absence of a significant change in blood pressure within 5 minutes of standing or upright tilt.[13] [14] POTS appears to result from a failure of the peripheral vasculature to appropriately vasoconstrict under orthostatic

TABLE 27-1 -- ETIOLOGIES OF SYNCOPE

Vascular
Anatomical
Subclavian steal
Orthostatic
Drug-induced
Hypovolemia
Primary disorders of autonomic failure
Pure autonomic failure (Bradbury-Eggleston syndrome)
Multiple system atrophy (Shy-Drager syndrome)
Parkinson's disease with autonomic failure
Secondary neurogenic
Postprandial (in the elderly)
Postural orthostatic tachycardia syndrome (POTS)
Reflex-mediated

Neurally mediated syncope/vasovagal syncope

Carotid sinus hypersensitivity

Situational (cough, defecation, micturition, swallow)

Glossopharyngeal syncope

Trigeminal neuralgia

Cardiac

Anatomical

Aortic dissection
Aortic stenosis
Atrial myxoma
Cardiac tamponade
Hypertrophic cardiomyopathy
Mitral stenosis
Myocardial ischemia/infarction
Pulmonary embolism
Pulmonary hypertension

Arrhythmias

Bradyarrhythmias

Atrioventricular block
Pacemaker malfunction
Sinus node dysfunction/bradycardia

Tachyarrhythmias

Supraventricular tachycardia
Ventricular tachycardia
Torsades de pointes/long QT syndrome

Neurological/Cerebrovascular

Arnold Chiari malformation
Migraine
Seizures (partial complex, temporal lobe)

Transient ischemic attack/vertebrobasilar insufficiency/cerebrovascular accident

Metabolic/Miscellaneous

Metabolic

Hyperventilation (hypocapnea)
Hypoglycemia
Hypoxemia
Drugs/alcohol
Miscellaneous
Psychogenic syncope
Hysterical
Panic disorder
Anxiety disorder
Cerebral syncope
Hemorrhage

Unknown

stress. POTS may also be associated with syncope due to neurally mediated hypotension (see later). In some patients, the postural orthostatic tachycardia syndrome may result from an abnormality in the clearance of norepinephrine from the synaptic cleft.[14A] Approximately 90 percent of norepinephrine that is released into the synaptic cleft is cleared by uptake into the neuron by the norepinephrine transporter. A recent report identified a mutation in the norepinephrine transporter gene in a family with several affected family members.[14A]

REFLEX-MEDIATED SYNCOPE.

There are many reflex-mediated

TABLE 27-2 -- CAUSES OF ORTHOSTATIC HYPOTENSION

Drugs
Diuretics
Alpha-adrenergic blocking drugs
Terazosin (Hytrin), labetalol
Adrenergic neuron blocking drugs
Guanethidine
Angiotensin-converting enzyme inhibitors
Antidepressants
Monoamine oxidase inhibitors
Alcohol
Diuretics
Ganglion-blocking drugs
Hexamethonium, mecamylamine
Tranquilizers
Phenothiazines, barbiturates
Vasodilators
Prazosin, hydralazine, calcium channel blockers
Centrally acting hypotensive drugs
Methyldopa, clonidine
Primary Disorders of Autonomic Failures

Pure autonomic failure (Bradbury-Eggleston syndrome)
Multiple system atrophy (Shy-Drager syndrome)
Parkinson's disease with autonomic failure

Secondary Neurogenic

Aging
Autoimmune disease
Guillain-Barre syndrome, mixed connective tissue disease, rheumatoid arthritis
Eaton-Lambert syndrome, systemic lupus erythematosus
Carcinomatosis autonomic neuropathy
Central brain lesions
Multiple sclerosis, Wernicke's encephalopathy
Vascular lesions or tumors involving the hypothalmus and midbrain
Dopamine beta-hydroxylase deficiency
Familial hyperbradykinism
General medical disorders
Diabetes, amyloid, alcoholism, renal failure
Hereditary sensory neuropathies, dominant or recessive
Infections of the nervous system
Human immunodeficiency virus infection, Chagas' disease, botulism, syphillis, botulism
Metabolic disease
Vitamin B_{12} deficiency, porphyria, Fabry's disease, Tangier disease
Spinal cord lesions

Adapted from Bannister SR (ed): Autonomic Failure. 2nd ed. Oxford, Oxford University Press, 1988, p 8.

syncopal syndromes (see Table 27-1) . In each case, the reflex is composed of a trigger (the afferent limb) and a response (the efferent limb). This group of reflex-mediated syncopal syndromes has in common the response limb of the reflex, which consists of increased vagal tone and a withdrawal of peripheral sympathetic tone and leads to bradycardia, vasodilation, and, ultimately, hypotension, presyncope, or syncope. What distinguishes these causes of syncope are the specific triggers. For example, micturition syncope results from activation of mechanoreceptors in the bladder; defecation syncope results from neural inputs from gut wall tension receptors; and swallowing syncope results from afferent neural impulses arising from the upper gastrointestinal tract. The two most common types of reflex-mediated syncope, carotid sinus hypersensitivity and neurally mediated hypotension, are discussed later.

The term*neurally mediated hypotension/syncope* (also known as neurocardiogenic, vasodepressor, and vasovagal syncope and as "fainting") has been used to describe a common abnormality of blood pressure regulation characterized by the abrupt onset of hypotension with or without

bradycardia. Triggers associated with the development of neurally mediated syncope are those that either reduce ventricular filling or increase catecholamine secretion. These include the sight of blood, pain, prolonged standing, a warm environment or hot shower, and stressful situations. Under these types of situations, patients with this condition develop severe lightheadedness and/or syncope. It has been proposed that these clinical phenomena result from a paradoxical reflex that is initiated when ventricular preload is reduced by venous pooling. This leads to a reduction in cardiac output and blood pressure, which is sensed by arterial baroreceptors. The resultant increased catecholamine levels, combined with reduced venous filling, leads to a vigorously contracting volume-depleted ventricle. The heart itself is involved in this reflex by virtue of the presence of mechanoreceptors, or C-fibers, consisting of nonmyelinated fibers found in the atria, ventricles, and the pulmonary artery.[15] [16] [17] [18] [19] It has been proposed that vigorous contraction of a volume-depleted ventricle leads to activation of these receptors in susceptible individuals. These afferent C-fibers project centrally to the dorsal vagal nucleus of the medulla, leading to a "paradoxic" withdrawal of peripheral sympathetic tone and an increase in vagal tone, which, in turn, causes vasodilation and bradycardia. The ultimate clinical consequences are syncope or presyncope. Not all neurally mediated syncope results from activation of mechanoreceptors. In humans, it is well known that the sight of blood or extreme emotion can trigger syncope. These observations suggest that higher neural centers can also participate in the pathophysiology of vasovagal syncope. In addition, central mechanisms can contribute to the production of neurally mediated syncope.[18] [20]

Syncope due to carotid sinus hypersensitivity results from stimulation of carotid sinus baroreceptors, which are located in the internal carotid artery above the bifurcation of the common carotid artery. This condition is diagnosed by applying gentle pressure over the carotid pulsation just below the angle of the jaw, where the carotid bifurcation is located. Pressure should be applied unilaterally for approximately 5 seconds, after first listening for a carotid bruit. It has recently been reported that the sensitivity of diagnosing carotid sinus hypersensitivity can be increased, with no change in specificity, by performing carotid sinus massage during 60- or 70-degree upright tilt.[21A] [21B] The normal response to carotid sinus massage is a transient decrease in the sinus rate and/or slowing of atrioventricular (AV) conduction. Three types of abnormal responses have been described: (1) the cardioinhibitory response, characterized by marked bradycardia (>3-second pause); (2) the vasodepressor type, characterized by a 50-mm Hg fall in the systolic blood pressure in the absence of bradycardia; and (3) the mixed response. Carotid sinus hypersensitivity is commonly detected in patients with syncope. One study reported the presence of carotid sinus hypersensitivity in 65 of 279 patients (23 percent) who presented to the emergency department with falls.[21] It is important to recognize that carotid sinus hypersensitivity is also commonly observed in asymptomatic elderly patients, with carotid sinus hypersensitivity identified in one study in more than one third of asymptomatic patients undergoing cardiac catheterization for coronary artery disease. Because of this, the diagnosis of carotid sinus hypersensitivity should be approached cautiously after excluding alternative causes of syncope.

Cardiac Causes of Syncope

Cardiac causes of syncope, particularly tachyarrhythmias and bradyarrhythmias, are the second most common causes, accounting for 10 to 20 percent of syncopal episodes.

Ventricular tachycardia is the most common tachyarrhythmia that can cause syncope. Supraventricular arrhythmias can also cause syncope, although the great majority of patients with supraventricular arrhythmias present with less severe symptoms such as palpitations, dyspnea, and lightheadedness. Bradyarrhythmias that can result in syncope include sick sinus syndrome as well as AV block. Anatomical causes of syncope result from obstruction to blood flow, such as a massive pulmonary embolus, an atrial myxoma, and/or aortic stenosis.

Neurological Causes of Syncope

Neurological causes of syncope, including migraines, seizures, Arnold Chiari malformations, and transient ischemic attacks, are surprisingly uncommon causes of syncope, accounting for less than 10 percent of all cases of syncope. The majority of patients in whom a "neurological" cause of syncope is established are found in fact to have had a seizure rather than true syncope.[5]

Metabolic/Miscellaneous Causes of Syncope

Metabolic causes of syncope are rare, accounting for less than 5 percent of syncopal episodes. The most common metabolic causes of syncope are hypoglycemia, hypoxia, and hyperventilation. The establishment of hypoglycemia as the cause of syncope requires demonstration of hypoglycemia during the syncopal episode. Although the mechanism of hyperventilation-induced syncope has been generally considered to be due to a reduction in cerebral blood flow, a recent study demonstrated that hyperventilation alone was not sufficient to cause syncope. This suggests that hyperventilation-induced syncope may also have a psychological component.[22] Psychiatric disorders may also cause syncope. It has been reported that up to 25 percent of patients with syncope of unknown origin may have psychiatric disorders for which syncope is one of the presenting symptoms.[23] Cerebral syncope is a rare, recently described cause of syncope resulting from cerebral vasoconstriction induced by orthostatic stress.[24]

Relationship Between Prognoses and the Cause of Syncope

The prognosis of patients with syncope varies greatly with diagnosis. Syncope of unknown origin or syncope due to a noncardiac etiology (including reflex mediated syncope) is generally associated with a benign prognosis. In contrast, syncope due to a cardiac cause is associated with a 30 percent mortality at 1 year.

DIAGNOSTIC TESTS

Identification of the precise cause of syncope is often challenging. Because syncope usually occurs sporadically and infrequently, it is extremely difficult to either examine a patient or obtain an electrocardiogram (ECG) during an episode of syncope. For this reason, the primary goal in the evaluation of a patient with syncope is to arrive at a presumptive determination of the cause of syncope.

History and Physical Examination

The history and physical examination is the most important component of the evaluation of a patient with syncope.[5] [25] [26] [27] In one prospective series of 433 patients a diagnosis was established based on the history and physical examination in 144 patients, representing 58 percent of those patients in whom a diagnosis was established.[5] When taking a clinical history, particular attention should then be focused on (1) determining if the patient experienced true syncope as compared with a transient alteration in consciousness without loss of postural tone; (2) determining if the patient has a history of cardiac disease or if a family history of cardiac disease, syncope, or sudden death exists;

TABLE 27-3 -- DIFFERENTIATING SYNCOPE DUE TO NEURALLY MEDIATED HYPOTENSION, ARRHYTHMIAS, AND SEIZURES

	NEURALLY MEDIATED HYPOTENSION	ARRHYTHMIAS	SEIZURE
Demographics/Clinical Setting	Female>male gender Younger age (<55 yr) More episodes (>2) Standing, warm room, emotional upset	Male>female gender Older age (>54 yr) Fewer episodes (<3) Any setting	Younger age (<45 yr) Any setting
Premonitory Symptoms	Longer duration (>5 sec) Palpitations Blurred vision Nausea Warmth Diaphoresis Lightheadedness	Shorter duration (<6 sec) Palpitations less common	Sudden onset or brief aura (deja vu, olfactory, gustatory, visual)

Observations During the Event	Pallor Diaphoretic Dilated pupils Slow pulse, low blood pressure Incontinence may occur Brief clonic movements may occur	Blue, not pale Incontinence can occur Brief clonic movements can occur	Blue face, no pallor Frothing at the mouth Prolonged syncope (duration >5 minutes) Tongue biting Horizontal eye deviation Elevated pulse and blood pressure Incontinence more likely* Tonic clonic movements if grand mal
Residual Symptoms	Residual symptoms common Prolonged fatigue common (>90%) Oriented	Residual symptoms uncommon (unless prolonged unconsciousness) Oriented	Residual symptoms common Aching muscles Disoriented Fatigue Headache Slow recovery

*May be observed with any of these causes of syncope buy more common with seizures.

(3) identifying medications that may have played a role in syncope; (4) quantifying the number and chronicity of prior episodes; (5) identifying precipitating factors including body position; and (6) quantifying the type and duration of prodromal and recovery symptoms. The features of the clinical history that are most useful in determining whether syncope resulted from neurally mediated hypotension, an arrhythmia, or a seizure are summarized in Table 27-3` . It is also important to search to identify additional precipitating factors that may suggest a specific type of syncope. For example, carotid sinus syncope should be suspected if a patient reports syncope in response to head rotation and cough syncope should be suspected if syncope occurs in association with cough. The presence of akinetic or petit mal seizures can be recognized by the patient's lack of responsiveness in the absence of a loss of postural tone. Temporal lobe seizures last several minutes and are characterized by confusion, changes in the level of consciousness, and autonomic signs such as flushing. Vertebrobasilar insufficiency should be considered as the cause of syncope if syncope occurs in association with other symptoms of brain stem ischemia (i.e., diplopia, tinnitus, focal weakness or sensory loss, vertigo, or dysarthria). Migraine-mediated syncope is often associated with a throbbing unilateral headache, scintillating scotomata, and nausea.

After obtaining a careful history, evaluation should continue with a physical examination including the determination of orthostatic vital signs. Particular attention should focus on

determining if structural heart disease is present, defining the patient's level of hydration and orthostatic vital signs, and detecting the presence of significant neurologic abnormalities suggestive of a dysautonomia or a cerebrovascular accident.

Blood Tests

The routine use of blood tests, such as serum electrolytes, glucose, and hematocrit levels generally has low diagnostic value. Nonetheless, these tests are commonly obtained as part of the evaluation of a patient with syncope.

Carotid Sinus Massage

Carotid sinus hypersensitivity is diagnosed by carotid massage, as outlined earlier.

Tilt-Table Testing (See Chap. 23.)

Tilt-table testing is a standard diagnostic test for evaluating patients with syncope.[28] [28A] [29] [30] [31] To the extent that tilt-table testing provides diagnostic evidence indicating susceptibility to neurally mediated syncope, it is generally considered the "gold standard" for establishing this diagnosis. The American College of Cardiology recently published an Expert Consensus Document that contains specific recommendations for performing and interpreting the results of this test.[28] Upright tilt-table testing is performed for 30 to 45 minutes at an angle of approximately 70 degrees. In general, a positive response to tilt-table testing is defined as the development of syncope or presyncope in association with hypotension and/or bradycardia. Positive responses to tilt-table testing can be divided into mixed, cardioinhibitory, and vasodepressor categories[31] (Table 27-4) . The sensitivity of the test can be increased, with an associated fall in specificity, by the use of longer tilt durations, steeper tilt angles, and provocative agents such as isoproterenol, nitroglycerin, or edrophonium.[28] [28A] In the absence of pharmacologic provocation, the specificity of the test has been estimated to be 90 percent.[28] [29] There is general agreement that

TABLE 27-4 -- CLASSIFICATION OF HEART RATE AND HEMODYNAMIC RESPONSES TO TILT-TABLE TESTING

Type 1: Mixed
Heart rate rises initially and then falls, but the ventricular rate does not fall to less than 40 beats/min or falls to 40 beats/min for less than 10 seconds with or without asystole for less than 3 seconds. Blood pressure rises initially and then falls before heart rate falls.
Type 2A: Cardioinhibitory

Heart rate rises initially and then falls to a ventricular rate of less than 40 beats/min for greater than 10 seconds, or asystole occurs for greater than 3 seconds. Blood pressure rises initially and then falls before heart rate falls.
Type 2B: Cardioinhibitory
Heart rate rises initially and then falls to a ventricular rate of less than 40 beats/min for more than 10 seconds, or asystole occurs for more than 3 seconds. Blood pressure rises initially and only falls to hypotensive levels less than 80 mm Hg systolic at or after onset of rapid and severe heart rate fall.
Type 3: Pure Vasodepressor
Heart rate rises progressively and does not fall more than 10% from peak at time of syncope. Blood pressure falls to cause syncope.

upright tilt-table testing is indicated in patients with (1) recurrent syncope or a single syncopal episode in a high-risk patient who either has no evidence of structural heart disease or in whom other causes of syncope have been excluded, (2) evaluation of patients in whom the causes of syncope have been determined (e.g., asystole) but in whom the presence of neurally mediated syncope on upright tilt would influence treatment, and (3) as part of the evaluation of patients with exercise-related syncope. There is also general agreement that upright tilt-table testing is not necessary for patients who have experienced only a single syncopal episode that was highly typical for neurally mediated syncope and during which no injury occurred. Tilt-table testing is not useful in establishing a diagnosis of situation syncope (i.e., postmicturition syncope[32]).

Echocardiography

Although echocardiograms are commonly used in the evaluation of patients with syncope, little objective evidence exists to support their use in patients with a normal physical examination and a normal ECG.[33] [34] [35] [36] The rationale for obtaining an echocardiogram in patients with syncope is to risk stratify the patient by excluding the possibility of occult cardiac disease not apparent after the history, physical examination, and electrocardiography. If detected, the presence of impaired ventricular function or significant valvular dysfunction would suggest a cardiac cause of syncope that would predict a worse long-term prognosis.

Stress Tests, Cardiac Catheterization

Myocardial ischemia is an unlikely cause of syncope and, when present, is usually accompanied by angina. As such, exercise stress testing and cardiac catheterization are unlikely to establish a diagnosis in patients presenting with syncope unless the clinical suspicion of ischemia is high. The use of stress tests in the evaluation of a patient with syncope is best reserved for patients in whom syncope or presyncope occurred during or immediately after exertion or in association with chest pain. They might also be considered in young individuals with recurrent syncope during exertion

when other causes of syncope have been excluded to rule out anomalous coronary arteries. Even among patients with syncope during exertion it is highly unlikely that exercise stress testing will trigger another event. Patients suspected of having severe aortic stenosis or obstructive hypertrophic cardiomyopathy should not undergo exercise stress testing, because it may precipitate a cardiac arrest.

Electrocardiography

The 12-lead ECG is a standard component in the work-up of a patient with syncope. The initial ECG results in establishment of a diagnosis in approximately 5 percent of patients and suggests a diagnosis in another 5 percent of patients.[5] Specific findings that may identify the probable cause of syncope include QT prolongation (long QT syndrome), the presence of a short PR interval and a delta wave (Wolff-Parkinson-White syndrome), evidence of an acute myocardial infarction, and high-grade AV block. Less specific findings that may suggest potential causes of syncope that can be later confirmed with directed testing include evidence for a prior myocardial infarction, bundle branch block, ventricular hypertrophy, ventricular premature beats, and T wave inversion in the right precordial leads with an incomplete right bundle branch block pattern, suggestive of right ventricular dysplasia. Another recently identified syndrome that should be searched for is the Brugada syndrome, which is characterized by a right bundle branch block pattern with persistent ST segment elevation in leads V_1 to V_3 . This syndrome is associated with a high incidence of sudden cardiac death.[37] [38] The finding of a normal ECG suggests that a cardiac cause of syncope is unlikely.

Signal-Averaged Electrocardiography

Signal-averaged electrocardiography (SAECG) is a noninvasive technique used for detection of low-amplitude signals in the terminal portion of the QRS complex (late potentials), which are a substrate for malignant ventricular arrhythmias. In contrast to a standard ECG, obtaining a SAECG is not considered a standard part of the evaluation of a patient with syncope.[39]

Holter Recording

Continuous ECG monitoring using telemetry and/or Holter recording is commonly performed in patients with syncope. The information provided by ECG recording at the time of syncope is extremely valuable because it allows an arrhythmic cause of syncope to be established or excluded. However, because of the infrequent and sporadic nature of syncope, the diagnostic yield of Holter recording is low. The likelihood of experiencing an episode of syncope while wearing a Holter recorder in an unselected population of patients with syncope is approximately 0.1 percent. Although detection of asymptomatic sinus bradycardia, AV block, or nonsustained supraventricular or ventricular arrhythmias can suggest an arrhythmic cause of syncope, it is important to recognize that unless syncope or presyncope accompanies these arrhythmias they are likely to be incidental findings and should not be assumed to be the cause of syncope. Another inherent limitation of Holter recording is that it requires that the patient experience another

episode of syncope to establish a diagnosis. For these reasons, the clinical situation in which Holter recording is most likely to be diagnostic is when used in the occasional patient with very frequent (i.e., daily) episodes of syncope or presyncope.

Event Recorders

Transtelephonic event recorders are small, portable ECG recording devices that are carried or worn continuously by the patient and can be activated by the patient to record a rhythm strip. The tracings can be stored and transmitted over telephone lines at a later time. Some event recorders, referred to as continuous loop event recorders, are worn

continuously and allow capture of both retrospective and prospective ECG recordings, whereas other types of event recorders record only when activated by the patient. Continuous loop event recorders are preferred when used in the evaluation of a patient with syncope. Event recorders are especially useful for patients with infrequent episodes of presyncope or syncope, particularly once potentially malignant causes of syncope have been excluded.[40] [41] One recent study reported the diagnostic utility of event recorders in 62 patients with syncope.[41] The device was recommended either after a nondiagnostic electrophysiology (EP) test or in patients with syncope that occurred in the absence of structural heart disease. During a recording period of 4 weeks, 20 patients (32 percent) experienced symptoms and activated the device. An arrhythmia was observed in association with symptoms in 8 of these patients.

Implantable Event Recorders

In some patients, episodes of syncope are extremely infrequent, occurring once or twice a year. In this patient population a traditional event recorder is unlikely to be diagnostic because of the prolonged length of recording that would be needed to successfully record an event. To address this, an implantable event recorder has been developed (Medtronic Reveal, Minneapolis, MN). This smaller device (61×19×8 mm) with a projected longevity of 24 months incorporates two electrodes within its can and is implanted in the subcutaneous tissue of the chest.[42]

Electrophysiology Testing

The results of EP testing can be useful in establishing a diagnosis of sick sinus syndrome, heart block, supraventricular tachycardia, or ventricular tachycardia in patients with syncope. The indications for EP testing in the evaluation of patients with syncope have recently been established based on an American College of Cardiologists/American Heart Association Task Force report.[43] There is general agreement that EP testing should be performed in patients with suspected structural heart disease and unexplained syncope (Class I indication) and that it should not be performed in patients with a known cause of syncope for whom treatment will not be influenced by the findings of the test (Class III indication). The role of EP testing in

evaluating patients with recurrent unexplained syncope who do not have structural heart disease and have had a negative tilt test remains controversial (see Chap. 23) .

Sinus node function is evaluated during EP testing primarily by determining the sinus node recovery time (SNRT). The SNRT is defined as the interval between the last paced atrial depolarization and the first spontaneous atrial depolarization resulting from activation of the sinus node. A corrected SNRT (SNRT -- sinus cycle length) greater than 525 msec is generally considered abnormal.[43] Identification of sinus node dysfunction as the cause of syncope is an uncommon finding during EP tests (<5 percent).[44] [45] It is also important to note that the absence of evidence of sinus node dysfunction during EP testing does not exclude a bradyarrhythmia as the cause of syncope. During EP testing, AV conduction is assessed by measuring the His bundle to ventricular conduction time (HV interval) and also by determining the response of AV conduction to incremental atrial pacing. The findings obtained during EP testing that allow AV block to be established as the probable cause of syncope include an HV interval greater than or equal to 100 msec or an infra-His block observed spontaneously or during atrial pacing.[43] [44] [45] [46] Completion of a standard EP test will allow accurate identification of most types of supraventricular arrhythmias that may have caused syncope. The study should be repeated during an isoproterenol infusion to increase the sensitivity of the study, particularly for detecting idiopathic ventricular tachycardia or AV nodal reentrant tachycardia. A supraventricular arrhythmia is diagnosed as the probable cause of syncope in less than 5 percent of patients who undergo EP testing for evaluation of syncope of unknown origin.[6] [43] [44] [45] [47] Ventricular tachycardia is the most common abnormality uncovered during EP testing in patients with syncope. An EP test is interpreted as positive for ventricular tachycardia when sustained monomorphic ventricular tachycardia is induced. The induction of polymorphic ventricular tachycardia, ventricular fibrillation, and nonsustained ventricular tachycardia have been considered to represent nonspecific responses to EP testing. Among studies that have reported the results of EP testing in evaluating patients with syncope, identification of ventricular tachycardia as the probable cause of syncope is reported in approximately 20 percent of patients.[6] [43] [44] [45]

Approximately one third of patients with syncope of unknown origin referred for EP testing will have a presumptive diagnosis established.[6] Clinical factors that have been identified as predictors of a positive response to EP testing include impaired ventricular function, male sex, prior myocardial infarction, bundle branch block, injury, and nonsustained ventricular tachycardia. The remaining two thirds of patients with a normal response to EP testing are generally considered to be at low risk of sudden cardiac death. It is important to recognize however that EP testing does not always identify the arrhythmic cause of syncope because transient abnormalities such as those caused by ischemia or fluctuations in autonomic tone may be missed.[48] In addition, recent studies have suggested that EP testing may have less predictive value in patients with markedly impaired ventricular function and particularly those with an idiopathic dilated cardiomyopathy. Middlekauff and colleagues[49] [50] have called attention to the strong link between syncope and sudden cardiac death in patients with syncope and congestive heart failure and also to the poor negative predictive value of EP testing in patients with reduced ventricular function. Another recent study[51] reported that 7 of 14 patients with an idiopathic dilated cardiomyopathy who presented with syncope, had a negative EP test, and underwent placement of an implantable defibrillator received

appropriate shocks for ventricular arrhythmias during 24 months of follow-up.[51] These findings suggest that more sensitive diagnostic tests to evaluate patient risk of sudden death and/or greater use of implantable defibrillators may be needed in patients with an idiopathic dilated cardiomyopathy who present with syncope.

Tests to Screen for Neurological Causes of Syncope

Syncope, as an isolated symptom, is rarely due to a neurological cause. In most large published series, neurological causes of syncope are established in less than 5 percent of patients. As a result, widespread use of tests to screen for neurologic conditions rarely are diagnostic. In many institutions, computed tomography, electroencephalography, and carotid duplex scans are overused, being obtained in more than 50 percent of patients with syncope. A diagnosis is almost never uncovered that was not first suspected based on a careful history and neurologic examination.[5] [52] One study indicated that 29 percent of patients with treatment-resistant epilepsy or suspected nonepileptic seizures have an underlying cardiovascular cause of syncope such as neurally mediated hypotension, carotid sinus hypersensitivity, or transient AV block.[53]

APPROACH TO THE EVALUATION OF PATIENTS WITH SYNCOPE

Figure 27-1 outlines an approach to the diagnostic evaluation of a patient presenting with syncope. The initial evaluation

Figure 27-1 Diagnostic evaluation of syncope. TTT=tilt table testing, EPS=electrophysiologic studies.

begins with a careful history, physical examination, and 12-lead ECG. Various clinical features can help suggest a specific cause of the syncope (Table 27-5) . Based on this initial evaluation performed either in an emergency department or outpatient setting, the probable cause of syncope can be identified in approximately 30 percent of patients. Common causes of syncope that can be identified at this initial stage include orthostatic hypotension, situational syncope, and often neurally mediated syncope. This initial evaluation should also allow identification of patients who likely had a seizure, rather than syncope. In another large group of patients the probable cause of syncope can be suspected and later confirmed with directed diagnostic testing. Causes of syncope that would fall into this category include syncope due to critical aortic stenosis, neurally mediated syncope with a suggestive but not diagnostic clinical presentation, arrhythmias due to the Wolff-Parkinson-White syndrome, or right ventricular dysplasia, as well as neurologic causes of syncope that can be further evaluated with directed testing. Among the remaining patients, the next step in the evaluation depends on the presence of structural heart disease as well as the physician's clinical suspicion that an arrhythmia may have been the cause of syncope. An echocardiogram is often obtained at this point

to help determine if structural heart disease is present. If the patient has significant structural heart disease or a clinical history suggestive of an arrhythmia, an EP test would be an appropriate next step. On the other hand, if structural heart disease is absent and the clinical history is not suggestive of an arrhythmia, the evaluation can be continued either with a tilt test, event monitor, or clinical follow-up, depending on the severity and chronicity of the patient's symptoms. With the use of this approach a probable cause of syncope can be determined in 75 percent of patients.[6]

PATIENT MANAGEMENT

The approach to treatment of a patient with syncope depends largely on the diagnosis that is established. For example,

TABLE 27-5 -- CLINICAL FEATURES SUGGESTIVE OF SPECIFIC CAUSES

SYMPTOM OR FINDING	DIAGNOSTIC CONSIDERATION
After sudden unexpected pain, unpleasant sight, sound, or smell	Vasovagal syncope
During or immediately after micturition, cough, swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Bradycardia or vasodepressor reaction
On standing	Orthostatic hypotension
Prolonged standing at attention	Vasovagal syncope
Well-trained athlete after exertion	Neurally mediated
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Aortic stenosis, pulmonary hypertension, pulmonary embolus, mitral stenosis, idiopathic hypertrophic subaortic stenosis, coronary artery disease, neurally mediated
With head rotation, pressure on carotid sinus (as in tumors, shaving, tight collars)	Carotid sinus syncope
Associated with vertigo, dysarthria, diplopia, and other motor and sensory symptoms of brain stem ischemia	Transient ischemic attack, subclavian steal, basilar artery migraine
With arm exercise	Subclavian steal
Confusion after episode	Seizure

From Kapoor WN: Syncope and hypotension.In Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 868.

the appropriate treatment of a patient with syncope due to AV block or sick sinus syndrome would likely involve placement of a permanent pacemaker; treatment of a patient with syncope due to the Wolff-Parkinson White syndrome would likely involve catheter ablation; and treatment of a patient with syncope due to ventricular tachycardia would likely involve placement of an implantable defibrillator. For other types of syncope, optimal patient management may involve discontinuation of an offending pharmacological agent, an increase in salt intake, or patient education.

Other issues that need to be considered include the indication for hospitalization of a patient with syncope and duration of driving restrictions. There have been no studies that have evaluated the indications for hospital admission among patients with syncope. Generally, hospital admission is indicated when there is concern regarding a potentially life-threatening cause of syncope or when significant injury has occurred. It would therefore be prudent to hospitalize a 65-year-old man with a prior history of a myocardial infarction and heart failure who presents with an initial episode of syncope that occurs without warning or residual symptoms. In this type of patient, the probability of ventricular tachycardia as the cause of syncope is high. On the other hand, the evaluation of a young patient who presents with a clinical history suggestive of neurally mediated syncope and no clinical evidence of cardiac disease could be performed as an outpatient.

Physicians who care for patients with syncope are after asked to address the issue of driving risk. Patients who experience syncope while driving pose a risk both to themselves and to others. Although some would argue that all patients with syncope should never drive again because of the theoretical possibility of developing a recurrence, this is an impractical solution that will be ignored by many patients. Factors that should be considered when making a recommendation for a particular patient include (1) the potential for recurrent syncope, (2) the presence and duration of warning symptoms, (3) whether syncope occurs while seated or only when standing, (4) how often and in what capacity does the patient drive, and (5) are there any state laws that may be applicable? When considering these issues, physicians should note that acute illnesses, including syncope, are unlikely to cause a motor vehicle accident. The American Heart Association and the Canadian Cardiovascular Society have published guidelines concerning this issue.[54] [55] For noncommercial drivers, it is generally recommended that driving be restricted for several months. If the patient remains asymptomatic, driving can be resumed several months later.

Neurally Mediated Syncope

Because neurally mediated syncope is so common, therapy will be outlined in detail.

Treatment begins with a careful history with particular attention focused on identifying precipitating factors, quantifying the degree of salt intake and current medication use, and determining if the patient has a prior history of peripheral edema, hypertension, asthma, or other conditions that may alter the approach used to treat neurally mediated syncope. For many patients, particularly those with infrequent episodes associated with an identifiable precipitant, education about avoidance of predisposing factors and a moderate increase in salt intake is effective treatment. For others, treatment involves removal or avoidance of drugs that predispose one to orthostatic hypotension or volume depletion, such as vasodilators and diuretics. Treatment with pharmacologic agents is usually targeted at patients in whom syncope is recurrent or has been associated with physical injury. The medications that are generally considered to be most effective in the treatment of neurally mediated syncope include beta blockers, serotonin reuptake inhibitors, and midodrine.[56] [57] [58] [59] [60] [61] [61A] Although fludrocortisone is widely used in the treatment of neurally mediated syncope, particularly in children, its efficacy has never been demonstrated with a randomized clinical trial.[61] A recent study has reported that "orthostatic training," performed by standing the patient for 40 minutes twice daily, is effective in the treatment of neurally mediated hypotension in adolescents.[61B] For most patients, first-line therapy includes a combination of increased salt intake (>3 gm/day) and beta-blocker therapy. If ineffective, treatment with fludrocortisone, midodrine, or a serotonin reuptake inhibitor such as paroxetine can be considered. Although pacemakers have also been demonstrated to be valuable in the treatment of some patients with neurally mediated syncope, they are generally considered in patients who fail attempts at pharmacologic therapy and have demonstrated a predominantly cardioinhibitory response during tilt-table testing.[62] Because of the profound implications of pacemaker implantation, particular restraint should be exercised when considering the implantation of a pacemaker in a young person. The development of asystole during tilt-table testing is not considered to be an absolute indication for pacemaker implantation.[63]

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Part IV - HYPERTENSIVE AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Chapter 28 - Systemic Hypertension: Mechanisms and Diagnosis

NORMAN M. KAPLAN

Definitions, Prevalence, and Consequences of Hypertension

Hypertension, despite its widely recognized high prevalence and associated danger, remains inadequately treated in the majority of patients. In the representative sample of the U.S. population examined in the 1991-1994 National Health and Nutrition Examination Survey (NHANES III), only 27 percent of hypertensives had their blood pressure well controlled, as defined by a reading below 140/90 mm Hg[1] (Fig. 28-1) . Although most cases of hypertension had been identified previously, only about half of

hypertensives were currently being treated. Similarly inadequate rates of control have been noted among patients managed in health maintenance organizations[2] and Veterans Affairs clinics.[3] Moreover, cardiovascular mortality remains higher even in presumably well treated hypertensives than in nonhypertensives.[4]

Despite these disturbing figures, management of hypertension is now the leading indication for both visits to physicians and the use of prescription drugs in the United States. According to the National Ambulatory Care Survey, over 100 million office visits related to hypertension were made in 1997.[5] Clearly, more attention is being directed toward hypertension, but adequate hypertension control remains elusive, in large part because of the asymptomatic nature of the disease for the first 15 to 20 years, even as it progressively damages the cardiovascular system.[6] Asymptomatic patients are often unwilling to alter life style or take medication to forestall some far-off, poorly perceived danger, particularly when they are made uncomfortable in the process.

In view of these built-in barriers to effective control of the individual patient, population-wide application of preventive measures becomes inherently more attractive. Although the specific mechanisms for most hypertension remain unknown, it is highly likely that the process could be slowed, if not prevented, by the prevention of obesity, moderate reduction in sodium intake, higher levels of physical activity, and avoidance of excessive alcohol consumption.[6] Since hypertension will eventually develop in most people during their lifetime, the need for more widespread adoption of potentially effective and totally safe preventive measures is obvious. In the meantime, better management

Figure 28-1 Percentages of U.S. adult men and women aged 18 to 74 years identified in the National Health and Nutrition Examination Survey (NHANES), 1991-1994, with hypertension diagnosed (left-hand bars), treated (middle), and controlled (right). Hypertension was defined as blood pressure of 140/90 or above. (Adapted from Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 157:2413, 1997. Copyright 1997, American Medical Association.)

of those already afflicted must be practiced, starting with careful documentation of the diagnosis.

DEFINITION OF HYPERTENSION

Blood pressure is distributed in a typical bell-shaped curve within the overall population (Fig. 28-2) . As seen in the 12-year experience of the almost 350,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT), the long-term risks for cardiovascular mortality associated with various levels of pressure rise progressively over the entire range of blood pressure, with no threshold that clearly identifies potential

danger. Therefore, the definition of hypertension is somewhat arbitrary and usually taken as that level of pressure associated with a doubling of long-term risk. Perhaps the best operational definition is "the level at which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction."

The issue of what blood pressure level should be taken to signify hypertension is further complicated by its typically marked variability. Such variability is seldom recognized by the relatively few office readings taken by most practitioners but can easily be identified by automatically recorded measurements taken throughout the day and night (Fig. 28-3) . This variability can often be attributed to physical activity or emotional stress but is frequently without obvious cause.

In a few patients, markedly elevated levels clearly indicate serious disease requiring immediate treatment. However, in most cases, initial readings are not high enough to indicate immediate danger, and the diagnosis of hypertension should be substantiated by repeated readings. The reason for such caution is obvious: The diagnosis of hypertension imposes psychological and socioeconomic burdens on an individual and usually implies the need for commitment to lifelong therapy.

Both transient and persistent elevations in pressure are common when it is taken in the physician's office or hospital. To identify "white coat" hypertension, more widespread use of out-of-the-office readings, either with semiautomatic inexpensive devices or with automatic ambulatory recorders, is encouraged both to establish the diagnosis and to monitor the patient's response to therapy.[1] A large body of data provides normal ranges for both home self-recorded[7] and automatic ambulatory measurements.[8] Both average about 10/5 mm Hg lower than the average of multiple office readings. A closer correlation between the presence of various types of target organ damage, specifically, left ventricular hypertrophy (LVH), carotid wall thickness, proteinuria, and retinopathy, has been noted with ambulatory levels than with office levels.[9] However, in the absence of adequate long-term follow-up evidence of the risks associated with either home or ambulatory monitoring, office readings should continue to be the basis for the diagnosis and management of hypertension.

OUT-OF-THE-OFFICE MEASUREMENTS.

Whenever possible, office readings should be supplemented by out-of-the-office measurements, particularly when there is an apparent

Figure 28-2 *Left,* Percent distribution of systolic blood pressure (SBP) for men screened for the Multiple Risk Factor Intervention Trial who were 35 to 57 years old and had no history of myocardial infarction (*n* = 347,978) *(shaded bars)* and corresponding 12-year rates of cardiovascular mortality by SBP level adjusted for age, race, total serum cholesterol level, cigarettes smoked per day, reported use of medications for diabetes mellitus, and estimated household income (using census tract of residence). *Right,* Same as at the *left,* except distribution of diastolic blood pressure (DBP) (*n* = 356,222). (From National High Blood Pressure Education Program Working Group: National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. Arch Intern Med

153:186, 1993. Copyright 1993, American Medical Association.)

Figure 28-3 Computer printout of blood pressure readings obtained by ambulatory blood pressure monitoring over a 24-hour period beginning at 9 A.M. in a 50-year-old man with hypertension receiving no therapy. The patient slept from midnight until 6 A.M.*Solid circles* = heart rate. (From Zachariah PK, Sheps SG, Smith RL: Defining the roles of home and ambulatory monitoring. Diagnosis 10:39, 1988. © Medical Economics Publishing Company, Inc., Pradell, NJ. All rights reserved.)

discrepancy between the level of blood pressure and the degree of target organ damage, in which case white coat hypertension should be suspected. Pickering has provided a scheme for the use of home and ambulatory monitoring in such a circumstance[10] (Fig. 28-4) . In as many as half of patients with office readings that remain elevated despite the use of three or more drugs, hypertension in as many as half is found to be well controlled by out-of-the-office readings.[11] Purely white coat hypertension, that is, persistently elevated office readings but persistently normal out-of-the-office readings, is found in 20 to 30 percent of patients. Most are found to be free of the target organ damage and metabolic abnormalities (dyslipidemia, hyperinsulinemia) that are often found in patients with sustained hypertension,[12] and follow-up for up to 10 years has found no increase in cardiovascular events.[13] Therefore, close observation and life style modifications but not antihypertensive drug therapy seem appropriate management for such patients.

Figure 28-4 Schema for evaluation of hypertensive patients by use of clinic, home, and ambulatory monitoring of blood pressure. (From Pickering TG: Blood pressure measurement and detection of hypertension. Lancet 344:31, 1994. © by The Lancet Ltd., 1994.)

In addition to their role in the recognition of white coat hypertension, out-of-the-office readings are essential for the recognition of persistently elevated pressures soon after awakening, when the largest proportion of sudden deaths, myocardial infarctions, and strokes occur.[14] Increased awareness of the role of the abrupt and marked rise in pressure after awakening in the etiology of these early morning cardiovascular catastrophes has prompted therapeutic strategies to ensure control of hypertension at that time, including late evening dosing with currently available medications and the development of tablets that are delayed in releasing active drug so that they can be taken at bedtime but not become active until the hours before awakening.[15]

In view of the usual nocturnal fall in pressure (see Fig. 28-3) , addition of the maximal antihypertensive effect of medication taken before bedtime could incite myocardial and cerebral ischemia during sleep. Therefore, the best way to blunt the early morning surge in pressure is to use formulations that provide full 24-hour coverage and to take them as

early in the morning as possible.

Although a nocturnal fall in pressure is usual, various groups of hypertensives who have a more serious degree of target organ damage or subsequent major cardiovascular events have been noted to have little or no nocturnal fall.[16] These groups include patients with LVH, diabetes, or renal damage and blacks. Recognition of abnormal nocturnal patterns of blood pressure, presumably adding an additional stress to the cardiovascular system, is a potential indication for more widespread use of automatic recordings.

BLOOD PRESSURE RESPONSE TO EXERCISE.

Another source of potentially useful prognostic information is the blood pressure response to exercise, usually ascertained by treadmill testing. An exaggerated response in normotensive adults, defined as a systolic pressure rise of more than 60 mm Hg at 5 minutes of exercise (6.3 METs) or more than 70 mm Hg at 10 minutes (8.1 METs) or a diastolic rise of more than 10 mm Hg at any time, was associated with a 3-fold greater likelihood of hypertension developing over the next 5 to 15 years.[17] Such patients had a 3.6 times greater risk ratio for major cardiovascular events over an 8-year follow-up than did those without an exaggerated response during exercise.[18]

DOCUMENTATION OF HYPERTENSION.

For most patients who are in no immediate danger from markedly elevated pressure, i.e., below approximately 170/110 mm Hg, the following guidelines are offered:

TABLE 28-1 -- GUIDELINES IN MEASURING BLOOD PRESSURE

Conditions for the Patient
Posture
For patients who are older than 65 yr, diabetic, or receiving antihypertensive therapy, check for postural changes by taking readings immediately and 2 min after patient stands
Sitting pressures are usually adequate for routine follow-up. Patient should sit quietly with back supported for 5 min and arm supported at level of heart
Circumstances
No caffeine for preceding hour
No smoking for preceding 15 min
No exogenous adrenergic stimulants, e.g., phenylephrine in nasal decongestants or eyedrops for pupillary dilation

Quiet, warm setting

Home readings taken under varying circumstances and 24-hr ambulatory recordings may be preferable and more accurate in predicting subsequent cardiovascular disease

Equipment

Cuff size: The bladder should encircle and cover two-thirds of the length of the arm; if not, place the bladder over the brachial artery; if bladder is too small, spuriously high readings may result

Manometer: Aneroid gauges should be calibrated every 6 mo against a mercury manometer

For infants, use ultrasound equipment, e.g., the Doppler method

Technique

Number of readings

On each occasion, take at least 2 readings separated by as much time as practical. If readings vary by more than 5 mm Hg, take additional readings until 2 are close

For diagnosis, obtain at least 3 sets of readings at least a week apart

Initially, take pressure in both arms; if pressure differs, use arm with higher pressure

If arm pressure is elevated, take pressure in one leg, particularly in patients younger than 30 yr

Performance

Inflate the bladder quickly to a pressure 20 mm Hg above the systolic, as recognized by disappearance of the radial pulse

Deflate the bladder 3 mm Hg every second

Record the Korotkoff phase V (disappearance) except in little children, in whom use of phase IV (muffling) may be preferable

If Korotkoff sounds are weak, have the patient raise the arm and open and close the hand 5-10 times, after which the bladder should be inflated quickly

Recordings

Note the pressure, patient position, which arm, and cuff size (e.g., 140/90, seated, right arm, large adult cuff)

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1. Multiple readings should be obtained with appropriate technique (Table 28-1) . If possible, the readings should be taken under varying conditions and at various times for at least 4 to 6 weeks with a semiautomatic home device. If the diagnosis must be established more rapidly, a set of readings obtained by an automatic monitor over a single 24-hour period will be adequate.
2. Although the logical approach would be to calculate the average values from multiple readings when deciding whether hypertension is present, even a single high measurement should not be disregarded. In large populations, a single set of casual measurements has been found to predict a greater likelihood of

subsequent cardiovascular disease.[19] However, such elevated measurements do not necessarily predict either fixed hypertension or increased risk for each individual. For example, in one study only 10.8 percent of 719 men aged 18 to 30 with initial systolic values of 140 to 170 began to exhibit systolic pressures persistently above 140 over the next 12 to 15 years.[20] Nonetheless, persistently elevated pressures were found 2.3 times more often among those with initially high readings, obviously placing them at higher risk.

3. Systolic elevations pose a risk that is equal to or greater than that posed by diastolic elevations, and a wide pulse pressure is the most potent predictor of cardiovascular risk.[21] isolated systolic hypertension, as commonly seen among the elderly, presents a risk for both stroke and myocardial infarction.[19]
4. The elderly often have sclerotic brachial arteries that may not become occluded until very high pressures are exerted by the balloon; therefore, cuff diastolic levels may be considerably higher than those measured intraarterially. In patients with high cuff readings but little or no hypertensive retinopathy, cardiac hypertrophy, or other evidence of longstanding hypertension, "pseudohypertension" should be suspected and ruled out before treatment is begun.
5. Elderly persons with elevated systolic pressure should be monitored carefully for significant falls in pressure either with sudden upright posture or after meals.[22] These changes probably reflect a progressive loss of baroreceptor responsiveness with age. This condition makes the elderly particularly susceptible to marked orthostatic hypotension after even small decreases in vascular volume.

For the individual patient, hypertension can be definitively diagnosed when most readings are at a level known to be associated with a significantly higher cardiovascular risk without treatment. The recommendations of the Sixth Joint National Committee (JNC/6) are shown in Table 28-2 .[1] Note that systolic levels of 130 to 139 mm Hg and diastolic levels of 85 to 89 mm Hg are classified as *high normal blood pressure,* a recommendation stemming from prospective observations of over 420,000 people for 6 to 25 years wherein a doubling of the risk for stroke was seen among those with mean diastolic blood pressure of 85 mm Hg when compared with those with a mean of 76 mm Hg.[23] Therefore, persons with relatively high systolic or diastolic pressures should be advised that they may be at increased risk and counseled to follow better health habits in the hope of slowing the progression toward definite hypertension.

The criteria shown in Table 28-2 are based on at least three sets of measurements taken over at least a 3-month interval. Even more readings may be needed to establish a patient's usual level.

Even though they are diagnosed as hypertensive, not all persons with usual levels above 140/90 mm Hg need be treated with drugs, although all should be advised to use the various life style modifications described in Chapter 29 . As recommended in both the 1997 JNC-6 report[1] and the 1999 World Health Organization-International Society of Hypertension (WHO-ISH) guidelines,[24] the threshold for institution

TABLE 28-2 -- CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGED 18 YEARS AND OLDER*

	BLOOD PRESSURE (mm Hg)

CATEGORY	Systolic		Diastolic
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	180	or	N 110

*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressure levels fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mm Hg should be classified as stage 2 hypertension, and 174/120 mm Hg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as systolic blood pressure 140 mm Hg or greater and diastolic blood pressure less than 90 mm Hg and staged approximately (e.g., 170/82 mm Hg is defined as stage 2 isolated systolic hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify the presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment (see Table 28-5) .

Optimal blood pressure with respect to cardiovascular risk is less than 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.

Based on the average of two or more readings taken at each of two or more visits after an initial screening.

TABLE 28-3 -- NINTY-FIFTH PERCENTILE OF BLOOD PRESSURE BY SELECTED AGES IN GIRLS AND BOYS IN THE 50TH AND 75TH HEIGHT PERCENTILES

	GIRLS'SBP/DBP		BOYS' SBP/DBP	
AGE (yr)	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

Adapted from The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 157:2413, 1997. Copyright 1997, American Medical Association. DBP=diastolic blood pressure; SBP= systolic blood pressure.

of drug therapy should be based on the overall cardiovascular risk profile, as noted on p. 973 .

BORDERLINE HYPERTENSION.

In view of the usual variability in blood pressure levels, the term *labile* is inappropriate for describing diastolic pressures that only occasionally exceed 90 mm Hg. Instead, the term *borderline* should be used. In 30 to 40 percent of patients whose initial diastolic measurement exceeds 90 mm Hg, repeat readings taken soon after will be well below this value.[25] Such patients should be advised that their blood pressure level is *borderline elevated* and should be checked at least annually while they follow general health measures.

HYPERTENSION IN CHILDREN AND ADOLESCENTS (see also Chap. 45).

Upper limits of normal in children of various ages were proposed in the JNC-6 report[1] (Table 28-3) . Premature labeling of children whose readings are above these limits as hypertensive should be avoided since long-time tracking is only now being carried out.[26] Appropriate management for asymptomatic children with sustained elevations in blood pressure has not been established. Although many maintain similarly high readings over 3- to 4-year periods, most become normotensive. Such patients should be monitored carefully, with particular emphasis placed on regular exercise and weight reduction for those who are overweight in the hope of preventing progression of the disease. If life style modifications are not successful, antihypertensive agents should probably be prescribed for those with sustained hypertension.

PREVALENCE OF HYPERTENSION

From the criteria shown in Table 28-2 , the prevalence of hypertension in the United States rises progressively with age in both men and women[27] (Fig. 28-5) . The prevalence of hypertension among blacks is greater at every age beyond adolescence, and they have a higher proportion of more severe disease with a higher mortality rate than whites at every level of income.[28]

SECONDARY HYPERTENSION.

Among the large number of people with hypertension, it is helpful to know whether some secondary process--perhaps curable by surgery or more easily controlled by a specific drug--may be present (Table 28-4) so that the clinician can determine whether more definitive diagnostic testing is in order. Most surveys to determine the relative proportion of various secondary diseases are biased as a result of the selection process, with only

the increasingly suspect population "funneled" to an investigator interested in a particular disease. Thus, estimates as high as 20 percent for certain secondary forms of hypertension have been reported; however, these figures do not reflect the incidence in the population at large. Estimates more likely to be indicative of the situation in usual clinical practice are shown in Table 28-5 .[29] [30] [31] The closest approximation of usual medical practice is the survey by Rudnick and associates of middle-class white patients seen in a family practice in Hamilton, Ontario, Canada, from 1965 to 1974.[29] In this as in the other surveys, many of the

Figure 28-5 Prevalence of high blood pressure by age and race or ethnicity for men and women 18 years and older in the U.S. population. *Based on a sample size that did not meet the minimum requirements of the National Health and Nutrition Examination Survey (NHANES) III design or relative SEM greater than 30%. (Data from NHANES III. From Burt VL, Whelton P, Roccella EJ, et al: Prevalence of hypertension in the US adult population: Results from the Third National Health and Nutrition Examination Survey 1988-91. Hypertension 25:305-313, 1995.)

TABLE 28-4 -- TYPES OF HYPERTENSION

Systolic and Diastolic Hypertension
Primary, essential, or idiopathic
Identifiable (secondary)
Renal
Renal parenchymal disease
Acute glomerulonephritis
Chronic nephritis
Polycystic disease
Diabetic nephropathy
Hydronephrosis
Renovascular
Renal artery stenosis
Intrarenal vasculitis
Renin-producing tumors
Renoprival
Primary sodium retention (Liddle syndrome, Gordon syndrome)
Endocrine

- Acromegaly
- Hypothyroidism
- Hyperthyroidism
- Hypercalcemia (hyperparathyroidism)
- Adrenal
  - Cortical
    - Cushing syndrome
    - Primary aldosteronism
    - Congenital adrenal hyperplasia
    - Apparent mineralocorticoid excess (licorice)
  - Medullary: Pheochromocytoma
- Extraadrenal chromaffin tumors
- Carcinoid
- Exogenous hormones
  - Estrogen
  - Glucocorticoids
  - Mineralocorticoids
  - Sympathomimetics
  - Tyramine-containing foods and monoamine oxidase inhibitors

Coarctation of the aorta

Pregnancy-induced hypertension

Neurological disorders

- Increased intracranial pressure
  - Brain tumor
  - Encephalitis
  - Respiratory acidosis
- Sleep apnea
- Quadriplegia
- Acute porphyria
- Familial dysautonomia
- Lead poisoning
- Guillain-Barre syndrome

Acute stress, including surgery

- Psychogenic hyperventilation

Hypoglycemia
Burns
Pancreatitis
Alcohol withdrawal
Sickle cell crisis
Postresuscitation
Postoperative
Increased intravascular volume
Alcohol and drug use

Systolic Hypertension

Increased cardiac output
Aortic valvular insufficiency
Arteriovenous fistula, patent ductus
Thyrotoxicosis
Paget disease of bone
Beriberi
Hyperkinetic circulation
Rigidity of the aorta

patients underwent intravenous pyelography (IVP) in addition to providing a history and undergoing a physical examination and routine urine and blood tests. Although a few patients with secondary diseases may have been

TABLE 28-5 -- FREQUENCY OF VARIOUS DIAGNOSES IN HYPERTENSIVE SUBJECTS

DIAGNOSIS	RUDNICK ET AL.[29]	SINCLAIR ET AL.[30]	ANDERSON ET AL.[31] *
Essential hypertension	94%	92.1%	89.5%
Chronic renal disease	5%	5.6%	1.8%
Renovascular disease	0.2%	0.7%	3.3%
Coarctation of arota	0.2%		
Primary aldosteronism		0.3%	1.5%
Cushing syndrome	0.2%	0.1%	0.6%
Pheochromocytoma		0.1%	0.3%
Oral contraceptive induced	0.2%	1.0%	
No. of patients	665	3783	4429

Data from Rudnick KV, Sackett DL, Hirst S, Holmes C: Hypertension in family practice. Can Med Assoc J 117:492, 1977; Sinclair AM, Isles CG, Brown I, et al: Secondary hypertension in a blood pressure clinic. Arch Intern Med 147:1289, 1987; Anderson GH Jr, Blakemann N, Streeten DHP: The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. J Hypertens 12:609, 1994.

*The patients screened by Anderson and colleagues were referred for evaluation of secondary causes; those screened by Rudnick and Sinclair were all those seen in a primary setting.

missed, the similarity of data strongly supports the view that more than 90 percent of all hypertensive persons will have no recognizable cause; i.e., they have essential or primary hypertension.

THE CHANGING NATURE OF CHILDHOOD HYPERTENSION (see also p. 956).

Even among children, secondary hypertension is less common than indicated by previous surveys of hospital-based populations. As more apparently normal children are being screened and more are found to be hypertensive, the clinical manifestation of childhood hypertension is changing from that of a rare and serious disease, usually related to renal damage, to a more common and generally asymptomatic process, in most cases without recognizable cause.[26] Some prepubertal hypertensive children do not have recognizable secondary diseases, whereas most identified after puberty have primary hypertension.

SCREENING FOR SECONDARY HYPERTENSION

Because of the relatively low frequency of the various secondary diseases, the clinician should be selective in carrying out various screening and diagnostic tests. The presence of features *inappropriate* for the usual uncomplicated primary hypertension is an indication for additional tests (Table 28-6) . However, for the 9 in 10 hypertensive patients without these features, a hematocrit, urine analysis, automated blood biochemical profile (including plasma glucose, potassium, creatinine, and total and high-density lipoprotein cholesterol), and an electrocardiogram are all that is required. Although some would include other tests, an inordinate number of screening tests for relatively rare diseases will increase the likelihood of a false-positive result. For example, according to Bayes' theorem, at a prevalence rate of 2 percent for renovascular hypertension, which is probably higher than seen in the overall hypertensive population, the predictive

TABLE 28-6 -- FEATURES OF "INAPPROPRIATE" HYPERTENSION

Onset before age 20 or after age 50
Level of blood pressure >180/110 mm Hg
Organ damage
Funduscopic findings of grade 2 or higher
Serum creatinine >1.5 mg/100 ml
Cardiomegaly (on radiograph) or left ventricular hypertrophy (on electrocardiogram)
Features indicative of secondary causes
Unprovoked hypokalemia
Abdominal bruit
Variable pressures with tachycardia, sweating, tremor
Family history of renal disease
Poor response to therapy that is usually effective

value of an IVP or isotopic renogram suggestive of this diagnosis is only 10 percent, and an abnormal IVP or renogram is more likely to be a false-positive result than be true-positive and indicate a specific diagnosis.[32]

NATURAL HISTORY OF UNTREATED HYPERTENSION

A meta-analysis of nine major prospective observational studies involving 420,000 individuals free of known coronary or cerebral vascular disease at baseline who were monitored for 6 to 25 years (mean of 10 years) shows a "direct, continuous and apparently independent association" of diastolic blood pressure with both stroke and coronary heart disease[23] (Fig. 28-6) . The data indicate that prolonged increases in the usual diastolic pressure of 5 and 10 mm Hg were associated with at least 34 and 56 percent increases in stroke risk and with at least 21 and 37 percent increases in coronary heart disease risk, respectively.

SYMPTOMS AND SIGNS.

Because uncomplicated hypertension is almost always asymptomatic, a person may be unaware of the consequent progressive cardiovascular damage for as long as 10 to 20 years. Only if blood pressure is measured frequently and people are made aware that hypertension may be harmful even if asymptomatic will the majority of people with unrecognized or inadequately treated hypertension be managed effectively. Symptoms often attributed to hypertension--headache, tinnitus, dizziness, and fainting--may be observed just as commonly in the normotensive population. Moreover, many symptoms attributed to the elevated blood pressure are psychogenic in origin, often reflecting hyperventilation induced by anxiety over the diagnosis of a lifelong, insidious disease that threatens well-being and survival.[33] Even headache, long considered a frequent symptom of hypertension, is poorly related to the level of blood pressure, as noted in 10 to 20 percent of those with diastolic blood pressure levels from below 90 to above 120

mm Hg.[34]

COURSE OF UNTREATED HYPERTENSION.

As noted in Figure 28-6 , even minimal hypertension is accompanied by significant increases in coronary disease and stroke. However, these figures may be misleading since they seem to imply that most hypertensives, including those with minimally elevated pressure, will experience adverse consequences of hypertension, and rather quickly. The issue is well identified in the data from the Pooling Project,[35] which includes multiple prospective follow-up studies, including the Framingham cohort. These data indicate that white men with diastolic pressures of 80 to 87 mm Hg had a 52 percent greater *relative* risk of having a major coronary event over an 8.6-year period than did those with diastolic pressures below 80. However, this large increased *relative* risk translates to an *absolute* excess risk of only 3.5 men per 100 over the 8.6-year interval. Obviously, the majority of those with even higher diastolic pressures did not suffer a major coronary event.

Nonetheless, because so many persons have hypertension, the fact that even a minority of them will suffer a premature cardiovascular event in the course of their disease makes hypertension a major societal problem. In fact, when the death rates for various levels of diastolic blood pressure are multiplied by the proportion of people in the population who have these various levels, the majority of excess deaths attributable to hypertension are found to occur among those with minimally elevated pressure (see Fig. 28-2).

As the public and the medical profession have become aware of the overall societal consequences of even mild hypertension, enthusiasm for early recognition and aggressive treatment of hypertension has continued to mount. A closer look at the issue of deciding on the need for therapy is provided in Chapter 29 . However, further consideration of the natural course of hypertension, as it applies to the individual patient, is needed to answer a basic question: Are the blood pressure and the consequent risk high enough to justify medical intervention? Unless the risk is high enough to mandate some form of intervention, there seems to be no need to identify and label the person as hypertensive since psychological and socioeconomic burdens accompany this label; unless risks clearly outweigh these burdens, caution is obviously advised. A cogent view of this issue has been offered by Rose.[36]

> In reality the care of the symptomless hypertensive person is preventive medicine, not therapeutics. If a preventive mea- sure exposes many people to a small risk, the harm it does may readily . . . outweigh the benefits, since these are re- ceived by relatively few. . . . We may thus be unable to iden- tify that small level of harm to individuals from long-term in- tervention that would be sufficient to make that line of prevention unprofitable or even harmful. Consequently we cannot accept long-term mass preventive medication.

We are thus left with a dilemma: For hypertensive individuals as a group, even those with the least elevated pressures, risk is increased; for the individual hypertensive, the

risk may not justify the labeling or treatment of the condition.

ASSESSMENT OF INDIVIDUAL RISK

Guidelines are available to help practitioners resolve this dilemma in dealing with the individual patient. These guidelines are based on the overall assessment of cardiovascular risk and the biological aggressiveness of the hypertension. They are intended to apply only to those with stage 1 (formerly referred to as mild) hypertension, that is, diastolic

Figure 28-6 The relative risks of stroke and coronary heart disease (CHD), estimated from the combined results of prospective observational studies, for each of five categories of diastolic blood pressure (DBP). (Estimates of the usual DBP in each baseline DBP category are taken from mean DBP values 4 years postbaseline in the Framingham Study.) The solid squares represent disease risks in each category relative to risk in the whole study population; the sizes of the squares are proportional to the number of events in each DBP category, and 95 percent confidence intervals for the estimates of relative risk are denoted by vertical lines. (From MacMahon S, Peto R, Cutler J, et al: Blood pressure and coronary heart disease: Part 1, prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. Lancet 335:765, 1990. © by the Lancet Ltd., 1990.)

Figure 28-7 Estimated 10-year risk of coronary artery disease in hypothetical 55-year-old men and women according to levels of various risk factors. Lipid units are milligrams per deciliter. (From O'Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: Lessons from observational studies. J Hypertens 16(Suppl 6):3, 1998.)

pressure between 90 and 99 mm Hg; those with diastolic levels persistently at or above 100 mm Hg have been shown to be at high enough risk from the hypertension per se to justify immediate intervention. Recall, however, that most hypertensives are in the range between 90 and 99 mm Hg (see Fig. 28-2). On the other hand, patients at high overall cardiovascular risk even with high normal blood pressure are deemed to be in need of active drug therapy.[1]

OVERALL CARDIOVASCULAR RISK.

The Framingham Study and other epidemiological surveys have clearly defined certain risk factors for premature cardiovascular disease in addition to hypertension (see Chap. 31). For varying levels of blood pressure, the Framingham data (available in the *Coronary and Stroke Risk Handbooks* published by the American Heart Association) show the increasing likelihood of a vascular event over the next 10 years for both men and women at various ages as more and more risk factors are added.[19] For example, a 55-year-old man with a systolic blood pressure of 160 mm Hg who is otherwise at low

risk would have a 13.7 percent chance of a vascular event in the next 10 years (Fig. 28-7) . A man of the same age with the same pressure but with all the additional risk factors (elevated serum total cholesterol, low high-density lipoprotein cholesterol, cigarette smoking, glucose intolerance, and LVH on the electrocardiogram) has a 59.5 percent chance. Obviously, the higher the overall risk, the more intensive the interventions should be.

An interesting--and disturbing--connection between untreated hypertension and *hypercholesterolemia* has been noted in multiple populations.[37] This connection may be mediated through insulin resistance and hyperinsulinemia and is anticipated in those with upper body obesity[38] but may also be found in nonobese hypertensives. Clearly, through this association, hypertensives are often burdened with an even greater risk than that imposed by their blood pressure alone.

Complications of Hypertension

The higher the level of blood pressure, the more likely that various cardiovascular diseases will develop prematurely through acceleration of atherosclerosis, the pathological hallmark of uncontrolled hypertension. If untreated, about 50 percent of hypertensive patients die of coronary heart disease or congestive failure, about 33 percent of stroke, and 10 to 15 percent of renal failure. Those with rapidly accelerating hypertension die more frequently of renal failure, as do those who are diabetic once proteinuria or other evidence of nephropathy develops. It is easy to underestimate the role of hypertension in producing the underlying vascular damage that leads to these cardiovascular catastrophes. Death is usually attributed to stroke or myocardial infarction instead of to the hypertension that was largely responsible. Moreover, hypertension may not persist after a myocardial infarction or stroke.

In general, the vascular complications of hypertension can be considered as either "hypertensive" or "atherosclerotic" (Table 28-7) . The former are more directly caused by the increased blood pressure per se and can be prevented by lowering this level; the latter have more multiple causations. Although hypertension may represent the most significant of the known risk factors for atherosclerosis in quantitative terms, lowering blood pressure may not by itself halt the atherosclerotic process.

The path from hypertension to vascular disease probably involves three interrelated processes: *pulsatile flow, endothelial cell dysfunction,* and *smooth muscle cell hypertrophy.* Higher systolic pressures are probably more responsible for these changes than are lower diastolic levels, which provides an explanation for the closer approximation of cardiovascular risk to systolic pressure and pulse pressure.

These three interrelated processes are probably responsible for the arteriolar and arterial sclerosis that is the usual consequence of longstanding hypertension; the subsequent target organ damage (see below) should be included in the overall assessment of hypertension risk. Beyond damage to the eyes, heart, brain, and kidney, large vessels such as the aorta may be directly affected and be at risk for aneurysms and dissection.

Target Organ Damage

The biological aggressiveness of a given level of hypertension varies among individuals. This inherent propensity to induce vascular damage can best be ascertained by examination of the eyes, heart, and kidney.

FUNDUSCOPIC EXAMINATION.

As described by Keith and associates in 1939, vascular changes in the fundus reflect both hypertensive retinopathy and arteriosclerotic retinopathy[39] (see Fig. 4-1). The two processes first induce

TABLE 28-7 -- VASCULAR COMPLICATIONS OF HYPERTENSION

HYPERTENSIVE	ATHEROSCLEROTIC
Accelerated-malignant phase	Coronary heart disease
Hemorrhagic stroke	Sudden death
Congestive heart failure	Other arrhythmias
Nephrosclerosis	Atherothrombotic stroke
Aortic dissection	Peripheral vascular disease

Adapted from Smith WM: Treatment of mild hypertension. Results of a ten-year intervention trial. Circ Res 25(Suppl 1):98, 1977. By permission of the American Heart Association.

narrowing of the arteriolar lumen (grade 1) and then sclerosis of the adventitia and/or thickening of the arteriolar wall, visible as arteriovenous nicking (grade 2). Progressive hypertension induces rupture of small vessels, seen as hemorrhage and exudate (grade 3) and eventually papilledema (grade 4). The grade 3 and 4 changes are clearly indicative of an accelerated-malignant form of hypertension, whereas the lesser changes have been correlated with other evidence of target organ damage.[40]

CARDIAC INVOLVEMENT.

Hypertension places increased tension on the left ventricular myocardium that is manifested as stiffness and hypertrophy, which accelerates the development of atherosclerosis within the coronary vessels. The combination of increased demand and lessened supply increases the likelihood of myocardial ischemia and thereby leads to a higher incidence of myocardial infarction, sudden death, arrhythmias, and congestive failure in hypertensives (see Figs. 28-2 and Fig. 28-6).

Abnormalities in Left Ventricular Function.

Even before LVH develops, changes in both systolic and diastolic function may be seen. Those with minimally increased left ventricular muscle mass may have supernormal contractility as reflected by an increased inotropic state with a high percentage of fractional shortening and increased wall stress.[41] The earliest functional cardiac changes in hypertension are in left ventricular diastolic function, with prolongation and incoordination of isovolumic relaxation, a reduced rate of rapid filling, and an increase in the relative amplitude of the *a* wave, probably caused by increased passive stiffness[42] (see Chap. 15).

With increasing hemodynamic load, either systolic or diastolic dysfunction may evolve and progress to different forms of congestive heart failure[43] (Fig. 28-8) . In addition, impaired coronary flow reserve and thallium perfusion defects may be observed in hypertensives without obstructive coronary disease.[44] The syndrome of severe concentric hypertrophy with a small ventricular cavity leading to dyspnea and pulmonary congestion has been most frequently

Figure 28-8 Consequences of systolic and diastolic dysfunction related to hypertension. *A,* Systolic dysfunction and congestive heart failure caused by impaired ventricular contraction may occur late in the evolution of hypertensive heart disease. *B,* Diastolic dysfunction is the most common manifestation of the effect of hypertension on cardiac function and can also lead to congestive heart failure from increased filling pressures. LV = left ventricular. (From Shepherd RFJ, Zachariah PK, Shub C: Hypertension and left ventricular diastolic function. Mayo Clin Proc 64:1521, 1989. By permission of the Mayo Foundation.)

Figure 28-9 Mean left ventricular mass by sex and by systolic pressure, including participants taking antihypertensive medications. These data were obtained by M-mode echocardiograms taken on 2226 men and 2746 women aged 17 to 90 years in the Framingham Study, cohort examination 16 and offspring cycle 2, 1979 to 1983. (From Savage DD, Levy D, Danneberg AL, et al,: Association of echocardiographic left ventricular mass with body size, blood pressure and physical activity [the Framingham Study]. Am J Cardiol 65:371, 1990.)

reported in black hypertensive women.[45] Moreover, blacks are at a higher risk for progression to heart failure and death from left ventricular dysfunction than are similarly treated whites.[46]

Left Ventricular Hypertrophy.

Hypertrophy as a response to the increased afterload associated with elevated systemic vascular resistance can be viewed as necessary and protective up to a certain point. Beyond that point, a variety of dysfunctions accompany LVH.

In the past, LVH was recognized on electrocardiography (see Chap. 5) by increased

voltage of QRS complexes, intrinsicoid deflection over lead V_2 or V_3 greater than 0.06 seconds, and ST segment depression greater than 0.5 mm. Increasingly, echocardiography is being used (see Chap. 7) because it is much more sensitive in recognizing early cardiac involvement. By echocardiography, left ventricular mass is shown to progressively increase with increases in blood pressure[47] (Fig. 28-9) . Left ventricular mass is greater in those whose pressure does not fall during sleep because of a more persistent pressure load.[48]

The pathogenesis of LVH involves a number of variables other than the pressure load, one of which is hemodynamic volume load. Devereux and colleagues[48] found a closer correlation between left ventricular stroke volume and left ventricular mass with diastolic than with systolic blood pressure. Other determinants are obesity,[49] levels of sympathetic nervous system and renin-angiotensin activity, and whole blood viscosity, presumably by way of its influence on peripheral resistance. The correlation is much closer between LVH and pressure readings taken during the stress of work by ambulatory monitoring than between LVH and casual pressure readings.[50]

Different patterns of hypertrophy may evolve, often starting with asymmetrical left ventricular remodeling from isolated septal thickening, which has been noted in 22 percent of untreated hypertensives with normal total left ventricular mass.[51] The pattern of LVH may have important prognostic implications. In a 10-year follow-up of 253 hypertensives, all-cause mortality was higher and cardiovascular events were most frequent in those with *concentric* LVH.[52] The degree of increased muscle mass is a strong and independent risk factor for cardiac mortality over and above the extent of coronary artery disease.[47] In addition, the risk of ventricular arrhythmias is increased at least twofold in the presence of LVH.[53]

Since the presence of LVH may connote a number of deleterious effects of hypertension on cardiac function, a great deal of effort has been expended in showing that treatment of hypertension will cause LVH to regress. Treatment with all antihypertensive drugs except those that further activate sympathetic nervous system activity, e.g., direct vasodilators such as hydralazine when used alone, has been shown to cause LVH regression.[54] With regression, left ventricular function usually improves and cardiovascular morbidity decreases.[55]

Features of Coronary Artery Disease.

As detailed elsewhere (see Chap. 31), hypertension is a major risk factor for myocardial ischemia and infarction. Moreover, in the Framingham cohort, the prevalence of silent myocardial infarction was significantly increased in hypertensive subjects, and they were also more susceptible to silent ischemia and sudden death,[56] as well as having a greater risk for mortality after an initial myocardial infarction.[57] Beyond these multiple additional risks associated with hypertension, a higher incidence of cardiovascular mortality has also been recognized when elevated diastolic blood pressures are

reduced to levels below 80 mm Hg.[58] This J-shaped curve probably reflects a reduction in perfusion pressure through coronary vessels either narrowed or having impaired vasodilatory reserve in the presence of hypertrophied myocardium.

RENAL FUNCTION.

Renal dysfunction too subtle to be recognized may be responsible for the development of most cases of essential hypertension. As discussed on p. 952 , increased renal retention of salt and water may be a mechanism initiating primary hypertension, but the retention is so small that it escapes detection. With detailed study, both structural damage and functional derangements reflecting intraglomerular hypertension often reflected by microalbuminuria can be found in most hypertensive persons. Microalbuminuria in hypertensives has been correlated with both insulin resistance[59] and evidence of endothelial cell dysfunction.[60] As hypertension-induced nephrosclerosis proceeds, the plasma creatinine level begins to rise, and eventually, renal insufficiency with uremia may develop, thus making hypertension a leading cause of end-stage renal disease (ESRD), particularly in blacks.[61]

CEREBRAL INVOLVEMENT.

Hypertension may accelerate cognitive decline with age.[62] Hypertension, particularly systolic, is a major risk factor for initial and recurrent stroke and for transient ischemic attacks caused by extracranial atherosclerosis.[63] Usually with, but sometimes without, hypertension, increasing left ventricular mass on echocardiography is associated with a progressively higher risk for stroke.[64] Blood pressure usually rises further during the acute phases of a stroke, and caution is advised in lowering blood pressure during this crucial period.

On the basis of the aforementioned assessments of overall cardiovascular risk and severity of hypertension, it should be possible to determine the approximate risk status and prognosis for individual patients, which can most easily be accomplished with the Framingham data, as described on page 948 .

SHORT-TERM COURSE OF LOW-RISK HYPERTENSION.

Data on the 4-year experiences of over 1600 "low-risk" hypertensives who served as controls in the Australian Therapeutic Trial document the validity of this assessment.[65] To enter this placebo-versus-drug trial, the patients had to be free of all identifiable cardiovascular disease, with the second set of diastolic pressures between 95 and 109 mm Hg. Thus, they could be considered "low-risk" hypertensives. Over the next 4 years, in the majority of these patients, who were given placebo tablets but neither nondrug nor drug therapy, blood pressures *dropped progressively* from an average of 157/102 to 144/91 mm Hg. Diastolic pressure was below 95 mm Hg in 47.5 percent at the end of the trial. The fall in blood pressure was not related to any recognizable change in the patients' status; similar decreases occurred independent of changes in or stability of body weight. Of great interest was the lack of excess morbidity and mortality among

those whose diastolic pressure remained below 100 mm Hg.

These results strongly support the view that certain patients can be characterized as being at relatively low risk and can therefore safely do without drug therapy long enough for the clinician to monitor both their blood pressure levels over time and the effectiveness of nondrug measures, if indicated. The large number of patients whose pressure fell and the high average degree of fall may seem surprising, but none of these patients started with any identifiable cardiovascular disease or complications of hypertension. Moreover, placebo may be more effective than no therapy.

THE POTENTIAL FOR PROGRESSION.

Although these data reflect the benign nature of "low-risk" hypertension over the short term, it should be noted that diastolic blood pressure rose above 110 mm

TABLE 28-8 -- COMPONENTS OF CARDIOVASCULAR RISK STRATIFICATION IN PATIENTS WITH HYPERTENSION

Major Risk Factors
Smoking
Dyslipidemia
Diabetes mellitus
Age >60 yr
Sex (men and postmenopausal women)
Family history of cardiovascular disease:
Women <65 yr or men >55 yr
Target Organ Damage/Clinical Cardiovascular Disease
Heart diseases
Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure
Stroke or transient ischemic attack
Nephropathy
Peripheral arterial disease
Retinopathy

From The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 157:2413. 1997. Copyright 1997, American Medical Association.

Hg in 12 percent of the non-drug-treated patients in the Australian trial. Therefore, continued monitoring of blood pressure levels is obviously needed for all patients with even the mildest "low-risk" hypertension.

A SYNTHESIS OF RISK.

As first clearly articulated by a group of New Zealand physicians,[66] the degree of risk from hypertension can be categorized with reasonable accuracy by taking into account (1) the level of blood pressure, (2) the biological nature of the hypertension based on the degree of target organ damage, and (3) the coexistence of other risks. The JNC-6 report provides a stratification of risk into three groups based on known components of risk (Table 28-8) and levels of blood pressure, which are, in turn, used as the basis for deciding upon initial treatment (Table 28-9) . According to this stratification, active drug therapy is recommended for high-risk patients even if blood pressure is only high normal, whereas life style modifications are recommended for low-risk patients even if blood pressure is as high as 159/99 mm Hg. Similar recommendations have been made in the 1999 WHO-ISH guidelines.[24]

It is obvious that since the course of the blood pressure cannot be predicted with certainty, even hypertensives who are not treated should be monitored, and recognition of their hypertension should motivate them to follow good health habits. In this way, no harm should be done, and the potential benefit may be considerable if progression of the disease can be slowed by life style modifications.

MECHANISMS OF PRIMARY (ESSENTIAL) HYPERTENSION

No single or specific cause is known for most hypertension, and the condition is referred to as *primary* in preference to *essential.* Since persistent hypertension can develop only in response to an increase in cardiac output or a rise in peripheral resistance, defects may be present in one or more of the multiple factors that affect these two forces (Fig. 28-10) . The interplay of various derangements in factors affecting cardiac output and peripheral resistance may precipitate the disease, and these abnormalities may differ in both type and degree in different patients.

TABLE 28-9 -- RISK STRATIFICATION AND TREATMENT*

BLOOD PRESSURE STAGES (mm Hg)	RISK GROUP A (NO RISK FACTORS: NO TOD/CCD)	RISK GROUP B (AT LEAST 1 RISK FACTOR, NOT INCLUDING DIABETES: NO TOD/CCD)	RISK GROUP C (TOD/CCD AND/OR DIABETES, WITH OR WITHOUT OTHER RISK FACTORS)
High normal (130-139/85-89)	Life style modification	Life style modification	Drug therapy
Stage 1 (140-159/90-99)	Life style modification (up to 12 mo)	Life style modification (up to 6 mo)	Drug therapy

Stages 2 and 3 (>160/>100)	Drug therapy	Drug therapy	Drug therapy

CCD=clinical cardiovascular disease; TOD=target organ disease.*From The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 157:2413. 1997. Copyright 1997, American Medical Association.*

*Note: For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as "stage 1, risk group C," and recommended for immediate initiation of pharmacological treatment. Life style modification should be adjunctive therapy for all patients recommended for pharmacological therapy.

Hemodynamic Patterns

Before describing specific abnormalities in the various factors shown in Figure 28-10 to affect the basic equation blood pressure = cardiac output × peripheral resistance (BP = CO × PR), the hemodynamic patterns that have been measured in patients with hypertension will be considered. One cautionary factor should be kept in mind: Development of the disease is slow and gradual. By the time that blood pressure becomes elevated, the initiating factors may no longer be apparent because they may have been "normalized" by multiple compensatory interactions. Nonetheless, when a group of untreated young hypertensive patients was studied initially, cardiac output was normal or slightly increased and peripheral resistance was normal.[67] Over the next 20 years, cardiac output fell progressively while peripheral resistance rose. In a much larger study involving over 2600 subjects in Framingham who were monitored for 4 years by echocardiography, an increased cardiac index and end-systolic wall stress were related to the development of hypertension,[68] and in a 10-year follow-up of 4700 young people, an increased heart rate, presumably associated with a reflection of increased cardiac output, has been found to be a predictor of future hypertension.[69]

Regardless of how hypertension begins, the eventual primacy of increased resistance can be shown even in models of hypertension that feature an initial increase in fluid volume and cardiac output.[6]

Genetic Predisposition

As discussed in Chapter 56 and shown in Fig. 28-10 , genetic alterations may initiate the cascade to permanent hypertension. In studies of twins and family members in which the degree of familial aggregation of blood pressure levels is compared with the closeness of genetic sharing, the genetic contributions have been estimated to range from 30 to 60 percent.[70] Unquestionably, environment plays some role, and Harrap[70] offers as a working model an interaction between genes and environment "in which the average population pressure is determined by environment, but blood pressure rank

within the distribution is decided largely by genes."

Three rare forms of hypertension have been found to be

Figure 28-10 Some of the factors involved in the control of blood pressure that affect the basic equation Blood pressure = cardiac output (CO) × peripheral resistance (PR). Cellular hyperplasia may be seen along with hypertrophy. (From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 45.)

caused by a monogenic abnormality: glucocorticoid-remediable aldosteronism, Liddle syndrome, and apparent mineralocorticoid excess.[71] In addition, polymorphism of genes involving the renin-angiotensin system,[72] aldosterone synthesis,[73] and adrenergic receptors[74] has been noted to be more common in hypertensive than normotensive patients.

If genetic markers of a predisposition for the development of hypertension are found, specific environmental manipulations could then be directed toward susceptible subjects.[75] For now, children and siblings of hypertensives should be more carefully screened. They should be vigorously advised to avoid environmental factors known to aggravate hypertension and increase cardiovascular risk (e.g., smoking, inactivity, and excess sodium).

The Fetal Environment

Environmental factors may come into play very early. Low birth weight as a consequence of fetal undernutrition is followed by an increased incidence of high blood pressure later in life.[76] Brenner and Chertow hypothesized that a decreased number of nephrons from intrauterine growth retardation could very well serve as this permanent, irreparable defect that eventuates in hypertension [77] (Fig. 28-11) . In their words:

> This hypothesis draws on observations suggesting (1) a direct relationship between birth weight and nephron number, (2) an inverse relationship between birth weight and childhood, adolescent, and adult blood pressures, and (3) an inverse relationship between nephron number and blood pressure, irrespective of whether neph- ron number is reduced congenitally or in postnatal life (as from partial renal ablation or acquired renal disease).

This hypothesis fits nicely with Brenner's explanation for the inexorable progression of renal damage once it begins and the concept that hypertension may begin by renal sodium retention induced by the decreased filtration surface area.[78]

Renal Retention of Excess Dietary Sodium

A considerable amount of circumstantial evidence supports a role for sodium in the genesis of hypertension (Table 28-10) . To induce hypertension, some of that excess sodium must be retained by the kidneys. Such retention could arise in a number of ways, including

Figure 28-11 The risk of essential hypertension and progressive renal injury developing in adult life is increased as a result of congenital oligonephropathy, an inborn deficit of filtration surface area (FSA) caused by impaired renal development. Low birth weight resulting from intrauterine growth retardation or prematurity contributes to this oligonephropathy. Systemic and glomerular hypertension in later life results in progressive glomerular sclerosis, further reducing FSA and thereby perpetuating a vicious cycle that leads, in the extreme, to end-stage renal failure. (From Brenner BM, Chertow GM: Congenital oligonephropathy: An inborn cause of adult hypertension and progressive renal injury? Curr Opin Nephrol Hypertens 2:691, 1993.)

TABLE 28-10 -- EVIDENCE FOR A ROLE OF SODIUM IN PRIMARY (ESSENTIAL) HYPERTENSION

In multiple populations, the rise in blood pressure with age is directly correlated with increasing levels of sodium intake.
Multiple, scattered groups who consume little sodium (less than 50 mmol/d) have little or no hypertension. When they consume more sodium, hypertension appears.
Hypertension develops in animals given sodium loads, if genetically predisposed.
In some people, large sodium loads given over short periods cause an increase in vascular resistance and blood pressure.
An increased concentration of sodium is present in the vascular tissue and blood cells of most hypertensives.
Sodium restriction to a level below 100 mmol/d will lower blood pressure in most people. The antihypertensive action in diuretics requires an initial natriuresis.

A decrease in filtration surface by a congenital or acquired deficiency in nephron number or function.[78]

A resetting of the normal pressure-natriuresis relationship wherein a rise in pressure invokes an immediate increase in renal sodium excretion, thereby shrinking fluid volume and returning the pressure to normal. Guyton has long argued for a resetting of this relationship as a fundamental defect that must be present to explain the persistence of elevated pressure.[79]

Nephron heterogeneity, which is hypothesized by Sealey and coworkers[80] as the presence of "a subpopulation of nephrons that is ischemic either from afferent arteriolar vasoconstriction or from an intrinsic narrowing of the lumen. Renin

secretion from this subgroup of nephrons is tonically elevated. This increased renin secretion then interferes with the compensatory capacity of intermingled normal nephrons to adaptively excrete sodium and, consequently, perturbs overall blood pressure homeostasis."

An acquired inhibitor of the sodium pump[81] or other abnormalities in sodium transport.[82]

Deficient responsiveness to atrial natriuretic hormone.[83]

Thus, more than enough ways are available to incite renal retention of even a very small bit of the excess sodium typically ingested that could eventually expand body fluid volume. Variations in sensitivity to sodium have also been noted and may explain why only some people respond to excess sodium and others do not.[84]

Those who are more sodium sensitive have been found to have more markers of endothelial damage,[85] nondipping of nocturnal blood pressure, [86] and increased mortality[87] than do those who are less sodium sensitive. Sodium sensitivity is more common among normotensive blacks and is associated with sodium-induced renal vasoconstriction.[88] Both the pressor sensitivity and renal vasoconstriction were reversed by increased intake of potassium bicarbonate, thus supporting a role for reduced potassium intake as a contributor to the excess number of cases of hypertension found in people of low-socioeconomic status.[89]

Vascular Hypertrophy

Both excess sodium intake and renal sodium retention would presumably work primarily on increasing fluid volume and cardiac output. A number of other factors may work primarily on the second part of the equation BP = CO × PR (see Fig. 28-10). Most of these factors can cause both functional contraction and structural remodeling and hypertrophy.

Multiple vasoactive substances act as growth factors for vascular hypertrophy. These pressor-growth promoters may result in both vascular contraction and hypertrophy simultaneously,

but perpetuation of hypertension involves hypertrophy. Various hormonal mediators may serve as the initiator of what eventuates as increased peripheral resistance. From the study of certain "pure" forms of hormonally induced hypertension, Lever and Harrap[90] have postulated that

Most forms of secondary hypertension have two pressor mecha- nisms: a primary cause, e.g., renal clip, and a second process, which is slow to develop, capable of maintaining hypertension after removal of the primary

> cause, and probably self-perpetuating in nature. We suggest that essential hypertension also has two mechanisms, both based upon cardiovascular hypertrophy: (1) a growth-promoting process in children (equivalent to the primary cause in secondary hypertension) and (2) a self-perpetuating mechanism in adults.

These investigators have built on the original proposal of Folkow[91] of a "positive feedback interaction" wherein even mild functional pressor influences, if repeatedly exerted, may lead to structural hypertrophy, which in turn reinforces and perpetuates the elevated pressure (Fig. 28-12) . Lever and Harrap[90] have added two hypotheses to Folkow's first: a reinforcement of the hypertrophic response to stimuli that initially raise the pressure, e.g., defects in the vascular cell membrane, and the action of various trophic mechanisms that may cause vascular hypertrophy directly (the "slow pressor mechanism").

This scheme to explain an immediate pressor action and a slow hypertrophic effect is thought to be common to the action of pressor-growth promoters. When present in high concentrations over long periods, as with angiotensin II in renal artery stenosis, each of these pressor-growth promoters causes hypertension. Moreover, when the source of the excess pressor-growth promoter is removed, hypertension may recede slowly, presumably reflecting the time needed to reverse vascular hypertrophy.

No marked excess of any known pressor hormone is identifiable in the majority of hypertensive patients. Nonetheless, a lesser excess of one or more may have been responsible for initiation of a process sustained by the positive feedback postulated by Folkow[91] and the trophic effects emphasized by Lever and Harrap.[90] This sequence encompasses a variety of specific initiating mechanisms that accentuate and maintain the hypertension by a nonspecific feedback-trophic mechanism (Fig. 28-12) . If this double process is fundamental to the pathogenesis of primary hypertension, the difficulty in recognizing the initiating causal factor is easily explained. As formulated by Lever[92]

> The primary cause of hypertension will be most apparent in the early stages; in the later stages, the cause will be con- cealed by an increasing contribution from hypertrophy... A particular form of hypertension may wrongly be judged to have "no known cause" because each mechanism considered is insufficiently abnormal by itself to have produced the hypertension. The cause of essential hypertension may have been considered already but rejected for this reason.

Figure 28-12 Hypotheses for the initiation and maintenance of hypertension. *A,* Folkow's first proposal that minor overactivity of a pressor mechanism (A) raises blood pressure slightly, which initiates positive feedback (BCB) and a progressive rise in blood pressure. *B,* As in *A* with two additional signals: D, an abnormal or "reinforced" hypertrophic response to pressure; and E, increase in a humoral agent causing hypertrophy directly. (From Lever AF and Harrap SB: Essential hypertension: A disorder of growth with origins in childhood? J Hypertens 10:101, 1992.)

Neurohumoral Causes of Primary Hypertension

A large number of circulating hormones and locally acting substances may be involved in the development of hypertension. Support exists for each of those shown as potential instigators in Figure 28-10 . They will be considered in the order shown without attempting to prioritize their role. In addition to these hypertrophic changes, capillary rarefaction[93] and impaired microvascular dilation [94] may also be involved in the pathogenesis of hypertension.

Sympathetic Nervous Hyperactivity

Young hypertensives tend to have increased levels of circulating catecholamines, augmented sympathetic nerve traffic in muscles, faster heart rate,[69] and heightened vascular reactivity to alpha-adrenergic agonists.[95] These changes could raise blood pressure in a number of ways--either alone or in concert with stimulation of renin release by catecholamines--by causing arteriolar and venous constriction, by increasing cardiac output, or by altering the normal renal pressure-volume relationship. In addition to cardiac stimulation by sympathetic activity, vagal inhibitory responses to baroreceptors and other stimuli may also be important. In humans with denervated transplanted hearts, both pulse and blood pressure fail to display the usual nocturnal fall, and hypertension is frequent.[96] The transient increase in epinephrine during stress reactions may invoke a more prolonged pressor response by facilitating the release of norepinephrine from sympathetic neurons but this mechanism could not be demonstrated in humans.[97]

Repetitive stress or an accentuated, exaggerated response to stress is the logical means by which sympathetic activation would arise. Young hypertensives tend to be hyperresponsive,[95] and at least among middle-aged men in Framingham, the development of hypertension over an 18- to 20-year period was associated with heightened anxiety and anger intensity and suppressed expression of anger at baseline.[98] Moreover, in the 29-year-old normotensives in the Tecumseh Blood Pressure study, increased sympathetic activity was closely correlated with higher hematocrit levels, presumably reflecting a decrease in plasma volume from vasoconstriction[99]

The Tecumseh subjects with higher plasma catecholamine levels also tended to have higher plasma renin activity (PRA). Other investigators have noted that hypertensives with high PRA had more anxiety, suppressed anger, and susceptibility to emotional distress.[100] Obviously, the sympathetic and renin mechanisms may be connected in various ways.

Sympathetic nervous activity could be activated from the brain without the mediation of stress or emotional distress. Hypertension has been induced in animals by various neurogenic defects. An intriguing association has been reported but not documented between essential hypertension and compression of the ventrolateral medulla by loops of the posterior inferior cerebellar artery or an ectatic vertebral artery seen by magnetic

resonance tomography.[101]

Whatever the specific role of sympathetic activity in the pathogenesis of hypertension, it appears to be involved in the increased cardiovascular morbidity and mortality that affect hypertensive patients during the early morning hours. Increased alpha-sympathetic activity occurs in the early morning in association with the preawakening increase in rapid eye movement (REM) sleep and the assumption of upright posture after overnight recumbency.[102] As a consequence of the increased sympathetic activity, blood pressure rises abruptly and markedly. This rise must be at least partly responsible for the increase in cardiovascular catastrophes in the early morning hours.[14]

Renin-Angiotensin System

Both as a direct pressor and as a growth promoter, the renin-angiotensin mechanism may also be involved in the pathogenesis of hypertension. All functions of renin are mediated through the synthesis of angiotensin II. This system is the primary stimulus for the secretion of aldosterone and hence mediates mineralocorticoid responses to varying sodium intake and volume load. When sodium intake is reduced or effective plasma volume shrinks, the increase in renin-angiotensin II stimulates aldosterone secretion, which in turn is responsible for a portion of the enhanced

Figure 28-13 Overall scheme of the renin-angiotensin mechanism indicating the site of action of angiotensin II type I receptor antagonist.

renal retention of sodium and water (Fig. 28-13) . As noted elsewhere (see Chap. 64), aldosterone may have additional roles including a contribution to myocardial fibrosis and to baroreceptor dysfunction.[103]

According to the feedback shown in Fig. 26-13 , any rise in blood pressure inhibits release of renin from the renal juxtaglomerular cells. Therefore, primary (essential) hypertension would be expected to be accompanied by low, suppressed levels of PRA. However, when large populations of hypertensives are surveyed, only about 30 percent have low PRA, whereas 50 percent have normal levels and the remaining 20 percent have high levels.[104]

NORMAL- AND HIGH-RENIN HYPERTENSION

A number of explanations have been offered for these "inappropriately normal" or high levels, beyond the proportion expected in a normal gaussian distribution curve. One of the more attractive is the concept of "nephron heterogeneity" described by Sealey and colleagues,[80] which assumes a mixture of normal and ischemic nephrons caused by

afferent arteriolar narrowing. Excess renin from the ischemic nephrons could raise the total blood renin level to varying degrees and cause some persons to have normal- or high-renin hypertension.

This hypothesis is similar to that proposed by Goldblatt, who believed that "the primary cause of essential hypertension in man is intrarenal obliterative vascular disease, from any cause, usually arterial and arteriolar sclerosis, or any other condition which brings about the same disturbance of intrarenal hemodynamics."[105] When Goldblatt placed the clamp on the main renal arteries in canine studies, he was trying to explain the pathogenesis of primary (essential) hypertension rather than what he ended up explaining: the pathogenesis of renovascular hypertension. Nonetheless, his experimental concept is the basis for the more modern model of Sealey and colleagues. The elevated renin from the ischemic population of nephrons, although diluted in the systemic circulation, provides the "normal" renin levels that are usual in patients with primary hypertension who would otherwise be expected to shut down renin secretion and in whom levels would be low. These diluted levels are still high enough to impair sodium excretion in the nonischemic hyperfiltering nephrons but are too low to support efferent tone in the ischemic nephrons, thereby reducing sodium excretion in them as well.

Sealey and associates' concept of nephron heterogeneity differs from Brunner and associates' concept of nephron scarcity previously noted.[105] Nevertheless, Sealey and colleagues agree that "a reduction in nephron number related to either age or ischemia could amplify the impaired sodium excretion and promote hypertension."[80]

The renin-angiotensin system is active in multiple organs, either from in situ synthesis of various components or by transport from renal juxtaglomerular cells through the circulation. Most of the important pathophysiological effects are mediated through the angiotensin II type I receptor,[106] but some effects may involve the type II receptor[107] (Fig. 28-13) . The presence of the complete system in endothelial cells, the brain, the heart, and the adrenal cortex[108] broadens the potential roles of this mechanism far beyond its previously accepted boundaries.

Hyperinsulinemia/Insulin Resistance

An association between hypertension and hyperinsulinemia has been recognized for many years, particularly with accompanying obesity but also in nonobese hypertensives.[37] The association does not apply to some ethnic groups such as Pima Indians, but it has been found in blacks and Asians, as well as whites.

All obese people are hyperinsulinemic secondary to insulin resistance and even more so if the obesity is predominantly visceral, i.e., abdominal or upper body, wherein decreased hepatic uptake of insulin contributes to the hyperinsulinemia. The hyperinsulinemia of hypertension also arises as a consequence of resistance to the effects of insulin on peripheral glucose utilization.[109] The cause of the insulin resistance is unknown. It could reflect a simple inability of insulin to reach skeletal muscle cells, wherein its major peripheral actions on glucose metabolism occur. This impairment may in turn result from a defect in the usual vasodilatory effect of insulin mediated through

increased synthesis of nitric oxide (NO), which normally counters the multiple pressor effects of insulin[110] (Fig. 28-14) . These pressor effects, in addition to activation of sympathetic activity, include a trophic action on vascular hypertrophy, increased renal sodium reabsorption, and structural changes in the myocardium.[111]

Figure 28-14 *Left,* Insulin's actions in normal humans. Although insulin causes a marked increase in sympathetic neural outflow, which would be expected to increase blood pressure, it also causes vasodilation, which would decrease blood pressure. The net effect of these two opposing influences is no change or a slight decrease in blood pressure. There may be an imbalance between the sympathetic and vascular actions of insulin in conditions such as obesity or hypertension. *Right,* Insulin may cause potentiated sympathetic activation or attenuated vasodilation. An imbalance between these pressor and depressor actions of insulin may result in elevated blood pressure. (From Anderson EA, Mark AL: Cardiovascular and sympathetic actions of insulin: The insulin hypothesis of hypertension revisited. Cardiovasc Risk Factors 3:159, 1993.)

Figure 28-15 Endothelium-derived vasoactive substances. Various blood- and platelet-derived substances can activate specific receptors (open circles) on the endothelial membrane to release relaxing factors such as nitric oxide (NO), prostacyclin (PGI_2), and an endothelium-derived hyperpolarizing factor (EDHF). Other contracting factors are released, such as endothelin-1 (ET-1), angiotensin (A), and thromboxane A_2 (TXA_2), as well as prostaglandin H_2 (PGH_2). ACE = angiotensin-converting enzyme; Ach = acetylcholine; 5HT = 5-hydroxytryptamine, or serotonin; BK = bradykinin; ECE = endothelin-converting enzyme; L -Arg = L - arginine; NOS = nitric oxide synthase; O_2^- = superoxide; TGF-beta = transforming growth factor-beta; Thr = thrombin. (From Ruschitzka F, Corti R, Noll G, Luscher TF: A rationale for treatment of endothelial dysfunction in hypertension. J Hyperten 17(Suppl 1):25-35, 1999.)

The failure of vasodilation to antagonize the multiple pressor effects of insulin presumably eventuates in a rise in blood pressure that may be either a primary cause of hypertension or, at least, a secondary potentiator. In addition, the underlying insulin resistance is often associated with a full syndrome, including dyslipidemia and diabetes along with hypertension, which combine to be a major risk factor for premature coronary disease.[37]

Endothelial Cell Dysfunction

The impairment of normal vasodilation seen in the insulin resistance syndrome has been shown to involve failure to synthesize the normal endothelium-derived relaxing factor NO.[112] Lack of NO synthesis is one of the rapidly increasing pieces of evidence for an active role for endothelial cells, now known to be the source of multiple relaxing and constricting substances, most having a local, paracrine influence on underlying smooth muscle cells (Fig. 28-15) .

NITRIC OXIDE (see Chap. 34).

Hypertensive patients have been shown to have a reduced vasodilatory response to various stimuli of NO release that appears to be independent of the etiology of the hypertension and the degree of gross vascular structural alteration.[113] [114] Impaired NOmediated vasodilation may promote abnormal vascular remodeling[115] and may be involved in the greater propensity for vascular damage in blacks than in white.[116] NO-mediated forearm responsiveness has been restored by normalization of blood pressure by antihypertensive drugs with different modes of action.[117]

ENDOTHELIN.

A number of endothelium-derived constricting factors are shown in the middle portion of Fig. 28-15 . Of these, endothelin-1 appears to be of particular importance because it causes pronounced and prolonged vasoconstriction and because inhibitors of its synthesis or binding cause significant vasodilation.[118] Its role in human hypertension, however, remains uncertain.

OTHER POSSIBLE MECHANISMS

The preceding description of the possible roles of the various mechanisms portrayed in Figure 28-10 does not exhaust the list of putative contributors to the pathogenesis of primary hypertension.

The role of other pressor hormones in human hypertension remains unknown. Similarly, a number of vasodepressor hormones are known, but their function, too, remains uncertain. These hormones include kallikrein,[119] medullipin, a renomedullary lipid,[120] and adrenomedullin.[121]

Contributions from excesses of various minerals, particularly lead,[122] and changing ratios among dietary sodium, potassium, calcium, and magnesium have also been postulated.[123] Support for these and other proposed mechanisms is meager, and the overall schemes involving intracellular sodium and calcium and the pressor-growth promoter mechanisms for vascular hypertrophy seem more than adequate to explain the pathogenesis of primary hypertension. However, a number of associations between hypertension and other conditions have been noted and may offer additional insight into the potential causes and possible prevention of the disease.

ASSOCIATION OF HYPERTENSION WITH OTHER CONDITIONS

OBESITY.

Hypertension is more common among obese individuals and adds to their increased risk for ischemic heart disease, particularly if it is abdominal or visceral in location.[124] In the Framingham offspring study, adiposity, as measured by subscapular skinfold thickness,

was the major controllable contributor to hypertension.[125] Even small amounts of weight gain are associated with a marked increase in the incidence of hypertension[126] and coronary mortality.[127] Unfortunately, there is a worldwide epidemic of obesity, perhaps most widespread in the United States, where the prevalence of obesity, defined as a body mass index above 30, increased by 50 percent from 1980 to 1995.[128] Obesity is rapidly increasing among U.S. children, and children seem particularly vulnerable to the hypertensive effects of weight gain.[26] Therefore, avoidance of childhood obesity in the hope of avoiding subsequent hypertension is important. The evidence that weight reduction will lower established hypertension is discussed on p. 976 .

SLEEP APNEA.

One of the contributors to the hypertension in obese persons is sleep apnea. Snoring and sleep apnea are often associated with hypertension, which may in turn be induced by increased sympathetic activity and

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endothelin release in response to hypoxemia during apnea.[129]

PHYSICAL INACTIVITY.

Physical fitness may help prevent hypertension, and persons who are already hypertensive may lower their blood pressure by means of regular isotonic exercise. The relationship may involve insulin resistance because increased resistance was coupled with low physical fitness in normotensive men with a family history of hypertension.[130] Regular exercise may prevent hypertension and thereby protect against the development of cardiovascular disease. Among 16,936 Harvard male alumni monitored for 16 to 50 years, those who did not engage in vigorous sports play were at 35 percent greater risk for the development of hypertension regardless of whether they had higher blood pressures while at Harvard, a family history of hypertension, or obesity--factors that also increased the risk of hypertension.[131]

ALCOHOL INTAKE.

Alcohol in small amounts (less than two usual portions a day) provides protection from coronary disease, stroke, and atherosclerosis[132] but in larger amounts (more than two portions a day and even more so when drunk in binges), alcohol increases blood pressure.[133] The reduction in coronary disease in persons who ingest small amounts of alcohol may reflect an improvement in lipid profile, a reduction in factors that encourage thrombosis, and an improvement in insulin sensitivity.[134]

The pressor effect of larger amounts of alcohol primarily reflects an increase in cardiac output and heart rate, possibly a consequence of increased sympathetic nerve activity.[135] Alcohol also alters cell membranes and allows more calcium to enter,

perhaps by inhibition of sodium transport.[136]

SMOKING (see also p. 976).

Cigarette smoking raises blood pressure, probably through the nicotine-induced release of norepinephrine from adrenergic nerve endings. In addition, smoking causes an acute and marked reduction in radial artery compliance independent of the increase in blood pressure.[137] When smokers quit, a trivial rise in blood pressure may occur, probably reflecting a gain in weight.

HEMATOLOGICAL FINDINGS.

Polycythemia vera is frequently associated with hypertension (see Chap. 69). More common is a "pseudo-" or "stress" polycythemia with a high hematocrit[99] and increased blood viscosity but contracted plasma volume, as well as normal red cell mass and serum erythropoietin levels. High white blood cell counts are predictive of the development of hypertension.[138]

HYPERURICEMIA.

Hyperuricemia is present in 25 to 50 percent of individuals with untreated primary hypertension, about five times the frequency found in normotensive persons. Hyperuricemia probably reflects decreased renal blood flow, presumably a reflection of nephrosclerosis. In addition to these conditions often associated with hypertension, distinctive features of hypertension may be important in various special groups of people.

HYPERTENSION IN SPECIAL GROUPS

Blacks

Although, on average, blood pressure in blacks is not higher than that in whites during adolescence,[26] adult blacks have hypertension more frequently, with higher rates of morbidity and mortality. These higher rates may reflect a higher incidence of low birth weight from intrauterine growth retardation[76] a lesser tendency for the pressure to fall during sleep,[139] greater degrees of LVH, [46] and impaired NO-induced vasodilation,[116] but the lower socioeconomic status and lesser access to adequate, health care of blacks as a group are probably more important.[28] In particular, blacks suffer more renal damage, even with effective blood pressure control, which leads to a significantly greater prevalence of end-stage disease.[61] When given a high-sodium diet, most blacks but not whites tend to have renal vasoconstriction[88] and an increase in the glomerular filtration rate (GFR),[140] thus providing a possible mechanism for increased glomerular sclerosis.[140] Hypertension in blacks has been characterized as having a relatively greater component of fluid volume excess, including a higher prevalence of low PRA and greater responsiveness to diuretic therapy.[84]

Perhaps blacks evolved the physiological machinery that would offer protection in their ancestral habitat, i.e., hot, arid climates in which avid sodium conservation was necessary for survival because the diet was relatively low in sodium. When they migrate to areas where sodium intake is excessive, they are then more susceptible to "sodium overload." In addition, blacks may also be more susceptible to hypertension because as a group they tend to ingest less potassium.[89]

Women

In general, women suffer less cardiovascular morbidity and mortality than men do for any degree of hypertension.[19] Moreover, before menopause, hypertension is less common in women than in men, perhaps reflecting the lower blood volume afforded women by menses. Eventually, however, more women than men have a hypertension-related cardiovascular complication because there are more elderly women than elderly men and hypertension is both more common and more dangerous in the elderly.[141]

Children and Adolescents (see also Chap. 45)

As in adults, care is needed in establishing the presence of persistently elevated blood pressure in children when using the upper limits of normal shown in Table 28-3 . Recall that these are the averages of the first blood pressure value obtained; since the pressure usually falls on repeated measurements, levels below those shown in Table 28-3 may be abnormally high for a given child. In addition, the recent inclusion of height along with age and weight to the nomograms for children and adolescents probably improves their diagnostic accuracy.[1] The significance of readings above the 95th percentile in an asymptomatic child remains uncertain since tracking of blood pressure as children grow older does not tend to be persistent; the positive predictive value of a blood pressure reading above the 95th percentile in a 10-year-old boy being at a hypertensive level at age 20 is only 0.44.[142] Moreover, the sensitivity of this high blood pressure in a 10-year-old to detect hypertension 10 years later is only 0.17.

Nonetheless, most authorities[26] agree that children with "significant" hypertension (levels above the 95th percentile) should be given a limited work-up for target organ damage and secondary causes (perhaps including an echocardiogram and probably including a renal isotopic scan); if these tests are negative, the children should be carefully monitored and given nonpharmacological therapy. Those with "severe" hypertension (levels above the 99th percentile) should be more rapidly and completely evaluated and given appropriate pharmacological therapy.

EPIDEMIOLOGY.

The older the child, the more likely the hypertension is of unknown cause, i.e., primary or essential. In prepubertal children, chronic hypertension is more likely caused by congenital or acquired renal parenchymal or vascular disease[143] (Table 28-11) .

In adolescents, primary hypertension is the most likely diagnosis. Factors that increase the likelihood for early onset of hypertension include a positive family history of hypertension, obesity, poor physical fitness, and an increase in thickness of the interventricular septum during systole on echocardiography. Among black children, a greater blood pressure reactivity to stress may also be predictive.[144]

TABLE 28-11 -- MOST COMMON CAUSES OF CHRONIC HYPERTENSION IN CHILDHOOD

Newborn
Renal artery stenosis or thrombosis
Congenital renal structural abnormalities
Coarctation of the aorta
Bronchopulmonary dysplasia
Infancy to 6 yr
Renal structural and inflammatory diseases
Coarctation of the aorta
Renal artery stenosis
Wilms tumor
6-10 yr
Renal structural and inflammatory diseases
Renal artery stenosis
Essential (primary) hypertension
Renal parenchymal diseases
Adolescence
Primary hypertension
Renal parenchymal diseases
From Loggie JMH: Hypertension in children. Heart Dis Stroke May/June:147, 1994.

MANAGEMENT.

Once persistently elevated blood pressure is identified in children and adolescents and an appropriate work-up has been performed, weight reduction if the patient is overweight, regular dynamic exercise, and moderate restriction of dietary sodium should be encouraged. Those deemed to be in need of drug therapy are usually treated in the way adults are managed, as described in the next chapter and in Chapter 45 .

The Elderly

As more people live longer, more hypertension, particularly systolic, will be seen. By the usual criteria of the average of three blood pressure measurements on one occasion at or above 140 mm Hg systolic and/or 90 mm Hg diastolic or the taking of antihypertensive medication, 54 percent of men and women aged 65 to 74 have hypertension; among blacks, the prevalence is 72 percent.[27] In elderly patients with significant hypertension of recent onset, chronic renal disease or atherosclerotic renovascular disease is more likely to be found.

The risks of both pure systolic and combined systolic and diastolic hypertension at every level are greater in the elderly than in younger patients as a result of the adverse effects of age-related atherosclerosis and concomitant conditions. It comes as no surprise that the elderly achieved even greater reductions in coronary disease and heart failure by effective therapy than did younger hypertensives in multiple clinical trials.[1]

The elderly may display two features that reflect age-related cardiovascular changes. The first is pseudohypertension from markedly sclerotic arteries that do not collapse under the blood pressure cuff and therefore result in much higher cuff pressures than present within the vessels. If the arteries feel rigid but the patient has few retinal or cardiac findings to go along with marked hypertension, direct intraarterial measurements may be needed before therapy is begun to avoid inordinate lowering of a blood pressure that is not in fact elevated. The second feature, seen in 20 to 30 percent of the elderly, is postural and postprandial hypotension, which usually reflects a progressive loss of baroreceptor responsiveness with age.[22] A standing blood pressure should always be taken in patients older than 65 years, particularly if seated or supine hypertension is noted; if postural hypotension is present, maneuvers to overcome the precipitous falls in pressure should be attempted before the seated and supine hypertension is cautiously treated. More about the special therapeutic challenges often found in the elderly is provided in the next chapter.

Patients with Diabetes Mellitus (see also Chap. 63)

Hypertension and diabetes coexist more commonly than predicted by chance. They act in a synergistic manner to markedly accelerate cardiovascular damage, which is in turn responsible for the premature disabilities and higher rates of mortality that afflict diabetics. Among some 1500 diabetics monitored by Danish investigators, 51 percent of the insulin-dependent diabetics and 80 percent of the noninsulin-dependent diabetics had blood pressures above 140/90 mm Hg.[145] In more than half of these hypertensive diabetics, isolated systolic hypertension was noted.

Not only is hypertension more common in diabetics, but it also tends to be more persistent, with less of the usual nocturnal fall in pressure. The absence of a nocturnal fall in pressure may reflect autonomic neuropathy or incipient diabetic nephropathy.

The presence of hypertension increases all of the microvascular and macrovascular

complications observes in diabetes. Even at the initial diagnosis of diabetes, the presence of hypertension is associated with about a doubling of the prevalence of microalbuminuria, LVH, and electrocardiographic signs of myocardial ischemia.[146] These newly diagnosed diabetics were monitored for about 5 years, and those with hypertension suffered almost a twofold greater incidence of cardiovascular morbidity and mortality than did the nonhypertensive diabetics.

When hypertensive, patients with diabetes mellitus may confront some unusual problems. With progressive renal insufficiency, they may have few functional juxtaglomerular cells, and as a result, the syndrome of hyporeninemic hypoaldosteronism may appear, usually manifested by hyperkalemia. If hypoglycemia develops because of too much insulin or other drugs, severe hypertension may occur as a result of stimulated sympathetic nervous activity.

Diabetics are also susceptible to special problems associated with antihypertensive therapy. High doses of both diuretics and beta blockers may worsen diabetic control, probably by inducing further insulin resistance.[146A] Those who are prone to hypoglycemia may have difficulties with beta-blocking agents since these drugs blunt their protective catecholamine response, and severe hypoglycemia may develop with sweating as the only warning. Diabetic neuropathy may add to the postural hypotension and impotence that frequently complicate antihypertensive therapy. Diabetic nephropathy will impair sodium excretion and diminish the effectiveness of diuretics. On the other hand, successful control of hyperglycemia and blood pressure reduction will protect such patients from the otherwise inexorable progress of diabetic nephropathy. As will be noted in the next chapter, diabetic hypertensives are provided even better protection against cardiovascular morbidity and mortality than are nondiabetics when their blood pressure is lowered with antihypertensive drugs.[147]

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Identifiable (Secondary) Forms of Hypertension (See Tables 28-4 and 28-5 , p. 946)

Oral Contraceptive and Postmenopausal Estrogen Use

The use of estrogen-containing oral contraceptive pills is probably the most common cause of secondary hypertension in young women. Most women who take them experience a slight rise in blood pressure, and hypertension develops in about 5 percent (i.e., blood pressure above 140/90 mm Hg) within 5 years of oral contraceptive use. This incidence is more than twice that seen among women of the same age who do not use these agents. Although the hypertension is usually mild, it may persist after oral contraceptive use is discontinued, it may be severe, and it is almost certainly a factor in the increased cardiovascular mortality seen among young women who take these agents.[148] Despite these facts, these drugs have provided effective and safe birth control for millions of women, and the need for oral contraceptives remains.

The dangers of oral contraceptives should be kept in proper perspective. While it is true that use of these drugs is associated with increased morbidity and mortality, the *absolute* numbers are quite small, and overall mortality from cardiovascular disease has been declining progressively among women in the United States at a rate equal to that noted among American men. Moreover, the risks appear to have been lessened by more careful selection of users and lower doses of hormones.[149] Most adverse effects occur in women who smoke and have other cardiovascular risk factors and who take formulations with more than 50 mug of estrogen. Thus, the currently used low-estrogen

and low-progesterone forms seem quite safe for the purposes of temporary birth control.

INCIDENCE.

The best data on the incidence of oral contraceptive-induced hypertension came from a large study of the Royal College of General Practitioners. The incidence of hypertension was 2.6 times greater among 23,000 pill users than 23,000 nonusers, with pill users having a 5 percent incidence over 5 years of oral contraceptive use.[150] In addition, this incidence increased with longer duration of pill use, being only slightly higher than that in controls during the first year but rising to almost 3 times higher by the fifth year. In a much smaller, but more carefully performed, prospective study of 186 Scottish women, systolic pressure rose in 164 (by more than 25 mm Hg in 8) and diastolic pressure rose in 150 (by more than 20 mm Hg in 2) during the first 2 years of oral contraceptive use.[151] After 3 years, the mean rise in 83 of these women was 9.2 mm Hg. The current use of smaller amounts of estrogen (20 to 35 mug) than the 50 mug taken by most of these women may induce less hypertension.

CLINICAL FEATURES.

The likelihood of hypertension developing among women using oral contraceptives is much greater in those who are older than 35 or obese or who drink large quantities of alcohol. The presence of hypertension during a prior pregnancy increases this likelihood, but not enough to preclude pill use in such women who require contraception. In most women the hypertension is mild; however, in some it may accelerate rapidly and cause severe renal damage. When use of the pill is discontinued, blood pressure falls to normal within 3 to 6 months in about half the patients. Whether the pill caused permanent hypertension in the other half or just uncovered primary hypertension at an earlier time is not clear.

MECHANISMS OF HYPERTENSION.

Oral contraceptive use probably causes hypertension by volume expansion since both estrogens and the synthetic progestogens used in oral contraceptive pills cause sodium retention. Although plasma renin levels rise in response to increased levels of angiotensinogen, angiotensin-converting enzyme (ACE) inhibition did not alter blood pressure any more in women with oral contraceptive-induced hypertension than in women with essential hypertension.[152] In keeping with the probable role of hyperinsulinemia in other hypertensive states (see p. 954) hyperinsulinemia may be involved in oral contraceptive-induced hypertension as well because plasma insulin levels are increased after the start of oral contraceptive use, a finding reflective of peripheral insulin resistance.[153]

MANAGEMENT.

The use of estrogen-containing oral contraceptives should be restricted in women older than 35, particularly if they also smoke or are hypertensive or obese. Women given the pill should be properly monitored as follows: (1) The supply should be limited initially to

3 months and thereafter to 6 months; (2) they should be required to return for a blood pressure check before an additional supply is provided; and (3) If blood pressure has risen, an alternative contraceptive should be offered. If the pill remains the only acceptable contraceptive, the elevated blood pressure can be reduced with appropriate therapy. In view of the possible role of aldosterone, use of a diuretic-spironolactone combination seems appropriate. In those who stop taking oral contraceptives, evaluation for secondary hypertensive diseases should be postponed for at least 3 months to allow changes in the renin-angiotensin-aldosterone system to remit. If the hypertension does not recede, additional work-up and therapy may be needed.

POSTMENOPAUSAL ESTROGEN USE.

Millions of women use estrogen for its potential benefits after menopause. It does not appear to induce hypertension, even though it does induce the various changes in the renin-angiotensin-aldosterone system seen with oral contraceptive use.[154] Moreover, the majority of case-control studies have shown a significantly *lower* mortality rate from coronary artery disease among postmenopausal estrogen users than nonusers.[155] Such cardioprotection probably reflects improvement in endothelium-dependent, flow-mediated vasodilation, either from a direct effect on endothelial function or through changes in blood lipids.[156]

Renal Parenchymal Disease

In the overall population, renal parenchymal disease is the most common cause of secondary hypertension and is responsible for 2 to 5 percent of cases (see Table 28-5). As chronic glomerulonephritis has become less common, hypertensive nephrosclerosis and diabetic nephropathy have become the most common causes of ESRD.[157] The higher prevalence of hypertension among U.S. blacks is probably responsible for their significantly higher rate of ESRD, with hypertension as the underlying cause in as many as half of these patients.[61]

Not only does hypertension cause renal failure and renal failure cause hypertension, but also more subtle renal dysfunction may be involved in patients with primary hypertension. As discussed earlier (see p. 952), the kidneys may initiate the hemodynamic cascade eventuating in primary hypertension. As that disease progresses, some renal dysfunction is demonstrable in most patients; progressive renal damage is the end result and is the cause of death in perhaps 10 percent of hypertensives. Since early treatment of hypertension will probably protect against nephrosclerosis, there is hope that improved control of hypertension will slow the progression and reduce the frequency of ESRD.

In hypertension with renal parenchymal disease the sequence of progressively worsening renal damage is (1) acute renal diseases that are often reversible, (2) unilateral and bilateral diseases without renal insufficiency, (3) chronic renal disease with renal insufficiency, and

(4) hypertension in the anephric state and after renal transplantation.

ACUTE RENAL DISEASES.

Hypertension may appear with any sudden, severe insult to the kidneys that either markedly impairs excretion of salt and water, which leads to volume expansion, or reduces renal blood flow, which sets off the renin-angiotension-aldosterone mechanism. Bilateral ureteral obstruction is an example of the former; sudden bilateral renal artery occlusion, as by emboli, is an example of the latter. Relief of either may dramatically reverse severe hypertension. Such reversal of hypertension has been particularly striking in men with high-pressure chronic retention of urine, who may manifest both renal failure and severe hypertension, both of which may be ameliorated by relief of the obstruction.[158] Some of the collagen diseases may also produce rapidly progressive renal damage. The more common acute processes are glomerulonephritis and oliguric renal failure.

ACUTE GLOMERULONEPHRITIS.

Although the classic syndrome of type-specific poststreptococcal nephritis has become much less common, glomerular lesions of various types may be associated with hypertension. Moreover, although the epidemic poststreptococcal disease is usually self-limited, the disease in some patients follows a progressive, smoldering course that may lead to renal insufficiency. Typically, hypertension accompanies the fluid retention of acute renal injury and is best relieved by sodium and fluid restriction and potent diuretics. Dialysis and parenteral antihypertensive drugs may be needed if encephalopathy supervenes. In milder cases, the hypertension recedes as the edema is relieved.

ACUTE OLIGURIC RENAL FAILURE.

Acute renal failure may occur after hypotension, particularly in patients in whom renin levels are already high, such as those with cirrhosis and ascites or at the end of pregnancy. The release of even more renin by decreased blood pressure and effective circulating blood volume may flood the renal vasculature and cause such intense renal vasoconstriction that renal function shuts down. Hypertension in this setting is not usually an important problem and can be controlled by preventing volume overload. High doses of furosemide may be helpful, but dialysis is often needed. When acute renal failure occurs in the setting of accelerated or malignant hypertension, aggressive therapy (including dialysis) may be followed by sustained recovery of renal function.[159] The use of nonsteroidal antiinflammatory agents may cause acute renal failure, usually in the setting of chronic renal damage.[160]

VASCULITIS.

Rapidly progressive renal deterioration with severe hypertension occurs not infrequently during the course of scleroderma and other forms of vasculitis (see Chap. 67). Therapy with antihypertensives, particularly ACE inhibitors, may reverse the process.[161]

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY.

As this procedure has been increasingly used to treat nephrolithiasis, at least transient rises in blood pressure have been observed in 20 to 30 percent of patients, but persistent hypertension is unusual.[162]

RENAL DISEASE WITHOUT RENAL INSUFFICIENCY.

Although an entire kidney may be removed without obvious effect and no rise in blood pressure, hypertension may be associated with unilateral and bilateral renal parenchymal diseases in the absence of significant renal insufficiency. Even though such hypertension may reflect other unrecognized processes, most likely it is caused by activation of the renin-angiotensin-aldosterone mechanism. However, in some patients whose hypertension has been relieved by correction of a renal defect, the levels of renin have not been high.

UNILATERAL PARENCHYMAL RENAL DISEASE.

A number of unilateral kidney diseases may be associated with hypertension, and in some of these diseases the affected kidney is shrunken. Nonetheless, most small kidneys do not cause hypertension, and when they are indiscriminately removed from patients with hypertension, the condition is relieved in only about 25 percent. Of that 25 percent, most have arterial occlusive disease, either as the primary cause of the renal atrophy or secondary to irregular scarring of the parenchyma.

POLYCYSTIC KIDNEY DISEASE.

Although patients with adult polycystic kidney disease usually progress to renal insufficiency, some retain reasonably normal GFRs and display no azotemia. Hypertension, although more common in those with renal failure, is present in perhaps half of those with a normal GFR and probably reflects variable degrees of both renin excess and fluid retention.[163]

CHRONIC PYELONEPHRITIS.

The relationship between pyelonephritis and hypertension is multifaceted: Pyelonephritis, either unilateral or bilateral, may cause hypertension, and hypertensive individuals may be more susceptible to renal infection. In pyelonephritic patients with hypertension but fairly normal renal function, renin levels are high,[164] probably from

interstitial scarring with obstruction of intrarenal vessels.

CHRONIC RENAL DISEASES WITH RENAL INSUFFICIENCY.

Because dialysis and transplantation prolong the lives of more patients with renal insufficiency, their hypertension must be dealt with over much longer periods. In most patients with renal insufficiency, hypertension is predominantly caused by volume overload resulting from an inability of the reduced functioning renal mass to handle the usual sodium and water intake. With proper attention to sodium and water intake and, if needed, adequate dialysis, control of blood pressure may not be particularly difficult. Unfortunately, some patients are much more fragile and alternate between low and high pressure, and some are much more resistant, presumably because of a greater contribution of high renin levels to the hypertension. Moreover, their pressures may not fall much during sleep, which poses an additional burden on the heart and vasculature. Nonetheless, with judicious use of available therapy, hypertension should not be a major problem for most patients with renal insufficiency.

Three aspects of hypertension with ESRD should be recognized: (1) Hypertension contributes to the cardiovascular diseases that are the cause of death in about half of patients with ESRD; (2) renal damage may progress despite apparent control of hypertension, particularly among blacks;[165] and (3) a significant proportion of cases of ESRD may reflect bilateral renovascular disease that may be made worse by antihypertensive drug therapy but markedly improved by revascularization.[166]

In view of increasing evidence that glomerular capillary hypertension is responsible for the progressive loss of renal function once renal damage begins (see Fig. 28-11), aggressive reduction of intraglomerular hypertension to prevent further renal loss is being actively pursued. ACE inhibitors maybe particularly effective in this regard.[165]

Diabetic Nephropathy (see also Chap. 63).

Hypertension often accompanies diabetic nephropathy as a result of an inability to handle volume loads because of loss of nephrons secondary to progressive intercapillary glomerulosclerosis. As shown in Figure 28-16 , intrarenal hypertension accelerates the progress of the glomerulosclerosis, and antihypertensive therapy has been shown to slow the progression of renal damage.[167] Although more effective relief of glomerular capillary hypertension may be possible with ACE inhibitors, long-term protection has been obtained with traditional antihypertensive drugs, not including ACE inhibitors.[168] As common as it is, hypertension may not be as severe or as likely to progress to an accelerated-malignant phase in diabetics with nephropathy for two reasons: First, these patients often have diminished intravascular volume because of the hypoalbuminemia of the nephrotic syndrome, and second, they have low renin levels, presumably because of hyalinization of juxtaglomerular cells, which may be manifested as hyporeninemic hypoaldosteronism.

Analgesic Nephropathy.

In addition to the acute renal insufficiency that may accompany the inhibition of renal prostaglandins by nonsteroidal antiinflammatory agents,[160] permanent interstitial renal damage may supervene after prolonged exposure to analgesics, particularly phenacetin and, to a lesser degree, acetaminophen.[169] Until late in their course, these patients have a greater propensity for salt wasting and may therefore have less severe hypertension.

HYPERTENSION DURING CHRONIC DIALYSIS AND AFTER RENAL TRANSPLANTATION.

In patients with ESRD, blood pressure depends mainly on body fluid volume. Hypertension may be accentuated by the accumulation of endogenous inhibitors of nitric oxide (NO) synthase because of withdrawal of the vasodilation provided by NO. As these inhibitors are removed during dialysis, NO may contribute to hemodialysis-induced hypotension.[170] With neither the vasoconstrictor effects of renal renin nor the vasodepressor actions of various renal hormones, blood pressure may be particularly labile and sensitive to changes in adrenergic activity. Among patients receiving maintenance

Figure 28-16 Pivotal role of glomerular hypertension in the initiation and progression of structural injury. (From Anderson S, Brenner BM: Progressive renal disease: A disorder of adaptation. QJM 70:185, 1989.)

hemodialysis every 48 hours, elevated blood pressures tend to fall progressively after dialysis is completed, remain depressed during the remainder of the first 24 hours, and rise again during the second day as a consequence of excessive fluid retention.[171] Thus, antihypertension therapy may be needed only on the days between dialysis.

Although successful renal transplantation may cure primary hypertension, various problems may result, with about half of the recipients becoming hypertensive within 1 year.[172] These problems include stenosis of the renal artery at the site of anastomosis, rejection reactions, high doses of adrenal steroids and cyclosporine, and excess renin derived from the retained diseased kidneys. ACE inhibitor therapy may obviate the need to remove the native diseased kidneys to relieve hypertension caused by their persistent secretion of renin. The source of the donor kidney may also play a role in the subsequent development of hypertension in the recipient: More hypertension has been observed when donors had a family history of hypertension or when the donors had died of subarachnoid hemorrhage and had probably been hypertensive.[173]

Renovascular Hypertension

Renovascular hypertension is among the most common secondary forms of hypertension and is not easily recognizable. Although no more than 1 percent of all

adults with hypertension have renovascular hypertension (see Table 28-5), the prevalence is much higher in those with sudden onset of severe hypertension and other suggestive features[174] (Table 28-12) . Mann and Pickering classified patients into those with a low, moderate, and high "clinical index of suspicion" as a guide to the selection of additional work-up for renovascular hypertension. Those with characteristics listed under moderate are considered to have a 5 to 15 percent likelihood of the diagnosis and are therefore in need of a noninvasive screening test. Those with characteristics listed under high are considered to have a greater than 25 percent likelihood of the diagnosis and renal arteriography should be the initial test.

Renovascular disease is found less commonly in black hypertensives than in whites,[175] but it should be looked for when accompanied by the features described in Table 28-12 .

CLASSIFICATION.

In adults, the two major types of renovascular disease tend to appear at different times and affect the sexes differently (Table 28-13) . Atherosclerotic disease affecting mainly the proximal third of the main renal artery is seen mostly in older men. Fibroplastic disease involving mainly the distal two-thirds and branches of the renal arteries appears most commonly in younger women. Overall, about two-thirds of cases are caused by atherosclerotic disease and one-third by fibroplastic disease. While the nonatherosclerotic stenoses involve all layers of the renal artery, the most common is medial fibroplasia.

A number of other intrinsic and extrinsic causes of renovascular hypertension are known, including cholesterol emboli

TABLE 28-12 -- TESTING FOR RENOVASCULAR HYPERTENSION: CLINICAL INDEX OF SUSPICION AS A GUIDE TO SELECTING PATIENTS FOR WORK-UP

Low (Should Not Be Tested)
Borderline, mild, or moderate hypertension, in the absence of clinical clues
Moderate (Noninvasive Tests Recommended)
Severe hypertension (diastolic blood pressure greater than 120 mm Hg) Hypertension refractory to standard therapy Abrupt onset of sustained, moderate to severe hypertension at age <20 or age >50 Hypertension with a suggestive abdominal bruit (long, high pitched, and localized to the region of the renal artery) Moderate hypertension (diastolic blood pressure exceeding 105 mm Hg) in a smoker, in a patient with evidence of occlusive vascular disease (cerebrovascular, coronary, peripheral vascular), or in a patient with unexplained but stable elevation of serum creatinine Normalization of blood pressure by an angiotensin-converting enzyme inhibitor in a patient with moderate or severe hypertension (particularly a smoker or a patient with recent onset of hypertension)

High (May Consider Proceeding Directly to Arteriography)

Severe hypertension (diastolic blood pressure greater than 120 mm Hg with either progressive renal insufficiency or refractoriness to aggressive treatment, particularly in a patient who has been a smoker or has other evidence of occlusive arterial disease)
Accelerated or malignant hypertension (grade III or IV retinopathy)
Hypertension with recent elevation of serum creatinine, either unexplained or reversibly induced by an angiotensin-converting enzyme inhibitor
Moderate to severe hypertension with incidentally detected asymmetry of renal size

Reproduced with permission from Mann SJ, Pickering TG: Detection of renovascular hypertension. State of the art: 1992. Ann Intern Med *117*:845, 1992.

TABLE 28-13 -- FEATURES OF THE TWO MAJOR FORMS OF RENAL ARTERY DISEASE

CAUSE	INCIDENCE (%)	AGE (yr)	LOCATION OF LESION IN RENAL ARTERY	NATURAL HISTORY
Atherosclerosis	65	>50	Proximal 2 cm; branch disease rare	Progression in 50%, often to total occlusion
Fibromuscular dysplasias				
Intimal	1-2	Birth-25	Midportion of main renal artery and/or branches	Progression in most cases; dissection and/or thrombosis common
Medial	30	25-50	Distal segment of main renal artery and/or branches	Progression in 33%; dissection and/or thrombosis rare
Periarterial	1-2	15-30	Middle to distal segments of main renal artery or branches	Progression in most cases; dissection and/or thrombosis common

From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 306.

within the renal artery or compression of this vessel by nearby tumors. Most renovascular hypertension develops from partial obstruction of one main renal artery, but only a branch need be involved; segmental disease was found in 11 percent of cases in one large series.[176] On the other hand, if apparent complete occlusion of the

renal artery is slow in developing, enough collateral flow will become available to preserve viability of the kidney. In this way, the seemingly nonfunctioning kidney may be responsible for continued renin secretion and hypertension. If recognized, such totally occluded vessels can sometimes be repaired, with return of renal function and relief of hypertension. [177]

Renovascular stenosis is often bilateral, although usually one side is clearly predominant. The possibility of bilateral disease should be suspected in those with renal insufficiency, particularly if rapidly progressive oliguric renal failure develops without evidence of obstructive uropathy and even more so if it develops after the start of ACE inhibitor therapy.[178]

MECHANISMS.

After Goldblatt produced renovascular hypertension in the dog in 1934, confusion arose because of the use of one-kidney models, which are more appropriate to the study of renal parenchymal hypertension. The sequence of changes in the two-kidney (one-clip) model and in patients with renovascular hypertension almost certainly starts with the release of increased amounts of renin when sufficient ischemia is induced to diminish pulse pressure against the juxtaglomerular cells in the renal afferent arterioles. A reduction in renal perfusion pressure by 50 percent leads to an immediate and persistent increase in renin secretion from the ischemic kidney, along with suppression of secretion from the contralateral one. With time, renin levels fall (but not to the low level expected from the elevated blood pressure), accompanied by an expanded body fluid volume and increased cardiac output.

DIAGNOSIS.

The presence of the clinical features listed under moderate suspicion for renovascular hypertension in Table 28-12 , found in perhaps 5 to 10 percent of all hypertensives, indicates the need for a screening test for renovascular hypertension. A positive screening test, or very strong clinical features, calls for more definitive confirmatory tests. Recurrent flash pulmonary edema has been associated with renovascular hypertension,[179] so this clinical manifestation should be added to the indication for diagnostic work-up.

Some patients have renovascular hypertension but none of the clinical features listed in Table 28-12 , and they clinically resemble patients with mild primary hypertension. Nonetheless, these features should be used to exclude the majority of hypertensives from additional work-up and to identify the 10 percent or so who should undergo a work-up.

Functional Diagnostic Tests.

Isotopic renography and plasma renin measurements after an oral captopril challenge are currently the best initial tests in patients with the suggestive clinical features listed under moderate in Table 28-12 , to be followed by renal arteriography and then renal

vein renin assays. The latter procedure may not be needed if isotopic renography after captopril indicates significant renal ischemia in the kidney with renal artery disease by arteriography. In some centers with facilities dedicated to the performance of renal artery duplex sonography, that procedure is being used for initial screening,[180] and in the future, intravascular ultrasound will probably be used.[181] In addition, contrast-enhanced magnetic resonance arteriography may be even more reliable, particularly for visualizing accessory renal arteries.[182]

The captopril challenge test depends on abrupt inhibition of circulating angiotensin II by the ACE inhibitor, which removes the major support for perfusion through a stenotic renal artery to a kidney. The acutely ischemic kidney immediately releases more renin and undergoes a marked decrease in glomerular filtration and renal blood flow. Therefore, both plasma renin level and isotopic flow through the kidneys 1 hour after a single 50-mg dose of the ACE inhibitor should be measured. To measure the plasma renin response, the patient should have normal sodium dietary intake and not be taking diuretics and ACE inhibitors; if possible, other antihypertensive medications should be withdrawn for at least a week.[183] After the patient sits for 30 minutes, venous blood is obtained for basal PRA, and 50 mg of captopril is given orally. At 60 minutes, another blood sample for stimulated PRA is obtained. The authors have subsequently reported a high prevalence of false-positive responses in patients with high baseline renin levels.[183] Others report sensitivity ranging from 0.73 to 1.0 and specificity ranging from 0.73 to 0.95.[184]

Performance of isotopic renography 1 hour after the oral captopril dose provides additional diagnostic information in most but not all series.[185] The renogram may use labeled hippurate, a measure of renal blood flow, or diethylenetriaminepentaacetic acid (DTPA) or mercaptoacetyltriglycine (MAG3), measures of the GFR. If the postcaptopril test shows a significant difference between the two kidneys, the procedure should be repeated without captopril to document the ischemic origin of the differences in blood flow or GFR. With captopril renography, renal vein renin measurements are needed less often to localize the affected side when renovascular disease is bilateral.

MANAGEMENT

Medical.

The availability of ACE inhibitors may be considered a two-edged sword; one edge provides better control of renovascular hypertension than may be possible with other antihypertensive medications, while the other edge exposes the already ischemic kidney to further loss of blood flow by removing the high levels of angiotensin II that were supporting its circulation. Calcium entry blockers and other antihypertensive drugs may be almost as effective as ACE inhibitors and perhaps safer.[186]

Angioplasty (see also Chap. 42).

Angioplasty has been shown to improve (at least transiently) 60 to 70 percent of patients, more with fibromuscular disease than with atherosclerosis, as is also the case for surgery. Ostial lesions may be successfully managed by placement of an arterial stent, which will probably be performed more frequently to improve the results of angioplasty.[187]

Surgery.

Surgical repair has been shown to relieve renovascular hypertension in an increasing number of patients, including the elderly and those with renal insufficiency.[188] Most agree that surgery is indicated in patients whose hypertension is not well controlled or whose renal function deteriorates with medical therapy and in those with only a transient response to angioplasty or in whom lesions are not amenable to that procedure, more to preserve renal function than to relieve hypertension and before serum creatinine rises above 3 mg/dl.[189]

RENIN-SECRETING TUMORS

Made up of juxtaglomerular cells or hemangiopericytomas, these tumors have been found mostly in young patients with severe hypertension, very high renin levels in both peripheral blood and the kidney harboring the tumor, and secondary aldosteronism manifested by hypokalemia.[190] The tumor can generally be recognized by selective renal angiography, usually performed for suspected renovascular hypertension, although a few are extrarenal. More commonly, children with Wilms tumors (nephroblastoma) may have hypertension and high plasma renin and prorenin levels that revert to normal after nephrectomy.[191]

Adrenal Causes of Hypertension (see Chap. 64)

Adrenal causes of hypertension include primary excesses of aldosterone, cortisol, and catecholamines; more rarely, excess deoxycorticosterone (DOC) is present along with congenital adrenal hyperplasia. Together, these conditions cause less than 1 percent of all hypertensive diseases, although as will be noted, primary aldosteronism may be more common than previously thought. Each can usually be recognized with relative ease, and patients suspected of having these disorders can be screened by readily available tests. More of a problem than the diagnosis of these adrenal disorders is the need to exclude their presence because of the increasing identification of incidental adrenal masses when abdominal computed tomography (CT) is done to diagnose intraabdominal pathology. Unsuspected adrenal tumors have been found in 1 to 2 percent of abdominal CT scans obtained for reasons unrelated to the adrenal gland. Most of these "incidentalomas" appear to be nonfunctional on the basis of normal basal adrenal hormone levels. However, when more detailed studies are done, a significant number show incomplete suppression of cortisol by dexamethasone, i.e., subclinical Cushing disease that does not appear to progress to overt hypercortisolism, and a few

have unsuspected catecholamine hypersecretion.[192] Nonfunctioning adenomas have significantly less lipid content than do functioning adenomas by chemical-shift magnetic resonance imaging (MRI),[193] so this procedure may have clinical usefulness. The threat of malignancy can probably be best excluded by adrenal scintigraphy with NP-59, a radioiodinated derivative of cholesterol.[194] Benign lesions almost always take up the isotope, while malignant ones almost always do not. Most tumors larger than 4 cm are resected since a significant number of them are malignant.

Primary Aldosteronism (See also Chap. 64)

This disease is relatively rare in unselected populations (see Table 28-5), although it has been recognized in considerably more patients screened by a plasma aldosterone/renin activity ratio.[195]

PATHOPHYSIOLOGY.

Primary aldosterone excess usually arises from solitary benign adenomas. As diagnostic tests have improved and become more readily available, larger numbers of patients with minimal features have been recognized.[196] Many of these patients have been found to have bilateral adrenal hyperplasia, the number averaging about one-third of all cases of aldosteronism.

MINERALOCORTICAL HYPERTENSION.

In addition to the usual forms of primary aldosteronism, two unusual but interesting variants have been identified. One, familial glucocorticoid-suppressible aldosteronism, is caused by a mutation in the genes involved in coding for the aldosterone synthase enzyme normally found only in the outer zone glomerulosa and the 11-beta-hydroxylase enzyme in the zone fasciculata.[197] The chimeric gene induces an enzyme that catalyzes the synthesis of 18-hydroxylated cortisol in the zona fasciculata. Since this zone is under the control of adrenocorticotropic hormone (ACTH), the glucocorticoid suppressibility of the syndrome is explained. Since a few patients with classic primary aldosteronism show glucocorticoid suppression, the diagnosis should be made by genetic testing for the chimeric gene.[198]

The other unusual form of mineralocorticoid hypertension is caused by deficiency of the enzyme 11-beta-hydroxysteroid dehydrogenase (11beta-OHSD) in the renal tubule, where it normally converts cortisol (which has the ability to act on the mineralocorticoid receptor) to cortisone (which does not). Persistence of high levels of cortisol induces all the features of mineralocorticoid excess. The 11beta-OHSD enzyme may be congenitally absent (the syndrome of apparent mineralocorticoid excess) or inhibited by the glycyrrhetenic acid contained in licorice.[199] Another unusual syndrome with hypertension and hypokalemia but suppressed mineralocorticoid secretion is Liddle syndrome, wherein the kidney reabsorbs excess sodium and wastes potassium because of a mutation in the beta or gamma subunits of the epithelial sodium channel.[200]

Whatever the source, excess mineralocorticoid usually causes hypertension and hypokalemia, defined as a plasma potassium level below 3.2 mEq/liter. Very rarely, mineralocorticoid excess has been recognized in normotensive persons.[201] Not so rarely, hypokalemia may be absent or only intermittent, but in most patients with adenomas, persistent hypokalemia is observed.[196]

The hypertension begins as a volume overload but soon converts, as apparently do all forms of hypertension, to increased peripheral resistance. Hypertension may be severe, and cardiovascular complications, particularly stroke, common.[202] In association with the increased pressure and expanded blood volume, renin secretion is suppressed. Although this finding has been almost invariable with hyperaldosteronism, the overwhelming majority of hypertensive patients with suppressed renin do not have mineralocorticoid excess.

DIAGNOSIS.

Serious consideration should be given to the diagnosis of primary aldosteronism when hypertension and hypokalemia coexist. If normokalemic patients with the disease are missed, little will be lost as long as the patients are protected by appropriate treatment of the hypertension. Since such treatment is likely to include a diuretic, significant hypokalemia will probably soon become manifested and make the diagnosis obvious. If hypokalemia is present, excessive urinary potassium excretion (above 30 mmol/day) is strongly suggestive of mineralocorticoid excess.

A high plasma aldosterone/renin ratio in plasma is a useful screening test that can be performed immediately upon recognition of hypokalemia in a hypertensive patient, but with the knowledge that a high ratio may reflect only a suppressed renin level. Therefore, not only should plasma renin levels be low, but plasma aldosterone levels should be elevated, with a ratio of well above 30.[203] Although this ratio is being increasingly used to screen for primary aldosteronism,

it has not always been found to be abnormal in patients with the syndrome.[204] Therefore, the finding of increased urinary aldosterone levels or failure to suppress plasma aldosterone levels by volume expansion or by a single dose of an ACE inhibitor also may be useful.[203]

ESTABLISHING THE PATHOLOGY.

Once the diagnosis of primary aldosteronism is made, the type of adrenal pathology should be determined, and only patients with a tumor should be subjected to surgery and those with bilateral hyperplasia treated by medical therapy. The best initial study is adrenal CT or MRI (Fig. 28-17) . However, the ability of these scans to identify hitherto

hidden degrees of adrenal pathology may engender confusion; the usual nodularity seen in the remainder of a gland that harbors a solitary adrenal adenoma may give the appearance of bilateral hyperplasia, and some larger hyperplastic nodules may look like adenomas.[205] Therefore, unless the scan is unequivocal, additional tests to discriminate between adenoma and hyperplasia should be done (Fig. 28-17) .

Various maneuvers are available.[196] Basal levels of serum 18-hydroxycorticosterone (18-OHB) and changes in plasma aldosterone levels after 2 hours of upright posture from 8 A.M.to 10 A.M.usually distinguish patients with adenomas (who generally have basal 18-OHB levels above 65 ng/dl and falls in plasma aldosterone in the upright posture) from those with bilateral hyperplasia (who usually have basal 18-OHB levels below 50 ng/dl and postural rises in plasma aldosterone presumably invoked by their supersensitivity to posture-mediated rises in renin-angiotensin). In addition, most adenomas but few hyperplastic glands secrete increased amounts of 18-hydroxylated cortisol, which suggests that they harbor similar mutant genes as found in the glucocorticoid-suppressible syndrome. If the type of adrenal disorder is still uncertain, bilateral adrenal vein catheterization with analysis of venous aldosterone and cortisol levels should be performed by radiologists who are experienced with the technique.

THERAPY.

Once the diagnosis of primary aldosteronism is made and the type of adrenal disorder has been established, the choice of therapy is fairly easy: Patients with a solitary adenoma should have the tumor resected, now more and more frequently done by laparoscopic surgery. Those with bilateral hyperplasia should be treated with spironolactone (see Chap. 64) and, if necessary, a thiazide diuretic or other antihypertensive drugs. Fortunately, the doses of spironolactone required for chronic therapy are usually low enough to avoid bothersome side effects. When an adenoma is resected, about half of patients will become normotensive, while the others, although improved, remain hypertensive, either from preexisting primary hypertension or from renal damage caused by prolonged secondary hypertension.[206]

CUSHING SYNDROME (see also Chap. 64)

Hypertension occurs in about 80 percent of patients with Cushing syndrome.[207] If left untreated, it can cause marked LVH and congestive heart failure. As with hypertension of other endocrine causes, the longer it is present, the less likely it is to disappear when the underlying cause is relieved.

MECHANISM OF HYPERTENSION.

Blood pressure may increase for a number of reasons. Secretion of mineralocorticoids may also be increased along with cortisol. The excess cortisol may overwhelm the ability of renal 11beta-OHSD to convert it to the inactive cortisone, and renal mineralocorticoid receptors are activated by the excess cortisol to retain sodium and expand fluid volume.[199] Cortisol stimulates the synthesis of renin substrate and the expression of angiotensin II receptors, which may be responsible for enhanced pressor

effects.[208]

DIAGNOSIS.

The syndrome should be suspected in patients with truncal obesity, thin skin, muscle weakness, and osteoporosis. If clinical features are suggestive, the diagnosis can be either ruled out or virtually ensured by the measurement of free cortisol in a 24-hour urine sample or the simple overnight *dexamethasone suppression test.* [209] In normal subjects, the level of plasma cortisol in a sample drawn at 8 A.M.after a bedtime dose of 1 mg of dexamethasone should be below 2 mug/100 mg. If the level is higher, additional work-up is in order to establish both the diagnosis of cortisol excess and the pathological type. The 1-mg overnight suppression test has a specificity of 87%; the traditional 2-mg/day (0.5 mg every 6 hours) or 48-hour low-dose dexamethasone screening test has been recommended since it provides almost 100% specificity.[207]

When an abnormal screening test is present, some would immediately perform pituitary and adrenal CT or MRI scans to elucidate the type of pathology. However, most authorities continue to recommend as additional high-dose dexamethasone suppression test at 2.0 mg every 6 hours for 2 days, with measurement of urinary free cortisol excretion and plasma cortisol levels. If Cushing syndrome is caused by excess pituitary ACTH drive with bilateral adrenal hyperplasia, urinary free cortisol will be suppressed to below 40 percent of the control value with the 2.0-mg dose. Plasma ACTH assays provide an additional means of differentiating pituitary and ectopic ACTH excess from adrenal tumors with ACTH suppression.[207] The response to corticotropin-releasing hormone and inferior petrosal sinus sampling may help identify a pituitary cause of the syndrome.

THERAPY.

In about two-thirds of patients with Cushing syndrome, the process begins with overproduction of ACTH by the pituitary, which leads to bilateral adrenal hyperplasia. Although pituitary hyperfunction may reflect a hypothalamic disorder, the majority of patients have discrete pituitary adenomas that can usually be resected by selective transsphenoidal microsurgery.

If an adrenal tumor is present, it should be removed surgically. With earlier diagnosis and more selective surgical therapy, it is hoped that more patents with Cushing syndrome will be cured without a need for lifelong glucocorticoid replacement therapy and with permanent relief of their hypertension. Temporarily and rarely permanently, therapy may require one of a number of medical approaches.[210]

CONGENITAL ADRENAL HYPERPLASIA.

Two other enzymatic defects may induce hypertension by interfering with cortisol biosynthesis. Low levels of cortisol lead to increased ACTH, which increases the accumulation of precursors

Figure 28-17 Flow diagram for the progressive work-up of confirmed primary aldosteronism, with additional steps to take when initial studies are aberrant. Rare, angiotensin II-responsive adenomas may demonstrate features of hyperplasia but lateralize by venous sampling or scintigraphy. On the other hand, primary adrenal hyperplasia may demonstrate features of an adenoma except for equally high steroid levels by venous sampling. *GRA* = glucocorticoid-remediable aldosteronism; *18-OH-B* = 18-hydroxycorticosterone; *18-oxo-F* = 8-hydrocortisol. (From Kaplan NM: Primary aldosteronism. *In* Kaplan NM [ed]: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 378.)

proximal to the enzymatic block, specifically, DOC, which induces mineralocorticoid hypertension. The more common of these is *11-hydroxylase deficiency* which has been attributed to various mutations in the gene [211] and leads to virilization (from excessive androgens) and hypertension with hypokalemia (from excessive DOC). The other is *17-hydroxylase deficiency,* which also causes hypertension from excess DOC but, in addition, causes failure of secondary sexual development because sex hormones are also deficient.[212] Affected children are hypertensive, but the defect in sex hormone synthesis may not become obvious until after puberty. Thereafter, affected males display ambiguity of sexual development and fail to mature.

PHEOCHROMOCYTOMA (see also Chap. 64)

The wild fluctuations in blood pressure and dramatic symptoms of pheochromocytoma usually alert both the patient and the physician to the possibility of this diagnosis. However, such fluctuations may be missed, or as occurs in half the patients, the hypertension may be persistent.[212A] The symptoms may be incorrectly ascribed to psychoneurosis by practitioners not sensitized to "spells," which usually represent menopausal hot flushes or anxiety-induced hyperventilation.[33] Panic attacks may simulate a "pheo spell."[213] Unfortunately, if the diagnosis of pheochromocytoma is missed, severe complications may arise from exceedingly high blood pressure and damage to the heart by catecholamines (see Chap. 64). Stroke and hypertensive crises with encephalopathy and retinal hemorrhage may occur, probably because blood pressure levels soar in vessels unprepared by a chronic hypertensive condition. Fortunately, a simple and inexpensive test will detect the disease with virtual certainty, so diagnostic indecision should be minimized.

PATHOPHYSIOLOGY.

The cells of the sympathetic nervous system arise from the primitive neural crest as primitive stem cells called *sympathogonia.* These cells differentiate into ganglion cells, neuroblasts, and chromaffin cells. Tumors develop from each of these cell types; ganglioneuromas and neuroblastomas usually occur in children, whereas tumors arising from chromaffin cells, i.e., pheochromocytomas, occur at all ages anywhere along the sympathetic chain and rarely in aberrant sites.[214] About 15 percent of

pheochromocytomas are extraadrenal; nonsecreting ones are called *paragangliomas* or *chemodectomas*.

Of the 85 percent of pheochromocytomas that arise in the adrenal medulla, 10 percent are bilateral and another 10 percent are malignant. Multiple adrenal tumors are particularly common in patients with simple familial pheochromocytoma and multiple endocrine neoplasia (MEN) type 2A in association with medullary carcinoma of the thyroid (Sipple syndrome) or with mucosal ganglioneuromas in addition (type 2B). The MEN-2 syndromes are inherited as autosomal dominants with mutations on chromosome 10.[215] Diffuse medullary hyperplasia may precede the development of tumors, and the tumors may in fact reflect extreme degrees of nodular hyperplasia. About 20% of cases of Von Hippel-Lindau disease with retinal angiomas and multiple other tumors are associated with a pheochromocytoma[216] as are 1% of cases of type 1 neurofibromatosis.[217]

Secretion from nonfamilial pheochromocytomas varies considerably, with small tumors tending to secrete larger proportions of active catecholamines. If the predominant secretion is epinephrine, which is formed primarily in the adrenal medulla, the symptoms reflect its effects--mainly systolic hypertension caused by increased cardiac output, tachycardia, sweating, flushing, and apprehension. If norepinephrine is predominantly secreted, as from some of the adrenal tumors and from almost all extraadrenal tumors, the symptoms include both systolic and diastolic hypertension from peripheral vasoconstriction but less tachycardia, palpitations, and anxiety. The hemodynamic features of 24 untreated patients with surgically proven pheochromocytomas were quite similar to those found in 24 untreated patients of similar sex, age, weight, and blood pressure with primary hypertension, with increased total peripheral resistance as the primary mechanism in both groups.[218]

DIAGNOSIS.

Many more hypertensive patients have variable blood pressure and "spells" than the 0.1 percent or so who harbor a pheochromocytoma. Spells with paroxysmal hypertension may occur with a number of stresses, and a large number of conditions may involve transient catecholamine release. A pheochromocytoma should be suspected in patients with hypertension that is either paroxysmal or persistent and accompanied by the symptoms and signs listed in Table 28-14 . In addition, children and patients with rapidly accelerating hypertension should be screened. Those whose tumors secrete predominantly epinephrine are prone to postural hypotension from a contracted blood volume and blunted sympathetic reflex tone. Suspicion should be heightened if activities such as bending over, exercise, palpation of the abdomen, smoking, or dipping snuff cause repetitive spells that begin abruptly, advance rapidly, and subside within minutes.

High levels of catecholamines may induce myocarditis (Chap. 48) , which may progress to cardiomyopathy and left ventricular failure.

TABLE 28-14 -- FEATURES SUGGGESTIVE OF PHEOCHROMOCYTOMA

Hypertension: Persistent or Paroxysmal

Markedly variable blood pressures (± orthostatic hypotension)
Sudden paroxysms (± subsequent hypertension) in relation to
  Stress: anesthesia, angiography, parturition
  Pharmacological provocation: histamine, nicotine, caffeine, beta blockers, glucocorticoids, tricyclic antidepressants
  Manipulation of tumors: abdominal palpation, urination
Rare patients persistently normotensive
Unusual settings
  Childhood, pregnancy, familial
  Multiple endocrine adenomas: medullary carcinoma of the thyroid (MEN-2), mucosal neuromas (MEN-2B)
  Neurocutaneous lesions: neurofibromatosis

Associated Symptoms

Sudden spells with headache, sweating, palpitations, nervousness, nausea, and vomiting
Pain in chest or abdomen

Associated Signs
Sweating, tachycardia, arrhythmia, pallor, weight loss

MEN=multiple endocrine neoplasia.

Electrocardiographic changes of ischemia may also be seen. Beta blockers given to such patients may raise the pressure and induce coronary spasm through blockade of beta-mediated vasodilation.

LABORATORY CONFIRMATION.

The easiest and best procedure is either a 24-hour or spot urine assay for total metanephrine.[219] This catecholamine metabolite is least affected by various interfering substances, including antihypertensive drugs, with the exception of labetalol, which may cause markedly elevated levels of all catecholamines.[220] In addition to the effects of labetalol, urinary metanephrine excretion is increased if patients are taking sympathomimetic or dopaminergic drugs or are under acute, severe stress such as an acute myocardial infarction or severe congestive heart failure. Interference with the measurement of metanephrine may occur for the next few days after the use of radiographic contrast media containing methylglucamine and lead to a falsely low value. Therefore, the urine should be collected before coronary angiography or other such procedures are done.

If urine assays are equivocal, measurement of a plasma norepinephrine level 3 hours after a single 0.3-mg oral dose of the adrenergic inhibitor clonidine has been shown to separate nonpheochromocytoma patients, whose levels are suppressed, from those with disease whose levels are not suppressed.[218]

LOCALIZATION OF THE TUMOR.

Once the diagnosis has been made, medical therapy should be started and the tumor localized by CT or MRI, which usually demonstrates these typically large tumors with ease. Radioisotopes that localize in chromaffin tissue are available and of additional help in the few patients in whom localization is not possible by CT or MRI.

THERAPY.

Once diagnosed and localized, pheochromocytomas should be resected. Although preoperative alpha-adrenergic blockade has been recommended, fewer operative and postoperative problems were encountered in patients who had been treated with a calcium channel blocker.[221] If the tumor is unresectable, chronic medical therapy with the alpha blocker phenoxybenzamine (Dibenzyline) or the inhibitor of catechol synthesis alphamethyltyrosine (Demser) can be used.

Other Causes of Hypertension

A host of other causes of hypertension are known (see Table 28-4). One that is probably becoming more common is ingestion of various drugs--prescribed (e.g., cyclosporine or tacrolimus[222] and erythropoietin[223]), over the counter (e.g., phenylpropanolamine), and illicit (e.g., cocaine). Obstructive sleep apnea has been well characterized as a cause of significant, but reversible, hypertension. [224]

COARCTATION OF THE AORTA (seeChaps. 43 and 44).

Congenital narrowing of the aorta may occur at any level of the thoracic or abdominal aorta. It is usually found just beyond the origin of the left subclavian artery or distal to the insertion of the ligamentum arteriosum. The coarctation may be localized or more diffuse. Other cardiac anomalies usually accompany the latter and give rise to considerable mortality during the first year of life, although operative

treatment of both the coarctation and associated anomalies may reduce the mortality rate. With less severe postductal lesions, damage is more insidious, and symptoms may not appear until the teenage years or later.

Hypertension in the arms and weak or absent femoral pulses are the classic features of coarctation. The pathogenesis of the hypertension may be more complicated than simple mechanical obstruction; a generalized vasoconstrictor mechanism is likely to be involved and may be either renin-angiotensin or sympathetic nervous activity.[225] The lesion may be detected by two-dimensional echocardiography, and aortography proves the diagnosis. The obstruction should be corrected in early childhood either by surgery[226] or by angioplasty.[227] Immediately after either, blood pressure may transiently rise even further, and mesenteric arteritis may develop. These changes may reflect very

high levels of renin-angiotensin and catecholamines and can be prevented by the prophylactic use of beta blockers.

HORMONAL DISTURBANCES.

Hypertension is seen in as many as half of patients with a variety of hormonal disturbances, including acromegaly,[228] hypothyroidism,[229] and hyperparathyroidism. Diagnosis of the latter two conditions has been made easier by readily available blood tests, and affected hypertensives may be relieved of their high blood pressure by correction of the hormonal disturbance. Such relief happens more frequently with hypothyroidism than with hyperparathyroidism.[230]

Hypertension after Cardiac Surgery

Transient hypertension may develop postoperatively for various reasons: pain, physical and emotional excitement, hypoxia, hypercapnia, and excessive volume loads. More severe hypertension has been noted to follow a number of cardiovascular surgical procedures:

1. *Coronary bypass surgery.* The incidence, exceeding 33 percent, is far higher than after other major cardiac or noncardiac surgery, except after heart transplantation. The hemodynamic pattern of increased peripheral resistance can be explained by the markedly elevated plasma catecholamine levels measured in such patients in the presence of normal renin-angiotensin levels.[231] In patients who had previously received beta blocker therapy, postoperative hypertension may also reflect a rebound phenomenon. Therefore, continuation of beta blocker therapy through the perioperative period is likely to reduce the frequency of the problem. If it occurs, parenteral therapy is often required, and intravenous nicardipine has been found to be very effective.[232]
2. *Aortic valve replacement.* Transient hypertension may give way to more permanent hypertension. In one series, 53 percent of 116 patients were hypertensive 5 years after surgery, and hypertension was a major determinant of late failure of the homograft valve.[233]
3. *Closure of an atrial septal defect.*[234]
4. *Cardiac transplantation.* After cardiac denervation and with current immunosuppression consisting of cyclosporine or tacrolimus and high doses of adrenal steroids, hypertension is almost invariable and can be resistant to intensive therapy.[235] Ambulatory monitoring should be performed since a considerable "white coat" effect has been noted and, therefore, more intensive therapy may not be required.[236]

HYPERTENSION DURING PREGNANCY (see also Chap. 65)

In as many as 10 percent of first pregnancies in previously normotensive women, hypertension appears after 20 weeks, i.e., *gestational hypertension,* and may progress to *preeclampsia* when the hypertension is complicated by proteinuria, edema, or hematological or hepatic abnormalities or progress to *eclampsia,* with cerebral

symptoms leading to convulsions.[237] Women with hypertension predating pregnancy have an even higher incidence of *preeclampsia* and a greater likelihood of early delivery of small-for-gestational-age babies,[238] who are in turn more prone to the development of hypertension as adults.[76]

Gestational hypertension is of unknown cause but occurs more frequently in primigravid women or in subsequent pregnancies with a different father, thus suggesting an immunological mechanism. Additional predisposing factors include increased age, black race, multiple gestations, concomitant heart or renal disease, and chronic hypertension.[239] Endothelial cell dysfunction may be an underlying defect.[240]

The diagnosis is usually based on a rise in pressure of 30/15 mm Hg or more to a level above 140/90. Although some measure the Korotkoff fourth sound (muffling), the fifth sound (disappearance) is closer to the true diastolic and should be used.

CLINICAL FEATURES.

The features shown in Table 28-15 should help distinguish gestational hypertension and preeclampsia from chronic, primary hypertension. The distinction should be made because management and prognosis are different: Gestational hypertension is self-limited and rarely recurs in subsequent pregnancies, whereas chronic hypertension progresses and usually complicates subsequent pregnancies. Separation may be difficult because of a lack of knowledge of prepregnancy blood pressure and because of the usual tendency for high pressure to fall considerably during the middle trimester so that hypertension present before pregnancy may not be recognized.

In gestational hypertension, the blood pressure usually rises only late in pregnancy. Among 84 patients with an onset of hypertension before 37 weeks' gestation, 55 had renal disease documented by kidney biopsy 6 months postpartum, when morphological changes caused solely by gestational hypertension should have subsided.[241] Gestational hypertension was the diagnosis in only 10 percent of primiparous women with onset of hypertension before 37 weeks, whereas it was the diagnosis in three-fourths of primigravid women with onset of hypertension after 37 weeks.

The hemodynamic features of gestational hypertension are a further rise in cardiac output than usually seen in normal pregnancy, accompanied by profound vasoconstriction that reduces intravascular capacity even more than blood volume.[242] The mother may be particularly vulnerable to encephalopathy because of her previously normal

TABLE 28-15 -- DIFFERENCES BETWEEN PREECLAMPSIA AND CHRONIC HYPERTENSION

FEATURE	PREECLAMPSIA	CHRONIC HYPERTENSION
Age (yr)	Young (<20)	Older (>30)
Parity	Primigravida	Multigravida

Onset	After 20 wk of pregnancy	Before 20 wk of pregnancy
Weight gain and edema	Sudden	Gradual
Systolic blood pressure	<160	>160
Funduscopic findings	Spasm, edema	Arteriovenous nicking, exudates
Proteinuria	Present	Absent
Plasma uric acid	Increased	Normal
Blood pressure after delivery	Normal	Elevated

blood pressure. As is described in more detail below, cerebral blood flow is normally maintained constant over a fairly narrow range of mean arterial pressure, roughly between 60 and 100 mm Hg in normotensive individuals. In a previously normotensive young woman, an acute rise in blood pressure to 150/100 mm Hg may exceed the upper limit of autoregulation and result in a "breakthrough" of cerebral blood flow (acute dilation) that leads to cerebral edema, convulsions, and all the clinical manifestations of eclampsia.

PREVENTION.

Beyond delay of pregnancy until after the teens and better prenatal care, no other manuever has been shown to prevent preeclampsia, including low doses of aspirin[243] or supplemental calcium.[244]

Treatment

GESTATIONAL HYPERTENSION.

Women with gestational hypertension and their fetuses can be protected from excessive morbidity and mortality by maneuvers that lower blood pressure without impairing uteroplacental perfusion. These maneuvers include modified bed rest, a nutritious diet with normal amounts of sodium, and antihypertensive agents when diastolic blood pressure above 100 mm Hg indicates impairment in renal function and predisposition to overt eclampsia.

> However, as noted by Redman and Roberts, the cure is achieved by delivery, which removes the diseased tissue--the placenta. In short, the need is to deliver before it is too late. To achieve this apparently simple end, the clinician must detect the symptomless prodromal condition by screening all

pregnant women, admit to hospital those with advanced preeclampsia so as to keep track of an unpredictable situation, and time preemptive delivery to maxi- mize the safety of mother and baby.[245]

Caution is advised in the use of drugs for mild gestational hypertension, traditionally limited to methyldopa. Drug treatment of maternal blood pressure does not improve perinatal outcome and may be associated with fetal growth retardation. Most authorities recommend antihypertensive drugs only if diastolic pressures remain above 100 mm Hg.[246] The only drugs that are contraindicated are ACE inhibitors and angiotensin II receptor blockers because of their propensity to induce neonatal renal failure.[246]

If the syndrome advances and eclampsia threatens before the 32nd week of gestation, expectant management (bed rest, oral antihypertensives, and intensive fetal monitoring) provides better eventual outcomes than does more aggressive therapy (glucocorticoids for 48 hours followed by delivery either by induction or cesarean section).[246] If parenteral antihypertensives are needed, hydralazine works well.

CHRONIC HYPERTENSION.

If pregnancy begins while a woman is receiving antihypertensive drug therapy, the medications, including diuretics, are usually continued in the belief that the mother should be protected and that the fetus will not suffer from any sudden hemodynamic shifts such as occur when therapy is first begun. However, despite modern treatment, the incidence of perinatal mortality and fetal growth retardation remains higher in patients with chronic hypertension.[238]

MANAGEMENT OF ECLAMPSIA.

With appropriate care of gestational hypertension, eclampsia hardly ever supervenes; when it does, however, maternal and fetal mortality remain very high. Excellent results have been reported with the use of magnesium sulfate to prevent convulsions.[247] Patients with severe eclampsia who have persistent oliguria after a fluid challenge should undergo hemodynamic monitoring since management may require additional volume or a reduction in preload or afterload.

CONSEQUENCES OF PREGNANCY-RELATED HYPERTENSION.

The long-term prognosis of women with gestational hypertension is excellent. When 200 women with the most severe form, eclampsia, were monitored for up to 44 years, the distribution of blood pressure was identical to that in the general population.[248] Chesley concluded that "eclampsia neither is a sign of latent essential hypertension nor causes hypertension." Nonetheless, when compared with women who were normotensive, the overall prognosis for women who had hypertension during pregnancy is not as good, probably because of causes other than preeclampsia, including unrecognized chronic primary hypertension.[249]

After delivery, transient or persistent hypertension may develop in the mother. In many,

early primary hypertension may have been masked by the hemodynamic changes of pregnancy. Postpartum heart failure may develop in some women; the heart failure may be an idiopathic cardiomyopathy but is usually related to hypertension, preexisting heart disease, or complications of pregnancy.[250]

HYPERTENSIVE CRISIS

DEFINITIONS.

A number of clinical circumstances may require rapid reduction of blood pressure (Table 28-16) . These circumstances may be separated into *emergencies,* which require immediate reduction of blood pressure (within 1 hour), and *urgencies,* which can be treated more slowly. A persistent diastolic pressure exceeding 130 mm Hg is often associated with acute vascular damage; some patients may suffer vascular damage from lower levels of pressure, while others manage to withstand even higher levels without apparent harm. As discussed below, the rapidity of the rise may be more important than the absolute level in producing acute vascular damage. Therefore, in practice, all patients with diastolic blood pressure above 130 mm Hg should be treated, some more rapidly with parenteral drugs and others more slowly with oral agents, as described on p. 991 .

When the rise in pressure causes retinal hemorrhage, exudates, or papilledema, the term *accelerated-malignant hypertension* is used. *Hypertensive encephalopathy* is characterized

TABLE 28-16 -- CIRCUMSTANCES REQUIRING RAPID TREATMENT OF HYPERTENSION

Accelerated-malignant hypertension with papilledema
Cerebrovascular
  Hypertensive encephalopathy
  Atherothrombotic brain infarction with severe hypertension
  Intracerebral hemorrhage
  Subarachnoid hemorrhage
Cardiac
  Acute aortic dissection
  Acute left ventricular failure
  Acute or impending myocardial infarction
  After coronary bypass surgery
Renal
  Acute glomerulonephritis
  Renal crises from collagen-vascular diseases
  Severe hypertension after kidney transplantation
Excessive circulating cathecholamines
  Pheochromocytoma crisis
  Food or drug interactions with monoamine oxidase inhibitors
  Sympathomimetic drug use (cocaine)
  Rebound hypertension after sudden cessation of antihypertensive drugs
Eclampsia
Surgical
  Severe hypertension in patients requiring immediate surgery
  Postoperative hypertension
  Postoperative bleeding from vascular suture lines
Severe body burns
Severe epistaxis

From Kaplan NM: Management of hypertensive emergencies. Lancet 344:1335, 1994.
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by headache, irritability, alterations in consciousness, and other manifestations of central nervous dysfunction with sudden and marked elevations in blood pressure. Symptoms can be reversed by a reduction in pressure.

INCIDENCE.

In less than 1 percent of patients with primary hypertension, the disease progresses to an accelerated-malignant phase. Although the incidence is probably falling as a consequence of more widespread treatment of hypertension, no difference was found in the numbers of patients seen in Birmingham, England, from 1970 to 1993,[251] reflecting the very low rates of control of hypertension in England.

Any hypertensive disease can initiate a crisis. Some, including pheochromocytoma and

renovascular hypertension, do so at a higher rate than seen with primary hypertension. However, since hypertension is of unknown cause in over 90 percent of all patients, most hypertensive crises appear in the setting of preexisting primary hypertension.

PATHOPHYSIOLOGY.

Whenever blood pressure rises and remains above a critical level, various processes set off a series of local and systemic effects that cause further rises in pressure and vascular damage eventuating in accelerated-malignant hypertension

Studies in animals and humans by Strandgaard and Paulson have elucidated the mechanism of hypertensive encephalopathy.[252] First, they directly measured the caliber of pial arterioles over the cerebral cortex in cats whose blood pressure was varied over a wide range of infusion by vasodilators or angiotensin II. As the pressure fell, the arterioles became dilated; as the pressure rose, they become constricted. Thus, constant cerebral blood flow was maintained by means of autoregulation, which is dependent on the cerebral sympathetic nerves. However, when mean arterial pressure rose above 180 mm Hg, the tightly constricted vessels could no longer withstand the pressure and suddenly dilated. This dilation began in an irregular manner, first in areas with less muscle tone and then diffusely with production of generalized vasodilation. This "breakthrough" of cerebral blood flow hyperperfuses the brain under high pressure and thereby causes leakage of fluid into the perivascular tissue and results in cerebral edema and the syndrome of hypertensive encephalopathy.

In human subjects, cerebral blood flow was measured repetitively by an isotopic technique while blood pressure was lowered or raised with vasodilators or vasoconstrictors in a manner similar to that used in the animal studies.[252] Curves depicting cerebral blood flow as a function of arterial pressure demonstrated autoregulation with a constancy of flow over mean pressures in normotensive persons from about 60 to 120 mm Hg and in hypertensive patients from about 110 to 180 mm Hg (Fig. 28-18) . This "shift to the right" in hypertensive patients is the result of structural thickening of the arterioles as an adaptation to the chronically elevated pressure. When pressure was raised beyond the upper limit of autoregulation, the same "breakthrough"

Figure 28-18 Idealized curves of cerebral blood flow at varying levels of systemic blood pressure in normotensive and hypertensive subjects. Rightward shift is shown in autoregulation with chronic hypertension. (Adapted from Strandgaard S, Olesen J, Skinhtoi E, Lassen NA: Autoregulation of brain circulation in severe arterial hypertension. BMJ 1:507, 1973.)

TABLE 28-17 -- CLINICAL CHARACTERISTICS OF HYPERTENSIVE CRISIS

Blood pressure: Usually >140 mm Hg diastolic
Funduscopic findings: Hemorrhage, exudate, papilledema
Neurological status: Headache, confusion, somnolence, stupor, visual loss, focal deficits, seizures, coma
Cardiac findings: Prominent apical impulse, cardiac enlargement, congestive failure
Renal: Oliguria, azotemia
Gastrointestinal: Nausea, vomiting

From Kaplan NM: Clinical Hypertension. 6th ed. Baltimore, Williams & Wilkins, 1994, p 283.

with hyperperfusion occurred as was seen in the animal studies. In previously normotensive persons whose vessels have not been altered by prior exposure to high pressure, breakthrough occurred at a mean arterial pressure of about 120 mm Hg; in hypertensive patients, the breakthrough occurred at about 180 mm Hg.

These studies confirm clinical observations. In previously normotensive persons, severe encephalopathy occurs with relatively little hypertension. In children with acute glomerulonephritis and in women with eclampsia, convulsions may occur as a result of hypertensive encephalopathy with blood pressure readings as low as 150/100 mm Hg. Obviously, chronically hypertensive patients withstand such pressures without difficulty; however, when pressure increases significantly, encephalopathy may also develop even in these patients.

MANIFESTATIONS AND COURSE.

The symptoms and signs of hypertensive crises are usually dramatic (Table 28-17) . However, some patients may be relatively asymptomatic despite markedly elevated pressure and extensive organ damage. Young black men are particularly prone to hypertensive crisis with severe renal insufficiency but little obvious prior distress. When the blood pressure is sufficiently high to induce encephalopathy or accelerated-malignant hypertension, the following clinical features are frequently present:

1. Renal insufficiency with protein and red cells in the urine and azotemia; acute oliguric renal failure may also develop.
2. Elevated levels of plasma renin from the diffuse intrarenal ischemia resulting in secondary aldosteronism, often manifested by hypokalemia. Although not causal, the secondarily elevated renin and aldosterone levels most likely exacerbate the hypertensive process.
3. Microangiopathic hemolytic anemia with red cell fragmentation and intravascular coagulation.
4. Cardiac size and function may *not* be abnormal in those in whom malignant hypertension suddenly develops.

If left untreated, patients die quickly of brain damage or more gradually of renal damage. Before effective therapy was available, less than 25 percent of patients with malignant hypertension survived 1 year and only 1 percent survived 5 years.[253] With therapy

including renal dialysis, over 90 percent survive 1 year and about 80 percent survive 5 years. Death in patients with severe hypertension is usually

TABLE 28-18 -- CONDITIONS TO BE DIFFERENTIATED FROM A HYPERTENSIVE CRISIS

Acute left ventricular failure
Uremia from any cause, particularly with volume overload
Cerebrovascular accident
Subarachnoid hemorrhage
Brain tumor
Head injury
Epilepsy (postictal)
Collagen diseases, particularly lupus, with cerebral vasculitis
Encephalitis
Overdose and withdrawal from narcotics, amphetamines, etc.
Hypercalcemia
Acute anxiety with hyperventilation syndrome

from stroke or renal failure if it occurs in the first few years after onset. If therapy keeps patients alive for longer than 5 years, death will usually be due to coronary artery disease, in which case factors other than the high pressure per se are probably also involved.

DIFFERENTIAL DIAGNOSIS.

The presence of hypertensive encephalopathy or accelerated-malignant hypertension demands immediate, aggressive therapy to lower blood pressure effectively, often before the specific cause is known. However, certain serious diseases, as well as psychogenic problems, i.e., acute anxiety with hyperventilation or panic attacks, can mimic a hypertensive crisis (Table 28-18) and management of these conditions obviously requires different diagnostic and therapeutic approaches. In particular, blood pressure should not be lowered too abruptly in a patient with a stroke.[254] Specific therapy for hypertensive crises is described in the next chapter (p. 991).

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HYPERTENSIVE CRISES

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Chapter 29 - Systemic Hypertension: Therapy

NORMAN M. KAPLAN

As noted at the beginning of Chapter 28 , the number of patients being treated for hypertension has expanded markedly during the past 25 years so that it is now the leading reason for office visits to physicians. Nonetheless, in various developed countries--from the United Kingdom and Canada, which have national health schemes that cover everyone, to the United States, with its sporadic coverage--only 15 to 30 percent of hypertensive patients have their disease under good control.[1] This apparent paradox of expanded coverage but continued poor control is not the consequence of either the ineffectiveness of available therapy or an unwillingness of physicians to provide it. In controlled trials, most patients with the most prevalent form of hypertension, previously called "mild" but now referred to as grade 1, i.e., diastolic blood pressure (DBP) between 90 and 100 mm Hg, achieve excellent control with one of many drugs.[2] Relatively few patients are truly resistant to therapy.[3]

The problem derives from the inherent nature of hypertension: induced by common but unhealthy life styles, asymptomatic and persistent, with overt consequences delayed by 10 to 30 years so that the costs of therapy, both in money and in adverse effects, seem on the surface to outweigh benefits to be derived from adherence to the regimen. Furthermore, behind the inherent nature of the disease that often interferes with

patients' adherence to their physician's requests, there lurks yet another disquieting feature of the therapy of most hypertension: It may not benefit the majority of patients who adhere faithfully to their treatment.[4] Even among such elderly patients as enrolled in the Systolic Hypertension in the Elderly Program (SHEP) trial, 111 would need to be treated for 5 years to prevent one cardiovascular death and 19 treated to prevent one cardiovascular event.[5] Because of the costs and side effects of therapy, caution is needed in the use of medication as a preventive measure.[6]

Yet another element, the issue of cost-effectiveness, has been introduced into the debate about the value of treating all patients with any degree of hypertension.[7] As the escalating costs of health care consume a greater share of society's resources, two opposing forces have risen: one, the need for less expensive illness care, and the other, the relatively large cost of prevention when indiscriminately applied to low-risk subjects. Therefore, it is likely that the calls for more selective and targeted antihypertensive therapy will be more widely listened to in the future.

We examine the evidence for benefits of therapy and then apply this evidence to the criteria for the initiation of therapy for individual patients.

BENEFITS OF THERAPY

The treatment of hypertension is aimed not at simple reduction of blood pressure but at prevention of the cardiovascular complications that are known to accompany the high pressure. During the past 30 years, many randomized, controlled trials (RCTs) have tested the ability of antihypertensive drugs--primarily diuretics and adrenergic inhibitors--to prevent strokes and heart attacks. Although such RCTs have limited ability to aid in clinical decisions about individual patients,[8] few other aspects of clinical practice have as strong an evidence base as does the treatment of hypertension.

A series of meta-analyses have portrayed the effects of therapy in a progressively enlarging number of completed trials.[9] [10] [11] They have shown a uniform and persistent reduction in morbidity and mortality from stroke averaging 40 percent, a reduction that exactly fits what was predicted from epidemiological evidence if the attributable risk had been completely reversed.[12] On the other hand, the impact on coronary artery disease reported in 1990 was only 14 percent,[9] below the 20 to 25 percent predicted if the risk attributed to blood pressure had been completely reversed.[12] By 1997, however, data from three reported trials enrolling elderly patients[5] [13] [14] brought the overall impact on coronary events to a 16 percent reduction, with confidence limits of 8 to 23 percent, which overlap the excess 20 to 25 percent risk predicted from epidemiological evidence (Fig. 29-1) . The protection against stroke has been shown to apply even to patients older than 80 years.[11] In the six trials that included 1670 patients older than 80 years, the half who were treated with either diuretics or dihydropyridine calcium antagonists had a 36 percent reduction in stroke, a 39 percent reduction in heart failure, and a statistically significant 22 percent reduction in major coronary events.[11]

The explanation for the progressively better results in the RCTs likely reflects the inclusion of higher-risk subjects. As shown in Figure 29-2 , absolute benefit in stroke prevention is progressively greater, the higher the stroke rate event in the placebo

group.[15] In a like manner, benefits of treatment were first documented for patients with severe hypertension,[16] then for those with moderate disease, and only later for those with lesser degrees of hypertension.[17]

The difficulty in showing clear benefits of treatment in the larger part of the hypertensive population, those with stage 1 or blood pressures from 140/90 to 160/100 mm Hg (see Table 28-2) must be reconciled with the fact that even though their individual risk is relatively low, their sheer

Figure 29-1 Meta-analysis of randomized, placebo-controlled clinical trials in hypertension according to first-line treatment strategy. Trials indicate number of trials with at least one endpoint of interest. For these comparisons, the numbers of participants randomized to active treatment and placebo, respectively, were 7768 and 12,075 for high-dose diuretic therapy, 4305 and 5116 for low-dose diuretic therapy, and 6736 and 12,147 for beta-blocker therapy. Because the Medical Research Council trials included two active arms, the placebo group is included twice in these totals (for diuretic comparison and for beta-blocker comparison). The total numbers of participants randomized to active and control therapy were 24,294 and 23,926, respectively. RR = relative risk; CI = confidence interval; HDFP = Hypertension Detection and Follow-up Program. (Data from Psaty BM, Smith NL, Siscovick DS, et al: Health outcomes associated with antihypertensive therapies used as first-line agents. JAMA 277:739, 1997.)

number causes them to make a major contribution to the overall population risk from hypertension, as shown in Figure 28-2 . This fact has given rise to two important guidelines for clinical practice: first, the critical need for prevention of hypertension by population-wide life style modifications[18] ; second, the rationale for considering blood pressure in the larger context of overall cardiovascular risk.

THRESHOLD FOR THERAPY

The value of life style modifications is documented in the next section of this chapter. The rationale for a broader look at risk beyond blood pressure was first formalized by a group of investigators from New Zealand[19] and has now been incorporated into both the 1997 report of the U.S. Joint National Committee (JNC-6)[20] and the 1999 World Health Organization-International Society of Hypertension (WHO-ISH) guidelines.[1] The basis for risk assessment and stratification provided in JNC-6 are shown in Tables 28-8 and 28-9 (pp. 950 , 951). The somewhat more detailed list of factors influencing risk in the 1999 WHO-ISH report is shown in Table 29-1 . The stratification in both reports is similar, with a fourth "very high" risk group having associated clinical conditions added in the WHO-ISH report, as are the recommendations for management: Low-risk patients with blood pressures as high as 159/99 mm Hg should be given life style modification; high-risk patients with blood pressures as low as 130/85 mm Hg should be immediately started on drug therapy (see Table 28-9) . The WHO-ISH report provides additional data on the absolute effects of treatment on cardiovascular risk (Table 29-2) . As shown, relatively small benefits have been seen in RCTs of about 5 years' duration in low-risk patients, although with more intensive therapy to lower blood pressure by 20/10 mm Hg,

they too can achieve more impressive protection.

All in all, these recommendations have placed the decision to treat individual patients with different levels of blood pressure and degrees of overall cardiovascular risk into a much more rational framework. Lest practitioners be concerned about the recommendation to withhold drug therapy from low-risk patients with blood pressure as high as 159/99 mm Hg, recall the experience of the placebo-treated half of the patients in the Australian trial[21] : Over 4 years, the average DBP fell below 95 mm Hg in 47.5 percent of patients with baseline DBP of 95 to 109 mm Hg, and increased morbidity and mortality were seen only in those whose average DBP remained above 100 mm Hg.

If drug therapy is not given, close surveillance of all patients must be provided, because from 10 to 17 percent of the placebo-treated patients in various trials had progression of their blood pressure to a level above that considered an indication for active treatment. Moreover, all patients should be strongly advised to use the appropriate life style modifications described beginning on page 975 .

Systolic Pressure in the Elderly

The New Zealand recommendations are that therapy be given to the elderly at lower levels of pressure because they "generally have a higher absolute risk of cardiovascular disease and therefore derive greater benefit from treatment."[19] The elderly achieved even greater protection from coronary disease in three trials. Furthermore, protection from congestive heart failure was even more impressive, therapy reducing the incidence by over 50 percent.[5] [13] Moreover,

TABLE 29-1 -- FACTORS INFLUENCING PROGNOSIS

Risk Factors for Cardiovascular Diseases	Target-Organ Damage	Associated Clinical Conditions

Used for Risk Stratification Levels of systolic and diastolic blood pressure (grades 1-3) Men >55 yr Women >65 yr Smoking Total cholesterol level >6.5 mol/liter (250 mg/dl) Diabetes Family history of premature cardiovascular diseaes	Left ventricular hypertrophy (electrocardiogram, echocardiogram, or radiograph) Proteinuria and/or slight elevation of plasma creatinine concentration (1.2-2.0 mg/dl) Ultrasound or radiological evidence of atherosclerotic plaque (carotid, ilac, and femoral arteries, aorta) Generalized or focal narrowing of the retinal arteries	Cerebrovascular disease Ischemic stroke Cerebral hemorrhage Transient ischemic attack Heart disease Myocardial infarction Angina Coronary revascularization Congestive heart failure Renal disease Diabetic nephropathy Renal failure (plasma creatinine concentration >2.0 mg/dl) Vascular disease Dissecting aneurysm Symptomatic arterial disease Advanced hypertensive retinopathy Hemorrhages or exudates Papilledema

Other Factors Adversely Influencing Prognosis

Reduced high-density lipoprotein cholesterol
Raised low-density lipoprotein cholesterol
Microalbuminuria in diabetes
Impaired glucose intolerance
Obesity
Sedentary life style
Raised fibrinogen level
High-risk socioeconomic group
High-risk ethnic group
High-risk geographical region

From Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hypertens 17:151-183, 1999.

Figure 29-2 Comparison of proportionate or relative *(top)* and absolute *(bottom)* benefit from reduction in the incidence of stroke in the six trials in the elderly, as well as in one other with similar design but in which the absolute risk of stroke was much lower. Event rates are for fatal and nonfatal stroke combined. Aust = Australian study; EWPHE = European Working Party on High Blood Pressure in the Elderly trial;

Coope = Cooper and Warrender; MRC = Medical Research Council trials; SHEP = Systolic Hypertension in the Elderly Program trial; STOP = Swedish Trial in Old Patients with Hypertension. (From Lever AF, Ramsay LE: Treatment of hypertension in the elderly. J Hypertens 13:571-579, 1995.)

TABLE 29-2 -- ABSOLUTE EFFECTS OF TREATMENT ON CARDIOVASCULAR RISK

From the results of randomized, controlled trials, it appears that each reduction of 10 to 14 mm Hg in systolic blood pressure and 5 to 6 mm Hg in diastolic blood pressure confers about two-fifths less stroke, one-sixth less coronary heart disease, and, in Western populations, one-third fewer major cardiovascular events overall.

In patients with grade I hypertension, monotherapy with most agents produces reductions in blood pressure of about 10/5 mm Hg. In patients with higher grades of hypertension, it is possible to achieve sustained blood pressure reductions of 20/10 mm Hg or more, particularly if combination drug therapy is used.

The estimated absolute effects of such blood pressure reductions on cardiovascular disease (CVD) risk (fatal plus nonfatal stroke or myocardial infarction) are as follows:

		Absolute Treatment Effects (CVD Events Prevented per 1000 Patients-Years)	
Patient Group	**Absolute Risk (CVD Events over 10yr)(%)**	***10/5 mm Hg***	***20/10 mm Hg***
Low risk	<15	<5	<9
Medium risk	15-20	5-7	8-11
High risk	20-30	7-10	11-17
Very high risk	>30	>10	>17

Between these strata, the estimated absolute treatment benefits range from less than five events prevented per thousand patient-years of treatment (low risk) to more than 17 events prevented per thousand patient-years of treatment (very high risk).

The absolute benefits for stroke and coronary artery disease will be augmented by smaller absolute benefits for congestive heart failure and renal disease.

These estimates of benefit are based on relative risk reductions observed in trials of about 5 years' duration. Longer-term treatment over decades could produce larger risk reductions.

From Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hyperten 17:151, 1999.

not included in Figure 29-1 are the results of the Syst-Eur trial, in which a long-acting dihydropyridine calcium antagonist, nitrendipine, was found to provide significant reductions in stroke and coronary events[22] and dementia[23] and particularly impressive protection against all endpoints among the diabetic patients enrolled in the trial.[24] Similar protection against stroke and coronary mortality has been shown in a similar trial of elderly Chinese with systolic hypertension.[25] Based on the four trials in the elderly patients with pure systolic hypertension, the need to consider systolic levels in the decision to treat is obvious. In fact, the difference between the typically elevated systolic levels and the usually lower diastolic levels, i.e., a widened pulse pressure in the elderly is most predictive of future cardiovascular risk.[26]

USE OF SURROGATE ENDPOINTS.

All of the preceding discourse on the benefits of therapy and the threshold for treatment has involved "hard" endpoints: morbidity and mortality. Some argue that softer endpoints should also be taken into account, using as surrogates one or another sign of cardiovascular damage that may be easier to assess and quicker to appear. These include regression of left ventricular hypertrophy or carotid artery stenosis and reduction of proteinuria. Most, however, hold to the need for the hard endpoints.

GOAL OF THERAPY

Once having decided to treat, the clinician must consider the goal of therapy. In the past, most physicians assumed that the effects of reduction of blood pressure on cardiovascular risk would fit a straight line downward (line A in Fig. 29-3) , [27] justifying the opinion "the lower, the better." However, as noted, data from large trials indicated a more gradual decline in risk when pressures were reduced to moderate levels (line B in Fig. 29-3) , DBP approximately 95 mm Hg in the IPPPSH trial.[28] Subsequently, Cruickshank[29] called attention to a J curve (line C in Fig. 29-3) , reflecting a progressive fall in risk as pressure is lowered, but only to a certain level; below that level, the risk for coronary ischemic events rises again.

Additional evidence for the J curve has been added to the six retrospective studies analyzed by Cruickshank, including two prospective studies of sizable numbers of patients.[30] [31] The apparent propensity to induce myocardial ischemia when pressures are lowered below a certain critical threshold may not apply to other vital organs. Therefore, maximal protection against stroke or renal damage may require greater reductions in pressure than the coronary circulation can safely handle.

Because the presence of a J curve could reflect lower blood pressures as a consequence of coronary disease rather than a cause, the Hypertension Optimal Treatment (HOT) trial was performed.[32] Almost 19,000 patients with initial mean blood pressure of 170/105 mm Hg were randomly allocated to one of three target diastolic pressures: 90, 85, or 80 mm Hg. Treatment was based on a long-acting dihydropyridine

calcium antagonist, felodipine, with additional drugs added to achieve the desired goal. Diastolic pressures were significantly reduced by more than 20 mm Hg in all three groups, but at the end, only 4 mm Hg separated them, so it was not possible to prove or disprove a J curve. The least cardiovascular mortality was seen at a blood pressure of 139/86 mm Hg; the least morbidity, at 138/83 mm Hg (Fig. 29-4) . In the absence of a placebo group, the absolute degree of protection could not be ascertained, but most of the benefit was noted in the 1500 diabetic patients who had a 51 percent reduction in major cardiovascular events in those in the below 80 mm Hg target group compared with the below 90 mm Hg target group.

Even though a J curve is suggested in the left portion of the lowest panel, the major positive result of this massive trial is that the safest blood pressure for most patients is less than 140/85 mm Hg, a level that only a small minority of patients are now achieving. As noted in JNC-6 and WHO-ISH guidelines, the goal must be less than 140/90 mm Hg for most patients, including the elderly, and less than 130/85 mm Hg for those at high risk, including all diabetic persons.

Figure 29-3 Three models representing hypothetical relationships between levels of blood pressure and risk of cardiovascular disease. (From Epstein FH: Proceedings of the XVth International Congress of Therapeutics, September 5-9, 1979. Brussels, Excerpta Medica, 1980.)

Even though the current guidelines have clarified the questions of whom to treat with drugs for mild hypertension and how much the pressure should be reduced, each patient must be considered separately, taking various factors into account. The foregoing discussion should indicate the wisdom of withholding drug therapy from many of these patients, at least until the effects of time and life style modifications have been given a chance, thereby avoiding too fast and too great reductions in pressure.

Once good control of blood pressure in a patient has been achieved, it may be possible to reduce or withdraw drug therapy. Perhaps one fourth of patients who have initially mild hypertension and who achieve good control with therapy will remain normotensive for at least 1 year after their therapy is stopped.[33] However, such patients need to remain under observation.

LIFE STYLE MODIFICATIONS

Interest in the use of various nondrug therapies, better called life style modifications, for the treatment of hypertension has risen markedly in the past few years, yet many practitioners either do not use them or use them in a casual, perfunctory manner. This hesitant attitude can be attributed both to the sparseness of firm evidence indicating that these therapies succeed and to the difficulty many have faced in convincing patients to adhere to them. This situation is likely to change: Evidence for the effectiveness of these approaches in lowering blood pressure is growing,[34] [35] techniques for improving adherence are being popularized, and patients seem increasingly willing to adopt changes in life style. These changes come at a propitious time, when many more individuals are being identified as hypertensive and are considered in need of lowering

of

Figure 29-4 Estimated incidence with 95 percent confidence intervals of cardiovascular events *(top three panels)* and mortality *(bottom panel)* blood pressure in the 18,790 hypertensive patients treated in the Hypertension Optimal Treatment (HOT) trial. (From Hansson L, Zanchetti A, Carruthers SG, et al: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment [HOT] randomised trial. Lancet 351:1755, 1998.)

blood pressure. Although most have turned first to drugs, the evidence presented in the previous section suggests that these can be safely withheld from many hypertensive individuals to allow life style modifications a chance to be effective. The need for strong and immediately effective therapy was clear when the majority of patients had fairly severe hypertension; however, as a larger number of patients with mild hypertension have entered the picture, a more gradual approach to their treatment seems more appropriate. In addition, increasing awareness of the need to address other risk factors, such as dyslipidemia and glucose intolerance, along with hypertension has given additional emphasis to the value of life style modifications that can favorably affect them as well.

Just as the increased awareness of the problem of patients' frequent poor adherence to drug therapy has led to attempts to improve the situation, similar attention toward adherence to life style modifications is likely to improve their effectiveness. These measures should be introduced gradually and gently. Too many and too drastic changes in life style may discourage patients from accepting them. Eventually, however, all hypertensive patients should benefit from moderate restriction of dietary salt, reduction of excess body weight, regular exercise, and moderation of alcohol intake.[20] The ability of these life style modifications to prevent hypertension has not been documented, although fewer subjects with high-normal pressures proceed into hypertension over 3 to 7 years while they practice these modalities.[36] [37] Because hypertension slowly develops over 20 to 40 years and normotensive persons have little if any decline in blood pressure even with potent antihypertensive drugs, the failure to lower blood pressure or prevent hypertension in a few years should not be taken as proof that these life style changes will not work over longer intervals.

AVOIDANCE OF TOBACCO.

The major pressor effect of tobacco is easily missed because patients are not allowed to smoke in places where blood pressures are recorded. With automatic monitoring, the effect is easy to demonstrate[38] (Fig. 29-5) , and blood pressure immediately falls when smokers quit.[39] Patients who smoke or dip snuff should be strongly and repeatedly told to stop. Failing that, they should be advised to monitor their blood pressure while they smoke because such pressures are at least partially responsible for increased risks for

cardiovascular disease and should be the target of antihypertensive therapy.

WEIGHT REDUCTION.

Relatively small increases in body weight increase the incidence of hypertension,[40] and even small decreases in excess weight lower blood pressure.[34] In a review of adequately controlled intervention studies, a

Figure 29-5 Changes in systolic blood pressure (SBP) over 15 minutes after smoking the first cigarette of the day within the first 5 minutes (solid circles), during no activity (open-circles), and during sham smoking (triangles) in normotensive smokers. (From Groppelli A, Giorgi DMA, Omboni S, et al: Blood pressure and heart rate response to repeated smoking before and after beta blockade and selective alpha$_1$ -inhibition. J Hypertens 10:495, 1992.)

1.0-kg decrease in body weight was accompanied by an average reduction of 1.6/1.3 mm Hg in blood pressure.[41] The fall in blood pressure may reflect many effects including improvements in insulin sensitivity, amelioration of sleep apnea, and decreased sensitivity to sodium. Although the rate of recidivism among obese persons is high, an attempt at weight reduction in all obese hypertensive patients should be made, using whatever level of caloric restriction a patient is able to maintain.

DIETARY SODIUM RESTRICTION.

On page 952 , evidence incriminating the typically high sodium content of the diet of persons living in developed, industrialized societies was presented as a cause of hypertension. Once hypertension is present, modest salt restriction may help lower the blood pressure. In a review by Cutler and colleagues of 32 well-controlled intervention studies in which daily intake (based on urinary sodium excretion) was reduced by a median of 77 mmol/24 hr, blood pressures fell an average of 4.8/2.5 mm Hg in the hypertensive individual.[42] There is probably a dose-response relation--the more sodium reduction, the greater the blood pressure decline. In a small but well-controlled study, the reduction in blood pressure was shown to be 8/5 mm Hg on a daily sodium intake of 100 mmol and 16/9 mm Hg on a 50 mmol/day intake.[43]

However, rigid degrees of sodium restriction are not only difficult for patients to achieve but may also be counterproductive.[44] The marked stimulation of renin-aldosterone and sympathetic nervous activity that accompanies rigid sodium restriction may prevent the blood pressure from falling and increase the amount of potassium wastage if diuretics are concomitantly used. Not all hypertensive persons respond to a moderate degree of sodium restriction to the recommended level of 100 mmol sodium, or 2.4 gm/day. Blacks and elderly patients may be more responsive to sodium restriction, perhaps

because of their lower renin responsiveness.

Even if the blood pressure does not fall with moderate degrees of sodium restriction, patients may still benefit: improved beta-adrenergic responsiveness.[45] Increased antihypertensive effectiveness of other drugs[46] less diuretic-induced potassium wastage, and reduction in left ventricular hypertrophy[47] all have been reported among patients on moderate sodium restriction. Although there is no certainty that moderate sodium restriction will help, the little evidence suggesting that it will hurt[48] has been shown to be invalid.[49] In overweight persons, a lower sodium intake was associated with a reduced risk of cardiovascular disease.[49]

Therefore, I consider sodium restriction to be useful for all persons, as a preventive measure in those who are normotensive and, more certainly, as partial therapy in those who are hypertensive. The easiest way to accomplish moderate sodium restriction is to substitute natural foods for processed foods, because natural foods are low in sodium and high in potassium whereas most processed foods have had sodium added and potassium removed. It is hoped that food processors will gradually reduce the large amounts of salt they often add to processed foods, but in the meantime, patients should be asked to avoid those foods whose label indicates more than 300 mg of sodium per portion. Additional guidelines include the following:

1. Add no sodium chloride to food during cooking or at the table.
2. If a salty taste is desired, use a half sodium and half potassium chloride preparation (such as Lite Salt) or a pure potassium chloride substitute.
3. Avoid or minimize the use of "fast foods," many of which have high sodium content.
4. Recognize the sodium content of some antacids and proprietary medications. (For example, Alka-Seltzer contains more than 500 mg of sodium; Rolaids is virtually sodium free.)

POTASSIUM SUPPLEMENTATION.

Some of the advantages of a lower sodium intake may relate to its tendency to increase body potassium content, both by a coincidental increase in dietary potassium intake and by a decrease in potassium wastage if diuretics are being used. Potassium deficiency exerts many effects that may increase blood pressure, and potassium infusions increase the vasodilating effect of acetylcholine, apparently through the nitric oxide pathway.[50] Potassium supplements have been shown to reduce the blood pressure an average of 3.1/2.0 mm Hg in 33 RCTs published before July 1995.[51] Nonetheless, potassium supplements are too costly and potentially hazardous for routine use in normolcalemic hypertensive persons. Patients should be protected from potassium depletion and encouraged to increase dietary potassium intake, which may be enough to lower blood pressure.

MAGNESIUM SUPPLEMENTATION.

Only a few controlled trials find an effect on blood pressure with magnesium

supplements.[52] However, those who are magnesium depleted may not be able to replete concomitant potassium deficiency.[53]

CALCIUM SUPPLEMENTATION.

An increase in free calcium concentration in vascular smooth muscle cells may be a final step in the pathogenesis of primary hypertension. Nonetheless, some hypertensive patients have a lower calcium intake and higher urinary calcium excretion than do normotensive persons.[54] In 42 mostly short-term studies of either calcium supplements (in 33) or dietary intervention (in 9) in 4560 nonpregnant adults, the blood pressure fell 1.44/0.84 mm Hg.[55] Because calcium supplements sometimes raise blood pressure and increase the risk of kidney stones, the best course is to ensure that calcium intake is not inadvertently reduced by reduction of milk and cheese consumption in an attempt to reduce saturated fat and sodium intake when supplemental calcium is not taken.

OTHER DIETARY CHANGES.

Significant reductions in blood pressure were observed in hypertensive persons who ate a diet rich in fruits and vegetables, an effect that was further accentuated when low-fat dairy foods were substituted for high-fat foods.[35] The effect was greater in hypertensive than in normotensive persons and in blacks than in whites. This fall in blood pressure, accomplished without change in sodium or caloric intake, could reflect increases in fiber, potassium, or other ingredients. Some lowering of the blood pressure has been noted in studies of a lacto-ovo-vegetarian diet,[56] high fiber intake,[57] and high doses of omega-3 fatty acids from fish oil.[58] Consumption of dried garlic powder lowered diastolic pressure in four of seven trials compared with placebo.[59]

In 11 carefully controlled trials involving 522 subjects who consumed an average of 5 cups of caffeine-containing coffee, the mean blood pressure rose 2.4/1.2 mm Hg.[60] An even greater effect was noted in elderly hypertensive individuals.[61] Even though consumption of tea has been found to be associated with a lower risk of myocardial infarction,[62] it too may raise blood pressure.[63]

MODERATION OF ALCOHOL.

Moderate alcohol consumption, less than 1 oz of ethanol per day, does not increase the prevalence of hypertension. Heavier drinking clearly exerts a pressor effect that makes *alcohol abuse the most common cause of reversible hypertension.*[64] One to two portions of alcohol-containing beverages a day, containing 0.5 to 1.0 oz of ethanol, need not be prohibited, particularly because fewer coronary events[65] and strokes[66] have been noted in those who consume that amount.

PHYSICAL EXERCISE.

Although the systolic pressure rises considerably during dynamic (aerobic) exercise, vascular compliance increases[67] and resting blood pressure usually falls[68] in hypertensive persons after regular exercise programs. Even in obese individuals,

cardiorespiratory fitness is associated with lower cardiovascular disease mortality.[69] Although pure static exercise acutely raises both systolic and diastolic pressures, repetitive circuit weight training also lowers blood pressure.[70]

RELAXATION TECHNIQUES.

A review of 26 reports of various forms of relaxation--transcendental meditation, yoga, biofeedback, psychotherapy--reports that they were no more effective in lowering blood pressure than were sham controls.[71]

COMBINED THERAPIES

When several life style modifications are combined, additional antihypertensive effects may accrue. The best study is the placebo arm of the Treatment of Mild Hypertension Study (TOMHS),[2] in which 234 mildly hypertensive persons followed a 48-month regimen of moderate sodium restriction, weight loss, regular exercise, and moderation of alcohol use. Despite relatively small changes in weight (average loss of 6.6 lbs), sodium intake (reduction of 10 percent), exercise level, and alcohol consumption, these patients had an 8.6/8.6 mm Hg decline in blood pressure at the end of the 4-year program. Moreover, they experienced improvements in lipid profile and reduction in left ventricular mass.

THE POTENTIAL OF LIFE STYLE MODIFICATIONS

Part of the antihypertensive effect reported in this and other trials of life style modification may be attributable to the nonspecific reduction in blood pressure so often noted when repeated readings are taken. Such decreases may reflect a statistical regression toward the mean, a placebo effect, or relief of anxiety and stress with time. The same phenomenon is probably also responsible for much of the initial response to drug therapy, so that success may be attributed to both drugs and nondrugs when it is deserved by neither.

Nonetheless, increasingly long and strong evidence from controlled studies attests to the efficacy of multifaceted nondrug programs to reduce the blood pressure. Whether such success can be achieved by individual practitioners is uncertain. However, because help is available, including various educational materials for patients, professional assistants such as dietitians and psychologists, and groups organized for weight reduction, exercise, and relaxation therapies, the effort seems both increasingly easy and likely to be successful in lowering blood pressure.

ANTIHYPERTENSIVE DRUG THERAPY

If the life style modifications just described are not followed or prove to be ineffective, or

if the level of hypertension at the onset is so high that immediate drug therapy is deemed necessary, the general guidelines listed in Table 29-3 should be helpful in improving patients' adherence to lifelong treatment.

General Guidelines

The guidelines listed in Table 29-3 are all aimed at providing effective 24-hour control of hypertension in a manner that encourages adherence to the regimen. The approach is based on known pharmacological principles and proven ways to improve adherence. It is designed for the 90 percent of patients with fairly mild hypertension, in whom a gradual approach is feasible.

Once the selection of the most appropriate agent for initial therapy has been made (by a process that is discussed further in the next section), a relatively low dose of a single drug should be started, aiming for a reduction of 5 to 10 mm Hg in blood pressure at each step. Many physicians, by nature and training, desire to control a patient's hypertension rapidly and completely. Regardless of which drugs are used, this approach often leads to undue fatigue,

TABLE 29-3 -- GENERAL GUIDELINES TO IMPROVE PATIENTS' ADHERENCE TO ANTIHYPERTENSIVE THERAPY

1. Be aware of the problem of nonadherence and be alert to signs of patients' nonadherence.
2. Establish the goal of therapy: to reduce blood pressure to normotensive levels with minimal or no side effects.
3. Educate the patient about the disease and its treatment.
   a. Involve the patient in decision-making.
   b. Encourage family support.
4. Maintain contact with the patient.
   a. Encourage visits and calls to allied health personnel.
   b. Allow the pharmacist to monitor therapy.
   c. Give feedback to the patient via home blood pressure readings.
   d. Make contact with patients who do not return.
5. Keep care inexpensive and simple.
   a. Do the least work-up needed to rule out secondary causes.
   b. Obtain follow-up laboratory data only yearly unless indicated more often.
   c. Use home blood pressure readings.
   d. Use nondrug, no-cost therapies.
   e. Use the fewest daily doses of drugs needed.
   f. If appropriate, use combination tablets.
   g. Tailor medication to daily routines.
6. Prescribe according to pharmacological principles.

a. Add one drug at a time.
b. Start with small doses, aiming for 5 to 10 mm Hg reductions at each step.
c. Prevent volume overload with adequate diuretic and sodium restriction.
d. Take medication immediately on awakening or after 4A.M. if patient awakens to void.
e. Ensure 24-hour effectiveness by home or ambulatory monitoring.
f. Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy.
g. Be willing to stop unsuccessful therapy and try a different approach.
h. Adjust therapy to ameliorate side effects that do not spontaneously disappear.

From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 188.

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weakness, and postural dizziness, which many patients find intolerable, particularly when they felt well before therapy was begun. Although hypokalemia and other electrolyte abnormalities may be responsible for some of these symptoms, a more likely explanation has been provided by the studies of Strandgaard and Haunso.[72] As shown in Figure 29-6 , they demonstrated the constancy of cerebral blood flow by autoregulation over a range of mean arterial pressures from about 60 to 120 mm Hg in normal subjects and from 110 to 180 mm Hg in patients with hypertension. This shift to the right protects hypertensive patients from a surge of blood flow, which could cause cerebral edema. However, the shift also predisposes hypertensive patients to cerebral ischemia when blood pressure is lowered.

Figure 29-6 Mean cerebral blood flow autoregulation curves from normotensive, severely hypertensive, and effectively treated hypertensive patients are shown. (Modified from Strandgaard [Circulation 53:720, 1976.] From Strandgaard S, HaunsO S: Why does antihypertensive treatment prevent stroke but not myocardial infarction? Lancet 2:658, 1987. © by the Lancet Ltd.)

Figure 29-7 Theoretical therapeutic and toxic logarithmic-linear dose-response curves. The horizontal axis is a logarithmic scale with arbitrary dose units. The vertical axis is a linear scale showing percentage of maximum possible response. See text for discussion. (From Fagan TC: Remembering the lessons of basic pharmacology. Arch Intern Med 154:1430, 1994. Copyright 1994 American Medical Association.)

The lower limit of autoregulation necessary to preserve a constant cerebral blood flow in hypertensive patients is a mean of about 110 mm Hg. Thus, acutely lowering the pressure from 160/110 mm Hg (mean=127) to 140/85 mm Hg (mean=102) may induce cerebral hypoperfusion, although hypotension in the accepted sense has not been produced. This provides an explanation for what many patients experience at the start of antihypertensive therapy, i.e., manifestations of cerebral hypoperfusion, even though

blood pressure levels do not seem inordinately low.

Thus, the approach to antihypertensive therapy should be gradual in order to avoid symptoms related to overly aggressive blood pressure reduction. Fortunately, as shown in the middle of Figure 29-6 , if therapy is continued for a period, the curve of cerebral autoregulation shifts back toward normal, allowing patients to tolerate greater reductions in blood pressure without experiencing symptoms.

STARTING DOSAGES.

The need to start with a fairly small dose also reflects a greater responsiveness of some patients to doses of medication that may be appropriate for the majority. All drugs exert increasing effect with increasing doses, portrayed by a log-linear dose-response curve[73] (Fig. 29-7) . However, different patients require different absolute amounts of drug for their own dose response.

As a hypothetical example, for the majority of patients, 50 mg of the beta blocker atenolol would provide a moderate response, shown as point A on the therapeutic effect curve, whereas a dose of 25 mg would provide only a minimal response. At dose A, providing the significant albeit partial response, the side effects would be minimal, as shown by point A
on the curve of toxic effect. If a starting dose of 100 mg were used, the therapeutic effect would be near maximal (point B) but the side effects would be much greater as well (point B
). Therefore, a lower starting dose is preferable for most patients.

However, the response to a given dose is not the same for all patients but rather assumes a bell-shaped curve; some patients are very sensitive to that dose and some very resistant, the majority having a moderate response. Therefore, a significant minority of patients--the very sensitive ones--would obtain a near-maximal response to the 25-mg dose and would better be started on 12.5 mg in order to achieve a moderate therapeutic effect (point A) with minimal side effects (point A
). Without knowing how individual patients will respond, the safest and easiest approach is to start at a dose that probably is not enough for most patients.

The situation was well described by Herxheimer.[74] "For a new drug to penetrate the market quickly, it should be rapidly effective in a high proportion of patients and simple to use. To achieve this, the dosage of the first prescription is therefore commonly set at about the ED_{90} level, i.e., the dose which the early clinical (phase 2) studies have been shown to be effective in 90 percent of the target population, provided that the unwanted effects at this dose are considered acceptable. In 25 percent of patients, a smaller--perhaps much smaller--dose (the ED_{25}) will be effective. The patients in this quartile are the most sensitive to the drug and are liable to receive far more than they need if they are given the ED_{90} . They are also likely to be more sensitive to the dose-related side effects of the drug."

As I have written,[75] Herxheimer goes on to recommend a logical solution: Starting

doses should be less than the usual maximal effective dose. For this to be effective, however, physicians must be willing to start most patients with a dose of medication that will not be fully effective. As he states, "The disadvantage from the marketing standpoint is that for the majority of patients the dose must be titrated. That is time-consuming for doctors and patients and more difficult to explain to them. A drug requiring dose titration cannot be presented as the 'quick fix', the instant good news that marketing departments love."[74] The quick fix is inappropriate for most hypertensive patients. To allow for autoregulation of blood flow to maintain perfusion to vital organs when perfusion pressure is lowered, the decline in pressure should be relatively small and gradual.[75] More precipitous reductions in pressure, as frequently occur with larger starting doses, may induce considerable hypoperfusion that results in symptoms that are at least bothersome (fatigue, impotence) and that may be potentially hazardous (postural hypotension, coronary ischemia). It is far better to start low and go slow.[75]

DRUG COMBINATIONS.

Combinations of smaller doses of two drugs from different classes have been marketed to take advantage of the differences in the dose-response curves for therapeutic and toxic (side) effects shown in Figure 29-7 .[20] By combining two drugs, each at a dose near point A, a greater antihypertensive effect is provided (up to point B), but because the side effects are not additive for different classes of drugs, they remain at point A . A combination of low doses of a beta blocker (bisoprolol) and a diuretic (hydrochlorothiazide) has been approved for initial therapy for hypertension, after it was shown to provide antihypertensive efficacy far beyond that of each component but with no more side effects than with each separately.[76] More low-dose combinations are likely to become available. For the 50 percent or so of patients who do not respond to their initial therapy, combinations of two, three, or four drugs are needed.[32] Many of these can be provided in single tablets, thereby reducing cost and possibly improving adherence.[77]

COMPLETE COVERAGE WITH ONCE DAILY DOSING.

A number of choices within each of the six major classes of antihypertensive drugs now available provide full 24-hour efficacy. Therefore, single daily dosing should be feasible for virtually all patients, thereby improving adherence to therapy. Moreover, the use of longer-acting agents avoids the potential of inducing too great a peak effect in order to provide an adequate effect at the end of the dosing interval (the trough). As seen in Figure 29-8 , moderate doses of various formulations of calcium antagonists provide similar peak effects but different trough effects at the end of 24 hours.[78] Moreover, because many patients occasionally skip a dose of their drugs, there is an additional value in using agents with inherently long duration of action that covers the skipped dose as well (Fig. 29-9) .

Long-acting choices are available within each class.[20] However, because patients differ not only in terms of degree of response but also in terms of the duration of effect, the prudent course is to document the patient's response at the end of the dosing interval by home or ambulatory monitoring. With this approach, the abrupt surge in blood pressure that occurs on awakening will be blunted, and, it is hoped, patients can be

better protected from the increased incidence of cardiovascular catastrophes at this critical time.[79]

If short-acting medications are taken at bedtime to ensure coverage in the early morning, ischemia to vital organs might be induced by the combination of the maximal effect of the drug within the first 3 to 6 hours after intake and the usual nocturnal decline in pressure.[80] Therefore, the safest course is to take medications with 24-hour duration of action as early in the morning as possible, as early as 4 or 5 A.M. if the patient awakens to urinate.

THE INITIAL CHOICE.

The initial choice of antihypertensive therapy is perhaps the most important decision made

Figure 29-8 Trough blood pressure changes (red bars), peak blood pressure changes (pink bars), and trough-to-peak ratios (numbers) observed after treatment with various calcium antagonists. All drugs were given on a once-daily basis. V = verapamil; NT = nitrendipine; D = diltiazem extended release; N GITS = nifedipine gastrointestinal therapeutic system; A = amlodipine; SBP = systolic blood pressure; DBP = diastolic blood pressure. *P < 0.05; **P < 0.01 versus baseline (From Mancia G, Cattaneo BM, Omboni S, Grassi G: Clinical benefits of a consistent reduction in blood pressure. J Hypertens 16 [Suppl 6]:S35, 1998.)

in the treatment process. That drug is likely to be effective in about half the patients and, if no significant overt side effects occur, may be taken for many years. If the choice is ineffective or bothersome, the patient's confidence may be shaken, postponing or preventing adequate control. Two guidelines by expert committees have been published.[1] [20] The JNC-6 recommends diuretics or beta blockers as initial therapy for the relatively small portion of patients with uncomplicated hypertension, and drugs from all of the six major classes for patients with either a compelling indication or a comorbid condition that has been shown to respond well to a particular therapy.[20] The 1999 WHO-ISH

Figure 29-9 Forty-eight-hour systolic and diastolic blood pressure profile in 24 elderly subjects with isolated systolic hypertension. The 48-hour monitoring was done at the end of a 6-month administration of amlodipine at a dose of 5 to 10 mg daily and in the pretreatment placebo period. Amlodipine was administered at the beginning of the 48-hour monitoring period while the subsequent dose to be given 24 hours later was purposely missed. (From Mancia G, Cattaneo BM, Omboni S, Grassi G: Clinical benefits of a consistent reduction in blood pressure. J Hypertens 16 [Suppl 6]:S35, 1998.)

TABLE 29-4 -- GUIDELINES FOR SELECTING DRUG TREATMENT

CLASS OF DRUG	COMPELLING INDICATIONS	POSSIBLE INDICATIONS	COMPELLING CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidemia Sexually active men
Beta blockers	Angina After myocardial infarction Tachyarrhythmias	Heart failure Pregnancy Diabetes	Asthma and COPD Heart block*	Dyslipidemia Athletes and physically active patients Peripheral vascular disease
ACE inhibitors	Heart failure Left ventricular dysfunction After myocardial infarction Diabetic nephropathy		Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Calcium antagonists	Angina Elderly patients Systolic hypertension	Peripheral vascular disease	Heart block	Congestive heart failure
Alpha blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidemia		Orthostatic hypotension
Angiotensin II antagonists	ACE inhibitor cough	Heart failure	Pregnancy Bilateral renal artery stenosis Hyperkalemia	

COPD=chronic obstructive pulmonary disease.

*Grade 2 or 3 atrioventricular block;

grade 2 or 3 atrioventricular block with verapamil or diltiazem;

verapamil or diltiazem. ACE=angiotensin-converting enzyme;

guidelines broaden the number of compelling indications (Table 29-4) but give equal weight to all classes of drugs if there are no specific reasons to use one, stating that

"There is as yet no evidence that the main benefits of treating hypertension are due to any particular drug property rather than to lowering of blood pressure per se."[1]

In practice, little difference remains between these two major guidelines. Until the many additional trials comparing different types of drugs now in progress are completed,[81] these guidelines should be followed. Appropriately individualized therapy will thereby be provided, maximizing the potential for a good fit between patient need and drug potential.

SUBSTITUTION.

Even after a careful attempt to select the most appropriate drug for an individual patient, the choice may be either ineffectual in perhaps a third or unacceptable because of side effects in another 10 to 20 percent of all patients. Although the overall effectiveness of all approved drugs is about equal in the general population, individual patients show considerable variability in their response to different drugs.[82] Therefore, the physician must be willing to discontinue the initial choice and try a drug from another category. In a more structured trial-and-error approach that has been described, each patient is put through several double-blind, randomized crossover trials against placebos to determine the best drug.[83] However, this approach probably is too much trouble for most physicians and patients. Although other approaches have been recommended, including one based on the renin profile,[84] the general principles shown in Tables 29-3 and 29-4 should serve well to ensure that each patient receives a drug likely to provide good control and few side effects.

For patients with more severe hypertension, in whom the first choice can be expected to be only partially effective, the stepped-care approach is logical. A diuretic enhances the effectiveness of most other drugs used, preventing the "pseudotolerance" that develops because of the fluid retention that frequently follows the use of some adrenergic blocking drugs and vasodilators. Increasingly, an angiotensin-converting enzyme (ACE) inhibitor or calcium antagonist is being chosen as the second or third drug when triple therapy is needed.

THE GOAL OF THERAPY.

As discussed earlier, caution is advised in lowering diastolic pressure below 80 mm Hg, the apparent nadir of the J curve, particularly in patients prone to coronary disease. On the other hand, lower levels are needed in high-risk patients such as those with diabetes and nephropathy.[85] The overriding problem is not that a few patients may be endangered by too aggressive therapy but rather that even with presumably adequate current therapy, maximal protection against cardiovascular complications is not being provided.[86] Recall that twice as many hypertensive patients in the United States are being treated as are being controlled to a blood pressure of 140/90 mm Hg, providing reasonable protection to only 27 percent of patients.[20]

DIURETICS (See also Chap. 18)

Diuretics useful in the treatment of hypertension may be divided into four major groups by their primary site of action within the tubule, starting in the proximal portion and moving to the collecting duct[86A] [86B] : (1) agents acting on the proximal tubule, such as carbonic anhydrase inhibitors, which have limited antihypertensive efficacy; (2) loop diuretics; (3) thiazides and related sulfonamide compounds; and (4) potassium-sparing agents. A thiazide is the usual choice, often in combination with a potassium-sparing agent. Loop diuretics should be reserved for those patients with renal insufficiency or resistant hypertension.

MECHANISM OF ACTION.

All diuretics initally lower the blood pressure by increasing urinary sodium excretion and by reducing plasma volume, extracellular fluid volume, and cardiac output. Within 6 to 8 weeks, the lowered plasma, extracellular fluid volume, and cardiac output return toward normal. At this point and beyond, the lower blood pressure is related to a decline in peripheral resistance, thereby improving the underlying hemodynamic defect of hypertension. The mechanism responsible for the lowered peripheral resistance may involve potassium channel activation,[87] but initial diuresis is needed because diuretics fail to lower the blood pressure when the excreted sodium is returned or when given to patients who have nonfunctioning kidneys and are undergoing long-term dialysis. With the shrinkage in blood volume and lower blood pressure, increased secretion of renin and aldosterone retards the

continued sodium diuresis. Both renin-induced vasoconstriction and aldosterone-induced sodium retention prevent continued diminution of body fluids and progressive reduction in blood pressure while diuretic therapy is continued.

CLINICAL EFFECTS.

With continuous diuretic therapy, blood pressure usually falls about 10 mm Hg, although the degree depends on various factors, including the initial height of the pressure, the quantity of sodium ingested, the adequacy of renal function, and the intensity of the counterregulatory renin-aldosterone response.[87A] The antihypertensive effect of the diuretic persists indefinitely, although it may be overwhelmed by dietary sodium intake exceeding 8 gm/day.

If other antihypertensive drugs are used, a diuretic may also be needed. Without a concomitant diuretic, antihypertensive drugs that do not block the renin-aldosterone mechanism may cause sodium retention. This mechanism probably reflects the success of the drugs in lowering the blood pressure and may involve the abnormal renal pressure-natriuresis relationship that is presumably present in primary hypertension. Just as more pressure is needed to excrete a given load of sodium in a hypertensive

individual, so does a lowering of pressure toward normal incite sodium retention.

The critical need for adequate diuretic therapy to keep intravascular volume diminished has been repeatedly documented.[88] Therefore, diuretics are likely to continue to be widely used in antihypertensive therapy. Drugs that inhibit the renin-aldosterone mechanism, such as ACE inhibitors, or drugs that induce some natriuresis themselves, such as calcium antagonists, may continue to work without the need for concomitant diuretics. However, a diuretic enhances the effectiveness of all other types of drugs, including calcium antagonists.[89]

DOSAGE AND CHOICE OF AGENT.

Most patients with mild to moderate hypertension and serum creatinine concentrations less than 2.0 mg/dl respond to the lower doses of the various diuretics listed in Table 29-5 . An amount equivalent to 12.5 mg of hydrochlorothiazide is usually adequate; larger doses have some additional antihypertensive effect but at the price of additional potassium wastage and insulin resistance. For uncomplicated hypertension, a moderately long-acting thiazide is a logical choice, and a single morning dose of hydrochlorothiazide provides a 24-hour antihypertensive effect. The nonthiazide agent indapamide has special properties that make it an attractive choice; it seldom disturbs lipid or glucose levels.[90] With renal failure, manifested by a serum creatinine level exceeding 2.0 mg/dl or creatinine clearance less than 25 ml/min, thiazides are usually not effective, and repeated doses of furosemide, one or two doses of torsemide, or a single dose of metolazone is needed.

SIDE EFFECTS.

A number of biochemical changes often accompany successful diuresis, including a decrease in plasma potassium level and increases in glucose, insulin, and cholesterol levels (Fig. 29-10) . Most of these are minimized or absent with low doses of diuretic.

Hypokalemia.

The degree of potassium wastage and hypokalemia is directly related to the dose of diuretic; serum potassium level falls an average of 0.7 mmol/liter with 50 mg of hydrochlorothiazide 0.4 with 25, and little if any with 12.5.[91] Hypokalemia due to high doses of diuretic may precipitate potentially hazardous ventricular ectopic activity and increase the risk of primary cardiac arrest,[92] even in patients not known to be susceptible because of concomitant digitalis therapy or myocardial irritability.

Most patients are unaware of mild diuretic-induced hypokalemia, although it may contribute to leg cramps, polyuria, and muscle weakness, but subtle interference with antihypertensive therapy may accompany even mild hypokalemia, and correction of hypokalemia may result in a reduction in blood pressure.[93]

TABLE 29-5 -- DIURETICS AND POTASSIUM-SPARING AGENTS

AGENT	DAILY DOSE (mg)	DURATION OF ACTION (hr)
Thiazides		
Bendroflumethiazide (Naturetin)	01.25-5.0	>18
Benzthiazide (Aquatag, Exna)	12.5-50	12-18
Chlorothiazide (Diruil)	125-500	6-12
Cyclothiazide (Anhydron)	0.125-1	18-24
Hydrochlorothiazide (Esidrix, HydroDIURIL, Oretic)	6.25-50	12-18
Hydroflumethiazide (Saluron)	12.5-50	18-24
Methyclothiazide (Enduron)	2.5-5.0	>24
Polythiazide (Renese)	1-4	24-48
Trichlormethiazide (Metahydrin, Naqua)	1-4	>24
Related Sulfonamide Compounds		
Chlorthalidone (Hygroton)	12.5-50	24-72
Indapamide (Lozol)	1.25-2.5	24
Metolazone (Mykrox, Zaroxolyn)	0.5-10	24
Quinethazone (Hydromox)	25-100	18-24
Loop Diuretics		
Bumetanide (Bumex)	0.5-5	4-6
Ethacrynic acid (Edecrin)	25-100	12
Furosemide (Lasix)	40-480	4-6
Torsemide (Demadex)	5-40	12
Potassium-Sparing Agents		
Amiloride (Midamor)	5-10	24
Spironolactone (Aldactone)	25-100	8-12
Triamterene (Dyrenium)	50-100	12

From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 190.

Prevention of hypokalemia is preferable to correction of potassium deficiency. The following maneuvers should help prevent diuretic-induced hypokalemia:

Use the smallest dose of diuretic needed.

Use a moderately long-acting (12- to 18-hour) diuretic, such as hydrocholorothiazide, because longer-acting drugs (e.g., chlorthalidone) may increase potassium loss.

Restrict sodium intake to less than 100 mmol/day (i.e., 2.4 gm sodium).

Increase dietary potassium intake.

Restrict concomitant use of laxatives.

Use a combination of a thiazide with a potassium-sparing agent except in patients with renal insufficiency or in association with an ACE inhibitor or angiotensin II-receptor blocker.

Concomitant use of a beta blocker or an ACE inhibitor diminishes potassium loss by blunting the diuretic-induced rise in renin-aldosterone.

If hypokalemia is to be treated, these principles should be followed, along with some form of supplemental potassium. Potassium chloride is preferred for correction of the associated alkalosis. If tolerated, granular potassium chloride can be given as a salt substitute; extra potassium will thereby be provided while sodium intake is reduced. Caution is necessary when supplemental potassium chloride is given to older patients with borderline renal function, in whom hyperkalemia may be induced.

HYPOMAGNESEMIA.

In some patients, concomitant diuretic-induced magnesium deficiency prevents restoration of intracellular deficits of potassium[94] so that hypomagnesemia should be corrected. Magnesium

Figure 29-10 The mechanisms by which chronic diuretic therapy may lead to various complications. The mechanism for hypercholesterolemia remains in question, although it is shown as arising via hypokalemia. Cl = Clearance; PRA = plasma renin activity; GFR = glomerular filtration rate. (From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 193.)

deficiency may also be responsible for some of the arrhythmias ascribed to hypokalemia.

HYPERURICEMIA.

The serum uric acid level is elevated in as many as one-third of untreated hypertensive patients. With long-term high-dose diuretic therapy, hyperuricemia appears in another

third of patients, probably as a consequence of increased proximal tubular reabsorption accompanying volume contraction. Diuretic-induced hyperuricemia may precipitate acute gout, most frequently in those who are obese and consume large amounts of alcohol.[95] Because asymptomatic hyperuricemia does not cause urate deposition, most investigators agree that it need not be treated. If therapy is used, a uricosuric drug such as probenecid should be given.

HYPERLIPIDEMIA.

Serum cholesterol levels often rise after diuretic therapy, but after 1 year, no adverse effects were noted in those who responded to smaller doses.[96]

HYPERGLYCEMIA AND INSULIN RESISTANCE.

High doses of diuretics may impair glucose tolerance and precipitate diabetes mellitus, probably because they increase insulin resistance and hyperinsulinemia.[97] The manner by which diuretics increase insulin resistance is uncertain, but in view of the many potential pressor actions of hyperinsulinemia (see Chap. 28) , this could be a significant problem.

HYPERCALCEMIA.

A slight rise in serum calcium levels, less than 0.5 mg/dl, is frequent with thiazide diuretic therapy, at least in part because increased calcium reabsorption accompanies the increased sodium reabsorption in the proximal tubule induced by contraction of extracellular fluid volume.[98] The rise is of little concern except in patients with previously unrecognized hyperparathyroidism, who may experience a much more marked rise. On the other hand, the diuretic-induced positive calcium balance is associated with a reduction in the incidence of osteoporosis in the elderly.[99]

IMPOTENCE.

An increase in the incidence of impotence was noted among men who took 15 mg of chlorthalidone, the diuretic being the only one of five classes of agents attended by this effect.[100]

RENAL CELL CARCINOMA.

A significant increase in renal cell carcinoma among diuretic users was found in a search of nine case control and three cohort studies.[101] Methodological problems are inherent in this type of analysis,[102] and the overall positive effects of diuretic use far outweigh their hazard, a situation similar to oral contraceptive use.

LOOP DIURETICS.

Loop diuretics are usually needed in the treatment of hypertensive patients with renal

failure, defined here as a serum creatinine level exceeding approximately 2.0 mg/dl. Furosemide has been most widely used, although either torsemide or metolazone may be as effective, and each requires only a single daily dose. Many physicians use furosemide in the management of uncomplicated hypertension, but this drug provides less antihypertensive action when given once or twice a day than do longer-acting diuretics, which maintain a slight volume contraction.

POTASSIUM-SPARING AGENTS.

These drugs are normally used in combination with a thiazide diuretic. Of the three currently available, one (spironolactone) is an aldosterone antagonist; the other two (triamterene and amiloride) are direct inhibitors of potassium secretion. In combination with a thiazide diuretic, they diminish the amount of potassium wasting. Although they are more expensive than thiazides alone, they may decrease the total cost of therapy by reducing the need to monitor and treat potassium depletion. Moreover, low doses of spironolactone may prevent myocardial fibrosis and reduce mortality in patients with heart failure.[103]

An Overview of Diuretics in Hypertension

Diuretics have been effective for the treatment of millions of hypertensive patients during the past 40 years. They reduce DBP and maintain it below 90 mm Hg in about half of all hypertensive patients, providing the same degree of effectiveness as most other antihypertensive drugs. In two groups that constitute a rather large portion of the hypertensive population, the elderly and blacks, diuretics may be particularly effective.[104] One-half of a diuretic tablet per day is usually all that is needed, minimizing cost and maximizing adherence to therapy. Even lower doses, i.e., 6.25 mg of hydrochlorothiazide, may be adequate when combined with other drugs.[76]

The side effects of high-dose diuretic therapy are usually not overly bothersome, but the hypokalemia, hypercholesterolemia, hyperinsulinemia, and worsening of glucose tolerance that often accompany prolonged high-dose diuretic therapy gave rise to concerns about their long-term benignity. However, lower doses are usually just as potent as higher doses in lowering the blood pressure and less likely to induce metabolic mischief.[91] Therefore, the advocacy of low-dose diuretic therapy in the 1997 JNC-6 report[20] and the 1999 WHO-ISH report[1] is appropriate.

ADRENERGIC INHIBITORS

A number of drugs that inhibit the adrenergic nervous system are available, including some that act centrally on vasomotor center activity, peripherally on neuronal catecholamine

TABLE 29-6 -- ADRENERGIC INHIBITORS USED IN TREATMENT OF HYPERTENSION

Peripheral Neuronal Inhibitors

Reserpine
Guanethidine (Ismelin)
Guanadrel (Hylorel)
Bethanidine (Tenathan)

Central Adrenergic Inhibitors

Methyldopa (Aldomet)
Clonidine (Catapres)
Guanabenz (Wytensin)
Guanfacine (Tenex)

Alpha-Receptor Blockers

$Alpha_1$ and $alpha_2$ receptor

Phenoxybenzamine (Dibenzyline)
Phentolamine (Regitine)

$Alpha_1$ receptor

Doxazosin (Cardura)
Prazosin (Minipress)
Terazosin (Hytrin)

Beta-Receptor Blocker

Acebutolol (Sectral)
Atenolol (Tenormin)
Betaxolol (Kerlone)
Bisoprolol (Zebeta)
Carteolol (Cartrol)
Metoprolol (Lopressor, Toprol)
Nadolol (Corgard)
Penbutolol (Levatol)
Pindolol (Visken)
Propranolol (Inderal)
Timolol (Blocadren)

Alpha- and Beta-Receptor Blocker

Labetalol (Normodyne, Trandate)
Carvedilol (Coreg)

discharge, or by blocking alpha- and/or beta-adrenergic receptors (Table 29-6) ; some act at numerous sites. Figure 29-11 , a schematic view of the ending of an adrenergic nerve and the effector cell with its receptors, depicts how some of these drugs act. When the nerve is stimulated, norepinephrine, which is synthesized intraneuronally and stored in granules, is released into the synaptic

Figure 29-11 Simplified schematic view of the adrenergic nerve ending showing that norepinephrine (NE) is released from its storage granules when the nerve is stimulated and enters the synaptic cleft to bind to alpha$_1$ and beta receptors on the effector cell (postsynaptic). In addition, a short feedback loop exists, in which NE binds to alpha$_2$ and beta receptors on the neuron (presynaptic), to inhibit or to stimulate further release, respectively.

cleft. It binds to postsynaptic alpha- and beta-adrenergic receptors and thereby initiates various intracellular processes. In vascular smooth muscle, alpha stimulation causes constriction and beta stimulation causes relaxation. In the central vasomotor centers, sympathetic outflow is inhibited by alpha stimulation; the effect of central beta stimulation is unknown.

An important aspect of sympathetic activity involves the feedback of norepinephrine to alpha- and beta-adrenergic receptors located on the neuronal surface, i.e., presynaptic receptors. Presynaptic alpha-adrenergic receptor activation inhibits release, whereas presynaptic beta activation stimulates further norepinephrine release. The presynaptic receptors probably has a role in the action of some of the drugs to be discussed.

Elucidation and quantification of the various actions of these drugs remain incomplete. The listing in Table 29-6 is based on the predominant site of action according to currently available data. The action of beta-adrenergic receptor blockers involves a peripheral effect, but they almost certainly also act on central vasomotor mechanisms.

Drugs That Act Within the Neuron

Reserpine, guanethidine, and related compounds act differently to inhibit the release of norepinephrine from peripheral adrenergic neurons.

RESERPINE.

Reserpine, the most active and widely used of the derivatives of the rauwolfia alkaloids, depletes the postganglionic adrenergic neurons of norepinephrine by inhibiting its uptake into storage vesicles, exposing it to degradation by cytoplasmic monoamine oxidase. The peripheral effect is predominant, although the drug enters the brain and depletes central catecholamine stores as well. This probably accounts for the sedation and depression accompanying reserpine use. The drug has certain advantages. Only one dose a day is needed; in combination with a diuretic, the antihypertensive effect is significant, greater than that noted with nitrendipine in one comparative study[105] ; little postural hypotension is noted; and many patients experience no side effects. The drug has a relatively flat dose-response curve, so that a dose of only 0.05 mg/day gives almost as much antihypertensive effect as 0.125 or 0.25 mg/day but fewer side effects. Although it remains popular in some places and is recommended as an inexpensive choice where resources are limited,[1] reserpine has progressively declined in use

because it has no commercial sponsor.

GUANETHIDINE.

This agent and a series of related guanidine compounds, including guanadrel, bethanidine, and debrisoquine, act by inhibiting the release of norepinephrine from the adrenergic neurons, perhaps by a local anesthetic-like effect on the neuronal membrane. In order to act, the drug must be transported actively into the nerve through an amine pump.

Their low lipid solubility prevents guanidine compounds from entering the brain, so that sedation, depression, and other side effects involving the central nervous system do not occur. The initial predominant hemodynamic effect is decreased cardiac output: after continued use, peripheral resistance declines. Blood pressure is reduced further when the patient is upright, owing to gravitational pooling of blood in the legs, because compensatory sympathetic nervous system-mediated vasoconstriction is blocked. This results in the most common side effect, postural hypotension. Unlike reserpine, guanethidine has a steep dose-response curve, so that it can be successfully used in treating hypertension of any degree in daily doses of 10 to 300 mg. Like reserpine, it has a long biological half-life and may be given once daily. As other drugs have become available, guanethidine and related compounds have been relegated mainly to the treatment of severe hypertension unresponsive to all other agents.

Drugs That Act on Receptors

Predominantly Central Alpha Agonists

Until the mid-1980's, methyldopa was the most widely used of the adrenergic receptor blockers, but its use has declined as beta blockers and other drugs have become more popular. In addition, three other drugs--clonidine, guanabenz, and guanfacine, which act similarly to methyldopa but have fewer serious side effects--have become available.

METHYLDOPA.

The primary site of action of methyldopa is within the central nervous system, where alpha-methylnorepinephrine, derived from methyldopa, is released from adrenergic neurons and stimulates central alpha-adrenergic receptors, reducing the sympathetic outflow from the central nervous system.[106] The blood pressure mainly falls as a result of a decrease in peripheral resistance with little effect on cardiac output. Renal blood flow is well maintained, and significant postural hypotension is unusual. Therefore, the drug has been used in hypertensive patients with renal failure or cerebrovascular disease and remains the most commonly used agent for pregnancy-induced

hypertension (see Chaps. 28 and 65) .

Methyldopa need be given no more than twice daily, in doses ranging from 250 to 3000 mg/day.

Side effects include some that are common to centrally acting drugs that reduce sympathetic outflow: sedation, dry mouth, impotence, and galactorrhea. However, methyldopa causes some unique side effects that are probably of an autoimmune nature, because a positive antinuclear antibody test result occurs in about 10 percent of patients who take the drug, and red cell autoantibodies occur in about 20 percent. Clinically apparent hemolytic anemia is rare, probably because methyldopa also impairs reticuloendothelial function so that antibody-sensitized cells are not removed from the circulation and hemolyzed. Inflammatory disorders in various organs have been reported, most commonly involving the liver (with diffuse parenchymal injury similar to viral hepatitis).[107]

CLONIDINE.

Although of different structure, clonidine shares many features with methyldopa. It probably acts at the same central sites, has similar antihypertensive efficacy, and causes many of the same bothersome but less serious side effects (e.g., sedation, dry mouth). It does not, however, induce the autoimmune and inflammatory side effects.

As an alpha-adrenergic receptor agonist, the drug also acts on presynaptic alpha receptors and inhibits norepinephrine release, and plasma catecholamine levels fall.[108] The drug has a fairly short biological half-life, so that when it is discontinued, the inhibition of norepinephrine release disappears within about 12 to 18 hours, and plasma catecholamine levels rise. This is probably responsible for the rapid rebound of the blood pressure to pretreatment levels and the occasional appearance of withdrawal symptoms, including tachycardia, restlessness, and sweating. If the rebound requires treatment, clonidine may be reintroduced or alpha-adrenergic receptor antagonists given.

Clonidine is available in a *transdermal* preparation, which may provide smoother blood pressure control for as long as 7 days with fewer side effects. However, bothersome skin rashes preclude its use in perhaps one-fourth of patients.

GUANABENZ.

This drug differs in structure but shares many characteristics with both methyldopa and clonidine, acting primarily as a central alpha agonist. It may differ, however, in not causing fluid retention.

GUANFACINE.

This drug is also similar to clonidine but is longer acting, which enables once-a-day

dosing and minimizes rebound hypertension.[109]

Alpha-Adrenergic Receptor Antagonists

Before 1977, the only alpha blockers used to treat hypertension were phenoxybenzamine (Dibenzyline) and phentolamine (Regitine). These drugs are effective in acutely lowering blood pressure, but their effects are offset by an accompanying increase in cardiac output, and side effects are frequent and bothersome. Their limited efficacy may reflect their blockade of presynaptic alpha-adrenergic receptors, which interferes with the feedback inhibition of norepinephrine release (see Fig. 29-11) . Increased catecholamine release would then blunt the action of postsynaptic alpha-adrenergic receptor blockade. Their use has largely been limited to the treatment of patients with pheochromocytomas.

PRAZOSIN.

This was the first of a group of selective antagonists of the postsynaptic alpha$_1$ receptors. By blocking alpha-mediated vasoconstriction, prazosin induces a decline in peripheral resistance with both venous and arteriolar dilation. Because the presynaptic alpha-adrenergic receptor is left unblocked, the feedback loop for the inhibition of norepinephrine release is intact, an action that is also certainly responsible for the greater antihypertensive effect of the drug and the absence of concomitant tachycardia, tolerance, and renin release. Inhibition of norepinephrine release may also account for the propensity toward greater first-dose reductions in blood pressure.

OTHER ALPHA BLOCKERS.

Two other alpha blockers, terazosin and doxazosin, have slower onset and longer duration of action, so they may be given once daily with less propensity for first-dose hypotension.

Selective alpha blockers are as effective as other first-line antihypertensives.[2] When given to patients whose condition is poorly controlled on standard triple therapy (diuretic, beta blocker, and vasodilator), they may reduce blood pressure even more than anticipated. They can be safely and effectively used by patients with renal failure. The favorable hemodynamic changes--a fall in peripheral resistance with maintenance of cardiac output--make them an attractive choice for patients who wish to remain physically active. In addition, blood lipids are not adversely altered and may actually improve with alpha blockers, unlike the adverse effects observed with diuretics and beta blockers.[110] Moreover, improved insulin sensitivity with lesser rises in plasma glucose and insulin levels after a glucose load has been observed with alpha blockers.[111] Alpha blockers decrease the smooth muscle tone of the bladder neck and prostate, relieving the obstructive symptoms of prostatism.[112] They are then an excellent choice for older men with hypertension and benign prostatic hypertrophy.

In a large, double-blind, randomized trial of older patients (>55 years) with hypertension (ALLHAT), the alpha adrenergic blocker doxazosin, when compared with the diuretic

chlorthalidone, was associated with significantly higher risks for stroke and congestive heart failure.[112A]

Side effects, beyond first-dose postural hypotension, include the nonspecific effects of lower blood pressure, such as dizziness, weakness, fatigue, and headaches. Most patients, however, find the drugs easy to take, with little sedation, dry mouth, or impotence.

Beta-Adrenergic Receptor Antagonists (See also Chaps. 23 and 37)

In the 1980's, beta-adrenergic receptor blockers became the most popular form of antihypertensive therapy after diuretics, reflecting their relative effectiveness and freedom from many bothersome side effects. For the majority of patients, beta blockers are usually easy to take, because somnolence, dry mouth, and impotence are seldom encountered. Because beta blockers have been found to reduce mortality if taken either before or after acute myocardial infarction[113] (i.e., secondary prevention), it was assumed that they might offer special protection against initial coronary events, i.e., primary prevention. However, in four large clinical trials, a beta blocker provided less protection than did a low-dose diuretic (see Fig. 29-1) .[10] Nevertheless, their efficacy in treatment of congestive heart failure will likely stimulate their use.[114]

THE VARIOUS BETA BLOCKERS.

Beta blockers now available in the United States are listed in Table 29-6 , and others are available in other countries. A number of agents with additional vasodilatory effects are available elsewhere; these may be free of many of the unfavorable hemodynamic and adverse effects of currently available agents. Pharmacologically, those now available differ considerably from one another with respect to degree of absorption, protein binding, and bioavailability. However, the three most important differences affecting their clinical use are cardioselectivity, intrinsic sympathomimetic activity, and lipid solubility. Despite these differences, they all seem to be about equally as effective as antihypertensives.

Cardioselectivity.

As seen in Figure 29-12 , beta blockers can be classified by their degree of cardioselectivity relative to their blocking effect on the $beta_1$ -adrenergic receptors in the heart compared with that on the $beta_2$ receptors in the bronchi, peripheral blood vessels, and elsewhere.

Figure 29-12 Classification of beta-adrenergic receptor blockers based on cardioselectivity and intrinsic

sympathomimetic activity (ISA). Those not approved for use in the United States are in italics. (From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 206.)

Such cardioselectivity can be easily shown using small doses in acute studies; with the rather high doses used to treat hypertension, much of this selectivity is lost.

Intrinsic Sympathomimetic Activity (ISA).

Some of these drugs have ISA, interacting with beta receptors to cause a measurable agonist response but at the same time blocking the greater agonist effects of endogenous catecholamines. As a result, although in usual doses they lower the blood pressure about the same degree as do other beta blockers, they cause a smaller decline in heart rate, cardiac output, and renin levels.

Lipid Solubility.

Atenolol and nadolol are among the least lipid soluble of the beta blockers. Because they do not enter the brain as readily, they may cause fewer central nervous system side effects.[115]

Mechanism of Action.

Despite these and other differences, the various beta blockers now available are approximately equipotent as antihypertensive agents. A number of possible mechanisms are likely to be involved in their antihypertensive action. In those without ISA, cardiac output falls 15 to 20 percent and renin release is reduced about 60 percent. Central nervous system beta-adrenergic receptor blockade may reduce sympathetic discharge, but similar antihypertensive effects are seen with those drugs that are more lipid soluble, and therefore in high concentration within the central nervous system, and those that are less lipid soluble.

At the same time that beta blockers lower blood pressure through various means, their blockade of peripheral beta-adrenergic receptors inhibits vasodilation, leaving alpha receptors open to catecholamine-mediated vasoconstriction. Over time, however, vascular resistance tends to return to normal, which presumably preserves the antihypertensive effect of a reduced cardiac output.[116]

Clinical Effects.

Even in small doses, beta blockers begin to lower the blood pressure within a few hours. Although progressively higher doses have usually been given, careful study has shown a near-maximal effect from smaller doses. For example, in a double-blind crossover study involving 24 patients, 40 mg of propranolol twice a day provided the same antihypertensive effects as 80, 160, or 240 mg twice a day.[116A] The degree of blood pressure reduction is at least comparable to that noted with other antihypertensive drugs.[2] Beta blockers may be particularly well suited for younger and middle-aged hypertensive patients, especially nonblacks, and for patients with myocardial ischemia

and high levels of stress.[113] Because the hemodynamic responses to stress are reduced, however, they may interfere with athletic performance.[117]

SPECIAL USES FOR BETA BLOCKERS

COEXISTING ISCHEMIC HEART DISEASE.

Even without evidence that beta blockers protect patients from initial coronary events, the antiarrhythmic and antianginal effects of these drugs make them especially valuable in hypertensive patients with coexisting coronary disease.

COEXISTING HEART FAILURE.

As described elsewhere (see Chap. 18) , beta blockers have been found to reduce mortality in patients with congestive heart failure.[114]

PATIENTS WITH HYPERKINETIC HYPERTENSION.

Some hypertensive patients have increased cardiac output that may persist for many years. Beta blockers are particularly effective in such patients, but a reduction in exercise capacity may necessitate restriction of their use in young athletes.

PATIENTS WITH MARKED ANXIETY.

The somatic manifestations of anxiety--tremor, sweating, and tachycardia--can be helped, without the undesirable effects of methods commonly used to control anxiety, such as alcohol and tranquilizers.

PERIOPERATIVE STRESS.

The ultra-short-acting cardioselective agent esmolol has been successfully used to prevent postintubation tachycardia and hypertension,[118] and atenolol protects patients with coronary disease during surgery.[119]

SIDE EFFECTS.

Most of the side effects of beta blockers relate to their major pharmacological action, the blockade of beta-adrenergic receptors. Certain concomitant problems may worsen when beta-adrenergic receptors are blocked, including peripheral vascular disease and bronchospasm.

The most common side effect is fatigue, which is probably a consequence of decreased cardiac output and the decreased cerebral blood flow that may accompany successful lowering of the blood pressure by any drug (see Fig. 29-6) . More direct effects on the central nervous system--insomnia, nightmares, and hallucinations--occur in some

patients. An association with depression appears to be accounted for by various confounding variables.[120]

Diabetic patients may have additional problems with beta blockers, more so with nonselective ones. The responses to hypoglycemia, both the symptoms and the counterregulatory hormonal changes that raise blood glucose levels, are partially dependent on sympathetic nervous activity. Diabetic patients who are susceptible to hypoglycemia may not be aware of the usual warning signals and may not rebound as quickly. The majority of noninsulin-dependent diabetic patients can take these drugs without difficulty, although their diabetes may be exacerbated, probably from beta blocker interference with insulin sensitivity.[111]

When a beta blocker is discontinued, angina pectoris and myocardial infarction may occur.[121] Because patients with hypertension are more susceptible to coronary disease, they should be weaned gradually and given appropriate coronary vasodilator therapy. Perturbations of lipoprotein metabolism accompany the use of beta blockers.[122] Nonselective agents cause greater rises in triglycerides and reductions in cardioprotective high-density lipoprotein-cholesterol levels, whereas ISA agents cause less or no effect and some agents such as celiprolol may raise high-density lipoprotein cholesterol levels. Patients with renal failure may take beta blockers without additional hazard, although modest reductions in renal blood flow and glomerular filtration rate have been measured, presumably from renal vasoconstriction.

Caution is advised in the use of beta blockers in patients suspected of harboring a pheochromocytoma (Chaps. 28 and 64) , because unopposed alpha-adrenergic agonist action may precipitate a serious hypertensive crisis if this disease is present. The use of beta blockers during pregnancy has been clouded by scattered case reports of various fetal problems. Moreover, prospective studies have found that the use of beta blockers during pregnancy may lead to fetal growth retardation.[123]

AN OVERVIEW OF BETA BLOCKERS IN HYPERTENSION.

Beta blockers are specifically recommended for hypertensive patients with concomitant coronary disease, particularly after a myocardial infarction, congestive heart failure, or tachyarrhythmias[1] (see Table 29-4) . If a beta blocker is chosen, those agents that are more cardioselective and lipid insoluble offer the likelihood of fewer perturbations of lipid and carbohydrate metabolism and greater patient adherence to therapy; only one dose a day is needed, and side effects probably are minimized. In patients with heart failure, the initial dose should be very small (e.g., metoprolol 12.5 mg twice daily) and gradually increased to the maintenance dose (100 to 200 mg twice daily) (see Chap. 18) .

The combination of an alpha and a beta blocker in a single molecule is available in the

forms of labetalol and carvedilol, the latter agent approved for treatment of heart failure as well. The fall in pressure mainly results from a decrease in peripheral resistance, with little or no decline in cardiac output.[124] The most bothersome side effects are related to postural hypotension; the most serious side effect is hepatotoxicity. Intravenous labetalol is used to treat hypertensive emergencies.

VASODILATORS

In the past, direct-acting arteriolar vasodilators were used mainly as third drugs, when combinations of a diuretic and adrenergic blocker failed to control blood pressure. However, with the availability of vasodilators of different types that can be easily tolerated when used as first or second drugs, wider and earlier application of vasodilators in therapy of hypertension has begun (Table 29-7) .

Direct Vasodilators

Hydralazine is the most widely used agent of this type. Minoxidil is more potent but is usually reserved for patients with severe, refractory hypertension associated with renal failure.[20] Nitroprusside and nitroglycerin are given intravenously for hypertensive crises and are discussed on page 991 .

HYDRALAZINE.

From the early 1970's, hydralazine, in combination with a diuretic and a beta blocker, was used frequently to treat severe hypertension. The drug acts directly to relax the smooth muscle in precapillary resistance vessels, with little or no effect on postcapillary venous capacitance vessels. As a result, blood pressure falls by a reduction in peripheral resistance, but in the process a number of compensatory processes, which are activated by the arterial baroreceptor arc, blunt the decrease in pressure and cause side effects. With concomitant use of a diuretic to overcome the tendency for fluid retention and an adrenergic inhibitor to prevent the reflex increase in sympathetic activity and rise in renin, the vasodilator is more effective and causes few, if any, side effects. Without the protection conferred by concomitant use of an adrenergic blocker, numerous side effects (tachycardia, flushing, headache, and precipitation of angina) may occur.

The drug need be given only twice a day. Its daily dose should be kept below 400 mg to prevent the lupus-like syndrome that appears in 10 to 20 percent of patients who receive more. This reaction, although uncomfortable to the patient, is almost always reversible. The reaction is uncommon with daily doses of 200 mg or less and is more common in slow acetylators of the drug.

MINOXIDIL.

This drug vasodilates by opening potassium channels in vascular smooth muscle. Its hemodynamic effects are similar to those of hydralazine, but minoxidil is even more effective and may be used once a day. It is particularly useful in patients with severe

hypertension and renal failure. Even more than with hydralazine, diuretics and adrenergic receptor blockers must be used with minoxidil to prevent the reflex increase in cardiac output and fluid retention. Pericardial effusions have appeared in about 3 percent of those given minoxidil,

TABLE 29-7 -- VASODILATOR DRUGS USED TO TREAT HYPERTENSION

DRUG	RELATIVE ACTION ON ARTERIES (A) OR VEINS (V)
Direct	
Hydralazine	A > > V
Minoxidil	A > > V
Nitroprusside	A=V
Nitroglycerin	V > A
Calcium entry blockers	A > > V
Converting enzyme inhibitors	A > V
Alpha blockers	A=V

TABLE 29-8 -- PHARMACOLOGICAL EFFECTS OF CALCIUM ANTAGONISTS

	DILTIAZEM	VERAPAMIL	DIHYDROPYRIDINES
Heart rate			-
Myocardial contractility			-
Nodal conduction			-
Periphral vasodilation			

Indicates decrease;

increase;

in some without renal or cardiac failure. The drug also causes hair to grow profusely, and the facial hirsutism precludes use of the drug in most women.

Calcium Antagonists (See also Chap. 37)

These drugs have become the most popular class of agents used in the treatment of hypertension. They differ in both their sites and modes of action (Table 29-8) , with major pharmacological differences between the various dihydropyridines.[125] Dihydropyridines have the greatest peripheral vasodilatory action,[126] with little effect on cardiac automaticity, conduction, or contractility. However, comparative trials have shown that verapamil and diltiazem, which do affect these properties, are also effective antihypertensives, and they may cause fewer side effects related to vasodilation, such as flushing and ankle edema.

Calcium antagonists are effective in hypertensive patients of all ages and races[104] and in hypertensive diabetics.[104A] In a large comparative trial, verapamil was more effective than chlorthalidone in promoting regression of carotid intima-media thickness and preventing cardiovascular events.[127] Even more impressively, therapy based on the dihydropyridine nitrendipine provided even greater protection to elderly patients with isolated systolic hypertension in the Syst-Eur trial[22] than did chlorthalidone in the SHEP trial,[5] particularly in those in the two trials with diabetes accompanying the hypertension.[24] Dihydropyridines were also the foundation of therapy in other large trials that found significant reductions in cardiovascular events.[25] [32]

Calcium antagonists may cause at least an initial natriuresis, probably by producing renal vasodilation,[128] which may obviate the need for concurrent diuretic therapy. In fact, unlike all other antihypertensive agents, they may have their effectiveness reduced rather than enhanced by concomitant dietary sodium restriction,[129] whereas most careful studies show an enhancement of their effect by concomitant diuretic therapy.[89] Their renal vasodilatory effect allows glomerular filtration rate and renal blood flow to be well maintained as they reduce systemic blood pressure.[130] Because they act primarily to dilate afferent arterioles, these agents could accelerate a decline in renal function by increasing flow within the glomeruli. Although they may not decrease proteinuria as well as ACE inhibitors, they seem to preserve renal function as well.[131]

A potentially serious adverse effect of the use of calcium antagonists to treat hypertension was described in a case-control study in which more hypertensive patients who had a myocardial infarction were taking short-acting calcium antagonists than were hypertensive patients who had not had an infarct.[132] The most likely explanation for the finding is exclusion bias, which is an inherent problem with case-control studies in which the cases are at greater risk for the complication than the controls; i.e., higher-risk patients are excluded from the control group but not from the case group. Specifically, short-acting calcium antagonists, which were not approved for the treatment of hypertension

and which were more expensive and more difficult to use because they require three doses a day compared with the other approved antihypertensive agents, were probably given to patients considered at higher risk for coronary events. Similar case-control

studies claiming that the use of reserpine was associated with a threefold increase in breast cancer were subsequently shown to be erroneous because of exclusion bias.[133] The decrease in coronary events in large randomized controlled trials with *long-acting* dihydropyridines[22] [25] [32] is the best proof of the safety of these agents. Similar claims based on case-control studies that calcium anatgonists increase cancer and gastrointestinal bleeding also have not been confirmed.[134] [135]

Along with freedom from most of the side effects accompanying other classes, calcium antagonists may be unique in not having their antihypertensive efficacy blunted by nonsteroidal antiinflammatory agents (NSAIDs).[136]

Liquid nifedipine has been used effectively to reduce high levels of blood pressure quickly, but the occasional occurrence of cerebral and myocardial ischemia has prompted a call for discontinuation of the practice.[137] Intravenous nicardipine is available for hypertensive emergencies.[138]

Renin-Angiotensin Inhibitors (See also Chap. 18)

Activity of the renin-angiotensin system (see Fig. 28-13) may be inhibited in four ways (Fig. 29-13), three of which can be applied clinically. The first, use of beta-adrenergic receptor blockers to inhibit the release of renin, was discussed earlier (p. 986). The second, direct inhibition of renin activity by specific renin inhibitors, is being investigated.[139] The third, inhibition of the enzyme that converts the inactive decapeptide angiotensin I to the active octapeptide angiotensin II, is being widely used with orally effective ACE inhibitors. The fourth approach to inhibiting the renin-angiotensin system, blockade of angiotensin's actions by a competitive receptor blocker, is now the basis for the fastest growing class of antihypertensive agents.[140] The AII receptor blockers (ARBs) may offer additional benefits, but their immediate advantage is the absence of cough that often accompanies ACE inhibitors, as well as less angioedema. In the absence of outcome data, both JNC-6[20] and WHO-ISH [1] guidelines recommend their use only if an ACE inhibitor cannot be tolerated. The ARBs are considered after the ACE inhibitors.

MECHANISM OF ACTION.

The first of these ACE inhibitors, captopril, was synthesized as a specific inhibitor of the converting enzyme that, in the classical pathway shown in Figure 29-13 , breaks the peptidyldipeptide bond in angiotensin I, preventing the enzyme from attaching to and splitting the angiotensin I structure. Because angiotensin II cannot be formed and angiotensin I is inactive, the ACE inhibitor paralyzes the classical renin-angiotensin system, thereby removing the effects of most endogenous angiotensin II as both a vasoconstrictor and a stimulant to aldosterone synthesis.

Interestingly, with long-term use of ACE inhibitors, the plasma angiotensin II levels actually return to previous level while the blood pressure remains lowered[141] ; this suggests that the antihypertensive effect may involve other mechanisms. Because the same enzyme that converts angiotensin I to angiotensin II is also responsible for inactivation of the vasodilating hormone bradykinin, by inhibiting the breakdown of

bradykinin, ACE inhibitors increase the concentration of a vasodilating hormone while they decrease the concentration of a vasoconstrictor hormone. The increased plasma kinin levels may contribute to the vasodilation and improvement in insulin sensitivity observed with ACE inhibitors, but they are also responsible for the most common and bothersome side effect of their use, a dry, hacking cough.[140] ACE inhibitors may also vasodilate by increasing levels of vasodilatory prostaglandins and decreasing levels of vasoconstricting endothelins.[142]

Regardless of their mechanism of action, ACE inhibitors lower blood pressure mainly by reducing peripheral resistance with little, if any, effect on heart rate, cardiac output, or body fluid volumes, likely reflecting preservation of baroreceptor reflexes.[143] Their vasodilating effect may also involve restoration of endothelium-dependent relaxation by nitric oxide.[144] As a consequence, resistance arteries become less thickened and more responsive.[145]

CLINICAL USE.

In patients with uncomplicated primary hypertension, ACE inhibitors provide antihypertensive effects that are equal to those with other classes,[146] but they are less effective in blacks,[104] perhaps because blacks tend to have lower renin levels. They are equally effective in elderly and younger hypertensive patients. In the large controlled CAPPP trial, in which captopril-based therapy was compared with conventional therapy with diuretic and beta blockers, the two approaches provided essentially identical protection against cardiovascular morbidity and mortality.[146] As a consequence of these results, the WHO-ISH guidelines include ACE inhibitors as a choice for initial therapy.[1] In view of the impressive reduction in morbidity

Figure 29-13 The four sites of action of inhibitors of the renin-angiotensin system. J-G = Juxtaglomerular apparatus; CE = converting enzyme. (From Kaplan NM: Clinical Hypertension. 7th ed. Baltimore, Williams & Wilkins, 1998, p 223.)Risk Factors for Cardiovascular Diseases Left ventricular hypertrophy (electrocardiogram), Associated Clinical Conditions

and mortality with ramipril in the HOPE trial of high-risk patients,[146A] the use of ACE inhibitors will almost certainly increase.

The initial dose of ACE inhibitor may precipitate a rather dramatic but transient fall in blood pressure[147] that likely reflects a higher level of renin-angiotensin and that could be a harbinger of the presence of renovascular hypertension. Because the therapeutic response will be potentiated by concomitant intravascular volume contraction from a low-sodium diet or diuretics, caution should be taken in starting an ACE inhibitor in those who might be most responsive. The response to an ACE inhibitor is usually well maintained, perhaps because its suppression of aldosterone mitigates the tendency

toward volume expansion that often antagonizes the effects of other antihypertensives.

These drugs have been a mixed blessing for patients with renovascular hypertension. On the one hand, the response of plasma renin level to a single dose of captopril may provide a simple diagnostic test for the disease. More importantly, they usually control the blood pressure effectively.[148] On the other hand, the removal of the high levels of angiotensin II that they produce may deprive the stenotic kidney of the hormonal drive to its blood flow, thereby causing a marked decline in renal perfusion so that patients with solitary kidneys or bilateral disease may develop acute and sometimes persistent renal failure.[149]

Patients with intraglomerular hypertension, specifically those with diabetic nephropathy or reduced renal functional mass due to other forms of renal parenchymal disease, may benefit especially from the reduction in efferent arteriolar resistance that follows reduction in angiotensin II. The clinical evidence for modulation of the progressive loss of renal function in diabetic and nondiabetic nephropathy is now unequivocal.[150] Whether this effect is quantitatively better with ACE inhibitors than that provided by other drugs is less certain. ACE inhibitors have been widely used in diabetic hypertensive patients, in part on the basis of earlier reports of their ability to improve insulin sensitivity. However, more recent data do not confirm the effect on insulin sensitivity.[151] More impressively, ACE inhibitor-based therapy was somewhat *less* effective in preventing diabetic complications than was beta-blocker therapy in the large and long United Kingdom Prospective Diabetes Study.[152] Therefore, the need for ACE inhibitors is considered as compelling for diabetic patients with nephropathy, hypertensive patients with heart failure, or systolic dysfunction after a myocardial infarction,[20] but these agents should be considered as equal to other classes in most other circumstances. Nonetheless, they may be the best tolerated antihypertensive agent[153] (along with ARBs), so their use will continue to grow.

SIDE EFFECTS.

Most patients who take an ACE inhibitor experience neither the side effects nor the biochemical changes often accompanying other drugs that may be of even more concern even though they are not so obvious; neither rises in lipids, glucose, or uric acid nor reductions in potassium levels are noted.

To be sure, ACE inhibitors may cause both specific and nonspecific adverse effects. Among the specific ones are rash, loss of taste, and leukopenia. In addition, they may cause a hypersensitivity reaction with angioneurotic edema or a cough, although often persistent, that is infrequently associated with pulmonary dysfunction.[154] The cough, affecting more than 10 percent of women and about half as many men, may not disappear for 3 weeks after the ACE inhibitor is discontinued.[155] If a cough appears in a patient who needs an ACE inhibitor, an ARB should be substituted.

There is at least a potential problem for those patients taking an ACE inhibitor and coincidentally developing volume depletion, as from gastroenteritis, because they may be unable to marshal the compensatory homeostatic responses

TABLE 29-9 -- CLINICAL PHARMACOLOGY OF AVAILABLE ANGIOTENSIN II RECEPTOR BLOCKERS

COMPOUND	ACTIVE METABOLITE	FOOD EFFECT	HALF-LIFE (hr)
Candesartan (Atacand)	Prodrug	No	9-10
Irbesartan (Avapro)	No	No	11-15
Losartan (Cozaar)	Yes	Modest	2-4
Telmisartan (Micardis)	No	No	18-24
Valsartan (Diovan)	No	Moderate	6-8

that involve increased angiotensin II and aldosterone. Finally, patients with renal insufficiency or on potassium supplements or sparing agents may not be able to excrete potassium loads and therefore may develop hyperkalemia.

ANGIOTENSIN II RECEPTOR BLOCKERS

As the number of these agents being marketed quickly increases, they will be more widely used even in the absence of many outcome data. Those now available (Table 29-9) differ little save for a longer duration of action and perhaps a greater dose-response curve with the newer ones than with the first, losartan.[155] As more outcome data become available, ARBs may become an initial choice for many hypertensive patients. However, their price may be a consideration. Moreover, considering their presumed ability to block the response to angiotensin II more completely, they may end up being used in combination with ACE inhibitors.[140]

Other Vasodilators

Various other forms of antihypertensive therapy are under investigation. These include endothelin receptor antagonists[156] and agents that inhibit both the ACE and neutral endopeptidase, thereby increasing atrial natriuretic hormone.[157] The distant future may see the application of gene therapy.[158]

SPECIAL CONSIDERATIONS IN THERAPY

RESISTANT HYPERTENSION.

There are numerous causes of resistance to therapy, usually defined as the failure of DBP to fall below 90 mm Hg despite the use of three or more drugs.[88] Patients often do not respond well because they do not take their medications. On the other hand, what appears to be a poor response based on office readings of blood pressure may be disclosed to be an adequate response when ambulatory or home readings are obtained.[159] However, a number of factors may be responsible for a poor response even if the appropriate medication is taken regularly (Table 29-10) . Most common is volume overload owing either to inadequate diuretic or to excessive dietary sodium

intake. Larger doses or more potent diuretics often bring resistant hypertension under control.

Resistance is particularly common in patients with visceral obesity and associated insulin resistance.[160] A frequently overlooked cause is the interference by NSAIDs or aspirin[161] with virtually all antihypertensive drugs, with the exception of calcium antagonists and possibly ARBs.[162]

Resistance can usually be overcome by adequate doses of a diuretic, a calcium antagonist, and an ACE inhibitor.

ANESTHESIA IN HYPERTENSIVE PATIENTS.

In the absence of significant cardiac dysfunction, hypertension adds little to the cardiovascular risks of surgery.[163] If possible, however, hypertension should be well controlled by means of medications before anesthesia and surgery to reduce the

TABLE 29-10 -- CAUSES OF INADEQUATE RESPONSIVENESS TO THERAPY

Pseudoresistance	
"White coat" or office elevations	
Pseudohypertension in the elderly	
Nonadherence to Therapy	
Side effects of medication	
Cost of medication	
Lack of consistent and continuous primary care	
Inconvenient and chaotic dosing schedules	
Instructions not understood	
Inadequate patient education	
Organic brain syndrome (e.g., memory deficit)	
Drug-Related Causes	
Doses too low	
Inappropriate combinations (e.g., two centrally acting adrenergic inhibitors)	
Rapid inactivation (e.g., hydralazine)	
Drug interactions	
Nonsteroidal antiinflammatory drug	
Sympathomimetics	Oral contraceptives
Nasal decongestants	Adrenal steroids
Appetite suppressants	Licorice (chewing tobacco)
Cocaine	Cyclosporine
Caffeine	Erythropoietin
Antidepressants (MAO inhibitors, tricyclics)	Cholestyramine

Excessive volume contraction with stimulation of rennin-aldosterone
Hypokalemia (usually diuretic induced)
Rebound after clonidine withdrawal

Associated Conditions

Smoking
Increasing obesity
Sleep apnea
Insulin resistance/hyperinsulinemia
Ethanol intake more than 1 ounce/day (>3 portions)
Anxiety-induced hyperventilation or panic attacks
Chronic pain
Intense vasoconstriction (Raynaud's, arteritis)

Secondary Hypertension

Renal insufficiency
Renovascular hypertension
Pheochromocytoma
Primary aldosteronism

Volume Overload

Excess sodium intake
Progressive renal damage (nephrosclerosis)
Fluid retention due to reduction of blood pressure
Inadequate diuretic therapy

Modified from Joint National Committee, Sixth Report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure (JNC VI). Arch Intern Med 157:2413, 1997. Copyright 1997 American Medical Association.

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risk of myocardial ischemia.[164] Therefore, patients taking antihypertensive medications should continue these drugs, as long as the anesthesiologist is aware of their use and takes reasonable precautions to prevent wide swings in pressure. The very short-acting beta blocker esmolol has been successful in preventing surges in blood pressure during intubation,[118] and the use of atenolol protected coronary patients undergoing noncardiac surgery.[119]

Hypertension is often observed during and immediately after coronary bypass surgery (see p. 965); various intravenous agents have been successfully used to lower the pressure. Nitroprusside has been the usual choice during the postoperative period, but toxicity, often in the form of loss of consciousness and cyanide or thiocyanate toxicity, may develop in those who are critically ill and given the drug for prolonged periods. Esmolol, labetalol, or nicardipine may be a better choice.[165]

HYPERTENSIVE CHILDREN (see also p. 956 and Chap. 45) .

Almost nothing is known about the effects of various antihypertensive medications given to children over long periods. In the absence of adequate data, an approach similar to that advocated for adults is advised.[166] Emphasis should be placed on weight reduction in hypertensive children who are obese, in the hope of attempting to control

hypertension without the need for drug therapy.

HYPERTENSION DURING PREGNANCY.

This topic is discussed in Chapter 65 .

HYPERTENSION IN THE ELDERLY.

As noted on page 957 , a few elderly persons may have high blood pressure as measured by the sphygmomanometer but may have less or no hypertension when direct intraarterial readings are made, i.e., pseudohypertension due to rigid arteries that do not collapse under the cuff.

If either the systolic pressure alone or both systolic and diastolic levels are elevated, careful lowering of blood pressure with either diuretics[5] or dihydropyridine calcium antagonists[22] has been unequivocally documented to reduce cardiovascular morbidity in older hypertensive patients extending to those older than 80 years.[11] Care is needed because they may have a number of problems with the medications (Table 29-11) . In view of the reduced effectiveness of the baroceptor reflex and the failure of peripheral resistance to rise appropriately with standing,[167] drugs with a propensity to cause postural hypotension should be avoided, and all drugs should be given in slowly increasing doses to prevent excessive lowering of the pressure.

For those who start with systolic pressures exceeding 160 mm Hg, the goal of therapy should be a level around 140 mm Hg with little concern about further reductions in already low diastolic levels.[167A]

PATIENTS WITH HYPERTENSION AND DIABETES.

Special attention should be given to diabetic patients with hypertension. The two commonly coexist and multiply the cardiovascular risks of each alone. Fortunately, evidence from several trials now documents the protection provided by *intensive* control of hypertension, preferably in concert with management of the diabetes and the dyslipidemia that commonly accompanies the two.[24] [32] [85] [152] Most diabetic hypertensive patients need two or more antihypertensive drugs to bring their pressure to below 130/85 mm Hg, which is likely the highest level that should be tolerated.

An ACE inhibitor should be included if proteinuria is present. A diuretic and a beta blocker are appropriate, and a long-acting dihydropyridine will likely be required.[104A] Concerns about possible adverse effects of calcium antagonists in diabetic patients[168] have been absolved by their

TABLE 29-11 -- FACTORS THAT MIGHT CONTRIBUTE TO INCREASED RISK OF PHARMACOLOGICAL TREATMENT OF HYPERTENSION IN THE ELDERLY

FACTORS	POTENTIAL COMPLICATIONS

Diminished baroreceptor activity	Orthostatic hypotension
Decreased intravascular volume	Orthostatic hypotension, dehydration
Sensitivity to hypokalemia	Arrhythmia, muscle weakness
Decreased renal and hepatic function	Drug accumulation
Polypharmacy	Drug interaction
Central nervous system changes	Depression, confusion

even greater protective effects in diabetic than nondiabetic persons,[24] [32] including those with nephropathy.[169]

HYPERTENSIVE PATIENTS WITH IMPOTENCE.

Erectile dysfunction is common in hypertensive patients, even more so in those who are also diabetic.[170] The problem may be exacerbated by diuretic therapy, even in appropriately low doses.[100] Fortunately, sildenafil usually returns erectile ability, but caution is advised with antihypertensive drugs.[171] The potential for hypotension, well recognized with concomitant nitrate therapy, may also appear with other vasodilators, although to a lesser degree.

HYPERTENSION WITH CONGESTIVE HEART FAILURE.

Cardiac output may fall so markedly in hypertensive patients who are in heart failure with systolic dysfunction that their blood pressure is reduced, obscuring the degree of hypertension; often, however, the DBP is raised by intense vasoconstriction while the systolic pressure falls as a result of the reduced stroke volume. Lowering the blood pressure may, by itself, relieve the heart failure. Chronic unloading has been most efficiently accomplished with ACE inhibitors, and beta blockers have been shown to further reduce morbidity and mortality in ACE inhibitor-treated patients in heart failure.[172] Caution is needed for those elderly hypertensive patients with diastolic dysfunction related to marked left ventricular hypertrophy, because unloaders may worsen their status, whereas beta blockers or calcium antagonists may be beneficial.

As noted in Chapter 28 , left ventricular hypertrophy is frequently found by echocardiography, even in patients with mild hypertension. All antihypertensive drugs except direct vasodilators have been shown to regress left ventricular hypertrophy and regression may continue for as long as 5 years of treatment.[173]

HYPERTENSION WITH ISCHEMIC HEART DISEASE.

The coexistence of ischemic heart disease makes antihypertensive therapy even more

essential, because relief of the hypertension may ameliorate the coronary disease. Beta blockers and calcium antagonists are particularly useful if angina or arrhythmias are present. Caution is needed to avoid decreased coronary perfusion that may be responsible for the J curve seen in several trials[32] (see p. 975).

The often markedly high levels of blood pressure during the early phase of an acute myocardial infarction may reflect sympathetic nervous hyperreactivity to pain. Antihypertensive drugs that do not decrease cardiac output may be cautiously utilized in the immediate postinfarction period, whereas beta blockers[174] and ACE inhibitors[175] have been shown to provide long-term benefit.

THERAPY FOR HYPERTENSIVE CRISES

When DBP exceeds 140 mm Hg, rapidly progressive damage to the arterial vasculature is demonstrable experimentally, and a surge of cerebral blood flow may rapidly lead to encephalopathy (p. 966). If such high pressures persist or if there are any signs of encephalopathy, the pressures should be lowered using parenteral agents in those patients considered to be in immediate danger or with oral agents in those who are alert and in no other acute distress.

A number of drugs for this purpose are currently available (Table 29-12) . If diastolic pressure exceeds 140 mm Hg and the patient has any complications, such as an aortic dissection, a constant infusion of nitroprusside is most effective and almost always lowers the pressure to the desired level. Constant monitoring with an intraarterial line is mandatory because a slightly excessive dose may lower the pressure abruptly to levels that induce shock. The potency and rapidity of action of nitroprusside have made it the treatment of choice for life-threatening hypertension. However, nitroprusside acts as a venous and arteriolar dilator, so that venous return and cardiac output are lowered and intracranial pressures may increase. Therefore, other parenteral agents are being more widely used. These include labetalol and the calcium antagonist nicardipine.[165]

With any of these agents, intravenous furosemide is often needed to lower the blood pressure further and prevent retention of salt and water. Diuretics should not be given if volume depletion is initially present.

For patients in less immediate danger, oral therapy may be used. Almost every drug has been used and most will, with repeated doses, reduce high pressures. The prior preference for liquid nifedipine by mouth or sublingually has been deflated because of occasional ischemic complications from too rapid reduction in blood pressure.[137] Oral doses of other short-acting formulations may be used, including furosemide, propranolol, captopril, or felodipine. A safer course for any patients, particularly if their current high pressures are simply a reflection of stopping previously effective oral medication and they are asymptomatic, is simply to restart that medication and monitor their response

TABLE 29-12 -- PARENTERAL DRUGS FOR TREATMENT OF HYPERTENSIVE EMERGENCY (IN ORDER OF RAPIDITY OF ACTION)

DRUG	DOSAGE	ONSET OF ACTION	ADVERSE EFFECTS
Vasodilators			
Nitroprusside (Nipride, Nitropress)	0.25-10 mug/kg/min as IV infusion	Instantaneous	Nausea, vomiting, muscle twitching, sweating, thiocyanate intoxication
Nitroglycerin	5-100 mug/min as IV infusion	2-5 min	Tachycardia, flushing, headache, vomiting, methemoglobinemia
Nicardipine (Cardene)	5-15 mg/hr IV	5-10 min	Tachycardia, headache, flushing, local phlebitis
Hydralazine (Apresoline)	10-20 mg IV 10-50 mg IM	10-20 min 20-30 min	Tachycardia, flushing, headache, vomiting, aggravation of angina
Enalapril (Vasotec IV)	1.25-5 mg q 6 hr	15 min	Precipitous fall in blood pressure in high renin states; response variable
Fenoldopam (Corlopam)	0.1-0.3 mug/kg/min	<5 min	Tachycardia, headache, nausea, flushing
Adrenergic inhibitors			
Phentolamine (Regitine)	5-15 mg IV	1-2 min	Tachycardia, flushing
Esmolol (Brevibloc)	500 mug/kg/min for 4 min, then 150-300 mug/kg/min IV	1-2 min	Hypotension
Labetalol (Normodyne, Trandate)	20-80 mg IV bolus every 10 min 2 mg/min IV infusion	5-10 min	Vomiting, scalp tingling, burning in throat, postural hypotension, dizziness, nausea

closely. If their nonadherence to therapy was caused by side effects, appropriate changes should be made.

Most centers are seeing fewer patients in hypertensive crisis, presumably because more patients are diagnosed and treated before the disease enters this malignant

course. The continued successful treatment of many more hypertensive persons will prevent the more frequent long-range cardiovascular complications of hypertension.

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Chapter 30 - The Vascular Biology of Atherosclerosis

PETER LIBBY

A remarkable evolution in concepts concerning the pathogenesis of atherosclerosis occurred in the 20th century. This disease has a venerable history, having left traces in the arteries of Egyptian mummies.[1] Apparently uncommon in antiquity, atherosclerosis became epidemic as populations increasingly survived early mortality caused by infectious diseases and as many societies adopted dietary habits that may promote atherosclerosis.

At the end of the 19th century, the first edition of Osler's *Textbook of Medicine* articulated a rather fatalistic view of atheroma as an inevitable degenerative process that affected arteries, which were structures viewed by many of his contemporaries as mere conduits: "In the make-up of the machine bad material was used in the tubing."[2] Indeed, until very recently internists and cardiologists generally viewed arteries as inanimate tubes rather than living, dynamic tissue. Over 100 years ago, Virchow recognized the participation of cells in atherogenesis. A controversy raged between Virchow, who viewed atheroma as a proliferative disease,[3] and Rokitansky, who believed that atheroma derived from healing and resorption of thrombi.[4] In the early part of the 20th century, Anitschkow and Chalatow used dietary modulation to produce fatty lesions in the arteries of rabbits and ultimately identified cholesterol as the culprit.[5]

These observations, followed by the characterization of human lipoprotein particles at mid century, promoted the concept of insudation of lipids as a cause for atherosclerosis. At the beginning of the new millennium, we have learned enough about atherosclerosis to recognize that elements of all of these pathogenic theories participate in atherogenesis. This chapter summarizes evidence from human studies, animal experimentation, and in vitro work, and highlights a synoptic view of atherogenesis, taking into account advances in vascular biology that have enabled us to achieve a deeper understanding of the process.

Acquaintance with the vascular biology of atherosclerosis should prove useful to the practitioner. Our daily contact with this common disease lulls us into a complacent belief that we understand it better than we actually do. For example, we are just beginning to learn why atherosclerosis affects certain regions of the arterial tree preferentially and why its clinical manifestations occur only at certain times. Atherosclerosis can involve both large and medium-sized arteries diffusely. Postmortem and intravascular ultrasound studies have revealed widespread intimal thickening in patients with atherosclerosis and, indeed, in many asymptomatic human adults.[6] At the same time, atherosclerosis is a focal disease that constricts some areas of affected vessels much more than others. Understanding of the biological basis of the predilection of certain sites to develop atheroma is just beginning to emerge.[7]

Atherosclerosis also displays heterogeneity in time, being a disease with both chronic and acute manifestations. Few human diseases have a longer "incubation" period than atherosclerosis, which begins to affect arteries of many North Americans in the second and third decades of life (Fig. 30-1) .[7] Yet typically, symptoms of atherosclerosis do not occur until several decades later, characteristically occurring even later in women. Despite this indolent time course and prolonged period of clinical inactivity, the dreaded complications of atheroma such as myocardial infarction, unstable angina, or stroke typically occur suddenly.

Another poorly understood aspect of atherogenesis is its role in causing narrowing, or stenosis, of some vessels and ectasia of others. Typically, we fear stenoses in coronary atherosclerosis. However, aneurysm is a common manifestation of this disease in other vessels, including the aorta. Even in the life history of a single atherosclerotic lesion, a phase of ectasia known as positive remodeling, or compensatory enlargement, precedes the formation of stenotic lesions.[8] [9] Contemporary vascular biology is beginning to shed light on some of these apparent contradictions, or paradoxes, in understanding atherosclerosis.

STRUCTURE OF THE NORMAL ARTERY

The Intima

Understanding the pathogenesis of atherosclerosis first requires knowledge of the structure and biology of the normal artery and its indigenous cell types. Normal arteries have a well-developed trilaminar structure (Fig. 30-2) . The innermost layer, the tunica intima, is thin at birth in humans and many nonhuman species. Although often depicted as a monolayer of endothelial cells abutting directly on a basal lamina, the structure of

the adult human intima is actually much more complex and heterogeneous. The endothelial cell of the arterial intima constitutes the crucial contact surface with blood. Arterial endothelial cells possess many highly regulated mechanisms of capital importance in vascular homeostasis that often go awry during the pathogenesis of arterial diseases.

Figure 30-1 A schematic life history of an atherosclerotic lesion. In westernized societies, and increasingly in developing countries, atherogenesis begins in early life. Lesion evolution usually occurs slowly over decades, often progressing in a asymptomatic manner or eventually causing stable symptoms related to embarrassment of flow, such as angina pectoris or intermittent claudication. For the first part of the life history of the lesion, growth proceeds abluminally, in an outward direction preserving the lumen (compensatory enlargement or "positive remodeling"). A minority of lesions will produce thrombotic complications, leading to clinical manifestations such as the unstable coronary syndromes, thrombotic stroke, or critical limb ischemia.

Figure 30-2 The structures of normal arteries. *A,* Elastic artery. Note the concentric laminae of elastic tissue that form sandwiches with successive layers of smooth muscle cells. Each level of the elastic arterial tree has a characteristic number of elastic laminae. *B,* Muscular artery. The smooth muscle cells are surrounded by a collagenous matrix but lack the concentric rings of well-organized elastic tissue character istic of the larger arteries.

Figure 30-3 The endothelial thrombotic balance. This diagram depicts the anticoagulant profibrinolytic functions of the endothelial cell *(left)* and certain procoagulant and antifibrinolytic functions *(right).* t-PA=tissue type plasminogen activator; PGI_2 =prostacyclin; PA_i =plasminogen activator inhibitor; vWf= von Willebrand factor.

For example, the endothelial cell provides one of the only surfaces, either natural or synthetic, that can maintain blood in a liquid state during protracted contact (Fig. 30-3). This remarkable blood compatibility derives in part from the expression of heparan sulfate proteoglycan molecules on the surface of the endothelial cell. These molecules, like heparin, serve as a cofactor for antithrombin III, causing a conformational change that allows this inhibitor to bind to and inactivate thrombin. The surface of the endothelial cell also contains thrombomodulin, which binds thrombin molecules and can exert antithrombotic properties by activating proteins S and C. Should a thrombus begin to form, the normal endothelial cell possesses potent fibrinolytic mechanisms associated with its surface. In this regard, the endothelial cell can produce both tissue and urokinase type plasminogen activators. These enzymes catalyze the activation of plasminogen to form plasmin, a fibrinolytic enzyme. (For a complete discussion of the role of endothelium in hemostasis and fibrinolysis, see Chap. 62.)

The endothelial monolayer rests upon a basement membrane containing nonfibrillar collagen types, such as type IV collagen, laminin, fibronectin, and other extracellular matrix molecules.[10] With aging, human arteries develop a more complex intima containing arterial smooth muscle cells and fibrillar forms of interstitial collagen (types I and III). The smooth muscle cell produces these extracellular matrix constituents of the arterial intima. The presence of a more complex intima, known by pathologists as diffuse intimal thickening, characterizes most adult human arteries. Some locales in the arterial tree tend to develop thicker intimas than other regions, even in the absence of atherosclerosis.[11] For example, the proximal left anterior descending coronary artery often contains an intimal cushion of smooth muscle cells more fully developed than that in typical arteries. (See also Chap. 41.) The diffuse intimal thickening process does not necessarily go hand in hand with lipid accumulation and may occur in individuals without substantial burdens of atheroma. The internal elastic membrane bounds the tunica intima abluminally and serves as the border between the intimal layer and the underlying tunica media.

The Tunica Media

The tunica media lies under the media and internal elastic lamina. The media of elastic arteries such as the aorta have well-developed concentric layers of smooth muscle cells, interleaved with layers of elastin-rich extracellular matrix (see Fig. 30-2 *A*). This structure appears well adapted to the storage of the kinetic energy of left ventricular systole by the walls of great arteries. The lamellar structure also doubtless contributes to the structural integrity of the arterial trunks. The media of smaller muscular arteries usually have a less-stereotyped organization (see Fig. 30-2 *B*). Smooth muscle cells in these smaller arteries generally reside within the surrounding matrix in a more continuous than lamellar array. The smooth muscle cells in normal arteries are generally quiescent from the standpoint of growth control. That is, rates of cell division and cell death are quite low.[12] In the normal artery, a state of homeostasis of extracellular matrix also typically prevails. Because extracellular matrix neither accumulates nor atrophies, rates of matrix synthesis and dissolution must balance each other under normal conditions. The external elastic lamina bounds the tunica media abluminally, forming the border with the adventitial layer.

The Adventitia

The adventitia of arteries has typically received little attention, although appreciation of its potential roles in arterial homeostasis and pathology has recently increased. The adventitia contains collagen fibrils in a looser array than usually encountered in the intima. Vasa vasorum and nerve endings localize in this outermost layer of the arterial wall. The cellular population in the adventitia is more sparse than in other arterial layers. Cells encountered in this layer include fibroblasts and mast cells (see Fig. 30-2) .

INITIATION OF ATHEROSCLEROSIS

Extracellular Lipid Accumulation

The first steps in atherogenesis in humans remain largely conjectural. However, integration of observations of tissues obtained from young humans with the results of experimental studies of atherogenesis in animals provides hints in this regard. On initiation of an atherogenic diet rich in cholesterol and saturated fat, one of the first ultrastructural alterations is an accumulation of small lipoprotein particles in the intima (Fig. 30-4 ,*1*).[13] These lipoprotein particles appear to decorate the proteoglycan of the arterial intima and tend to coalesce into aggregates (Fig. 30-5) .[14] [15] Detailed kinetic studies of labeled lipoprotein particles indi

Figure 30-4 Schematic of the evolution of the atherosclerotic plaque. *1,* Accumulation of lipoprotein particles in the intima. The modification of these lipoproteins is depicted by the darker color. Modifica tions include oxidation and glycation. *2,* Oxidative stress including products found in modified lipopro teins can induce local cytokine elaboration. *3,* The cytokines thus induce increased expression of adhesion molecules for leukocytes that cause their attachment and chemoattractant molecules that direct their migration into the intima. *4,* Blood monocytes, on entering the artery wall in response to chemoattractant cytokines such as monocyte chemoattractant protein 1 (MCP-1), encounter stimuli such as macrophage colony stimulating factor (M-CSF) that can augment their expression of scavenger receptors. *5,* Scavenger receptors mediate the uptake of modified lipoprotein particles and promote the development of foam cells. Macrophage foam cells are a source of mediators such as further cytokines and effector molecules such as hypochlorous acid, superoxide anion (O_2 -), and matrix metalloproteinases. *6,* Smooth muscle cells in the intima divide, and other smooth muscle cells migrate into the intima from the media. *7,* Smooth muscle cells can then divide and elaborate extracellular matrix, promoting extracellular matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibrofatty lesion. *8,* In later stages, calcification can occur (not depicted) and fibrosis continues, sometimes accompanied by smooth muscle cell death (including programmed cell death, or apoptosis), yielding a relatively acellular fibrous capsule surrounding a lipid-rich core that may also contain dying or dead cells and their detritus. LDL\m4\low-density lipoprotein; IL-1 = interleukin-1.

Figure 30-5 Scanning electron micrograph of a freeze etch preparation of rabbit aorta that received an intravenous injection of human low-density lipoprotein (LDL). Round LDL particles decorate the strands of proteoglycan found in the subendothelial region of the intima. By binding LDL particles, proteoglycan molecules can retard their traversal of the intima and promote their accumulation. Proteoglycan-associated LDL appears particularly susceptible to oxidative modification. Accumulation of extracellular lipoprotein particles is one of the first morphological changes noted after initiation of an atherogenic diet in experimental animals. (From Nievelstein PF, Fogelman AM, Mottino G, et al: Lipid accumulation in rabbit aortic intima 2 hours after bolus infusion of low density lipoprotein: A deep-etch and immunolocalization study of ultrarapidly frozen tissue. Arterioscler Thromb Vasc Biol 11:1795-1805, 1991.)

cate that a prolonged residence time characterizes sites of early lesion formation in rabbits. [16] [17] The binding of lipoproteins to proteoglycan in the intima captures and

retains these particles, accounting for their prolonged residence time.[15] Lipoprotein particles bound to proteoglycan appear to exhibit increased susceptibility to oxidative or other chemical modifications, considered by many to be an important component of the pathogenesis of early atherosclerosis (see Fig. 30-4 ,*2*).[15] [19] [21] Other studies suggest that permeability of the endothelial monolayer increases at sites of lesion predilection to low-density lipoprotein (LDL).[22] Contributors to oxidative stress in the nascent atheroma could include the nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate-dependent oxidases expressed by vascular cells[23] and lipoxygenases expressed by infiltrating leukocytes.[24] In addition to oxidation, aggregation, enzymatic processing due to sphingomyelinase, and glycation (see Chap. 63) can modify LDL in the intima.

Leukocyte Recruitment

The second morphologically definable event in the initiation of atheroma is leukocyte recruitment and accumulation (see Fig. 30-4 ,*3*). The normal endothelial cell generally resists adhesive interactions with leukocytes. Even in inflamed tissues, most recruitment and trafficking of leukocytes occurs in postcapillary venules, not in arteries. However, very early after initiation of hypercholesterolemia, leukocytes adhere to the endothelium and diapedese between endothelial cell junctions to enter the intima, where they begin to accumulate lipids and transform into foam cells (Fig. 30-6) .[25] In addition to the monocyte, T lymphocytes also tend to accumulate in early human and animal atherosclerotic lesions.[26] [27]

The expression of certain leukocyte adhesion molecules on the surface of the endothelial cell regulates the adherence of monocytes and T cells to the endothelium. Two broad categories of leukocyte adhesion molecules exist (Table 30-1) .[28] Members of the immunoglobulin superfamily include structures such as vascular cell adhesion molecule-1 (VCAM-1).[29] [32] This adhesion molecule has particular interest in the context of early atherogenesis because it interacts with an integrin (very late antigen-4 [VLA-4]) characteristically expressed by only those classes of leukocytes that accumulate in nascent atheroma, monocytes, and T cells. Moreover, studies in rabbits and mice have shown expression of VCAM-1 on endothelial cells overlying very early atheromatous lesions.[30] Another member of the immunoglobulin superfamily of leukocyte adhesion molecules is intercellular adhesion molecule-1.[33] [34] This molecule is more promiscuous, both in the types of leukocytes it binds and because of its wide and constitutive expression at low levels by endothelial cells in many parts of the circulation.

Selectins constitute the other broad category of leukocyte adhesion molecules. The prototypical selectin, E-selectin (E for "endothelial," the cell type that selectively expresses this particular family member), probably has little to do with early atherogenesis. E-selectin preferentially recruits polymorphonuclear leukocytes, a cell type seldom found in early atheroma (but an essential protagonist in acute inflammation and host defenses against bacterial pathogens). Moreover, endothelial cells overlying atheroma do not express high levels of this adhesion molecule. Other members of this family, including P-selectin (P for "platelet," the original source of this adhesion molecule), may play a greater role in leukocyte recruitment in atheroma, because endothelial cells overlying human atheroma do express this adhesion molecule.[34] [36]

Selectins tend to promote saltatory or rolling locomotion of leukocytes over the endothelium. Adhesion molecules belonging to the immunoglobulin superfamily tend to promote tighter adhesive interactions and immobilization of leukocytes.[28]

Figure 30-6 Electron microscopy of leukocyte interactions with the artery wall in hypercholesterolemic nonhuman primates. *A* and *B,* Scanning electron micrographs that demonstrate the adhesion of mononuclear phagocytes to the intact endothelium 12 days after initiating a hypercholesterolemic diet in rabbits. *C* and *D,* Transmission electron micrographs. Note the abundant interdigitations and intimate association of the monocyte with the endothelium in *C.* In *D,* a monocyte appears to diapedese between two endothelial cells to enter the intima. (From Faggiotto A, Ross R, Harker L: Studies of hypercholesterolemia in the nonhuman primate: I. Changes that lead to fatty streak formation. Arteriosclerosis 4:323-340, 1984.)

Once adherent to the endothelium, leukocytes must receive a signal to penetrate the endothelial and enter the arterial wall (see Figs. 30-4 , *4* and 30-6 *C*). The current concept of directed migration of leukocytes involves the action of protein molecules known as chemoattractant cytokines, or chemokines.[37] Two groups of chemokines have particular interest in recruiting the mononuclear cells characteristic of the early atheroma. One such molecule, known

TABLE 30-1 -- EXAMPLES OF ENDOTHELIAL-LEUKOCYTE ADHESION MOLECULES

NAME	ABBREVIATION	COGNATE LIGAND	LEUKOCYTES BOUND
Vascular cell adhesion molecule-1	VCAM-1	VLA-4 integrin	Monocytes Lymphocytes
Intercellular adhesion molecule-1	ICAM-1	CD11a integrin (LFA-1) CD11b integrin (Mac-1)	Many classes
E-selectin	Formerly ELAM-1	Sialyl-Lewis x	Granulocytes>monocytes>memory T cells
P-selectin	Formerly GMP-140	PSGL-1	Monocytes; lymphocytes; granulocytes
L-selectin		PSGL-1; mucosal vascular addressin (MAdCAM-1)	Expressed on the leukocytes

as monocyte chemoattractant protein-1 (MCP-1), is produced by the endothelium in response to oxidized lipoprotein and other stimuli. Cells intrinsic to the normal artery, including endothelium and smooth muscle, can produce this chemokine when stimulated by inflammatory mediators, as do many other cell types.[38] , [39] MCP-1 selectively promotes the directed migration, or chemotaxis, of monocytes. Studies conducted with genetically modified mice lacking MCP-1 or its receptor CCR-2 have delayed and attenuated atheroma formation when placed on an atherosclerosis-prone, hyperlipidemic genetic background.[40] , [41] Human atherosclerotic lesions express increased levels of MCP-1 compared with uninvolved vessels.[42] Thus, MCP-1 appears causally related to monocyte recruitment during atherogenesis in vivo. Another group of chemoattractant cytokines may heighten lymphocyte accumulation in plaques. Atheromas express a trio of lymphocyte-selective chemokines (interferon-inducible protein 10 [IP-10], interferon-inducible T-cell alpha chemoattractant [I-TAC], monokine induced by interferon-gamma [MIG]).[43] Interferon gamma, a cytokine known to be present in atheromatous plaques, induces the genes encoding this family of T cell chemoattractants.

The Focality of Lesion Formation

The spatial heterogeneity of atherosclerosis has proven challenging to explain in mechanistic terms. Equal concentrations of blood-borne risk factors such as lipoproteins bathe the endothelium throughout the vasculature. It is difficult to envisage how injury due to inhaling cigarette smoke could produce any local rather than global effect on arteries. Yet, atheroma typically form focally, as revealed by studies of morphology, lipid accumulation, and adhesion molecule expression. Some have invoked a multicentric origin hypothesis of atherogenesis, positing that atheromas arise as benign leiomyomas of the artery wall.[44] The monotypia of various molecular markers such as glucose-6-phosphate dehydrogenase isoforms in individual atheroma supports this "monoclonal hypothesis" of atherogenesis.[45] However, the location of sites of lesion predilection at proximal portions of arteries after branch points or bifurcations at flow dividers suggests a hydrodynamic basis for early lesion development. Arteries without many branches (e.g., the internal mammary or radial arteries) tend not to develop atherosclerosis. (See also Chap. 41.)

Two concepts that can help understand how local flow disturbances might render certain foci sites of lesion predilection. Locally disturbed flow could induce alterations that promote the steps of early atherogenesis. Alternatively, the laminar flow that usually prevails at sites that do *not* tend to develop early lesions may elicit antiatherogenic homeostatic mechanisms (atheroprotective functions).[7] The endothelial cell experiences the laminar shear stress of normal flow and the disturbed flow (usually yielding decreased shear stress) at predilected sites. In vitro data suggest that laminar shear stress can augment the expression of genes that may protect against atherosclerosis, including forms of the enzymes superoxide dismutase or nitric oxide synthase.[46] Superoxide dismutase can reduce oxidative stress by catabolizing the reactive and injurious superoxide anion. Endothelial nitric oxide synthase produces the

well-known endogenous vasodilator nitric oxide (NO). However, beyond its vasodilating actions, NO can resist inflammatory activation of endothelial functions such as expression of the adhesion molecule VCAM-1.[47] Nitric oxide appears to exert this antiinflammatory action at the level of gene expression by interfering with the transcriptional regulator nuclear factor kappa B (NFkappaB). Nitric oxide actually increases the production of an intracellular inhibitor (IkappaBalpha) of this important transcription factor.[48] The NFkappaB system regulates numerous genes involved in inflammatory responses in general, and in atherogenesis in particular.[49] These examples show how basic vascular biology is beginning to yield insight into previously obscure yet important aspects of atherogenesis. Future study of the molecular regulation of vascular cell function by mechanical stimuli promises to clarify further the mechanisms of lesion formation at particular sites in the circulation.

Likewise, study of vascular developmental biology may aid understanding of the tendency of certain arteries to develop atherosclerosis at different rates and in different ways. Smooth muscle cells vary in embryological origin in different regions.[50] For example, upper body arteries can recruit smooth muscle from neurectoderm, whereas in the lower body smooth muscle cells derive principally from mesoderm. Coronary artery smooth muscle cells arise from an Anlage known as the proepicardial organ.[51] How this heterogeneity in the origin of smooth muscle cells might impact human atherosclerosis and may help explain some of the poorly understood issues regarding dispersion of atheroma in time and space remains intriguing yet speculative. (See also Chap. 41.)

Intracellular Lipid Accumulation: Foam Cell Formation

The monocyte, once recruited to the arterial intima, can there imbibe lipid and become a foam cell, or lipid-laden macrophage (see Fig. 30-4 ,*5*). Whereas most cells can express the classical cell surface receptor for LDL, that receptor does not mediate foam cell formation. This is evident clinically, because patients lacking functional LDL receptors (familial hypercholesterolemia homozygotes) still develop tendinous xanthomas filled with foamy macrophages. The LDL receptor does not mediate foam cell formation because of its exquisite regulation by cholesterol. As soon as a cell collects enough cholesterol from LDL capture for its metabolic needs, an elegant transcriptional control mechanism quenches expression of the receptor (see also Chap. 31) .

Instead of the classical LDL receptor, various molecules known as "scavenger" receptors appear to mediate the excessive lipid uptake characteristic of foam cell formation.[52] , [53] The longest studied of these receptors belong to the scavenger receptor-A family. These surface molecules bind modified rather than native lipoproteins and apparently participate in their internalization. Atherosclerosis-prone mice with mutations that delete functional scavenger receptor-A have less exuberant fatty lesion formation than those with functional scavenger receptor-A molecules.[54] Other receptors that bind modified lipoprotein and that may participate in foam cell formation include CD36 and macrosialin, the latter exhibiting preferential binding specificity for oxidized forms of LDL (see Table 31-3) .

Once macrophages have taken up residence in the intima and become foam cells, they

not infrequently replicate. The factors that trigger macrophage cell division in the atherosclerotic plaque likely include macrophage colony-stimulating factor (M-CSF). This co-mitogen and survival factor for mononuclear phagocytes exists in human and experimental atheromatous lesions. Atherosclerosis-prone mice lacking functional M-CSF have retarded fatty lesion development.[55] , [56] Other candidates for macrophage mitogens or co-mitogens include interleukin-3 and granulocyte-macrophage colony-stimulating factor.

Thus far, the scenario of the evolving atheroma has invoked only leukocytes, principally the macrophage. The precursor lesion, known as the fatty streak, consists mainly of accumulations of such lipid-engorged leukocytes. Fatty streaks may occur in children and in societies less affected by the atherosclerosis pandemic than the developed Western nations. Moreover, in experimental animals, withdrawal of the atherogenic diet or treatment with drugs that lower lipoprotein levels in plasma can reduce the extent of established lesions. Thus, fatty streaks composed primarily of macrophages are likely reversible, at least to some extent.

THE EVOLUTION OF ATHEROMA

Smooth Muscle Cell Migration and Proliferation

Whereas the early events in atheroma initiation involve primarily altered endothelial function and recruitment and accumulation of leukocytes, the subsequent evolution of atheroma into more complex plaques involves smooth muscle cells as well (see Fig. 30-4 ,*6* and *7*).[57] Smooth muscle cells in the normal arterial tunica media differ considerably from those in the intima of an evolving atheroma. Although some smooth muscle cells likely arrive in the arterial intima early in life, others that accumulate in advancing atheroma likely arise from cells that have migrated from the underlying media into the intima.[11] , [57] The chemoattractants for smooth muscle cells likely include molecules such as platelet-derived growth factor (PDGF), a potent smooth muscle cell chemoattractant secreted by activated macrophages and overexpressed in human atherosclerosis.[58] These smooth muscle cells in the atherosclerotic intima can also multiply by cell division. Estimated rates of division of smooth muscle cells in the human atherosclerotic lesion are on the order of less than 1 percent.[59] However, considerable smooth muscle cell accumulation may occur over the decades of lesion evolution.

Smooth muscle cells in the atherosclerotic intima appear to exhibit a less mature phenotype than the quiescent smooth muscle cells in the normal arterial medial layer. Instead of expressing primarily isoforms of smooth muscle myosin characteristic of adult smooth muscle cells, those in the intima have higher levels of the embryonic isoform of smooth muscle myosin.[60] Thus, smooth muscle cells in the intima seem to recapitulate an embryonic phenotype. These intimal smooth muscle cells in atheroma appear morphologically distinct as well. They contain more rough endoplasmic reticulum and

fewer contractile fibers than do normal medial smooth muscle cells.

Although replication of smooth muscle cells in the steady state appears indolent in mature human atheroma, bursts of smooth muscle cell replication may occur during the life history of a given atheromatous lesion. For example, and as will be discussed in considerable detail later, episodes of plaque disruption with thrombosis may expose smooth muscle cells to potent mitogens, including the coagulation factor thrombin itself. Thus, accumulation of smooth muscle cells during atherosclerosis and growth of the intima may not occur in a continuous and linear fashion. Rather, "crises" may punctuate the history of an atheroma, during which bursts of smooth muscle replication and/or migration may occur (Fig. 30-7) .

Smooth Muscle Cell Death During Atherogenesis

In addition to smooth muscle cell replication, death of these cells may also participate in complication of the atherosclerotic plaque (see Fig. 30-4 ,*8*). At least some smooth muscle cells in advanced human atheroma exhibit fragmentation of their nuclear DNA characteristic of programmed cell death, or apoptosis.[61] [63] Apoptosis may occur in response to inflammatory cytokines known to be present in the evolving atheroma.[64] In addition to soluble cytokines that may trigger programmed cell death, the T cells in atheroma may participate in eliminating some smooth muscle cells. In particular, certain T cell populations known to accumulate in plaques can express *fas* ligand on their surface. *Fas* ligand can engage *fas* on the surface of smooth muscle cells and, in conjunction with soluble proinflammatory cytokines, lead to death of the smooth muscle cell.[65]

Thus, smooth muscle cell accumulation in the growing atherosclerotic plaque probably results from a tug-of-war between cell replication and cell death. Contemporary cell and molecular biological research has identified candidates

Figure 30-7 The time course of atherosclerosis. Traditional teaching held that atheroma formation followed an inexorably progressive course with age, depicted in the curve in the left panel. Current thinking suggests an alternative model, a step function rather than a monotonically upward course of lesion evolution in time (curve in right panel). According to this latter model, "crises" can punctuate periods of relative quiescence during the life history of a lesion. Such crises might follow an episode of plaque disruption, with mural thrombosis, and healing, yielding a spurt in smooth muscle proliferation and matrix deposition. Intraplaque hemorrhage due to rupture of a friable microvessel might produce a similar scenario. Such episodes might usually be clinically inapparent. Extravascular events such as an intercurrent infection with systemic cytokinemia or endotoxemia could elicit an "echo" at the level of the artery wall, evoking a round of local cytokine gene expression by "professional" inflammatory leukocytes resident in the lesion. The episodic model of plaque progression shown on the right fits human angiographic data better than the continuous function depicted on the left.

for mediating both the replication and attrition of smooth muscle cells, a concept that

originated from the careful morphological observations of Virchow almost a century and a half ago.[3] Referring to the smooth muscle cells in the intima, Virchow noted that early atherogenesis involves a "multiplication of their nuclei." However, he recognized that cells in lesions can "hurry on to their own destruction" because of death of smooth muscle cells.

The Arterial Extracellular Matrix

Extracellular matrix rather than cells themselves makes up much of the volume of an advanced atherosclerotic plaque. Thus, extracellular constituents of plaque also require consideration. The major extracellular matrix macromolecules that accumulate in atheromas include interstitial collagens (types I and III) and proteoglycans such as versican, biglycan, aggrecan, and decorin.[10] Elastin fibers may also accumulate in atherosclerotic plaques. The vascular smooth muscle cell produces these matrix molecules in disease, just as it does during development and maintenance of the normal artery (see Fig. 30-4 ,*7*). Stimuli for excessive collagen production by smooth muscle cells include PDGF and transforming growth factor-beta (TGF-beta), both constituents of platelet granules and products of many cell types found in lesions.[66]

Much like the accumulation of smooth muscle cells, extracellular matrix secretion also depends on a balance. In this case, the biosynthesis of the extracellular matrix molecules counters breakdown catalyzed in part by catabolic enzymes known as matrix metalloproteinases (MMPs).[67] , [68] Dissolution of extracellular matrix macromolecules undoubtedly plays a role in migration of smooth muscle cells as they penetrate into the intima from the media through a dense extracellular matrix, traversing the elastin-rich internal elastic lamina. In injured arteries, overexpression of inhibitors of such proteinases (known as tissue inhibitors of metalloproteinases [TIMPs]) can delay smooth muscle accumulation in the intima.[69]

Extracellular matrix dissolution also likely plays a role in arterial remodeling that accompanies lesion growth. During the first part of the life history of an atheromatous lesion, growth of the plaque is outward, in an abluminal direction, rather than inward in a way that would lead to luminal stenosis[8] , [9] (see Fig. 30-1). This outward growth of the intima leads to an increase in caliber of the entire artery. This so-called positive remodeling or compensatory enlargement must involve turnover of extracellular matrix molecules to accommodate the circumferential growth of the artery. Luminal stenosis tends to occur only after the plaque burden exceeds some 40 percent of the cross-sectional area of the artery.[8]

Angiogenesis in Plaques

The smooth muscle cell is not alone in its proliferation and migration within the evolving atherosclerotic plaque. Endothelial migration and replication also occur as plaques develop in microcirculation, characterized by plexuses of newly formed vessels.[70] Such plaque neovessels usually require special stains for visualization. However, histological examination with appropriate markers for endothelial cells reveals a rich neovascularization in evolving plaques. These microvessels likely form in response to angiogenic peptides overexpressed in atheroma. These angiogenesis factors include

acidic and basic fibroblast growth factors (human BGFs I and II),[71] vascular endothelial growth factor (VEGF),[72] , [73] and oncostatin M.[74]

These microvessels within plaques probably have considerable functional significance. For example, the abundant microvessels in plaques provide a relatively large surface area for the trafficking of leukocytes, which could include both entry and exit of leukocytes. Indeed, in the advanced human atherosclerotic plaque, microvascular endothelium displays the mononuclear-selective adhesion molecules such as VCAM-1 much more prominently than does the macrovascular endothelium overlying the plaque.[75] The microvascularization of plaques may also allow growth of the plaque overcoming diffusion limitations on oxygen and nutrient supply, in analogy with the concept of tumor angiogenic factors and growth of malignant lesions. Consistent with this view, administration of inhibitors of angiogenesis to mice with experimentally induced atheromas limits lesion expansion.[76] Finally, the plaque microvessels may be friable and prone to rupture like the neovessels in the diabetic retina. Hemorrhage and thrombosis in situ could promote a local round of smooth muscle cell proliferation and matrix accumulation in the area immediately adjacent to the microvascular disruption. This scenario illustrates a special case of one of the "crises" described earlier in the evolution of the atheromatous plaque (see Fig. 30-7) . Attempts to augment myocardial perfusion by enhancing new vessel growth by transfer of angiogenic proteins or their genes might have adverse effects on lesion growth or clinical complications of atheroma by these mechanisms.

Plaque Mineralization

Plaques often develop areas of calcification as they evolve. Indeed, both Virchow and Rokitansky recognized morphological features of bone formation in atherosclerotic plaques in early microscopic descriptions of atherosclerosis.[3] [4] In recent years, understanding of the mechanism of mineralization during evolution of atherosclerotic plaques has advanced.[77] Some subpopulations of smooth muscle cells may foster calcification by enhanced secretion of cytokines such as bone morphogenetic proteins, homologues of TGF-beta. Atheromatous plaques may also contain proteins with gamma carboxylated glutamic acid residues specialized in sequestering calcium and thus promoting mineralization.

COMPLICATIONS OF ATHEROSCLEROSIS

Arterial Stenoses and Their Clinical Implications

The process of initiation and evolution of the atherosclerotic plaque generally takes place over many years, during which the affected person often has no symptoms. After the plaque burden exceeds the capacity of the artery to remodel outward, encroachment on the arterial lumen begins. Eventually the stenoses may progress to a degree that impedes blood flow through the artery. Lesions that produce stenoses of greater than some 60 percent can cause flow limitations under conditions of increased demand. In the coronary tree such obstructive lesions may cause symptoms such as angina pectoris. Thus, the symptomatic phase of atherosclerosis usually occurs many decades after lesion initiation (see Fig. 30-1). The development of chronic stable angina pectoris

or intermittent claudication on increased demand is a common presentation of this type of atherosclerotic disease. During this chronic asymptomatic or stable phase of lesion evolution, growth probably occurs discontinuously, with periods of relative quiescence punctuated by episodes of rapid progression (see Fig. 30-7). Human angiographic studies support this discontinuous growth of coronary artery stenoses.[78] [79]

However, in many cases of myocardial infarction no history of prior stable angina heralds the acute event. In some cases, this mode of transition from the chronic stable or asymptomatic phase of coronary atherosclerosis may result from progressive intimal growth and critical narrowing of the vessel due to a high-grade stenosis. Several kinds of clinical observation over the last several years, however, suggest that most myocardial infarctions result not from

critical blockages but from lesions that produce stenoses that do not limit flow. For example, in individuals who have undergone coronary arteriography in the months preceding myocardial infarction, the culprit lesion most often shows less than 50 percent stenosis. In a compilation of four such serial angiographic studies, only approximately 15 percent of acute myocardial infarctions arose from lesions with degrees of stenosis greater than 60 percent on an antecedent angiogram.[80] [81]

Instead of progressive growth of the intimal lesion to a critical stenosis, we now recognize that thrombosis, complicating a not necessarily occlusive plaque, most often causes episodes of unstable angina or acute myocardial infarction. Angiographic studies performed in individuals undergoing thrombolysis support this view. In one such study, almost half of patients undergoing thrombolysis for a first myocardial infarction had an underlying stenosis of less than 50 percent once the acute thrombus was lysed.[82]

It is a misconception, however, that small atheromas cause most myocardial infarction. Indeed, culprit lesions of acute myocardial infarction actually may be sizable. However, they may not produce a critical luminal narrowing because of the phenomenon of compensatory enlargement. Studies using intravascular ultrasonography, a cross-sectional imaging modality, to examine culprit lesions of acute myocardial infarction support this concept[83] (see also Chap. 12) . Of course, critical stenoses do cause myocardial infarctions. In fact, the high-grade stenoses are more likely to cause acute myocardial infarction than nonocclusive lesions.[80] However, because the noncritical stenoses by far outnumber the tight focal lesions in a given coronary tree, the lesser stenoses cause more infarctions even though their individual probability of causing a myocardial infarction is less than that of the high-grade stenoses.

Thrombosis and Atheroma Complication

This evolution in our view of the pathogenesis of the acute coronary syndromes places new emphasis on thrombosis as the critical mechanism of transition from chronic to

acute atherosclerosis. In the past decade we have seen considerable progress in our understanding of the mechanisms of coronary thrombosis. We now appreciate that a physical disruption of the atherosclerotic plaque commonly causes acute thrombosis.[68] [80] [84] Two major modes of plaque disruption provoke most coronary thrombi. The first mechanism, accounting for some two thirds of acute myocardial infarctions, involves a fracture of the plaque's fibrous cap (Fig. 30-8 *A*).[80] The second mode involves a superficial erosion of the intima (see Fig. 30-8 *B*), accounting for up to a fourth of acute myocardial infarctions in highly selected referral cases from medical examiners who have studied individuals who succumbed to sudden cardiac death.[85] Superficial erosion appears more frequently in women than in men as a mechanism of coronary sudden death.[86] [87]

Plaque Rupture and Thrombosis

The rupture of the plaque's fibrous cap probably reflects an imbalance between the forces that impinge on the plaque's cap and the mechanical strength of the fibrous cap.[88] Interstitial forms of collagen provide most of the biomechanical resistance to disruption to the fibrous cap. Hence, the metabolism of collagen probably participates in regulating the propensity of a plaque to rupture. Factors that decrease collagen synthesis by smooth muscle cells can impair their ability to repair and maintain the plaque's fibrous cap. For example, the T cell-derived cytokine interferon gamma po

Figure 30-8 Mechanisms of plaque disruption. Advanced atherosclerotic plaques can promote thrombosis by disruption. Fracture of the plaque's protective fibrous cap accounts for three fourths of fatal coronary thromboses. *A,* When the fibrous cap ruptures, blood with its coagulation factors can contact the tissue factor within the plaque, notably associated with plaque macrophages, although also found as acellular particles and on smooth muscle cells. *B,* The remainder of fatal coronary plaque disruptions appear to occur because of a superficial erosion of the endothelial layer exposing the blood and platelets to the subendothelial basement membrane containing collagen platelet activation and thrombosis.

Figure 30-9 A schematic relating extracellular matrix metabolism to intimal inflammation during athero genesis. The lymphocyte can elaborate gamma interferon (IFN-gamma) that inhibits smooth muscle cell collagen production. The lymphocyte can also signal either by elaboration of soluble mediators or by contact activation of macrophages. Other cytokines produced in response to products of oxidized lipoproteins, among other stimuli, can further activate the macrophage. The activated phagocyte can release collagen- degrading matrix metalloproteinases and elastolytic enzymes, including certain nonmetalloenzymes such as cathepsins S and K. These enzymes promote matrix catabolism. Thus, in states characterized by heightened intimal inflammation, the extracellular matrix that confers biomechanical strength to the plaque's fibrous cap is under double attack: decreased synthesis and increased degradation. This results in a weakening and thinning of the fibrous cap, features associated in pathological studies with fatal atheromatous plaque disruptions and thrombosis. TNF-alpha = tumor necrosis factor-alpha; M-CSF = macrophage colony stimulat ing factor; MCP-1 = monocyte chemoattractant protein-1. (After Libby P: The molecular bases of the acute coronary syndromes. Circulation 91:2844-2850, 1995. Copyright 1995, American Heart Association.)

tently inhibits smooth muscle cell collagen synthesis (Fig. 30-9) .[66] On the other hand, as already noted, certain mediators released from degranulating platelets can increase

smooth muscle cell collagen synthesis, tending to reinforce the plaque's fibrous structure. Such mediators include TGF-beta and PDGF contained in platelet granules.[66]

In addition to reduced de novo collagen synthesis by smooth muscle cells, increased catabolism of the extracellular matrix macromolecules that comprise the fibrous cap can also contribute to weakening this structure and rendering it susceptible to rupture, and hence thrombosis. The same matrix-degrading enzymes thought to contribute to smooth muscle migration and arterial remodeling may contribute to weakening of the fibrous cap as well (see Fig. 30-9) . [67] [68] , Macrophages in advanced human atheromas overexpress matrix metalloproteinases and elastolytic cathepsins that can break down the collagen and elastin of the arterial extracellular matrix.[89] [91] Thus, the strength of the plaque's fibrous cap is under dynamic regulation, linking the inflammatory response in the intima with the molecular determinants of plaque stability and, hence, the thrombotic complications of atheroma. The thinning of the plaque's fibrous cap, a result of reduced collagen synthesis and increased degradation, probably explains why pathological studies have shown that a thin fibrous cap characterizes atherosclerotic plaques that have ruptured and caused fatal myocardial infarction.[92] [93]

Another feature of the so-called vulnerable atherosclerotic plaque defined by pathological analysis is a relative lack of smooth muscle cells.[94] As explained earlier, inflammatory mediators both soluble and associated with the surface of T lymphocytes can provoke programmed cell death of smooth muscle cells. "Dropout" of smooth muscle cells from regions of local inflammation within plaques probably contributes to the relative lack of smooth muscle cells at places where plaques rupture.[63] Because these cells are the source of the newly synthesized collagen needed to repair and maintain the matrix of the fibrous cap, the lack of smooth muscle cells may contribute to weakening of the fibrous cap and, hence, the propensity of that plaque to rupture.[68]

A prominent accumulation of macrophages and a large lipid pool is a third microanatomical feature of the so-called vulnerable atherosclerotic plaque.[94] From a strictly biomechanical viewpoint, a large lipid pool can serve to concentrate biomechanical forces on the shoulder regions of plaques, which are common sites of rupture of the fibrous cap.[95] [96] From a metabolic standpoint, the activated macrophage characteristic of the plaque's core region produces the proinflammatory cytokines and the matrix-degrading enzymes thought to regulate aspects of matrix catabolism and smooth muscle cell apoptosis in turn.[97] The success of lipid-lowering therapy in reducing the incidence of acute myocardial infarction or unstable angina in patients at risk may result from a reduced accumulation of lipid and decrease in inflammation. Recent animal studies and monitoring of peripheral markers of inflammation in humans support this concept. (See also Chap. 31.)

Thrombosis Due to Superficial Erosion of Plaques

The foregoing section discusses the pathophysiology of rupture of the plaque's fibrous cap. The pathobiology of superficial erosion is much less well understood. In experimental atherosclerosis in the nonhuman primate areas of endothelial loss and platelet deposition occur in the more advanced plaques (Fig. 30-10) . In humans,

superficial erosion appears

more likely to cause fatal acute myocardial infarction in women and in individuals with hypertriglyceridemia and diabetes mellitus.[85] [87] However, the underlying molecular mechanisms remain obscure. Apoptosis of endothelial cells could contribute to desquamation of endothelial cells in areas of superficial erosion. Likewise, matrix metalloproteinases such as certain gelatinases specialized in degrading the nonfibrillar collagen found in the basement membrane (e.g., collagen type IV) might also sever the tetherings of the endothelial cell to the subjacent basal lamina and promote their desquamation.

Most plaque disruptions do not give rise to clinically apparent coronary events. Careful pathoanatomical examination of hearts obtained from individuals who have succumbed to noncardiac death have shown a surprisingly high incidence of focal plaque disruptions with limited mural thrombi. Moreover, hearts fixed immediately after explantation from individuals with severe but chronic stable coronary atherosclerosis and who had undergone transplantation for ischemic cardiomyopathy show similarly evidence for ongoing but asymptomatic plaque disruption.[84] Experimentally, in atherosclerotic nonhuman primates, mural

Figure 30-10 Superficial erosion of experimental atherosclerotic lesions shown by scanning electron microscopy. *A,* In the low-power view, the rent in endothelium is evident. Leukocytes have adhered to the subendothelium, which is beginning to be covered with a carpet of platelets. *B,* The high-power view shows a field selected from the center of *A* that shows the leukocytes and platelets adherent to the subendothelium. (From Faggiotto A, Ross R: Studies of hypercholesterolemia in the nonhuman primate: II. Fatty streak conversion to fibrous plaque. Arteriosclerosis 4:341-356, 1984.)

Figure 30-11 Platelet thrombus complicating a plaque disruption in experimental atherosclerosis. This transmission electron micrograph shows a cross section of macrophage studded with platelets that have clumped to form a microscopic thrombus. (From Faggiotto A, Ross R, Harker L: Studies of hypercholesterolemia in the nonhuman primate: I. Changes that lead to fatty streak formation. Arteriosclerosis 4:323-340, 1984.)

platelet thrombi can complicate plaque erosions without causing arterial occlusion (Fig. 30-11) .[102] Therefore, repetitive cycles of plaque disruption, thrombosis in situ, and healing probably contribute to lesion evolution and plaque growth. Such episodes of thrombosis and healing constitute one type of "crisis" in the history of a plaque that may cause a burst of smooth muscle cell proliferation, migration, and matrix synthesis. The

TGF-beta and PDGF released from platelet granules stimulate collagen synthesis by smooth muscle cells.[66] Thrombin, generated at sites of mural thrombosis, potently stimulates smooth muscle cell proliferation.[103] The late stage or "burned out" fibrous and calcific atheroma may represent a late stage of a plaque previously rich in lipid and vulnerable but now rendered fibrous and hypocellular owing to a wound-healing response mediated by the products of thrombosis.

SPECIAL CASES OF ARTERIOSCLEROSIS

Restenosis after Arterial Intervention (See also Chap. 38)

The problem of restenosis after percutaneous arterial intervention represents a special case of arteriosclerosis. After balloon angioplasty, luminal narrowing recurs in approximately one third of cases within 6 months (see also Chap. 38) . Initially, work on the pathophysiology of restenosis after angioplasty focused on smooth muscle proliferation.[104] A good deal of the thinking regarding the pathobiology of restenosis depended on extension to the human situation of the results of withdrawal of an overinflated balloon in a previously normal rat carotid artery. Study of this very well standardized preparation promoted precise understanding of the kinetics of intimal thickening after this type of injury. Furthermore, these studies identified a role for PDGF in stimulating smooth muscle cell migration and basic fibroblast growth factor in triggering smooth muscle cell proliferation in the rat carotid artery after injury.[105] [107] However, the attempts to transfer this information to human restenosis met with considerable frustration. This disparity between the balloon withdrawal injury of animals arteries and human restenosis is not surprising. The substrate of the animal studies was usually a normal rather than atherosclerotic artery, with all the attendant cellular and molecular differences highlighted earlier. Moreover, a high-pressure inflation of an angioplasty balloon only vaguely resembles the overinflated balloon withdrawal injury commonly practiced in rats.

Although smooth muscle cell proliferation appears prominent in the simple experimental models of intimal thickening, observations on human specimens showed relatively low rates of smooth muscle cell proliferation and called into question therapeutic targeting of this process. Moreover, intravascular ultrasound studies in humans, and considerable evidence from animal experimentation, suggested that a substantial proportion of the loss of luminal caliber after balloon angioplasty resulted from a constriction of the vessel from the adventitial side ("negative remodeling").[108] These observations renewed interest in adventitial inflammation with scar formation and wound contraction as a mechanism of arterial constriction after balloon angioplasty.[109] [110]

The widespread introduction of stents has changed the face of the restenosis problem. The process of in-stent stenosis, in contrast to restenosis after balloon angioplasty, depends uniquely on intimal thickening, as opposed to "negative remodeling." The stent provides a firm scaffold that prevents constriction from the adventitia. Histological analyses reveal that a great deal of the volume of the in-stent restenotic lesion is made up of "myxomatous" tissue, comprising occasional stellate smooth muscle cells embedded in a loose and highly hydrated extracellular matrix.

The introduction of stents has reduced the clinical impact of restenosis because of the very effective increase in luminal diameter achieved by this technique. Even if a considerable degree of lumen loss occurs due to intimal thickening, the luminal caliber remains sufficient to alleviate the patient's symptoms because of the excellent dilatation achieved. Currently, radiation treatment, presumably targeting smooth muscle proliferation and matrix synthesis, is under evaluation as a therapeutic approach to limiting in-stent stenosis (see Chap. 38).

Accelerated Arteriosclerosis after Transplantation (See also Chap. 20)

Since the advent of effective immunosuppressive therapy such as cyclosporine, the major limitation to long-term survival

of cardiac allografts is the development of an accelerated form of arterial hyperplastic disease (see also Chap. 20.)

Figure 30-12 Comparison of usual atherosclerosis and transplantation arteriosclerosis. Usual atherosclerosis *(left panel)* characteristically forms an eccentric lesion with a lipid core and fibrous capsule. In contrast, the lesion of transplantation-associated accelerated arteriosclerosis *(right panel)* characteristically has a concentric intimal expansion without a clear central lipid core.

I favor the term *arteriosclerosis* (hardening of the arteries) rather than *atherosclerosis* (gruel-hardening) to describe this process because of the inconstant association with lipids (the "gruel" in atherosclerosis). [111] This form of arterial disease often presents a diagnostic challenge. The patient may not experience typical anginal symptoms due to the interruption of cardiac denervation after transplantation. In addition, graft coronary disease is concentric and diffuse, not only affecting the proximal epicardial coronary vessels but also penetrating smaller intramyocardial branches (Fig. 30-12) . [112] For this reason, the angiogram, well suited to visualize focal and eccentric stenoses, consistently underestimates the degree of transplantation arteriosclerosis.[113]

In most centers, a majority of patients undergoing transplantation have atherosclerotic disease and ischemic cardiomyopathy. However, a sizable minority undergo heart transplantation for idiopathic dilated cardiomyopathy and may have few risk factors for atherosclerosis. Even in the absence of traditional risk factors, this latter group of individuals shares the risk of developing accelerated arteriosclerosis. This observation suggests that the pathophysiology of this form of accelerated arteriosclerosis differs from that of usual atherosclerosis.

The selective involvement of the engrafted vessels with sparing of the host's native arteries suggests that accelerated arteriopathy does not merely result from the

immunosuppressive therapy or other systemic factors in the transplantation recipient. Rather, these observations suggest that the immunological differences between the host and the recipient vessels might contribute to the pathogenesis of this disease. Considerable evidence from both human and experimental studies currently supports this viewpoint. Endothelial cells in the transplanted coronary arteries express histocompatibility antigens that can engender an allogeneic immune response from host T cells.[114] The activated T cells can secrete cytokines (e.g., interferon gamma) that can augment histocompatibility gene expression, recruit leukocytes by induction of adhesion molecules, and activate macrophages to produce smooth muscle cell chemoattractants and growth factors. Interruption of interferon gamma signaling can prevent experimental graft coronary disease in mice.[115] This disease appears to occur despite cyclosporine therapy, because this immunosuppressant is relatively ineffective as a suppressor of the endothelial allogeneic response. These observations hold out the hope that combinations of cyclosporine with other immunosuppressive agents that more effectively suppress the endothelial allogeneic response may prove an effective therapy to retard or prevent graft arteriosclerosis.

The data just summarized suggest that graft arteriosclerosis represents an extreme case of immunologically driven arterial hyperplasia (Fig. 30-13) that can happen in the absence of other risk factors.[111] On the other extreme, patients with homozygous familial hypercholesterolemia can develop fatal atherosclerosis in the first decade of life due solely to an elevation in LDL. The vast majority of patients with atherosclerosis fall somewhere between these two extremes. Analysis of usual atherosclerotic lesions shows evidence for a chronic immune response and lipid accumulation. Therefore, by studying the extreme cases, such as transplantation arteriopathy and familial hypercholesterolemia, one can gain insight into elements of the pathophysiology that contribute to the multifactorial form of atherosclerosis that affects the majority of patients.

Figure 30-13 A multifactorial view of the pathogenesis of atherosclerosis. This diagram depicts two extreme cases of atherosclerosis. One *(far left side)* represents accelerated arteriosclerosis that can occur in the transplanted heart in the absence of traditional coronary risk factors. This disease likely represents primarily immune-mediated arterial intimal disease. The other extreme *(far right side)* depicts the case of a child who may succumb to rampant atherosclerosis in the first decade of life due solely to an elevated low density lipoprotein (LDL) caused by a mutation in the LDL receptor (homozygous familial hypercholesterolemia). Between these two extremes lie the vast majority of patients with atherosclerosis, probably involving various mixtures of immune and inflammatory and/or lipoprotein-mediated disease. One can further consider that this diagram extends to a third dimension that would involve other candidate risk factors such as homocysteine, lipoprotein(a), infection, tobacco abuse, and so on.

Aneurysmal Disease (See also Chap. 40)

Atherosclerosis produces not only stenoses but also aneurysmal disease. Why does a single disease process manifest itself in directionally opposite manner, for example, most commonly producing stenoses in the coronary arteries but causing ectasia of the abdominal aorta? In particular, aneurysmal disease characteristically affects the infrarenal abdominal aorta. This region is highly prone to the development of atherosclerosis. Data from the Pathobiological Determinants of Atherosclerosis In Youth

Study (PDAY) show that the dorsal surface of the infrarenal abdominal aorta has a particular predilection for development of fatty streaks and raised lesions in Americans younger than age 35 who succumbed for noncardiac reasons.[116] [118] Because of the absence of vasa vasorum the relative lack of blood supply to the tunica media in this portion of the abdominal aorta might explain the regional susceptibility of this portion of the arterial tree to aneurysm formation. In addition, the lumbar lordosis of the biped human may alter the hydrodynamics of blood flow in the distal aorta, yielding flow disturbances that may promote lesion formation.

Histological examination shows considerable distinction between occlusive atherosclerotic disease and aneurysmal disease. In typical coronary artery atherosclerosis, expansion of the intimal lesion produces stenotic lesions. The tunica media underlying the expanded intima is often thinned, but its general structure remains relatively well preserved. In contrast, transmural destruction of the arterial architecture occurs in aneurysmal disease. In particular, the usually well-defined laminar structure of the normal tunica media disappears with loss of the elastic laminae. The medial smooth muscle cells, usually well preserved in typical stenotic lesions, are notable for their paucity in the media of advanced aortic aneurysms.

Study of the pathophysiology that underlies these anatomical pathological findings has proven frustrating. Informative animal models are not available. The human specimens obtainable for analysis generally represent the late stages of this disease. Nonetheless, recent work has

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identified several mechanisms that may underlie the peculiar pathology of aneurysmal disease. Widespread destruction of the elastic laminae suggests a role for degradation of elastin, collagen, and other constituents of the arterial extracellular matrix. Many studies have documented overexpression of matrix-degrading proteinases including matrix metalloproteinases in human aortic aneurysm specimens.[119] [121]

Thus, heightened elastolysis may explain the breakdown of the usually ordered structure of the tunica media in this disease. In addition, aortic aneurysms show evidence for considerable inflammation, particularly in the adventitia.[122] The lymphocytes that characteristically abound on the adventitial side of aneurysmal tissue suggest that apoptosis of smooth muscle cells triggered by inflammatory mediators including soluble cytokines and *fas* ligand, elaborated by these inflammatory cells, may contribute to smooth muscle cell destruction, and promote aneurysm formation.[123] Although extracellular matrix degradation and smooth muscle cell death also occur in sites where atherosclerosis causes stenosis, they appear to predominate in regions of aneurysm formation and to affect the tunica media much more extensively, for reasons that remain obscure.

Infection and Atherosclerosis

Recently, interest has increased in the possibility that infections may cause atherosclerosis. A considerable body of seroepidemiological evidence supports a role for certain bacteria, notably *Chlamydia pneumoniae*, and certain viruses, notably *cytomegalovirus* (CMV), in the etiology of atherosclerosis.[124] [125] The seroepidemiological studies have spurred a number of in vivo and in vitro experiments that lend varying degrees of support to this concept. In evaluation of the seroepidemiological evidence, several caveats apply. First, confounding factors should be carefully considered.[126] For example, smokers may have a higher incidence of bronchitis due to *C. pneumoniae*. Therefore, evidence for infection with *C. pneumoniae* may merely serve as a marker for tobacco use, a known risk factor for atherosclerotic events. Additionally, a strong bias favors publication of positive studies as opposed to negative studies. Thus, meta-analyses of seroepidemiological studies may be slanted toward the positive merely because of underreporting of negative studies. Finally, atherosclerosis is a common and virtually ubiquitous disease in developed countries. In most societies, many adults have serological evidence of prior infections with Herpesviridae, such as CMV, and respiratory pathogens, such as *C. pneumoniae*. It is difficult to sort out coincidence from causality when the majority of the population studied has evidence of both infection and atherosclerosis. (See also Chap. 31.)

Although proof that bacteria or viruses can cause atherosclerosis remains elusive, it is quite plausible that infections may potentiate the action of traditional risk factors, such as hypercholesterolemia. Based on the vascular biology of atherosclerosis discussed in this chapter, a number of scenarios might apply. First, cells within the atheroma itself may be a site for infection. For example, macrophages existing in an established atherosclerotic lesion might become infected with *C. pneumoniae*, which could spur their activation and accelerate the inflammatory pathways that are currently believed to operate within the atherosclerotic intima. Specific microbial products such as lipopolysaccharides, heat-shock proteins, or other virulence factors might act locally at the level of the artery wall to potentiate atherosclerosis in infected lesions.[127] [133]

Extravascular infection might also influence the development of atheromatous lesions and provoke their complication. For example, circulating endotoxin or cytokines produced in response to a remote infection can act locally at the level of the artery wall to promote the activation of vascular cells and of leukocytes in preexisting lesions, producing an "echo" at the level of the artery wall of a remote infection.[134] Also, the acute phase response to an infection in a nonvascular site might affect the incidence of thrombotic complications of atherosclerosis by increasing fibrinogen or plasminogen activator inhibitor-1 (PAI-1) or otherwise altering the balance between coagulation and fibrinolysis. Such disturbance in the prevailing prothrombotic, fibrinolytic balance may critically influence whether a given plaque disruption will produce a clinically inapparent transient or nonocclusive thrombus or sustained and occlusive thrombi that could cause an acute coronary event.

Acute infections might also produce hemodynamic alterations that could trigger coronary events. For example, the tachycardia and increased metabolic demands of fever could augment the oxygen requirements of the heart, precipitating ischemia in an otherwise compensated individual. These various scenarios illustrate how infectious

processes, either local in the atheroma or extravascular, might aggravate atherogenesis, particularly in preexisting lesions or in concert with traditional risk factors. Currently, a number of well-designed trials are critically testing the hypothesis that treatment with antibiotics can reduce recurrent coronary events in survivors of myocardial infarction. The results of such studies will be forthcoming in the next several years. However, even if these studies were positive, they would not establish a role for a particular infectious agent, nor could they prove that the antibiotic effect of the agents tested, rather than some other action not related to their antimicrobial effect, could produce benefit.

Acknowledgment

This chapter is dedicated to the memory of Dr. Russell Ross, author of the chapter on atherosclerosis in the last three editions of this text. Dr. Ross died unexpectedly in March of 1999 and was thus unable to participate in authoring this chapter, as had been planned.

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Chapter 31 - Risk Factors for Atherosclerotic Disease

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Cardiovascular disease is the single most common cause of death in the developed world and accounts for almost 1 million fatalities in the United States alone each year. Of these cardiovascular deaths, nearly half result directly from coronary artery disease and another 20 percent from stroke (see Chap. 1) . Given our current understanding of the pathophysiology of atherothrombosis (see Chap. 30) , it is historically surprising that the conceptual basis for considering specific "cardiovascular risk factors" did not formally exist until the initial findings of the Framingham Heart Study began to appear in the early 1960s.[1] [2]

From an epidemiological perspective, a "risk factor" is a characteristic or feature of an individual or population that is present early in life and is associated with an increased risk of developing future disease. The risk factor of interest may be a behavior (e.g., smoking), an inherited trait (e.g., family history), or a laboratory measurement (e.g., cholesterol). For a risk factor to be considered causal, the marker of interest must predate the onset of disease and must have biological plausibility. Most risk factors used in daily practice have demonstrated a consistent graded-response effect and are

substantiated by a large series of consistent prospective studies in broad population groups. Several risk factors such as hyperlipidemia and hypertension are modifiable, and trials have demonstrated that lowering these factors reduces vascular risk.

This chapter reviews the epidemiological evidence underlying the conventional atherosclerotic risk factors of hyperlipidemia, smoking, hypertension, insulin resistance and diabetes, physical activity, obesity, and hormone status, as well as general strategies for reducing risk related to these factors. However, it has become increasingly clear that not all coronary events occur in individuals with traditional risk factors and that in some individuals isolated abnormalities of hemostasis and thrombosis appear to play critical roles.[3] In particular, nearly half of all instances of myocardial infarction in the United States occur among individuals without overt hyperlipidemia.[4] Thus, this chapter also reviews in detail a series of novel atherosclerotic risk factors, including homocysteine, fibrinogen, and lipoprotein(a) (Lp[a]), as well as indices of fibrinolytic function (e.g., tissue-type plasminogen activator [t-PA] and plasminogen activator inhibitor 1 [PAI-1]) and markers of inflammation (e.g., high-sensitivity C-reactive protein (hs-CRP). Strategies for reducing coronary risk, often through modification of the factors outlined here, are provided in Chapter 32 and the pharmacotherapy of lipid disorders is dealt with more specifically in Chapter 33 .

Despite recent advances,[5] coronary artery disease will continue to play a major role well into the 21st century[6] (see also Chap. 1) . Thus, risk prediction algorithms such as those developed in the Framingham Heart Study or by the European Consortium[1] will remain important for patient care (see Chap. 32) . However, risk reduction strategies targeted solely at high-risk individuals are not the only viable approach to coronary prevention. For a disease as common as atherosclerosis, population-based strategies can also be highly effective, particularly for primary prevention. To date, population-wide reductions in cigarette consumption, hyperlipidemia, and blood pressure have been reported for the United States.[7] [8] Determining whether similar programs to increase physical activity, reduce the prevalence of hyperinsulinemia, or directly target novel risk factors for atherosclerosis can further reduce coronary heart disease rates presents a major challenge for the future.[8A] [8B] [8C]

DYSLIPIDEMIA

The Lipid Hypothesis (See also Chap. 30)

HISTORICAL CONSIDERATIONS.

The role of cholesterol in the pathogenesis of atherosclerotic heart disease remained controversial until surprisingly recently.[9] Early experiments by Anitschow on cholesterol-fed animals and the later identification of cholesterol as an important constituent of the plaque furnished landmark clues in the case against cholesterol in the pathogenesis of cardiovascular diseases.[10] As early mortality due to communicable diseases subsided, chronic diseases, especially atherosclerosis, became the most important causes of mortality and disability[11] in the latter part of the 20th century (see Chaps. 1 and 32) . The importance of serum (or plasma) cholesterol emerged not only from the large epidemiological studies conducted after World War II but also from a

large body of epidemiological data that include the Seven Country Study, the Ni-Hon-San study, the Northwick Park study, and, more recently, the Prospective Cardiovascular Munster (PROCAM) study.[9] [12] Further refinements in analytical methodologies, especially the use of the ultracentrifuge (which allows separation of plasma lipoproteins), provided important data on the relationship between low-density lipoproteins (LDL) and possibly very low-density lipoproteins (VLDL) and coronary artery disease.[13] The role of high-density lipoproteins (HDL) as a protective fraction also emerged.[14] Despite these results, until recently, enthusiasm for treating patients with drugs to lower cholesterol lagged for two reasons: (1) the drugs themselves had undesired effects and (2) little direct evidence actually demonstrated reduced morbidity and mortality.

Data regarding the role of diet in cardiovascular diseases only added to the confusion. The Seven Country Study[15] provided compelling data that plasma cholesterol levels correlated much more with saturated fat intake than with dietary cholesterol. Furthermore, there was a strong and graded relationship between saturated fat intake,

serum cholesterol, and the incidence of coronary heart disease. Dietary cholesterol had a much weaker correlation with coronary heart disease, an often overlooked but important point. Many intervention studies with earlier generations of lipid-lowering drugs showed a reduction of coronary events, but no change in total mortality and a tendency toward increased noncardiovascular deaths (see Chap. 33 for an extensive discussion of clinical trials of lipid lowering). These findings led to a sober reevaluation of the lipid hypothesis. However, recent trials, notably those using hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors, have established beyond a doubt that lipid-lowering therapy in high-risk or even moderate-risk subjects reduces cardiovascular morbidity and mortality.

We advocate use of the more general term *dyslipoproteinemia* in place of hyperlipidemia to describe disorders of the lipid and lipoprotein transport pathways. Dyslipidemia encompasses disorders that include low HDL but average total plasma cholesterol levels, very commonly encountered in clinical practice. Despite their prevalence, most dyslipoproteinemias have few, if any, symptoms and only rarely cause clinical signs evident on physical examination. Proper recognition and management of dyslipidemia thus requires a working knowledge of elements of lipid metabolism.

The Lipid Transport System

Plasma Lipids

The lipid transport system has evolved to ferry hydrophobic molecules (fat) from sites of synthesis to sites of utilization. Not surprisingly, the proteins (apolipoproteins) that mediate this process are remarkably well conserved throughout evolution. Most apolipoproteins probably derive from an ancestral gene and contain alpha-helical

domains with an amphipathic structure allowing the interface between the aqueous environment of plasma and the phospholipid constituents of the lipoprotein.[16] Four major types of lipids circulate in plasma: cholesterol and cholesteryl esters, phospholipids, and triglycerides.

CHOLESTEROL.

This is a polycyclic molecule that is waxy and water insoluble. It is an essential component of mammalian cell membranes and serves as the substrate for synthesis of corticosteroid hormones and bile acids. All cells require cholesterol for their membranes and tightly regulate its production. Most cholesterol in plasma circulates in the form of cholesteryl esters, with a fatty acid moiety linked to its weakly polar hydroxyl group.

TRIGLYCERIDES.

These are composed of glycerol (a 3-carbon alcohol), covalently linked to three fatty acids chains. The fatty acids vary in both chain length and presence of single (monounsaturated) or multiple (polyunsaturated) double bonds. Triglyceride molecules are nonpolar and hydrophobic.

PHOSPHOLIPIDS.

All cellular membranes contain phospholipids and glycerol molecules, with two of its hydroxyl groups esterified with fatty acids of various chain length and saturation. The third carbon is attached to a phosphate group, which is linked to one of four molecules: choline (phosphatidyl choline--or lecithin), ethanolamine (phosphatidylethanolamine), serine (phosphatidyl serine), or inositol (phosphatidylinositol). A related phospholipid, sphingomyelin, is a critical component of the plasma membrane and functions in the formation of membrane microdomains. Phospholipids also participate in signal transduction pathways after hydrolysis by membrane-associated phospholipases.

Lipoproteins

Lipoprotein particles provide water-soluble packages of hydrophobic lipids permitting their transport in blood. Lipoproteins contain an envelope of phospholipids and some free cholesterol, as well as a core of triglycerides or cholesteryl esters (Fig. 31-1). Lipoproteins vary in origin, size, density in an aqueous environment (plasma), lipid, and apolipoprotein content (Fig. 31-2 , Table 31-1) .[17] Ultracentrifugation separates lipoproteins according to their density in plasma (density 1.006 gm/ml). The triglyceride-rich lipoproteins consisting of chylomicrons and VLDL float in the ultracentrifuge (density < 1.006 gm/ml). The rest of the ultracentrifuged plasma contains LDL, HDL and Lp(a). More convenient methods of separation have now replaced ultracentrifugation for many practical purposes.[13] [18]

Apolipoproteins, Receptors, and Processing Proteins

The protein moieties of lipoproteins known as apolipoproteins (Table 31-2) have four major roles: (1) they assemble and secrete the lipoprotein (apo B_{100} and B_{48}); (2) they provide structural integrity to the lipoprotein (apo B, apo E, apo AI, apo AII); (3) they act as co-activators of enzymes (apo AI, CII, CIII) (Table 31-3) ; and (4) they bind or dock to specific receptors and proteins for cellular uptake (apo AI, B_{100} , E). The role of several apolipoproteins (AIV, D, and J) remains incompletely understood.

Identification and characterization of proteins that regulate the synthesis, secretion, and metabolic fate of lipoproteins has allowed crucial understanding of cellular biology and provided targets for drug

Figure 31-1 Structure of lipoproteins. Phospholipids are oriented with their polar head toward the aqueous environment of plasma. Free cholesterol is inserted within the phospholipid layer. The core of the lipoprotein is made up of cholesteryl esters and triglycerides. Apolipoproteins provide structural integrity to the lipoprotein and act as cofactors for enzymes or as ligands for various receptors. (From Grundy SM: Cholesterol and Atherosclerosis: Diagnosis and Treatment. Philadelphia, JB Lippincott, 1990.)

Figure 31-2 Relative size of plasma lipoproteins according to their hydrated density.

development. The discovery of the LDL receptor (LDL-R) constituted a landmark in understanding how cells take up complex molecules by receptor-mediated endocytosis.[19] The level of LDL-R expression depends exquisitely on cellular cholesterol content, decreasing when supplies are sufficient. The discovery of the LDL-R set the stage for molecular characterization of several other lipoprotein receptors. We now recognize several receptors for VLDL that bind to specific epitopes on VLDL but not on LDL.[20] [21] Apo E is the apparent preferred ligand for the LDL receptor-related peptide (LRP), which mediates the uptake of chylomicron remnants and VLDL.[22] LRP interacts with hepatic lipase. In addition, a novel receptor, the lipolysis-stimulated receptor (LSR), is expressed in response to free fatty acids.[23]

Macrophages can express receptors that bind modified (especially oxidized) lipoproteins. Such scavenger receptors mediate the uptake of oxidized LDL into macrophages (see also Chap. 30) .[24] This mechanism contributes to the removal of modified lipoproteins from the arterial intimal layer, where they can provoke an inflammatory reaction. Lipid-laden macrophages may exit the artery wall and become engulfed in the reticuloendothelial system. In contrast to the LDL-R, cellular cholesterol sufficiency does not suppress scavenger receptors. Therefore, macrophages can rapidly become lipid-laden foam cells under conditions of cholesterol excess and form fatty streaks.[25] Endothelial cells can also take up modified lipoproteins through specific

receptors such as Lox-1.[26] Receptors for HDL have engendered

TABLE 31-1 -- PLASMA LIPOPROTEIN COMPOSITION

	ORIGIN	DENSITY (gm/ml)	SIZE (nm)	%PROTEIN	CHOLESTEROL IN PLASMA*	TRIGLYCERIDE IN PLASMA
Chylomicrons	Intestine	<0.95	100-1000	1-2	0.0	0
VLDL	Liver	<1.006	40-50	10	0.1-0.4	0.2-1.2
IDL	VLDL	1.006-1.019	25-30	18	0.1-0.3	0.1-0.3
LDL	IDL	1.019-1.063	20-25	25	1.5-3.5	0.2-0.4
HDL	Tissues	1.063-1.210	6-10	40-55	0.9-1.6	0.1-0.2
Lp(a)	Liver	1.051-1.082	25	30-50		

*in mmol/L; for mg/dl, multiply by 38.67.

in mmol/L; for mg/dl, multiply by 88.5.

TABLE 31-2 -- APOLIPOPROTEINS

	PREDOMINANT LIPOPROTEIN	MOLECULAR WEIGHT (daltons)	PLASMA CONCENTRATION (mg/dl)	CHROMOSOME	ROLE
Apo AI	HDL	28,300	90-160	11q23	ACAT activation, structural
Apo AII	HDL	17,000	25-45	1q21-23	Structural
Apo AIV	HDL	45,000	10-20	11q23	Structural, absorption
Apo B100	LDL, VLDL	512,000	50-150	2q23-24	Structural, LDL-R binding
Apo B48	Chylomicrons	241,000	0-100	2q23-24	Structural
Apo CI	Chylomicrons	6,631	5-6	19q13.2	TRL metabolism
Apo CII	Chylo, VLDL	8,837	3-5	19q13.2	LPL activation

Apo CIII	Chylo, VLDL	8,764	10-14	11q23	LPL inhibition
Apo D	HDL	33,000	4-7	3q26.2	LCAT
Apo E	Chylo rem, IDL	34,000	2-8	19q13.2	LDL-R, ApoE-R binding
Apo J	HDL	70,000	10	18p21	Complement system
Apo(a)	Lp(a)	250,000-800,000	0-200	6q27	Tissue injury ?

TABLE 31-3 -- EXAMPLES OF LIPOPROTEINS, THEIR PROCESSING ENZYMES, AND THEIR RECEPTORS

ABBREVIATION	NAME	ROLE	HUMAN DISEASE
LPL	Lipoprotein lipase	Triglyceride hydrolysis	Hyperchylomicronemia
HL	Hepatic lipase	Triglyceride hydrolysis	Remnant accumulation
MTP	Microsomal triglyceride transfer	Apo B assembly	Abetalipoproteinemia
LCAT	Lecithin:cholesterol acyl transferase	Cholesterol esterification	LCAT deficiency, low HDL
ACAT1	Acyl:CoA cholesterol acyl transferase	Cholesterol esterification	Cellular cholesterol esterification
ACAT2	Acyl:CoA cholesterol acyl transferase	Cholesterol esterification	Rough ER cholesterol esterification
NPC1	Niemann-Pick C gene product	?	Niemann-Pick type C
LDL-R	Low-density lipoprotein receptor	LDL uptake	Familial hypercholesterolemia
VLDL-R	VLDL receptor	VLDL uptake	
Apo E-R	ApoE containing lipoproteins	TRL uptake	
SR-B1	Scavenger receptor B1	HDL CE uptake	

LIPE	Hormone sensitive lipase	Fatty acid release from adipocytes	
MSR	Scavenger receptor	OxLDL uptake	Oxidized lipoprotein uptake, macrophage
Lox1	Scavenger receptor	OxLDL uptake, endothelium	Oxidized lipoprotein uptake, endothelium
LRP1	LDL-R related protein	Chylomicron remnants	
LRP2	LDL-R related protein 2 (megalin)	Protease uptake, apo J	
ABC1/CERP	Cholesterol efflux regulatory protein	Cellular cholesterol efflux	Tangier disease
CD36	Oxidized LDL receptor	OxLDL uptake	
CD68	Macrosialin: oxidized LDL receptor	OxLDL uptake	
Cubilin	Apo AI receptor	Renal HDL clearance	

considerable debate. Of the receptors that have been postulated, several are strong candidates. The only HDL receptor clearly identified is a protein of the scavenger receptor class B, SR-B1.[27] SR-B1 binds HDL (and LDL and VLDL as well, but with less affinity). Animal data show that SR-B1 mediates the selective uptake of HDL cholesteryl esters in steroidogenic tissues (Fig. 31-3 *A*). Recent work has characterized other putative HDL receptors.[28] For example, cubilin, probably in concert with megalin (both of which are proteins expressed by resorptive epithelial cells), appears to mediate renal clearance of HDL.[28A] [28B]

Physiology of Lipoprotein Transport

The lipid transport system has two predominant roles: (1) the efficient transport of triglycerides from the gut and the liver to sites of utilization or storage (fat tissue or muscle) and (2) the transport of the cholesterol molecule to peripheral tissues, for membrane synthesis, for steroid hormone production, or to the liver for bile acid synthesis (Fig. 31-4) . Lipoproteins also deliver essential fatty acids that the human body must derive from dietary sources.

THE FATE OF DIETARY FAT.

Most dietary fat consists of triglycerides. For an individual consuming 2000 Kcal/day, with 30 percent in the form of fat, this represents approximately 66 gm of triglycerides per day and the intake of cholesterol is approximately 250 mg. On ingestion, fats are emulsified in the bowel by bile salts and form micelles before being hydrolyzed by

pancreatic lipases into free fatty acids and monoglycerides or diglycerides. The fatty acids are reassembled into very large lipoproteins, the chylomicron, inside the intestinal cell and then secreted in the portal circulation (see Fig. 31-4 ,*1*).

Chylomicrons contain apo B48, which is the amino-terminal component of apo B100. In the intestine, the apo B gene is modified during transcription into messenger RNA with a substitution of a uracil for a cytosine by an apo B48-editing enzyme. This mechanism, which involves the deamination of cytosine, leads to a termination codon at residue 2153 and a truncated form of apo B.[29] Only intestinal cells contain this apo B-editing complex (apoBec). Chylomicrons rapidly enter the plasma compartment in the postprandial phase. In capillaries of adipose tissue or muscle cells, chylomicrons in the peripheral circulation encounter lipoprotein lipase (LPL), an enzyme attached to heparan sulfate on the luminal side of endothelial cells (see Fig. 31-4 ,*2*).

LPL activity is modulated by apo CII (an activator of LPL) and by apo CIII (an inhibitor). LPL has broad specificity for triglycerides; it cleaves all fatty acyl residues attached to glycerol, generating three molecules of free fatty acid for each molecule of glycerol. The fatty acids are rapidly taken up by muscle cells for energy utilization, a process requiring insulin, or by adipose cells for storage. Fatty acids can also bind to fatty acid-binding proteins and reach the liver, where they will be repackaged in VLDL. Peripheral resistance to insulin may therefore increase the flux of free fatty acids to the liver, with a consequent increase in VLDL secretion and increased apo B particles in plasma. As discussed later, this is one of the consequences of insulin resistance syndrome. The chylomicron remnants contain apo E and are taken up by the liver for degradation and reutilization of its core constituents (see Fig. 31-4 ,*3*).

HEPATIC LIPOPROTEIN SYNTHESIS: AN ALTERNATIVE SOURCE OF FAT FOR ENERGY SUPPLY.

Food is not always available and dietary fat content is not always constant. The body, therefore, must ensure readily available triglyceride molecules for energy demands. This is done by hepatic secretion of triglyceride-rich VLDL particles that contain apo B100 as their main lipoprotein (see Figs. 31-2 and 31-4 ,*4;* Table 31-1) . Apo B48 lacks the domain recognized by the LDL-R present in apo B100. VLDL particles undergo the same catabolic pathway as chylomicrons by lipoprotein lipase (see Fig. 31-4 ,*2*).

REMODELING OF TRIGLYCERIDE-RICH LIPOPROTEIN: A ROLE IN REVERSE CHOLESTEROL TRANSPORT.

Whether derived from diet or hepatic synthesis, triglyceride-rich lipoproteins undergo hydrolysis by LPL. At this stage, an exchange of proteins and lipids takes place: VLDL particles (and chylomicrons) acquire apo Cs and apo E, in part, from HDL particles. A cholesterol ester transfer protein (CETP) mediates net exchange of VLDL triglycerides for cholesteryl esters from HDL (see Fig. 31-4 ,*6* and *9*). Such bidirectional transfer of constituents between lipoproteins serves several purposes. It allows lipoproteins to acquire specific apolipoproteins that will dictate their metabolic fate. It also allows the transfer of cholesterol from HDL to VLDL remnants so it can be metabolized in the liver. Both of these roles contribute to reverse cholesterol transport, a pathway that can

promote export of cholesterol from the vessel wall.

FORMATION OF LDL FROM VLDL

Lipoprotein lipase partly depletes VLDL of triglycerides, and the exchanges just discussed enrich the particles in cholesterol and apo E while they shed several other apolipoproteins (especially the C apolipoproteins). The resultant VLDL remnants are called intermediate-density lipoproteins (IDL) and can be either taken up by the liver by means of its apo E moiety (see Fig. 31-4 ,*3*) or be further delipidated by hepatic lipase to form an LDL particle (see Fig. 31-4 ,*6*). There are at least four receptors for triglyceride-rich lipoproteins: the VLDL receptor, the remnant receptor, the LDL-R (also called the apo B/E receptor), and the LDL-related protein (LRP).[22] A common feature of most hepatic receptors is their recognition of apo E, which mediates uptake of several classes of lipoproteins, including VLDL and IDL. The interaction of apo E with its ligand is complex and involves the "docking" of triglyceride-rich lipoproteins on heparan sulfate proteoglycans (HSPG) before presentation of the ligand to its receptor.[30] LDL particles contain mostly cholesterol and apo B100. Normally, LDL particles contain only 4 to 8 percent of their mass as triglycerides. Under certain circumstances, especially in conditions of elevated levels of triglycerides, LDL particles can be enriched in triglycerides and depleted in core cholesteryl esters, making them smaller and denser.

Cells can either make the cholesterol they require from acetate (a pathway with at least 33 steps) or capture it from LDL particles using the LDL-R (see Fig. 31-3 *A*). The LDL-R localizes in a region of the plasma membrane rich in the protein clathrin (clathrin-coated pits) (see Figs. 31-3 *B* and 31-4,*7*). After binding of LDL to the receptor, clathrin polymerizes and forms an endosome that contains LDL

Figure 31-3 Cellular cholesterol homeostasis in various tissues. *A,* Selective uptake of cholesterol. Examples of steroidogenic tissues include the adrenal cortex and the gonads. *B,* LDL-receptor pathway (hepatic cell). *C,* Cellular cholesterol efflux (peripheral cell). *D,* Adipocyte. ASP = acylation stimulating protein; SER = smooth endoplasmic reticulum; RER = rough endoplasmic reticulum; Lys = lysosome; CERP = cholesterol efflux regulatory protein (product of the ABC 1 gene); HMG CoA Red = hydroxylmethylglutaryl coenzyme A reductase; LDL-R = LDL receptor; Apo = apolipoprotein; ACAT = Acyl coenzyme A: cholesterol acyl transferase.

bound to its receptor, a portion of the plasma membrane, and clathrin. This internalized particle then fuses with a lysosome containing cholesteryl ester hydrolase, which releases free cholesterol and proteinases that degrade apo B. The unbound LDL-R then recycles to the plasma membrane.[19] The disorder familial hypercholesterolemia (FH) results from mutations of the LDL-R gene.

REGULATION OF INTRACELLULAR CHOLESTEROL METABOLISM.

Several mechanisms closely control cellular cholesterol content. Cholesterol synthesis in the smooth endoplasmic reticulum (by means of HMG CoA reductase) and receptor-mediated endocytosis of LDL or selective free cholesterol uptake from LDL are controlled transcriptionally by a factor known as the steroid-responsive element-binding protein (SREBP).[31] Other regulatory mechanisms include cholesterol efflux from plasma membrane to cholesterol acceptor particles (predominantly HDL) and intracellular cholesterol esterification through the enzyme acyl-CoA:cholesteryl acyltransferase (ACAT) (see Fig. 31-3 *B*). The cholesterol content in membranes regulates the amount of ACAT at the protein level. (Humans have two forms of ACAT: ACAT1 probably mediates cellular cholesterol esterification for storage in the cytosolic compartment, whereas ACAT2 appears to mediate cholesterol esterification in the endoplasmic reticular lumen for lipoprotein assembly and secretion.[32]) The cholesterol efflux pathway appears to be regulated through the adenosine triphosphate (ATP) binding cassette 1 (*ABC1*) gene, which produces cholesterol efflux regulatory protein (CERP) (see Fig. 31-3 *C*). [33] [34] [35] In conditions of cellular cholesterol excess, the cell can decrease its input of cholesterol by reducing the de novo synthesis

Figure 31-4 Schematic diagram of the lipid transport system. Apo = apolipoprotein; LPL = lipoprotein lipase; HL = hepatic lipase; CETP = cholesteryl ester transfer protein; LCAT = lecithin cholesterol acyl transferase; FFA = free fatty acids; numbers are keyed to explanations in the text.

of cholesterol and decrease the amount that enters the cell by means of the LDL-R, thus decreasing the amount stored as cholesteryl esters. The cell can also promote the removal of cholesterol by increasing the movement of cholesterol to the plasma membrane for efflux by means of the ATP-1 gene product.[36]

HDL AND REVERSE CHOLESTEROL TRANSPORT.

Plasma levels of HDL-C correlate inversely with the presence of coronary artery disease. Several mechanisms may underlie HDL's atheroprotective effects, including reverse cholesterol transport and limiting lipoprotein oxidation.[37] [38] HDL metabolism is complex and only partly understood.

The components of HDL derive from several sources and undergo metabolism at different sites. Both the intestine and the liver produce the main protein of HDL, apo AI. Apo AI acquires phospholipids from cell membranes and from phospholipids shed during hydrolysis of triglyceride-rich lipoproteins. Because these nascent HDL particles contain little or no cholesterol, they have no central lipophilic core, are discoid, and are not currently measured by standard laboratory tests, although they can mediate reverse cholesterol transport. On reaching a cell membrane, these nascent HDL particles can capture membrane-associated cholesterol and promote the efflux of free cholesterol

onto other HDL particles (see Fig. 31-4 ,*8*). The free cholesterol will then be esterified by the plasma enzyme lecithin:cholesterol acyl transferase (LCAT), an enzyme activated by apo AI (see Fig. 31-4 ,*8*). LCAT transfers an acyl chain (a fatty acid) from the R2 position of a phospholipid to the 3
OH residue of cholesterol, resulting in the formation of a cholesteryl ester. Because cholesteryl esters are hydrophobic, they move to the core of the lipoprotein, whereby the HDL particle now assumes a spherical configuration. This particle is an HDL_3 . With further cholesterol esterification, the HDL increases in size to become an HDL_2 , which is more buoyant than an HDL_3 . Cholesterol within HDL particles can be exchanged with triglyceride-rich lipoproteins by means of CETP, which mediates an equimolar exchange of cholesterol from HDL to triglyceride-rich lipoproteins and triglyceride movement from triglyceride-rich lipoproteins onto HDL (see Fig. 31-4 ,*9*). Such triglyceride-enriched HDL particles are denoted HDL_{2b} . Hepatic lipase can hydrolyze triglycerides within these HDL_{2b} , converting them back to HDL_3 particles. One mechanism of reverse cholesterol transport involves the uptake by HDL of cellular cholesterol, its esterification by LCAT, its transport by large HDL particles, and its exchange for one triglyceride molecule from a triglyceride-rich lipoprotein by CETP. The cholesterol molecule, originally on an HDL particle and now on a triglyceride-rich lipoprotein or LDL particle, can then be taken up by hepatic receptors that recognize apo E. Therefore, HDL particles act as a shuttle between tissue cholesterol, triglyceride-rich lipoproteins, and the liver.

Classification of Lipoprotein Disorders

Because time and new knowledge having brought necessary changes, there are several classifications of lipoprotein disorders. The prototypical classification of lipoprotein relied on the measurement of total plasma cholesterol and triglycerides and on analysis of lipoprotein patterns after separation by electrophoresis. This classification recognized elevations of chylomicrons (type I), VLDL or pre-beta lipoproteins (type IV), "broad beta" disease (or type III hyperlipoproteinemia), beta lipoproteins (LDL) (type II), and elevations of both chylomicrons and VLDL (type V). In addition, the combined elevations in pre-beta (VLDL) and beta (LDL) lipoproteins were recognized as type IIb hyperlipoproteinemia. Although it still provides a useful conceptual framework after nearly 40 years, this classification has some drawbacks. It does not include HDL cholesterol nor does it differentiate severe monogenic lipoprotein disorders from the more common polygenic disorders. Subsequently, the World Health Organization, the European Atherosclerosis Society, and, more recently, the National Cholesterol Education Program have classified lipoprotein disorders on the basis of arbitrary cut-points. Most guidelines specify that lipid profiles should be measured after an overnight fast. However, postprandial dyslipidemia may contribute to coronary risk and is not assessed under these conditions.[39]

A clinically practical approach describes the lipoprotein disorder by the absolute plasma levels of lipids (cholesterol and triglycerides) and lipoprotein cholesterol levels (LDL-C and HDL-C). This biochemical characterization provides a context for the clinical manifestations. For example, a young patient presenting with eruptive xanthomas and a plasma triglyceride level of 11.3 mmol/liter (1000 mg/dl) is likely to have familial

hyperchylomicronemia. An obese,

hypertensive middle-aged man with a cholesterol of 6.4 mmol/liter (247 mg/dl), triglycerides of 3.1 mmol/liter (274 mg/dl), a HDL-C level of 0.8 mmol/liter (31 mg/ml), and a calculated LDL of 4.2 mmol/liter (162 mg/dl) is very likely to have the metabolic syndrome with insulin resistance. This finding suggests concomitant clinical disorders such as hypertension and hyperglycemia. Current evidence does not establish that measurement of apolipoproteins AI and B or of LDL particle size adds substantial information to that provided by the conventional lipid profile. Taken as a single measurement, the apo B level provides information on the number of potentially atherogenic particles. Similarly, LDL particle size correlates highly with readily measured plasma HDL-C and triglyceride levels and does not appear to be an independent cardiovascular risk factor.[40] The presence of small, dense LDL particles may be related to features of the "metabolic syndrome," characterized by the presence of abdominal obesity, peripheral insulin resistance, high blood pressure, and a dyslipoproteinemia with elevated plasma triglycerides and reduced HDL-C levels. In some studies, improvement in LDL particle size has correlated with angiographic improvement of coronary artery disease. It remains to be determined whether in addition to LDL particle number reduction, a change in LDL particle size will bring further clinical benefit.

Genetic Lipoprotein Disorders

Knowledge of the genetics of lipoprotein metabolism is rapidly expanding. Monogenic disorders tend to be infrequent or very rare, with the exception of FH. Disorders that appear heritable on careful family study may be difficult to characterize unambiguously because of age, gender, gene-gene, and environmental interactions. Most lipoprotein disorders encountered clinically result from the interaction of increasing age, lack of physical exercise, weight gain, inadequate diet, and genetic makeup of the individual. A useful resource for the identification of genes related to heart disease is the Online Mendelian Inheritance in Man web site, OMIM, from the Johns Hopkins University in Baltimore, Maryland (MIM: #144250:1994). The web site can be accessed at http://www.ncbi.nlm.nih.gov/omim/ (see also Chap. 56) .

For clinical purposes, this discussion will divide genetic lipoprotein disorders into those that affect LDL, Lp(a), remnant lipoproteins, triglyceride-rich lipoproteins (chylomicrons and VLDL), and HDL (Table 31-4) . Within each of these, genetic disorders can cause an excess or a deficiency of a specific class of lipoprotein. The genes involved in these genetic lipoprotein disorders are identified in Table 31-4 .

GENETIC DISORDERS OF LOW-DENSITY LIPOPROTEINS (TYPE II HYPERLIPIDEMIA).

Familial hypercholesterolemia is the most thoroughly studied lipoprotein disorder.[19] Affected subjects present with an elevated LDL-C level greater than the 95th percentile

for age and gender. In adulthood, clinical manifestations include corneal arcus, tendinous xanthomas over the extensor tendons (metacarpophalangeal joints, Achilles tendons), and xanthelasmas. The transmission is autosomal codominant, and the prevalence of FH is estimated at approximately 1:500, although this prevalence is higher in populations with founder effects (see Chap. 56) . Men with heterozygous FH usually develop clinical coronary artery disease by the third to fourth decade, whereas it occurs in women 8 to 10 years later. Elevated plasma LDL-C, the presence of a family history of premature coronary artery disease, and the presence of xanthomas establish the diagnosis clinically. Molecular diagnosis is sometimes required. Defects at the LDL-R gene that alter the function of the LDL-R protein and its function cause FH (see Fig. 31-4, *7*) by allowing accumulation of LDL particles

TABLE 31-4 -- GENETIC LIPOPROTEIN DISORDERS

	GENE	STEP SHOWN IN FIGURE 31-4
LDL Particles		
Familial hypercholesterolemia	LDL-R	7
Familial defective apo B-100	Apo B	7
Abetalipoproteinemia	MTP	
Hypobetalipoproteinemia	ApoB	
Familial phytosterolemia	?	
Lp(a)		
Familial Lp(a) hyperlipoproteinemia	Apo(a)	
Remnant Lipoproteins		
Dysbetalipoproteinemia type III	Apo E	3
Hepatic lipase deficiency	HL	6
Triglyceride-Rich Lipoproteins		
Lipoprotein lipase deficiency	LPL	2
Apo CII deficiency	Apo CII	2
Familial hypertriglyceridemia	Polygenic	
Chylomicron retention disease	?	
Familial combined hyperlipidemia	Polygenic	
HDL Particles		
Apo AI deficiency	Apo AI	
Familial HDL deficiency/Tangier disease	ABC1/CERP	
Familial LCAT deficiency syndromes	LCAT	8
CETP deficiency	CETP	9

in plasma. There are five classes of LDL-R defects at the cellular level, including lack of RNA synthesis (large LDL-R gene truncations), unstable RNA synthesis, abnormal protein folding and intracellular degradation, recycling defective protein, and decreased binding affinity to its ligands. To date, well over 200 mutations of the LDL-R gene have been identified see http://www.umd.necker.fr and http://www.ud.ac.uk/fh/.[41]

ABNORMAL APOLIPOPROTEIN B.

Mutations within the apo B gene, leading to an abnormal ligand-receptor interaction, can cause a form of FH clinically indistinguishable from FH. This disorder, called familial defective apo B 100 (FDB), results from several mutations at the postulated binding site to the LDL-R (see Fig. 31-4 ,*7*). [42] These consist of apo $B_{Arg3500Gln}$, apo $B_{Arg3500Trp}$, and apo $B_{Arg3531Cys}$. The apo $B_{Arg3500Gln}$ results from a G
A substitution at nucleotide 3500 within exon 26 of the apo B gene. The defective apo B has a reduced affinity (20 to 30 percent of control) for the LDL-R.[43] LDL particles with the defective apo B have a plasma half-life threefold to fourfold longer than normal LDL and may thus undergo oxidative modifications that can enhance their atherogenic potential. Affected subjects usually have elevated LDL-C levels, up to 400 mg/dl (10.4 mmol/liter), but they may also have normal levels. The reasons for the variability of plasma LDL-C levels remain unexplained. The prevalence of FDB is about the same as for FH (1/500). In subjects with the classic presentation of FH, the prevalence of FDB is reported to be 1/50 to 1/20. Mutations within the apo B gene may lead to truncations of the mature apo B_{100} peptide. Many such mutations cause a syndrome of reduced LDL-C and VLDL-C, but with little or no clinical manifestations and no known risk of cardiovascular disease. Truncation of the apo B moiety close to its amino terminus impairs the ability of the truncated apo B moiety to bind lipids, leading to a syndrome similar to abetalipoproteinemia.

ABETALIPOPROTEINEMIA.

Abetalipoproteinemia is a rare recessive lipoprotein disorder of infancy characterized by mental retardation and growth abnormalities. It is caused by a mutation in gene encoding the microsomal triglyceride transfer protein (MTP), which is required for assembly of apo B-containing lipoproteins in the liver and

the intestine. [44] As a result of such mutations, no apo B-containing lipoproteins are found in plasma, with a resulting marked deficiency of fat-soluble vitamins (A, D, E, and K) that circulate in lipoproteins.

PHYTOSTEROLEMIA.

A rare condition of increased intestinal absorption and decreased excretion of plant sterols (sitosterol and campesterol) can mimic clinical features of severe FH, with

extensive xanthoma formation and premature atherosclerosis.[45] However, patients with phytosterolemia have normal or reduced plasma cholesterol and triglyceride levels. The diagnosis requires specialized analysis of plasma sterols, revealing an elevation in sitosterol, campesterol, cholestanol, sitostanol, and campestanol. Although the molecular defect remains unknown, positional cloning techniques have localized the defect to chromosome 2p21.[46]

LIPOPROTEIN (a).

Lipoprotein(a)--Lp(a), pronounced "lp little a" to distinguish it from apolipoprotein A--consists of an LDL particle covalently linked to one molecule of apo (a).[47] The apo (a) moiety has a high degree of homology with plasminogen. There are multiple repeats of one of the kringle motifs (kringle IV) within the apo (a) gene, varying in number from 12 to over 40 in each individual. Plasma Lp(a) levels correlate inversely with the number of kringle repeats and, therefore, with the molecular weight of apo (a). Prospective epidemiological studies have yielded controversial data on the association between Lp(a) and coronary artery disease, as discussed in more detail later.

TRIGLYCERIDE-RICH LIPOPROTEINS.

Elevation of plasma triglyceride levels is most often seen in the presence of obesity and of a diet rich in calories, sugars, and saturated fats in diabetic subjects; it is a component of the metabolic syndrome. Severe elevation of plasma triglyceride levels results from genetic disorders of the processing enzymes or apolipoproteins.

FAMILIAL HYPERTRIGLYCERIDEMIA.

Familial hypertriglyceridemia (type IV hyperlipoproteinemia) is not associated with clinical signs such as corneal arcus, xanthoma, and xanthelasmas. Plasma levels of triglycerides and of VLDL-C and VLDL triglycerides are moderately to markedly elevated; the LDL-C is usually low, and the HDL-C is also reduced. The total cholesterol value is normal or elevated, depending on VLDL-C levels. Fasting plasma concentrations of triglycerides are in the range of 2.3 to 5.7 mmol/liter (200-500 mg/dl). After a meal, plasma triglyceride levels may exceed 11.3 mmol/liter (1000 mg/dl). The disorder is found in first-degree relatives, but phenotypic variability is related to gender, age, hormone use (especially estrogens), and diet. Alcohol intake is a potent stimulus for hypertriglyceridemia in these subjects, as is caloric and carbohydrate intake. The relationship with coronary artery disease is not as strong or as consistent as with familial combined hyperlipidemia. Depending on the criteria used, the prevalence of familial hypertriglyceridemia ranges from 1:100 to 1:50. The disorder is highly heterogeneous and likely results from several genes, with a strong environmental influence.[48] Familial glycerolemia, an unrelated chromosome X-linked genetic disorder, may mimic familial hypertriglyceridemia because most measurement techniques for triglycerides use the measurement of glycerol after enzymatic hydrolysis of triglyceride.[49] The diagnosis of familial hyperglycerolemia therefore requires ultracentrifugation of plasma and analysis of glycerol.

The metabolic defect in familial hypertriglyceridemia causes hepatic overproduction of VLDL (see Fig. 31-4 ,*4*); the catabolism (uptake) of VLDL particles may be normal or reduced. Lipolysis by LPL does not appear to be a limiting factor, although the triglyceride load, especially in the postprandial state, may limit processing of VLDL particles. The genetic basis of familial hypertriglyceridemia is unknown, and the candidate gene approach to find the gene(s) involved (apo B, LDL, apo CIII) has been unfruitful. Treatment is based first on lifestyle modifications, including withdrawal of hormones (estrogens and progesterone), limiting alcohol intake, reducing caloric intake, and increasing exercise. The decision to treat this disorder with medications depends on global cardiovascular risk.

TYPE V HYPERLIPIDEMIA

An infrequent disorder characterized by severe elevation in plasma triglyceride levels (both VLDL and chylomicrons) is associated with a fat-rich diet, obesity, and poorly controlled diabetes. Recognized as type V hyperlipidemia, the pathogenesis is multifactorial and results from overproduction of both VLDL and chylomicrons and decreased catabolism of these particles.

FAMILIAL HYPERCHYLOMICRONEMIA

In this rare disorder, also know as type I hyperlipidemia, severe hypertriglyceridemia occurs with elevations in fasting plasma levels of triglycerides greater than 11.3 mmol/liter (>1000 mg/dl). Affected individuals do not necessarily have increased coronary risk, but they do have recurrent bouts of pancreatitis and eruptive xanthomas. Interestingly, severe hypertriglyceridemia may also be associated with xerostomia and xerophthalmia and with abnormalities in behavior. The hyperchylomicronemia results from a markedly reduced or absent LPL activity or, more rarely, by the absence of its activator, apo CII (see Table 31-3 , Fig. 31-4 ,*2*). [50] [51] These deficiencies lead to a lack of hydrolysis of chylomicrons and VLDL and to accumulation of these lipoproteins in plasma, especially in the postprandial phase. Extreme elevations of plasma triglycerides of more than 11.3 mmol/liter (>10,000 mg/dl) can occur. The plasma from a patient with very high triglyceride levels is milky white; and after a specimen stands overnight in a refrigerator, a clear band of chylomicrons appears at its top. The prevalence of mutations at the *LPL* gene locus are relatively frequent in populations with a founder effect (see also Chap. 56) . Multiple mutations at the *LPL* gene locus have been identified, with LPL_{188} , $LPL_{Asn291Ser}$, and LPL_{207} being frequently associated with hyperchylomicronemia. There are at least 60 LPL mutations that cause LPL deficiency.[52] Heterozygotes for the disorder tend to have an increase in fasting plasma triglyceride levels and smaller, denser LDL particles. Many patients with complete LPL deficiency present in childhood with failure to thrive and recurrent bouts of pancreatitis. Consistent with the importance of the role of LPL, mice deficient in this enzyme have a lethal phenotype.[53]

Treatment of acute pancreatitis in patients with familial hyperchylomicronemia consists of intravenous hydration and avoidance of fat in the diet (including in parenteral

nutrition). Rarely, plasma filtration may be required. Chronic treatment includes avoidance of alcohol and dietary fats. The use of short-chain fatty acids (which are not incorporated in chylomicrons) can make the diet more palatable.

TYPE III HYPERLIPOPROTEINEMIA

Type III hyperlipoproteinemia, also referred to as dysbetalipoproteinemia or "broad beta disease," is a rare genetic lipoprotein disorder characterized by an accumulation in plasma of remnant lipoprotein particles.[54] Agarose gel electrophoresis of the lipoproteins yields a typical pattern of a broad band between the pre-beta (VLDL) and beta (LDL) lipoproteins, hence its name. Affected individuals clearly have increased cardiovascular risk. Clinical features include tuberous xanthomas and palmar striated xanthomas, which are pathognomonic of the disease. The total plasma cholesterol level is increased, as are triglyceride levels; the HDL-C value is reduced. Remnant lipoproteins (partly catabolized chylomicrons and VLDL) accumulate in plasma and are enriched in cholesterol esters. The defect is due to abnormal apo E that does not bind to hepatic receptors using apo E as a ligand, initially the LDL receptor (see Fig. 31-4 ,*3*). Patients with type III hyperlipoproteinemia have increased ratio of VLDL-C to triglycerides, normally less than 0.7 in mmol/liter (< 0.30 in mg/dl), owing to cholesteryl ester enrichment of remnant particles. The diagnosis includes plasma ultracentrifugation for lipoprotein separation, lipoprotein electrophoresis, and apo E phenotyping or genotyping.

There are three common alleles for apo E: apo E2, E3, and E4. Patients with type III hyperlipoproteinemia have the apo E2/2 phenotype or genotype. The apo E2 allele has markedly decreased binding to the apo B:E (LDL) receptor. Normal populations have a prevalence of the apo E2/2 genotype of 0.7 to 1.0 percent. Type III hyperlipoproteinemia is only seen in approximately 1 percent of subjects bearing the apo E2/2 phenotype. The reasons for the relative rarity of type III dyslipoproteinemia (or low penetrance of the E2/2 genotype) are not fully understood. A second "hit" may enable the full expression of the disorder. Other rare mutations of the apo E gene can also cause type III hyperlipoproteinemia.[55] Apo E-deficient mice currently serve as one useful model for the study of atherosclerosis. Type III dyslipoproteinemia generally responds well to dietary therapy and to correction of other metabolic abnormalities (diabetes, obesity). In some cases it requires drug therapy, such as with fibric acid derivatives or statins.

FAMILIAL COMBINED HYPERLIPIDEMIA.

One of the most common familial lipoprotein disorders is familial combined hyperlipoproteinemia (FCH). Described initially in survivors of myocardial infarction,[56] FCH has undergone several definitions since its original description. The presence in several members of the same family of elevated total cholesterol and/or triglycerides based on arbitrary cut-points defines FCH. The disorder must be identified in at least one first-degree relative for a diagnosis of FCH. The biochemical abnormalities include the elevation of plasma total and LDL-C (> 90th or 95th percentile), and/or an elevation of plasma triglycerides (> 90th to 95th percentile), a type IIb lipoprotein phenotype, a reduction in HDL-C, and elevation in apo B levels; small, dense LDL particles are frequently seen. Measurement of LDL-C and, in some cases, apo B levels can further

characterize this disorder. Because of the lack of a clear-cut clinical or biochemical marker, there is considerable overlap between FCH, familial dyslipidemic hypertension, the insulin-resistance metabolic syndrome, and hyperapobetalipoproteinemia.

There are few clinical features of FCH; corneal arcus, xanthomas, and xanthelasmas occur infrequently. The underlying metabolic disorder appears to be hepatic overproduction of apo B-containing lipoproteins, delayed postprandial triglyceride-rich lipoprotein clearance, and increased flux of free fatty acids (FFA) to the liver. Experimental data have shown that hepatic apo B secretion is substrate driven, the most important substrates being FFA and cholesteryl esters. The increased delivery of FFA to the liver that occurs in states of insulin resistance augments hepatic apo B secretion.

Genetic heterogeneity probably underlies FCH. The prevalence of FCH is reported at approximately 1:50 and accounts for 10 to 20 percent of patients with premature coronary artery disease.[57] FCH has complex genetics. Initially considered to be an autosomal codominant trait, a more complex mode of inheritance may pertain. Phenotypical expression of the disease varies with gender, age, diet, and comorbid states such as obesity and lack of exercise. Initial reports of linkage with the apo AI-CIII-AIV and LPL genes have not been substantiated. A novel locus on chromosome 1 in Finnish families appears promising in the identification of genes related to FCH.[58]

Recent reports of the acylation stimulating protein (ASP) pathway suggests that abnormal peripheral uptake of FFA may underlie some cases of FCH and the insulin-resistance metabolic syndrome (see Fig. 31-3 *D*). ASP regulates FFA uptake by tissues. According to this scheme, increased flux of FFAs to the liver caused by this decreased uptake and utilization at the periphery drives hepatic apo B-containing lipoprotein assembly and secretion.[59]

Abnormalities of HDL Metabolism

Observational studies have consistently linked a reduced plasma level of HDL-C to the development or presence of coronary artery disease. Most cases of reduced HDL-C result secondarily from elevated plasma triglycerides or apo B levels. These abnormalities often cluster with other features of the insulin-resistant metabolic syndrome (see also Chap. 63) . Familial hyperchylomicronemia, familial hypertriglyceridemia, and FCH are all associated with reduced HDL-C levels. Primary forms of low HDL-C, although less common, also are associated with premature coronary artery disease. Close study of these abnormalities has shed new light on the complex metabolism of HDL particles. Genetic disorders can cause either decreased production of HDL or abnormal maturation and increased catabolism of HDL or its primary apoprotein, AI.

Primary defects affecting production of HDL particles consist predominantly in apo

AI-CIII-AIV gene defects. There are approximately a dozen reported mutations affecting the structure of apo AI[38] [60] with a marked reduction in HDL-C levels. Not all these defects cause premature cardiovascular disease. Clinical presentations can vary from extensive, atypical xanthomatosis and corneal infiltration of lipids to no manifestations. The treatment of these apo AI gene defects is generally unsuccessful in raising HDL-C levels. Other mutations of apo AI accelerate apo AI catabolism and may not be linked with cardiovascular disease. One such mutation, apo AI_{Milano} (apo $AI_{Arg173Cys}$), may be associated with longevity.[60] Genetic defects in the HDL-processing enzymes give rise to interesting phenotypes. Deficiencies of LCAT, which catalyzes the formation of cholesteryl esters in plasma, cause corneal infiltration of neutral lipids and hematological abnormalities because of abnormal constitution of red blood cell membranes. LCAT deficiency can cause an entity called "fish eye disease" because of the characteristic pattern of corneal infiltration observed in affected individuals.[61]

Patients with absent CETP have very elevated HDL-C levels, enriched in cholesteryl esters.[62] Because CETP facilitates the transfer of HDL cholesteryl esters into triglyceride-rich lipoproteins, a deficiency of this enzyme causes accumulation of cholesteryl esters within HDL particles. Despite the high HDL levels, CETP may not afford protection against coronary artery disease.[63]

A rare disorder of HDL deficiency was first identified in a proband from the island of Tangier in the Chesapeake Bay in the United States. The proband has markedly enlarged yellow tonsils and a near absence of HDL-C. His sister was also affected, and the entity was named Tangier disease.[64] Since then, at least 50 cases have been reported worldwide.[65] The cellular defect in Tangier disease has been identified as a reduced cellular cholesterol efflux in skin fibroblasts from affected subjects.[36] A more common entity, familial HDL deficiency, also results from decreased cellular cholesterol efflux. The genetic defect in Tangier disease and in familial HDL deficiency has been identified as a result of mutations of *ABC1,* which encodes CERP (see Fig. 31-3 *C*). [33] [34] [35]

OTHER CHOLESTEROL TRANSPORT DEFECTS

Niemann-Pick disease type C is a disorder of lysosomal cholesterol transport. Mental retardation and neurological manifestations occur frequently in patients with Niemann-Pick disease type C. The cellular phenotype includes markedly decreased (acid) sphingomyelinase activity, reduced cholesterol esterification, and a cellular cholesterol transport defect involving the Golgi apparatus. Unlike Tangier disease/familial HDL deficiency, the cellular defect in Niemann-Pick disease type C appears therefore to be proximal to the transport of cholesterol to the plasma membrane. The gene for Niemann-Pick disease type C (*NPC1*), mapped to the chromosomal location 18q21, encodes a 1278-amino acid protein of as yet unknown function. The *NPC1* gene product shares homology with the morphogen receptor "patched" and the SREBP cleavage activating protein (SCAP).[66] [67]

Secondary Causes of Dyslipidemia

Several clinical disorders secondarily alter lipoprotein status (Table 31-5) .[68]

HORMONAL CAUSES OF DYSLIPIDEMIA (see also Chap. 64) .

Hypothyroidism often causes elevated levels of LDL-C, triglycerides, or both. An elevated thyroid stimulating hormone (TSH) value is key to the diagnosis, and the lipoprotein abnormalities often revert to normal once the thyroid status is corrected. Rarely, hypothyroidism may uncover a genetic lipoprotein disorder such as type III hyperlipidemia. A TSH level should be obtained on all patients with unexplained elevations in triglyceride levels.

Estrogens can increase plasma triglyceride levels and HDL-C owing to increases in hepatic VLDL secretion and apo AI secretion (see also Chap. 58) . In postmenopausal women, estrogens may reduce LDL-C by 0-15%. Rarely, pregnancy, in a woman with LPL deficiency, severely increases plasma triglyceride levels. Such cases present a serious threat to mother and child and must be referred to specialized centers. Male sex hormones and anabolic steroids may increase hepatic lipase activity and have been used in the treatment of hypertriglyceridemia in men. Growth hormone use reduces LDL-C and increases

TABLE 31-5 -- SECONDARY CAUSES OF DYSLIPOPROTEINEMIAS

Metabolic
Diabetes Lipodystrophy Glycogen storage disorders
Renal
Chronic renal failure Glomerulonephritis Nephrotic syndrome
Liver Disease
Obstructive liver disease Cirrhosis
Hormonal
Estrogens Progesterones Growth hormone Thyroid disorders (hypothyroidism)
Lifestyle

Physical inactivity
Obesity
Diet rich in fats, saturated fats
Alcohol intake

Medications
Immunosuppressive agents
Corticosteroids
Retinoids
Highly active antiretroviral therapy
Thiazides
Beta-adrenergic blockers

HDL-C but is not recommended in the treatment of lipoprotein disorders.

METABOLIC CAUSES OF DYSLIPIDEMIA.

The constellation of metabolic abnormalities seen in the insulin-resistance metabolic syndrome currently constitutes the most frequent secondary cause of dyslipidemia (see also Chap. 63) . The findings of increased visceral fat (abdominal obesity), elevated blood pressure, and peripheral insulin resistance frequently cluster with increased plasma triglyceride levels and a reduced HDL-C level. Elevated plasma triglyceride levels and a low HDL-C value often accompany overt diabetes, especially type II adult-onset diabetes.[69] These abnormalities have prognostic implications in patients with type II diabetes. Although type II diabetics often do not have marked elevations in LDL-C levels, those with coronary artery disease benefit from lipid-lowering therapy with a statin.[70] One recent angiographic trial (Flu Diabetes Atherosclerosis Intervention Study [DAIS]) showed slowed progression in diabetic patients treated with a fibric acid derivative, fenofibrate, which lowered triglyceride levels and raised HDL-C levels.[71] Poorly controlled diabetes, obesity, and moderate to severe hyperglycemia can yield severe hypertriglyceridemia with chylomicronemia and increased VLDL. Subjects with juvenile diabetes may also present with severe hypertriglyceridemia when the diabetes is poorly controlled. Familial lipodystrophy (complete or partial) may be associated with increased VLDL secretion. In glycogen storage disorders, elevated plasma triglyceride levels are often encountered.

RENAL DISORDERS AND DYSLIPIDEMIA.

Glomerulonephritis or protein-losing nephropathies can cause a marked increase in secretion of hepatic lipoproteins, elevating LDL-C levels, which may approach the levels seen in FH.[72] [73] In contrast, patients with chronic renal failure have a pattern of hypertriglyceridemia with reduced HDL-C. Patients on hemodialysis or chronic ambulatory peritoneal dialysis also exhibit similar lipoprotein changes. Many

hemodialysis patients have elevations in Lp(a). After organ transplantation, the immunosuppressive regimen (glucocorticoids and systemic immunosuppressive drugs) can contribute to elevation in triglyceride levels and a reduced HDL-C level.

LIVER DISEASE AND DYSLIPIDEMIA.

Obstructive liver disease, especially primary biliary cirrhosis, may lead to the formation of an abnormal lipoprotein termed lipoprotein-x (Lp-x).[74] This type of lipoprotein is found in LCAT deficiency and consists of an LDL-like particle, but with a marked reduction in cholesteryl esters. Extensive xanthoma formation on the face and palmar areas can result from accumulation of Lp-x.

DYSLIPIDEMIA ASSOCIATED WITH THERAPY FOR ACQUIRED IMMUNODEFICIENCY SYNDROME (See also Chap. 68) .

The introduction of inhibitors of a major protease of human immunodeficiency virus-1 (HIV-1) has markedly prolonged the survival of infected individuals.[75] Although HIV protease inhibitors have emerged as the cornerstone of highly active antiretroviral therapy (HAART), these agents can cause secondary dyslipidemia.[76] [77] Treatment with HAART results in increased levels of triglyceride-rich lipoprotein particles, such as VLDL.[78] In addition to the rise in total cholesterol and triglyceride levels, HAART causes a concomitant decrease in HDL levels. Reminiscent of the diabetic dyslipidemic syndrome, these changes in lipoprotein profile go hand in hand with hyperinsulinemia and insulin resistance.[79] Moreover, there is a striking and prevalent association of HAART with lipodystrophy. Specifically, patients receiving HAART often have a decreased peripheral accumulation of adipose tissue, while central adiposity increases. Although in most instances, the lipodystrophy is mild to moderate, more striking alterations can occur, including development of a "buffalo hump."[80] Potential clinical consequences of HAART-associated dyslipidemia may include premature atherosclerosis and pancreatitis due to hypertriglyceridemia.

The mechanism of HAART-associated dyslipidemia remains obscure. Recent metabolic studies have shown maintained levels of LPL but decreased levels of hepatic lipase, and evidence for increased production of VLDL. Interestingly, the HIV protease active site has homology to two receptors involved in lipid metabolism.[81] The lipoprotein-related receptor has regions of approximately 60 percent sequence similarity with the HIV protease. Thus, HIV protease inhibitors might interfere with the function of this remnant receptor involved in clearing certain triglyceride-rich lipoprotein particles. The HIV protease also shares sequence similarity with regions of a retinoid binding protein known as CRAB1.[81] [82] By binding to CRAB1, HIV protease inhibitors might interfere with the synthesis of *cis*-9-retinoic acid. The retinoic acids are, of course, classic ligands for the retinoid X receptor (RXR). When liganded RXR pairs with another nuclear receptor, PPAR gamma, and forms an active transcription factor known to control adipocyte differentiation and insulin sensitivity.[83] Thus, the HIV protease inhibitors might interfere with the activation of these transcription factors and contribute to the lipodystrophy and insulin resistance.

Management.

The treatment of HAART-associated dyslipidemia requires control of triglyceride levels, particularly in patients with or at risk for pancreatitis. Treatment with fibric acid derivatives may help in this regard. No systematic information exists yet regarding the effect of lipid-lowering therapy on outcomes in individuals with HAART-associated dyslipidemia. However, reports of management of this dyslipidemia with fibric acid derivatives alone, or in combination with HMG CoA reductase inhibitors, have appeared. Because agents included in HAART can interfere with the metabolism of concomitantly administered drugs due to changes in cytochrome p450 isoform function, addition of lipid-lowering agents to HAART requires careful consideration of potential drug interactions.

OTHER MEDICATIONS.

Several medications commonly cause alterations in lipoproteins.[68] Thiazide diuretics can increase plasma triglyceride levels. Beta blockers, especially the non-$beta_1$-selective agents, increase triglycerides and lower HDL-C levels. Retinoic acid can increase triglyceride levels, sometimes dramatically. Corticosteroids and immunosuppressive agents can increase plasma triglyceride levels.[84] Because transplantation recipients and patients on this class of drugs generally have an increase in cardiovascular risk, this secondary hyperlipidemia may warrant treatment (see also Chap. 30) .[85] Estrogens can increase plasma HDL-C significantly and may also increase triglyceride concentrations, sometimes substantially.[86] [87]

LIFESTYLE FACTORS CONTRIBUTING TO DYSLIPIDEMIA.

Factors contributing to obesity, such as an imbalance between caloric intake and energy expenditure, lack of physical activity, and a diet rich in saturated fats and refined sugars, contribute in large part to the lipid and lipoprotein lipid levels within a population. In clinical practice, many dyslipoproteinemias other than the genetic forms mentioned earlier share important environmental components. Lifestyle changes (diet, exercise, reduction of abdominal obesity) remain the cornerstone of the treatment of most dyslipidemias. (See later and Chap. 32 for more information on exercise and obesity.) The effects of marked alterations in lifestyle,[88] reduction in dietary fats, especially saturated fats,[89] and exercise[90] can improve cardiovascular prognosis (see later and Chap. 32) . Translating these findings into practice, however, has been more difficult. For instance, dietary manipulations as performed in a physician's office lead to relatively small reductions in plasma lipid and lipoprotein cholesterol levels.[91]

Management of Lipoprotein Disorders

GENERAL APPROACHES.

Cardiologists must consider evaluation and management of dyslipidemia an integral part

of their practice. Two major questions confront the

clinician treating patients with lipoprotein disorders. First, are there secondary causes for the dyslipoproteinemia and, second, what risk does this disorder have for the patient's health? The clinical evaluation should include a thorough history, including a complete family history that may reveal clues about genetic etiology and genetic susceptibility to cardiovascular disease. Most patients with dyslipoproteinemias have few symptoms. Exceptions include those with severe hypertriglyceridemia, who may present with acute pancreatitis, and those with familial lipoprotein disorders, who have cutaneous manifestations (xanthomas, xanthelasmas). Other risk factors should be sought (cigarette smoking, diabetes) along with secondary causes (diet, physical activity, alcohol intake). Concomitant medication use should be investigated; alternative treatments should be considered that avoid alterations in the lipid profile.

The physical examination should include a search for xanthomas (in extensor tendons, including hands, elbows, knees, Achilles' tendons, as well as palmar xanthomas), the presence of xanthelasmas, and corneal arcus, corneal opacifications. Blood pressure, waist circumference, weight, and height should be recorded, and signs of vascular compromise must be carefully examined. A complete cardiovascular examination must be performed. The diagnosis of lipoprotein disorders is based on laboratory measurements (Table 31-6) . The lipid profile generally suffices for most lipoprotein disorders, and specialized laboratories can refine the diagnosis and provide expertise for extreme cases. Additional tests (e.g., measurement of apolipoprotein levels or of LDL particle size) increase cost and may not add predictive power beyond that of the lipid profile but may help to refine the diagnosis. It is advisable to stop all lipid-lowering therapy for 1 month before measuring a lipid profile during initial evaluation. Except in severe hypertriglyceridemia, this measure is unlikely to have a clinically significant adverse effect.

At least two lipid profiles should be obtained, and secondary causes should be explored by the measurement of TSH and glucose. Baseline aspartate and alanine aminotransferases and creatinine kinase should also be obtained in candidates for drug therapy.

SPECIFIC TREATMENTS.

The therapeutic options consist of lifestyle modifications, treatment of secondary causes, if possible, diet, and medications (see Chap. 33 for an extensive discussion of pharmacotherapy). The diet should have three objectives: (1) it should allow the patient to reach and maintain ideal body weight; (2) it should provide a well-balanced diet with fruits, vegetables, and grains; and (3) it should be restricted in saturated fats and refined carbohydrates.[92] The services of a professional dietitian prove valuable in this regard. Present guidelines recommend a diet in which protein intake represents 15 to 20 percent of calories and fats represent 25 to 30 percent (with only one third from

saturated fats).[93] The remaining calories are obtained from carbohydrates. Cholesterol intake is limited to less than 300 mg/d. Alcohol is not part of the current recommendations, although up to 2 drinks per day is associated with decreased cardiovascular deaths in many studies. The high cost of alcohol-related accidents, violent deaths, and liver disease, however, makes any recommendation regarding alcohol intake controversial. Although dietary changes should be instituted in most if not all the clinically relevant dyslipidemias, medications should be concomitantly initiated along with dietary changes in high-risk subjects, because in many cases the patient's diet may be insufficient to reach target levels.

Chapter 33 reviews in detail the evidence base supporting the use of lipid-lowering interventions (pharmacological and nonpharmacological) in clinical trials. This section is provided as a "how to" guide to the use of currently available lipid-lowering agents.[68]

RESINS.

The bile acid-binding resins act to interrupt the enterohepatic circulation of bile acids by inhibiting their reabsorbtion in the intestine (bile acids that contain cholesterol are more than 90 percent reabsorbed through this pathway). Their main indication is as adjunctive therapy in patients with severe hypercholesterolemia due to increased LDL-C. Because bile acid binding resins are not absorbed systemically (they remain in the intestine and are eliminated in the stool), they are considered safe in children. Cholestyramine (Questran) is used in 9-gm unit doses (containing 4 grams of anhydrous resin) as powder, and colestipol (Colestid) is used in 5-gm unit doses; a 1-gm tablet of colestipol is available. Effective doses range from two to six unit doses per day, always taken with meals. The side effects are predominantly gastrointestinal, with constipation, a sensation of fullness, and gastrointestinal discomfort being the most important ones. Hypertriglyceridemia can result from the use of these drugs. Decreased drug absorption dictates careful scheduling of medications 1 hour before or 3 hours after taking bile acid-binding resins. Bile acid-binding resins can be used in combination with statins in cases of severe hypercholesterolemia.

HMG CoA REDUCTASE INHIBITORS (STATINS).

The development of the statins has led to a further validation of the lipid hypothesis. Their target is the rate-limiting enzyme for cholesterol synthesis. Under treatment, maintenance of cellular cholesterol homeostasis involves increased expression of the LDL-R and decreased rate of cholesteryl ester formation. These changes increase LDL-C clearance from plasma and decrease hepatic production of VLDL and LDL. The statins are generally very well tolerated; side effects include hepatotoxicity and myositis, which necessitate discontinuation of the drug in approximately 1 percent of patients. The currently available drugs include fluvastatin (Lescol), 20 to 80 mg/d; lovastatin (Mevacor), 20 to 80 mg/d; pravastatin (Pravachol), 20 to 40 mg/day; simvastatin (Zocor) 10 to 80 mg/d; atorvastatin (Lipitor) 10 to 80 mg/d; and cerivastatin (Baycol), 0.2 to 0.4 mg/d. There is considerable debate regarding the degree to which these drugs exert beneficial effects on cellular function independent from their effects on cholesterol

TABLE 31-6 -- LABORATORY TESTS FOR THE DIAGNOSIS OF LIPOPROTEIN DISORDERS

LIPID PROFILE	MAY HELP IN DIAGNOSIS	SPECIALIZED CENTERS	RESEARCH TOOLS
Cholesterol	Lipoprotein separation by UTC	LDL particle size	Molecular diagnosis
Triglycerides	Apo B	LPL assay	
HDL-C	Apo AI	LCAT assay	
LDL-C*	Apo E genotype/phenotype	Apo E levels	
	Lp(a)	Apolipoprotein separation by PAGE	
		LDL-R assay	
		Apo CII, CIII	

PAGE=polyacrylamide gel electrophoresis.

Ultracentrifugation.
*Calculated as LDL-C=Cholesterol - (Triglycerides/2.2+HDL-C) in mmol/liter (or triglycerides divided by 5 in mg/dl); valid for triglycerides < 4.5 mmol/liter (<400 mg/dl). LDL-C can also be directly measured in plasma.

homeostasis. Concomitant therapy with drugs that interfere with the metabolism of statins by inhibiting cytochromes P-450, 3A4, or 2C9 can increase plasma concentrations of statins. Such agents include certain antibiotics, antifungal medications, antiviral drugs, grapefruit juice, amiodarone, and several others.[68]

FIBRIC ACID DERIVATIVES (FIBRATES).

There are currently three derivatives of fibric acid available in the United States and two more in Canada and Europe. Gemfibrozil (Lopid) is used at a standard dose of 600 mg twice daily and is indicated in hypertriglyceridemia and in the secondary prevention of cardiovascular diseases in patients with a low HDL-C. These latter recommendations are based on the Veterans Administration HDL Intervention Trial (VA-HIT). Fenofibrate (Tricor, Lipidil Micro) is used to treat hypertriglyceridemia and combined hyperlipoproteinemia. The dose is 200 mg/d, and a new formulation is available to vary the dose from 67 mg (especially in renal failure) to 200 mg/d. Clofibrate (Atromid) is still available in some centers, although its use has declined since the introduction of newer molecules. Ciprofibrate (Lypanthyl, Lipanor) and bezafibrate (Bezalip) are more widely

used in Europe. The main indication for the use of fibrates is hypertriglyceridemia when diet and lifestyle changes are not sufficient. Another indication is the prevention of cardiovascular diseases in patients with elevated plasma triglycerides and low HDL-C. The mechanism of action results in part from their interaction with the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPARalpha) that regulates the transcription of the LPL, apo CII, and apo AI genes and may also have direct antiinflammatory effects at the level of the artery wall.[94] The undesired effects of fibrates include cutaneous manifestations, gastrointestinal effects (abdominal discomfort, increased bile lithogenicity), erectile dysfunction, elevated serum aminotransferases, interaction with oral anticoagulants and elevated plasma homocysteine, especially with fenofibrate and, to a lesser extent, with bezafibrate.[95] Because fibrates increase apoB transcription, a consequent rise in LDL-C levels often occurs in patients with hypertriglyceridemia treated with this class of medications.

NICOTINIC ACID (NIACIN).

Niacin has been used for decades for the treatment of dyslipidemias and is particularly effective in increasing HDL-C and lowering triglyceride levels. The effect of niacin on LDL-C is more modest. Effective doses of niacin are in the range of 3000 mg/d, in three separate doses. It is preferable to use an escalating dose schedule to reach the full dose in 2 to 3 weeks rather than starting with the full dose. Aspirin may ameliorate niacin-induced skin flushing. Niacin decreases the hepatic secretion of VLDL from the liver and decreased FFA mobilization for the periphery. Although niacin has been shown in the long-term follow-up of the Coronary Drug Project to decrease mortality at 15 years,[96] important and sometimes life-threatening side effects and now the development of statins have hampered use of niacin. Side effects of niacin include flushing, hyperuricemia, hyperglycemia, hepatotoxicity, acanthosis nigricans, and gastritis. Long-acting niacin has the advantage of a once- or twice-daily dosing schedule, but older preparations of slow-release niacin were potentially more hepatotoxic.

FISH OILS.

Fish oils are rich in polyunsaturated fatty acids with the first double bond in the omega-3 position, such as eicosapentaenoic acid or docosahexaenoic acid. These fatty acids have been found to lower plasma triglyceride levels and to have antithrombotic and perhaps antiinflammatory properties.[97] [98] Although they have been used in the treatment of hypertriglyceridemia, their use is reserved in cases of severe hypertriglyceridemia refractory to conventional therapy. Fish oils decrease VLDL synthesis and decrease VLDL apo B. The response to fish oils depends on dose. A significant benefit on plasma triglyceride levels requires a daily intake of 10 to 15 gm of eicosapentaenoic acid or docosahexaenoic acid.

MONITORING.

After initiation of medical therapy, the response should be checked within the first 3 months, along with transaminases and creatinine kinase. Thereafter, clinical judgment should dictate the interval between follow-up visits. Although frequent visits are probably

not useful in the detection of serious side effects, they serve to encourage compliance, adherence to diet, and lifestyle changes.

OTHER MEDICATIONS.

Probucol has modest effects on plasma lipoprotein levels and antioxidant properties. The lack of conclusive evidence that probucol has beneficial effects led to its withdrawal. Recent studies indicate that it may have a role in the prevention of restenosis after coronary angioplasty if used before the procedure.[99] In the absence of documented hypothyroidism, thyroxine has no role as a lipid modulator.

DIETARY SUPPLEMENTS ("NUTRACEUTICALS").

The armamentarium for lipid-lowering intervention now includes products available directly to the public as food or dietary supplements. Many patients will ask their physicians about these so-called "neutraceuticals" learned of in the lay press, by word-of-mouth, or advertising. Such products currently marketed in the United States include Benechol and Take Control, formulated as margarine-like spreads, in salad dressings, and in snack bars. These products contain plant sterols (phytosterols) that interfere with intestinal absorption of cholesterol.[100] [101] The typical adult daily diet includes about 0.1 percent phytosterols. Consumption of 2 to 3 gm/d of plant sterols can lower LDL-C 10 to 15 percent with few untoward effects.[100] [101] [102] Combination of these products with statins may help some patients achieve an LDL-C goal.[103] However, the formulations are high calorie and would be best substituted for butter or margarine already included in the patient's diet. The suggested intake of three servings a day, especially if used on bread, might increase body weight. Also, phytosterol-enriched foods containing *trans*-fatty acids or saturated fat (sometimes included in the salad dressings and snack bars) might have a less salubrious effect on the lipid profile.

Other dietary products patients may take or ask about include psyllium, folate (commonly found enriched in food), natural phytoestrogens, soy, green tea, and synthetic fat substitutes (olean).[104] Cholestin, a controversial over-the-counter dietary supplement, contains a biologically active statin derived from a red yeast found on rice.[105] When devising treatment plans and counseling patients, the physician should bear in mind that scant clinical trial evidence currently shows cardiovascular event reduction with neutraceuticals. Patients should not supplant indicated lipid-lowering medications of proven cardiovascular benefit with untested dietary supplements.

AGGRESSIVE MEASURES FOR TREATING REFRACTORY ELEVATION OF LDL.

Cases of severe hypercholesterolemia, especially in homozygous hypercholesterolemia, can only be treated by an extracorporeal LDL elimination technique. These techniques are based on selective filtration, adsorption, or precipitation of LDL (or apo B-containing particles) after plasma apheresis. Such techniques are only available in highly specialized centers but may dramatically reduce the risk of developing cardiovascular

disease and improve survival.[106]

GENE THERAPY: A FUTURE APPROACH TO DYSLIPIDEMIA?

Severe, homozygous monogenic disorders will eventually be treated by gene therapy. The initial trials of gene therapy in homozygous FH have not led to a major improvement and have largely been abandoned.[107] However, the lifelong burden of these rare disorders and the potential for cure makes this approach very appealing. Other diseases, such as abetalipoproteinemia, LPL deficiency, Niemann-Pick disease type C, phytosterolemia, and Tangier disease, may become therapeutic targets for gene therapy. If

the approach to correct these disorders is successful, the more widely spread application of gene-based therapies to reduce potential cardiovascular risk will become a daunting medical, social, and ethical problem.

DRUG DEVELOPMENT AND FUTURE DIRECTIONS

Novel proteins that regulate the synthesis of lipids have become therapeutic targets for drug development. A good example has been the development of competitive inhibitors of HMG CoA reductase leading to statins. These drugs have an important impact on cardiovascular morbidity and mortality reduction in high-risk individuals (see Chap. 33) . Inhibitors of pancreatic lipases are currently used to treat obesity. Future potential drug targets might include inhibition of apo B secretion by inhibiting the microsomal triglyceride transfer protein (MTP), which is crucial in the assembly of apo B-containing lipoproteins.[44] [108] Reports of hepatic steatosis in animal studies may limit the use of this approach in humans. Selective inhibition of ACAT may also provide a therapeutic target to inhibit cholesterol absorption through the intestinal wall and reduce apo B-containing lipoprotein secretion from the liver.[109] Drugs that increase cellular cholesterol efflux to increase HDL-C levels may also prove useful in the treatment of dyslipoproteinemias.

The development of novel pharmaceutical agents for the treatment of lipoprotein disorders will likely continue because cardiovascular disease due to atherosclerosis represents the largest burden of disease for the near future.[6] [11] Better targeting of high-risk individuals[93] will allow optimization of expensive therapies. We may witness the development of new "nutraceuticals" to aid the dietary management of dyslipidemia. The "genomics revolution" will foster the burgeoning field of pharmacogenetics and might soon permit treatment of patients tailored to their genetic make-up.[110] Genetic screening will become a useful clinical tool as technology improves and rapid genotyping for diagnostic and prognostic purposes becomes available for clinicians. Beyond issues of cost, the ethics of screening for genetic predisposition to disease and access to information present daunting challenges. The discovery that the apo E4 allele confers risk of early-onset Alzheimer's disease illustrates the kind of complexity we will

encounter more frequently in the postgenomic era.[111]

SMOKING

Cigarette consumption constitutes the single most important modifiable risk factor for coronary artery disease and the leading preventable cause of death in the United States, where it accounts for over 400,000 deaths annually.[112] Despite the relative stability in prevalence of current smokers in the United States at 25 percent,[113] rates of tobacco use are increasing among adolescents and young adults.[114] Close to 1 million young Americans begin smoking each year.[115] Although increased recognition of the hazards of smoking might be hoped to slow these trends, nearly 1 billion individuals now smoke worldwide.[116] Smoking has a particularly staggering impact in the Third World: almost one-half billion individuals worldwide will eventually die of smoking-related complications.[117] Even among nonsmokers, we now recognize that inhaled smoke, whether from passive exposure or from cigar and pipe consumption, also greatly increases coronary risk.[118] [119]

Landmark studies in the early 1950s first reported strong positive associations between cigarette exposure and coronary heart disease. Over the next 40 years, an exceptionally consistent series of prospective studies have clearly documented

Figure 31-5 Relative risks of death due to coronary artery disease *(top)* and stroke *(bottom)* according to level of daily cigarette consumption. (Adapted from The Health Benefits of Smoking Cessation: A Report from the Surgeon General, 1990.)

the effects of smoking on coronary risk. These studies suggest that, compared with nonsmokers, those who consume 20 or more cigarettes daily have a twofold to threefold increase in total coronary heart disease. Moreover, these effects depend on dose; consumption of as few as one to four cigarettes daily increases coronary artery disease risk.[120] Smoking acts synergistically with oral contraceptive agents, placing younger women at even higher relative risk. In addition to myocardial infarction, cigarette consumption directly relates to increased rates of sudden death, aortic aneurysm formation, symptomatic peripheral vascular disease, and ischemic stroke. As for coronary disease, the risk of stroke directly increases with the number of cigarettes consumed.[121] (Fig. 31-5) .

Smoking affects atherothrombosis by several mechanisms. In addition to accelerating atherosclerotic progression,[122] long-term smoking may enhance oxidation of LDL-C and reduce levels of HDL-C.[123] [124] Smoking also impairs endothelium-dependent coronary artery vasodilation[125] [126] ; has multiple adverse hemostatic effects[127] ; increases inflammatory markers such as CRP, soluble intercellular adhesion molecule-1 (ICAM-1), and fibrinogen[128] [129] ; causes spontaneous platelet aggregation [130] ; and increases monocyte adhesion to endothelial cells.[131] Compared with nonsmokers, smokers have an increased prevalence of coronary spasm[132] and may have reduced thresholds for ventricular arrhythmia.

SMOKING CESSATION (see also Chap. 32) .

Cessation of cigarette consumption constitutes the single most important intervention in preventive cardiology. Smoking cessation

alone reduces the risk of a first heart attack by nearly 65 percent.[133] Trials of nicotine replacement therapy using either transdermal nicotine[134] [135] or nicotine chewing gum have both proven to greatly increase abstention rates after cessation. Such pharmacological programs, as well as physician-guided counseling, are cost effective and should be provided as a standard prevention service.[136] Patients need to recognize that "low yield" cigarettes do not appear to reduce risks of myocardial infarction.[137] Unfortunately, although the elevated cardiovascular risks associated with smoking decrease significantly after cessation, the risks of cancer of the lungs, pancreas, and stomach persist for more than a decade, as do the risks of developing chronic obstructive pulmonary disease. Thus, primary prevention remains the most important population-based component of any smoking reduction strategy.

HYPERTENSION (See also Chaps. 28 , 29 , and 32)

In contrast to cigarette consumption, hypertension is often a silent cardiovascular risk factor. Of the estimated 50 million Americans with high blood pressure, almost a third evade diagnosis and only a fourth receive effective treatment.[138] Elevated levels of blood pressure consistently correlate with elevated risks of stroke and myocardial infarction (see Fig. 28-6). An early meta-analysis that evaluated over 5500 cardiovascular events found a 27 percent increase in risk of coronary heart disease and a 42 percent increase in risk of ischemic stroke for every 7 mm Hg elevation of diastolic blood pressure.[139] Although hypertension often clusters with insulin resistance and obesity, the risk imposed by hypertension increases in the presence of other cardiovascular risk factors.

Even among individuals without diastolic hypertension, isolated increases in systolic pressure are a risk factor. Isolated systolic hypertension markedly increases risk for nonfatal myocardial infarction and cardiovascular death among both general population samples[140] and apparently low-risk groups.[141] Pulse pressure, a potential surrogate for vascular wall stiffness, also potently predicts both first and recurrent myocardial infarction.[142] Interestingly, both isolated systolic hypertension and pulse pressure independently predict coronary risk.

The pathophysiology and treatment of hypertension are discussed at length in Chapters 28 and 29 . In regard to treatment, blood pressure reduction greatly reduces risk, even among individuals with mild to moderate hypertension. In overview analyses, pharmacological reductions in diastolic blood pressure of 5 to 6 mm Hg appear to reduce the risk of stroke by over 40 percent, the risk of vascular mortality by 21 percent,

and the risk of coronary heart disease by 14 percent.[143] In the elderly, randomized trial data have also indicated the efficacy of treating isolated systolic hypertension.[144] [145] Among compliant patients, sodium reduction and weight loss can be effective.[146] However, not all patients respond to such measures, and the long-term success of non-pharmacologic approaches to hypertension control has often proven disappointing. Thus, although the most recent report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure continues to stress weight loss, alcohol reduction, increased physical activity, and sodium restriction as first-line approaches, the proportion of hypertensive patients being treated pharmacologically will continue to increase. As with smoking cessation, programs of blood pressure control have consistently been found cost effective.[147]

INSULIN RESISTANCE AND DIABETES (See also Chap. 63)

Three fourths of all deaths among diabetic patients result from coronary heart disease.[148] Compared to unaffected individuals, diabetic patients have a greater atherosclerotic burden both in the major arteries and in the microvascular circulation. Not surprisingly, diabetic patients have substantially increased rates of atherosclerotic complications both in the settings of primary prevention and after coronary interventional procedures.[149] Thus, insulin resistance and diabetes rank among the major cardiovascular risk factors.

Patients with diabetes have threefold to fivefold increased rates of future cardiovascular events,[150] with even higher rates reported among diabetic women.[151] The risk of coronary disease among premenopausal diabetic women resembles that of nondiabetic men, indicating that diabetes largely mitigates the protective effects of female gender.[152] However, although hyperglycemia is associated closely with microvascular disease, insulin resistance itself promotes atherosclerosis even before it produces frank diabetes.[153] Recent studies corroborate the role of insulin resistance as an independent risk factor for atherothrombosis.[154] This finding has prompted recommendations for increased surveillance for the insulin resistance syndrome, a cluster of glucose intolerance and hyperinsulinemia accompanied by hypertriglyceridemia, low HDL levels, and a predominance of small dense LDL particles. Insulin resistance also produces a prothrombotic state due to increased levels of PAI-1 and fibrinogen.[155] [156] [157]

In addition to these systemic metabolic abnormalities, hyperglycemia causes accumulation of advanced glycation end products inculpated in vascular damage[158] (see Chap. 63) . Furthermore, diabetic patients have markedly impaired endothelial and smooth muscle function[159] [160] and appear to have increased leukocyte adhesion to vascular endothelium, a critical early step in atherogenesis. Diabetic nephropathy, detected by microalbuminuria, accelerates these adverse processes. Among individuals with non-insulin-dependent diabetes, microalbuminuria predicts both cardiovascular and all cause mortality.[161] [161A]

Despite evidence concerning pathophysiological abnormalities associated with diabetes and epidemiological data describing increased hazards associated with hyperglycemia, few clinical trials have evaluated whether improved glycemic control improves cardiovascular risk. The Diabetes Complications and Control Trial of strict glycemic

control among insulin-dependent diabetics reported benefits on microvascular endpoints but did not find significant benefits on coronary event rates.[162] Similarly, the United Kingdom Prospective Diabetes Study found only marginal benefit for improved glycemic control among non-insulin-dependent diabetics.[163] Thus, as outlined later, exercise, diet, avoidance of obesity, and aggressive control of other risk factors remain primary targets for risk reduction in type II diabetic populations.[163A]

EXERCISE AND OBESITY

Regular physical exercise reduces myocardial oxygen demand and increases exercise capacity, both of which are associated with lower levels of coronary risk[164] (see also Chap. 39) . A consistent series of prospective studies have demonstrated an association between levels of physical activity and reduced rates of cardiovascular morbidity and all-cause mortality[90] [165] [166] [167] [167A] [167B] [167C] [167D] (Fig. 31-6) . For example, in a prospective evaluation of Harvard alumni initially free of apparent cardiovascular disease, those men with the highest

Figure 31-6 Prospective studies of physical activity and the risk of subsequent cardiovascular mortality. (From Pate RR, Pratt M, Blair SN, et al: Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA 273:402-407, 1995. Copyright 1995, American Medical Association.)

levels of activity at baseline had a 40 percent reduction in nonfatal cardiovascular events and a 24 percent reduction in cardiovascular death compared with those with sedentary lifestyles.[165] Whereas the level of exercise in early life predicts long-term exercise pattern, significant reductions in subsequent risk also applied to individuals who were initially sedentary but later increased exercise levels.[90] Thus, increasing exercise levels even in mid to late life reduces coronary risk in men[168] and women.[169] Rates of stroke also decline among those with life-long exercise habits, independent of hypertension.[170] [171]

Mortality data suggest that over 200,000 deaths result from physical inactivity annually in the United States.[172] Thus, a recent joint statement from the Centers for Disease Control and Prevention and the American College of Sports Medicine recommends that every American should accumulate at least 30 minutes of moderate-intensity physical activity daily.[173] Similarly, the American Heart Association has recommended an exercise energy expenditure approaching 2000 calories each week, a level of exercise that can be achieved with modest daily exertion.[174] Regrettably, only 25 percent of the American population achieve this level of activity and another 25 percent participate in no leisure-time physical activity at all.[175] Thus, recommendations from physicians to increase exercise levels play an important role in coronary risk reduction, particularly among the elderly, women, and those of lower socioeconomic status whose exercise

rates tend to be lower.

The mechanisms by which exercise lowers cardiovascular risk remain uncertain but likely include favorable effects on blood pressure,[176] weight control, lipid profiles, [177] and improved glucose tolerance.[178] [179] Exercise also improves endothelial function, enhances fibrinolysis, reduces platelet reactivity, and reduces propensity for in situ thrombosis.[180] [181] [182]

Weight reduction programs should include exercise as a critical component, a particularly effective measure when combined with dietary restriction.[183] It is important to recognize that obesity itself is associated with substantially increased cardiovascular risk, regardless of activity levels. For example, the Nurses Health Study revealed a direct linear relation between body mass index and subsequent risk of coronary heart disease.[184] Modest weight gain in mid to late adulthood also increases risks of coronary disease among both men and women,[185] [186] as does the distribution of body fat. Recent studies indicate that the waist-to-hip ratio, a surrogate for centripetal or abdominal obesity, is an independent marker of vascular risk both in women and older men.[187] [188]

Controversy remains as to whether obesity itself is a true risk factor for cardiovascular disease or whether its impact on vascular risk is mediated solely through interrelations with glucose intolerance, insulin resistance, hypertension, physical inactivity, and dyslipidemia. Nonetheless, obesity is epidemic in the United States and weight control must play a fundamental role in all preventive cardiology practices, preferably in conjunction with advice regarding diet and exercise.[92] [189]

MENTAL STRESS AND CARDIOVASCULAR RISK

The adrenergic stimulation of mental stress can clearly augment myocardial oxygen requirements and aggravate myocardial ischemia. Mental stress can cause coronary vasoconstiction, particularly in atherosclerotic coronary arteries, and hence can influence myocardial oxygen supply as well.[190] Myocardial ischemia provokable by mental stress can predict future coronary events.[191] [192] Catecholamines can also promote alterations in thrombosis and coagulation that might favor clot formation and stability. These factors may well trigger complications of preexisiting atherosclerotic lesions. The increase in coronary death documented during missile attacks or natural disasters such as earthquakes support this concept.[193]

What remains less certain is the effect of mental stress per se on the development of atherosclerosis.[194] Studies in this regard have proven challenging because the metrics for mental stress lend themselves less well to controlled clinical trials than other more readily quantified risk factors. Behavioral interventions, often combined with dietary changes, have proven in some studies to decrease atherosclerosis or its manifestations.[194] Ongoing studies such as the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, which include specific interventions that target psychosocial factors, should shed light on this elusive but potentially important contributor to cardiovascular risk.[195]

ESTROGEN STATUS (See also Chap. 58)

Before menopause, women have lower age-adjusted incidence and mortality rates for coronary heart disease than men. Gender-specific incidence rates converge after menopause, suggesting a major role for estrogen in delaying progression of atherosclerosis. Much of this effect results from beneficial actions of estrogen on lipid fractions. In studies of exogenous oral estrogen replacement therapy such as the Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial, estrogen reduces LDL-C by 10 to 15 percent while increasing HDL-C, apo A1, and triglycerides.[86] The mechanism of this effect from oral estrogen results partly from a first-pass action in the liver that augments LDL catabolism while reducing activity of hepatic lipase with subsequent promotion of hepatic HDL uptake.[196]

The lipid effects of estrogen, however, explain only part of the apparent cardiovascular benefits enjoyed by premenopausal women and women taking hormone replacement therapy.[197] In observational studies, even women without dyslipidemia appear to benefit from hormone replacement therapy.[198] Estrogen must therefore have other potentially beneficial effects.[199] These likely include direct vascular mechanisms such as improved endothelial-dependent vasomotion,[200] [201] reduced LDL oxidation,[202] altered adhesion molecule levels,[203] increased fibrinolytic capacity,[204] and enhanced glucose metabolism.[205]

Despite these data, exogenous estrogen use among young women as a form of oral contraception is associated with increased rates of intravascular thrombosis, including deep vein thrombosis and pulmonary embolism as well as myocardial infarction and stroke. These effects are particularly prominent among smokers such that women who continue to smoke should use alternative forms of contraception.[206] Although low-dose oral contraceptive preparations may have an improved toxicity profile,[207] the incidence of pathological thrombosis remains high among smokers using low-dose oral contraceptives.[208] [209]

By contrast, among postmenopausal women using hormone replacement therapy, prospective observational studies suggest that estrogen use reduces cardiovascular risk by 35 to 45 percent.[210] [211] In one study, estrogen users had an adjusted relative risk of coronary heart disease 40 percent lower than that of nonusers[212] as well as reduced rates of all-cause mortality.[213] However, the clinical utility of estrogen replacement therapy remains controversial for several reasons: (1) observational studies are prone to bias and it remains possible that estrogen use is a marker for improved access to health care or differences in socioeconomic and educational levels, which in turn result in lowered rates of cardiovascular disease[214] ; (2) the potential risks of estrogen use including endometrial cancer, gallstones, venous thrombosis, and possibly breast cancer[215] require patient-specific decisions concerning this therapy[216] ; (3) data from the randomized, double-blind Heart and Estrogen/progestin Replacement Study (HERS)

of women with preexisting coronary disease found no evidence of a difference in risk for nonfatal myocardial infarction or cardiovascular death between women assigned to combined hormone replacement or to placebo (relative risk = 0.99).[217] In that study, time-trend subgroup analyses suggest a possible early hazard with hormone initiation as well as later benefits, although these observed differences may well be due to chance effects. Post-hoc analysis of the HERS suggests that women with elevated Lp(a) levels at the outset of the study may have derived benefit from the hormone therapy.[218] Thus, at least in this secondary prevention setting, data from available randomized trials are at apparent odds with observational evidence and thus underscore the need for successful completion of the federally funded Women's Health Initiative randomized trial. Randomized trials of selective estrogen receptor modulators (SERMS)[219] [220] in the secondary prevention of cardiovascular disease are also underway (see Chap. 58) .

NOVEL ATHEROSCLEROTIC RISK FACTORS

Despite the importance of blood lipids, half of all myocardial infarctions occur among individuals without overt hyperlipidemia. [221] Several novel markers of atherothrombotic risk have emerged from epidemiological studies and might prove useful clincially. However, when considering adoption of screening for any new cardiovascular risk factor, clinicians need to consider[222] whether there is a standardized and reproducible assay for the marker of interest[223] ; whether there is a consistent series of prospective studies demonstrating that baseline elevations of a given parameter predict future risk; and whether the novel marker adds to the predictive value of lipid screening.[224] This section applies these basic epidemiological requirements to five promising novel markers of cardiovascular risk: total plasma homocysteine, fibrinogen, Lp(a), fibrinolytic function as ascertained by t-PA or PAI-1 antigens, and markers of low-grade inflammation such as hs-CRP (Fig. 31-7) , Table 31-7) . Physicians should also consider the relative magnitude of novel markers in terms of risk prediction, particularly in comparison to lipid screening. Figure 31-7 shows data describing the relative efficacy of several variables measured at baseline in one cohort of middle-aged men, the Physicians' Health Study.

Homocysteine

Homocysteine is a sulfhydryl-containing amino acid derived from the demethylation of dietary methionine. Patients with rare inherited defects of methionine metabolism can develop severe hyperhomocystinemia (plasma levels > 100 mumol/liter) and can have premature atherothrombosis. The mechanisms that account for these effects remain uncertain but may include endothelial toxicity, accelerated oxidation of LDL-C, impairment of endothelial-derived relaxing factor, and reduced flow-mediated arterial vasodilation.[225] [226] [227] [228]

In contrast to severe hyperhomocystinemia, mild to moderate elevations of homocysteine (plasma levels > 15 mumol/liter) are common in general populations, primarily due to insufficient dietary intake of folic acid.[229] Other patient groups that tend to have elevated homocysteine levels include those with common polymorphisms in the methylene tetrahydrofolate reductase gene (*MTHFR*), those receiving folate antagonists

such as methotrexate and carbamazepine, and those with impaired homocysteine metabolism due to hypothyroidism or to renal insufficiency.[230] [231]

In most clinical settings, total plasma homocysteine (the combination of free homocysteine, bound homocystine, and mixed disulfides) is measured by high-performance liquid chromatography, although reliable and less expensive immunoassay

Figure 31-7 Relative risks of future myocardial infarction among apparently healthy middle aged men according to baseline levels of lipoprotein(a) (Lp[a]), D -dimer, total plasma homocysteine (tHCY), total cholesterol (TC), fibrinogen, soluble intercellular adhesion molecule type-1 (sICAM-1), tissue type plasminogen activator antigen (tPA:ag), the total to HDL cholesterol ratio (TC:HDLC), interleukin-6 (IL-6), high sensitivity C reactive protein (hs-CRP), and the combination of hs-CRP and the TC:HDLC ratio. For consistency, risks are computed for those in the top quartile compared with the bottom quartile. (From Ridker PM: Novel risk factors and markers for coronary disease. Adv Intern Med 45:391-418, 2000.)

TABLE 31-7 -- ASSESSMENT OF THE CLINICAL UTILITY OF NOVEL MARKERS OF CARDIOVASCULAR RISK

MARKER	ASSAY CONDITIONS STANDARDIZED?	PROSPECTIVE STUDIES CONSISTENT?	ADDITIVE TO TOTAL AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROL?
Lipoprotein(a)	No	Yes/no	Yes/no
Total homocysteine	Yes	Yes/no	Yes/no
Tissue-type plasminogen activator and plasminogen activator inhibitor	Yes/no	Yes	Yes/no
Fibrinogen	Yes/no	Yes	Yes
High-sensitivity C-reactive protein	Yes	Yes	Yes

From Ridker PM: Evaluating novel cardiovascular risk factors: Can we better predict heart attacks? Ann Intern Med 130:933-937, 1999.

techniques now exist. Although a nonfasting evaluation of total plasma homocysteine suffices for most clinical purposes, measurement of homocysteine levels 2 to 6 hours after ingestion of an oral methionine load (0.1 gm/kg body mass) can identify individuals with impaired homocysteine metabolism despite normal fasting levels.

A large series of cross-sectional and retrospective studies indicate a positive relationship between mild to moderate hyperhomocystinemia and atherosclerosis; on average, those with plasma levels above 15 mumol/liter appear to have a relative risk one and one-half to two times higher than individuals with lower levels.[232] [233] However, because homocysteine levels increase after myocardial infarction and stroke,[234] [235] such data cannot be used to establish a cause-and-effect relationship.

By contrast, prospective epidemiological studies (where homocysteine levels are ascertained before the onset of cardiovascular events) have provided mixed data. For example, although positive prospective studies have been reported among apparently healthy middle-aged men[236] [237] [238] and women[239] [240] as well as among those with known coronary atherosclerosis,[241] it is important to recognize that several high-quality prospective studies have found no relationship between baseline homocysteine levels and subsequent vascular risk.[242] [243] [244] Furthermore, although some studies have found positive associations both among those taking and not taking multivitamins,[239] this effect lacks consistency. Finally, in some of the "positive" cohort studies, no evidence of association was seen with longer-term follow-up.[245] Thus, prospective studies of hyperhomocystinemia do not provide consistent evidence of association (Fig. 31-8). Moreover, the width of the 95 percent confidence intervals in these studies indicates a modest magnitude of any true increase in risk associated with homocysteine, perhaps limited to those individuals with markedly elevated levels. Due in part to this lack of compelling epidemiological data, current recommendations from both the American Heart Association and the American College of Cardiology do not recommend population-based screening for homocysteine.[230] The observation that mutation in the *MTHFR* gene leads to hyperhomocysteinemia but not to increased vascular risk also reduces enthusiasm for screening, at least from a genetic perspective.[246]

Recent fortification of the United States food supply with folate to reduce the risk of neural tube defects[247] also complicates clinical issues in terms of screening for hyperhomocystinemia. Since its initiation in 1992, the addition

Figure 31-8 Prospective studies of homocysteine as a risk factor for future cardiovascular events in populations free of clinical disease. PHS = Physicians' Health Study; MRFIT = Multiple Risk Factor Intervention Trial; BUPA = British United Provident Association; ARIC = Atherosclerosis Risk in Communities; WHS = Women's Health Study. (From Ridker PM: Novel risk factors and markers for coronary disease. Adv Intern Med 45:391-418, 2000.)

of small amounts of folic acid to enriched flour and grain products has resulted in a 9 to 10 percent drop in mean population homocysteine levels and an almost 50 percent drop in the number of individuals with homocysteine levels within the moderately elevated range.[248] Thus, the number of individuals potentially identifiable by general screening

has decreased considerably over just a few years.

In some patient groups, such as those with premature atherosclerosis, an absence of other risk factors or in the setting of renal failure, homocysteine screening may have increased utility. Folic acid, given in doses of up to 400 mug/d, can be expected to reduce homocysteine levels approximately 25 percent, whereas the addition of vitamin B_{12} will likely reduce levels another 7 percent.[249] Because this therapy is inexpensive and has low toxicity in the absence of vitamin B_{12} deficiency, vitamin supplementation may be a more cost-effective approach for high-risk groups than screening.[230] No randomized trial data are available that demonstrate that reducing homocysteine levels reduces coronary risk.

Fibrinogen

Plasma fibrinogen critically influences platelet aggregation and blood viscosity, interacts with plasminogen binding, and in combination with thrombin mediates the final step in clot formation.[250] In addition, fibrinogen associates positively with age, obesity, smoking, diabetes, and LDL-C and inversely with HDL-C, alcohol use, physical activity, and exercise level.[251] [252]

Given these relationships, it is not surprising that fibrinogen was among the first "novel" risk factors to be evaluated in epidemiological studies. Early reports from the Gothenburg,[253] Northwick Park,[254] and Framingham[255] heart studies all found significant positive associations between fibrinogen and future risk of cardiovascular events. A series of prospective studies have since confirmed these results,[256] [257] [258] [259] [260] [261] and a recent meta-analysis indicates that the relative risk of future cardiovascular events is 1.8 times higher for individuals in the top as compared with the bottom tertile of baseline fibrinogen concentration.[262] Women may have higher risks, although confounding by the effects of hormone replacement therapy limit interpretation of available studies.[263] Plasma viscosity, determined in part by fibrinogen level, also predicts cardiovascular risk.[264] [265]

Due to the consistency of these data, many consider fibrinogen an independent marker of risk for coronary heart disease.[266] However, two issues have limited clinical screening for fibinogen to improve risk prediction: (1) inadequate standardization between competing laboratory techniques and (2) wide intraindividual variation in plasma levels over time.[267] In addition, because smoking and estrogen replacement therapy appear to have opposite effects on fibrinogen levels,[127] [268] [269] care must be taken when interpreting results for these subgroups. Furthermore, the magnitude to which fibrinogen assessment improves coronary risk prediction models has varied widely in different studies[270] [271]

Despite major genetic determinants of fibrinogen concentration,[272] [273] substantial variation in plasma levels results from environmental factors. Smoking cessation, increased exercise, and weight loss can reduce fibrinogen concentration. Fibric acid derivatives also reduce fibrinogen, apparently through a PPAR-alpha mechanism.[274] [275] However, results of the Bezafibrate Infarction Prevention Trial do not show a significant

decrease in vascular risk despite an overall 9 percent reduction in fibrinogen due to drug administration.[276] Furthermore, although hormone replacement therapy also reduces fibrinogen levels, this effect did not translate into a net clinical benefit among participants in HERS.[217]

Fibrinogen elevation occurs as part of the acute-phase response and may thus be associated with risk owing to its role as a marker of systemic inflammation. However, as is reviewed later in this chapter, other markers of inflammation such as hs-CRP appear to be more powerful than fibrinogen in terms of risk prediction

Lipoprotein(a)

As described on page 1017 , Lp(a) consists of an LDL particle with its apo B-100 component linked by a disulfide bridge to apo(a), a variable length protein that has sequence homology to plasminogen.[47] The apo(a) component of Lp(a) is a complex molecule composed in part of varying numbers of cysteine-rich kringle repeats that result in great heterogeneity. Plasma Lp(a) concentrations vary inversely with apo(a) isoform size but may vary even within isoform size based on differential levels of production.[277] Underlying its molecular complexity, more than 25 heritable isoforms of Lp(a) exist.[47] This molecular variability has clinical import because Lp(a) levels vary widely across ethnic groups.

Although the normal function of Lp(a) is unknown, the close homology between Lp(a) and plasminogen has raised the possibility that this unusual lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen for binding on the endothelial surface.[278] More recent data demonstrate accumulation of Lp(a) and co-localization with fibrin within atherosclerotic lesions, both in stable patients and among those with unstable angina pectoris.[279] [280] Apo(a) may also induce monocyte chemotactic activity in the vascular endothelium,[281] whereas Lp(a) may increase release of PAI.[282] Thus, several mechanisms may contribute to a role for Lp(a) in atherothrombosis.

Many retrospective and cross-sectional studies suggest a positive association between Lp(a) and vascular risk. However, as in the case of homocysteine, levels of Lp(a) increase after acute ischemia and such studies cannot reliably determine causality. Prospective studies of Lp(a) avoid this bias but have not always found consistent evidence of association. For example, although several prospective studies employing plasma based assays for either apo(a) or for Lp(a) mass concentration have reported a positive, graded association,[258] [283] [284] [285] several other well-designed prospective studies have not demonstrated these effects.[286] [287] [288] [289] Electrophoretic detection of pre-beta-lipoprotein, a surrogate for Lp(a), has also been associated with increased vascular risk.[290] [291] However, these studies reported inconsistent data between men and women and between the endpoints of myocardial infarction and stroke. Thus, available prospective studies do not establish the importance of Lp (a) as a marker for all future cardiovascular events or whether any increased risk is restricted to those with the highest levels or an absence of other traditional risk factors.

Beyond these considerations, several practical issues limit the utility of Lp (a) screening. First, commercially available tests for Lp(a) lack sufficient standardization and there

remains no consensus among clinical chemists on how best to measure this highly polymorphic molecule. This issue hampers reproducibility between laboratories, greatly reducing clinical efficacy.[292] Second, Lp(a) levels vary widely among different racial groups, with the African-American population tending to have more individuals in the higher range.[293] Scant evidence establishes the predictive value of Lp(a) for many ethnic groups, including African-Americans.[294] Similarly, the predictive value of Lp(a) in women is controversial.[295] Third, even in the positive studies of Lp(a), it is unclear whether evaluation of this lipoprotein adds to the predictive value of total and HDL-C. Indeed, LDL reduction markedly reduces any adverse hazard associated with Lp(a).[296]

Whereas niacin can modestly reduce Lp(a) levels, specific Lp(a)-lowering therapies are not available. For all of these reasons, most authorities do not recommend general Lp(a) screening.[297] However, as with homocysteine, special situations may warrant Lp(a) evaluation, such as young individuals who have suffered infarction yet who appear to lack other traditional risk factors.

Markers of Fibrinolytic Function (PAI-1, t-PA, Clot Lysis, and D

-Dimer)Impaired fibrinolysis can result from an imbalance between the clot-dissolving enyzmes tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA) and their endogenous inhibitors, primarily PAI-1. Plasma levels of PAI-1 peak in the morning whereas concentrations of t-PA demonstrate a less prominent circadian variation.[298] On this basis, a relative hypofibrinolytic state may prevail in the morning that, along with increased platelet reactivity, may contribute to the increased risk of myocardial infarction seen in this time period.[299] Visceral obesity yields enhanced PAI-1 production from adipocytes, and thus impaired fibrinolysis may help explain how weight gain and obesity influence atherothrombosis.[300] [301] [302] Individuals with the insulin resistance syndrome commonly have impaired fibrinolysis.[303] [304]

Clinically, patients with isolated PAI-1 deficiencies have excess rates of hemorrhage whereas animals with genetically mediated PAI-1 excess may develop spontaneous thrombosis.[305] [305A] However, a role for either t-PA or PAI-1 in the development of venous thrombosis remains controversial because retrospective studies may fail to account for acute-phase effects[306] and available prospective studies have not provided consistent evidence of association.[307]

By contrast, a highly consistent series of prospective studies have linked abnormalities of fibrinolysis to increased risk of arterial thrombosis. For example, prospective associations exist between PAI-1 antigen and activity levels and the risk of first and recurrent myocardial infarction.[251] [271] [308] [309] Perhaps paradoxically, individuals at risk for future coronary as well as cerebral thrombosis consistently have elevated levels of circulating t-PA antigen.[304] [310] [311] [312] [313] These latter effects may represent evidence of underlying endothelial dysfunction among individuals at risk or of direct relationships between t-PA and PAI-1, or they may represent a biological response to impaired

fibrinolysis. In this regard, reduced clot lysis time, an overall indicator of net fibrinolytic function, also predicts coronary risk.[314] Finally, several studies indicate that levels of D-dimer, a peptide released by plasmin's action on fibrin, also predict myocardial infraction, peripheral atherothrombosis, and recurrent coronary events.[315] [316] [317]

Despite these data, the clinical use of fibrinolytic markers to determine coronary risk may offer little marginal value. Direct measurement of PAI-1 activity is difficult in clinical settings and requires special anticoagulants and precise phlebotomy techniques to avoid degranulation of platelets, a rich source of PAI-1. In addition, these markers, particularly PAI-1, have wide circadian variation. Furthermore, few data indicate that assessment of fibrinolytic markers adds substantially to clinical risk prediction models.[3]

The recognition that fibrinolytic function contributes to atherothrombotic risk has nonetheless yielded several practical clinical applications. For example, PAI-1-resistant thrombolytic agents may provide a means to increase the efficacy of fibrinolytic therapy for acute myocardial infarction. Furthermore, the renin-angiotensin system plays an important role in the regulation of fibrinolysis, and at least two randomized trials have shown the ability of angiotensin-converting enzyme inhibitors to influence favorably the balance between t-PA and PAI-1.[318] [319] Finally, genetic polymorphism in the promoter of the PAI-1 gene appears to be associated with elevated levels of PAI-1 expression,[320] [321] although whether this increases risk of myocardial infarction remains uncertain.[322] [323]

Markers of Inflammation (hs-CRP, ICAM-1, and IL-6)

INFLAMMATION CHARACTERIZES ALL PHASES OF ATHEROSCLEROSIS.

As reviewed in Chapter 30 , inflammation characterizes all phases of atherosclerosis.[324] [325] Formation of the fatty streak, the earliest phase of atherogenesis, involves recruitment of leukocytes due to expression of leukocyte adhesion molecules on endothelial cells in turn triggered by primary proinflammatory cytokines such as interleukin (IL)-1 or tumor necrosis factor-alpha. Subsequent migration of inflammatory cells into the subendothelial space requires chemotaxis controlled by chemokines induced by the primary cytokines.[326] Mononuclear cells within this initial infiltrate as well as intrinsic vascular cells subsequently release growth factors that stimulate proliferation of the smooth muscle cells and hence the progression of plaques. Finally, the thrombotic complications of plaques often involve physical disruption, usually associated with signs of inflammation.[327] [328] Other proinflammatory cytokines such as CD154 (CD40 ligand) can induce tissue factor procoagulant expression and promote thrombus

Figure 31-9 Pathways by which vascular and extravascular sources of inflammation result in circulating levels of inflammatory markers associated with atherothrombosis. CRP=C-reactive protein; HSP=heat shock protein; ICAM-1=intercellular adhesion molecule-1; IL-1 = interleukin-1; SAA=serum amyloid A; TNF-alpha = tumor necrosis factor-alpha. (Adapted from Libby P, Ridker PM: Novel inflammatory markers of coronary risk: Theory versus practice Circulation 100:1148-1150, 1999. Copyright 1999, American

Heart Association.)

Figure 31-10 (Figure Not Available) Baseline plasma concentration of hs-CRP and the risk of future cardiovascular events among apparently healthy men and women. CHS/RHPP=Cardiovascular Health Study/Rural Health Promotion Project; Helsinki=Helsinki Heart Study; MONICA=Monitoring trends and determinants in Cardiovascular disease; MRFIT=Multiple Risk Factor Intervention Trial; PHS=Physician's Health Study; WHS=Women's Health Study.

formation.[329] Thus, the inflammatory response participates in every stage of atherothrombosis.

The primary proinflammatory cytokines IL-1 and tumor necrosis factor-alpha induce, in turn, the expression of another cytokine, IL-6. We have dubbed IL-6 a "messenger" cytokine because it can act remotely to change the program of protein synthesis in the liver from "housekeeping" proteins (e.g., albumin) to a family of proteins known collectively as acute-phase reactants. In this manner, local inflammation (in this case, the artery wall) can produce a reflection in the peripheral blood. We envisage this cytokine cascade orchestrating the expression of effector molecules (e.g., the adhesion molecules) as a biochemical pathway, similar to those encountered in intermediary metabolism (Fig. 31-9) .

MARKERS OF INFLAMMATION PREDICT FUTURE RISK OF VASCULAR EVENTS.

Given this underlying pathophysiology, it is not surprising that several markers of low-grade systemic inflammation have also proven useful for cardiovascular risk prediction.[330] [331] These markers include nonspecific acute-phase reactants such as hs-CRP, adhesion molecules such as ICAM-1, which are involved in mononuclear cell attachment to the vascular endothelium, and cytokines such as IL-6 and tumor necrosis factor. Each of these inflammatory markers can be measured in plasma and may thus provide a window on the inflammatory processes at the level of the arterial wall.

It remains unclear to what extent the acute-phase reactants serve merely as markers or themselves act as effectors of pathological responses. A large body of consistent evidence validates the use of acute-phase reactants such as CRP and serum amyloid A as markers of risk (see later). The evidence regarding their roles as direct mediators of pathology remains much more speculative. Nonetheless, CRP may activate complement and thus participate in sustaining inflammation. Serum amyloid A can bind to HDL particles, perhaps rendering them less protective against vascular inflammation.[332] Fibrinogen, another acute-phase protein, clearly can participate in coagulation, as discussed earlier.

Among the inflammatory markers, hs-CRP will likely prove the most clinically useful because it is easy and inexpensive to measure with commercial assays.[333] CRP has proven to have strong predictive value both among currently healthy men[334] [334A] [334B] and women[331] [335] as well as among the elderly,[336] high-risk smokers,[337] those with

stable[338] and unstable angina pectoris,[339] [340] and those with prior myocardial infarction.[341] In these studies, individuals with hs-CRP levels in the upper quartile had relative risks of future vascular events three to four times higher than individuals with lower levels, effects that were independent of all other traditional cardiovascular risk factors (Fig. 31-10) (Figure Not Available) . Moreover, plasma levels of hs-CRP appear to add to the predictive value of plasma lipid measurements, and thus may provide an improved method to determine future vascular risk[342] (Fig. 31-11) .

In one recent large-scale prospective evaluation of 12 different inflammatory and lipid markers of risk, hs-CRP proved to be the single best predictor of future vascular thrombosis.[331] Moreover, in multivariate analysis, only hs-CRP or the total cholesterol:HDL-C ratio independently predicted risk. Importantly, levels of hs-CRP as well as the

Figure 31-11 Relative risks for future myocardial infarction among currently healthy men according to baseline tertile of the total to HDL-cholesterol ratio and to baseline tertile of hs-CRP. From Ridker PM, Glynn R, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 97:2007-2011, 1998. Copyright 1998, American Heart Association.)

inflammatory markers serum amyloid A, soluble ICAM-1, and IL-6 all predicted future vascular risk. Interestingly, these variables establish increased risk even among those with LDL-C levels below 130 mg/dl, the threshold for pharmacotherapy mandated by National Cholesterol Education Program (NCEP) Adult Treatment Program-2 (ATP-2) guidelines (Fig. 31-12) . [331] Thus, the clinical use of inflammatory markers may help to identify individuals at higher risk for myocardial infarction despite not meeting criteria for treatment based on the lipid profile.

For many clinicians, it may seem surprising that markers of inflammation such as CRP have such potent predictive value. After all, as a classic acute-phase reactant, levels of CRP increase several hundredfold in response to injury or infection and increase with a variety of inflammatory stimuli.[343] However, as long as hs-CRP is not measured within 2 to 3 weeks of an acute inflammatory stimulus (e.g., intercurrent infection), levels in a given individual are quite stable over long periods.

TREATMENTS CAN MODIFY MARKERS OF INFLAMMATION.

Evidence also suggests that hs-CRP may represent a modifiable risk marker. In a randomized trial of low-dose aspirin, the relative efficacy of this agent in decreasing coronary risk was greatest among those with evidence of low-grade inflammation as determined by hs-CRP but was sequentially smaller as levels of hs-CRP declined, data

that suggest potentially important antiinflammatory effects for aspirin.[334]

Similarly, in the Cholesterol and Recurrent Events (CARE) trial, the attributable risk reduction associated with pravastatin was greater among individuals with a persistent inflammatory response as determined by hs-CRP, such that statin therapy attenuated almost completely the elevated risk associated with inflammation.[341] Moreover, therapy with pravastatin in the CARE trial significantly reduced levels of hs-CRP over a 5-year period.[344] This finding corroborates in humans experimental studies that suggest that lipid lowering attenuates inflammation[345] [346] and that the use of statins reduces macrophage content and activity within atheromatous plaque.[347] [348] [349] Thus, lipid lowering by statins appears to mitigate the inflammatory processes that undermine plaque stability. Nonpharmacological methods to reduce hs-CRP include weight reduction and exercise.[350] [351] By contrast, cross-sectional[352] [353] and randomized data indicate that hormone replacement therapy may augment levels of hs-CRP.[354]

MECHANISMS OF INFLAMMATORY MARKER ELEVATIONS.

Although the mechanisms underlying CRP as a risk factor remain uncertain, the low-grade inflammation detected by hs-CRP probably serves as an indirect marker of an enhanced cytokine[355] response to a variety of inflammatory stimuli that ultimately proves critical both for plaque progression and plaque rupture (see Fig. 31-9. Plasma levels of the "messenger" cytokine IL-6 , the primary driver of hepatic CRP synthesis, also predict future myocardial infarction among currently healthy men[356] as well as total mortality in the elderly.[357] Furthermore, individuals with

Figure 31-12 The value of hs-CRP, serum amyloid A (SAA), soluble intercellular adhesion molecule (sICAM-1), and interleukin-6 as predictors of future vascular risk among women with high, medium, and low levels of total cholesterol. (From Ridker PM, Hennekens CH, Buring JE, et al: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 342:836-843, 2000.)

acute coronary syndromes have elevated levels of IL-6, and this cytokine has both short- and long-term prognostic value among those with and without overt plaque rupture.[358] [359] Upstream effectors of IL-6 production also serve as markers of future vascular risk. Individuals with increased vascular risk also have elevated levels of tumor necrosis factor-alpha and IL-1 isoforms, which in turn may stimulate IL-6 expression.[359] [360] Cellular adhesion molecules responsible for recruitment of monocytes into the intima also appear to have a predictive role in vascular disease. In particular, those at risk for future coronary artery disease and stroke have elevated levels of soluble forms of ICAM-1 at baseline.[331] [361] [362] Soluble forms of other adhesion molecules that reflect endothelial activation or platelet adhesion may also indicate vascular disease progression.[129]

Sources of stimuli for the smoldering inflammatory response include not only the vessel wall itself but also extravascular sites. Extravascular foci of chronic infection might include the gingiva, the bronchi, the urinary tract (including the prostate), or diverticular disease. Chronic infection with agents such as *Chlamydia pneumoniae, Helicobacter pylori,* herpes simplex virus, or cytomegalovirus can lead to systemic inflammation. Such observations have heightened interest in the hypothesis that infection may contribute to coronary risk[363] [364] (see also Chap. 30) . Several cross-sectional and retrospective studies that suggest an increased prevalence of infection among individuals with known coronary disease support this hypothesis.[365] [366] [367] In addition, several studies have identified *Chlamydia* species[368] [369] as well as viral particles[367] [370] in atheromatous lesions. On the other hand, interpreting these data requires considerable caution. First, retrospective studies are prone to considerable confounding and the presence of infection may represent a result rather than a cause of atherosclerotic disease.[371] For example, several large-scale prospective studies have not found evidence that prior exposure to either *Chlamydia pneumoniae, Helicobacter pylori,* cytomegalovirus, or herpes viruses is associated with increased risk of future cardiovascular events.[372] [373] [374] [375] [376] Furthermore, recovery of infectious particles within atheromatous plaque does not prove causation but may simply represent an innocent commensal colonization.

It is thus uncertain whether infection plays an important etiological role in atherthrombosis. Available clinical trials of antibiotic therapy have been underpowered to demonstrate either a true benefit or a meaningful null result. It is important to recognize, however, several mechanisms by which infection might contribute to plaque instability. For example, *Chlamydia* species have been reported to induce macrophage foam cell formation and increase procoagulant activity.[377] [378] Human atheromas often contain chlamydial heat shock protein 60 (HSP-60), an effector of activation of macrophages, endothelium, and matrix metalloproteinase expression.[379] [380] [381] Ongoing large-scale clinical trials of antibiotic therapies in the setting of chronic and acute infarction will help resolve these controversies. Although the proximal stimuli remain unproven at this time, overwhelming evidence supports a major role for inflammation in atherosclerosis and establishes the clinical utility of measurement of the inflammatory response in identifying individuals at high risk for plaque rupture.

FUTURE DIRECTIONS IN CORONARY RISK ASSESSMENT

Although available data demonstrate the considerable potential of inflammatory markers such as hs-CRP to improve coronary risk prediction, determining the full utility of inflammatory markers as adjuncts to lipid screening in individual patients will require further clinical studies. The observation that elevated levels of CRP, IL-6, tumor necrosis factor, IL-1RA, and soluble ICAM-1 all associate with future vascular events provides a potent stimulus to consider targeted antiinflammatory therapies as a novel method to both treat and prevent vascular thrombosis.

Aside from inflammatory markers, future strategies to detect vascular risk will likely take several forms. Imaging techniques including carotid and intravascular ultrasonography, electron-beam computed tomography (CT), and magnetic resonance imaging all hold

promise as methods to identify silent atheroma and perhaps vulnerable plaque.[330] Similarly, testing for endothelium-dependent vasodilation has proven highly effective in specialized research settings. However, each of these techniques requires carefully designed prospective evaluations to determine their clinical utility. Just as the extent of stenosis determined at coronary angiography does not necessarily predict plaque rupture, it is not at all certain that other imaging techniques will overcome this inherent limitation. For example, a recent study of coronary calcification as detected by electron-beam CT has found that this method does not predict accurately near-term vascular events, even in high-risk settings.[382] Furthermore, imaging studies and the consequences of false-positive testing can entrain considerable costs. Indeed, a recent American Heart Association position paper has advised against the use of electron-beam CT for coronary calcium scoring as a routine screening tool at present.

An alternative approach to improving risk prediction would be expansion of current lipid screening algorithms to include other vascular markers with a firm pathophysiological basis such as homocysteine, LDL particle size, Lp(a), or hs-CRP. Advantages of this approach include relatively low cost, a recognition that such variables could add to simple lipid screening in assessing the risk of thrombotic complications of atheroma, and their firm basis in pathophysiology. Moreover, in contrast to imaging techniques, abundant prospective data already exist for many of these markers that can guide clinicians in their use. This approach seems promising because inflammatory markers appear to add to the predictive value of lipid screening and provide a window onto clinically relevant plaque biology.

The "genomics revolution" mentioned earlier in relation to pharmacogenomics will also doubtless open new vistas of cardiovascular risk prediction. Over the next decade, considerable attention will focus on genetic detection of thrombotic risk. For venous thrombosis, genetic detection of factor V Leiden and of a common polymorphism in the promoter of the prothrombin gene have already entered clinical practice and have utility for targeting secondary prevention. In contrast, although family history contributes importantly to determining risk of myocardial infarction or stroke, studies of single gene polymorphisms and arterial thrombosis have proven disappointing, limiting enthusiasm for the use of genetic screening for abnormalities of hemostasis, thrombosis, and inflammation at present.[383] Nonetheless, screening of multiple loci and haplotyping hold the promise of better targeted pharmaceutical approaches based partly on genetic screening and will likely provide major avenues for coronary risk reduction in the future.

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Chapter 32 - Primary and Secondary Prevention of Coronary Heart Disease

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The public health importance of both primary and secondary prevention of coronary heart disease (CHD) is indisputable. In view of the prevalence of CHD, preventing even a small proportion of cases would save thousands of lives, avoid inestimable suffering, and save billions of health care dollars. In addition, measures that prevent CHD may also mitigate other manifestations of atherosclerosis such as stroke and peripheral artery disease. Because cardiovascular diseases will become the number one killer worldwide early in the 21st century,[1] widespread deployment of affordable preventive strategies will be essential for both developed and developing countries.[2]

While researchers have made great strides in identifying a large number of life style, biochemical, and genetic factors potentially associated with CHD, the process of disease prevention must push beyond understanding disease mechanisms and identifying risk factors toward establishing intervention strategies that definitively reduce risk. Weighing the benefits of given interventions against their risks and costs has led to

the establishment of guidelines for health providers and the general public. Implementing these guidelines, however, remains a difficult task.

DEVELOPMENT OF PREVENTIVE INTERVENTIONS

The multifactorial nature of atherogenesis makes the process of prevention complex. Potential risk factors for atherosclerotic disease include nonmodifiable factors such as age, sex, and race; behavioral characteristics such as smoking and physical activity; and biochemical variables such as the serum cholesterol level. Many factors are useful in assessing an individual's risk of development of a first or subsequent event. However, while predictive value is *necessary* to infer that modification of a risk factor will lead to reduced risk, it is not *sufficient*. Several additional steps are needed. First, the factor must be easy and inexpensive to measure--a major potential limitation for expensive techniques such as electron beam computed tomography. Second, the false-positive rate associated with screening must be low to avoid unnecessary and potentially hazardous consequences. Third, the benefit of intervention must clearly exceed any risks and be worth the cost. Finally, the intervention must be implemented in appropriate populations. Some factors, such as age, gender, and family history, are useful in assessing risk but are not modifiable. These factors will be considered only in the context of their ability to help us determine global risk.

Assessing Causality of a Given Factor

A crucial step in developing preventive strategies is the establishment of cause and effect. Consistent data from several types of research are needed to establish a causal relationship between exposure and disease (Table 32-1) . Basic research is providing insight into the mechanisms underlying atherogenesis and can help elucidate potential interventions to modify these effects. It is in the area of drug development that basic research has been particularly successful. The role of epidemiology in the development of preventive strategies involves a number of complementary methods, including descriptive studies (cross-sectional surveys and cross-cultural analyses), analytical studies (case-control and prospective cohort studies), and intervention studies (randomized trials).

DESCRIPTIVE STUDIES.

Descriptive studies include case reports, case series, cross-sectional surveys, cross-cultural

TABLE 32-1 -- TYPES OF STUDIES USED IN ESTABLISHING PREVENTIVE STRATEGIES

Basic research
In vitro studies
Animal studies
Clinical investigation

- Epidemiological studies
  - Descriptive studies
    - Case reports
    - Cross-sectional surveys
    - Cross-cultural comparison studies
    - Temporal trend studies
  - Analytical studies
  - Observational
    - Case-control studies
    - Cohort studies
  - Intervention (randomized trials)
- Cost efficacy studies
- Meta-analyses

studies, and studies of population-based temporal trends. These studies are valuable primarily for their generation of hypotheses that can be tested in more analytical settings. The major contribution of descriptive studies, particularly cross-cultural studies and studies of temporal trends, has been the demonstration that environmental factors play an important role in the development of atherosclerotic disease. The higher rates of heart disease in northern Europe than southern Europe,[3] the differences in cardiovascular disease rates among industrialized and less developed nations,[1] and changing rates of heart disease over the past three decades in the United States (Fig. 32-1) and other industrialized nations all support critical environmental components in the pathogenesis of atherosclerosis. Migration studies, such as the Ni-Hon-San Study, which showed increasing heart disease rates as Japanese men migrated from Japan to Honolulu and San Francisco, indicated that behavioral and environmental factors could explain a large portion of the cross-cultural differences in heart disease rates.[4] However, preventive strategies cannot be based solely on descriptive studies because their design prevents adequate control for potential factors that may confound apparent associations.

OBSERVATIONAL ANALYTICAL STUDIES.

In contrast to descriptive studies, observational analytical studies (case-control and prospective cohort studies) give researchers greater control over potential confounders. Observational studies suffer less from the biases of descriptive data since both outcome and exposure data are available for each individual in the study population, thus offering

the possibility of better control for many potential confounders.

Case-Control Studies.

Case-control studies are designed to identify cases of a particular disease and appropriately matched controls and to compare the exposure status of potential risk factors typically ascertained at the time that disease status is established. Although case-control studies are more efficient and less costly than prospective cohort studies, recall bias may have an impact on risk estimates since exposure status is ascertained *after* the onset of disease. The selection process used to identify both cases and matched controls may also introduce bias since selected cases or controls may not adequately represent the intended source populations.

Prospective Cohort Studies.

In these studies, researchers ascertain exposure status at the beginning of the study and monitor individuals for the development of subsequent events. Prospective cohort studies are thus less subject to the biases of case-control studies because exposure data are collected *before* the development of disease. Furthermore, selection bias is less of an issue because subjects are not initially chosen on the basis of their disease status.

Case-control and prospective cohort studies are extremely useful in establishing risk attributable to a single factor, particularly when the effect of a given factor is large. Thus, as is the case for smoking and lung cancer, it is neither necessary nor ethical to conduct randomized trials to establish causality. On the other hand, when searching for small to moderate effects, the amount of uncontrolled confounding in observational studies may be as large as the probable risk reduction itself. In such cases, randomized trials are essential for confirming association. Even when causality is not in question, trials help quantify the magnitude of an intervention's effect. In addition, when the intervention is associated with competing risks and benefits, randomized trials are needed to determine the net clinical effect of the intervention. For example, observational studies indicate that estrogen replacement therapy may confer a protective effect in terms of coronary heart disease, but these benefits must be weighed against the potential increased risk of breast and uterine cancer.

Assessment of Benefits and Risks of Intervention

Once a factor has been established as causally related to disease, interventions to modify the factor must be developed and tested. This critical element in prevention is necessary because the magnitude of associated risk is not necessarily related to the magnitude of benefit derived from the intervention. Such lack of correlation may be due to the inability of the intervention to achieve the necessary change, or a change in the parameter may not result in the necessary change in risk in a proportional manner. An example is the difference between the observed risk associated with a 1-mm Hg rise in blood pressure and the lower than anticipated benefit on CHD derived from reducing blood pressure by this amount.[5] [6] Similarly, while elevated levels of homocysteine have

been implicated as a risk factor for CHD and while folic acid reduces homocysteine levels, evidence from randomized trials indicating that reducing homocysteine levels with folic acid reduces vascular risk is not yet available.

In addition to providing information on the causal nature of an association, randomized trials generally provide the best data on the magnitude of benefit and risk from a given intervention. This information is essential for assessing cost efficacy and developing preventive strategies.

Figure 32-1 Change in age-adjusted mortality from coronary heart disease (CHD), stroke, and all causes in the United States, 1950 to 1996. CVD=cardiovascular disease. *(From 1998 Chartbook on Cardiovascular, Lung, and Blood Diseases. Bethesda, MD, National Institutes of Health, National Heart, Lung and Blood Institute, 1998, p 21.)*

Meta-Analysis

In some instances, data from individual randomized trials or observational studies fail to establish a clear risk or benefit, possibly because of small sample size. In these cases, it may be helpful to pool data from several studies in an overview, or meta-analysis. Pooling data is difficult if major differences exist in study design, interventional strategies, or definitions of exposure variables or outcome measures. Meta-analyses must be interpreted cautiously because the results may depend on the underlying assumptions dictating which studies were included or how data were summarized. Publication bias may also influence the results since it is often difficult to gain access to unpublished data for inclusion in the meta-analysis.

Cost Efficacy of Preventive Interventions (see also Chap. 2)

Once reasonable estimates of benefit and risk have been established for a given factor, cost-effectiveness analyses can be helpful in establishing guidelines for intervention. The common currency used to compare interventions is the quality-adjusted life-year (QALY) or disability-adjusted life-year (DALY). As with estimates derived from meta-analyses, those from cost- and risk-benefit analyses are dependent on the underlying assumptions made in a given analysis. In particular, because prevention measures have a long time horizon (decades or more), the consequences of initial assumptions can be much more significant than those of interventions with a short time horizon. Nonetheless,

Figure 32-2 Coronary heart disease (CHD) score sheets for calculating 10-year CHD risk according to age, total cholesterol (TC) (or low-density lipoprotein cholesterol [LDL-C]), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking. *A,* Score sheet for men based on the Framingham experience in men 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 mg/dl (or LDL of 100 to 129 mg/dl), HDL-C of 45 mg/dl, no diabetes, and no smoking. *B,* Score sheet for women based on the Framingham experience in women 30 to 74 years old at baseline. Aerage risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 mg/dl (or LDL of 100 to 129 mg/dl), HDL-C of 55 mg/dl, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts=points. *(From Wilson PW, D'Agostino RB, Levy D, et al: Prediction of coronary heart disease using risk factor categories. Circulation 97:1837-1847, 1998. By permission of the American Heart Association, Inc.)*

the cost-effectiveness of interventions to prevent heart disease is important because of both the prevalence of CHD and the high cost of treatment.

Cost-effectiveness estimates are calculated as the ratio of net cost to the gain in life expectancy. Interventions with an incremental cost-effectiveness ratio of less than $40,000 per QALY are comparable to other chronic interventions such as hypertension management and hemodialysis. Those with a cost-effectiveness ratio under $20,000 per QALY are very favorable, while those exceeding $40,000 per QALY tend to be higher than generally accepted by most insurers.

Assessing Absolute Risk

The cost efficacy of any intervention varies according to global risk in a given individual or population. Thus, a fundamental step in establishing a preventive strategy involves assessing an individual's risk of development of clinically relevant outcomes. To illustrate this concept, assume that an intervention reduces mortality by 25 percent in both primary and secondary prevention. Furthermore, assume that a high-risk individual with CHD has a 20 percent chance of death from cardiovascular disease over the next 10 years while a low-risk individual has a 1 percent chance of death over the same period. To save a life among those at high risk, one would have to treat only 20 patients (4 of whom are destined to die) for 10 years so that a 25 percent relative risk reduction would result in 1 life saved (3 deaths instead of 4). On the other hand, one would have to treat 400 low-risk patients (4 of whom are also destined to die) so that the same 25 percent relative risk reduction would yield 3 deaths instead of 4. Thus, the total cost per

lives saved is considerably lower among individuals at higher absolute risk.

Investigators with the Framingham Heart Study have developed a useful tool to assess

risk of a first cardiovascular event based on age, gender, total or low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure, and history of diabetes and cigarette smoking[7] (Fig. 32-2) . Point-based weights are assigned to the presence and/or level of each risk factor. Once the points have been assigned and summed, the total score can be translated to an estimated absolute risk of a CHD event occurring within the next 10 years.

The European Society of Cardiology has also assembled

Figure 32-3 Risk assessment tool using cholesterol levels, blood pressure, and smoking status devised by a European task force on coronary prevention. *(From Wood D, De Backer G, Faergeman O, et al: Prevention of Coronary Heart Disease in Clinical Practice. Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Eur Heart J 19:1434-1503, 1998.)*

recommendations for the prevention of heart disease that stratify preventive interventions according to whether a patient is at high, intermediate, or low risk.[8] Those with known CHD constitute the highest-risk category because most of these individuals have a greater than 20 percent chance of subsequent events over the next 10 years. Individuals without known CHD are assessed for risk with a modified Framingham assessment tool. This tool, presented in a series of easy-to-use charts, allows clinicians to assess risk over the next 10 years based on age, gender, smoking status, diabetes, level of cholesterol, and blood pressure (Fig. 32-3) . Those for whom the risk of a primary event exceeds 20 percent over the next 10 years are recommended for aggressive management. Those for whom risk is lower are prescribed a less intense and less costly approach. The major difference between the Framingham and the European Society of Cardiology scores is the absence of HDL cholesterol from the European formula, which was omitted because it is not routinely measured in general population screening in some countries.

Risk assessment scales are also available from the Framingham investigators for the secondary prevention of myocardial infarction and stroke. However, since all patients with prior evidence of cardiovascular disease are at high risk for recurrent events and require aggressive preventive efforts, the utility of these tools is unclear.

Primary Versus Secondary Prevention

A crude means of determining absolute risk is embedded in the concept of primary versus secondary prevention. While most factors that predict a first CHD event also predict subsequent events, the relative cost efficacy of an intervention for primary prevention versus secondary prevention varies. Preventive interventions tend to be more cost-effective in secondary prevention: Since absolute risk among those with known disease is higher, fewer higher-risk individuals require treatment to save one life in comparison to those at lower risk, even if relative risk reductions are identical in both

groups.

Assessing an individual's absolute risk enables cost-effective targeting of interventions. Accordingly, the National Cholesterol Education Program (NCEP) and the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) use absolute risk to gauge the level of intensity of intervention. Guidelines from the NCEP Adult Treatment Panel II adjust treatment cut points and goals according to the level of underlying risk.[9] Individuals with clinical manifestations of CHD should receive the most aggressive lipid-lowering therapy (LDL goal of <100 mg/dl), while therapy can be less aggressive among those without overt CHD and two or more risk factors (LDL goal of <130 mg/dl) and least aggressive among those with no CHD and fewer than two risk factors (LDL goal of 160 mg/dl). Similarly, the JNC VI guidelines stratify interventions according to baseline risk[10] (see also Chap. 29) , while the American Diabetes Association recommends a tiered approach to management[11] (see Chap. 63) .

Incidence, Prevalence, and Population Attributable Risk

Sound public policy also requires evaluation of the impact of different factors on the *population*. Population risk depends not only on the strength of the factor-disease association and the benefit of intervention, but also on how common the factor is in the general population. These concepts are captured in incidence, prevalence, and population attributable risk. While incidence rates reflect the frequency of new cases of disease over a given period, prevalence reflects the proportion of individuals with a given condition or factor at a single point. Population attributable risk, or how much of the population's risk of disease is attributable to a given factor, is driven by the proportion of the public with a given risk factor and the magnitude of the associated risk.

Population attributable risk also reflects the shape of the relationship between the exposure and the disease. Many factors increase risk in a linear fashion, so population attributable risk can be computed against an ideal standard or a low-risk individual. For example, the relationship between hypertension and heart disease and stroke is linear. Thus, lowering blood pressure at any level in the pathological range reduces risk. In contrast, the shape of the risk curve for obesity appears nonlinear, with risk increasing logarithmically (Fig. 32-4) . Thus, each incremental pound gained is associated with much more risk in those who are already overweight. Population attributable risk is an important concept for determining resource allocation between various preventive interventions.

Implementation of Preventive Strategies

Three complementary approaches may be used to reduce the population burden of cardiovascular disease: (1) therapeutic interventions for secondary prevention in patients with known cardiovascular disease, (2) identification and targeting of high-risk individuals for primary prevention through mass screening or case finding, and (3) general recommendations disseminated throughout the population. Each of these approaches has merit in different situations. For example, targeted interventions such as specialized cardiac rehabilitation and life style programs show the greatest efficacy

among motivated individuals who hope to avoid a recurrent myocardial infarction, whereas mass screening programs for high blood pressure and hyperlipidemia are cost-effective. Population-wide campaigns against cigarette smoking offer an example of an effective public health approach.

Figure 32-4 Association between body mass index and relative risk of nonfatal myocardial infarction and fatal coronary heart disease among women. Light bars show the relative risks adjusted for age, and dark bars show the relative risks adjusted for age and smoking. The vertical lines represent 95 percent confidence intervals. (Reprinted, by permission, from Manson JE, Colditz GA, Stampfer MJ, et al: A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 322:882-889, 1990.)

Classification of Interventions for Modifiable Risk Factors

Implementation of preventive strategies requires a practical, systematic approach to prioritizing interventions and allocating resources. The American College of Cardiology's Bethesda conferences placed risk factors into four categories according to the likelihood that modification of the factor will result in lower risk.[12] These categories include (1) factors for which interventions have been proved to reduce risk; (2) factors for which interventions are likely to lower the incidence of events; (3) factors clearly associated with CHD risk that, if modified, might lower the incidence of coronary events; and (4) factors associated with CHD risk that cannot be modified or, if modified, are not likely to decrease risk (Table 32-2) . Adapting this useful classification scheme to clinical practice requires consideration of cost efficacy. We present a modified classification scheme of interventions for major modifiable risk factors that is based not only on the strength of the association and evidence of benefit of intervention but also on cost efficacy (Table 32-3) .

CLASS 1 INTERVENTIONS.

These interventions have a clear causal relationship with heart disease (Table 32-4) . Solid data, generally from randomized clinical trials, demonstrate the magnitude of the intervention's benefit, as well as its risks and cost. Cigarette smoking, hypercholesterolemia, and hypertension are causally related to CHD, and the corresponding interventions--smoking cessation, cholesterol reduction, and blood pressure management--are all cost-effective in both primary and secondary prevention. For management of hypertension and hyperlipidemia, extensive trial and cost efficacy data enable a tiered approach based on baseline absolute risk. Other pharmacological approaches proven to be beneficial and cost-effective include aspirin, beta blockers, and angiotensin-converting enzyme (ACE) inhibitors in secondary prevention and aspirin in some instances of primary prevention.

CLASS 2 INTERVENTIONS.

Class 2 includes interventions for which the available data (largely basic research and human observational studies) strongly indicate a causal relationship and suggest that intervention will probably reduce the incidence of events but for which data on the benefits, risks, and costs of intervention are limited. Class 2 factors that clearly increase the risk of CHD include diabetes, low HDL and high triglyceride levels, obesity, physical inactivity, and menopause. Light to moderate alcohol consumption appears to reduce the risk of CHD. Trial data on interventions are forthcoming for several of these factors,

TABLE 32-2 -- EVIDENCE SUPPORTING THE ASSOCIATION OF RISK FACTORS WITH CARDIO DISEASE, THE USEFULLNESS OF MEASURING THEM, AND THEIR RESPONSIVENESS TO INT

RISK FACTOR	EVIDENCE FOR ASSOCIATION WITH CVD			RESPONSE T
	Epidemiological	Clinical Trials	CLINICAL MEASUREMENT: USEFUL?	Nonpharmacological Therapy
Category I (Risk Factors for which Interventions Have Been Proved to Lower CVD Risk)				
Cigarette smoking	+++	++	+++	+++
LDL cholesterol	+++	+++	+++	+++
High-fat/high-cholesterol diet	+++	++	++	++
Hypertension	+++	+++ (Stroke)	+++	+
Left ventricular hypertrophy	+++	+	++	--
Category II (Risk Factors for which Interventions Are Likely to Lower CVD Risk)				
Diabetes mellitus	+++	+	+++	++
Physical inactivity	+++	++	++	++
HDL cholesterol	+++	+	+++	++
Triglycerides; small, dense LDL	++	++	+++	++
Obesity	+++	--	+++	++
Postmenopausal status (women)	+++	--	+++	--
Category III (Factors Associated with Increased CVD Risk that if Modified, Might Lower Risk)				
Psychosocial factors	++	+	+++	+

Lipoprotein (a)	+	--	+	--	
Homocysteine	++	--	+	++	
Oxidative stress	+	--	--	+	
No alcohol consumption	+++	--	++	++	
Category IV (Factors Associated with Increased CVD Risk but Cannot be Modified)					
Age	+++	--	+++	--	
Male gender	+++	--	+++	--	
Low socioeconomic status	+++	--	++	--	
Family history of earlyonset CVD	+++	--	+++	--	

+=weak, somewhat consistent evidence; ++=moderately strong, rather consistent evidence; +++=very consistent evidence; --=poor or nonexistent evidence. CVD=cardiovascular disease; HDL=high-density LDL=low-density lipoprotein.

Modified from Pearson TA, McBride PE, Miller NH, Smith SC: 27th Bethesda Conference: Matching th risk factor management with the hazard for coronary disease events. Task Force 8. Organization of pr cardiology service. J Am Coll Cardiol 27:1039-1047, 1996.

TABLE 32-3 -- CLASSIFICATION SCHEME FOR MODIFIABLE RISK FACTORS

Class 1

Basic research and human observational studies indicate a clear causal relationship

Intervention data (typically from randomized trials) demonstrate the magnitude of the benefit and risk

Interventions are cost-effective

Class 2

Basic research and human observational studies indicate a causal relationship

Intervention data from large-scale trials are limited

Lack of adequate intervention data precludes determination of cost-effectiveness

Class 3

Basic research and human observational studies demonstrate associations, but the independent nature of a causal relationship is not yet clear

Interventions are not yet available or have not been adequately tested

such as hormone replacement therapy after menopause. For other factors, such as

alcohol intake, there may never be data from large-scale randomized trials. Despite this limitation, class 2 interventions are useful in assessing global risk and have the potential to lower the risk of initial or recurrent CHD. While it makes sense to invest more resources to modify these factors in individuals at highest risk, guidelines for class 2 factors do not generally distinguish between high- and low-risk individuals.

CLASS 3 INTERVENTIONS.

These interventions are currently under active investigation. For many factors in this class, data are incomplete and an independent causal relationship with CHD cannot be inferred. For others, such as homocysteine and C-reactive protein, where data are promising, interventions are not yet available or widely tested even though causal relationships are apparent. Thus, while these factors may have utility for risk assessment, their role in preventing CHD is uncertain. For these reasons, dietary practices such as the consumption of nutritional supplements, psychological factors, and other novel biochemical and genetic markers are currently considered class 3 factors.

In several instances an intervention has proven efficacy in secondary prevention but data are not yet available to support that intervention in primary prevention. For this reason, a factor may be a class 1 intervention for secondary prevention but a class 2 intervention with respect to primary prevention.

CLASS 1 INTERVENTIONS

Cigarette Smoking (See Chap. 31)

PREVALENCE.

In the United States, per capita cigarette consumption rose dramatically in the first half of the 20th century. Over 65 percent of men born between 1911 and 1920 were smoking by 1945.[13] Annual per capita consumption of cigarettes hit an astonishing 4345 (more than 200 packs per year) in 1963.[14] The prevalence of smoking among adult men peaked at 55 percent in 1955 and, among women, 10 years later at 34 percent. [15] Since then, smoking rates have declined substantially, although the rate of decline differs by gender. Among men, smoking rates have declined by approximately half, while among women, rates have dropped by only one-third, primarily because of increasing smoking rates among women younger than 30 years. By 1997, approximately 27 percent of men aged 18 and older were current smokers, as compared with 22 percent of women.[16] Smoking rates tend to be higher among blacks, those with lower socioeconomic status, and those with a high school education or less.[16] Most alarming, smoking rates are increasing among children, with the prevalence of smoking among high school seniors rising from 30 percent in the mid-1980s to approximately 36.5 percent by 1997.[17]

ASSOCIATED RISK.

Smoking cigarettes increases the risk of CHD (see Chap. 31) . By the middle of the 20th century, seminal studies linking smoking and heart disease had been published by English and colleagues,[18] Doll and Hill,[19] and Hammond and Horn.[20] The Surgeon General's report in 1964 reaffirmed the epidemiological relationship between the two,[21] and by 1983 the Surgeon General firmly established cigarette smoking as the leading avoidable cause of cardiovascular disease.[22] The Surgeon General's 1989 report presented definitive data from observational case-control and cohort studies, largely among men, that demonstrated that smoking increases CHD mortality by 50 percent, that it doubles the incidence of CHD, and that the risk increases with age and with the number of cigarettes smoked.[14] Similar increases in the relative risk for CHD have been observed among women.[23] [24]

In the United States, cigarette smoking is the leading preventable cause of death and accounts for an estimated 430,000 deaths each year--more than 40 percent of which result from cardiovascular disease--and more than 7 million years of potential life lost.[25] Worldwide, smoking rates continue to rise, with the greatest increases in the developing world.[26] [27]

TABLE 32-4 -- CARDIOVASCULAR DISEASE RISK FACTORS AND INTERVENTIONS

RISK FACTOR	INTERVENTION	SECONDARY PREVENTION	PRIMARY PREVENTION
Cigarette smoking	Smoking cessation	Class 1	Class 1
High cholesterol	Cholesterol lowering	Class 1	Class 1
High blood pressure	Blood pressure management	Class 1	Class 1
	Aspirin therapy	Class 1	Class 2
	Beta blockers	Class 1	--
	ACE inhibitors	Class 1	--
	Oral anticoagulants	Class 1/2	--
Diabetes	Diabetes control	Class 2	Class 2
Low HDL	Increase HDL	Class 1/2	Class 2
High triglycerides	Triglyceride lowering	Class 2	Class 2
Physical inactivity	Increase activity	Class 2	Class 2
Obesity	Weight reduction	Class 2	Class 2
Menopause	Hormone replacement therapy	Class 2	Class 2

	Moderate alcohol consumption	Class 2/3	Class 2/3
Dietary factors	Improved diet	Class 3	Class 3

ACE=angiotensin-converting enzyme; HDL=high-density lipoprotein.

BENEFIT OF INTERVENTION.

While data from large-scale, randomized trials concerning the risk reduction associated with smoking cessation are limited, observational studies demonstrate clear benefits of smoking cessation. Smokers who quit reduce their excess risk of a coronary event by 50 percent in the first year or two after cessation, with much of this gain in the first few months. This period is followed by a more gradual decline, with the risk of former smokers approaching that of never smokers after 5 to 15 years.[28]

COST EFFICACY.

Smoking cessation is highly cost-effective. The intervention is usually short term and thus low cost. In fact, smoking cessation programs generally cost less than continued smoking. The gains in life expectancy are large, and the younger an individual stops smoking, the larger the potential gain--a 35-year-old male smoker may add 3 years to his life expectancy upon cessation. Costs vary, depending on the intensity of intervention and the use of pharmacological agents, with $1100 to $4500 (in 1995 dollars) spent for every QALY saved.[29]

GUIDELINES/RECOMMENDATIONS.

The U.S. Preventive Services Task Force recommends screening for smoking at every office visit.[30] Most people who give up smoking do not use an organized cessation program. Since the risks associated with smoking increase linearly with the number of cigarettes smoked, a modest reduction in smoking will probably reduce the risk. However, smoking reduction--as opposed to smoking cessation--is not an acceptable strategy, in view of the addictive nature of smoking and the tendency to increase smoking over time. The efficacy of smoking intervention programs ranges from a 6 percent 1-year success rate for physician counseling to 18 percent for self-help programs and 20 to 40 percent for pharmacological interventions with nicotine gum or patches. The use of antidepressant drugs also increases cessation rates.[31]

While it is important to counsel patients at all stages about the hazards of smoking and the benefits of quitting, the period soon after a cardiac event is an opportune time to encourage a patient to begin a smoking cessation effort.

FUTURE CHALLENGES.

In the United States, the prevalence of smoking is increasing among young women, particularly minority women. Worldwide, intense public health efforts are needed to reverse the alarming rise in smoking rates occurring in many developing countries.

Hypercholesterolemia (see also Chap. 31)

PREVALENCE.

Mean age-adjusted cholesterol levels have declined modestly in the United States since the early 1960s.[32] Even with this decline, the latest estimates suggest that half of all American adults have cholesterol levels greater than 200 mg/dl and that 20 percent of American adults have cholesterol levels of 240 mg or greater.[32] [33]

ASSOCIATED RISK.

Elevated serum cholesterol is causally associated with increased risk of CHD. Specifically, a 10 percent increase in serum cholesterol is associated with a 20 to 30 percent increase in risk for CHD, and elevations earlier in life may be associated with higher increases in risk.[34] [35] [36]

BENEFIT OF INTERVENTION (see Chap. 33) .

Clear benefits have been demonstrated for dietary and pharmacological treatments that lower serum cholesterol.[36A] Treatment aimed at lowering serum cholesterol by 10 percent reduces the risk of CHD death by 15 percent.[37] Treatment for more than 5 years yields a 25 percent reduction in CHD events.[36] Thus, long-term compliance is important for successful intervention.

Although early randomized trials generally showed a reduction in the risk of both fatal and nonfatal CHD in both primary and secondary prevention trials, some studies suggested that cholesterol lowering increased the risk of nonvascular mortality. Recently completed large-scale primary and secondary prevention trials using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) confirm the reductions in fatal and nonfatal CHD and also provide reassuring data that cholesterol reduction does not increase the risk of nonvascular mortality.[38] [39] [40] [41] [42] A recent meta-analysis of these five primary and secondary trials (30,817 participants and more than 166,000 person-years of follow-up) demonstrated that statin therapy reduced the risk of major coronary events by 31 percent and all-cause mortality by 21 percent, with similar reductions in men and women, as well as in those younger and older than 65.[43] Cholesterol-lowering trials also demonstrate reductions in stroke.[44] [45]

COST EFFICACY (see Chap. 2) .

The cost efficacy of nonpharmacological interventions to lower LDL cholesterol is unclear. Pharmacological intervention, however, is clearly cost-effective under certain conditions, and available data permit tailoring recommendations to the level of baseline CHD risk. Early analyses of cholesterol reduction for secondary prevention (which used data from cholestyramine trials) resulted in very costly interventions, largely because the available drugs were relatively ineffective. In contrast, data for statin therapy is remarkably consistent.

For example, in the Scandinavian Simvastatin Survival Study, the direct cost per life-year saved was $5400 for men and $10,500 for women.[46] As expected, cost decreased as the baseline cholesterol level increased. For example, the direct cost per life saved was $11,400 for a man with a baseline total cholesterol of 213 mg/dl (5.5 mmol/liter) and $6700 for a man with a cholesterol level of 309 mg/dl (8.0 mmol/liter). Furthermore, the direct cost tended to be lower with increasing age, a finding in stark contrast to estimates based on the Coronary Heart Disease Policy Model.[47] [48] In further analyses of the Scandinavian Simvastatin Survival Study, the indirect cost per life-year saved was $1600 for men and $5100 for women.[46] Thus, the overall, incremental costs of treatment for secondary prevention were very attractive by most standards.

Cost-effectiveness data regarding statin therapy in primary prevention are limited. The Coronary Heart Disease Policy Model made estimates for lovastatin[47] and found that favorable cost per life-year was largely confined to middle-aged men with multiple coronary risk factors. However, if ongoing analyses based on the West of Scotland Coronary Prevention Study[39] and the Air Force/Texas Coronary Atherosclerosis Prevention Study[41] find that direct costs decrease with age for primary prevention, as they did for the Scandinavian Simvastatin Survival Study analysis of secondary prevention, cost-effectiveness estimates may prove more favorable for primary prevention in the elderly than the middle-aged.

GUIDELINES/RECOMMENDATIONS.

All patients with cardiovascular disease should be screened for serum cholesterol levels. In primary prevention, some controversy remains regarding screening, with the NCEP recommending screening of all adults older than 20 years[10] and the American College of Physicians (ACP) recommending screening only for men ages 35 to 65 and women ages 45 to 65. [49]

TREATMENT.

To reduce the prevalence of hyperlipidemia in the United States, the NCEP issued its first *Adult Treatment Panel* report in 1988[50] and a second report in 1993. [9] A third report is under way. The current guidelines recommend nonpharmacological interventions for approximately 30 percent of American adults and cholesterol-lowering drugs for about 7 percent. The goals of intervention are based on the level of CHD risk for an individual (Fig. 32-5) .

For primary prevention, the NCEP recommends as first-line strategy a step 1 diet to lower fat intake to 30 percent of total calories, with saturated fat accounting for less than 10 percent of fat intake and cholesterol intake limited to 300 mg/d per day. Carbohydrates should account for 55

Figure 32-5 Algorithm for lipid-lowering therapy based on findings from intervention trials. CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides. *(From Ansell BJ, Watson KE, Fogelman AM: An evidence-based assessment of the NCEP Adult Treatment Guidelines Panel II guidelines. National Cholesterol Education Program. JAMA 282:2051-2057, 1999. Copyright 1999, American Medical Association.)*

percent of calories and protein for 15 percent. If after 3 months of dietary therapy the LDL goals are not met, the step 2 diet is recommended--less than 7 percent of calories from saturated fat and 10 percent from polyunsaturated fat with the remainder in monounsaturated fat (13 percent). Cholesterol intake is limited to 200 mg/d per day. Protein and carbohydrate intake is similar to step 1.

Since patients may find it difficult to understand percent calories, it can be helpful to translate these guidelines into grams of fat, protein, and other dietary constituents, the reporting of which is now mandated on labels of all food sold in the United States. Professional counseling with a dietitian may also be helpful. If dietary therapy does not achieve the target LDL level, drug therapy should be started (see Chap. 33) . In all cases, drug therapy should be an adjunct to dietary therapy and increased physical activity.

Guidelines from the European Society of Cardiology also have three tiers.[8] While the target is identical for all patients--total cholesterol of 190 mg/dl (5.0 mmol/liter) or less and LDL cholesterol of 115 mg/dl (3.0 mmol/liter) or less--the timing and intensity of drug therapy are different. For individuals with CHD, diet and drug therapy are initiated simultaneously. In primary prevention, if either the absolute 10-year risk of a CHD event or the projected risk at 60 years is greater than 20 percent, life style modifications are recommended and lipids are checked in 3 months (Fig. 32-6) . If at 3 months the total or LDL cholesterol level is above target, drug therapy may be instituted. For those with

Figure 32-6 Algorithm for lipid-lowering therapy devised by the Second Joint Task Force of European and Other Societies on Coronary Prevention. CHD=coronary heart disease; HDL=high-density

lipoprotein; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol. *(From Wood D, De Backer G, Faergeman O, et al: Prevention of Coronary Heart Disease in Clinical Practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. Eur Heart J 19:1434-1503, 1998.)*

a current or projected risk of less than 20 percent, life style advice but not drug therapy is recommended.

FUTURE CHALLENGES.

Additional randomized trial data will need to clarify the role of screening and treatment in older individuals and for stroke prevention. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) is currently testing whether reductions in plasma cholesterol levels with pravastatin will reduce the risk of major vascular events in approximately 5500 high-risk elderly subjects,[51] while the Risk Evaluation and Stroke Prevention in the Elderly--Cerivastatin Trial (RESPECT) is evaluating cerivastatin in the prevention of stroke. Although cholesterol levels are falling or stable in industrialized countries, they are rising in developing countries as "Western" diets are increasingly adopted.

Hypertension (see also Chaps. 28 , 29 , and 31)

PREVALENCE.

Approximately 30 percent of American adults are hypertensive, as defined by JNC VI.[32] [52] The prevalence of hypertension is greater among blacks than whites and among men than women; moreover, the prevalence of hypertension clearly increases with older age, from 9 percent of those aged 19 to 24 years to 75 percent of those older than 75 years.

ASSOCIATED RISK.

Elevated systolic or diastolic blood pressure is clearly associated with an increased risk of CHD (see Chaps. 28 , 29 , and 31) . The best estimates for the magnitude of associated risk derive from a meta-analysis of nine large prospective observational studies with 420,000 participants who accrued over 4850 CHD events during follow-up.[7] A 7-mm Hg increase in diastolic blood pressure over any baseline reading was associated with a 27 percent increase in CHD risk and a 42 percent increase in stroke risk. The shape of the risk curve is linear.

BENEFIT OF INTERVENTION.

For patients with malignant hypertension (defined as diastolic blood pressure greater than 115 mm Hg), the benefits of pharmacological intervention are clear and uncontroversial. Beginning in the late 1960s, a number of randomized trials confirmed the protective effect of treating mild to moderate hypertension, and these early trial data led to the establishment of treatment guidelines in the 1970s.[53] [54] The most precise estimates of risk reduction have come from meta-analyses reporting that lowering diastolic blood pressure by 5 to 6 mm Hg results in a 42 percent reduction in the risk of

stroke and a 15 percent reduction in the risk of CHD events.[5] [55] A number of studies have demonstrated the utility of life style interventions, in particular, weight reduction and exercise, in reducing blood pressure. However, these trials have generally lacked the power to demonstrate a reduction in coronary events.

COST EFFICACY (see Chap. 2) .

Detection and management of hypertension are highly cost-effective. In general, for agents such as diuretics and beta blockers, the cost is

TABLE 32-5 -- CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGED 18 AND OLDER,* WITH RECOMMENDATIONS FOR FOLLOW-UP

CATEGORY	SYSTOLIC BP (mm Hg)	DIASTOLIC BP (mm Hg)	FOLLOW-UP
Optimal	<120 and	<80	Recheck in 2 yr
Normal	<130 and	<85	Recheck in 2 yr
High-normal	130-139 or	85-89	Recheck in 1 yr
Hypertension§			
Stage 1	140-159 or	90-99	Confirm within 2 mo
Stage 2	160-179 or	100-109	Evaluate or refer to source of care within 1 mo
Stage 3	180 or	100	Evaluate or refer to source of care immediately or within 1 wk, depending on clinical situation

From The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD, National Institutes Of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program, NIH Publication 98-4080, 1997.

*Not taking antihypertensive drugs and not acutely ill.

Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

Provide advice about life style modifications.
§Based on the average of two or more readings taken at each of two or more visits after an initial screening.

below $10,000 per QALY for patients with established CHD, even when blood pressure is only mildly elevated.[56] In primary prevention, cost ranges between $10,000 and $20,000 per QALY among individuals with moderate to severe elevations in blood pressure. However, the cost approaches an unacceptable range of $100,000 per QALY for higher-priced medications. In contrast to some estimates for lipid lowering, cost efficacy decreases with increasing age.

GUIDELINES/RECOMMENDATIONS.

The U.S. Preventive Services Task Force recommends routine blood pressure testing of all adults.[30] The JNC VI[10] defines six levels of blood pressure according to the risk imparted (Table 32-5) .

Recommendations for intervention from the JNC VI are based on the level of blood pressure and the level of absolute risk (Table 32-6) . Three strata of absolute risk are defined according to the presence or absence of target organ disease, clinical cardiovascular disease, diabetes, and cardiovascular risk factors such as smoking, hyperlipidemia, age older than 60 years, gender, and family history of early-onset cardiovascular disease. The JNC VI set a blood pressure goal of 140/90 for lower-risk patients and 130/85 for those with cardiovascular disease, diabetes, or proteinuria. Since the relationship of blood pressure to risk of cardiovascular disease is linear, a significant portion of the population's attributable risk occurs among those with blood pressure above the JNC VI optimal level of 120/80 and below the level of true hypertension. For all individuals with blood pressure of 130/85 or greater, JNC VI recommends life style modifications, including smoking cessation, weight reduction if needed, increased physical activity, limited alcohol intake, limited sodium intake, maintenance of adequate potassium and calcium intake, and adoption of a low-fat diet.

Initiation of drug therapy should depend on blood pressure and the absolute level of risk. For example, among individuals with blood pressure as high as 140 to 159/85 to 99 but who show no evidence of end-organ damage, vascular disease, or diabetes and who have no cardiovascular disease risk factors, life style modification is recommended for up to 12 months. In contrast, individuals with blood pressure of 130/85 and end-organ damage, diabetes, or cardiovascular disease warrant early initiation of drug therapy. The specific therapeutic agents recommended by JNC VI are provided in Table 32-7 and discussed at length in Chapter 29 .

Guidelines from the European Society of Cardiology stratify initial therapy somewhat differently[8] (Fig. 32-7) . Drug therapy is recommended for individuals with less than 20 percent absolute risk and blood pressure in excess of 160/95 only after at least 6 months of life style modification; for individuals with greater than 20 percent absolute risk if their blood pressure exceeds 140/90 after 3 months of life style modification; and for individuals whose blood pressure exceeds 180/100, regardless of absolute risk. As with the JNC VI recommendations, life style modifications should always be used as an adjunct to drug therapy.

FUTURE CHALLENGES.

In the developed world, the prevalence of hypertension is increasing as these populations

TABLE 32-6 -- RISK STRATIFICATION AND THERAPY FOR HYPERTENSION

BLOOD PRESSURE STAGES (mm Hg)	RISK GROUP A (No Risk Factors, No TOD/CCD)	RISK GROUP B (at Least 1 Risk Factor, Not Including Diabetes; No TOD/CCD)	RISK GROUP C (TOD/CCD and/or Diabetes, with or Without Other Risk Factors)
High-normal (130-139/85-89)	Life style modification[L]	Life style modification	Drug therapy
Stage 1 (140-159/90-99)	Life style modification (up to 12 mo)	Life style modification (up to 6 mo)	Drug therapy
Stages 2 and 3 (>160/>100)	Drug therapy	Drug therapy	Drug therapy

TOD/CCD=target organ disease/clinical cardiovascular disease (see Table 32-4) .

From The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD, National Institutes Of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program, NIH Publication 98-4080, 1997.

Life style modification should be adjunctive therapy for all patients recommended for pharmacological therapy.

For those with heart failure, renal insufficiency, or diabetes.

For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus life style modifications.

TABLE 32-7 -- CONSIDERATIONS FOR INDIVIDUALIZING ANTIHYPERTENSIVE DRUG THERAPY

INDICATION	SUGGESTED PHARMACOLOGICAL THERAPY
Diabetes mellitus (type 1) with proteinuria	ACE inhibitors

Heart failure	ACE inhibitors, diuretics
Isolated systolic hypertension (older patients)	Diuretics (preferred), calcium antagonists (long-acting dihydropyridine)
Myocardial infarction	Beta blockers (nonintrinsic sympathomimetic activity)
	ACE inhibitors (with systolic dysfunction)
Angina	Beta blockers, calcium antagonists
Benign prostatic hyperplasia	Alpha blockers

ACE=angiotensin-converting enzyme.

From The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD, National Institutes Of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program, NIH Publication 98-4080, 1997.

age. In the United States, the proportion of hypertensives managed appropriately has recently decreased, thus reversing a two-decade trend.[10] In developing countries, hypertension rates are rising rapidly with urbanization and changes in life style habits. The attributable risk for hypertension tends to be greater in the developing world because the low rates of detection and treatment in such countries result in a proportionately higher rate of hypertensive heart disease and stroke.[57]

Cardiac Protection with Aspirin, Beta Blockers, ACE Inhibitors

Several pharmacological interventions have proved highly effective in the secondary prevention of cardiovascular disease. Pharmacological reduction of risk during or immediately after the development of CHD has been demonstrated for thrombolytic agents, aspirin, beta blockers, and ACE inhibitors.[58]

ASPIRIN IN SECONDARY PREVENTION (see also Chaps. 35 , 36 , and 62) .

Aspirin therapy in patients with existing cardiovascular disease reduces the risk of subsequent events by 25 percent.[59] Recent meta-analyses demonstrate clear reductions in mortality and nonfatal cardiovascular disease events among those with prior myocardial infarction,

Figure 32-7 Primary prevention guide to blood pressure management. BP=blood pressure; CHD=coronary heart disease; DBP=diastolic BP; SBP=systolic BP. *(From Wood D, De Backer G, Faergeman O, et al: Prevention of Coronary Heart Disease in Clinical Practice. Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Eur Heart J 19:1434-1503, 1998.)*

stroke, bypass surgery, angioplasty, peripheral vascular surgery, or angina.[59] [60] Unless contraindicated, aspirin should be used by most patients with known cardiovascular disease. Other antiplatelet agents with demonstrated efficacy such as ticlopidine and clopidogrel should be considered for patients with aspirin allergy or intolerance. However, the cost efficacy of these agents remains to be determined and will clearly be less favorable than the cost efficacy of aspirin. In primary prevention, aspirin is a class 2 intervention (see below).

BETA BLOCKERS.

A number of trials have demonstrated the long-term efficacy of beta blockade after myocardial infarction in reducing mortality,[61] [62] and meta-analyses provide good estimates of the size of that benefit.[63] In longer-term secondary prevention, beta blockers lower the risk of a recurrent cardiovascular event by 18 percent.[64] Cross-trial comparisons suggest that the higher the level of beta blockade, as measured by heart rate reduction relative to the control group, the greater the benefit. Beta blockade after myocardial infarction is also extremely cost-effective.[65]

ACE INHIBITORS.

The benefit of ACE inhibitors among individuals at high risk for CHD events is substantial. Following myocardial infarction, the use of ACE inhibitors is associated with a 7 percent reduction in mortality at 30 days,[66] [67] [68] while among individuals with a low ejection fraction after myocardial infarction, total mortality is reduced by 26 percent[58] (see also Chap. 35) . Higher doses may afford greater protection.[69] Currently, an ACE inhibitor should be used in any patient with depressed systolic left ventricular function of less than 40 percent (see also Chap. 18) . Findings from the Heart Outcomes Prevention Evaluation (HOPE) Study suggest that the benefits of ACE inhibitors extend to those with clinical CHD (see Chap. 37) and diabetes, even in the absence of left ventricular dysfunction.[70]

RECOMMENDATIONS.

For secondary prevention, aspirin, beta blockers, and ACE inhibitors are cost-effective and should be considered standard therapy in appropriate patients--aspirin for any patient with cardiovascular disease, beta blockers after myocardial infarction, and ACE inhibitors in patients with a low ejection fraction, as well as in others with cardiovascular disease and diabetes. All three agents are recommended for secondary prevention by the American Heart Association, American College of Cardiology, and the European Society of Cardiology.

CLASS 2 INTERVENTIONS

Class 2 interventions relate to risk factors that appear to have strong causal associations with CHD risk and for which intervention has the potential to reduce risk but for which intervention data are limited (see Table 32-4) . Factors in this category include diabetes, HDL and triglycerides, obesity, physical inactivity, postmenopausal hormones, alcohol intake, and aspirin in primary prevention. In general, cost efficacy data are not available because of a lack of adequate intervention data.

Diabetes (see also Chap. 63)

PREVALENCE.

In the United States, nearly 16 million people have diabetes mellitus (DM); approximately 90 percent of cases are type II DM.[71] Fully one-third of people with diabetes are not aware they have this disease. The prevalence of DM will increase with the adoption of new recommendations revising the definition of diabetes to include those with a fasting plasma blood glucose level of 126 mg/dl or higher.[72] In addition, the prevalence of diabetes appears to have increased over the last decade, which may be a reflection of increasing body mass index (BMI).[71]

ASSOCIATED RISK.

Diabetes increases the risk of atherosclerotic disease, and CHD is a major complication of both type I and type II DM. By age 40, CHD is the leading cause of death in both diabetic males and females,[73] and a recent survey found that CHD was listed on 69 percent of death certificates in a representative national cohort of adults with diabetes.[74] Age-adjusted rates for CHD are two to three times higher among diabetic men and three to seven times higher among diabetic women than among their counterparts without diabetes.[75] The onset of clinically apparent CHD in those with type I DM occurs at an early age, with markedly increased risk by the third decade of life; risk is clearly related to the duration of disease.[76] [77] In the Danish Steno Hospital Study, mortality from myocardial infarction alone was 12.5 percent after 35 years of diabetes regardless of the age of onset.[78] Thus, individuals with diabetes must be considered at high risk for CHD, regardless of the presence or absence of other risk factors.

BENEFIT OF TREATMENT.

Maintaining normoglycemia may reduce the risk of microvascular (renal and eye) disease. However, data demonstrating reduced risk of CHD with tight glycemic control are scant. In the Diabetes Complications and Control Trial (DCCT), an apparent reduction in CHD events among patients with type I DM assigned to intensive therapy did not achieve statistical significance, possibly because of the small number of events in this relatively young cohort.[79] While oral hypoglycemic agents and insulin can improve glycemic control, their role in the reduction of risk from macrovascular complications of type II DM remains unclear.[80] [81] Interestingly, the recent HOPE trial showed that ACE inhibitor therapy could reduce onset of diabetes.[70] [81A]

GUIDELINES/RECOMMENDATIONS.

Diet and exercise are integral components of the treatment strategy for patients with diabetes. In many patients with type II DM, glycemic control can be achieved by modest weight loss through diet and exercise.[82] While tight control with insulin in type I DM is appropriate, its role in the prevention of CHD among those with type II DM remains unclear.

In contrast to patients with type I DM, those with type II DM are much more likely to have multiple coronary risk factors than is the case in the general population. Thus, aggressive modification of associated risk factors--including treatment of hypertension, aggressive reduction of serum cholesterol, reduction of weight, and increased physical activity--is of paramount importance in reducing the risk of CHD among people with diabetes. In addition, aspirin[83] and ACE inhibitors[70] have been demonstrated to have clear efficacy in reducing coronary events in this population.

HDL and Triglycerides (see also Chaps. 31 and 33)

PREVALENCE.

Low HDL and high triglyceride levels tend to coincide and often result from metabolic phenomena that are distinct from those leading to high levels of LDL cholesterol. Thus, low HDL and high triglyceride levels can occur alone or in combination with high LDL levels.

ASSOCIATED RISK.

HDL cholesterol has emerged as an important independent predictor of CHD--every 1 mg/dl decrease in HDL cholesterol causes a 3 to 4 percent increase in coronary artery disease.[84] [85] [86] Furthermore, an emerging body of evidence indicates that the ratio of total or LDL cholesterol to HDL cholesterol may be a better predictor of CHD risk than LDL alone. Data from the Physicians' Health Study, for example, suggest that a one-unit

decrease in this ratio (which is easily achievable with statin drugs) reduces the risk of myocardial infarction by 53 percent.[87]

Imprecision in triglyceride measurements, within-individual variability, and complex interactions between triglycerides and other lipid parameters may obscure the impact of triglycerides in the development of CHD. However, fasting triglyceride levels represent a useful marker of the risk for CHD, particularly when HDL levels are considered.[88] Trial data testing interventional strategies specifically targeted at individuals with low HDL or

elevated triglycerides in the setting of normal LDL levels are limited.

BENEFIT OF INTERVENTION.

Data from the Helsinki Heart Study demonstrate that gemfibrozil, an agent that increases HDL and lowers triglyceride levels, reduces risk among those with high total and LDL cholesterol.[89] In the more recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a 22 percent reduction in cardiovascular events was observed with gemfibrozil treatment in a population with low HDL (<40 mg/dliter [1.0 mmol/liter]).[90] This risk reduction occurred in the absence of any substantial change in LDL cholesterol, data that support the potential for agents targeted at HDL and triglyceride levels.

RECOMMENDATIONS.

Screening of patients with cardiovascular disease should include a full lipid profile, including total cholesterol, HDL, and fasting triglycerides. For patients without cardiovascular disease, screening for HDL remains controversial, with the NCEP recommending screening and the ACP recommending against it. Because the ratio of total cholesterol to HDL cholesterol is a powerful predictor of risk and aids in the detection of individuals who have elevated LDL despite moderate levels of total cholesterol, it seems prudent to check HDL along with total cholesterol.

All patients with low HDL and/or high triglycerides should receive recommendations for life style modifications that include a diet low in saturated fat and increased physical activity. In secondary prevention, individuals with high LDL who also have low HDL or high triglycerides should be treated aggressively and consideration given to combination therapy (see Chaps. 31 and 33) . In primary prevention, nonpharmacological interventions are warranted for individuals who have a normal LDL level but a low HDL and/or high triglycerides because trial data regarding drug therapy in such cases are insufficient. Intervention data regarding patients with isolated elevated triglyceride levels are needed.

Physical Inactivity (see also Chap. 39)

PREVALENCE.

Physical activity is an exceptionally common modifiable risk factor for CHD. In a study of all CHD deaths occurring in the United States in 1986, more than 205,000 were attributable to physical inactivity, second only to the 253,000 attributable to hypercholesterolemia.[91] While the number of adults in the United States considered to be sedentary declined from over 40 percent in the early 1970s to approximately 27 percent by the early 1990s, more than three-quarters of adults do not exercise regularly or take part in leisure time physical activity.[92] Older individuals, who are most at risk for cardiovascular disease, are less likely to be physically active than younger individuals, and women tend to be less active than men.

ASSOCIATED RISK.

Morris and colleagues first reported in the mid-1950s that CHD rates were lower among bus conductors and mail carriers than sedentary bus drivers and postal supervisors.[93] By incorporating estimates of leisure time activity in their analyses, these investigators found that civil servants with sedentary jobs who engaged in vigorous sports were half as likely to suffer myocardial infarction than were those who did not engage in leisure time physical activity.[94] Since then, a number of observational studies have reported similar inverse associations between activity level from work or play and CHD. In a meta-analysis of 27 observational cohort studies, the risk of CHD in sedentary individuals was almost twice that of active individuals after controlling for other coronary risk factors.[95] Long-term prospective studies of men and women consistently demonstrate that regular physical activity protects against death from CHD.[96] [97] [98] These benefits apply to activities as simple as brisk walking, which has been shown to reduce the risk of CHD in women[99] and men,[100] as well as the risk of type II diabetes.[101] Shifting even late in life from a sedentary life style to a more active one confers a reduction in mortality from CHD.[102] Physical activity is also associated with a decreased risk of stroke in men,[103] [104] primarily because of its beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance.

While no large-scale, randomized trials of physical activity are available, numerous trials of moderate size and duration have been conducted among healthy individuals, those at high risk for cardiovascular disease, and those with existing cardiovascular disease. Despite differences in design, these trials generally demonstrate a benefit.[105] The ideal intensity, frequency, and duration of physical activity, however, have still not been determined.

BENEFIT OF INTERVENTION.

While cessation of activity appears to result in increased risk of CHD, the lack of large-scale, randomized, primary prevention trials on the benefits of physical activity makes it difficult to determine the precise benefit of exercise in terms of CHD reduction. Physical activity does, however, have clearly demonstrated benefits on cardiovascular risk factors. Exercise increases HDL, reduces LDL[106] and triglycerides, increases insulin sensitivity,[107] and reduces resting blood pressure. [108]

In secondary prevention, cardiac rehabilitation programs with an exercise component tend to report benefit in reducing subsequent events. Pooled data from many of these trials suggest reductions in total and cardiovascular mortality of about 25 percent.[109]

RECOMMENDATIONS.

The U.S. Preventive Services Task Force recommends a discussion of physical activity with all patients. All patients, including those with cardiovascular disease, should be strongly encouraged to engage in regular physical activity.[109A] Structured exercise programs may enhance long-term compliance. For primary prevention, the surgeon

general's recommendation is an excellent starting point--every adult should accumulate 30 minutes of moderately intense physical activity on most, if not all days of the week.[92]

Obesity

PREVALENCE.

Since the late 1970s, the proportion of the U.S. population considered to be overweight (BMI
25.0) has risen dramatically from 43.3 percent in 1960 to 1962 to 54.9 percent in 1988 to 1994.[110] In the last decade of the 20th century, the proportion of people considered obese (BMI
30) increased from 12.0 percent in 1991 to 17.9 percent in 1998.[111] Obesity among children is also on the rise,[112] an alarming trend in view of the fact that early obesity is a strong predictor of later cardiovascular disease.[112A]

ASSOCIATED RISK.

Because of the use of various measures of obesity, reports on the magnitude of the association between obesity and CHD are conflicting. Considerable dispute on the independent status of obesity as a risk factor has also arisen because the impact of obesity on CHD risk

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may be mediated, at least in part, by other coronary risk factors such as hypertension, dyslipidemia, glucose intolerance, and possibly hemostatic factors. In prospective studies in men, obesity appears to have an independent effect even after controlling for other risk factors.[113] Among women, greater than a threefold increased risk of fatal and nonfatal CHD is noted in those with the highest BMI (BMI
29), as well as an 80 percent increase in CHD in moderately overweight women (BMI of 25 to 29) when lipoprotein abnormalities, blood pressure, and diabetes are not included in multivariate models.[114] Whether any increased risk associated with obesity remains after controlling for these factors is uncertain. However, obesity is clearly associated with CHD and is an important and easily assessed marker of risk. The distribution of body fat may also play a role in the development of CHD, with abdominal adiposity posing a substantially greater risk in both women[115] and men.[116] A waist circumference of 35 inches in women and 40 inches in men is an easily measured marker of increased CHD risk.

BENEFIT OF INTERVENTION.

No large-scale trials of weight reduction as an isolated intervention are available on which to estimate the benefits of this intervention. However, in view of the clear improvements in glucose tolerance, blood pressure, and lipoprotein profile with weight

loss, it is generally agreed that weight reduction has an important role in primary and secondary prevention programs.[105] [117] There is little consensus, however, on the ideal approach to weight reduction.[117A] Promoting life style changes to encourage weight reduction has been universally disappointing. While 25 percent of American men and 43 percent of American women may attempt to lose weight in any given year,[118] failure rates are exceedingly high. One reason may be that most individuals who are trying to lose weight are not following guidelines established by the National Heart, Lung, and Blood Institute[117] to reduce calorie intake and engage in at least 150 minutes of leisure time activity per week.[118] Effective treatment strategies generally involve a multifaceted approach, including dietary counseling, behavioral modification, increased physical activity, and psychosocial support.[119] [120] [121] Without precise estimates of the benefit and with substantial variability in the intervention strategy, it is currently impossible to estimate the cost/benefit ratio of this intervention.

RECOMMENDATIONS.

Weight reduction programs that include a structured exercise component should be considered in primary prevention for all obese (BMI >30) patients and in most overweight (BMI >25) patients with a history of CHD.

Postmenopausal Estrogen Therapy (see also Chap. 58)

RISK ASSOCIATED WITH MENOPAUSE.

In the United States, CHD is the number one cause of death in women by age 60.[122] While men exhibit a higher incidence of CHD at every age, as well as higher mortality rates from it, the gap narrows substantially after both natural menopause and bilateral oophorectomy.[123] Women seen with a first myocardial infarction tend to be older and have higher mortality than men with a first myocardial infarction. However, after adjustment for age and other indicators of severity and comorbidity, these differences are greatly attenuated.[124]

A wide range of factors may explain the increased risk of CHD after menopause, including adverse changes in lipid and glucose metabolism that result in an increase in LDL cholesterol and a decrease in HDL cholesterol, an increase in glucose intolerance, and changes in hemostatic factors and vascular function.[123] Endogenous estrogens appear to play a major role in reducing the risk of CHD in women. Substantial improvement in the lipoprotein profile, along with a reduction in LDL and an increase in HDL, is observed following the initiation of hormone replacement therapy.[125] [126] In addition, there appear to be protective effects on vascular function, as well as an apparent estrogen-related protection of LDL from oxidation.[127] Estrogens may also play one or more roles in maintaining normal hemostasis and improving glucose tolerance.

EFFECTS OF INTERVENTION.

The association between postmenopausal hormone therapy and CHD risk has been widely studied in case-control and prospective cohort studies. Overviews suggest that

treatment with estrogen reduces the risk of CHD by 44 percent.[128] [129] In the Nurses' Health Study, the largest prospective cohort study to address this question, current users of estrogen had about half the risk of CHD (relative risk, 0.51; 95 percent confidence interval, 0.37 to 0.70) as nonusers did.[130] The association appears even stronger among women with known CHD.[131] However, these data are limited by their observational nature, and it is quite possible that women who self-select for estrogen therapy engage in other protective behavior that confounds this relationship.

Large-scale, randomized trial data in primary or secondary prevention are inadequate to fully assess the risks and benefits of postmenopausal hormone replacement. Recent data from the Heart and Estrogen/Progestin Replacement Study (HERS) suggested that among women with underlying CHD, combined estrogen and progesterone did *not* result in a reduction in cardiovascular events after 4 years of treatment.[126] In primary prevention, the ongoing Women's Health Initiative[132] will address the risks and benefits of treating postmenopausal women with estrogen alone, as well as the use of estrogen and progestin in combination, versus placebo. The use of selective estrogen receptor modulators and phytoestrogens in cardiovascular risk prevention remains unproven (see also Chap. 58) . [132A]

RECOMMENDATIONS.

Until more definitive data are available, decisions to begin hormone replacement therapy should be based on a woman's baseline risk for cardiovascular and other diseases, such as hyperlipidemia, as well as her personal preferences.[133] On the basis of current data, there is no mandate to either initiate or discontinue hormone replacement therapy in view of the complex balance of potential benefits and risks.

Moderate Alcohol Consumption

Alcohol consumption has complex effects on cardiovascular disease. Observational studies demonstrate that heavy alcohol intake increases total mortality[134] [135] and cardiovascular disease mortality,[136] [137] while moderate alcohol intake appears to exert a protective effect on CHD in comparison to no alcohol intake in both primary[138] [139] [140] [141] and secondary prevention.[142] Mechanisms underlying the effect of moderate alcohol consumption, defined as one to two drinks daily, include raising HDL levels,[143] [144] as well as improving fibrinolytic capacity[145] [146] and reducing platelet aggregation.[147]

RECOMMENDATIONS.

While the association of alcohol and CHD is likely to be causal, any individual or public health recommendation must consider the complexity of alcohol's metabolic, physiological, and psychological effects. With alcohol, the difference between daily intake of small to moderate quantities and large quantities may be the difference between preventing and causing disease. For appropriate patients, a discussion of alcohol intake can be a part of routine preventive counseling. In general, one or two drinks per day may be safe for men. For women, because

of their generally smaller BMIs and potential differences in liver metabolism, lower levels may be more prudent. However, counseling must be individualized--other medical problems, including other coronary risk factors (particularly hypertension and diabetes), liver disease, tendency toward excess use, family history of alcoholism, and possibly a family history of breast and colon cancer, should be taken into account when discussing alcohol consumption.

Aspirin in Primary Prevention (see also Chap. 62)

Four large-scale trials, performed primarily in men, have assessed the benefits of low-dose aspirin in the prevention of cardiovascular disease.[148] [149] [150] [151] Taken together, these studies suggest a benefit of prophylactic aspirin in primary prevention among men; however, concerns over increased risk of hemorrhagic stroke have not been fully assessed.[152] For women, the Women's Health Study, which is scheduled to end in 2001, is addressing the benefit-to-risk ratio of aspirin therapy for primary prevention of cardiovascular disease.

RECOMMENDATIONS.

While aspirin in doses between 81 and 365 mg daily is widely used, both the American Heart Association[153] and the U.S. Preventive Services Task Force[30] agree that the data are still insufficient to recommend this approach for the primary prevention of cardiovascular disease in healthy individuals. However, both these groups acknowledge that the benefits may outweigh the possible harm (particularly hemorrhagic stroke) in those with risk factors for cardiovascular disease. The European Society of Cardiology recommends low-dose aspirin (75 mg) in primary prevention only for men at particularly high risk of CHD.[8]

Oral Anticoagulants (see also Chap. 62)

Oral anticoagulants prevent embolic events in patients with prosthetic heart valves and atrial fibrillation. Less certain is their role, either alone or in combination with aspirin, in the secondary prevention of events in those with CHD. The results of randomized controlled trials are inconsistent, a troubling issue because oral anticoagulants have significant bleeding side effects.

A recent meta-analysis provided a comprehensive summary of existing data on high-, moderate-, and low-intensity oral anticoagulants alone or in combination with aspirin versus placebo or aspirin alone.[154] In this analysis, high- and moderate-intensity oral anticoagulation reduced myocardial infarction and stroke rates when compared with placebo but increased the risk of hemorrhage. The combination of low-intensity oral anticoagulation plus aspirin did not appear to confer any benefit over aspirin alone, while the combination of moderate- or high-intensity oral anticoagulation plus aspirin did appear to offer promising benefits. These findings require confirmation from ongoing

clinical trials.

CLASS 3 INTERVENTIONS

Class 3 interventions relate to risk factors that are currently under investigation (see Table 32-4) . For some of them, a causal relationship with CHD cannot be determined because of limited data. For others, where causal relationships are apparent, interventions are not yet available or tested.

Diet

Diet is an important component of any prevention program inasmuch as weight reduction can improve dyslipidemia, hypertension, and diabetes. One of the most consistent findings in dietary research is that individuals who consume higher amounts of fresh fruits and vegetables have lower rates of heart disease[155] and stroke. [156] The U.S. Department of Agriculture recommends two to four servings of fresh fruit and three to five servings of fresh vegetables per day.

Two randomized clinical trials of dietary interventions are worth noting. In the Dietary Approaches to Stop Hypertension (DASH) Trial, 459 adults with systolic blood pressure less than 160 mm Hg and diastolic pressure less than 80 to 95 mm Hg were randomized to (1) a control diet low in fruits, vegetables, and dairy products and with a fat content of 37 percent; (2) a diet rich in fruits and vegetables; or (3) a combination diet rich in fruits, vegetables, and dairy products. Both of the intervention diets substantially reduced systolic and diastolic blood pressure in individuals with and without hypertension.[157] The Lyon Diet Heart Study randomized 605 survivors of a first myocardial infarction to a Mediterranean-type diet or a "prudent Western-type diet." After a mean follow-up of 46 months, the risk of cardiac death or acute myocardial infarction was 65 percent lower for those consuming the Mediterranean diet.[158]

Low-fat diets have been shown to reduce the risk of myocardial infarction in healthy individuals and may even cause regression of coronary artery disease.[159] In the opposite direction, saturated and *trans*-fatty acids[160] appear to increase the risk of CHD. Not surprisingly, there is lively controversy over the health effects of the amount and type of fat and carbohydrates. While it is generally agreed that a reduction in saturated fat intake reduces the risk of CHD, it is unclear whether it is best to replace these fats with complex carbohydrates or monounsaturated or polyunsaturated fats.

Specific Nutrients

Specific foods and micronutrients under investigation as agents for reducing the risk of cardiovascular disease include whole grains, fiber, fish and fish oils, folate, vitamin B_6 , antioxidants such as vitamin E, and soy protein. Observational studies tend to report lower rates of CHD events among those who take antioxidant vitamins and perhaps folate supplements; however, studies are inconsistent and the effects are modest.

ANTIOXIDANT VITAMINS.

Basic research strongly suggests that oxidative stress plays an important role in the development of atherosclerotic disease and that vitamin E may delay or prevent various steps in atherosclerosis. Human observational data are compatible with the possibility that vitamin E intake from either foods or supplements may reduce the risk of cardiovascular disease. However, randomized trial data are not yet sufficient to fully assess the role of vitamin E, vitamin C, or other antioxidants in the primary or secondary prevention of atherosclerotic disease. Most trials to date have been relatively short, particularly with respect to primary prevention. In addition, studies vary greatly in the dose and form of antioxidant vitamins. Recently completed secondary prevention trials raise the possibility that some of the benefit from observational epidemiology may have been overestimated.[161] [162]

The evidence available does not establish that vitamin E reduces the risk of cardiovascular disease. Longer follow-up of the completed trials, as well as ongoing trials, will provide valuable information upon which rational clinical decision-making for individuals and policy for the health of the general public can be reliably based. Although it remains unclear whether antioxidant supplementation will reduce the risks of chronic disease, consumption of fruits and vegetables high in these micronutrients is an important part of a healthy diet.

Psychosocial Factors (see also Chaps. 31 and 70)

Psychosocial factors such as depression,[163] [164] absence of social support,[165] and anger appear to contribute to an elevated risk of CHD, although further data are needed to confirm these relationships and establish the efficacy of interventional strategies.

Studies of therapeutic interventions, while not blinded, suggest a role for improving psychosocial factors as part of prevention programs, particularly in secondary prevention. The strongest evidence comes from post-myocardial infarction patients.[166] While abundant data suggest that stress and depression are prevalent and predict events after myocardial infarction, data on interventions are limited. A recent meta-analysis of 37 small studies of health education and stress management programs for CHD patients suggested that such efforts might reduce cardiac mortality by 34 percent and recurrent myocardial infarction by 29 percent, quite possibly through favorable effects on blood pressure, cholesterol, body weight, smoking behavior, physical activity, and dietary habits.[166] Trials of antidepressants following myocardial infarction are under way.

Novel Biochemical and Genetic Markers

Hemostatic and inflammatory markers, novel lipid parameters, cellular adhesion

molecules, indicators of prior infection, and markers of oxidative stress have all been linked to steps in atherogenesis, thrombosis, or cardiovascular disease events (see Chap. 30) . Several of these factors, such as C-reactive protein, fibrinogen, and extracellular adhesion molecules, are independent markers of coronary risk that add to the predictive value of cholesterol screening, whereas other factors such as homocysteine are easily treated with vitamin supplementation. The potential clinical utility of these markers[167] and current evidence regarding their modification are covered in Chapter 31 .

Thanks to recent advances, it is now possible to explore a number of gene polymorphisms that are associated with various coronary risk factors or directly with cardiovascular events. While genetic screening holds great promise for identifying individuals at risk for subsequent events, its role in primary or secondary prevention remains unclear. However, one can envision a time when genetic assays will play a role in identifying at-risk individuals and targeting therapies to reduce their risk of subsequent events.[168]

MULTIPLE-RISK FACTOR INTERVENTION PROGRAMS

While most prevention studies focus on changing a single factor, several have attempted to measure the impact of simultaneously changing multiple risk factors. In theory, the potential for synergistic effects between risk factors could lead to substantial reductions in risk that are multiplicative and offer the possibility of meaningful reductions in the risk of cardiovascular disease.[169]

Although these multiple-risk factor intervention trials (Table 32-8) have made major contributions to our understanding of cardiovascular risk, as well as our knowledge of what makes for effective--and ineffective--intervention strategies, their results have been mixed. It is clear that intervention on multiple levels can reduce risk factors and that this reduction can be sustained over time (Fig. 32-8) . In a Belgian study that was part of the World Health Organization (WHO) European Collaborative Trial in the Multifactorial Prevention of Coronary Heart Disease,[180] an intervention program composed of face-to-face counseling about eating habits, smoking, and physical activity substantially reduced predictors of coronary risk when compared with a control program that offered no such advice. The effect was sustained for 5 years.

A common result from multiple-risk factor intervention trials is a change in risk factor levels or composite scores among those receiving intervention. However, this change has not always translated into lower event rates. Explanations for this inconsistency include the possibility that the magnitude of intervention was too small or that control patients may also have improved their health habits over time. What is clear from these trials, however, is that multiple simultaneous interventions can reduce cardiovascular risk when the planned interventions are large enough and are adequately implemented.

In an analysis of seven multiple intervention trials, Kornitzer plotted change in the multiple logistic function of

Figure 32-8 In a multiple-risk factor intervention trial among workers in two Belgian factories, one receiving face-to-face advice on life style modification and the other receiving no such advice, a sustained and statistically significant reduction in the composite risk of coronary heart disease (CHD) was observed in the intervention group over the first 5 years of the 6-year study period. *(From Kornitzer M, De Backer G, Dramaix M, et al: Belgian heart disease prevention project: Incidence and mortality results. Lancet 1:1066-1070, 1983. © by The Lancet Ltd., 1983.)*

TABLE 32-8 -- MULTIPLE INTERVENTION TRIALS

TRIAL	POPULATION	INTERVENTION	CHANGE IN RISK FACTOR(S)	IMPACT ON ENDPOINT(S)
Multiple Risk Factor Intervention Trial[170]	12,866 men aged 35-57 at high risk for CHD; average 7-yr follow-up	Stepped care therapy for high BP, counseling for smoking cessation, and dietary advice for high cholesterol; *or* usual care	Coronary risk factors declined in both groups, though to a greater degree in intervention group	Nonsignificant change in CHD death: 17.9/1000 in intervention group, 19.3/1000 in usual care group
Oslo Trial[171]	1232 men aged 40-49 with coronary risk in upper quartile; 5-yr follow-up	Diet similar to AHA step 1, counseling to stop smoking; *or* usual care	LDL-C (13%), triglycerides (20%), tobacco consumption (45%), and weight were lower in intervention group than usual care group; in both groups, physical activity and BP unchanged vs. baseline	Significant reduction in fatal MI, nonfatal MI, sudden death, and cerebrovascular accidents in intervention vs. control; 55% decrease in CHD death and 32% decrease in total mortality

WHO Multifactorial Trial[172]	60,881 men aged 40-59 from 80 factories in Belgium, Italy, Poland, and United Kingdom; average 6 yr of intervention and follow-up	Educational materials or individual counseling regarding diet, smoking cessation, physical activity, and BP; drug therapy as needed for BP control; *or* no intervention	Coronary risk predictors were significantly lower in intervention group during first 5 yr of trial; by trial's end, differences were statistically significant only for high-risk subjects who received face-to-face counseling	Nonsignificant differences in all-cause mortality (-5.3%), total CHD (-10.2%; *p*=0.07), fatal CHD (6.9%), and nonfatal MI (-14.8%; *p*=0.06) for intervention group vs. nonintervention group
North Karelia Project[173]	11,992 men and women aged 25-59; 10-yr follow-up	Population-based prevention program with outreach for a smoking cessation, reducing BP and serum cholesterol and other CVD risk factors	In intervention group, 28% decrease in smoking, 3% decrease in serum cholesterol, and 3% decrease in BP vs. reference group	Age-adjusted CHD mortality decreased 22% in intervention group, 12% in reference group, and 11% in all of Finland (*p*0.05)
Goteborg Primary Prevention Trial[174]	Random sample of 20,000 men aged 47-55; average 10 yr of intervention and follow-up	Antihypertensive treatment in subjects with SBP >175 mm Hg or DBP >115 mm Hg, dietary advice for subjects with serum cholesterol levels >260 mg/dl, and smoking cessation advice; *or* usual care	BP, serum cholesterol, and smoking all decreased markedly in both intervention and control groups	No significant differences in total mortality, stroke, and CHD incidence

Minnesota Heart Health Program[175]	400,000 residents aged 30-74 of 6 (3 paired) Midwestern communities; 5- to 6-yr intervention program	Individual counseling and community outreach on decreasing BP and serum cholesterol, smoking cessation, and increasing physical activity; *or* no intervention	Generally favorable, though not statistically significant changes in intervention group vs. reference group	No significant difference in CAD death rate
Pawtucket Heart Health Program[176]	140,000 residents aged 18-64 of Pawtucket, RI, and a reference community; 7-yr intervention program	Community-wide educational programs designed to help individuals lower cholesterol and BP, stop smoking, maintain healthy weight, and increase physical activity	Small, not statistically significant decreases in serum cholesterol and BP in Pawtucket; slightly less smoking in the reference community	Projected CVD rates significantly (16%) less in Pawtucket during education program, but dropped to 8% after education program
Stanford Five-City Project[177]	320,300 residents of 5 California cities (2 intervention, 3 comparison); 5-yr intervention program	Individual counseling and community outreach regarding decreasing BP and serum cholesterol, smoking cessation, and increasing physical activity.	Statistically significant reductions in community averages of plasma cholesterol level (2%), BP (4%), resting pulse rate (3%), and smoking rate (13%) in intervention communities vs. reference communities	Decreased composite total mortality risk scores (15%) and CHD risk scores (16%) in intervention communities vs. reference communities

Lifestyle Heart Trial[169]	48 men and women aged 35-75 with ischemic heart disease; 4-yr intervention and follow-up	Low-fat vegetarian diet, moderate aerobic exercise, stress management training, smoking cessation, and group support; *or* usual care	After 4 yr, participants in intervention group were exercising more, practicing more stress management, and consuming less cholesterol and fewer fat calories than those in usual care group	In intervention group after 4 yr, significant reductions in frequency, duration, and severity of angina; fewer revascularizations (21% vs. 60%); and regression of atherosclerotic lesions (vs. continued worsening in usual care group)
Heidelberg Trial[178]	113 men and women recruited after coronary angiography for stable angina pectoris; 6-yr intervention and follow-up	Intervention group: AHA step 3 diet, 30 min of exercise daily, and two 60-min group counseling sessions per week; *or* advice about the AHA step 1 diet and encouragement of moderate aerobic exercise	Nonsignificant reductions in total cholesterol and triglycerides, maintenance of BMI, and significant increase in physical work capacity among those in intervention group	As assessed by coronary arteriography, significantly slower progression of coronary artery stenosis in intervention group, combined with significant improvements in myocardial perfusion
Stanford Coronary Risk Intervention Project[179]	300 men and women under age 75 without severe congestive heart failure, pulmonary disease, intermittent claudication, or noncardiac life-threatening illness	Low-fat diet (<20% of calories from fat and <75 mg of cholesterol/d), physical activity, and counseling for smoking cessation, with cholesterol-lowering medication as needed; *or* usual care with personal physician	Significant improvements in percent body fat, weight, BP, LDL-C, triglycerides, HDL-C, and exercise capacity in treatment group vs. controls	Although progression of coronary artery disease occurred in both groups, intervention group had a 47% lower rate of progression per individual and a 58% lower rate of progression in diseased vessel segments than reference group did

AHA=American Heart Association; BMI=body mass index; BP=blood pressure; CAD=coronary artery disease; CHD=coronary heart disease; CVD=cardiovascular disease; DBP=diastolic BP; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; SBP=systolic BP; WHO=World Health Organization.

TABLE 32-9 -- MODIFIABLE RISK FACTORS FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

Class 1 Risk Factors and Interventions in the Prevention of Cardiovascular Disease

FACTOR	EFFECT	INTERVENTION	COMMENT
Smoking	2- to 3-fold increased risk	Smoking cessation with behavior and pharmacological intervention	Smoking cessation results in a 60% reduction in CHD risk by 3 yr; about half of that benefit occurs in first 3-6 mo after quitting. Interventions are costeffective in both primary and secondary prevention
Hypercholesterolemia	10% increase in serum cholesterol increases risk of CVD by 20-30%	Dietary changes, lipid-lowering medications	Reduction in serum cholesterol by 10% reduces CVD death by 10% and CVD events by 18%. Treatment for >5 yr reduces CVD events by 25%. Extensive trial and cost efficacy data support a tiered approached based on underlying risk
Hypertension	7-mm Hg increase in BP over baseline increases risk of CVD by 27%	Life stye modifications, weight loss, limited alcohol intake, aerobic exercise, and medications	A 5- to 6-mm Hg reduction in BP results in 42% reduction in risk of stroke and 16% reduction in risk of CVD. Extensive trial and cost efficacy data support a tiered approached based on underlying risk.

Pharmacological Therapies

Aspirin in secondary prevention	Reduces CVD events by 25%	Daily low-dose aspirin	Reduces risk among those with any form of CVD
Beta blockers following MI	Reduces CVD events by 18%	Daily beta blocker use	Trial data suggest that the benefit may increase with increasing dose.
ACE inhibitors for patients with low EF and following MI	Reduces CVD events by 22% in those with low EF and by 7% following MI	Daily ACE inhibitor use	Trial data suggest that the benefit may increase with increasing dose

Class 2 Risk Factors and Interventions in the Prevention of Cardiovascular Disease

FACTOR	EFFECT	INTERVENTION	COMMENT
Insulin-dependent diabetes	Increases risk 2- to 4-fold in men and 3- to 7-fold in women	Maintaining normoglycemia with diet, exercise, weight management, and insulin	Trial data strongly suggest that tight control with insulin reduces risk of microvascular disease and may reduce the risk of CVD events
Noninsulin-dependent diabetes	Increases risk 2- to 4-fold in men and 3- to 7-fold in women	Maintaining normoglycemia with diet, exercise, weight management, oral agents, and insulin as needed	Tight control appears to reduce microvascular disease, but data on the risk of CHD are not available. Those with NIDDM are likely to have multiple coronary risk factors that should be aggressively modified
Elevated fasting triglyceride levels and lower HDL levels	Increases risk	Diet, exercise, and lipid-lowering therapy	HDL and triglyceride measures are useful markers of CHD risk, and limited trial data suggest that intervention reduces risk
Obesity and physical inactivity	Increases risk	Diet, exercise, and weight management programs	In addition to improving other CVD risk factors, maintaining ideal body weight and a physically active life style may reduce risk of MI as much as 50%, but trial data are limited

Menopause	Increases risk	Hormone Replacement Therapy (HRT)	HRT in postmenopausal women may reduce risk of CVD by 40-50%; however, risk of endometrial or breast cancer may increase. Trial data are limited
Moderate alcohol intake (one drink per day)	Decreases risk of MI by 30-50%	Discussion of alcohol intake with all patients	Risk/benefit ratio for moderate alcohol consumption may vary widely by gender and is based on underlying risk of CHD. Recommendations must be made individually with careful regard for conditions such as hypertension, diabetes, liver disease, history of alcohol abuse, risk of breast cancer, etc.
Pharmacological Therapies			
Aspirin in primary prevention	Pooled trial data in men suggest a 33% reduction in risk of first MI	Daily or alternate-day low-dose aspirin	Prophylactic aspirin use in older men, particularly with risk factors, may reduce risk of MI. Data among women are limited but forthcoming

Class 3 Factors and Interventions in the Prevention of Cardiovascular Disease

CATEGORY	SPECIFIC FACTORS	COMMENT
Dietary factors	Fruit and vegetable intake, type and amount of fat, type and amount of carbohydrate, fiber, *trans*-fatty acids, dietary antioxidants, dietary bioflavonoids, dietary folate, fish and fish oils, garlic, etc.	USDA recommends 5 servings of fruit and vegetables per day. Reduction in saturated and *trans*-fatty acid intake appears to be warranted
Dietary supplements	Multivitamins, antioxidant supplements, folate, vitamins B_{12} , and B_6 , fish oils, etc.	Randomized trials of antioxidant supplements have been disappointing. Randomized trial data on antioxidants and folate are forthcoming
Psychological factors	Depression, lack of social support, stress, type A personality, etc.	Trials of antidepressants in secondary prevention are forthcoming

Novel biochemical markers	Fibrinogen, homocysteine, LP(a), t-PA, von Willebrand factor, factor VII, C-reactive protein, soluble adhesion molecules (sICAM, sVCAM), antibodies to various infectious agents, measures of oxidative stress, etc.	Additional observational data are needed to clarify the role of these factors in clinical practice
Genetic markers	LDL receptor, factor V Leiden, ACE, etc.	Potential genetic markers and therapies are emerging at a rapid rate

ACE=angiotensin-converting enzyme; BP=blood pressure; CHD=coronary heart disease; CVD=cardiovascular disease; EF=ejection fraction; HDL=high-density lipoprotein; HRT=hormone replacement therapy; LDL=low-density lipoprotein; Lp(a)=lipoprotein little A antigen; MI=myocardial infarction; NIDDM=non-insulin-dependent diabetes mellitus; sICAM=soluble intercellular adhesion molecule; sVCAM=soluble vascular cell adhesion molecule; t-PA=tissue-type plasminogen activator; USDA=U.S. Department of Agriculture.

risk against the reduction in risk of CHD.[181] The strong linear relationship (Fig. 32-9) suggests that as long as risk factors are truly modified, event rates will also be reduced.

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SUMMARY OF RECOMMENDATIONS

The appropriate strategy for any given patient begins with assessment of the overall risk of a first or subsequent cardiovascular event. Patients can be classified into two broad groups: those with overt cardiovascular disease, including previous myocardial infarction, stroke, peripheral vascular disease, angina, or prior vascular procedure, and those without overt cardiovascular disease. Those without cardiovascular disease can be further subdivided into three risk strata: diabetics, high-risk nondiabetics, and low-risk nondiabetics. Those with cardiovascular disease and diabetes are generally straightforward to identify. Stratifying the remaining group requires the use of an algorithm such as those developed by the Framingham Heart Study (see Fig. 32-2) or the European Society of Cardiology (see Fig. 32-3).

Table 32-9 summarizes the interventional approach for each of the class 1 and 2 factors. Many of these activities can be undertaken by allied health professionals in a prevention program. Case management models of prevention have been demonstrated as useful among higher-risk groups following myocardial infarction or bypass surgery.[182] [183]

CONCLUSIONS

Current data strongly support a role for risk factor modification in both primary and secondary prevention of CHD. For three risk factors--cigarette smoking, elevated serum cholesterol, and hypertension--the strength and consistency of association with atherosclerotic disease indicate a causal relationship, and the benefits of intervention

are well documented

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in both primary and secondary prevention. There is little doubt that diabetes, low levels of HDL cholesterol, elevated levels of triglycerides, physical inactivity, obesity, and menopause increase the risk of CHD and that light to moderate alcohol consumption reduces the risk, but the precise magnitude of the effect attributable to intervention for these factors has been difficult to document.

The trends of several modifiable risk factors are troubling. As the population ages, the number of individuals with factors that put them at risk for cardiovascular disease will increase even if age-adjusted risk factor rates decline. Similarly, the number of people living with cardiovascular disease will increase, thus necessitating greater secondary preventive efforts. Obesity and physical inactivity are epidemic among all sectors of the population, including children. These factors will tend to increase rates of diabetes and hypertension and slow the favorable trends in mean lipid levels.

Primary and secondary prevention has contributed substantially to the reduction in CHD mortality rates. Yet much remains to be done. In addition to developing a better understanding of the mechanistic and epidemiological determinants of atherosclerotic disease, we must pay more attention to finding effective strategies for prioritizing factors in prevention programs, implementing existing guidelines for risk factor modification, and developing low-cost interventions for factors for which guidelines are not yet available. Many life style changes are difficult to achieve and even harder to maintain over the long term. Such interventions need to involve not only the affected individuals but also families, workplaces, schools, and even whole communities.

For clinicians, identifying a successful strategy for each patient is of critical importance. Further research on cost- and risk-benefit ratios will enable better targeting of interventions for maximal individual and societal benefit. More widespread use of multifaceted self-help and health professional-directed prevention programs should help sustain the decline in cardiovascular disease mortality rates in the United States.

Figure 32-9 For seven trials, four of which made up the World Health Organization (WHO) European Collaborative Trial in the Multifactorial Prevention of Coronary Heart Disease, Kornitzer plotted the difference in a composite risk factor score between treated and untreated groups and showed a statistically significant correlation between the magnitude of risk factor improvement and coronary heart disease (CHD) mortality. *(From Kornitzer M: Changing individual behavior. In Marmot M, Elliott P [eds]: Coronary Heart Disease Epidemiology: From Aetiology to Public Health. Oxford, Oxford University Press,*

1992, p 492.)

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Chapter 33 - Lipid-Lowering Trials

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The decline in age-adjusted cardiovascular mortality during the past three decades in the United States has been dramatic. The mechanisms that underlie this encouraging decline in death rates represent a multifactorial interplay between enhanced diagnostic capabilities coupled with improved capacity to treat both preclinical and advanced atherosclerotic disease, thanks to refinements in medical therapy and revascularization techniques. The ability to identify persons at risk well before the onset of symptomatic vascular disease has likewise improved and may account for some of the observed epidemiological benefit. Medical treatment for coronary artery disease has evolved rapidly over the past 15 years with significant improvements in antithrombotic and antiplatelet therapy, hypertension control with safe and well-tolerated medications, and new agents to alter the lipid profile.

The central tenet of the "lipid hypothesis" of coronary disease etiology that dyslipidemia is central to the process of atherosclerosis has now been validated by numerous pathological, epidemiological, genetic, and interventional trials (see Chap. 31) . Great strides have been made in the past 5 years to enhance the clinician's ability to identify--and direct effective therapies against--the involved abnormal lipid fraction,

which may include elevated total and low-density lipoprotein cholesterol (LDL-C), high triglycerides, low high-density lipoprotein cholesterol (HDL-C), and elevated lipoprotein (Lp)(a). In this chapter we discuss data from the more recent, representative epidemiological, angiographic and clinical lipid trials. Readers interested in the earlier classic trials (e.g., the Lipid Research Clinic Coronary Primary Prevention Trial, the Helsinki Heart Study) are referred to the fifth edition of *Heart Disease*.

EPIDEMIOLOGICAL STUDIES

A number of classic epidemiology studies (Seven Countries Study, Framingham Heart Study, Muenster, and others) have published recent updates, and new important information continues to be obtained from these trials.

Seven Countries Study

The Seven Countries Study measured total cholesterol levels at baseline in the years between 1958 and 1964 with subsequent 5-year and 10-year follow-up in the original cohort of 12,467 male subjects who were located at 16 centers in seven countries, including Europe, the United States, and Japan. The 25-year follow-up of the Seven Countries Study has been completed and the differences in cholesterol and cardiovascular mortality among the cohorts have been analyzed.[1] Considerable variability was observed in the mean cholesterol levels among nations, which ranged from 160 to 170 mg/dl in the Japanese cohort to 240 to 260 mg/dl in the United States and northern European population. The cholesterol levels correlated directly with the age-adjusted 25-year coronary heart disease (CHD) mortality rate, which was lowest in Japan (3.2 percent) and highest in northern Europe (20.3 percent) (Fig. 33-1). The low mortality in the Japanese cohort was present despite the relatively higher tobacco usage in this population compared with that in northern Europe (74.3 percent vs. 66.8 percent, respectively).

Although the absolute CHD mortality rates differed, the slopes of the event curves were comparable. The increase in risk associated with a 0.5-mg/dl increase in cholesterol was estimated. Only the relative risk in Japan did not differ from unity. In the other cohorts, the estimated increased relative risks ranged from 1.10 to 1.15. However, the power to detect a significant association in the Japanese cohort may be low because of the relatively few coronary patients and even fewer deaths due to CHD, possibly resulting from the low national cholesterol level in Japan. However, larger epidemiological studies performed with a similar trial design in China have demonstrated a positive linear relation between dyslipidemia and coronary mortality even at the extremely low cholesterol levels of the Chinese population. Cholesterol thus predicted the degree of CHD risk in different cultures, although the absolute level of significant clinical events associated with atherosclerosis was quite variable in the various countries analyzed in this trial. The changes in absolute CHD rates may be a function of dietary habits, favoring consumption of diets low in saturated fat and high in natural antioxidants that may have beneficial, anti-atherosclerotic effects.

Prospective Cardiovascular Muenster (PROCAM)

The PROCAM study reported that the epidemiological relation between dyslipidemia and coronary events could be correlated with an elevated total cholesterol to HDL-C ratio in combination with hypertriglyceridemia.[2] This observation corroborates a retrospective subset analysis in the Helsinki Heart Study, which demonstrated that 70 percent of the coronary events in this primary-prevention trial of gemfibrozil occurred in a similar subgroup of the total cohort that accounted for 10 percent of the randomized individuals.[3]

The PROCAM study has published 8-year follow-up data.[4] It analyzed a number of lipid parameters and clinical characteristics of 17,437 men (mean age 40.4 years) and 8,065 women (mean age 36 years). The PROCAM study implicated tobacco usage, diabetes mellitus, positive family history of myocardial infarction, and systolic blood pressure as independent predictors of risk for coronary disease in addition to the classic lipid parameters. The LDL-C:HDL-C ratio greater than 5, which had been used as a marker of increased risk in the earlier evaluations, was associated with a 19.2 percent probability of a patient developing a significant atherosclerotic event in the 8-year follow-up period. Additionally, in the subgroup of participants with the combination of hypertriglyceridemia with an adverse LDL-C:HDL-C ratio (> 5), the rate for developing a coronary event was approximately 26.9 percent. The risk for CHD

Figure 33-1 Seven Countries Study. Relationship between cholesterol and coronary heart disease (CHD) mortality rates. (From Verschuren WM, Jacobs DR, Bloemberg BP, et al: Serum total cholesterol and long-term coronary heart disease mortality in different cultures: Twenty-five-year follow-up of the seven countries study. JAMA 274:131-136, 1995. Copyright 1995, American Medical Association.)

was elevated approximately sixfold in this small subset of individuals (4.3 percent prevalence of this lipid constellation).

As have other epidemiological studies, the PROCAM study reported a J-shaped relation between cholesterol and mortality, with both low and high levels associated with increased deaths.[5] Previously, the validity and clinical implications of the J-shaped relation have been controversial and difficult to determine because of multiple confounding factors, such as poor health habits, alcoholism, malignancy, or cigarette smoking, that contribute potentially to a lower cholesterol and higher mortality. One interpretation of this relation has hypothesized that the increased mortality may be a deleterious consequence of low cholesterol levels and questioned the safety of aggressive lipid modification.

The PROCAM investigators analyzed smoking habits and malignancies and determined

that at high total cholesterol and LDL-C concentrations, the increased mortality was due to a higher death rate associated with coronary atherosclerosis. At the low levels, increased mortality was seen predominantly in smokers and could be related to an increase in smoking-related cancer deaths. Thus, in the PROCAM cohort, risks associated with smoking could explain the increased mortality at lower cholesterol levels.

The PROCAM study also extended the previously described data relating coronary mortality and hypertriglyceridemia as an independent risk factor for coronary events independent of HDL-C or LDL-C levels. Because of the inherent problems associated with epidemiological studies, the precise underlying mechanism or causality of the increased risk with this lipid pattern cannot be delineated. Possible mechanisms for this association include a link between hypertriglyceridemia and an increased incidence of atherosclerosis because of a propensity for hypercoagulability and persistence in the circulation of atherogenic subpopulations of triglyceride-rich particles.[6]

Framingham Heart Study

The Framingham Heart Study has provided a wealth of epidemiological information elucidating the relation between total cholesterol, LDL-C, HDL-C, and triglyceride levels and the risk for coronary atherosclerosis. Now extended to include the Offspring Study of the original cohort, the Framingham Heart Study has amplified the prior documentation of the increasing coronary risk associated with risk factor clustering.[7]

The Framingham investigators analyzed prospectively six metabolically linked risk factors, which include body mass index, systolic blood pressure, hypertriglyceridemia, glucose, cholesterol, and HDL-C levels. The Framingham Offspring Study examination from 1971 to 1974 analyzed measurements in 2406 men and 2569 women who ranged in age from 18 to 74 at the initial assessment. A risk factor sum that ranged from 0 to 6 was tabulated to determine the impact of risk factor clustering on the 16-year heart disease risk in these subjects. The Framingham Study previously reported the risk for developing coronary disease as a proportion of the associated risk factors. The prevalence of isolated risk factors occurred with a rate of approximately 30 percent, and clustering of three or more risk factors occurred in approximately 17 percent in both sexes, a finding compatible with a metabolic interrelation among the various elements of the risk factor profile. The risk factor sums of 0, 1, 2, and greater than 3 were associated with a 16-year relative risk for CHD of 1, 1.54, 2.02, and 2.39, respectively in male subjects, and 1, 1.21, 2.89, and 5.90, respectively in female subjects.

Obesity and weight gain were important determinants of risk factor clustering that raised the possibility that insulin resistance may be a predisposing cause, although insulin measurements were not available at the time of original evaluation. The Framingham Heart Study highlights the importance of risk factor clustering and places emphasis on the importance of weight control in middle-aged subjects to decrease the cardiac risk.

The Framingham investigators, using the concept of risk factor clustering, incorporated lipid and blood pressure categories from the National Cholesterol Education Program (NCEP) and Joint National Committee (JNC-V) recommendations for stratification and

control to establish probabilities for development of ischemic heart disease in primary prevention.[8] The cohort consisted of 5345 men and women whose age ranged from 30 to 74 years at baseline examination and who had 12 years of follow-up.

Using the concept of risk factor clustering in severity stratification, the Framingham group has developed a simple coronary disease prediction algorithm that predicts 10-year CHD risk in subjects who have no clinical evidence of overt atherosclerosis (see Fig. 31-2). Hypertension was categorized according to recommendations made by the JNC-V committee: optimal (systolic <120 mm Hg, diastolic <80 mm Hg); normal blood pressure (systolic 120-129 mm Hg, diastolic 80-84 mm Hg); high normal blood pressure (systolic 130-139 mm Hg, diastolic 85-89 mm Hg); hypertension stage I (140-159 mm Hg, diastolic 90-99 mm Hg); hypertension stage II-stage IV (systolic 160 mm Hg, diastolic > 100 mm Hg). Diabetes was considered to be present if the subject was currently under treatment with either oral hypoglycemic agents or insulin therapy. Total cholesterol was subdivided into four categories (<200 mg/dl, 200-239 mg/dl, 240-279 mg/dl, 280 mg/dl). LDL-C categories were less than 130 mg/dl, 130 to 159 mg/dl, and

more than 160 mg/dl. HDL-C categories were less than 35 mg/dl, 35 to 59 mg/dl, and more than 60 mg/dl. The age of the subject and the use of tobacco products were also considered.

During the 12-year follow-up evaluation, a total of 383 men and 227 women developed symptomatic CHD that showed a positive significant statistical correlation with the categories of blood pressure, total cholesterol, LDL-C, and HDL-C. The categorical approach using the clustering of concomitant risk factors and their severity was comparable to CHD prediction when the continuous variables were analyzed after assigning a risk. Approximately 28 percent of the CHD events in men and 29 percent in women were attributable to hypertension that exceeded the high normal range. The corresponding multivariable-adjusted risk associated with a cholesterol value of 200 mg/dl or greater was 27 percent in men and 34 percent in women. Obesity, degree of physical activity, and family history for heart disease were not used in the algorithm because the contribution of these important risk factors is difficult to quantify.

The Framingham investigators have also evaluated the association between elevated plasma Lp(a) and CHD in a prospective manner.[9] The Framingham Offspring Study analyzed a total of 2191 men who were 20 to 54 years of age at the time of evaluation. The subjects had no history of known coronary artery disease and were followed for the subsequent development of symptomatic atherosclerosis as manifest by angina pectoris, myocardial infarction, coronary insufficiency, or sudden cardiac death. The cohort was followed for a median period of 15.4 years, during which time 129 cardiac events occurred. Lp(a) contributed a relative risk for the development of symptomatic vascular disease of 1.9 when analyzed in a proportional hazards model. Lp(a) was determined to be an independent risk factor in this cohort comparable to the attributable risk of a total serum cholesterol in excess of 240 mg/dl or an HDL-C level of less than 35 mg/dl. Assays of Lp(a) with standardized precision have been developed and are

currently commercially available.

Copenhagen Male Study

The Copenhagen Male Study was initiated in 1970 as a prospective epidemiological trial that involved 6125 men who were eligible for the original study. In 1986, all survivors from the original trial were traced and invited to participate in a continuation of the trial. A total of 75 percent of the original cohort (3387 men with an average age of 63) agreed to participate in the follow-up. Subjects who had a history of acute myocardial infarction, stroke, or symptoms of coronary insufficiency were excluded, and 2906 men were eligible ultimately for this prospective study, which had an 8-year follow-up.[10]

The patients were categorized for both lipid and nonlipid risk factors for atherosclerosis according to tertiles of fasting triglyceride levels. Increasing triglyceride levels were associated with higher total and LDL cholesterol, higher systolic and diastolic blood pressure, higher body mass index, and a greater prevalence of hypertension and diabetes. Lower levels of HDL-C and physical activity were also associated with increasing triglyceride levels. Glucose levels were not measured, which prevented adjustment for the degree of glucose tolerance and glycemia. However, a relatively small number of patients in the Copenhagen Male Study carried the diagnosis of diabetes (1.1 percent, 1.5 percent, 3.0 percent in the increasing tertiles of triglyceride levels, respectively) and a smaller percent had glucosuria, which led the investigators to conclude that the majority of the patients did not have clinically significant diabetes.

During the follow-up period, a total of 229 subjects had an ischemic event, 66 of which were fatal. Total mortality was also documented, and a total of 426 men died during the trial. An association was found between triglyceride levels and the ischemic heart disease risk both overall and within each tertile of HDL-C, a relation that persisted with additional control for the potentially confounding effects of antihypertensive medications, sedentary life style, alcohol use, and socioeconomic class. Crude cumulative incidence rates of ischemic disease were 4.6 percent for the lowest tertile of triglyceride, 7.7 percent for the middle, and 11.5 percent for the highest third (p for trend <0.01). After controlling for other major risk factors, including HDL-C, the investigators found the relative risks for ischemic disease to be 1.5 (p=0.05) and 2.2 (p<0.001) for the middle and highest tertiles, respectively. Thus, the Copenhagen Male Study indicates that a gradient for risk for atherosclerosis can be demonstrated for increasing levels of triglycerides independent of other major risk factors. The Copenhagen Male Study further validates hypertriglyceridemia as an independent risk factor for coronary disease that may be considered in establishing a risk factor profile.

Johns Hopkins Precursor Study

The Johns Hopkins Precursor Study began in 1947 when an initial cohort of 1337 students who represented members of the graduating classes of 1948 to 1964 were enrolled. Beginning in 1949, serum cholesterol was measured in the nonfasting state in this cohort. A total of 1017 male students, whose average age at enrollment was 22 years, were followed for 27 to 42 years in an attempt to quantify the risk for cardiovascular disease and total mortality associated with serum cholesterol levels.[11]

The subjects were evaluated after graduation using annual questionnaires, and between 87 and 94 percent of the population responded at least once over any 5-year period. The vital status of more than 99 percent of the cohort had been established before evaluation of the data.

The subjects were analyzed for blood pressure and body mass index and a number of health habits. Of the men, 3.5 percent were hypertensive, defined as a systolic pressure in excess of 160 mm Hg and a diastolic pressure in excess of 95 mm Hg; 5 percent of the subjects were overweight, as defined by a body mass index greater than 27.8 kg/m^2 ; and, approximately 50 percent of the subjects smoked during medical school. Active physical training in the month before the initial examination was documented in 19 percent of the cohort. The average serum cholesterol at the beginning of the trial was 192 mg/dl. The cohort contributed a total of 27,871 person years of observation with a median follow-up of 30.5 years. A total of 125 cardiovascular disease events and 97 CHD events were reported during the follow-up period. A total of 95 participants died, and death was attributable to cardiovascular disease in 21 subjects, of which 18 had CHD. By 1985, only 10 subjects reported that they received hypolipidemic therapy and the mean cholesterol at the baseline examination of these subjects was 225 mg/dl. The prevalence of smoking decreased from 48 percent at baseline to 10.5 percent in 1986. The cumulative incidence of hypertension over the course of follow-up was 38.4 percent, and the cumulative incidence of diabetes was 6 percent.

Baseline serum cholesterol was strongly correlated with the subsequent incidence of CHD, which steadily increased for each quartile of serum cholesterol. In addition, there was a graded correlation between baseline serum cholesterol and subsequent fatal events. Multivariate analysis confirmed the relation for CHD and cholesterol. The Johns Hopkins Precursor Study clearly demonstrated a strong positive and progressive relation between dyslipidemia in early adult life and the subsequent incidence of CHD over approximately four decades of follow-up. Importantly, the risk

for cardiovascular disease was increased even among men whose serum cholesterol fell within the normal range.

Epidemiological studies are frequently confounded by socioeconomic considerations with an adverse health habit profile being more prevalent in patients with lower income levels, but the relatively homogeneous and high socioeconomic status in this cohort allows a reasonably unconfounded prospective assessment of the effect of cholesterol on mortality. The implication of the Johns Hopkins Precursor Study is that in generally healthy young males, the total serum cholesterol is a strong predictor of clinically evident cardiovascular disease occurring 25 years or more after the initial measurement.

DIET STUDIES

Lifestyle Heart Trial

The Lifestyle Heart Trial investigated the premise that comprehensive life style changes could alter the clinical and angiographic progression of coronary disease. The original trial analyzed both lipid and quantitative angiographic parameters after a 12-month intervention period that included intensive life style changes involving diet (strict vegetarian with 10 percent of calories obtained from fat), aerobic exercise, stress management, smoking cessation, and group psychosocial support. Comprehensive risk factor reduction resulted in a 37.2 percent reduction in LDL-C levels that was associated with a decrease of 91 percent in the frequency of anginal episodes. The Lifestyle Heart Trial also performed baseline and 12-month angiograms and demonstrated a striking improvement in the angiographic manifestations of CHD in the group randomized to intensive risk factor management. The intensive intervention group actually demonstrated angiographic regression to a 37.8 percent average percent diameter stenosis from a baseline of 40 percent stenosis. The usual care group demonstrated an increase in average percent diameter stenosis from 42.7 to 46.1 percent, suggesting progression.

The original Lifestyle Heart Trial was subsequently extended for a 5-year total trial duration and angiographic, clinical, and myocardial perfusion data were obtained.[12] A total of 48 subjects with moderate to severe CHD completed the 5-year follow-up. The experimental group decreased fat intake from approximately 30 percent of total calories to 8.5 percent. The average cholesterol intake had been 211 mg/d and was decreased to 18.6 mg/d. Patients in the experimental group lost 12.8 pounds after 5 years, compared with minimal changes in the control group. LDL-C, which had decreased by 40 percent at 12 months, remained 20 percent below baseline after 5 years of dietary and other hygienic interventions.

Striking angiographic changes were seen at the 5-year follow-up. In the intensive care group, the average baseline percent diameter stenosis was 41.3 percent; intensive therapy reduced this to 37.3 percent at 5 years. The control group, which demonstrated an average diameter stenosis of 40.7 percent at baseline, had increased to 51.9 percent stenosis at 5 years. This difference was highly statistically significant when analyzed with a between group two-tailed *t*-test (p=0.001).

Clinical events were tabulated, and the incidence of myocardial infarction, coronary angioplasty, coronary artery bypass surgical procedures, cardiac-related hospitalizations, and cardiac deaths were compared between the two groups. At 5 years, there were more total cardiac events in the control group compared with intensive therapy (45 events vs. 25 events, respectively). The Lifestyle Heart Trial emphasizes that comprehensive and rigorous modification of diet, smoking, exercise, and stress exposure in a highly motivated population may yield measurable benefits, using life style changes alone.

Lyon Diet Heart Study

The Lyon Diet Heart Study examined the effect of Mediterranean diet in a total of 605 subjects who had suffered an acute myocardial infarction. For a mean duration of 46 months per patient, the investigators compared the effect of a Mediterranean diet with that of a prudent Western-type diet on risk for recurrent coronary events.[13] The Mediterranean diet had fewer calories and a significantly lower content of both saturated fats and polyunsaturated fats relative to the Western diet. The composition of polyunsaturated fats in the Lyon Diet Heart Study consisted predominantly of oleic, linoleic, and linolenic, all of which were significantly increased when compared with the control diet.

A total of 275 cardiac events were documented during the 46-month follow-up period, and a significant reduction in recurrent event rates was achieved by the Mediterranean diet. At the 46-month follow-up period, the event rate for cardiac death and nonfatal myocardial infarction in the intervention group was 1.24 per 100 patients per year compared with 4.07 events per 100 patients per year in the control group (72 percent risk reduction, p=0.0001). All-cause mortality rate was also significantly reduced (56 percent risk reduction, p=0.03).

Multivariate analysis documented that the dietary pattern, cholesterol, hypertension, and leukocyte count were major independent and joint predictors of a nonfatal myocardial infarction or coronary death. Smoking was not independently related, but because the total prevalence of smokers in both groups was low (<20 percent) at the final visit, the impact of tobacco use was statistically inadequate for analysis. The protective effect of the Mediterranean diet in the Lyon Diet Heart Study was thus maintained up to a period of 4 years after an acute myocardial infarction. The composition of the Mediterranean diet appears to be cardioprotective and associated with improved outcomes in secondary prevention. This result emphasizes the importance of dietary therapy with optimal caloric and nutrient composition in patients with significant atherosclerosis.

Study on the Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 Fatty Acids (SCIMO)

SCIMO was a randomized, double-blind study conducted at a single center and was designed to assess the effects of a fish oil concentrate on coronary angiographic parameters as a primary endpoint after 24 months of therapy.[14] The patients were initially stratified according to three criteria: (1) angioplasty in the 6 months before randomization; (2) current hypolipidemic therapy; and (3) risk factor stratification. A total of 223 subjects were randomly assigned to receive either a fish oil capsule containing omega-3 fatty acids or a matching placebo.

The angiograms were visually analyzed by three experts with the determination of a global score as the primary endpoint. The coronary segments in the fish oil group demonstrated less progression and more regression compared with subjects in the control group when analyzed on an "intent to treat" basis (p=0.041). The induced angiographic changes increased in significance when the extent of analysis was limited to more compliant patients. A total of eight predefined clinical endpoints were reported in the placebo group compared with four in the patients randomized to receive fish oil, a

difference that did not reach statistical significance because of the small numbers.

Thus, treatment with omega-3 fatty acids resulted in less angiographic progression and more regression of coronary artery disease, overall, relative to placebo. This finding contrasts to those of previously described studies using marine fatty acids. Although SCIMO was not powered to evaluate clinical events, a beneficial trend was seen in the group randomized to receive omega-3 fatty acids. More data are needed on fish oil supplementation before definitive clinical recommendations can be made.

STATIN TRIALS

Angiographic

Statin Monotherapy

A number of angiographic trials using statin monotherapy have been performed that uniformly demonstrated benefit in altering the course of atherosclerosis (Table 33-1) .

Multicentre Anti-Atheroma Study

The Multicentre Anti-Atheroma Study (MAAS) was an angiographic trial that analyzed the effect of diet plus either 20 mg/d of simvastatin or placebo in a group of 381 subjects with documented coronary artery disease.[15] Quantitative angiographic analysis using the computer-assisted Cardiovascular Angiography Analysis System (CAAS) was performed to determine the mean lumen diameter for angiographically diseased segments, minimum lumen diameter, reference diameter, and percent diameter stenosis. Patients were included if they fell within the range of 30 to 67 years of age and had at least two coronary artery segments that were involved with atherosclerosis but not totally occluded. The patients were clinically stable in that angioplasty or bypass surgery was not considered to be absolutely necessary for control of symptoms or for management of a high-risk anatomic subgroup (severe triple-vessel or left main coronary artery disease). Exclusion criteria included prior coronary artery bypass surgery, recent myocardial infarction, unstable angina, significant hypertension, and congestive heart failure. The trial was conducted over a 48-month duration, at which time repeat angiography was performed.

Simvastatin plus diet therapy was successful in improving the lipid profile when compared with the changes induced by dietary intervention alone. A reduction in total cholesterol of 23 percent was achieved, which was accompanied by a 31 percent reduction in LDL-C. HDL-C levels were increased by 9 percent and triglyceride levels were reduced by 18 percent. The investigators analyzed a number of other lipid subfractions including apolipoprotein AI (APO AI), apolipoprotein B (APO B), and Lp(a). Lp(a) and APO AI were not significantly altered by simvastatin therapy, although a 28

percent reduction in levels of APO B was achieved.

Simvastatin therapy resulted in a beneficial alteration of the mean lumen diameter, minimum lumen diameter, and diameter stenoses when compared with diet alone. The patients were also classified as to their angiographic response to pharmacological or dietary interventions. Progression was the predominant angiographic picture in 54 patients randomized to placebo compared with 41 randomized to simvastatin. In the simvastatin group, 33 patients were classified as having undergone angiographic regression, compared with 20 in the placebo group. Thus, simvastatin therapy resulted in fewer patients experiencing angiographic progression and a higher proportion who demonstrated actual regression (p=0.02). Angiographic benefit was least evident in current smokers, who accounted for less than 25 percent of both treatment groups. Plaque stability was obtained in 94 patients randomized to simvastatin compared with 72 randomized to placebo. The MAAS trial was not powered for changes in mortality, but a total of 11 cardiac deaths occurred in the placebo group compared with 4 in the simvastatin group.

The MAAS trial was interpreted as demonstrating that improvement in both focal and diffuse coronary atherosclerosis could be induced by simvastatin. Fewer new lesions and complete occlusions were developed in the treatment group, and there were no significant differences in side effects or adverse reactions. Although the angiographic difference between treatment and control groups was small in absolute terms, the results of MAAS are consistent with other long-term angiographic trials.

Multicenter Coronary Intervention Study (CIS)

CIS was a 2.3-year, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the effect of diet plus either simvastatin, 40 mg/d, or placebo in 254 male subjects with documented atherosclerosis and hypercholesterolemia.[16] Mean baseline cholesterol values for all patients were approximately total cholesterol, 240 mg/dl, and LDL-C, 165 mg/dl. The primary endpoints of the CIS were a comparison of the global change score of the treated and control groups as determined by visual evaluation and the per-patient mean change of minimum lumen diameter evaluated quantitatively by the CAAS system.

Simvastatin therapy resulted in a significant improvement in the lipid profile relative to diet. A 35 percent reduction in LDL-C was achieved by simvastatin when compared with placebo. Total cholesterol was decreased by 28.5 percent, and triglycerides were decreased by 28 percent, both of which were statistically significant differences. Simvastatin therapy increased HDL-C by 6.1 percent, which was not statistically different from changes induced by diet.

TABLE 33-1 -- ANGIOGRAPHIC STUDIES OF STATIN MONOTHERAPY: MODEST VASCULAR CHANGES ARE ASSOCIATED WITH DISPROPORTIONATE EVENT REDUCTIONS

TRIAL (INTERVENTION)	% LDL-C REDUCTION Rx-Pbo	deltaMLD Rx_{final} -$Rx_{baseline}$	CORONARY EVENT REDUCTION (*p*VALUE)
PLAC I[20] (pravastatin)	29	-0.03	60% (p=0.05)
CCAIT[17] (lovastatin)	27.4	-0.02	22% (NS)
MAAS[15] (simvastatin)	31.4	-0.02 (diffuse disease)	22% (NS)
LCAS[25] (fluvastatin)	26.5	-0.03	24% (NS)

Rx=Treatment; Pbo-placebo; PLAC I=Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; CCAIT=Canadian Coronary Atherosclerosis Intervention Trial; MAAS=Multicentre Anti-Atheroma Study; LCAS=Lipoprotein and Coronary Atherosclerosis Study; NS=nonsignificant.

Follow-up angiography was obtained in 81 percent of the randomized patients. The mean global change score was +0.2 in the simvastatin group and +0.58 in the placebo group, representing a statistically significant decrease in the rate of progression in the group randomized to drug therapy (*p*=0.02). The mean quantitative change in minimum lumen diameter stenosis was -0.02 mm in the simvastatin group and -0.10 mm in the placebo group, again a statistically significant slowing of progression (*p*=0.002).

CANADIAN CORONARY ATHEROSCLEROSIS INTERVENTION TRIAL (CCAIT).

CCAIT was a double-blind, placebo-controlled, angiographic trial conducted over a 2-year period in 331 patients.[17] Angiograms were analyzed using the Cardiovascular Measurement System (CMS), which is a computer-based quantitative angiographic method for the determination of minimum lumen diameter. The CCAIT used relatively aggressive lipid-lowering therapy with lovastatin, which was begun at an initial dosage of 20 mg/d with the potential for titration up to 80 mg/d, which was intended to achieve an LDL-C level under 130 mg/dl. The CCAIT enrolled both men and women with a total cholesterol value between 220 and 300 mg/dl. Patients were excluded if triglyceride levels exceeded 500 mg/dl or if significant clinical instability was evident (ejection fraction <40 percent: left main coronary stenosis > 50 percent; recent myocardial infarction or unstable angina; or angioplasty within the 6 months before admission). The angiograms were analyzed in a quantitative manner and the investigators were blinded as to the treatment allocation or temporal sequence of the films. The primary endpoint was the coronary change score, which was defined as the per-patient mean of the minimum lumen diameter changes for all lesions that were greater than 25 percent obstructed on both angiograms. Secondary endpoints included the formation of new lesions, new total occlusions, presence of anatomic progression or regression, and the

coronary score of all lesions that were at least 50 percent obstructed at baseline.

Lovastatin therapy significantly improved the lipid profile when compared with placebo patients. Total cholesterol was decreased by 21 percent, which was accompanied by a decrease in LDL-C of 29 percent. HDL-C was increased by 7.3 percent, and triglyceride levels were decreased by 8 percent. Accompanying the change in LDL-C, APO B levels were decreased by 21 percent. The placebo group demonstrated little or no alteration of circulating lipid values. The target LDL-C was achieved in 69 percent of patients randomized to lovastatin, and the mean dosage was 36 mg/d. Dietary therapy alone reduced LDL-C to less than 130 mg/dl in 10 percent of the placebo patients.

Progression of atherosclerosis was significantly reduced by lovastatin therapy when analyzed using the change in coronary score. Minimum lumen diameter decreased by 0.05 mm in patients randomized to receive lovastatin, compared with 0.09 mm in the placebo group, indicating a significant slowing of the atherosclerotic process. Percent diameter stenosis was also increased to a lesser degree with lovastatin (1.66 percent increase with lovastatin compared with 2.89 percent increase with placebo). The majority of lesions that underwent anatomic progression were considered to be minimally obstructed (<50 percent occlusion) on the baseline angiogram. In the lovastatin group, 6.8 percent of these lesions progressed compared with 11.2 percent in the placebo group. Lovastatin also significantly reduced the development of new lesions: 16 percent of lovastatin patients developed new lesions compared with 32 percent of placebo patients.

The results of CCAIT demonstrate that lovastatin was able to diminish the rate of angiographic progression and to retard the development of new atherosclerotic lesions when compared with a placebo group. However, subjects who demonstrated anatomic regression or recanalization of previously totally occluded vessels were uncommon. The absolute change in coronary score between the two randomized groups is of comparable magnitude with other angiographic trials. Lovastatin therapy appeared to be more beneficial in subjects whose baseline LDL-C was above the median level of 176 mg/dl, implying enhanced angiographic benefit in the treatment of more severely dyslipidemic patients. However, a threshold value below which no treatment benefit could be documented was not established and emphasizes the importance of lipid lowering irrespective of baseline LDL-C levels in patients with known coronary disease. Reduction of new lesions may also have additional clinical importance when patients are followed for a longer period of time than the relatively brief 24-month trial period used in CCAIT.

REGRESSION GROWTH EVALUATION STATIN STUDY (REGRESS).

The Regression Growth Evaluation Statin Study (REGRESS) evaluated a patient cohort with coronary atherosclerosis and lipid levels that approximated the distribution within the general population.[18] Earlier clinical trials focused on subjects who were markedly dyslipidemic and who were believed to be at the highest level of risk for both angiographic progression and clinical events. Whereas severely dyslipidemic patients constitute a high-risk subgroup, they are relatively uncommon and thus not representative of the general population, a fact that renders extrapolation of the early

intervention trials to clinical practice problematic.

The REGRESS examined the role of pravastatin in a cohort that was representative of contemporary patient profiles. In addition to pharmacological and dietary interventions that alter the lipid profile, coronary interventions (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) were allowed. REGRESS was performed in a double-blind, placebo-controlled fashion over a 24-month trial duration. The patients were men with an average age of 56 years whose average cholesterol was 234 mg/dl (range 155-310 mg/dl). Patients were recruited from multiple centers on the basis of a qualifying angiogram that required the presence of at least one atherosclerotic lesion that was greater than or equal to a 50 percent obstruction. The primary endpoint of the trial was the alteration of the mean segment diameter and minimum lumen diameter when calculated on a per-patient basis. Pravastatin was used at a fixed dose of 40 mg/d, and a total of 885 subjects were randomized to receive either dietary therapy plus placebo or dietary therapy and pravastatin.

The administration of pravastatin resulted in a significant alteration of the lipid profile when compared with the group receiving dietary interventions alone. Total cholesterol was decreased by 20 percent, which was accompanied by a decrease in LDL-C of 29 percent. HDL-C was increased by 10 percent, and there was a 7 percent decrease in triglycerides. The changes in the lipid profile could be correlated with improvement in the angiographic parameters as defined by the primary endpoint of the trial. Mean segment diameter decreased by 0.06 mm in the pravastatin group compared with 0.10 mm in the placebo group. Pravastatin therapy thus demonstrated a reduction in the rate of the progression of atherosclerosis, as assessed by quantitative measurements of the mean segment diameter. Additionally, the minimum lumen diameter decreased by 0.03 mm in the group randomized to pravastatin and 0.09 mm in the placebo group. The benefit of pravastatin therapy was demonstrated across all baseline LDL-C quartiles, emphasizing the benefit of treating lipid disorders in patients with documented atherosclerosis irrespective of baseline lipid values. Pravastatin therapy reduced the risk for clinical events (89 percent of the pravastatin-treated patients were event free after 2 years vs. 81 percent of the placebo, p=0.002). It is interesting to note that the concomitant use of calcium

channel blockers in lipid-lowering therapy appears to have a synergistic effect in slowing the progression of coronary atherosclerosis in REGRESS, with fewer subjects who received combination therapy forming new lesions.[19]

PRAVASTATIN LIMITATION OF ATHEROSCLEROSIS IN THE CORONARY ARTERIES (PLAC-I).

PLAC-I was designed to examine the potential effects of pravastatin in patients with angiographically demonstrable CHD and mild to moderate hyperlipidemia.[20] The PLAC-I trial was conducted for a longer period of time (36 months) compared with other angiographic trials. Pravastatin was used at a fixed dose of 40 mg/d and was compared

with dietary therapy as the control group. Subjects randomized in PLAC-I had a mean LDL-C level of 164 mg/dl (inclusion range, 130-190 mg/dl). Subjects were not randomized if triglyceride levels exceeded 350 mg/dl after dietary therapy. Angiograms were analyzed using quantitative coronary angiography. Qualifying angiograms were required to demonstrate at least one lesion, causing a greater than 50 percent stenosis before randomization. Pravastatin therapy resulted in a significant reduction in the lipid profile, with total cholesterol being decreased by 19 percent and LDL-C by 28 percent. HDL-C was increased by 7 percent, and triglycerides were decreased by 8 percent. The dietary therapy used in the control group did not result in significant lipid changes.

The alterations in the lipid profile induced by pravastatin therapy were associated with a reduction in angiographic progression. The primary endpoint was the absolute change in mean lumen diameter that was reduced by 0.02 mm/yr in pravastatin patients compared with 0.04 mm/yr in the dietary group. The beneficial trend in the alteration of mean lumen diameter did not achieve statistical significance (p=0.16). However, the change in minimum lumen diameter was significantly improved by pravastatin therapy and demonstrated a decrease of 0.03 mm/yr compared with 0.05 mm/yr in the dietary group (p=0.04). The effectiveness of pravastatin therapy appeared to be more significant in lesions of less hemodynamic significance at baseline (<50 percent obstruction). Additionally, the number of new lesions was reduced by more than 50 percent in the patients taking pravastatin. Clinical events were also monitored, and a 60 percent reduction in fatal and nonfatal myocardial infarctions (p=0.05) was achieved in the pravastatin arm of the trial.

PRAVASTATIN ATHEROSCLEROSIS INTERVENTION PROGRAM.

The Pravastatin Atherosclerosis Intervention Program compiled the clinical results from the four major regression trials using pravastatin (PLAC-I, PLAC-II, REGRESS, and KAPS).[21] The trials had similar designs in that they were placebo-controlled, double-blind, regression studies using pravastatin monotherapy for a period of 24 to 36 months and were analyzed by vascular imaging (angiography or B-mode ultrasound). A total of 1891 participants were enrolled in these trials and were characterized by atherosclerosis in the presence of mild-to-moderate dyslipidemia. Pravastatin therapy resulted in a uniform reduction in LDL-C (27-28 percent), which was correlated with the subsequent rate of cardiac events. Whereas the cumulative absolute number of events was small, nonfatal and fatal myocardial infarction was reduced by 62 percent (p=0.001). Additionally, all-cause mortality was also evaluated and, although not reaching statistical significance, a 46 percent relative risk reduction was achieved. Reduction in stroke approached statistical significance with a 62 percent relative risk reduction (p=0.054). Pravastatin therapy was able to reduce each clinical outcome measurement and emphasized the potential benefit of statin therapy in angiographically demonstrable atherosclerosis even in the presence of mild dyslipidemia.

MONITORED ATHEROSCLEROSIS REGRESSION STUDY (MARS).

The Monitored Atherosclerosis Regression Study (MARS) was an angiographic trial in 270 male and female patients that analyzed the effect of lovastatin, 80 mg/d, versus placebo on progression of atherosclerosis.[22] The total cholesterol values in the MARS

trial ranged from 190 to 295 mg/dl, and angiographic requirements included at least two involved coronary segments with a minimum luminal narrowing in at least one vessel of 50 percent or greater (but not total occlusion). The MARS randomized both groups to receive dietary therapy, which consisted of 250 mg/d or less of cholesterol and 27 percent or less of the total calories obtained as fat. The primary endpoint was the per patient change in percent diameter stenosis using a blinded quantitative angiographic assessment. As a secondary endpoint, the global change score was determined, based on visual evaluation performed of expert angiographers who were blinded to treatment allocation and temporal sequence. Compared with baseline, lovastatin therapy lowered total cholesterol by 32 percent, which was accompanied by a decrease in LDL-C of 38 percent. APO B levels were decreased by 26 percent and HDL-C was increased by 8.5 percent. All of these were statistically significant changes.

The average percent diameter stenosis increased by 2.2 percent in patients who received dietary therapy alone and 1.6 percent in subjects randomized to lovastatin plus diet. The difference showed a favorable trend but was not statistically significant. However, when more angiographically significant lesions (> 50 percent luminal impingement at baseline) were analyzed, the average diameter stenosis was increased by 0.9 percent in placebo patients and decreased by 4.1 percent in lovastatin recipients, indicating highly statistically significant regression (p=0.005). Additionally, the visually analyzed mean global score was +0.9 and +0.4 in the diet and lovastatin group, respectively, indicating a slowing of progression (p=0.02). Twenty-eight lovastatin recipients had global change scores suggestive of regression, compared with only 13 patients randomized to dietary therapy alone (p=0.02).

The MARS also analyzed the role of triglyceride-rich lipoprotein particles in the progression of atherosclerotic lesions.[23] Although lovastatin significantly reduced the level of *cholesterol-rich* APO B-containing particles (designated as LpB), there was little effect on the more complex *triglyceride-rich* APO B-containing particles (designated as LpB_c). The latter set of lipoproteins were statistically higher in lovastatin-treated patients with progression in the study (p=0.02).

A possible explanation for this finding involves some discussion of triglyceride-rich lipoprotein metabolism. Apolipoprotein C-II (APO C-II) is the normally occurring activator of the endothelium-bound enzyme lipoprotein lipase, which is involved in the catabolism of triglyceride-rich VLDL and chylomicrons. Apolipoprotein C-III (APO C-III) appears to inhibit the activity of this enzyme. Thus, the relative concentrations of these apolipoproteins with opposing functions may play a role in the rate at which triglyceride-rich particles are catabolized. Increased amounts of APO C-III sequestered in HDL may be indicative of enhanced chylomicron and VLDL catabolism, thus decreasing the exposure of these potentially atherogenic particles to the vascular endothelium. This rationale seems to corroborate the findings in the placebo group, in which higher levels of triglyceride and APO C-III in very-low-density lipoprotein (VLDL)+LDL were associated with progression (p=0.05). In the combined groups, progressors had significantly higher on-trial triglycerides, VLDL-C, APO C-III in VLDL+LDL, APO C-III, APO B, and total cholesterol. Another important finding was that subjects who underwent angiographic progression had significantly lower levels of APO AI-containing particles (which include protective HDL) when compared with

nonprogressors.

The potential role of triglyceride-rich lipoproteins was also analyzed in the MARS trial using carotid arterial wall intimal media thickness.[24] Analytical ultracentrifugation was used to determine the levels of lipoprotein subclasses, including triglyceride-rich intermediate-density lipoprotein (IDL). The rate of atherosclerotic progression of the distal common carotid artery was determined by measuring intimal media thickness by high-resolution B-mode ultrasound at 6-month intervals during the trial. The major APO B-containing lipoproteins were analyzed, and IDL levels had a strong positive correlation with the degree of progression of carotid artery intimal thickness ($r=0.21$, $p<0.005$). Carotid artery thickness has been used in other trials as a surrogate measure for the subsequent risk for developing stroke and CHD. Because the normally performed measurements of LDL also include measurement of IDL, the risk for atherosclerosis that is generally attributed to LDL may be at least in part a consequence of lipoproteins within the IDL subfraction.

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LIPOPROTEIN AND CORONARY ATHEROSCLEROSIS STUDY (LCAS).

LCAS was an angiographic trial that analyzed the effect of fluvastatin on coronary atherosclerosis in 429 men and women (19 percent women), aged 35 to 75, with angiographic evidence of coronary disease but relatively normal LDL-C (mean LDL-C 146 mg/dl, inclusion range 115-190 mg/dl).[25] Patients qualified for randomization with an angiographically demonstrable stenosis of 35 to 75 percent using caliper measurements as a screening mechanism. Treatment was diet plus either placebo or fluvastatin, 20 mg twice a day. Because a number of angiographic and clinical trials had previously demonstrated angiographic and clinical benefits with lipid-lowering therapy, it was considered ethical to treat patients whose LDL-C levels remained above 160 mg/dl despite dietary intervention with adjunctive cholestyramine, up to 12 g/d. The cohort randomized to fluvastatin therapy demonstrated improvement in the lipid profile with an 18 percent reduction in total cholesterol and a 26.5 percent reduction in LDL-C. HDL-C levels were increased by 5.5 percent, and triglycerides were reduced by 10 percent. Dietary therapy as administered in the control patients had minimal impact on the lipid profile.

The primary angiographic endpoint was changed in the minimum lumen diameter, and fluvastatin therapy resulted in a 0.028-mm decrease in this endpoint compared with a 0.100-mm decrease in the placebo ($p<0.01$). The LCAS data were analyzed further based on subgroups of patients who received fluvastatin monotherapy and those who received adjunctive cholestyramine. Significant benefit was observed in monotherapy patients, with a decrease in minimum lumen diameter of 0.024 mm compared with 0.094 mm with placebo ($p<0.02$). A similar trend was also observed in the subgroup who received cholestyramine, although this result did not achieve statistical significance because of the small number of patients. The percent diameter stenosis increased by 0.6 percent in fluvastatin patients compared with a 2.8 percent increase in patients randomized to dietary therapy. Angiographic benefit was observed if the baseline LDL-C

was either above 160 mg/dl or below 130 mg/dl, suggesting no threshold of angiographic benefit. The formation of new lesions also was decreased with fluvastatin therapy compared with placebo (p=0.03). Although LCAS was powered to assess angiographic changes, clinical events also were monitored for safety reasons. A trend in reduction in clinical event rates was seen using both fatal and nonfatal cardiac events. Myocardial revascularizations were reduced by 21 percent, and the rate for any cardiac morbid or any fatal event was reduced by 24 percent. Neither reduction was statistically significant.

In a post-hoc analysis, subgroup analysis of the LCAS patients stratified by baseline HDL-C levels was performed.[26] [26A] Patients with HDL-C levels less than 35 mg/dl had significantly more progression of angiographically determined atherosclerosis when analyzed by the decrease in minimum lumen diameter (Fig. 33-2) . However, fluvastatin therapy in this subgroup also resulted in the greatest angiographic benefit and improved event-free survival. This analysis of the LCAS data suggests that angiographic benefit may be obtained in patients with relatively normal LDL-C levels and reduced HDL-C levels with statin therapy and foreshadows the clinical findings of the larger AFCAPS/TexCAPS to be discussed later.

POST CORONARY ARTERY BYPASS GRAFT (POST-CABG) TRIAL.

The Post Coronary Artery Bypass Graft (Post-CABG) trial examined the role of aggressive versus moderate lipid lowering in the prevention of atherosclerotic progression in saphenous vein bypass grafts. In addition, the potential role of low-dose warfarin as an antithrombotic and potentially antiatherosclerotic agent was addressed by the study's 2×2 factorial manner (aggressive vs. moderate×warfarin vs. no warfarin).[27] The Post-CABG study evaluated angiographic

Figure 33-2 Lipoprotein and Coronary Atherosclerosis Study (LCAS). In LCAS, which enrolled coronary artery disease (CAD) patients with mildly to moderately elevated LDL-C, patients with low HDL-C randomized to placebo had the most CAD progression at 2.5-year follow-up angiography. The low HDL-C subgroup also had the greatest benefit with fluvastatin therapy, although the primary effect of fluvastatin, like the other statins, is to reduce LDL-C. MLD=minimum lumen diameter; HDL-C=high-density lipoprotein cholesterol. (From Ballantyne CM, Herd JA, Ferlic LL, et al: Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy. Circulation 99:736-743, 1999. Copyright 1999, American Heart Association.)

progression in both native and saphenous vein grafts. Atherosclerosis in saphenous vein bypass grafts is a complex process involving intimal fibrous hyperplasia (which is a universal finding after the use of saphenous vein grafts as conduits) and classical graft atherosclerosis. Dyslipidemia is a significant modifiable risk factor for graft atherosclerosis in subjects who have undergone a coronary bypass operation. The annual rate of occlusion in saphenous vein grafts is significant and results in both recurrence of symptoms and increased utilization of health care resources with rehospitalization, angioplasty, and repeat operations.

Thrombosis is thought to play a significant role in obstruction of vein grafts, an

observation that provides the therapeutic rationale for the administration of warfarin in the Post-CABG trial. Warfarin had also been implicated as potentially playing a beneficial role in experimental atherosclerosis. The Post-CABG randomized 1351 men and women who had undergone bypass operations over a period of 1 to 11 years before the baseline angiogram. Qualifying lipids required the LDL-C level to fall between 130 and 175 mg/dl. At least one vein graft was required to be angiographically patent to qualify for randomization. The aggressive therapy group used an initial dosage of lovastatin of 40 mg/d, which could be uptitrated in an attempt to reduce LDL-C to less than 85 mg/dl. The moderate treatment group began lovastatin at 2.5 mg/d, and the dosage was doubled if necessary to achieve an LDL-C target level of less than 140 mg/dl. The Post-CABG trial was not a true statin monotherapy trial in that cholestyramine could be added if statin therapy did not achieve a level of at least 95 mg/dl in the aggressively treated group or 160 mg/dl in the moderate treatment group.

The Post-CABG trial used as its primary endpoint the mean per-patient percentage of initially patent grafts that had substantial progression of atherosclerosis (defined as a 0.6 mm or greater decrease in lumen diameter) using blinded computer-based quantitative angiography techniques. Aggressive therapy resulted in a significant reduction in LDL-C levels of approximately 40 percent from baseline, although the predefined goal of achieving LDL-C less than 85 mg/dl was not attained. The National Cholesterol Education Program guidelines for secondary prevention recommends an LDL-C level of less than 100 mg/dl, and lovastatin therapy was able to decrease LDL-C levels to a range between 93 and 97 mg/dl. In the moderate-treatment

group, an LDL-C reduction of approximately 15 percent achieved on-treatment LDL-C range between 132 and 136 mg/dl. Aggressive therapy did result in angiographic benefit, with 27 percent of the grafts in this group demonstrating progression compared with 39 percent of grafts for those who received moderate treatment ($p<0.001$). The addition of warfarin had no demonstrable benefit on the angiographic picture. The rate of revascularizations was 29 percent lower in the aggressive-treatment group than in the moderate-treatment group ($p=0.03$). The Post-CABG trial was the first trial to address the question of aggressive pharmacological lipid lowering versus a more moderate approach and the potential angiographic benefits of achieving LDL-C levels of less than 100 mg/dl as a predefined goal.

Combination Therapy

The two major combination therapy angiographic trials (Familial Atherosclerosis Treatment Study [FATS] and The Cholesterol Lowering Atherosclerosis Study [CLAS]) have been updated as to the mechanism of benefit of hypolipidemic therapy and the cumulative effects of long-term intensive treatment.

FAMILIAL ATHEROSCLEROSIS TREATMENT STUDY (FATS).

The FATS was originally performed as an angiographic trial that analyzed 146 men who were younger than 62 years of age at the time of randomization.[28] The entrance criteria were unique in that patients were selected on the basis of having an elevated level of APO B (
125 mg/dl), coronary atherosclerosis, and a family history of vascular disease. FATS was a 2 1/2 -year double-blind study that used both visual and quantitative analysis to assess the mean change in diameter stenosis and mean change in minimum luminal diameter in the 120 subjects who completed the study. Patients were randomized to one of three treatment groups: lovastatin, 20 mg twice a day, and colestipol, 10 g three times a day; nicotinic acid, 1 g four times a day, and colestipol, 10 g three times a day; or conventional therapy with diet, coupled with the potential to add colestipol if the LDL-C level remained elevated. The therapeutic interventions resulted in significant changes in LDL-C and HDL-C levels. The group randomized to receive lovastatin and colestipol lowered their LDL-C by 46 percent and raised their HDL-C by 15 percent. Nicotinic acid and colestipol therapy was associated with a reduction of 32 percent in LDL-C and an increase of 43 percent in HDL-C. Quantitative angiographic analysis revealed that 46 percent of the patients in the conventional therapy group demonstrated definite lesion progression in at least one of the nine proximal artery segments studied. Regression was the only change in 11 percent. By comparison, progression as the only change was less commonly documented among patients in the aggressive therapy group. Subjects who received lovastatin and colestipol had progression as the only change in 21 percent of the analyzed angiograms. Subjects who received niacin and colestipol had regression as the only change noted in 25 percent. Regression was documented more frequently in the lovastatin-colestipol and nicotinic acid-colestipol groups (32 percent and 39 percent, respectively, $p<0.005$). However, when the mean percentage change in stenosis was quantitatively determined, the absolute degree of change was relatively small. Colestipol-lovastatin resulted in a -0.7 percent change in stenosis, and colestipol-nicotinic acid resulted in a -0.9 percent change. The conventional therapy group demonstrated angiographic progression with an average of 2.1 percent increase in luminal stenosis.

Despite these relatively modest changes in angiographic appearance of the vessels, a significant impact on clinical cardiovascular events was demonstrated. The tabulation of clinical events included death, nonfatal myocardial infarction, or refractory ischemic symptoms that required revascularization. In the 52 patients originally assigned to conventional therapy, 11 events occurred compared with only 3 events in the 46 patients assigned to receive lovastatin-colestipol and 2 events in the 48 patients assigned to receive nicotinic acid-colestipol. Overall, intensive lipid therapy reduced the incidence of clinical events by 73 percent, which was statistically significant, with the majority of endpoints occurring in subjects with mild to moderate obstructions (<70 percent stenosis) at baseline.

The 10-year follow-up of the FATS trial has recently been presented. Subjects who completed the original 2.5-year angiographic study were offered the opportunity to continue indefinitely on triple therapy, which included nicotinic acid, 2.5 g/d, colestipol, 20 g/d, and lovastatin, 40 mg/d. A total of 75 patients agreed to continue in the trial and were followed for a period of 8 years. The remainder of the subjects were returned to their private physicians and received usual care (n=101). Triple therapy resulted in a

dramatic alteration of the lipid profile in the 75 patients who continued in the trial. Baseline LDL-C was decreased from 202 to 106 mg/dl, which compared with a decrease from 188 to 166 mg/dl in the usual care group. HDL-C was increased by triple therapy from 43 to 53 mg/dl compared with an increase from 38 to 40 mg/dl change associated with usual care. Triglyceride levels were increased in the usual care group (208 to 220 mg/dl), and a significant decrease in triglycerides from 210 to 134 mg/dl was achieved by triple therapy. Morbidity and mortality data were obtained, and a 19.8 percent death rate was demonstrated in the usual care group compared with 1.3 percent death rate in triple therapy. Cardiovascular events, which included both cardiovascular deaths and nonfatal MI, were also significantly altered by triple therapy. A total of 5.3 percent of the triple therapy patients had a cardiovascular event compared with a 14.8 percent event rate in the usual care group. FATS demonstrates the benefits of long-term and aggressive therapy, and the event curves diverged steadily over the 10-year duration of the trial.

CHOLESTEROL LOWERING ATHEROSCLEROSIS STUDY (CLAS)

The original CLAS evaluated the combination of nicotinic acid and colestipol in subjects who had undergone coronary artery bypass. CLAS-I randomized 188 nonsmoking males, aged 40 to 50 years, whose cholesterol levels ranged from 185 to 350 mg/dl to receive nicotinic acid (3-12 g/d) and colestipol (30 g/d) versus dietary therapy over a 2-year period. Combination drug therapy reduced total cholesterol by 27 percent, which was associated with an LDL-C reduction of 43 percent. Triglyceride levels decreased 22 percent, and HDL-C levels increased 37 percent. All induced lipid changes in the dietary group were less than 5 percent when compared with baseline. Regression was demonstrated in 16 percent of the intervention group and 4 percent of the dietary group, a statistically significant improvement with combination therapy. At 2 years, the mean global score in the drug treatment group was 0.3, compared with 0.8 in the placebo group, indicating a reduction in the overall progression of coronary disease.

In CLAS-II, 103 men completed an additional 2 years of follow-up, during which they maintained the induced changes in the lipid profile.[29] Global coronary score indicated progression in 48 percent of the drug treated group compared with 85 percent of patients in the placebo group. Regression was observed in 18 percent in the drug-treated group and 6 percent in the placebo, a difference that attained statistical significance (p=0.04).

Annual follow-up for an average of 7 years has been carried out in the subjects who completed the 24-month angiographic study.[30] The cohort was evaluated for clinical coronary events, and a total of 55 of the 162 subjects had one or more documented coronary events (need for revascularization, nonfatal myocardial infarction, or coronary death). Combination drug therapy resulted in a reduction in cardiac events (22 vs. 33), and a statistically significant relative risk reduction of 40 percent for coronary events was attained and fatal and nonfatal myocardial infarctions were reduced by 60 percent. The risk for clinical coronary events was related to the degree of lesion progression in the native vessels or in bypass grafts. Additionally, reduction in minimum luminal diameter also contributed significantly to predict coronary events. The implication of the 7-year CLAS follow-up was that changes in sequential coronary angiographic lesions

can be used as surrogate outcome measures for the risk for developing future clinical coronary events, thus providing justification for the utilization of shorter and less expensive trials of lipid and nonlipid therapies.

HARVARD ATHEROSCLEROSIS REVERSIBILITY PROJECT (HARP)

HARP was an angiographic trial of the effects of combination hypolipidemic treatment in a group of subjects with documented coronary artery disease whose cholesterol levels ranged between 182 and 250 mg/dl with a mean level of 213 mg/dl.[31] Eligible patients had a 30 percent or more narrowing of the luminal diameter of a major coronary artery as the qualifying lesion. Therapy targeted a total-cholesterol goal of less than 160 mg/dl, with an initial therapy of pravastatin,

40 mg/d. Nicotinic acid (1.5-3 g/d), cholestyramine (8-16 g/d), and gemfibrozil (600-1200 mg/d) were added sequentially, as needed, to achieve this goal. In addition to this target, treatment was intended to achieve a ratio of LDL-C to HDL-C of less than 2. The original cohort consisted of 91 predominantly male subjects with a mean age of 57 years, and 13 percent of the patients did not complete the trial. The final group consisted of 70 men and 9 women who underwent angiographic analysis. The baseline and follow-up angiograms were analyzed quantitatively by operators blinded to treatment status.

Compared with placebo, combination therapy resulted in significant alterations of the lipid profile. Total cholesterol was decreased by 28 percent, which was accompanied by a decrease in LDL-C and APO B levels of 41 percent and 31 percent, respectively. Triglycerides were decreased by 26 percent, and HDL-C rose 13 percent. Despite significant alterations of the lipid profile by pravastatin with the inclusion of nicotinic acid in 38 patients, cholestyramine in 24 patients, and gemfibrozil in 12 patients, no benefit was seen in coronary obstructions.

Combination therapy resulted in a decrease in minimum lumen diameter of 0.14 mm in the combination therapy group and 0.15 mm in the control group. Progression of stenosis occurred in 23 percent of lesions in the group receiving combination therapy and 28 percent in the control group. Definite regression occurred in 13 percent of both groups. Clinical events were also monitored, and no benefit to combination therapy was observed, although there was a nonsignificant beneficial trend in reduced incidence of cardiac events (10 patients with events in the control group and 6 in the combination-therapy group). Thus, HARP differs from other angiographic or clinical endpoint trials, which showed event benefit and slowing of the progression rate with lipid modification.

Although the trial did not report significant effects on progression, it was analyzed as to efficacy of stepped treatment in reaching NCEP lipid goals.[32] Approximately 70 percent of the treatment group in the HARP needed combination therapy to achieve the NCEP

goal of less than 100 mg/dl for patients with evidence of coronary disease. In 18 of the 35 patients with baseline LDL-C greater than 130 mg/dl, pravastatin monotherapy at 40 mg/d decreased the mean LDL-C cholesterol level to 100 mg/dl after 6 weeks of therapy. The addition of nicotinic acid achieved this goal for an additional 15 subjects, so that a total of 33 of 35 patients in this group reached target. Based on these findings, the HARP investigators advocated pravastatin and nicotinic acid or pravastatin and gemfibrozil as reasonably well-tolerated combination therapies that were most likely to achieve LDL-C target guidelines, reduce triglyceride, and increase HDL-C in this type of patient population.

HARP has also analyzed the influence of pretreatment LDL-C concentration on coronary disease.[33] As evidenced by the REGRESS and LCAS, the effect of treatment in "normocholesterolemic" patients would appear to be clinically relevant, because it addresses the epidemiological observation of relatively normal cholesterol values in patients who nevertheless develop evidence of atherosclerotic disease. As one explanation for the findings of this study, the HARP investigators hypothesized that alteration of LDL-C levels that fell in the normal range may demonstrate a differential impact on angiographically determined atherosclerosis when compared with the impact in patients with more significant dyslipidemia. A retrospective analysis of the HARP and other trials suggested that the improvement in coronary luminal measurements resulting from LDL-C modification may be most marked in those studies with initially more severe LDL-C elevations.

B-Mode Ultrasound Trials

ASYMPTOMATIC CAROTID ARTERY PROGRESSION STUDY (ACAPS)

The ACAPS was a randomized, double-blind, placebo-controlled clinical study in which lovastatin and warfarin were employed to analyze the progression of intimal medial thickness in the carotid arteries and the potential effect on cardiovascular events.[34] The patient cohort consisted of 919 asymptomatic men and women with an age range between 40 and 79 years with early carotid atherosclerosis defined by B-mode ultrasonography coupled with an LDL-C between the 60th and 90th percentiles. Low-dosage aspirin at 81 mg/d was recommended for all groups. Lovastatin was begun at an initial dosage of 20 mg/d and could be uptitrated to 40 mg/d. Warfarin was maintained at 1 mg/d. The goal of lipid therapy was to decrease LDL-C to a range of 90 to 110 mg/dl. The average daily dose of lovastatin in ACAPS was 26 mg/d and resulted in a 28 percent reduction in LDL-C. Minimal increases in HDL-C (ranging between 5 and 10 percent) were demonstrated.

Lovastatin therapy resulted in a significant benefit in the primary endpoint, which was the progression rate of the mean maximum intimal medial thickness. Based on ultrasound examination, an early increase in the progression rate in both the placebo and lovastatin groups over the initial 6- to 12-month period was followed by continued intimal thickening in the placebo group, as opposed to regression in the lovastatin group. Warfarin therapy did not result in significant alterations of the lipid profile or intimal thickness, although regular aspirin users demonstrated an increased benefit in LDL-C lowering with lovastatin administration. The changes in intimal medial thickness

in the ACAPS trial were similar to changes in luminal diameter that had been reported in coronary angiographic trials using lipid lowering with statins. Cardiovascular events were substantially fewer in the active therapy group, with a total of 14 events in the placebo group compared with 5 events in the lovastatin group (p=0.04). Total mortality was also analyzed, and eight deaths occurred in the placebo group compared with 1 death in the lovastatin group, a statistically significant difference (p=0.02).

The role of estrogen replacement therapy was evaluated in a subset analysis of the 186 postmenopausal women enrolled in the ACAPS.[35] A total of 34 percent of the women in the ACAPS trial were on estrogen therapy and had a more favorable lipid profile, which was characterized by an improved LDL-C to HDL-C ratio. Body mass index, baseline blood pressure, and intimal medial thickness were not different between women who used estrogen and those who did not. However, intimal medial thickness tended to progress in women who were not utilizing estrogen replacement and tended to regress among estrogen users (p=0.05). The changes in intimal medial thickness appeared to be independent of changes in lipoprotein concentrations. Lovastatin was associated with a 25 percent reduction of LDL-C in both users and nonusers of estrogen and had a significant impact on progression in these women. Although estrogen did not appear to have an additive effect with lovastatin, estrogen therapy may have an effect on intimal medial thickness in women not receiving active statin therapy and may aid in the slowing of progression of early carotid atherosclerosis.

KUOPIO ATHEROSCLEROSIS PREVENTION STUDY (KAPS)

The KAPS was a population-based primary-prevention trial that analyzed the effect of pravastatin on LDL-C lowering and atherosclerotic progression in both carotid and femoral arteries.[36] The KAPS was designed with a 2 1/2 -month placebo and dietary lead-in period followed by a 36-month controlled treatment period. The femoral and carotid arteries were analyzed using high-resolution B-mode ultrasonography to analyze the extent of maximum carotid and femoral intimal thickness in four arterial segments. Pravastatin therapy resulted in significant improvement in the lipid profile with a 21 percent reduction in total cholesterol that was accompanied by a 27 percent reduction in LDL-C. HDL-C was decreased by 1.9 percent, and triglycerides were decreased by 7.6 percent. Minimal changes of the lipid profile were achieved in the placebo group.

Analysis of the ultrasonography data demonstrated that the annual rate of the progression in the placebo group was dependent on the degree of baseline intimal medial thickness. Subjects with a higher baseline degree of atherosclerotic involvement had a greater rate of progression over the duration of the trial. However, in the group randomized to pravastatin, there was no relation between the rate of progression and baseline intimal thickness. When analyzed for the determination of the rate of change quantified by millimeters per year, the pravastatin group demonstrated basically a continuous nonincreasing rate of progression regardless of smoking status or original intimal thickness. In contrast, the placebo group showed progressively increasing rates of intimal thickening that reached as high as 0.08 mm/yr in the smoking population of KAPS. Placebo nonsmokers experienced an increased progression rate for intimal thickness of 0.04 mm/yr, whereas pravastatin therapy yielded a progression rate of less than 0.02 mm/yr in both smokers and nonsmokers. The rate of progression in the

pravastatin group was significantly slowed by approximately 45 percent relative to placebo. The beneficial effect of pravastatin was also enhanced in subjects with low levels of circulating alpha-tocopherol. Although the number of cardiovascular events in the pravastatin group was lower than in the placebo group, especially for myocardial infarctions, the difference was not statistically significant because of the relatively few events.

Clinical Trials: Primary Prevention

THE AIR FORCE/TEXAS CORONARY ATHEROSCLEROSIS PREVENTION STUDY (AFCAPS/TexCAPS).

The AFCAPS/TexCAPS examined the potential impact of statin monotherapy in a cohort of subjects that included both middle-aged men and women whose total cholesterol and LDL-C approximated the national average as determined by the National Health and Nutrition Examination Survey (NHANES) III.[37] The AFCAPS/TexCAPS patient population was also characterized by an HDL-C that was less than the national average. The AFCAPS/TexCAPS was designed in a prospective, randomized, double-blind, placebo-controlled fashion to test the hypothesis that primary prevention with a statin would reduce cardiac event rates in a relatively low-risk cohort of 6605 men and women with no clinical

TABLE 33-2 -- PRIMARY-PREVENTION TRIALS OF STATIN THERAPY

	PRIMARY PREVENTION	
	WOSCOPS [38]	**AFCAPS/TexCAPS** [37]
N (% women)	6596 (0)	6605 (15)
Duration (yr)	4.9	5.2
Intervention	Pravastatin, 40 mg/d	Lovastatin, 20-40 mg/d
Baseline lipids (mg/dL)		
TC	272	221
LDL-C	192	150
HDL-C	44	36 men; 40 women
TG	164	158
% Lipid Changes, Treatment vs. Placebo		
TC	-20	-19
LDL-C	-26	-26
HDL-C	+5	+5

TG	-12	-13
Endpoints (% Changes in Risk), Treatment vs. Placebo		
Nonfatal MI/CHD death	31	-25
Fatal/nonfatal MI	--	-40
Acute major coronary events	--	-37
Total mortality	-22	+3 (NS)
CHD mortality	-28	Too few
Revascularizations	-37	-33
Stroke	-11 (NS)	

HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A; WOSCOPS=West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; MI=myocardial infarction; CHD=coronary heart disease; NS=nonsignificant; bold=study's primary endpoint; --=not reported.

evidence of atherosclerosis (Table 33-2) . The cohort ranged from 45 to 73 years of age for men and 55 to 73 years of age for women. Patients were excluded if there were historical evidence or symptoms of a definite prior myocardial infarction, anginal syndrome, claudication, or stroke. The entrance lipid criteria were cholesterol levels between 180 and 264 mg/dl, LDL-C of 130 to 190 mg/dl, and HDL-C of 45 mg/dl or lower in men or 47 mg/dl or lower in women. In addition to having no clinical evidence of CHD, only 12 percent of this cohort were active smokers, 22 percent were hypertensive, and 2 percent were categorized as diabetic. AFCAPS/TexCAPS is one of the first intervention trials to randomize a significant number of female subjects (n=997).

The primary endpoint was the effect of lipid lowering with lovastatin on the rate of first acute major coronary events, defined as a composite endpoint including fatal or nonfatal myocardial infarction, unstable angina, and sudden cardiac death. The study was designed with a 90 to 97 percent power to detect a 30 to 35 percent reduction in the number of participants with primary endpoint events. The inclusion of unstable angina as an endpoint was a unique feature of the trial and required the presence of new-onset exertional angina and/or accelerated or rest angina that was characterized by several objective clinical criteria. Unstable angina was prospectively defined, and the clinical criteria for the diagnosis were rigorously applied, including at least one of the following: electrocardiographic changes characterized by 1 mm ST segment depression in addition to a corresponding reversible defect on a stress perfusion study; angiographic findings of at least 90 percent epicardial stenosis, 50 percent left main coronary disease; or electrocardiographic stress testing that was associated with 1 mm ST segment depression with pain and stenosis of at least 50 percent in a major epicardial vessel.

A number of secondary endpoints were also included for analysis, including two components of the primary endpoint assessed individually. The secondary events were

coronary revascularization procedures, unstable angina, fatal or nonfatal myocardial infarction, all fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality, and CHD mortality. The trial was not powered for alteration of total mortality, but a tertiary objective was to investigate safety parameters including potential changes in both total mortality and noncardiac causes of death (e.g., violent death and malignancy).

A total of 3304 patients were randomized to receive lovastatin, which was administered over a 5-year trial period. Lovastatin was begun at 20 mg/d and could be titrated upward to 40 mg/d if the response was determined to be inadequate (LDL-C in excess of 110 mg/dl after 3 months of therapy). Lovastatin had a significant effect on lipid values, with a reduction of LDL-C of 25 percent compared with baseline. Total cholesterol was reduced by 18 percent, and triglycerides were reduced by 15 percent. HDL-C was increased by 6 percent, and the LDL-C:HDL-C ratio was decreased by 28 percent. The group randomized to diet and placebo had no significant changes in the lipid profile. Lovastatin therapy was equally effective in both men and women. Titration to a higher dose of lovastatin was required in 50 percent of the subjects in the AFCAPS/TexCAPS. Forty-two percent of the subjects randomized to lovastatin achieved the LDL-C goal of 110 mg/dl compared with 3 percent of the placebo group. Of the group randomized to lovastatin, treatment lowered LDL-C to more than 130 mg/dl for 81 percent compared with 12 percent of the placebo patients.

Lovastatin therapy resulted in a statistically significant 37 percent reduction in the incidence of a primary endpoint event ($p<0.001$). A total of 183 subjects in the placebo group had at least one primary endpoint compared with 116 subjects in the lovastatin group. Life-table plots suggest that a difference between treatment and placebo event curves began in the first year of therapy and continued to diverge throughout the remaining years of the trial. In absolute terms, 11 subjects per 1000 patient-years in the placebo group suffered an event compared with 7 subjects per 1000 patient-years in the lovastatin group. Lovastatin therapy resulted in consistent reductions in event rates in the secondary endpoints: a 33 percent risk reduction in revascularizations ($p=0.001$), a 32 percent risk reduction in unstable angina ($p=0.02$), 40 percent risk reduction in nonfatal or fatal myocardial infarctions ($p=0.002$), and 25 percent risk reductions in both coronary and cardiovascular endpoints ($p=0.006$ and 0.003, respectively). Among patient subgroups in the cohort (e.g., women, smokers, and hypertensives), the benefit of lovastatin treatment was comparable with the benefit in the overall cohort. The safety analysis demonstrated no increase in noncardiac mortality with lovastatin therapy, and the discontinuation rate was similar in the placebo and lovastatin-treated groups.

The AFCAPS/TexCAPS is the first major clinical trial of a statin to demonstrate reductions in first coronary events in a low-risk subgroup whose profile approximates the general U.S. population (Fig. 33-3). Additionally, a large proportion of the patient population was recruited from a wellness center, indicating a concern by the participants for a healthful life style. Primary-prevention trials in the past had focused on male subjects with severe dyslipidemia (e.g., Lipid Research Clinics Primary Prevention Trial) and excluded women. These results indicate that primary prevention is clinically feasible in a low-risk population, and benefit was consistent across the range of baseline LDL-C tertiles (Fig. 33-4). Of greater controversy is the issue of cost of primary prevention in

this type of cohort.

Figure 33-3 The five large-scale trials of statin therapy have shown consistent relative risk reductions for nonfatal myocardial infarction (MI) or coronary heart disease (CHD) death, or comparable reported endpoint. In 4S, major coronary events included coronary death, nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest. LDL-C=low-density lipoprotein cholesterol; 4S=Scandinavian Simvastatin Survival Study; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; CARE=Cholesterol and Recurrent Events; WOSCOPS=West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study.

WEST OF SCOTLAND CORONARY PRIMARY PREVENTION STUDY (WOSCOPS).

WOSCOPS extended the role of statin therapy in primary prevention to a relatively high-risk cohort.[38] In a double-blind, placebo-controlled design, WOSCOPS evaluated the effects of either a fixed dose of pravastatin, 40 mg/d, or placebo over a 5-year period (see Table 33-2) . The primary endpoint of WOSCOPS was the combined incidence of nonfatal myocardial infarction or death from CHD. Additionally, WOSCOPS evaluated total mortality, death from cardiovascular cause, and the frequency of coronary revascularization procedures as secondary endpoints. The trial included patients with a history of documented myocardial infarction or a pathological Q wave and an entrance cholesterol level of at least 252 mg/dl. The WOSCOPS cohort had a number of characteristics that placed them in a relatively high-risk group despite the clinical absence of atherosclerosis as defined by a prior infarction. All subjects were men who averaged 55 years of age. The average cholesterol was 272 mg/dl, which was associated with an LDL-C of 192 mg/dl. Triglycerides averaged 164 mg/dl, and HDL-C was 44 mg/dl. Approximately 5 percent of the total cohort had a positive Rose Questionnaire for anginal symptoms, 3 percent reported intermittent claudication, and 78 percent of the patients were either current or ex-smokers.

WOSCOPS was analyzed on an "intent to treat" basis. Pravastatin therapy resulted in significant improvements in the lipid profile, even when analyzed with this conservative statistical protocol. Total cholesterol and LDL-C were decreased by 20 percent and 26 percent, respectively. Triglycerides were decreased by 12 percent, and HDL-C was increased by 5 percent. Diet plus placebo therapy resulted in no significant change in the lipid parameters from baseline. The benefits of pravastatin therapy in WOSCOPS may be underestimated because of the significant dropout rate, which was approximately 15 percent at 1 year, 19 percent at 2 years, 23 percent at 3 years, and 25 percent at 4 years. The placebo and pravastatin group had similar dropout rates at all periods during the trial. The use of an "intent to treat" analysis of the West of Scotland trial reduces the potential for introduction of bias but may also underestimate the beneficial impact of pravastatin therapy in this group.

A significant reduction of 31 percent was achieved in the primary endpoint. Total

mortality was reduced by 22 percent, which closely approached statistical significance (p=0.051). No increase in noncardiovascular death rates could be demonstrated in the pravastatin group. When taking into account suspected coronary events, death from CHD was decreased by 33 percent (p=0.042). WOSCOPS also reported 31 and 37 percent reductions of coronary angiography and revascularization procedures, respectively (p=0.007 and 0.009, respectively). In the pravastatin group, 116 subjects had incident cancers compared with 106 in the placebo group; the difference was not significant. The number of patients in WOSCOPS reporting myalgia or elevated liver enzymes were also comparable between the two groups.

The West of Scotland trial established the benefit of statin therapy in a high-risk cohort who qualified for primary prevention by the absence of a known myocardial infarction. Pravastatin therapy demonstrated a significant reduction in coronary death and nonfatal myocardial infarction, and the event curves began to diverge within the first 12 months of therapy.

Cost-Effectiveness (see also Chap. 2) .

Primary prevention has been criticized in even high-risk groups for economic considerations. However, WOSCOPS has been analyzed from the perspective of cost-effectiveness, using cost data derived from calculation of the number of subjects needed to be treated to prevent one event.[39] Pravastatin therapy in a cohort of male subjects with similar patient characteristics to the WOSCOPS trial would prevent one event in 31 subjects who began pravastatin therapy over a

Figure 33-4 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Consistent benefit was observed across tertiles of LDL-C and HDL-C. Treatment appeared to "neutralize" risk associated with a low HDL-C or an elevated LDL-C. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Endpoint rate is the rate of the first primary endpoint event per 1000 patient-years at risk. (Adapted from Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. JAMA 279:1615-1622, 1998. Copyright 1998, American Medical Association.)

5-year period. Restriction of therapy to the 40 percent of men at highest risk (20 percent event rate in 10 years, in accord with European guidelines) reduces the number needed to treat to 22.5. A conservative estimate of the feasibility of treating patients like those in WOSCOPS was determined to be well within the range of interventions that are considered to be cost effective (approximately £8200 [$13,000 US] per year of life saved).

Clinical Trials: Secondary Prevention

CHOLESTEROL AND RECURRENT EVENTS (CARE).

The CARE trial analyzed 4159 subjects (3583 men and 576 women) who had suffered an acute myocardial infarction between 3 and 20 months before randomization and whose total cholesterol levels at baseline were less than 240 mg/dl.[40] Additional lipid criteria required the LDL-C to be between 115 and 174 mg/dl and the fasting triglycerides to be less than 350 mg/dl. Women were excluded if they were premenopausal, and individuals with ejection fractions less than 25 percent were not allowed to be randomized. Pravastatin was administered at 40 mg/d in a fixed dose; cholestyramine, 8 to 16 g, could be added to the designated therapy if the LDL-C levels remained at 175 mg/dl or more after intensified dietary therapy in both groups. The primary endpoint analyzed in the CARE trial was nonfatal myocardial infarction and death from CHD, which included several fatal coronary events (sudden cardiac death, death during a coronary intervention, or mortality from other coronary causes). The CARE trial was designed with an 80 percent power to detect a 20 percent reduction in the number of recurrent primary-endpoint events with pravastatin and was conducted on an intent to treat analysis using two-sided *p* values (Table 33-3) .

Pravastatin therapy resulted in significant improvement in the lipid profile and was well tolerated (approximately 94 percent of the treatment group were still on the randomized medication during the final 12 months of the follow-up period). Additionally, 6 percent of the patients in either placebo or the pravastatin group required adjuvant cholestyramine therapy. LDL-C that averaged 139 mg/dl at the time of randomization was decreased by 32 percent to 98 mg/dl during the trial duration. The total cholesterol was approximately 20 percent lower when compared with the placebo group. The HDL-C level in the group randomized to pravastatin was 5 percent higher when compared with dietary therapy, and the triglyceride decrease was approximately 14 percent.

The improvements in the lipid profile relative to the dietary intervention resulted in a significant 24 percent reduction in the primary endpoint (p=0.003). In absolute terms, 13.2 percent of the dietary group had a qualifying recurrent event compared with 10.2 percent in the pravastatin group. In addition to the impact on the primary endpoint, the subjects randomized to pravastatin had a 26 percent reduction in the rate of coronary artery bypass procedures (p=0.005) and a 23 percent reduction in the rate of angioplasty (p<0.001).

The CARE trial was also analyzed for the effectiveness of pravastatin relative to the baseline lipids using a quartile analysis.[41] High levels of LDL-C were associated with a significantly elevated frequency of events. In the placebo group, the analysis demonstrated a 28 percent increase in risk for a primary-endpoint event for each 25 mg/dl increment in LDL-C. Additionally, an inverse relation between baseline HDL-C and cardiac events was demonstrated: 10 percent decrease in coronary risk for each 10 mg/dl increase in HDL-C levels. This analysis is compatible with the epidemiological curvilinear relation between cholesterol and coronary event rates.

Diabetes.

A number of subset analyses of the CARE trial have been performed, including evaluation of older subjects, diabetics, women, and persons with cerebrovascular disease. The CARE data base analyzed fasting blood sugar as part of the screening evaluation that allowed evaluation

TABLE 33-3 -- SECONDARY-PREVENTION TRIALS OF STATIN THERAPY

	SECONDARY PREVENTION		
	4S [48]	**CARE** [40]	**LIPID** [47]
N (% women)	4444(19)	4159(14)	9014(17)
Duration (yr)	5.4	5	6.1
Intervention	Simvastatin, 10-40 mg/d	Pravastatin, 40 mg/d	Pravastatin, 40 mg/d
Baseline lipids (mg/dL)			
TC	261	209	218
LDL-C	188	139	150
HDL-C	46	39	36
TG	135	155	138
% Lipid Changes, Treatment vs. Placebo			
TC	-26	-20	-18
LDL-C	-36	-28	-25
HDL-C	+7	+5	+5
TG	-17	-14	-11
Endpoints (% Changes in Risk), Treatment vs. Placebo			
Nonfatal MI/CHD death	-34	**-24**	-24
Fatal/nonfatal MI	-42	-25	-24
Acute major coronary events			-29
Total mortality	**-30**	-9 (NS)	-22
CHD mortality	-42	-20	**-24**
Revascularizations	-37	-27	-20
Stroke	-30	-31	-19

HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A; 4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; MI=myocardial infarction; CHD=coronary heart disease; NS=nonsignificant; bold=study's primary endpoint; --=not reported.

of subjects with either frank diabetes or impaired glucose tolerance (110-125 mg/dl). A total of 586 patients in the CARE trial (14.1 percent of the total cohort) met the criteria for definite diabetes.[42] The nondiabetic population was subdivided into subjects with normal fasting glucose levels (<110 mg/dl) or impaired glucose tolerance (fasting blood sugar of 110-125 mg/dl). Diabetics experienced more recurrent coronary events (defined as coronary death, nonfatal myocardial infarction, or revascularization in this analysis) than nondiabetics (37 vs. 25 percent event rates, respectively). Pravastatin therapy resulted in a 25 percent reduction in the expanded endpoint in the diabetic patients. In 342 patients (8 percent of all subjects) who had impaired glucose tolerance, the rate of recurrent events was higher compared with those with normal glucose. Pravastatin was associated with a 50 percent lower recurrence rate (p=0.05 for nonfatal myocardial infarction).

The Elderly.

The CARE study examined the effects of pravastatin therapy in older subjects.[43] A total of 1283 patients whose age ranged between 65 and 75 years were enrolled in the CARE study and were included in a subgroup analysis. The older subjects had a higher frequency of hypertension and diabetes and, in addition, were more likely to be women. The older patients were less likely to be current or past smokers or to have a family history of CHD. Pravastatin therapy resulted in a qualitatively similar improvement in the lipid profile in the older population when compared with the younger group and there was no significant difference when patients were stratified to being older or younger than 65 years of age. In the older cohort, pravastatin therapy reduced the risk for a major coronary event by 32 percent, which was highly significant (p<0.001), and coronary death was decreased by 45 percent (p=0.004). Additionally, stroke rates were decreased by 40 percent (p=0.03). The CARE study is compatible with the premise that older patients should not be excluded from secondary intervention on the basis of chronological age alone, because the analysis revealed that for every 1000 patients, aged 65 years or older, who were treated for 5 years, 225 cardiovascular hospitalizations would be avoided compared with 121 cardiovascular hospitalizations in patients younger than 65 years of age.

Women.

The CARE study enrolled 576 postmenopausal women whose average age was 61 years, and these subjects were analyzed in a subgroup evaluation.[44] The baseline

characteristics of the men and women in the CARE trial differed generally because the female subjects were older and had a higher prevalence of hypertension, diabetes, smoking, and a family history of coronary atherosclerosis. Women additionally had a higher mean total cholesterol and a higher HDL-C level when compared with men whereas the LDL and triglyceride levels were similar. Of the female patients in CARE, 10 percent were on estrogen replacement therapy and 3 percent were on progesterone. Risk reduction for combined coronary events was statistically significant for both women and men. The relative risk reduction for combined coronary events in women was 46 percent compared with 20 percent in men (p=0.001 for both, p=0.048 for the interaction), and the risk reduction occurred earlier with the pravastatin treatment group in women, separating at approximately 1 year. When the impact of therapy was analyzed in female subjects, approximately 228 cardiovascular events could be prevented by treating 1000 women, similar to the CARE population, with pravastatin for 5 years.

Stroke.

Another interesting finding from CARE was the reduction in risk for stroke, a prespecified endpoint in this trial. The CARE population was analyzed for the rates of both cerebrovascular accidents and transient ischemic attacks after myocardial infarction.[45] The risk factor profile in the patient groups was comparable, and no significant differences were observed. Additionally, equal proportions of both groups were using antiplatelet therapy during the trial (85 percent). The CARE cohort was documented with a total of 216 combined strokes or transient ischemic attacks (92 on pravastatin and 124 on placebo), which accounted for a 27 percent reduction in the combined rate of cerebrovascular events (p=0.02). A total of 128 completed strokes (52 on pravastatin vs. 76 in placebo) occurred. Pravastatin therapy resulted in a 32 percent reduction in the rate of acute strokes that was also statistically significant (p=0.03). The benefit of pravastatin therapy persisted in multivariate analysis when the data were adjusted for age, sex, hypertension, cigarette smoking, diabetes, left ventricular ejection fraction, and lipid levels. Epidemiological studies have long raised the question of whether lipid lowering would be associated with an increase in hemorrhagic strokes, possibly through the disruption of membrane integrity due to cholesterol lowering. The CARE study did not demonstrate a significant change in the incidence of hemorrhagic strokes (two with pravastatin vs. six with placebo). Pravastatin therapy thus significantly decreased the rate of both transient ischemic attacks and completed cerebrovascular accidents in a post-myocardial infarction cohort.

Inflammation (See also Chap. 31) .

The role of inflammation in the initiation and progression of atherosclerosis has been the focus of intense investigation, especially the predictiveness of C-reactive protein and serum amyloid A as markers of inflammation. The CARE trial was analyzed in a nested, case-controlled manner to investigate the correlation between risk and the levels of these markers, as determined from prerandomization blood samples from the 391 participants in the CARE trial who subsequently developed an acute myocardial infarction.[46] The patients who suffered an acute event were compared with age- and sex-matched controls. C-reactive protein and serum amyloid A were statistically

increased in patients with events when compared with control patients. The population was divided into quintiles on the basis of C-reactive protein, and the highest quintile demonstrated a relative risk for a subsequent recurrent event to be 75 percent greater than that of subjects in the lowest quintile. The group with the greatest risk had elevated levels of both markers. The risk associated with elevated C-reactive protein and serum amyloid A appeared to be attenuated with pravastatin treatment. This subgroup analysis suggests a role for statin therapy above and beyond the traditional concept that attributes all of the benefits of such interventions solely to modification of LDL-C.

The CARE trial was a landmark study that demonstrated significant improvement in fatal and nonfatal myocardial infarction in secondary prevention despite normal baseline cholesterol levels. Subgroup analysis of the CARE trial demonstrated reductions in stroke and improvement in diabetics, elderly patients, and women. The CARE trial emphasizes the clinical utility of statin therapy in secondary prevention even with cholesterol levels that would be considered to be within the normal range.

THE LONG-TERM INTERVENTION WITH PRAVASTATIN IN ISCHAEMIC DISEASE (LIPID).

LIPID was an extremely large secondary-prevention trial that evaluated pravastatin in 9014 patients over a period of 6.1 years.[47] Patients enrolled in the LIPID trial had a broad range of cholesterol levels (155-271 mg/dl) and also included a large number of women (17 percent) (see Table 33-3) . Subjects randomized in the LIPID trial ranged from 31 to 75 years of age and were considered for inclusion if they had suffered an acute myocardial infarction or had a diagnosis of unstable angina that was established between 3 and 36 months before randomization. On the basis of post-myocardial infarction status, 64 percent of patients qualified for randomization whereas 36 percent were enrolled after a diagnosis of unstable angina. Patients were allocated to receive dietary advice and either 40 mg of pravastatin versus placebo. The

primary endpoint of the lipid trial was death from CHD. A number of secondary outcomes were also tabulated, including all-cause mortality, death from CHD, nonfatal myocardial infarction, stroke, revascularization procedures, hospital days, and death due to heart failure.

Pravastatin therapy effectively lowered lipid values, with the total cholesterol level falling 39 mg/dl from the original average value of 218 mg/dl. The pravastatin-induced reduction in total cholesterol was 18 percent greater than the effect of dietary therapy alone in the placebo group. The median LDL-C in the group randomized to pravastatin was initially 150 mg/dl and was reduced by 25 percent compared with placebo. Median triglyceride level was 142 mg/dl and was reduced by 11 percent. HDL-C was increased by 5 percent.

The primary outcome was significantly and favorably altered by pravastatin therapy. Overall mortality was 22 percent less in the group randomized to pravastatin, which was

highly statistically significant (p<0.001). In absolute terms, 11 percent of subjects randomized to pravastatin suffered a fatal event, compared with 14.1 percent in the placebo group. The relative risk reduction by pravastatin in deaths from CHD was reduced by 24 percent compared with placebo (p<0.001). In absolute terms, death from CHD was 6.4 percent in subjects randomized to pravastatin compared with 8.3 percent in the placebo group. A number of secondary endpoints, including the incidence of myocardial infarction, revascularization procedures, hospitalization for unstable angina, stroke and hospital days, were also significantly reduced by pravastatin therapy. Pravastatin therapy did not result in an increase in noncardiac deaths, and there were actually fewer deaths from cancer, trauma, or suicide in the group randomized to drug therapy, although this did not achieve statistical significance.

The clinical qualifying event (myocardial infarction or unstable angina) did not alter clinical benefit from pravastatin. The subgroup who entered the LIPID trial on the basis of a previous myocardial infarction demonstrated a reduction in mortality from CHD of 23 percent (p=0.004), and overall mortality was 21 percent lower when these events were compared with the placebo group (p=0.002). The cohort of patients who qualified for LIPID by unstable angina criteria reduced both coronary and overall mortality by 26 percent (p=0.036 and 0.004, respectively). The LIPID investigators prespecified a number of subgroups for detailed analysis, including older, hypertensive, and diabetic patients and patients who were smokers. The analysis demonstrated no evidence of significant heterogeneity of the treatment effect in any of these subgroups, suggesting consistency with the overall 24 percent risk reduction for the entire LIPID cohort. The LIPID trial evaluated a number of safety parameters, including malignancy. A total of 403 primary cancers occurred in patients randomized to receive pravastatin compared with 417 cancers in the control group, indicating no increase in malignancy from statin therapy. Deaths from violent behavior, suicide, or accidents were also not increased in the treatment group. Laboratory variables, including liver function tests and creatine kinase levels associated with myopathy, were evaluated and were essentially similar in the two groups.

Because of its large and diverse population, the LIPID trial provides extremely strong evidence that pravastatin therapy in secondary prevention is of clinical benefit across a broad range of baseline cholesterol values and is associated with a reduction in total and cardiac mortality without an increase in noncardiac deaths. The LIPID investigators estimated that for every 1000 patients assigned to treatment with pravastatin over a period of 6 years, a total of 30 deaths, 28 nonfatal myocardial infarctions, and nine nonfatal strokes could be avoided with effective lipid-lowering therapy.

SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY (4S).

The Scandinavian Simvastatin Survival Study (4S) was a large-scale, double-blind, placebo-controlled trial that evaluated the effect of simvastatin therapy in dyslipidemic patients who were either myocardial infarction survivors (63 percent), patients with the anginal syndrome (21 percent), or both (16 percent) in a 5.4-year trial.[48] The age inclusion criteria ranged from 35 to 70 years. Selected exclusion criteria included documentation of a recent myocardial infarction (<6 months); congestive heart failure requiring digitalis, diuretics, or vasodilators; cardiomegaly; atrial fibrillation; significant

valvular heart disease; completed stroke; concomitant serious illness; premenopausal status with childbearing potential; or statin hypersensitivity. Screening cholesterol values were required to exceed 213 mg/dl before randomization, and the range of cholesterol values after a 2-week placebo and diet phase had to range between 213 and 310 mg/dl. Patients were randomly assigned to receive either placebo or 20 mg of simvastatin per day with the allowance of dosage titration in an attempt to reduce the serum cholesterol to 116 to 200 mg/dl.

The primary endpoint of the 4S trial was the impact of simvastatin on total mortality. A number of secondary endpoints were also determined and included major coronary events (coronary deaths, acute myocardial infarction, resuscitated cardiac arrest, and definite silent myocardial infarction). Tertiary endpoints were also evaluated by the 4S investigators, which included any coronary or atherosclerotic event, death, myocardial revascularization, hospital admission for acute coronary events, and health care costs. A total of 4444 subjects fulfilled the entry criteria, with the major reasons for exclusion being hypertriglyceridemia, unwillingness to participate in a clinical trial, and cholesterol levels outside the prescribed range.

Simvastatin therapy resulted in a significant beneficial alteration of the lipid profile. A total of 37 percent of the patients randomized to simvastatin were uptitrated to 40 mg in the first 6 months of the trial because of failure to achieve the predefined lipid goal. Placebo and diet therapy resulted in essentially minimal changes in the lipid group except for the induction of mild hypertriglyceridemia. In the simvastatin group, total cholesterol was reduced by 28 percent, which was accompanied by a reduction in LDL-C levels of 38 percent (see Table 33-3) . The patients with significant hypertriglyceridemia before randomization had been excluded, and simvastatin therapy resulted in a 15 percent decrease in the patients who had initial triglyceride levels within the prescribed range of the trial. HDL-C was increased by 8 percent. Approximately 72 percent of the simvastatin therapy cohort achieved the total cholesterol goal.

The primary endpoint was achieved by simvastatin therapy, with a highly statistically significant relative risk reduction of 30 percent (p=0.0003) (Fig. 33-5). The absolute number of deaths totaled 438, with 256 subjects dying in the placebo group compared with 182 patients in the simvastatin group. The absolute risk reduction was 4 percent. Adjustment for baseline covariates resulted in no difference in total mortality or other endpoints. Safety analysis revealed no statistically significant alteration in the number of deaths from noncardiovascular causes when the simvastatin and placebo groups were compared. Specifically, there was no increase in the incidence of malignancies or violent deaths associated with hypolipidemic therapy that had been implicated in other epidemiological and intervention trials. The total frequency of adverse experience was similar within the treated and placebo group. A total of 6 percent of the patients (who were equally distributed in both active therapy and placebo) discontinued the study medication secondary to adverse events. One case of clinically significant rhabdomyolysis was documented in the simvastatin group.

Figure 33-5 Scandinavian Simvastatin Survival Study (4S). Kaplan Meier curves for all-cause mortality. Number of patients at risk at the beginning of each year is shown below the horizontal axis. (From Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study [4S]. Lancet 344:1383-1389, 1994.)

The 4S study was a landmark trial and demonstrated clearly that statin therapy could reduce total mortality in a secondary prevention trial. The most significant impact on mortality was due to the reductions in cardiovascular events. A number of substudies were also performed and demonstrated that simvastatin therapy was effective in women and older patients (age > 60 years).[49] Cerebrovascular events and new carotid bruits were also significantly reduced by simvastatin therapy.[50] Lp(a) was also measured in the 4S study and was a major predictor of morbidity in major coronary events.[51] The impact on clinical events is compatible with the angiographic studies (e.g., MAAS, CIS), which demonstrated that simvastatin therapy was able to alter beneficially the progression of angiographically demonstrable coronary artery disease.

Comparison Trials

ATORVASTATIN VERSUS REVASCULARIZATION TREATMENT (AVERT).

The AVERT trial was designed to evaluate the potential benefits of aggressive lipid lowering with atorvastatin, 80 mg/d, on ischemic events in a cohort of patients with stable atherosclerosis who were scheduled to undergo a percutaneous revascularization procedure.[52] The AVERT trial was an 18-month, open-label, randomized, multicenter study that evaluated 341 patients who were scheduled for elective angioplasty. Qualification requirements included at least one native coronary vessel with 50 percent or greater stenosis and an LDL-C in excess of 115 mg/dl. Subjects were excluded if the triglyceride levels were in excess of 500 mg/dl, ejection fraction was less than 40 percent, or the patients could not complete 4 minutes of exercise on a Bruce treadmill. Additionally, patients were excluded if angiography revealed left main or triple-vessel coronary atherosclerosis. Recent unstable angina and myocardial infarction (<14 days) also were major exclusion criteria.

The primary endpoint in the AVERT trial was the composite incidence of ischemic events, defined as cardiac death, resuscitation after cardiac arrest, nonfatal myocardial infarction, stroke, worsening angina, or revascularization (coronary artery bypass graft or repeat angioplasty). The patients randomized to usual care received traditional balloon angioplasty, and approximately one third of the treated lesions underwent placement of an intravascular coronary stent. The patients treated with angioplasty were allowed to receive hypolipidemic therapy as part of usual care. Lipid-lowering drugs were administered in 73 percent of patients in this group at some time during the follow-up (71 percent of the total group received statins). The subjects randomized to receive atorvastatin had a significant reduction in lipid levels with an LDL-C decrease from mean baseline value 145 to 77 mg/dl (46 percent reduction). Total cholesterol was decreased from 223 to 151 mg/dl (31 percent reduction). Triglycerides were also

decreased from 168 to 139 mg/dl (11 percent reduction), and HDL-C increased from 45 to 47 mg/dl. The usual care group experienced a decrease in LDL-C from 147 to 119 mg/dl (18 percent reduction). Total cholesterol decreased from 222 to 197 mg/dl (10 percent decrease). Triglycerides increased from 161 to 165 mg/dl, and HDL-C increased from 43 to 46 mg/dl. Total cholesterol, LDL-C, and triglycerides were significantly improved by atorvastatin relative to usual care.

The composite endpoint of ischemic events was reduced by atorvastatin therapy. A total of 22 ischemic events occurred in the group randomized to receive aggressive lipid-lowering therapy compared with a total of 37 events in the usual care group (36 percent reduction, p=0.048). The difference in the treatment arms trended toward adjusted statistical significance because the significance level was reduced to 0.045 because of the performance of two interim analyses. An increase in ischemic events, especially as related to the potential for enhanced rate of repeat percutaneous revascularization, may be expected in the early period after angioplasty.

An early increase in events in the intervention group was seen in the Randomised Intervention Treatment of Angina (RITA-2) trial, which compared angioplasty with medical therapy, although the event rate in angioplasty and medical care groups converged at the completion of the trial.[53] However, in the AVERT study, the difference between usual care and aggressive medical therapy continued to remain separate during the trial period. The AVERT study was evaluated for safety, and there was no clinically significant differences in other adverse events. A total of 2.4 percent of patients in the atorvastatin group had persistently elevated levels of aspartate aminotransferase and alanine aminotransferase compared with no patients in the angioplasty and usual care group. Rhabdomyolysis was not seen in either group. Seventeen serious adverse events were reported in the atorvastatin group, although none was attributed to atorvastatin. Twenty-eight of the patients in the angioplasty group had serious adverse events; six of these patients had events attributable to the angioplasty.

FIBRATE TRIALS

Angiographic

BEZAFIBRATE CORONARY ATHEROSCLEROSIS INTERVENTION TRIAL (BECAIT)

BECAIT was a double-blind, placebo-controlled, randomized trial using bezafibrate in young (<45 years of age) male survivors of a first myocardial infarction.[54] The patients were treated for 3 months with a dietary intervention before randomization. The young, post-myocardial infarction patients were chosen due to the fact that the investigators had previously identified a number of hemostatic and metabolic disturbances, including elevated fibrinogen, insulin resistance, and a lipid triad (high triglycerides, low HDL-C, and small dense LDL) in these and similar subjects. The study was designed to examine the

feasibility of altering the angiographic progress of atherosclerosis with diet and bezafibrate. The mean minimum lumen diameter was used as an index of focal atherosclerosis at the site of most severe atherosclerotic narrowing in the analyzed segment. Mean segment diameter was calculated in all coronary segments irrespective of the presence of visually detectable atherosclerosis as a means to establish an index of diffuse disease.

BECAIT was conducted for a 5-year period and randomized 92 patients (of whom a total of 42 patients randomized to bezafibrate and 39 patients randomized to placebo completed the trial). Angiographic analysis demonstrated that the median change in minimum lumen diameter was, on average, 0.13 mm less in the bezafibrate group when compared with placebo (p=0.049). The difference in mean change in segment diameter was not significant, although a trend was demonstrated that was compatible with slowing progression of atherosclerosis.

A number of lipid and hemostatic parameters were measured. Fibrinogen concentrations fell significantly in the bezafibrate group when compared with dietary therapy. Additionally, the increase in APO AI was three times greater in patients treated with bezafibrate compared with placebo. Serum concentrations of APO B were also decreased significantly in patients treated with bezafibrate. In the placebo group, 11 of the 45 patients had a coronary event (three reinfarctions, one reinfarction plus coronary artery bypass, three percutaneous transluminal coronary angioplasties, four coronary artery bypass surgeries), compared with three cardiac events in the bezafibrate group (one sudden cardiac death, one reinfarction plus CABG, one reinfarction and coronary death) (p=0.02). The cumulative event rates began to diverge after 2 years of follow-up.

Subsequently, the investigators evaluated the relative effects of apolipoproteins, LDL particle size, and other lipoprotein variables on angiographic progression.[55] Analysis revealed that the on-trial HDL_3 cholesterol and APO B concentrations were independent predictors of alteration of mean luminal diameter (r=-0.23, p<0.05) and percent stenosis (r=0.30, p<0.01), respectively. Alteration in the level of small, dense LDL was not related to progression of coronary disease nor were VLDL lipid concentration levels. The major effect of bezafibrate was a decrease in the rate of progression of coronary occlusions that were associated with a less than 50 percent stenosis at baseline.[56]

BECAIT was a small trial but is important in that it emphasizes the effect of patient selection relative to drug therapy. Whereas the phenotypic pattern of alterations of the lipid parameters in BECAIT appears different relative to the induced changes in the statin angiographic trials, bezafibrate retarded the progression of atherosclerosis to a similar degree. Although the precise mechanism of the benefit of bezafibrate cannot be deduced from the BECAIT, the results may be caused by a combination of triglyceride lowering, fibrinogen lowering, or other mechanisms involved in lipoprotein composition or apolipoprotein levels, in addition to classic alteration of lipid parameters.

LOPID CORONARY ANGIOGRAPHY TRIAL (LOCAT)

The LOCAT study group analyzed the effect of gemfibrozil in a cohort of male coronary artery bypass patients.[57] Patients were excluded if the HDL-C exceeded 42.5 mg/dl, the LDL-C exceeded 174 mg/dl, or triglycerides were in excess of 354 mg/dl. Additionally, patients who consumed more than 20 cigarettes per week or who had left ventricular ejection fraction less than 35 percent were also excluded. All patients were begun on a diet that contained approximately 30 percent of the caloric intake from fat. Patients underwent angiography, which was analyzed in a blinded fashion by a single investigator using quantitative computer-assisted analysis (Cardiovascular Measurement System).

A total of 395 subjects were randomized to receive sustained-release gemfibrozil, 1200 mg/d, or to continue on dietary therapy. The follow-up in LOCAT was excellent, with 94 percent of originally randomized patients receiving a follow-up angiogram that was performed at 32 months after allocation to treatment or placebo groups. Gemfibrozil reduced triglycerides by 36 percent, which was associated with an increase in HDL-C of 21 percent from baseline. Minimal changes in total cholesterol and LDL-C were obtained, and reductions of 5.5 percent and 4.5 percent, respectively, were achieved by gemfibrozil therapy.

The primary angiographic endpoint was the determination of changes in the average diameter of segments and minimum luminal diameter. The change in per-patient mean of average diameter in the native coronary segment was -0.04 mm in the placebo group and -0.01 mm in the group randomized to gemfibrozil (p=0.009). The changes in minimum luminal diameter of vessels involved by stenotic lesions were -0.09 mm in the placebo group and -0.04 mm in the gemfibrozil group (p=0.002). New lesions were also analyzed, and a total of 14 percent of the patient population who were assigned to dietary therapy developed new lesions compared with 2 percent in the group assigned to gemfibrozil (p<0.001). A trend toward treatment benefit was also demonstrated both in the segments that were not grafted and the coronary vessels distal to graft insertions, although neither reached statistical significance.

The LOCAT trial emphasizes the clinical importance of determination of the lipid phenotype as a guide to pharmacological decisions. Although all hypolipidemic agents exert some effect on total cholesterol, LDL-C, HDL-C, and VLDL-C levels, fibric acid derivatives may play an important role in patients with isolated low HDL-C or mild to moderate hypertriglyceridemia. The angiographic outcome in the LOCAT trial, which was designed for the evaluation of the impact of therapy on low HDL-C, was qualitatively similar to that of other angiographic trials that used statin therapy in patients with atherosclerosis and dyslipidemia characterized predominantly by elevated total cholesterol or LDL-C.

B-Mode Ultrasound

THE ST. MARY'S, EALING, NORTHWICK PARK DIABETES CARDIOVASCULAR DISEASE PREVENTION (SENDCAP)

The SENDCAP study analyzed cardiac outcomes in subjects with type II diabetes in a double-blind, randomized, placebo-controlled trial using bezafibrate.[58] Men and women with type II diabetes with an age range of 25 to 35 years and no history of clinical cardiovascular disease were considered for randomization. Entry requirements included a serum cholesterol value greater than 200 mg/dl, HDL-C less than 43 mg/dl, and triglyceride levels above 160 mg/dl. Additionally, the total cholesterol to HDL-C ratio had to be in excess of 4.7. Patients were analyzed for clinical evidence of acute myocardial infarction using hospital records, serial electrocardiograms (evaluated by the Minnesota code), and enzyme changes. The primary endpoint of the SENDCAP trial was the change in carotid intima media thickness analyzed by B-mode ultrasound over a 3-year trial period.

A total of 164 subjects were initially randomized, and 128 remained in the study for 3 years with no significant differences in the dropout rates between patients randomized to diet plus placebo or bezafibrate. Bezafibrate therapy resulted in significant alterations of the lipid profile relative to the dietary group. Total cholesterol was decreased by 7 percent, which was accompanied by a reduction in serum triglycerides of 32 percent (both of which were statistically significant). HDL-C was increased by 6 percent, and the total cholesterol to HDL-C ratio was decreased by 12 percent, which also reached statistical significance. A trend toward reduction of fibrinogen was noted (-18 percent with bezafibrate vs. -6 percent with placebo) that did not reach statistical significance (p=0.08). The primary endpoint of the SENDCAP trial was not achieved, and alteration of the intimal medial thickness was minimal, resulting in an inability to differentiate the bezafibrate and placebo groups. However, despite the lack of change in carotid ultrasound parameters, a statistically significant reduction in ischemic changes on the electrocardiogram combined with documented heart attack was observed. A total of 7 percent of the bezafibrate group had a definite coronary event compared with 23 percent of the control population (p=0.01).

The lack of correlation between carotid measurements and cardiac events could not be definitely explained by the data, although the relatively short follow-up period may have played a role in the failure to achieve a statistically significant correlation. Additionally, diabetics may have vascular changes that were present early in the course of disease that may not be identifiable by changes in intimal medial thickness and, additionally, may not be amenable to alteration of the lipid profile. However, the SENDCAP study did emphasize the impact of diabetes on coronary risk and demonstrated that alteration of HDL-C and triglyceride levels in a diabetic population may play a role in the reduction of coronary events using fibric acid therapy. This finding is compatible with retrospective subset analysis of the Helsinki Heart Study and also the analyses of the diabetic subgroups in major statin prevention trials such as the CARE[42] and 4S.[59]

Clinical Fibrate Trials

VETERANS AFFAIRS COOPERATIVE STUDIES PROGRAM HIGH DENSITY LIPOPROTEIN CHOLESTEROL INTERVENTION

TRIAL (VA-HIT).

VA-HIT was a multicenter, randomized study that assessed the potential effects of gemfibrozil at a dose of 1200 mg/d versus dietary therapy on the incidence of cardiovascular events in 2531 men with known coronary artery disease associated with low HDL-C levels.[60] Enrollment criteria for HIT required the HDL-C to be 40 mg/dl or less or the LDL-C to be less than 140 mg/dl and triglycerides to be 300 mg/dl or less.

The mean age in the VA-HIT trial was 64 years with more than 75 percent of the patients older than 60 years of age. A total of 90 percent of patients enrolled in HIT were white. The participants in the HIT trial were characterized by body mass index of 29 kg/m^2 and a waist-hip ratio of 0.96, with a 25 percent prevalence of diabetes mellitus. Approximately 57 percent of the population were hypertensive

Figure 33-6 Veteran's Affairs HDL Intervention Trial (VA-HIT): summary of major results. MI=myocardial infarction; CHD=coronary heart disease. (From Rubins HB, Robins SJ, Collins D, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 341:410-418, 1999.)

and 20 percent were smokers. Baseline lipids in the HIT trial revealed a total cholesterol of 175 mg/dl, HDL-C of 32 mg/dl, LDL-C of 111 mg/dl, and triglycerides of 161 mg/dl. Gemfibrozil therapy resulted in essentially minimal alterations in total cholesterol and LDL levels. Total cholesterol was decreased by 4 percent compared with placebo, and no significant change was demonstrable with LDL-C concentrations. Triglycerides, on the other hand, were decreased by 31 percent and HDL-C increased by 6 percent. The primary endpoint of the HIT trial was the combination of coronary death and nonfatal myocardial infarction. Patients randomized to receive placebo accounted for 275 events compared with 219 events in the gemfibrozil group. The decline in coronary events represented a 22 percent risk reduction that was statistically significant (p=0.006) (Fig. 33-6). The event curves began to diverge at approximately 2 years after the beginning of the trial.

A number of safety analyses were performed, and there was no difference in death from malignancies or violent deaths, as had been inferred from prior studies; and the only adverse event observed more frequently in the gemfibrozil group was dyspepsia (40 percent in gemfibrozil group and 34 percent in placebo group). The VA-HIT is an important study that reinforces the importance of targeting low HDL-C as a major coronary risk factor.

OVERVIEW

A recent meta-analysis has assessed the efficacy of a variety of pharmacological

lipid-modifying interventions on the major mortality outcomes.[61] The MEDLINE database from 1966 to 1996 was searched for placebo-controlled trials of cholesterol-lowering intervention that reported mortality data. A total of 59 trials had been reported at the time of the analysis, involving 85,431 subjects randomized to lipid lowering and 87,729 control patients, although the large AFCAPS/TexCAPS and LIPID trials were not included. A number of pharmacological interventions were used, including statins (13 trials), fibrates (12 trials), bile acid sequestrants (8 trials), hormones (8 trials), nicotinic acid (2 trials), n-3 fatty acids (3 trials), and diet (16 trials). The mortality data were analyzed using a 95 percent confidence interval for each mode of cholesterol lowering and two-sided *p* values.

The trials that used statin therapy achieved the highest degree of cholesterol lowering, with an average cholesterol reduction of 22.9 percent. The statin trials were the only agents to demonstrate a statistically significant reduction of mortality due to CHD, with a 31 percent reduction in death rates (0.69 risk ratio with a 95 percent confidence interval: 0.59 to 0.80). The trials using resins demonstrated a risk ratio of borderline significance (0.71 risk ratio with a 95 percent confidence interval of 0.51 to 0.99). The summary estimates for coronary mortality did not reach statistical significance for the other interventions.

Earlier meta-analyses had raised the possibilities that cholesterol lowering was associated with increased noncardiac mortality. In this review, the statins and n-3 fatty acids demonstrated a significant reduction in total mortality. The decrease in all-cause mortality risk was 21 percent in the statin trials and 32 percent in trials of the n-3 fatty acids (although the n-3 fatty acid trials evaluated relatively fewer subjects); noncoronary mortality was not increased with either drug class. Of the trials summarized, only those of hormone therapy suggested a potentially deleterious effect, with an increased risk for mortality from noncoronary and all causes. These findings provide evidence that lipid-lowering therapy with the statin class is effective and safe. Multivariate meta-regression analysis suggested that the degree of cholesterol lowering was the most powerful factor in determining the difference in mortality reduction across these trials.

Concepts and Controversies in Lipid Management

The current body of clinical trial evidence demonstrates persuasively the potential benefits of lipid modification, especially in the judicious application of pharmacological interventions. The clinical trials have sparked vigorous discussion over a number of important clinical questions: What is the best course of treatment and who should receive it? Which lipids and other risk factors should be targeted for intervention or risk stratification? What should be the goal of lipid-modifying therapy?

What Is the Best Course of Treatment and Who Should Receive It?

Although specific treatment recommendations are outside the purview of this chapter, life style modification remains the first line of treatment for most patients. Because of the clear benefits reported in clinical trials, drug treatment merits additional consideration when appropriate. Early trials of resins or nicotinic acid have shown beneficial effects on

coronary events and angiographic progression. In comparison with statins, resins and nicotinic acid are generally not as well tolerated and there is less evidence concerning event reductions (e.g., total mortality). Of the fibrates, data with gemfibrozil have been the most conclusive, although newer trials of fibrate agents may add to the therapeutic implications of this group.

Available data support the use of simvastatin, pravastatin, and lovastatin to prevent clinical cardiovascular events and angiographic progression and of fluvastatin to prevent angiographic progression. Trials are ongoing or in development to assess the clinical efficacy of atorvastatin, cerivastatin, and fluvastatin. The five landmark, large-scale trials of the HMG-CoA reductase inhibitors (see Fig. 33-3) have shown consistent, statistically significant reductions in relative coronary risk on the order of 20 to 40 percent, although the individual populations studied varied by composition, geographical location, and absolute risk for such events.

Subgroup analyses of the studies' cohorts suggest statin therapy was generally beneficial in women, hypertensives, older patients, and diabetics. In AFCAPS/TexCAPS, lovastatin

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treatment appeared to neutralize the excess absolute risk associated with a risk factor, such as low HDL-C (see Fig. 33-4) or cigarette smoking. Pending the results of trials designed specifically to assess treatment effects in special populations such as the elderly, the overall benefit observed in these trials may be extended to the following groups: the majority (if not all) patients with established coronary disease (4S, CARE, LIPID), high-risk primary prevention (WOSCOPS), and low-to-moderate risk primary prevention (AFCAPS/TexCAPS) (Fig. 33-7).

In secondary prevention, LIPID and 4S reported significant reductions in all-cause mortality, proving not only safety but also improved survival. WOSCOPS, LIPID, and CARE employed a fixed dosage of pravastatin (40 mg/day), whereas drug titration was used in 4S (20 to 40 mg of simvastatin) and AFCAPS/TexCAPS (20 to 40 mg of lovastatin) to achieve a cholesterol target. In practice, the decision to use a fixed-dosage or a titration strategy to treat dyslipidemia should be at the discretion of the physician's judgment, although both approaches yielded clinical benefit in trials.

Given the clear benefit and safety of statin treatment across the continuum of baseline risk for coronary disease, the question becomes then, who should receive treatment? The answer is controversial. In primary prevention, some investigators have argued that the relatively modest absolute risk reductions achieved in some lower risk cohorts, such as that of AFCAPS/TexCAPS, are disproportionate to the potentially prohibitive costs of providing such treatment to the general population.[62] [62A] [62B] Joint European guidelines have recommended that global risk assessment guide the decision to intervene, with drug treatment reserved only for patients who have an estimated absolute CHD risk of at least 2 percent a year.[63] Although issues of cost-effectiveness are important in the

modern medical office, patients should not be excluded from at least the consideration of effective intervention on the basis of economics alone. It is likely that this issue will be revisited in the next iteration of U.S. guidelines of the NCEP.

Which Lipids and Other Risk Factors Should Be Targeted for Intervention or Risk Stratification?

The increasing emphasis on global risk assessment represents a promising avenue in refining the identification of patients at risk for CHD. Policymakers will need to reconcile such assessment with the current U.S. practice of using a target LDL-C goal, as well as incorporate triglyceride and HDL-C into a treatment algorithm that favors LDL-C. Clearly, the results of the VA-HIT support the need for this latter refinement because benefit accrued from treatment in the face of an unchanged level of LDL-C.[61] In AFCAPS/TexCAPS, patients with below-average HDL-C benefited from a statin, despite the fact that the major effect of treatment was in reducing LDL-C.[38] With the results of both VA-HIT and AFCAPS/TexCAPS to consider, an open question remains of whether statin or fibrate therapy would be the ideal therapy for a population with isolated low HDL-C. Also, it remains to be answered whether the current NCEP definition of low HDL-C (<35 mg/dL) is the appropriate one for defining the risk factor or whether a new definition or possibly a target goal of treatment for HDL-C will need to be developed.

Another important area of inquiry will be to dissect out the relative contributions of lipid modification versus nonlipid effects of statins (e.g., improving endothelial function, reducing inflammatory activity) to the observed risk reductions. In WOSCOPS, the investigators hypothesized that a greater than predicted decrease in events in the treatment group may be due to such effects related to pravastatin.[64]

Finally, the incorporation of other risk factors such as insulin resistance,[65] endothelial function,[65A] genetic markers, [66] and inflammatory markers,[67] like C-reactive protein,[68] may help to define more precisely the individuals who would benefit the most from statin therapy, at what level of dyslipidemia, and at what age intervention should begin.

What Should Be the Goal of Lipid-Modifying Therapy?

Benefit was seen across the spectrum of clinical events associated with atherosclerotic cardiovascular disease, including fatal and nonfatal MI, unstable angina, coronary mortality (in secondary prevention), and the number of coronary artery bypass grafts and angioplasty procedures. One of the unexpected findings was the significant reduction in stroke or cerebrovascular events (stroke+transient ischemic attacks) observed in the secondary-prevention trials.[69]

Based on 4S and AFCAPS/TexCAPS data, no threshold value of cholesterol could be identified below which clinical benefit was not achieved, although the benefit of treatment may become attenuated as the cholesterol value declines.[70] In contrast, CARE investigators have reported that CHD patients with a baseline LDL-C of less than 125 mg/dl did not benefit from treatment in this study.[71] Furthermore, in WOSCOPS, the investigators concluded that an approximately 24 percent reduction of LDL-C was all that was needed to achieve maximum clinical benefit and that further reductions were

without additional advantage.[64] These post-hoc analyses have fueled the discussion of whether the relation between risk reduction and LDL-C change is linear (i.e., a straight-line function) or curvilinear or whether a threshold exists below which no further benefit can be obtained.[72] [72A] Of the reported trials, only the Post-CABG study has compared prospectively the efficacy of an aggressive versus moderate lipid-lowering strategy in patients with CHD.[27] However, larger clinical-event studies such as the Treating to New Targets (TNT) of atorvastatin and the Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH) of simvastatin and folic acid are currently under way and have the potential to resolve this controversy.

Figure 33-7 Large-scale clinical trials have supported the lipid hypothesis. The pyramid reflects relative applicability to the overall population, with the greater number of individuals at the base and the fewest represented at the apex. 4S=Scandinavian Simvastatin Survival Study; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; CARE=Cholesterol and Recurrent Events; VA-HIT=Veteran's Affairs HDL Intervention Trial; WOSCOPS=West of Scotland Coronary Prevention Study; LRC-CPPT=Lipid Research Clinics Coronary Primary Prevention Trial; Helsinki=Helsinki Heart Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study.

CONCLUSIONS

The earlier clinical primary-prevention trials (Lipid Research Clinic Coronary Primary Prevention Trial and Helsinki Heart Study) demonstrated that cholesterol lowering with bile acid sequestrants or fibric acid derivatives could decrease coronary morbidity and mortality. The advent of the statins has revolutionized the ability to manage dyslipidemia using agents that are highly efficacious with a favorable risk-to-benefit ratio. The lipid hypothesis has been validated by the large-scale trials that demonstrate clinical benefit across the spectrum of risk factor profiles (Fig. 33-7) . Meta-analysis of the majority of available lipid-lowering trials demonstrates clear clinical benefits of such intervention. The case for secondary prevention with lipid modification is compelling. Current and renewed efforts should be directed at determining long-term safety effects with pharmacological intervention and at implementing effective risk factor reduction in primary-prevention patients at increased risk for clinical coronary events.

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Chapter 34 - Coronary Blood Flow and Myocardial Ischemia

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HYPOXIA AND ISCHEMIA

Ischemia is characterized by an imbalance between myocardial oxygen supply and demand (Fig. 34-1) (Figure Not Available) . In some situations this imbalance is caused by a reduction of blood flow and oxygen supply secondary to increased coronary vascular tone, intracoronary platelet aggregation, or thrombus formation (see Fig. 36-1) ; This condition, termed *supply ischemia* or *low-flow ischemia,* is responsible for myocardial infarction and most episodes of unstable angina. In other instances, usually in the presence of chronic coronary obstruction, exercise, tachycardia, or emotion leads to an increase in coronary blood flow that is insufficient to meet the rise in myocardial oxygen demand. This condition is termed *demand ischemia* or *high-flow ischemia*. It is responsible for many episodes of chronic stable angina. Typically, myocardial ischemia results from both an increase in oxygen demand and a reduction in myocardial oxygen supply. For example, although exercise leads to an overall increase in coronary blood flow, most of the additional flow is distributed toward the subepicardium, whereas

subendocardial blood flow may even drop below its resting level. The ischemia of the subendocardium is then caused by both an increase in myocardial oxygen demand and a reduction in regional blood flow. *Hypoxia* is the condition in which oxygen supply is reduced despite adequate perfusion. It may be present in asphyxiation, carbon monoxide poisoning, cyanotic congenital heart disease, and cor pulmonale.

Low-flow ischemia, in contrast to *high-flow ischemia or hypoxia*, is characterized not only by oxygen deprivation but also by inadequate removal of metabolites consequent to reduced perfusion and by loss of vascular turgor.[1] Coronary flow and coronary perfusion pressure augment left ventricular systolic performance (Gregg effect) and reduce left ventricular diastolic distensibility (Salisbury effect). Buildup of tissue metabolites, especially inorganic phosphate, reduces calcium sensitivity of myofilaments, thereby diminishing contractility. Accordingly, in patients with low-flow ischemia, left ventricular systolic performance is lower and left ventricular diastolic distensibility greater than when the same patients were exposed to high-flow ischemia or hypoxia[1] (Fig. 34-2) . Myocardial ischemia may be manifest as anginal discomfort, breathlessness, deviation of the ST segment on the electrocardiogram, reduced uptake of a tracer substance in myocardial perfusion images, or regional or global impairment of ventricular function.

In this chapter, we consider first the determinants of myocardial oxygen consumption, then the control of coronary blood flow, and, finally, the hemodynamic consequences of ischemia.

Figure 34-1 (Figure Not Available) Factors influencing myocardial oxygen supply and demand.*(From Ardehali A, Ports TA: Myocardial oxygen supply and demand. Chest 98:699, 1990.)*

Figure 34-2 Differences among the left ventricular hemodynamic responses during low-flow versus high-flow ischemia. Tracings from a patient undergoing cardiac catheterization and balloon coronary angioplasty of two surface leads (I and II) and one precordial lead (V_5) of the electrocardiogram; the left ventricular dP/dt signal; and the left ventricular pressure recording at rest, at cessation of pacing during pacing-induced angina, at the end of a regular angioplasty balloon coronary occlusion, and at the end of an equally long angioplasty balloon coronary occlusion with distal hypoxic perfusion. Left ventricular diastolic pressure was higher (and left ventricular compliance lower) during pacing angina and at the end of balloon coronary occlusion with distal perfusion of hypoxic fluid (examples of high-flow ischemia) than at the end of the regular balloon coronary occlusion (example of low-flow ischemia).*(From De Bruyne B, Bronzwaer JG, Heyndrickx GR, Paulus WJ: Comparative effects of ischemia and hypoxemia on left ventricular systolic and diastolic function in humans. Circulation 88:461, 1993. Copyright 1993, American Heart Association.)*

DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION

The heart is an aerobic organ; it relies almost exclusively on the oxidation of substrates for the generation of energy, and it can develop only a small oxygen debt. Therefore, in

a steady state, myocardial oxygen consumption (MV_{O_2}) provides an accurate measure of its total metabolism.[2] The total metabolism of the arrested, quiescent heart is only a small fraction of that of the working organ. The MV_{O_2} of the beating canine heart ranges from 8 to 15 ml/min/100 gm, whereas the MV_{O_2} of the noncontracting heart is approximately 1.5 ml/min/100 gm. The latter is required for those physiological processes not directly associated with contraction. Increases in the frequency of depolarization of the noncontracting heart are accompanied by only small increases of MV_{O_2} [2] [3] [4] (Tables 34-1 and 34-2) .

MYOCARDIAL TENSION.

As early as 1916 Evans and Matsuoka concluded from studies of the Starling heart-lung preparation that "there is a relation between the tension set up on contraction and the metabolism of the contractile tissue."[5] In a systematic investigation of the relative effects of ventricular pressure, stroke volume, and heart rate on MV_{O_2}, it was found that ventricular pressure development is a key determinant of MV_{O_2}. These investigations suggested that MV_{O_2} per beat correlates well with the area

TABLE 34-1 -- MYOCARDIAL O_2 CONSUMPTION COMPONENTS

	TOTAL: 6-8 ml/min/100 gm		
Distribution			
Basal	20%	Volume work	15%
Electrical	1%	Pressure work	64%
Effects on MV_{O_2} of 50% Increases In			
Wall stress	25%	Heart rate	50%
Contractility	45%	Volume work	4%
Pressure work	50%		

The table demonstrates the dominant contribution to myocardial O_2 consumption (MV_{O_2}) made by pressure work and prominent effects of increasing pressure work and heart rate on MV_{O_2}

From Gould KL: Coronary Artery Stenosis, New York, Elsevier, 1991, p 8.

under the left ventricular pressure curve, termed the *tension-time index.*[5A] Subsequently, it was emphasized that the myocardial wall tension time integral is a more accurate determinant of MV_{O_2} than is the developed pressure.[6] [7] Later studies demonstrated that frequency of contraction is an important determinant as well. An augmentation of heart rate elevates MV_{O_2} by increasing the frequency of tension development per unit of time, as well as by increasing contractility.[6] [8]

Rooke and Feigl have provided evidence that MV_{O_2} is influenced by the degree of myocardial shortening during ejection of stroke volume, although less so than by tension

development.[9] They also provided an experimental basis for the use of the systolic pressure-rate product as an estimate of MV_{O_2} in the clinical setting. This index, frequently referred to as "double product," is used widely to estimate changes in MV_{O_2} during stimuli such as exercise or pacing tachycardia, although with only limited accuracy.[10] Reexamination of the determinants of MV_{O_2} has emphasized that they correlate closely with the left ventricular systolic pressure volume area,[11] [12] which consists of the sum of the area within the systolic pressure-volume loop, that is, the external mechanical work and the end-systolic elastic potential energy in the ventricular wall, the area enclosed by the systolic pressure-volume trajectory, and the E_{max} line[12] [13] (Fig. 34-3) .

MYOCARDIAL CONTRACTILITY.

In addition to the systolic pressure-volume area and heart rate, myocardial contractility is the third major determinant of MV_{O_2} [13A] The net effect of positive inotropic stimuli (e.g., Ca^{2+} and catecholamines) on MV_{O_2} is the end result of their influence on two

TABLE 34-2 -- DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION

Tension development
Contractile state
Heart rate
Shortening against a load (Fenn effect)
Maintenance of cell viability in basal state
Depolarization
Activation
Maintenance of active state
Direct metabolic effect of catecholamines
Fatty acid uptake

Figure 34-3 Myocardial oxygen consumption correlates with the left ventricular pressure-volume area (PVA). PVA is the area in the P-V diagram that is circumscribed by the end-systolic P-V line (E-C), the end-diastolic P-V relation curve (D-A), and the systolic segment of P-V trajectory (E-A-B-C-E). PVA consists of the external work (EW) performed during systole and the end-systolic elastic potential energy (PE) stored in the ventricular wall at end systole. EW is the area within the P-V loop trajectory (A-B-C-D-A), and PE is the area between end-systolic P-V line and end-diastolic P-V relation curve to the left of EW (E-C-D-E).*(From Kameyama T, et al: Energy conversion efficiency in human left ventricle.*

Circulation 85:988, 1992. Copyright 1992, American Heart Association.)

major determinants that change in opposite direction in the intact heart.[2] These are wall tension, which declines as a consequence of reduction in heart size, and myocardial contractility, which, by definition, is augmented by inotropic stimuli. In the failing, dilated ventricle, the increased contractility reduces the left ventricular pressure and volume. On the basis of the Laplace relation, the reduction in ventricular volume leads to a reduction in myocardial tension, which reduces MVO_2 . However, the decrease in MVO_2 that might be expected to result from falling ventricular wall tension is opposed by the increase in contractility, which tends to augment MVO_2 . Thus, the change in MVO_2 consequent to an inotropic stimulus depends on the extent to which intramyocardial tension is reduced in relation to the extent to which contractility is augmented. In the absence of heart failure, drugs that stimulate myocardial contractility elevate MVO_2 because heart size and therefore wall tension are not reduced substantially and do not off-set the effect on metabolism of the stimulation of contractility.

It has been suggested by Suga that almost the entire increase in MVO_2 produced by the administration of positive inotropic agents such as Ca^{2+} and epinephrine results from the energy costs of enhanced excitation-contraction coupling.[11] Specifically, the increased energy costs result from the greater and more rapid Ca^{2+} uptake by the sarcoplasmic reticulum (see Chap. 14) as well as from the increased contractile activity, rather than from a direct stimulating effect of positive inotropic agents on basal myocardial metabolism. In experiments in which the relative effects of changes in tension development and in myocardial contractility on MVO_2 were assessed in the same heart, the quantitative effects of changes of MVO_2 in contractility and tension development were found to be both substantial and of the same order of magnitude.[14]

MVO_2 is also influenced by the substrate used. Specifically, it correlates directly with the fraction of energy derived from the metabolism of fatty acids, which varies directly with the arterial concentration of fatty acids and inversely with that of glucose and insulin.[15]

REGULATION OF CORONARY BLOOD FLOW

During diastole, when the aortic valve is closed, aortic diastolic pressure is transmitted without impediment through the dilated sinuses of Valsalva to the coronary ostia. The aortic arch and sinuses then act as a miniature reservoir, facilitating maintenance of relatively uniform coronary inflow through diastole. The major coronary arteries and their principal branches that course across the epicardial surface of the heart serve as conductance (or conduit) vessels. Normal epicardial coronary arteries in humans are typically 0.3 to 5 mm in caliber and do not offer appreciable resistance to blood flow. Even at the highest level of blood flow, there is no detectable pressure drop along the length of human epicardial arteries.[16] Conductance arteries give rise to arterioles, which are resistance vessels 10 to 200 mum in diameter across which a larger pressure drop occurs. The dense network of about 4000 capillaries per square millimeter ensures that each myocyte is adjacent to a capillary. Capillaries are not uniformly patent because precapillary sphincters appear to serve a regulatory function in accordance with the flow needs of the myocardium. This capillary density is reduced in the presence of

ventricular hypertrophy.

As in any vascular bed, blood flow in the coronary bed depends on the driving pressure and the resistance offered by this bed. Coronary vascular resistance, in turn, is regulated by several control mechanisms that will be reviewed: myocardial metabolism (metabolic control), endothelial (and other humoral) control, autoregulation, myogenic control, extravascular compressive forces, and neural control. These control mechanisms may be impaired in diseases and thereby contribute to the development of myocardial ischemia.

HETEROGENEITY IN THE CORONARY RESISTANCE VESSELS.

Experimental methods to visualize coronary resistance vessels in the beating hearts of animals have become available,[17] and it has been learned that arterioles are specialized according to their size. For example, metabolic vasodilation occurs predominantly in the smallest arterioles less than 30 mum; intermediate arterioles 30 to 60 mum are the principal site of myogenic regulation, whereas the large arterioles 100 to 150 mum appear to be the sites of flow-mediated dilation.[17] [18] The system of multiple valves permits fine control of the coronary circulation. For example, according to a scheme proposed by Chilian,[17] the smallest arterioles dilate during metabolic stress, resulting in reduced microvascular resistance and increased myocardial perfusion. As the upstream arteriolar pressure decreases owing to a fall in distending pressure, myogenic dilation of slightly larger arterioles upstream occurs and causes an additional decrease in resistance. Increased flow in the largest arterioles augments shear stress and triggers flow-mediated dilation, further reducing the resistance of this network. Thus, coronary arterioles appear to have specialized regulatory elements along their length that operate "in series" in an integrated manner.

Metabolic Regulation

RELATIONSHIP BETWEEN CORONARY BLOOD FLOW AND MYOCARDIAL OXYGEN CONSUMPTION.

Coronary blood flow is closely coupled to MV_{O_2} in normal hearts. [7] This linkage is necessary because (1) the myocardium depends almost entirely on aerobic metabolism; (2) the oxygen saturation of coronary venous blood is low (25 to 30 percent at rest), permitting little additional oxygen extraction; and (3) oxygen stores in the heart are meager.

Changes in myocardial oxygen requirement lead to alterations in coronary vascular resistance with great rapidity,

generally in less than 1 second. For example, occlusion of a coronary artery for less than 1 second produces an increase in coronary blood flow above baseline after release

of the occlusion.[19] This response is called *reactive hyperemia*. The mechanisms that link increases in metabolic activity to reductions in coronary vascular resistance have been investigated extensively, but uncertainty still remains regarding the role of various mediators released from the myocytes and the endothelium.

ADENOSINE.

Adenosine has been investigated most extensively.[20] Adenosine is formed by degradation of adenine nucleotides under conditions in which ATP utilization exceeds the capacity of myocardial cells to resynthesize high-energy phosphate compounds (a process dependent on oxidative phosphorylation in mitochondria). This results in the production of adenosine monophosphate (AMP), and the enzyme 5 -nucleotidase is responsible for the formation of adenosine from AMP[21] (Fig. 34-4) . Accordingly, adenosine diffuses from myocytes into the interstitial fluid and the coronary venous effluent.[22] [23] Adenosine is a powerful coronary dilator and is considered to be an important, perhaps the critical, mediator of local metabolic regulation.[22] [23] Its production increases at times of an imbalance in the supply-to-demand ratio for oxygen,[20] and the rise in the interstitial concentration of adenosine parallels the increase in coronary blood flow.[24]

Many investigators believe that adenosine fulfills most of the criteria of a metabolic regulator of blood flow.[20] However, inhibition of adenosine, either by its destruction by adenosine deaminase or by administration of adenosine receptor antagonists, does not always reduce the magnitude of the hyperemia in response to metabolic stimuli in animals[25] or humans.[24] Thus, despite its acknowledged importance, adenosine is almost certainly not the *only* vasoactive factor involved in the metabolic regulation of coronary blood flow. Others may include nitric oxide (NO), vasodilator prostaglandins, adenosine triphosphate (ATP)-sensitive K^+ channels (K^+_{ATP} channels; see later), as well as myocardial oxygen and carbon dioxide tensions.[26]

NITRIC OXIDE (NO).

This substance increases blood flow during metabolic stimuli. Inhibition of NO reduces the magnitude of metabolic dilation in animals[22] [23] [27] and in the peripheral[28] and coronary circulation in humans.[29] NO production is augmented in response to metabolic stimuli by at least two mechanisms. Hypoxia is a stimulus to release of NO from the endothelium.[30] Furthermore, NO is a principal mediator of flow-mediated dilation. Although hypoxia may initiate hyperemia, flow-mediated dilation sustains

Figure 34-4 Schematic depiction of a myocardial interstitial space, an arteriole, and a capillary with the localization of enzymes involved in the formation and fate of adenosine. Adenosine formed by 5 -nucleotidase from adenosine monophosphate (AMP) (which in turn arises from adenosine triphosphate) can enter the interstitial space. There it can induce arteriolar dilation and reenter the myocardial cell, where it is either phosphorylated to AMP by adenosine kinase or deaminated to inosine monophosphate (IMP) by adenosine deaminase, or it can enter the capillaries and leave the tissue. A large fraction of adenosine that crosses the capillary wall is deaminated to inosine, which in turn is split to hypoxanthine

and ribose-1-PO_4 by nucleoside phosphorylase located in the endothelial cells, pericytes, and erythrocytes. Most of the adenosine is taken up by the myocardial cells, and that escaping into the circulation is largely in the form of inosine and hypoxanthine. Because adenylic acid deaminase (which deaminates AMP to IMP) is in low concentration in heart muscle, the major degradative pathway from AMP is by means of dephosphorylation to adenosine. Open circles=adenosine deaminase; closed circles=adenylic acid deaminase; triangles=nucleoside phosphorylase; dashed lines=5 -nucleotidase; dotted lines=adenosine kinase.*(From Berne RM, Rubio R: Coronary circulation. In Berne RM, Sperelakis N, Geiger SR [eds]: Handbook of Physiology, Section 2. The Cardiovascular System. Bethesda, MD, American Physiological Society, 1979, p 924.)*

and amplifies it. In support of this, inhibition of nitric oxide attenuates the late phase of reactive hyperemia, when flow-mediated dilation would be expected to occur.[28]

OTHER METABOLIC MEDIATORS.

Inhibition of the synthesis of vasodilator prostaglandins[29] and inhibition of K^+_{ATP} channels[31] also reduces metabolic vasodilation. It is likely that vasoactive factors act in concert to regulate coronary flow in response to metabolic needs. A loss or inhibition of one mediator is compensated for by upregulation of others. Although the inhibition of K^+_{ATP} channels, adenosine, and NO individually has at most a modest effect on the increase in coronary blood flow during exercise in dogs, inhibition of all three simultaneously nearly abolishes the flow increase.[32]

Endothelial Control of Coronary Vascular Tone

Vasoactive agents that influence the tone of large and small coronary vessels can be carried in the blood plasma (e.g., epinephrine, vasopressin) or released from circulating blood elements such as platelets (e.g., serotonin, adenosine diphosphate) or from nerve endings in the vascular adventitia (e.g., norepinephrine, vasoactive intestinal peptide). Furthermore, vasoactive factors can be formed locally by the vascular endothelium.

The vascular endothelium performs a wide array of homeostatic functions within normal blood vessels. Located between the vascular lumen and the smooth muscle cells of the vessel wall, the monolayer of endothelial cells is able to transduce blood-borne signals, sense mechanical forces within the lumen, and regulate vascular tone through the production of a variety of factors.[33] [34] Endothelium produces both potent vasodilators, such as endothelium-derived relaxing factor (EDRF, NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictors, such as endothelin-1. Endothelium-derived vasoactive factors are of great interest because endothelium can be damaged by atherosclerosis and by cardiovascular risk factors. Endothelial dysfunction may then lead to disturbances in coronary blood flow, can contribute to the pathogenesis of myocardial ischemia, and is a central feature in the evolution of atherosclerosis and thrombosis[35] (Fig. 34-5) (see also Chap. 30) .

ENDOTHELIUM-DERIVED RELAXING FACTOR.

Perhaps the most important vasodilator substance produced by endothelial cells is endothelium-derived relaxing factor (EDRF).[36] The discovery of EDRF in 1980 by Furchgott resulted from the observation that intact endothelium is required for acetylcholine-induced vasodilation.[37] In the presence of endothelium, acetylcholine produces dose-dependent vasodilation. When the endothelium is removed, only constriction is induced by acetylcholine. It became apparent that acetylcholine has two distinct and opposite actions on blood vessels: an endothelium-mediated dilation and a smooth muscle-mediated constriction (Fig. 34-6) . In any blood vessel, the net response is related to the sum of these two actions. In most healthy arteries, endothelium-dependent vasodilation predominates over direct vasoconstriction.[33]

EDRF has been identified as the nitric oxide (NO) radical.[38] [39] NO is formed in endothelial cells from the substrate L-arginine by the action of NO synthase (Fig. 34-7) . In this reaction, the terminal nitrogen from the guanadino group of L-arginine gives rise to NO. This reaction requires molecular oxygen, tetrahydrobiopterin (THB_4), NADPH, flavin adenine dinucleotide, and flavin mononucleotide as cofactors and produces L-citrulline as a byproduct that can be recycled to L-arginine. The activity of the enzyme is controlled by calcium and calmodulin.[38] [39] The relaxing effect of NO is mediated by its diffusion to smooth muscle cells,

Figure 34-5 Normal and dysfunctional endothelial cells, with some of the functions adversely influenced by hypercholesterolemia and atherosclerosis, which may contribute to acute coronary syndromes. t-PA:PAI-1=the ratio of tissue plasminogen activator to plasminogen-activator inhibitor type 1. EDRF=endothelial derived relaxing factor.*(From Levine GN, Keaney JF, Vita JA: Cholesterol reduction in cardiovascular disease. N Engl J Med 332:312, 1995. Copyright 1995, Massachusetts Medical Society.)*

where it causes an activation of intracellular guanylate cyclase, a rise in cyclic guanosine monophosphate (GMP), and a consequent fall in intracellular calcium.[40] Once released from endothelial cells NO has a very short half-life, limited by interaction with other free radicals in tissues, principally superoxide, and by entering red blood cells to react with oxyhemoglobin.[41]

In many vascular beds, NO is released continuously, contributing to the maintenance of a vasodilator state. Aside from acetylcholine, the release of NO above this basal level is stimulated by products of thrombosis (thrombin), aggregating platelets (serotonin, ADP), other chemical stimuli (histamine, bradykinin), and increased shear stress resulting from an increase in blood flow; the latter is responsible for so-called flow-mediated vasodilation[33] (Fig. 34-8) .

Figure 34-6 Relaxation by acetylcholine (ACh) of rings of rabbit thoracic aorta precontracted by norepinephrine (NE). Aortic rings were exposed to increasing concentrations of ACh with endothelium either intact or removed by rubbing with a wooden applicator stick. This representative tracing shows loss of relaxation in response to ACh with removal of endothelium and appearance of mild constriction. *(From Furchgott RF: Role of endothelium in responses of vascular smooth muscle. Circ Res 53:557, 1983. Copyright 1983, American Heart Association.)*

Vasoconstrictors, such as alpha-adrenergic agonists, may also stimulate the release of NO. Although their net effect on the blood vessel may be vasoconstriction, the presence of an endothelium-dependent vasodilating influence attenuates this constriction. Only a few vasodilators can act independently of the endothelium and directly on vascular smooth muscle. These include the nitrovasodilators (e.g., nitroglycerin, nitroprusside) and prostacyclin.[33] Adenosine elicits both endothelium-independent and endothelium-dependent dilation; at high concentration of adenosine, endothelium-independent dilation dominates while NO contributes to the dilator effects of adenosine at lower adenosine concentration.[42]

ENDOTHELIUM-DEPENDENT VASODILATION IN HEALTHY HUMAN EPICARDIAL ARTERIES.

Endothelium-dependent vasodilation as an important mechanism has been documented in many vascular beds throughout animal kingdom, including mammals, birds, and reptiles. The importance of

Figure 34-7 Endothelial cell production of nitric oxide (NO) by the action of nitric oxide synthase (eNOS) on L-arginine. This reaction requires a number of cofactors such as tetrahydrobiopterin (BH_4), calmodulin, and NADPH. eNOS stimulation by vasodilator agonists or shear stress is mediated by rise in intracellular calcium (Ca^{2+}). NO may be broken down by free radicals (O_2^-), producing peroxinitrite ($OONO^-$), which is vasoinactive. NO acts on vascular smooth muscle cells to cause relaxation by activating guanylate cyclase (GC), thereby increasing intracellular cyclic guanosine monophosphate (cGMP).

NO secretion in vasodilation of healthy human epicardial arteries was first demonstrated by intracoronary infusion of acetylcholine at the time of cardiac catheterization.[33] This vasodilation can be inhibited by specifically blocking NO synthesis with N^G-monomethyl-L-arginine (L-NMMA). Likewise, L-NMMA inhibits flow-mediated dilation of human epicardial arteries.[29] Other endothelium-dependent substances that have been shown to dilate healthy human coronary arteries include serotonin, histamine, bradykinin, and substance P.[33]

IMPAIRMENT OF ENDOTHELIUM-DEPENDENT VASODILATION IN HUMAN EPICARDIAL ARTERIES.

Evidence has accumulated that the tendency to inappropriate vasoconstriction that characterizes atherosclerosis is related to vasodilator dysfunction of the endothelium,

permitting unopposed constriction of vascular smooth muscle. Responses to endothelium-dependent stimuli that dilate healthy human coronary arteries have been found to be markedly impaired in patients with both early and advanced atherosclerosis. Acetylcholine constricts atherosclerotic coronary arteries, reflecting the loss of NO and acetylcholine's unopposed

Figure 34-8 High-resolution ultrasound images of the human brachial artery at baseline; dilation during reactive hyperemia following the release of a 5-minute occlusion (i.e., flow-mediated dilation); and dilation after the administration of sublingual nitroglycerin (endothelium-independent dilation). This flow-mediated dilation is mediated principally by nitric oxide.

Figure 34-9 Mechanisms of endothelial dysfunction with cardiovascular risk factors. Cardiovascular risk factors, including cholesterol, reduce the bioavailability of nitric oxide by reducing the transcription (1) or stability (2) of messenger RNA encoding for nitric oxide synthase; (3) interfering with coupling of endothelial receptors to associated pertussis-sensitive G-proteins; (4 and 5) causing accumulation of asymmetric dimethyl arginine (ADM-arginine), a competitive antagonist to L-arginine, the substrate for nitric oxide synthesis; (6) reducing the availability of tetrahydrobiopterin (TBH_4), a cofactor for nitric oxide synthase; and (7) increasing the generation of superoxide (O_2^-), which combines with nitric oxide to generate a vasoinactive product $ONOO^-$

constrictor effects on vascular smooth muscle.[33] [43] Although abnormal vasomotor responses to acetylcholine have served as a convenient marker of endothelial dysfunction, the role of acetylcholine in the physiological regulation of vascular tone has not been established. The finding of endothelial vasodilator dysfunction in human coronary atherosclerosis has been confirmed for other more physiological stimuli that release NO, including serotonin, ADP, and increased coronary blood flow (flow-mediated dilation). For example, whereas serotonin, a product released from aggregating platelets, dilates normal human coronary arteries it constricts atherosclerotic arteries.[33] [44] [45]

The loss of endothelium-dependent dilation occurs early in atherosclerosis, even prior to its detection by angiography.[46] [47] This loss of NO bioavailability is related to risk factors for atherosclerosis[48] and is caused by reduced synthesis as well as accelerated breakdown of NO (Fig. 34-9) .

TABLE 34-3 -- RISK FACTORS ASSOCIATED WITH IMPAIRED ENDOTHELIUM-DEPENDENT VASODILATION

Dyslipidemia
Hypertension
Diabetes mellitus

Cigarette smoking
Menopause
Hyperhomocysteinemia
Aging
Family history of coronary artery disease
Mutations in eNOS

All of the traditional risk factors and several newly described risk factors have been shown to be associated with a loss of endothelium-dependent dilation in human arteries (Table 34-3) . One of the first risk factors found to be associated with loss of endothelium-dependent dilation was dyslipidemia.[33] Although native LDL may be involved in this process, there is much evidence that damaging effects on endothelial NO bioavailability are mediated by its most atherogenic forms, including oxidized LDL[49] [50] [51] and small, dense LDL particles.[33] Lipoprotein lipases act on triglyceride-rich particles, such as chylomicrons and very low-density lipoprotein, to produce remnant particles. Remnant particles are also highly atherogenic and associated with endothelial dysfunction and reduced NO.[52] Subjects with lipoprotein lipase deficiency, less able to generate remnant particles, have preserved endothelial function despite having a marked elevation in triglycerides.[53] Lipoprotein (a) also leads to a reduction in NO, especially when levels of LDL cholesterol are concomitantly elevated,[54] whereas HDL appears to be protective. [55]

Cause and effect between risk factors and loss of endothelial function was established when risk factors were introduced experimentally (and temporarily) into healthy volunteers. Infusion of high concentration of glucose (to mimic an aspect of diabetes mellitus),[56] methionine loading (to raise homocysteine concentration),[57] or ingestion of fatty meal (to raise the concentration of lipoprotein remnant particles)[58] promptly reduced the availability of NO. Surgical ovariectomy in women free of cardiovascular disease (which produces premature menopause) is also followed by a rapid loss of NO, which can be reversed with estrogen replacement therapy.[59] Mutations in the enzyme NO synthase can be associated with impaired production of NO and are clinically manifested by propensity to coronary vasospasm, hypertension, and myocardial infarction.[60] [61] [62] This genetic aberration provides further proof of the importance of the NO system in the clinical setting.

ENDOTHELIUM-DEPENDENT VASODILATION IN HUMAN CORONARY RESISTANCE VESSELS.

Endothelium-dependent vasodilation operates not only in large (conductance) arteries, but it is also an important mechanism that controls dilation in small (resistance) vessels (Fig. 34-10) . Studies in the human forearm have suggested that *continuous* basal release of NO is an important determinant of resting vascular resistance and blood flow. When a specific inhibitor of NO synthesis, L-NMMA, was infused into the forearm of healthy subjects, resting blood flow was cut in half.[63] Systemic administration of L-NMMA induces hypertension in normal volunteers, suggesting that NO acts to lower

systemic vascular resistance.[64] NO release also reduces basal coronary vascular resistance and contributes to dilation in response

Figure 34-10 Increase in coronary blood flow velocity in response to acetylcholine, an endothelium-dependent agonist, in a patient free of coronary atherosclerosis. Coronary blood flow velocity was measured with a Doppler flow wire and increased 2.4-fold during acetylcholine administration; this increase in flow velocity (and blood flow) is indicative of normal endothelial function of resistance arterioles.

to a variety of endothelium-dependent agonists.[43] However, L-NMMA typically inhibits less than half of the vasodilation *stimulated* by various agonists in coronary and most other resistance vessels, suggesting that factors other than NO may play a role in the dilation of arterioles.[43] [65] [66]

Although atherosclerosis does not directly involve resistance vessels, coronary risk factors markedly impair the responses of resistance vessels to endothelium-dependent vasodilator stimuli.[33] [67] [68] This may not be altogether surprising, because risk factors are "systemic" in nature, potentially affecting the endothelial lining of all blood vessels.[69] The close correlation between the extent of NO deficiency in coronary resistance vessels and the failure of coronary blood flow to respond appropriately to metabolic stimuli suggests that endothelial dysfunction in resistance vessels may be an important factor in preventing coronary blood flow from rising during times of increased metabolic stress.[70] An inadequate augmentation of coronary blood flow in the presence of an increased metabolic demand may represent one of the mechanisms by which disturbances in endothelial function can lead to the development of myocardial ischemia in the setting of risk factors and atherosclerosis.

ENDOTHELIAL DYSFUNCTION AS A CAUSE OF MYOCARDIAL ISCHEMIA.

Impairment of endothelial function that occurs in atherosclerosis and in the presence of risk factors for atherosclerosis plays an important role in the subsequent development of coronary syndromes. When superimposed on coronary artery stenoses, loss of endothelium-dependent dilation and resultant unopposed coronary constriction predisposes to myocardial ischemia.[71] Several studies have documented the physiological importance of this mechanism in patients with stable angina. With exercise, performed at the time of coronary angiography, epicardial arteries of healthy subjects were noted to dilate. In patients with stable angina, however, paradoxical vasoconstriction typically occurred at the site of coronary stenoses or even mildly irregular arterial segments.[72] Changes during exercise parallel the responses observed in response to the endothelium-dependent agent acetylcholine. Exercise causes dilation of the arteries with normal endothelium (evidenced by a normal response to acetylcholine) but constriction of vessels with evidence of endothelial dysfunction.

A similar pattern of dilation of normal coronary arteries and paradoxical constriction of atherosclerotic coronary arteries with dysfunctional endothelium has been observed with mental stress, the cold pressor test, and increase in heart rate.[68] [71] [73] These stimuli are normally accompanied by activation of the sympathetic nervous system, by an increase in circulating catecholamines, and by increases in coronary blood flow secondary to a rise in myocardial oxygen demand. In patients with dysfunctional endothelium,

Figure 34-11 Nitric oxide, a multipotent molecule, inhibits recruitment of inflammatory cells, including monocytes, into the subendothelial space and their differentiation into macrophages. Specifically, nitric oxide inhibits the production of proinflammatory cytokines and chemokines (e.g., monocyte chemotactic protein-1 [MCP-1], interleukin-6 [IL-6], and interleukin-8 [IL-8]), reduces the expression of leukocyte adhesion molecules (LAMs), and inhibits factors that facilitate differentiation of monocytes into macrophages (e.g., macrophage colony stimulating factor [M-CSF]).

Figure 34-12 Increase in coronary blood flow evoked by graded doses of acetylcholine in control subjects and patients with microvascular angina. The dose-dependent increases in coronary blood flow produced by acetylcholine were significantly smaller in patients with microvascular angina than in control subjects ($p<0.001$ by two-way analysis of variance). Bars indicate the standard deviation. *(From Egashira K, et al: Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. N Engl J Med 328:1659, 1993. Copyright 1993, Massachusetts Medical Society.)*

the loss of flow-mediated and catecholamine-stimulated NO release permits unopposed constriction by catecholamines. Thus, the loss of NO may contribute to impaired dilation or exaggerated constriction of epicardial and resistance vessels and thereby to myocardial ischemia. Conversely, improvement in endothelial vasodilator function, achieved by cholesterol lowering therapy, is paralleled by a reduction in myocardial ischemia.[74]

Plaque fissuring or rupture with superimposed platelet aggregation and thrombus is a hallmark of unstable angina and myocardial infarction, but coronary constriction also plays an important role in these conditions.[75] The products of platelet aggregation and thrombosis, although dilating normal arteries, can severely constrict the atherosclerotic arteries of patients with coronary disease. As already noted, intracoronary administration of serotonin, a product released by aggregating platelets, constricts atherosclerotic coronary arteries.[76] The clinical significance of these findings is supported by the observations that patients with unstable coronary syndromes and complex plaques demonstrate augmented release of serotonin into the coronary circulation.[76] Patients with a recent history of myocardial infarction or unstable angina show evidence of endothelial vasodilator dysfunction in the infarct-related artery when tested with acetylcholine that is more pronounced than in arteries with stable stenoses of similar severity.[77]

Reductions in NO are associated not only with enhanced vasoconstriction at sites of

disrupted atherosclerotic plaques but also with a predilection toward the destabilization of plaques. Such plaque destabilization is characterized by an infiltration of inflammatory cells, release of enzymes that degrade extracellular matrix, and thinning of the overlying fibrous cap with propensity to rupture.[68] [78] Enhanced production of highly thrombogenic tissue factor by inflammatory cells also plays a central role in this syndromes.[79] NO is a multipotent molecule (see Fig. 34-5) that inhibits the recruitment and differentiation of inflammatory cells by inhibiting the production of chemoattractant cytokines, leukocyte adhesion molecules, and factors that encourage the differentiation of monocytes into macrophages[75] (Fig. 34-11) . NO also reduces the production of tissue factor. For these reasons, nitric oxide has become viewed as an important antiatherogenic[80] and plaque stabilizing[68] molecule.

The coronary resistance vessels may be affected by endothelial dysfunction in the *absence* of obstructive epicardial artery disease. Impaired endothelium-dependent dilation of coronary resistance vessels accounts for some of the cases of syndrome X, that is, anginal discomfort, evidence of myocardial ischemia on stress testing, and angiographically normal coronary arteries[81] [82] (Fig. 34-12) (see also Chap. 37) .

MANAGEMENT OF ENDOTHELIAL DYSFUNCTION.

The use of cholesterol-lowering agents (statins or cholestyramine) in patients with hypercholesterolemia has led to a rapid and significant improvement in endothelium-dependent dilation of coronary and peripheral arteries in patients with hypercholesterolemia[33] [68] [83] [84] (Figs. 34-13 and 34-14) . Interestingly, such rapid improvement in endothelial function could not be demonstrated in patients with relatively low serum concentrations of cholesterol, a finding that has a clinical counterpart in the results of several recent clinical event trials.

Aggressive reduction in cholesterol is associated with improved myocardial perfusion on positron-emission tomography[85] and a reduction in myocardial ischemia.[74] [86] Cholesterol-lowering markedly reduced evidence of myocardial ischemia on ambulatory electrocardiographic monitoring in patients with stable coronary disease and hypercholesterolemia over a period of 4 to 6 months, a time period that parallels the observed improvement in endothelium-dependent dilation observed in similar patients and duration of treatment[74] [86] (Fig. 34-15) .

Other strategies are effective at restoring endothelium-dependent dilation, augmenting myocardial perfusion, and reducing the severity of myocardial ischemia or symptoms of angina. These include the use of angiotensin-converting enzyme inhibitors,[87] antioxidants[88] [89] and the oral administration of L-arginine.[89]

ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR.

Convincing evidence has accumulated that factors other than NO and prostacyclin (see

later) can mediate endothelium-dependent vasodilation by hyperpolarizing the underlying smooth muscle. This hyperpolarization occurs through activation of Ca^{2+} -activated K^+ channels in vascular smooth muscle cells and has been attributed to a diffusible factor termed *endothelium-derived hyperpolarizing factor (EDHF).*[90] EDHF appears to be far more important in small arterioles than in larger conduit arteries.[91] [92] It is released by many of the same stimuli that stimulate NO, including acetylcholine, bradykinin, substance P, and shear stress.[90] [93] [94] [95] Although there may be more than one EDHF molecule, cytochrome P450 (CYP)-dependent metabolites of arachidonic acid (AA), especially the epoxide 11,12-epoxyeicosatrienoic acid, fulfill the essential criteria as mediators of endothelium-dependent hyperpolarization.[96]

EDHF has been demonstrated in human coronary[91] and peripheral arterioles in vitro. NO inhibits the production of EDHF.[97] It has been therefore suggested that when diseases reduce NO bioavailability, release of this intrinsic inhibition may maintain endothelial vasodilator function by upregulation of EDHF.[90] [97] Nevertheless, aging and long-standing hypercholesterolemia appear to reduce EDHF as well as NO in human peripheral arterioles. Just as NO, EDHF (11,12-epoxyeicosatrienoic acid) is a multipotent molecule with antiinflammatory properties.[96] The full significance of EDHF in normal human coronary physiology and abnormal pathophysiology remains to be established and awaits the availability of specific inhibitors of this pathway.

PROSTACYCLIN.

This is a potent vasodilator derived from the endothelium through the actions of cyclooxygenase. The role of prostacyclin in the control of vascular tone in humans has been controversial, at least until recently.[29] Administration of aspirin has little effect on arterial blood pressure in humans, suggesting that inhibition of cyclooxygenase does not cause generalized systemic vasoconstriction. Administration of indomethacin does reduce resting coronary blood flow in humans.[98] It has been suggested, however, that these coronary constrictor effects of indomethacin are not due to inhibition of prostacyclin synthesis.[98]

Although vascular prostacyclin production under physiological conditions appears to be low, patients with atherosclerosis have increased prostacyclin production.[99] In patients with coronary atherosclerosis or risk factors, administration of aspirin to inhibit cyclooxygenase has revealed that prostacyclin contributes importantly to resting vasodilator tone in epicardial arteries and resistance arterioles

Figure 34-13 Mean (+SE) change in coronary artery diameter in response to serial infusions of acetylcholine at baseline and after 1 year of therapy in the three study groups. The improvement in the response from baseline to follow-up in the LDL-lowering-antioxidant group was significantly greater than that in the diet group ($p>0.05$). Negative numbers indicate vasoconstriction.*(From Anderson TJ, Meredith IT, Yeung AC, et al: The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 332:488, 1995. Copyright 1995, Massachusetts Medical Society.)*

Figure 34-14 Segment of the circumflex coronary artery at initial and follow-up (5.5 months) studies in a patient with coronary atherosclerosis assigned to lovastatin. Both left panels demonstrate baseline (control) arteriograms; both right panels demonstrate postacetylcholine arteriograms. Substantial vasoconstriction occurs in response to the peak infusion of acetylcholine in the initial study, with marked improvement (a mild vasodilator response) in the follow-up study.*(From Treasure CB, et al: Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 332:481, 1995. Copyright Massachusetts Medical Society.)*

and plays a role in flow-mediated coronary dilation and metabolic vasodilation.[29] Thus, the prostacyclin-mediated coronary vasodilation appears to be most important in a setting characterized by a deficiency of nitric oxide and may provide a useful compensatory mechanism.

ENDOTHELIUM-DERIVED CONSTRICTING FACTORS.

The endothelium not only mediates vasodilation but it is a source of vasoconstrictor factors as well (Fig. 34-16) . The best characterized of these are the endothelins.[100] [101] Endothelin-1 (ET-1) is a 21-amino-acid peptide that has a potent vasoconstrictor activity. Two other isoforms of endothelin have been discovered (ET-2 and ET-3), but endothelium produces only ET-1. Synthesis of ET-1 is complex, starting with a large precursor molecule, preproendothelin, which is processed to "big endothelin" and finally converted by the action of endothelin-converting enzyme to the fully active ET-1.[100]

Unlike NO, which can be released rapidly in response to vasodilator stimuli and then inactivated within seconds, ET-1-mediated constriction is slow in onset and lasts over minutes to hours.[100] [101] Agents that stimulate ET-1, such as thrombin, angiotensin II, epinephrine, or vasopressin, do so by de novo transcription of messenger RNA. On the basis of these considerations, it is likely that ET-1 contributes to the regulation of vascular tone primarily by exerting a tonic vasoconstrictor influence. In addition to its vasoactive properties, ET-1 also stimulates smooth muscle proliferation,[102] vascular remodeling,[103] and leukocyte adhesion and recruitment[104] ; it may thereby play a role in inflammation and in atherogenesis.

Plasma concentrations of ET-1 are elevated in a number of cardiovascular disorders,[101] [105] including hypercholesterolemia, hypertension, atherosclerosis, acute myocardial infarction, and congestive heart failure (see also Chap. 16) . Aside from the endothelium, macrophages and activated smooth muscle cells are a rich source of ET-1 in the vessel wall. These cells are numerous in vulnerable or ruptured plaques. Consistent with this finding the culprit plaques of patients with acute coronary syndromes express significantly greater ET-1 immunoreactivity than plaques of patients with stable angina.[106] These plaques are also rich in lipid, and oxidized LDL is a potent stimulus to ET-1 synthesis.[107] [108]

ENDOTHELIN RECEPTORS.

ET-1 exerts its vascular effects by binding to two specific receptors named ET_A and ET_B. ET_A receptors are present on vascular smooth muscle cells and promote vasoconstriction[109] and smooth muscle proliferation. [102] ET_B receptors are located on endothelial cells where they mediate endothelium-dependent dilation

Figure 34-15 Effect of cholesterol lowering or placebo over 6 months on the number of episodes of ischemic ST-segment depression in patients with coronary disease. Two of 20 in the placebo group vs. 13 of 20 in the treatment group show resolution of ischemia.*(From Andrews TC, Raby K, Barry J, et al: The effect of LDL cholesterol reduction on myocardial ischemia in patients with coronary disease. Circulation 95:324-328, 1997.)*

Figure 34-16 Endothelium-derived vasoactive substances. The endothelium is a source of relaxins (bottom right) and contracting (bottom left) factors. ACE=angiotensin converting enzyme; Ach=acetylcholine; ADP=adenosine diphosphate; BK=bradykinin; cAMP/cGMP=cyclic adenosine/guanosine monophosphate; ECE=endothelin-converting enzymes; EDHF=endothelium-derived hyperpolarizing factor; ET-1=endothelin-1; 5HT=5-hydroxytryptamine (serotonin); L-arg=L-arginine; NO=nitric oxide; PGH_2 =prostaglandin; PGI_2 =prostacyclin; TGF beta1=transforming growth factor beta1; Thr=thrombin; TXA_2 =thromboxane A_2. Circles represent receptors (AT=angiotensinergic; B=bradykinergic; M=muscarinic; P=purinergic; T=thrombin receptor).*(From Luscher TF, Noll G: The endothelium in coronary vascular control. In Braunwald E [ed]: Heart Disease--Update 3. Philadelphia, WB Saunders Company, 1995, p 2.)*

by releasing NO and are also located on smooth muscle cells where they mediate constriction.[110] Antagonists of the ET receptors and inhibitors of the endothelin-converting enzyme have become available and are helpful in assessing the role of ET-1 in cardiovascular diseases. Bosentan, a mixed ET_A /ET_B receptor antagonist, was found to lower blood pressure in patients with essential hypertension,[111] which suggests a role for ET-1 in the pathogenesis of hypertension.[112] Inhibition of ET_A receptor by intracoronary infusion of a specific antagonist BQ-123 results in significant dilation of normal human epicardial arteries. This finding suggests that ET-1, through the ET_A receptor, is important to the maintenance of tonic coronary tone in humans. The use of ET inhibitors will be helpful in assessing the role that ET-1 plays in exaggerated constriction in patients with atherosclerotic coronary arteries.

Autoregulation of Coronary Blood Flow

When sudden alterations in perfusion pressure are imposed in many arterial beds

(including the coronary), the resulting abrupt changes in blood flow are only transitory, with flow returning promptly to the previous steady-state level[113] (Fig. 34-17) . This ability to maintain myocardial perfusion at constant levels in the face of changing driving pressure is termed *autoregulation*. Demonstration of autoregulation in the coronary bed is difficult in intact animals because aortic pressure is not only the perfusion pressure for the coronary circulation, but it is also the afterload for the left ventricle, a major determinant of MV_{O_2} . Coronary autoregulation has therefore been studied under experimental conditions where the coronary circulation is cannulated and perfused separately. [114] Under such controlled conditions perfusion pressure is altered, but ventricular pressure, cardiac contractility and heart rate--the principal determinants of MV_{O_2} (see p. 1088)--are maintained constant and autoregulation is clearly evident. In dogs the upper limit of autoregulation is 130 mm Hg, whereas the lower limit of autoregulation is 40 mm Hg.[115] That is to say, when mean aortic pressure is within this range, coronary perfusion is relatively constant. When aortic pressure falls below 40 mm Hg, coronary blood flow precipitously declines. When aortic pressure exceeds 130 mm Hg, coronary flow rises sharply.

Although autoregulation cannot be studied in detail in humans, it is perhaps the principal reason why patients with coronary artery disease and epicardial stenoses do not have evidence of resting perfusion deficits or myocardial ischemia at all times! Reductions in perfusion pressure distal

Figure 34-17 Autoregulation of coronary blood flow in the beating dog heart. The point where the curves cross represents the control steady-state pressure and flow. A sudden, sustained charge in perfusion pressure caused an abrupt change in flow represented by the filled symbols and black line (transient flow). The open symbols and red line represent the steady-state flows obtained at each perfusion pressure. The points represented by triangles were obtained after blockade of cardiac prostaglandin synthesis with indomethacin. *(From Rubio K, Berne KM: Regulation of coronary blood flow. Prog Cardiovasc Dis 18:105, 1975.)*

to stenoses are compensated for by autoregulatory dilation of the resistance vessels. Recently, perfusion pressure distal to coronary stenoses was measured in patients with a pressure wire and myocardial perfusion in the same territory was assessed by positron emission tomography. Myocardial perfusion remained relatively constant over a pressure range of 45 to 125 mm Hg.[116] These data suggest that the autoregulatory range may be as large in humans as it is in conscious dogs.[115]

The ability of autoregulation to compensate for the effect of a proximal epicardial obstruction may be compromised in several clinical situations. A fall in aortic pressure can lower perfusion pressure distal to a stenosis below the critical levels at which autoregulation is effective, thereby compromising myocardial perfusion, intensifying myocardial ischemia, and increasing left ventricular filling pressure, which reduces the perfusion gradient further. These events may cause a vicious cycle, especially in

patients with left main or three-vessel coronary disease. Insertion of an intraaortic balloon pump in this setting raises diastolic perfusion pressure and restores coronary pressure so that autoregulation is reestablished and myocardial ischemia is lessened.

Chronic hypertension and left ventricular hypertrophy narrow the range of autoregulation, especially in the subendocardium, in which autoregulation is ordinarily more limited than in the subepicardium.[117] This amplifies the detrimental effects of coronary stenoses on myocardial perfusion and in patients with severe hypertrophy may lead to subendocardial ischemia even in the absence of coronary stenosis.

Conditions that alter the function of vascular smooth muscle in coronary arterioles attenuate autoregulation. For example, adenosine and dipyridamole abolish autoregulation. In the setting of stenoses, this may cause myocardial ischemia, especially in the subendocardium.[118] In endotoxemic shock, the myocardium produces massive amounts of nitric oxide, a potent vasodilator, which causes autoregulatory dysfunction and potentially predisposes to myocardial ischemia.[119]

MECHANISMS OF AUTOREGULATION

NITRIC OXIDE.

Evidence suggests a role for NO in coronary autoregulation. Inhibition of NO raises the lower autoregulatory threshold by about 15 mm Hg.[120] The involvement of NO may be related to the ability of the endothelium to sense changes in perfusion pressure through pressure-sensitive ion channels.[121] Currently, there is little evidence to support the role of adenosine or K^+_{ATP} in coronary autoregulation.[122]

MYOGENIC CONTROL.

Arteriolar smooth muscle reacts to increased intraluminal pressure by contracting. The consequent augmentation of resistance tends to return blood flow toward normal despite the higher perfusion pressure. This regulatory mechanism, referred to as *myogenic control*, is an important mechanism in some vascular beds. Although data demonstrate that myogenic responses are present in coronary resistance arteries,[123] their contribution to autoregulation is relatively small.[124]

Extravascular Compressive Forces

SYSTOLIC COMPRESSIVE FORCES.

Because systolic ventricular wall compresses intramyocardial vessels, most of the coronary blood flow to the left ventricle occurs during diastole. Thus, the contracting heart obstructs its own blood supply. At peak systole, there is even backflow in the coronary arteries, particularly in the intramural and small epicardial arteries.[125]

The extravascular systolic compressive force has two components. The first is left

ventricular systolic intracavitary pressure, which is transmitted fully to the subendocardium but falls off to almost zero at the epicardial surface. The second, and perhaps even more important, is the vascular narrowing caused by compression and bending of vascular arterioles coursing through the ventricular wall as the heart contracts.[126]

The important resistance to coronary blood flow caused by left ventricular systolic compression can be demonstrated experimentally in a beating heart perfused at constant pressure in which transient asystole is induced by vagal stimulation. At that point, coronary blood flow suddenly increases by approximately 50 percent because of the relief of the compressive effect.[127]

The "throttling" effect of systole on myocardial perfusion is particularly important when systolic intraventricular pressure is elevated to levels exceeding coronary perfusion, as occurs with obstruction to left ventricular outflow by valvular or subvalvular aortic stenosis,[128] or with severe aortic regurgitation.[129] Because an increase in heart rate augments the total duration of systolic time per minute during which coronary vascular compression occurs, while augmenting myocardial oxygen demand, tachycardia may cause myocardial ischemia. The importance of extravascular compressive forces is greatly magnified when coronary vascular tone is diminished[130] as may occur during administration of arteriolar vasodilators or during metabolic vasodilation associated with physical activity.

Because compressive forces exerted by the right ventricle are ordinarily far smaller than those of the left ventricle, ventricular perfusion is reduced but not interrupted during systole. When the right ventricular systolic pressure is elevated by disease (e.g., pulmonic stenosis), the phasic blood flow pattern of the arteries perfusing the right ventricle resembles that of the left ventricle.

DIASTOLIC COMPRESSIVE FORCES.

The coronary perfusion or effective driving pressure has been assumed to be the pressure gradient between the coronary arteries and the pressure in either the right atrium or the left ventricle in diastole, because coronary flow drains primarily into these two chambers during this phase of the cardiac cycle. When coronary perfusion pressure is lowered, diastolic blood flow ceases when coronary driving pressure reaches 40 to 50 mm Hg, the so-called pressure at zero flow (P_{zf}).[131] This pressure is determined largely by diastolic compressive forces.

Transmural Distribution of Myocardial Blood Flow

Extravascular compressive forces are greater in the subendocardium than in the subepicardial layer (Fig. 34-18) (Figure Not Available) . Subendocardial arterioles are particularly susceptible to compression as they arborize from long, transmural vessels.[132] Therefore, *systolic* flow is more reduced in the subendocardium than the subepicardium. Nevertheless, in conscious dogs under resting physiological conditions, the ratio of endocardial to epicardial flow averaged throughout the cardiac cycle is

approximately 1.25:1 due to preferential dilatation of the subendocardial arterioles, causing a large increase in diastolic flow in the subendocardium.[133] [134] The greater subendocardial blood flow appears to be secondary to the wall stress (and therefore oxygen consumption per unit weight), which is normally about 20 percent greater than that of subepicardial muscle.[135]

SUBENDOCARDIAL ISCHEMIA.

The subendocardium is more vulnerable to ischemic damage than the midmyocardium or subepicardium.[136] Epicardial coronary stenoses are associated with reductions in the subendocardial to subepicardial flow ratio.[134] When coronary arteries were constricted sufficiently to reduce total coronary flow to approximately 40 percent of control, endocardial to epicardial flow ratio fell from 1.16 at baseline to 0.37. This pattern of redistribution of flow away from the endocardium is further exaggerated during exercise, mental stress, and pacing-induced tachycardia.[137] Potent arteriolar vasodilators, such as dipyridamole or adenosine, also cause redistribution of blood flow from the endocardium to the epicardium.

Figure 34-18 (Figure Not Available) Cross-section of the left ventricular wall in diastole and systole. Factors involved in the susceptibility of the subendocardium to the development of ischemia include the greater dependence of this region on diastolic perfusion and the greater degree of shortening, and therefore of energy expenditure, of this region during systole.*(From Bell JR, Fox AC: Pathogenesis of subendocardial ischemia. Am J Med Sci 268:2, 1974.)*

When the absolute amount of blood flow is restricted, as in the presence of epicardial stenoses, this transmural redistribution leads to a "coronary steal," with the subendocardial flow even falling below resting values. Severe pressure-induced left ventricular hypertrophy,[133] as well as heart failure with elevated left ventricular end-diastolic pressure,[138] may also reduce the endocardial-to-epicardial flow ratio. When the markedly elevated left ventricular end-diastolic pressure in heart failure is corrected, subendocardial coronary flow reserve is restored and the endocardial-to-epicardial flow ratio is normalized.[138] Thus, impairment of endocardial perfusion in heart failure may be a direct consequence of the elevated left ventricular diastolic pressure and the *diastolic* compressive forces exerted on subendocardial perfusion.

A low subendocardial-to-subepicardial flow ratio can be increased by elevation of aortic pressure, which preferentially increases perfusion of the subendocardial region whose arterioles are maximally dilated and in which flow is pressure dependent. Overperfusion of the epicardial region is prevented by autoregulatory arteriolar constriction. Potent vasoconstrictors such as endothelin-1 and alphaadrenergic agonists[139] or inhibitors of adenosine-induced arteriolar dilation such as theophylline[140] cause arteriolar constriction and redistribution of blood flow to the endocardium. As long as the absolute blood flow is not reduced appreciably, this may result in lessening of myocardial ischemia. Reduction of myocardial oxygen demand, for example by beta blockers, also

decreases epicardial blood flow and increases perfusion pressure and thereby flow to the ischemic subendocardial region.[141]

Neural and Neurotransmitter Control

Coronary blood flow is controlled predominantly by local metabolic, autoregulatory and endothelial factors that match coronary blood flow to myocardial oxygen demand and to the driving perfusion pressure. Neural control of the coronary circulation complements these local effects.[142] Epicardial arteries and coronary arterioles are extensively innervated by sympathetic and parasympathetic fibers,[142] and adrenergic and muscarinic receptors are expressed in these locations.[143] [144] [145] Investigations of the control of coronary circulation by the autonomic nervous system have been challenging because autonomic activation almost invariably leads to changes in myocardial oxygen demand and, therefore myocardial blood flow, through alterations in heart rate, blood pressure, and contractility. Experiments have been designed to separate the direct from the indirect (metabolic) actions of the sympathetic and the parasympathetic nervous systems. The problems of investigating the sympathetic system are compounded by the opposing actions of vasoconstrictor alpha-adrenergic receptors and vasodilator beta-adrenergic receptors.

Sympathetic Control

ALPHA-ADRENERGIC VASOCONSTRICTION.

When its cardiac inotropic and chronotropic actions are blocked by beta-adrenoreceptor antagonists, electrical activation of sympathetic fibers results in coronary vasoconstriction. This constriction is mediated by means of alpha receptors (it is attenuated by alpha-adrenergic antagonists) and competes with metabolic regulation.[142] [142A]

Reflex Alpha-adrenergic Vasoconstriction.

The carotid baroreceptor reflex responds to changes in blood pressure. Hypotension leads to activation of sympathetic fibers and inhibition of vagal discharge. The resultant increase in myocardial oxygen demand and blood flow is countered by alpha-adrenergic mediated vasoconstriction.[142] [143] This restraint imposed by the alpha-adrenergic system results in increased myocardial oxygen extraction.[142] In humans, alpha-adrenergic coronary constriction can be demonstrated by activation of another reflex sympathetic pathway by the cold pressor test (immersion of a hand into ice-cold water). In some patients, the cold pressor stimulation results in coronary vasoconstriction that can be blocked by a selective $alpha_1$ -adrenergic antagonist.[146]

Alpha-adrenergic coronary vasoconstriction has also been observed during exercise in conscious dogs. During near-maximal exercise in dogs, myocardial oxygen delivery increased markedly but not maximally, because the increase in blood flow was blunted by alpha-adrenergic activation[147] (Fig. 34-19) . Feigl has proposed an explanation for the apparent paradox of sympathetic coronary constriction during exercise by its

potentially beneficial effects on the transmural distribution of blood in the left ventricular wall.[148] Alpha-adrenergic blockade during exercise results in adverse transmural flow redistribution away from the endocardium.[149] This effect of the alpha-adrenergic activation is not simply due to a reversal of intramural steal but is associated with a reduction in vascular compliance and backward arterial systolic blood flow with each systole.[142]

BETA-ADRENERGIC VASODILATION.

Under experimental conditions during which adrenergic activation does not alter myocardial oxygen demand, beta-receptor activation leads to coronary vasodilation. This is mediated predominantly by a $beta_1$ receptor in conduit arteries and by $beta_2$ receptors in resistance arterioles.[142]

PARASYMPATHETIC CONTROL

When myocardial oxygen demand is held constant, stimulation of the parasympathetic nervous system leads to dilation of epicardial arteries and coronary arterioles in dogs[143] and baboons,[150] whereas it leads to constriction in pigs.[151] This species variability can be accounted for by the dual actions of the neurotransmitter acetylcholine, which causes smooth muscle constriction and endothelium-dependent dilation by release of NO and other factors. Although release of acetylcholine from nerve terminals occurs at the medial-adventitial junction, sufficient amount diffuses to stimulate the endothelium. However, in pigs, muscarinic receptors are absent on the endothelium and only smooth muscle constriction is observed. In humans, the coronary response to acetylcholine is vasodilation in healthy subjects. However, vasoconstriction predominates in patients with atherosclerosis or its risk factors.[48]

REFLEX PARASYMPATHETIC VASODILATION.

Reflex parasympathetic control has been studied extensively in the canine circulation. Presumably, similar regulation applies to healthy humans with normal

Figure 34-19 Comparison of the effects of exercise on changes in mean left circumflex coronary blood flow (CBF, top panel) and late diastolic coronary resistance (LDCR, bottom panel) in the same dogs studied in the presence of beta-adrenergic receptor blockade with propranolol (solid lines) and combined beta- and alpha-adrenergic receptor blockades (broken lines). Increases in coronary blood flow and reductions in coronary resistance were greater after alpha blockade, indicating that sympathetic stimulation increases coronary vascular resistance during exercise by alpha-receptor stimulation. *(From Murray PA, Vatner SF: Alpha-adrenoceptor attenuation of the coronary vascular response to severe exercise in conscious dogs. Circ Res 45:654, 1979.)*

endothelial function but reflex parasympathetic control has not been characterized in patients with atherosclerosis or its risk factors. In dogs, parasympathetic reflex stimulation leads to coronary vasodilation through several pathways, including (1) carotid baroreceptors that respond to changing blood pressure, (2) carotid bodies that are activated by hypoxia and hypercarbia, and (3) cardiac mechanoreceptors that are stimulated by reduced cardiac filling or small end-systolic volume.[142]

Much remains to be learned about the neural control of the coronary circulation. As was noted previously, coronary arterioles have specialized functions according to their size, a feature that may facilitate finer control of blood flow. It is, therefore, of interest that sympathetic stimulation leads to dilation of the larger arterioles (through the beta-adrenergic system) and constriction of the smaller arterioles.[152] The physiological advantage of this specialized regulation will require further study.

Effects of Coronary Stenoses

Limitation of coronary blood flow imposed by atherosclerosis is related principally to the geometric features of stenoses, including their severity and length, their stiffness or partial distensibility permitting active or passive vasomotion, and the presence of superimposed platelet aggregation and thrombosis.

As blood traverses a stenosis, pressure (energy) is lost. Principles of fluid dynamics have been applied to estimate this pressure loss and validated in animals models as well as in patients. Although the formulas are complex, they can been simplified as follows:

where DeltaP is the pressure drop across a stenosis in millimeters of mercury (mm Hg), Q is the flow across the stenosis in milliliters per second, and d_{sten} is the minimal diameter of the stenosis lumen in millimeters. The first term accounts for viscous friction between layers of fluid in the stenotic segment leading to frictional energy losses. The second term reflects energy losses when the "pressure energy" of normal arterial flow is transferred first to the kinetic energy of high-velocity flow and then, at the exit from the stenosis, to the turbulent energy of distal flow eddies (separation losses due to disturbed laminar flow) (Fig. 34-20) .

RELATIONS BETWEEN CORONARY FLOW AND RESISTANCE.

At normal levels of coronary arterial flow, both frictional and separation losses contribute to the stenosis resistance and to the presence of a pressure gradient. As flow increases, separation losses, which increase with the square of the flow, become increasingly prominent and viscous losses become negligible. Thus, increases in blood flow and pressure drops across the stenosis are related in an exponential manner (Fig. 34-21) . Augmentation of coronary blood flow is associated with elevations in pressure gradient

across the stenotic orifice and reductions in poststenotic perfusion pressure (driving pressure for myocardial perfusion).

Brown and colleagues[153] have called attention to several common clinical situations in which reduction in poststenotic pressure contributes to the pathogenesis of myocardial ischemia. First, pharmacological dilators of coronary resistance arterioles, such as adenosine or dipyramidole, increase transstenotic blood flow and reduce poststenotic pressure. When subendocardial resistance vessels become near fully dilated their perfusion becomes pressure dependent (autoregulation fails). Redistribution of flow away from the subendocardium to the subepicardium develops. This is one mechanism of "coronary steal." Second, during physical activity, coronary blood flow rises to meet the increase in myocardial oxygen demand, leading to an increase in transstenotic pressure gradient and a fall in the distal perfusion pressure. This results in a reduction of blood flow from to the subendocardium while the flow to the subepicardium continues to increase, an effect similar to that observed with the administration of pharmacological vasodilators. Furthermore, the fall in intraluminal distending pressure may lead to a passive collapse of the artery at the site of the obstruction, exaggerating the degree of stenosis. Third, the reduced oxygen-carrying capacity of anemia is

Figure 34-20 Energy losses across a stenosis. The pressure gradient due to friction losses within the stenosis (DeltaP) is directly proportional to blood flow (Q), whereas separation losses at the exit to the stenosis due to formation of eddies increase with blood flow squared (Q^2). Separation losses predominate at high blood flows.

Figure 34-21 Relation between pressure reduction across a stenosis (DeltaP) and flow through the stenosis (Q). Relations are shown for concentric stenoses of 30, 50, 70, 80, and 90 percent internal diameter. The numbers in parentheses below each percent diameter stenosis represent residual luminal cross-sectional area, calculated on the basis of a normal internal diameter of 3 mm and cross-sectional area of 7.1 mm^2 . The level of flow corresponding to basal metabolic needs is represented by the vertical dotted line; stenosis resistances for this level of flow are shown as the dashed tangent lines to the individual pressure-flow relations. In the inset at right, stenosis resistance (R) is plotted as a function of degree of stenosis.*(From Klocke FJ: Measurements of coronary blood flow and degree of stenosis: Current clinical implications and continuing uncertainties. Newsletter of the Council on Clinical Cardiology of the American Heart Association. Vol 7, No. 3, July 1982.)*

compensated for by increase in coronary blood flow because the myocardium cannot increase its oxygen extraction significantly. This decreases poststenotic pressure and compromises subendocardial perfusion. Not surprisingly, therefore, anemia is poorly tolerated in patients with coronary artery disease.

SEVERITY OF STENOSIS.

At any level of blood flow, the single most important determinant of stenosis resistance is the minimum diameter of the stenosis. The transstenotic pressure drop is inversely proportional to the *fourth* power of the minimum luminal diameter. As a consequence, a relatively small change in luminal diameter (such as caused by active or passive vasomotion) is amplified to produce marked hemodynamic effects in the presence of severe stenoses (see Fig. 34-21) . For example, when the diameter stenosis is increased from 80 to 90 percent, the resistance of a stenosis rises nearly threefold.

ENTRANCE AND EXIT EFFECTS.

Blood flow velocity (kinetic energy) increases and pressure (static energy) decreases in a narrowed arterial segment. The conversion of static to kinetic energy would occur with little loss of energy if the flow remained laminar, according to the Bernoulli principle. Laminar flow can be preserved if the entrance and the exit of the stenotic segment taper gradually. However, most stenoses have abrupt transitions where energy losses associated with separation of laminar flow into eddy currents (vortices) occurs. The separation energy losses are particularly pronounced at the exits of stenoses.

LENGTH OF STENOSES.

For most stenoses, the length of the narrowing has only a modest effect on its physiological significance. However, in very long narrowed segments, significant turbulence occurs along the wall of the stenotic segment and energy is dissipated as heat when eddies impact on the wall; stenosis may become important under these conditions.

DYNAMIC CHANGES IN STENOSIS SEVERITY.

Examination of the morphology of pressure-fixed human coronary arteries has revealed eccentricity of atherosclerotic plaques. In many cases, plaques involve only a portion of the arterial wall whereas the remaining arc of the wall is relatively normal and often compliant. This provides a mechanism by which changes in vascular tone may alter luminal caliber and stenosis resistance. For example, most atherosclerotic stenoses in patients can dilate actively in response to nitroglycerin or constrict in response to acetylcholine, ergonovine, or alpha-adrenergic stimuli.

Dynamic changes in stenosis severity and resistance can also occur passively due to alterations in intraluminal distending pressure. Such changes can be demonstrated both in experimental models and in patients with coronary artery disease. As blood flow velocity rises in the stenotic segments, distending pressure falls, leading to passive collapse of a pliable segment. Passive collapse of a stenosis associated with the use of vasodilators occurs with agents that selectively dilate distal resistance vessels. The administration of dipyridamole to patients with coronary artery disease can cause narrowing of severely stenotic pliable segments as well as of the normal arterial segments distal to the stenoses. Passive collapse of pliable stenoses may also occur

when central aortic pressure is lowered.

EFFECTS OF CORONARY STENOSIS IN THE INTACT CORONARY BED.

The physiological effect of a coronary stenosis depends on the degree to which the resistance to flow caused by the stenosis can be compensated for by dilation of arterioles distal to the stenosis. Gould and Lipsomb concluded that in normal dogs, resting coronary flow is not altered until the constriction reaches at least 85 percent of the diameter. Therefore, resting coronary flow is not impeded by mild or moderate stenoses and is an insensitive measure for evaluation of coronary artery disease. *Maximal* coronary blood flow, however, begins to decline when diameter stenosis exceeds 30 to 45 percent (Fig. 34-22) . The capacity to increase coronary blood flow in response to

Figure 34-22 Relationship between resting (dashed line) and maximal coronary blood flow (solid line) and percentage of diameter stenosis in a dog. Progressive coronary stenosis was achieved by progressively narrowing a short segment of a proximal coronary artery. Resting coronary blood flow did not change until coronary diameter stenosis exceeded 80 percent.*(From Marcus ML: The Coronary Circulation in Health and Disease. New York, McGraw-Hill, 1983, and modified from Gould KL, Lipscomb L: Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 34:50, 1974.)*

increased oxygen demand is abolished when diameter stenosis exceeds 90 percent.

Insights derived from such animal studies must be applied cautiously in clinical practice. The simple use of relative percent diameter stenosis determined by coronary arteriography has important limitations, because it does not account for other geometric characteristics of the stenosis such as its absolute diameter, length, entrance and exit angles, or eccentricity. The determination of relative percent diameter narrowing may be misleading in the setting of diffuse disease where segments adjacent to the stenosis are also reduced in caliber. The hemodynamic effects of serial stenoses are also difficult to assess from arteriograms. It is not surprising, then, that the correlation between percent diameter stenosis and the physiological significance of a given obstruction in patients is poor, especially for lesions of moderate severity.[154] [155] [156] [157] [158]

Coronary Flow Reserve and Reactive Hyperemia

Severe myocardial ischemia produces maximal coronary dilation.[159] Therefore, when a coronary artery is occluded, release of the occlusion is followed by a marked increase in coronary flow. This response is termed *reactive hyperemia* (Fig. 34-23) . Reactive hyperemia follows an occlusion as short at 200 milliseconds. *Maximal reactive hyperemia* follows coronary occlusion of 20 seconds. Longer occlusion increases the

duration but not the amplitude of the hyperemic response.

Reactive hyperemia is partly a response driven by a requirement to repay oxygen debt. However, the hyperemic response is less pronounced when coronary arteries are perfused with deoxygenated blood for the same duration.[160] This suggests that factors other than the mere lack of oxygen stimulate the hyperemic response, including the local accumulation of adenosine (see p. 1090), prostacyclin (see p. 1095) and NO (see pp. 1090 , 1091 , 1092 , 1093 , and 1094).[28]

After the release of coronary occlusion, the coronary resistance vessels are maximally dilated. Under this condition, autoregulation is abolished and coronary blood flow is directly related to the driving pressure. Therefore, maximal hyperemic coronary blood flow is closely dependent on the coronary arterial (or central aortic) pressure at the time of the measurement.[161]

Assessment of the Physiological Significance of Coronary Stenoses

Because of the limitations inherent in coronary angiography, attention has been directed to using physiological approaches for determining the severity of coronary stenoses.

Figure 34-23 Mean coronary flow before, during, and after coronary occlusion. Arrow indicates the release of occlusion. Area A represents the flow debt, and area B its repayment. *(From Gould KL: Coronary Artery Stenosis. New York, Elsevier, 1991, p 13.)*

As noted earlier, maximal blood flow is a more sensitive stimulus for assessing the hemodynamic severity of stenoses than the resting blood flow. Three types of stimuli have been used to elicit maximal coronary blood flow in humans: transient coronary occlusion, pharmacological vasodilators, and metabolic stresses. In humans, coronary blood flow responses can be evaluated after a brief coronary occlusion with balloon angioplasty.[162] A potent stimulus causing a threefold or greater increase in blood flow coronary occlusion cannot be used for diagnostic purposes outside the angioplasty setting. Adenosine and papaverine are the principal pharmacological vasodilators used to elicit hyperemia. Adenosine can be administered by the intravenous or intracoronary route. It has a rapid onset and a brief duration of action and is generally safe. Papaverine is administered by the intracoronary route. It has a slower onset and a longer duration of action. Although it has been considered to be the gold standard for maximally stimulating blood flow, it tends to have more side effects. In appropriate concentrations, papaverine causes a maximal increase in coronary blood flow similar to that obtained with reactive hyperemia after balloon angioplasty.[162] Intense treadmill or bicycle exercise, a potent metabolic stimulus, also yield near maximal flow increases. Exercise is the most physiological stress particularly suited for the noninvasive laboratory, but it is difficult to apply at the time of catheterization. Rapid atrial pacing produces only modest, submaximal increases in coronary blood flow.[163]

INVASIVE MEASUREMENT OF FLOW RESERVE.

Several techniques for determining coronary flow reserve have been developed for use during cardiac catheterization. Doppler wires have a miniaturized Doppler crystal placed at the tip of an angioplasty guidewire, permitting measurement of phasic and mean coronary blood flow velocities.[155] [164] Because this technique does not measure absolute coronary blood flow, several indices of flow *velocity* have been used for assessing the physiological significance of coronary stenoses. Coronary flow velocity reserve is the ratio of maximum to baseline flow velocity. Patients with a coronary flow velocity ratio less than 2 typically have other, corroborating evidence of myocardial ischemia[165] and improve symptomatically with revascularization. Conversely, patients with a ratio greater than 2 usually lack other objective evidence of myocardial ischemia and have a favorable outcome with conservative management (Fig. 34-24) . Hence, flow velocity measurements can be helpful in the management of patients with coronary lesions of intermediate severity. Diastolic to systolic velocity ratio has also been used to evaluate stenosis severity. While in normal arteries, diastolic flow velocity far exceeds systolic velocity, the two are more equal distal to significant stenoses. A ratio less than 1.7 has been used to define significant coronary lesions.[166]

During coronary interventions, the Doppler guidewire can be used to judge the adequacy with which stenosis severity has been reduced. Patients with higher coronary flow reserve at completion of the procedure have a lower incidence of abrupt reocclusion and restenosis.[167]

Myocardial fractional flow reserve (FFR) is a recently developed index of the functional severity of coronary stenoses that is calculated only from simultaneous pressure measurements proximal and distal to a stenosis obtained with a pressure monitoring guidewire.[168] FFR represents the fraction of the normal maximal coronary flow that can be achieved in an artery in which flow is restricted by a coronary stenosis. The concept of FFR is founded in the observation noted previously, that during maximal hyperemia, myocardial perfusion is entirely pressure dependent. Therefore, maximal blood flow in the presence of a stenosis is determined by the driving pressure distal to the stenosis (Pd) while the theoretical normal maximal blood flow is determined by the pressure proximal to the stenosis (Pp).

Figure 34-24 Recording of blood flow velocity using a Doppler wire (schematic illustration in top panel) in the left anterior descending artery of a patient with an "intermediate" stenosis by angiography and exercise testing negative for ischemia. Blood flow velocity increased 3.5-fold after intracoronary (I.C.) adenosine (right lower panel) compared with baseline (left lower panel). Coronary flow velocity ratio (CFVR)=3.5 indicates that the "intermediate" stenosis is not hemodynamically significant.

FFR is calculated during maximal hyperemia, obtained with adenosine or papaverine as FFR = Pd/Pp.
FFR less than 0.75 is typically associated with other objective evidence of myocardial

ischemia (Fig. 34-25) . Measurement of FFR in patients with coronary stenoses of moderate severity has been shown to be a useful index of the functional severity of the stenoses and the need for coronary revascularization.[158] [169] [170] Measurement of FFR can also guide the adequacy of reducing coronary stenosis severity with balloon angioplasty[171] or stenting. [172]

NONINVASIVE MEASUREMENT OF FLOW RESERVE.

Radionuclide stress myocardial perfusion imaging (thallium-201, sestamibi) is used widely to quantify coronary flow reserve (see Chap. 9) . Some laboratories are using positron-emission tomography and nuclear magnetic resonance imaging for the same purpose.[173] [174] Flow reserve is typically assessed by these techniques during exercise or with pharmacological coronary vasodilators. In contrast to invasive techniques that measure an index of *absolute* flow reserve (an index related to the quotient of maximal and basal flow), cardiac imaging techniques assess *relative* coronary flow reserve by comparing the perfusion of ischemic regions of the left ventricle with presumably normally perfused reference regions.

Imaging techniques yield a less quantitative index of flow reserve than do catheter-based techniques. In addition, results can be misleading in the setting of diffuse coronary disease when a normal reference region is not available. However, unlike most measures of absolute flow reserve, relative flow reserve is independent of the loading conditions, because these affect all regions of the left ventricle equally. Taken together, absolute and relative coronary flow reserve provide a more complete description of physiological stenosis severity than does either alone.[175]

STENOSIS SEVERITY AND CLINICAL EVENTS.

There is a poor correlation between the severity of stenoses and their propensity to cause myocardial infarction, unstable angina, or sudden coronary death. Pathological studies have revealed that myocardial infarctions and unstable angina are most often caused by rupture of atherosclerotic plaques with formation of a superimposed occlusive thrombus (see Chap. 35) . The majority of atherosclerotic lesions responsible for these serious events are mild stenoses of inconsequential hemodynamic significance and are characterized by abundance of lipid, numerous inflammatory cells, and a thin, fragile fibrous cap.[75] [78] [176] These observations suggest that although measurements of coronary flow reserve may be useful in the assessment of the severity of stenoses and in the identification of lesions responsible for effort angina, they are *not* likely to identify the more dangerous plaques responsible for unstable angina, acute myocardial infarction, and ischemic sudden death.

Figure 34-25 Recording of arterial pressure (P) proximal to (by means of coronary catheter) and distal to (by means of a pressure wire) an "intermediate" stenosis in the left anterior descending coronary artery of a patient with exercise test positive for ischemia. Fractional flow reserve (FFR, a ratio of distal-to-proximal pressure after adenosine)=0.56 indicates that the "intermediate" stenosis is hemodynamically significant.

CORONARY COLLATERAL CIRCULATION AND ANGIOGENESIS

Coronary Collateral Vessels

After total or near-total occlusion or a coronary artery, perfusion of ischemic myocardium occurs by way of collaterals--vascular channels that interconnect epicardial arteries.[177] Preexisting collaterals are thin-walled structures ranging in diameter from 20 to 200 mum.[178] The density of preexisting collaterals varies greatly among different species.[179] Acute coronary occlusion produces no infarction at all in guinea pigs because of an exceptionally well developed network of preexisting collaterals. The dog has an intermediate density of preexisting collaterals that can deliver, on average, 5 to 10 percent of preocclusional, basal flow. Pigs, rats, and rabbits have virtually no preexisting collaterals, and infarcts develop rapidly and completely with acute coronary occlusion.[179] The density of preexisting collateral channels in humans appears to be somewhat more modest than in dogs.

COLLATERAL FORMATION (ARTERIOGENESIS)

Preexisting collaterals are normally closed and nonfunctional, because no pressure gradient exists between the arteries they connect. After coronary occlusion, the distal pressure drops precipitously and preexisting collaterals open virtually instantly. The transformation of preexisting collaterals into mature collaterals is called *arteriogenesis* and occurs in three stages. The initial stage (first 24 hours) involves *passive widening* of the preexisting channels facilitating increased flow. Endothelial cells become *activated* by increased blood flow velocity and shear stress and secrete proteolytic enzymes that fragment the basement membrane and dissolve extracellular matrix, an essential process in the upcoming migration of endothelial cells.[180] The second stage (1 day to 3 weeks) is characterized by *inflammation and cellular proliferation*. [177] [178] [181] [182] [183]

Monocytes migrate into the vascular wall and secrete cytokines and growth factors. This phase of vascular enlargement is marked by cellular proliferation involving the endothelium, smooth muscle cells, and fibroblasts.[177] [184] Endothelial cells and inflammatory cells also secrete matrix degrading enzymes, which create spaces necessary to accommodate the expanded collateral vessels as well as facilitate cell migration. These enzymes belong to the plasminogen activator/plasmin and matrix metalloproteinase families.[185] [186] Additional space for the larger vessels is created by the process of apoptosis.[177] [187] Over several weeks, endothelial and smooth muscle cells arrange themselves into circular and longitudinal layers. During these first two phases, the luminal diameter of collateral channels increases nearly 10-fold. The third stage of collateral maturation (3 weeks to 6 months) involves thickening of the vessel wall due to *deposition of extracellular matrix* and further cellular proliferation.[177] In its final stage, the mature collateral vessel may reach 1 mm in luminal diameter. Its three-layer structure is nearly indistinguishable from a normal coronary artery of the

same size.[177] [178]

MECHANISMS PROMOTING COLLATERAL GROWTH

SHEAR STRESS.

Mechanical forces determine the size of collateral channels in the early minutes and hours after coronary occlusion. Pressure gradients across preexisting rudimentary collaterals augment blood flow velocity and shear stress. Shear stress induces widespread functional changes in the endothelium, many of which reflect new gene expression. These include upregulation in leukocyte adhesion molecules[188] and increased production of proinflammatory cytokines (monocyte chemoattractant protein-1, tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor).[184] The end result of this process is an inflammatory environment.

INFLAMMATION.

Inflammatory cells are a rich source of matrix degrading enzymes (see earlier) and growth factors.[189] The invasion of inflammatory cells is rapidly followed by mitosis of endothelial and smooth muscle cells.[181]

GROWTH FACTORS.

More than 15 growth factors that can stimulate collateral growth (arteriogenesis) or angiogenesis have been identified.[180] [190] Among these, vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are believed to play the most important roles in vivo. Angiogenesis in response to VEGF is mediated by NO, and deficiency of NO (e.g., in the presence of coronary risk factors; see later) may account for impaired collateral formation in that setting.[191]

INHIBITORY FACTORS.

Growth factors can be detected in adult tissues in which endothelial cells are quiescent. Absence of angiogenesis in the presence of growth-promoting factors can be partly attributed to the presence of endogenous inhibitors of this process.[180] Potent angiogenesis inhibitors include angiostatin (a fragment of plasminogen),[192] endostatin (a proteolytic fragment of collagen XVIII),[193] and thrombospondin-1.[194] It is believed that the rate of angiogenesis is determined by a balance between stimulators and inhibitors.[194A]

HYPOXIA.

Tissue hypoxia is associated with rapid upregulation of VEGF. This increase in VEGF occurs by augmented mRNA synthesis and enhancement of its stability.[184] [195] [196] A hypoxia-sensitive element has been identified in the promoter region of VEGF gene.[197] Furthermore, hypoxia upregulates the number of VEGF receptors.[198] This latter

observation may provide an explanation by which intravenous administration of growth factors could induce angiogenesis preferentially and selectively in ischemic tissues.

Nevertheless, hypoxia is not likely an essential requirement for the formation of collaterals. In many cases, the collateral artery originates from a vessel far removed from the site of ischemia.[184]

SEVERITY OF OBSTRUCTION.

The severity of coronary obstruction is a critical determinant of the development of coronary collateral channels. In dogs, the growth of collaterals is not stimulated until a coronary stenosis reduces the luminal cross-sectional area by at least 80 percent. In patients, coronary collaterals do not develop until a coronary stenosis of at least 70 percent diameter narrowing is present. Beyond this threshold value, the growth of collateral channels is directly related to the severity of stenosis.[199]

CORONARY RISK FACTORS.

Patients with diabetes mellitus have an impaired ability to develop collateral blood vessels in the setting of obstructive coronary artery disease.[200] Similarly, rabbits with experimental hyperlipidemia have a limited collateral growth in response to arterial restriction.[201] Thus, the same risk factors that predispose to atherosclerosis may limit a major compensatory mechanism--formation of collateral pathways.

EXERCISE.

This has no effect on the preexisting (rudimentary) collaterals in the absence of coronary occlusions or stenoses. Even in the presence of severe coronary stenoses, the effects of exercise training have been inconsistent and overall neutral in animals.[179] In the clinical studies that used serial angiographic follow-up, increase in collaterals occurred with progression in the severity of coronary artery stenoses, rather than with long-term exercise programs.[202] The reduction of myocardial ischemia associated with exercise is likely the result of improved conditioning.

REGULATION OF COLLATERAL TONE.

The mature coronary collaterals can appreciably dilate or constrict in respond to vasoactive stimuli. The release of endogenous vasodilators NO[203] and prostacyclin maintains collaterals in a dilated state. Conditions that reduce endothelium-derived NO, including coronary risk factors, may reduce the dilator reserve of coronary collaterals, a condition correctable by the administration of exogenous nitrates.[203]

Conversely, serotonin[204] and vasopressin[205] constrict collaterals. Serotonin is released into the circulation during episodes of ischemia triggered by platelet aggregation or thrombosis and may exacerbate myocardial ischemia by reducing collateral blood flow.

CORONARY COLLATERALS IN PATIENTS WITH CORONARY ARTERY DISEASE.

Because coronary collaterals develop in patients whose symptoms of angina pectoris tend to be severe,[199] controversy arose in the past about their clinical utility.[179] However, it is now clear that coronary collaterals can mitigate the severity of myocardial ischemia[206] and, in acute myocardial infarction, collateral circulation can contribute significant amount of blood flow, decrease infarct size, improve left ventricular function, reduce the likelihood of left ventricular aneurysm formation, and improve survival.[207] [208]

Recently, it has become possible to quantify collateral blood flow in conscious humans undergoing coronary angioplasty. Coronary pressure distal to the site of angioplasty balloon occlusion (coronary wedge pressure) can be measured and reflects recruitable collateral perfusion.[209] Patients in whom recruitable collateral blood flow exceeded 28 percent of normal maximal myocardial blood flow were free of ischemia at the time of coronary occlusion induced by balloon angioplasty. Conversely, ischemia was frequently present at the time of coronary occlusion when recruitable collateral blood flow was less than 28 percent of normal maximal myocardial blood flow.[209] This approach has also shown that collateral circulation rarely provides blood flow increases adequate to meet the myocardial oxygen demand of maximal physical exercise; it is typically limited to less than 50 percent of maximal coronary flow reserve.[209]

Angiogenesis

Arteriogenesis (discussed earlier) refers to formation of mature collaterals by enlargement of *preexisting rudimentary collaterals*. Typically, epicardial collaterals fall into this category. *Angiogenesis* refers to *sprouting of new vessels* from preexisting blood vessels and usually results in formation of smaller, capillary-like structures. Subendocardial collaterals may be formed in this manner. In *therapeutic angiogenesis*, exogenous angiogenic growth factors (or genes encoding these growth factors) are administered to stimulate neovascularization of ischemic issues.[177] [190] [210] [210A]

MECHANISMS OF ANGIOGENESIS.

Angiogenic stimuli initiate activation of endothelial cells of capillaries or postcapillary venules. This results in local vasodilation, increased vascular permeability, and degradation of the basement membrane. Migration and proliferation of endothelial cells occurs with formation of capillary sprouts. Furthermore, endothelial proliferation elongates the sprouts and adjacent sprouts connect to form capillary loops that can carry blood flow. Maturation of the sprouts is associated with deposition of basement membrane.[180]

THERAPEUTIC ANGIOGENESIS: PRECLINICAL STUDIES.

Preclinical studies in several animal species have established that angiogenic growth factors can promote formation of new collateral channels in models of peripheral and myocardial ischemia.[190] [210] The angiogenic growth factors used in these studies were administered as recombinant protein or by gene transfer and included vascular endothelial growth factor (VEGF), fibroblast growth factor-1 (FGF-1) and FGF-2, hepatocyte growth factor (HGF), and hypoxia inducible factor-1 (HIF-1). Each of these growth factors can stimulate the critical steps in angiogenesis, including endothelial activation and mitogenesis and upregulation of matrix proteins and matrix proteinases.[210]

Much interest has focused on the role of VEGF because it is a potent angiogenic factor and because the receptors for VEGF are relatively specific for endothelial cells.[211] This specificity favors a targeted therapeutic response and limits the potential for pathological angiogenesis.[190] Four forms of VEGF are formed by alternative splicing of the messenger RNA from a single gene. These forms encode for protein molecules of 121, 165, 189, and 206 amino acids that vary in heparin-binding properties and therefore the avidity with which they bind to cell membranes and extracellular matrix. All forms of VEGF are mitogenic for endothelial cells.

FGF comprises a family of growth factors that are potent stimulants of angiogenesis. Unlike VEGF, FGF also stimulates the proliferation of smooth muscle cells and fibroblasts.

Although potentially associated with adverse effects, stimulation of smooth muscle cell growth and its incorporation into the vascular wall might permit formation of a muscular conduits resembling true collaterals rather than capillaries.

The initial demonstration by Isner and colleagues that intraarterial injection of VEGF augmented collateral formation in the ischemic rabbit hind limb has generated great interest in therapeutic angiogenesis[212] (Fig. 34-26) . Therapeutic angiogenesis has since been carried out successfully in several animal species for the treatment of peripheral ischemia using intraarterial and intramuscular routes of injection and for the treatment of myocardial ischemia using intracoronary, intravenous, intrapericardial, and intramyocardial routes of administration. In the rabbit hind limb model, morphometric analysis has revealed a significant increase in capillary density, accompanied by an increase in vascular conductance (a reduction in resistance).[181] Premortem angiography has also demonstrated growth of larger collaterals.[210] Whether these formed from preexisting rudimentary collaterals by arteriogenesis or whether they are

Figure 34-26 Selective internal iliac angiography of control rabbit performed at day 40 (control, untreated, top) and of vascular endothelial growth factor (VEGF)-treated rabbit at day 40 (bottom). VEGF was administered as a single intraarterial bolus into the internal iliac artery of rabbits with severe ipsilateral ischemia. The angiogram shown here has yielded angiographic scores of 0.17 and 0.41. Distal

reconstitution, barely apparent in the control group (arrows), was evident in the VEGF-treated group (arrows). Direct and linear extension of internal iliac artery to popliteal and/or saphenous arteries was also more evident in the VEGF-treated group (open arrows). *(From Takeshita S, et al: Therapeutic angiogenesis. J Clin Invest 93:662, 1994. Copyright, 1994 American Society of Clinical Investigation.)*

newly vessels formed by angiogenesis remains to be determined.

THERAPEUTIC ANGIOGENESIS: CLINICAL STUDIES.

Demonstration of successful angiogenesis in preclinical studies has led to its application in a number of small-scale trials. In patients with critical limb ischemia, the administration of VEGF by intramuscular injection of plasmid DNA resulted in improved angiographic evidence of collateral blood flow, healing of ulcers, and resolution of rest pain.[213] In another study, administration of FGF improved blood flow to the calf and reduced the symptoms of intermittent

claudication. [190] In patients with ischemic heart disease, administration of intramyocardial or intracoronary growth factors (VEGF or FGF) led to an improvement in myocardial perfusion and apparent reduction in symptoms.[214] [215] These early uncontrolled results, while exciting, need to be validated by controlled, randomized trials.

A number of issues will have to be addressed systematically to optimize therapeutic angiogenesis. These involve methodology (e.g., optimal angiogenic factor(s) and synergistic combinations; methods of delivery and dosing schedule) and potential for pathological angiogenesis at undesired sites (e.g., growth of tumors, proliferative retinopathy, progression of atherosclerosis). Furthermore, further advances in the understanding of the biology of angiogenesis are needed to create muscular collaterals with large perfusion capacity rather than a blush of capillaries.

THERAPEUTIC VASCULOGENESIS.

Vasculogenesis is the formation of new blood vessels that typically occurs during early embryonic development. Endothelial stem cells and circulating endothelial precursors, angioblasts, may persist into adult life.[216] The concept that circulating angioblasts could be harvested and used to create new blood vessels in adults is under investigation.[210]

CONSEQUENCES OF MYOCARDIAL ISCHEMIA

Myocardial Stunning (See also Chap. 14)

For four decades after Tennant and Wiggers's classic observation on the effects of coronary occlusion on myocardial contraction,[217] it was believed that transient severe

ischemia caused either irreversible cardiac injury, that is, infarction, or prompt recovery. However, in the 1970s Heyndrickx and colleagues reported that regional contraction remained depressed for more that 3 hours after a 5-minute coronary occlusion and for more than 6 hours after a 15-minute occlusion in conscious dogs.[218] It became clear that after a brief episode of severe ischemia, prolonged myocardial dysfunction with gradual return of contractile activity occurs, a condition termed *myocardial stunning* (Fig. 34-27) . Subsequently, myocardial stunning was observed by other investigators under a variety of additional experimental conditions, including multiple, brief episodes of ischemia; prolonged ischemia resulting in an admixture of myocardial necrosis and stunning of adjacent, viable myocardium; global myocardial ischemia (e.g., cardioplegia arrest); and stunning after exercise-induced ischemia.[219] [220] [221]

Myocardial stunning has been observed in patients with coronary artery disease in a variety of clinical conditions. It also has been observed after exercise-induced ischemia.

Persistent wall motion abnormalities can be observed by echocardiography at a time when chest pain, ST segment deviation, and regional perfusion had recovered.[219] [222] It affects both systolic and diastolic function.[223]

Clinically, global myocardial stunning occurs most frequently in patients who have undergone ischemic cardiac arrest during cardiopulmonary bypass, despite modern cardioplegia techniques.[224] Such hearts may not recover for days, and many patients require inotropic support. In patients with a myocardial infarction (both with and without the administration of thrombolytic therapy), stunned myocardium lies adjacent to infarcted myocardium. Improvement in ventricular function occurs gradually over the course of days to weeks.[219] [221] Myocardial stunning is also an important feature of unstable angina.[225]

Coronary angioplasty in patients parallels the observations in animal studies of brief coronary occlusion and reperfusion and provides a useful clinical model of stunning. Occlusions of 1 minute or less induce diastolic dysfunction,

Figure 34-27 Schematic diagram of stunned myocardium. During coronary occlusion, a wall motion abnormality of the left ventricle is present in the region supplied by the occluded artery. With relief of ischemia and reestablishment of coronary blood flow, there is a persistent wall motion abnormality despite reperfusion and viable myocytes. There is then gradual improvement in function that requires hours to days for recovery.*(From Kloner RA, Przyklenk K, Patel B: Altered myocardial states: The stunned and hibernating myocardium. Am J Med 86[Suppl 1A]:14, 1986.)*

whereas longer occlusions (over 5 minutes) induce systolic dysfunction that persists 24 to 36 hours.[219]

CELLULAR AND MOLECULAR MECHANISMS OF STUNNING.

A number of factors converge in the pathogenesis of myocardial stunning (see Fig. 14-35) . Probably, the three most important are (1) generation of oxygen derived free

radials, (2) calcium overload, and (3) reduced sensitivity of myofilaments to calcium and loss of myofilaments.[219] [220] These mechanisms interact synergistically in the pathophysiological process of stunning.

Transient myocardial ischemia followed by reperfusion results in increased production of superoxide radicals and hydroxyl radicals. Free radicals inactivate enzymes and cause lipid peroxidation. The generation of free radicals in the ischemia-reperfusion setting has been documented by a direct measurement (spin-trapping and aromatic hydroxylation techniques) and by reduction of stunning with administration of antioxidants. The damaging free radicals are generated in the first minute after reperfusion as antioxidant therapy can reduce stunning if administered at the time of reperfusion but not if it is begun 1 minute later. The presumed targets of oxygen derived free radicals include sarcolemmal Na^+ ,K^+ -ATPase and calcium-stimulated ATPase and, in the sarcoplasmic reticulum, calcium-stimulated ATPase. The result is increased influx of calcium through the sarcolemma, diminished calcium reuptake by the sarcoplasmic reticulum resulting in cellular calcium overload, and, ultimately, in impaired excitation-contraction coupling.[219] [220] Calcium overload can also activate enzymes that further damage the sarcolemma and sarcoplasmic reticulum. Ischemia followed by reperfusion also results in decreased calcium sensitivity of myofilaments, at least in part due to oxidation of critical thiol groups and in part due to partial proteolysis of troponin.[219] [220] [226] Recent evidence suggests that calcium overload may activate calpains, resulting in selective proteolysis of myofibrils.[220]

Although antioxidants are effective, they do not prevent stunning completely. It has been postulated that stunning involves two components, one related to ischemia (not responsive to antioxidants) and a larger component related to reperfusion.[219]

TREATMENT OF MYOCARDIAL STUNNING.

Myocardial stunning is an important clinical problem because it contributes to heart failure. Various therapies have been effective

in *preventing* stunning in the experimental setting, including antioxidants, angiotensin-converting enzyme inhibitors, calcium channel antagonists, and nitrates.[227] [228] Their effectiveness in the clinical setting remains to be established. Once stunning develops, it can be *reversed* with inotropic agents.

Hibernation (See also Chap. 14 and Chap. 37)

The term *hibernating myocardium* refers to the presence of impaired resting left ventricular function, owing to reduced coronary blood flow that can be restored toward normal by revascularization.[229] Hibernation was first noted in patients with coronary artery disease who had no evidence of ongoing ischemia yet whose left ventricular function improved after coronary artery bypass grafting. Even akinetic segments can

occasionally regain systolic contraction after revascularization. These observations led to the concept that myocardium can reduce its contractility (and myocardial oxygen demand) to match reduced perfusion, preserving its viability.[219] [230] [231]

Hibernating myocardium is present in approximately one third of patients with coronary artery disease and impaired left ventricular function.[232] [233] The time course of recovery of hibernating myocardium after revascularization is quite variable, ranging from days to months.[219] Slower recovery is typically associated with longer duration of hibernation. Revascularization can be effective whether achieved by coronary bypass grafting as described originally or by coronary angioplasty.[234]

Detection of hibernation (Fig. 37-18) is of great practical significance because it can alleviate symptoms of heart failure and, in the long term, can forestall myocardial necrosis (see later). Detection of hibernating myocardium consists of finding that akinetic or hypokinetic segments of the left ventricular segment are still viable (see Chaps. 9 and 13) . This viability can be detected either by the persistence of metabolic activity within the regions of dysfunctional myocardium or by demonstrating improvement in the contraction of the hibernating myocardial segment with appropriate stimulation, such as inotropic stimulation. The improvement in function would not have occurred if the dysfunction had been due to myocardial infarction and scarring.[231] None of the available methods for the detection of myocardial viability is clearly superior to others. Such methods include dobutamine stress echocardiography, thallium-201 redistribution study, imaging with technetium-99m sestamibi, and positron-emission tomography with agents that detect residual metabolic activity such as ^{18}F-fluorodeoxyglucose or ^{11}C-acetate.[219] [231]

Histopathological studies of hibernating myocardium have revealed changes consistent with myocyte dedifferentiation. It has been assumed that these findings are reversible after revascularization. However, areas of hibernating myocardium also show evidence of apoptosis,[194A] [235] necrosis, and fibrosis.[229] [236] Finding of these irreversible changes suggests that revascularization of hibernating myocardium should be performed on an urgent basis.

Unlike stunning, which was described first in the experimental laboratory, hibernation was described initially in the clinical setting, and suitable animal models have been lacking.

Therefore, the cellular and molecular basis of hibernation has not been as extensively investigated. A recent study suggested that in hibernation it is the mitochondria that sense hypoxia. Partial inhibition of cytochrome oxidase during hypoxia allows mitochondria to function as the oxygen sensors, limiting ATP utilization and oxygen consumption.[237]

HIBERNATION VERSUS REPETITIVE STUNNING (see Table 14-6) .

There is a debate as to whether hibernation is always caused by a chronic reduction in resting myocardial blood flow or whether, at least in some cases, the same syndrome

might be caused by repeat episodes of myocardial stunning. Animal models of short-term hibernation have clearly revealed that reductions in blood flow achieved by placement of stenoses are directly correlated with a decrease in contractile function.[238] [239] However, clinical studies have suggested that some patients with coronary artery disease who appear to have hibernating myocardium (poorly contracting but viable myocardium) have normal resting myocardial blood flow but diminished coronary flow reserve. It is likely that these patients suffer episodes of ischemia each time oxygen demand is increased. The final effect of multiple episodes of ischemia is cumulative stunning, mimicking hibernation.[238] [239]

Ultimately, with either scenario, revascularization therapy should improve left ventricular function.

Hemodynamic Consequences of Ischemia

Because the heart has virtually no stores of oxygen and relies almost entirely on aerobic metabolism, within seconds of coronary occlusion its relatively high rate of energy expenditure results in a sudden, striking decline of myocardial oxygen tension and impairment in left ventricular function. For example, sudden coronary occlusion in conscious dogs that produces regional myocardial ischemia is associated with evidence of systolic dysfunction within four beats of occlusion and diastolic dysfunction within nine beats.[240] Impairment of systolic and diastolic function are likely related to alterations in intracellular calcium handling, because calcium is ultimately responsible for regulating both systolic and diastolic function.[241] [242] Because left ventricular dysfunction is so readily induced by ischemia, its detection by echocardiography (see Chap. 7) or radionuclide imaging (see Chap. 9) has become a valuable diagnostic tool in the clinical diagnosis of coronary artery disease.[240]

Clinical evidence of heart failure occurs when regional asynergy is so severe and extensive that the uninvolved myocardium cannot sustain the normal hemodynamic burden (systolic failure). Symptoms of left ventricular failure usually develops when contraction ceases in 20 to 25 percent of the left ventricle. With loss of 40 percent or more of

Figure 34-28 Progression of cell death versus time after circumflex coronary occlusion in dogs. Necrosis occurs first in the subendocardial myocardium. With longer occlusions, a wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. In contrast, the lateral margins in the subendocardial region of the infarct are established as early as 40 minutes after occlusion and are sharply defined by the anatomic boundaries of the ischemic bed. AP=anterior papillary muscle; PP=posterior papillary muscle.*(From Reimer KA, Hill ML, Jennings RB: Prolonged depletion of ATP and of the adenine nucleotide pool due to delayed resynthesis of adenine nucleotides following reversible myocardial ischemic injury in dogs. J Mol Cell Cardiol 13:229, 1981.)*

Figure 34-29 *A,* Schematic diagram showing a transverse section through a canine left ventricle subjected to a permanent coronary occlusion without reperfusion. The white area represents nonischemic myocardium supplied by the nonoccluded vessel. The infarct (hatched area) is transmural or near-transmural. There are scattered zones of hemorrhage (solid black). A small layer of viable subendocardium is present that derives its oxygen directly from the ventricular cavity. Where collateral flow is high, there may be a small rim of surviving subepicardium (shaded areas). *B,* Schematic diagram showing a transverse section through a canine left ventricle subjected to coronary occlusion followed within 1 or 2 hours by coronary reperfusion. The hatched and solid black areas represent the infarct that is confined to the inner half of the myocardium. The solid black areas represent the zone of gross microvascular damage, including zones of no-reflow and hemorrhage. It is smaller than and contained within the total infarct. The remainder of the infarct without severe microvascular damage is represented by the hatched area and is located in the mid myocardium. The epicardial portion of the ischemic zone (stippled area) has been salvaged by coronary reperfusion. It is nonnecrotic but stunned (postischemic ventricular dysfunction) for hours to days after coronary reperfusion. *(From Braunwald E, Kloner RA: Myocardial reperfusion: A double-edged sword? J Clin Invest 76:1715, 1985. Copyright 1985, American Society for Clinical Investigation.)*

the left ventricular myocardium, severe pump failure ensues, and, if this loss is acute, cardiogenic shock may develop. A shift in the diastolic pressure-volume relationship (diastolic failure) increases the resistance to ventricular filling and leads to elevated ventricular filling pressures, causing symptoms of pulmonary congestion.[243]

The "Wavefront" of Necrosis

As already noted (see p. 1104), within seconds of a coronary occlusion, blood begins to flow through preexisting collateral channels to the occluded segment of the artery. Collateral flow is lowest and myocardial oxygen consumption highest in the subendocardium, and therefore ischemia is most severe in this region. In the normal myocardium, thickening and shortening are greater in the subendocardium, as is wall stress, accounting for the higher subendocardial energy requirements.[244] [245] Consistent with these findings, higher rates of metabolic activity, lower tissue oxygen tension,[246] and greater oxygen extraction have been found in this region.[247] As a consequence, ischemia becomes most severe and myocardial cells undergo necrosis first in the subendocardium, beginning as early as 15 to 20 minutes after coronary artery occlusion. Necrosis progresses toward the epicardium, gradually involving the less severely ischemic outer layers (Figs. 34-28 and 34-29) . The progression of the wavefront of necrosis[248] is slowed by the presence of residual blood flow when the coronary occlusion is incomplete or when mature collaterals are present at the time of occlusion.[248] The progression of the wavefront of necrosis is accelerated when myocardial ischemia is unusually severe, when collateral blood flow is low, in the presence of marked arterial hypotension (e.g., in patients in cardiogenic shock), and in the presence of elevated myocardial oxygen demand, as may be caused by inotropic stimulation, tachycardia, or fever.

In dogs with acute coronary occlusion, the subendocardial lateral boundaries of

myocardial infarcts are established early in the first hour, whereas the myocardial infarct enlarges in the transmural direction over 4 to 6 hours.[248] Transmural progression of myocardial infarction has also been observed in humans.[249] The recognition of the time-dependent progression of necrosis is the basis of interventions designed to arrest the progression of necrosis as rapidly as possible by reperfusion of occluded coronary arteries, using thrombolytic therapy or angioplasty (see Chap. 35) . Functional recovery that occurs in the subepicardial regions after reperfusion therapy is a mechanism for improvement in regional and global ejection fraction.[249]

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Chapter 35 - Acute Myocardial Infarction

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CHANGING PATTERNS IN CLINICAL CARE OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Despite impressive strides in diagnosis and management over the past three decades, acute myocardial infarction (AMI) continues to be a major public health problem in the industrialized world and is becoming an increasingly important problem in developing countries.[1] In the United States, nearly 1.0 million patients annually suffer from AMI.[2] More than 1 million patients with suggested AMI are admitted yearly to coronary care units (CCUs) in the United States.[2] Although the death rate from AMI has declined by about 30 percent over the past decade, its development is still a fatal event in approximately one third of patients. About 50 percent of the deaths associated with AMI occur within 1 hour of the event and are attributable to arrhythmias, most often ventricular fibrillation. Because AMI may strike an individual during the most productive years, it can have profoundly deleterious psychosocial and economic ramifications.

Of particular concern from a global perspective are projections from the World Heart Federation that the burden of disease in developing countries will become more closely

aligned with that now afflicting developed countries[2] [3] (see Chap. 1) . With a decline in infectious disease-related deaths accompanied by accelerated economic development and life style change promoting atherosclerosis, developing countries especially in Eastern Europe, Asia, and parts of Latin America are expected to experience a sharp increase in ischemic heart disease and AMI.[3] Given the wide disparity of available resources to treat AMI in developing countries, major efforts are needed on an international level to strengthen primary prevention programs at the community level.[1]

IMPROVEMENTS IN OUTCOME.

A steady decline in the mortality rate from AMI has been observed across several population groups since 1960.[1] [4] This appears to be caused by a fall in the incidence of AMI (replaced in part by an increase in the rate of unstable angina[5]) and a fall in the case-fatality rate once an MI has occurred[6] [7] (Fig. 35-1) .

Several phases in the management of patients have contributed to the decline in mortality from AMI.[8] [9] The "clinical observation phase" of coronary care consumed the first half of the 20th century and focused on a detailed recording of physical and laboratory findings; treatment consisted of strict bed rest and sedation. Subsequently, the "coronary care unit phase" beginning in the mid-1960s occurred and was notable for detailed analysis and vigorous management of cardiac arrhythmias. The "high-technology phase" was ushered in by the introduction of the pulmonary artery balloon flotation catheter, setting the stage for bedside hemodynamic monitoring and more precise management of heart failure and cardiogenic shock associated with AMI. The modern "reperfusion era" of coronary care was introduced by intracoronary and then intravenous thrombolysis, increased use of aspirin, and development of primary percutaneous transluminal coronary angioplasty (PTCA) and implantation of coronary stents for AMI. A battery of tests sometimes providing overlapping information was typically ordered during the high-technology phase.

Driven in large part by the need for cost-saving measures, contemporary care of patients with AMI has entered the "evidence-based coronary care phase" and is becoming increasingly influenced by managed care systems and guidelines for clinical practice[10] [11] Although increased responsibility has been placed in the hands of primary care physicians, they have begun to express concern about the potential adverse impact of an excessive increase in the scope of care they are being asked to provide.[12] Coronary care practice is better equipped than other areas of cardiology to face this transition from pathophysiologically based decision-making to evidence-based decision-making, given the rich data base of patients with suspected AMI studied in clinical trials and registries and efforts at summarizing a vast amount of data using metaanalysis.[13] [14] [15] [16] New therapies for AMI are being evaluated not only for evidence of safety and efficacy but also for their cost-effectiveness in caring for patients and their impact on quality of life. However, despite an abundance of cost-effectiveness information analyzed from a societal perspective with data from clinical trials, clinicians weighing the risk-benefit ratio at the bedside of an individual patient with AMI may have difficulty applying the findings for several reasons: uncertainty whether the benefits observed in a strictly defined trial population are applicable to a wider selection of

patients,[17] limited data on specific subgroups, variations

Figure 35-1 *A,* The impact of medical therapy for AMI on short-term mortality. In the pre-CCU era AMI short-term mortality (30-day) was estimated to be 30 percent. Implementation of the CCU concept with defibrillation, sophisticated hemodynamic monitoring, and beta blockade reduced this to 15 percent. A further mortality reduction was ushered in by the reperfusion era; combinations of thrombolysis, primary percutaneous transluminal coronary angioplasty, and aspirin are now employed. *(Modified from Antman EM: General hospital management. In Julian D, Braunwald E (eds): Management of Acute Myocardial Infarction. London, WB Saunders, 1994, p 31.) B,* Cumulative incidence of CHD death as function of time period of initial Q-wave MI. *(Modified from Guidry UC, et al: Temporal trends in event rates after Q-wave myocardial infarction: The Framingham Heart Study. Circulation 100:2054-2059, 1999. Copyright 1999, American Heart Association.)*

in the absolute level of baseline risk,[18] and variations in patient preferences. The information in this chapter on various treatment strategies should therefore be used as a guide and not a substitute for carefully reasoned clinical decision-making on a case-by-case basis.

LIMITATIONS OF CURRENT THERAPY AND VARIATIONS IN CLINICAL RESPONSE IN KEY SUBGROUPS.

Despite the gratifying success of medical therapy for AMI, several observations indicate that considerable room for improvement exists. The short-term mortality of patients with AMI who receive aggressive pharmacological reperfusion therapy as part of a randomized trial is in the range of 6.5 to 7.0 percent,[19] [20] [21] [22] whereas observational data bases such as The National Registry of Myocardial Infarction and Cooperative Cardiovascular Project suggest that the mortality rate in AMI patients is about 20 percent.[16] In addition, the mortality rate from AMI in patients enrolled in randomized trials is considerably lower than that observed among patients who are excluded from such trials.

Although the survival of elderly patients (> age 65) after AMI has improved significantly, advanced age consistently emerges as one of the principal determinants of mortality in AMI.[23] Despite reluctance to use potentially life-saving drug therapies in the elderly,[23A] [23B] cardiac catheterization and other invasive procedures are being performed more commonly at some point during hospitalization in elderly AMI patients. Nevertheless, evidence suggests that the greatest reductions in mortality for elderly patients are derived from those strategies employed during the first 24 hours, the time frame in which prompt and appropriate use of life-saving pharmacotherapy is of paramount importance, emphasizing the need to extend advances in drug therapy for AMI to the elderly.[24]

Despite trends toward greater use of mortality-reducing therapies such as thrombolytics, aspirin, and beta-adrenoceptor blockers in patients with AMI, these drugs still appear to

be underused.[25] [26] [27] [28] [29] [29A] Considerable variation exists in practice patterns for management of patients with AMI. This variation is seen not only on an international level but also regionally within countries[26] [30] and across medical specialties[26] [31] [32] ; such variations in practice are correlated with differences in outcome after AMI.[33] Intriguing data have indicated that mortality rates for AMI are lower in hospitals with a high clinical volume, a high rate of invasive procedures, and a top ranking in quality reports.[33] [34] [35] [35A]

Variation has also been observed in the treatment patterns of certain population subgroups with AMI, notably women and blacks.[29A] [36] Although the unadjusted rates of thrombolytic use and referral for cardiac catheterization and angioplasty are lower and unadjusted mortality rates are higher in women with AMI, gender differences are less apparent (but may not disappear entirely) once adjustment is made for baseline variables such as comorbidities and age[29A] [37] (see Chap. 58) . Of interest, after AMI, younger women but not older women have higher rates of in-hospital mortality than do men of the same age.[38]

Pathology

Almost all MIs result from coronary atherosclerosis, generally with superimposed coronary thrombosis. Nonatherogenic forms of coronary artery disease are discussed on pages 1123 and 1336, and causes of AMI without coronary atherosclerosis are shown in Table 35-1 .

Before the thrombolytic era, clinicians typically divided AMI patients into those suffering a Q-wave or non-Q-wave infarct, based on the evolution of the pattern on the electrocardiogram (ECG) over several days after AMI. The term "Q-wave infarction" was frequently considered to be virtually

TABLE 35-1 -- CAUSES OF MYOCARDIAL INFARCTION WITHOUT CORONARY ATHEROSCLEROSIS

CORONARY ARTERY DISEASE OTHER THAN ATHEROSCLEROSIS
Arteritis
Luetic
Granulomatous (Takayasu disease)
Polyarteritis nodosa
Mucocutaneous lymph node (Kawasaki) syndrome
Disseminated lupus erythematosus
Rheumatoid spondylitis

Ankylosing spondylitis

Trauma to coronary arteries

Laceration

Thrombosis

Iatrogenic

Radiation (radiation therapy for neoplasia)

Coronary mural thickening with metabolic disease or intimal

proliferative disease

Mucopolysaccharidoses (Hurler disease)

Homocysteinuria

Fabry disease

Amyloidosis

Juvenile intimal sclerosis (idiopathic arterial calcification of infancy)

Intimal hyperplasia associated with contraceptive steroids or with the postpartum period

Pseudoxanthoma elasticum

Coronary fibrosis caused by radiation therapy

Luminal narrowing by other mechanisms

Spasm of coronary arteries (Prinzmetal angina with normal coronary arteries)

Spasm after nitroglycerin withdrawal

Dissection of the aorta

Dissection of the coronary artery

EMBOLI TO CORONARY ARTERIES

Infective endocarditis

Nonbacterial thrombotic endocarditis

Prolapse of mitral valve

Mural thrombus from left atrium, left ventricle, or pulmonary veins

Prosthetic valve emboli

Cardiac myxoma

Associated with cardiopulmonary bypass surgery and coronary arteriography

Paradoxical emboli

Papillary fibroelastoma of the aortic valve ("fixed embolus")

Thrombi from intracardiac catheters or guidewires

CONGENITAL CORONARY ARTERY ANOMALIES

Anomalous origin of left coronary from pulmonary artery
Left coronary artery from anterior sinus of Valsalva
Coronary arteriovenous and arteriocameral fistulas
Coronary artery aneurysms
MYOCARDIAL OXYGEN DEMAND-SUPPLY DISPROPORTION
Aortic stenosis, all forms
Incomplete differentiation of the aortic valve
Aortic insufficiency
Carbon monoxide poisoning
Thyrotoxicosis
Prolonged hypotension
HEMATOLOGICAL (IN SITU THROMBOSIS)
Polycythemia vera
Thrombocytosis
Disseminated intravascular coagulation
Hypercoagulability, thrombosis, thrombocytopenic purpura
MISCELLANEOUS
Cocaine abuse
Myocardial contusion
Myocardial infarction with normal coronary arteries
Complication of cardic catheterization
Modified from Cheitlin M, et al: Myocardial infarction without atherosclerosis. JAMA 231:951, 1975. Copyright 1975, American Medical Association.

Figure 35-2 Nomenclature of acute coronary syndromes. Patients with ischemic discomfort may present with or without ST segment elevation on the ECG. The majority of patients with ST segment elevation (large arrows) ultimately develop a Q-wave acute myocardial infarction (QwMI), whereas a minority (small arrow) develop a non-Q-wave AMI (NQMI). Patients who present without ST segment elevation are either experiencing unstable angina or a non-ST segment elevation MI (NSTEMI). The distinction between these two diagnoses is ultimately made based on the presence or absence of a cardiac marker detected in the blood. Most patients with NSTEMI do not evolve a Q wave on the 12-lead ECG and are subsequently referred to as having sustained a non-Q-wave MI (NQMI); only a minority of NSTEMI patients develop a Q-wave AMI and are later diagnosed as having a Q-wave MI. The spectrum of clinical conditions ranging from unstable angina to non-Q-wave AMI comprise the acute coronary syndromes (ACS). *(From Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guidelines for the management of patients with unstable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J*

Am Coll Cardiol 36:970-1062, 2000.)

synonymous with "transmural infarction," whereas "non-Q-wave infarction" was often referred to as a "subendocardial infarction." Phibbs and colleagues have summarized the arguments that previous distinctions between Q-wave infarction and non-Q-wave infarction were based on erroneous interpretation of pathological data and should not serve as the basis for designing therapy.[39] A more suitable framework is based on the pathophysiology of AMI, leading to a reorganization of clinical presentations into what is now referred to as the *acute coronary syndromes* (Fig. 35-2) (see p. 1118).

ROLE OF ACUTE PLAQUE CHANGE

Slowly accruing high-grade stenoses of epicardial coronary arteries may progress to complete occlusion but do not usually precipitate AMI, probably because of the development of a rich collateral network (see p. 1123) over time. However, during the natural evolution of atherosclerotic plaques, especially those that are lipid laden, an abrupt and catastrophic transition may occur, characterized by plaque rupture. Evidence exists that some patients have a systemic predisposition to plaque rupture that is independent of traditional risk factors.[40] [40A] After plaque rupture there is exposure of substances that promote platelet activation and aggregation, thrombin generation, and, ultimately, thrombus formation[41] [42] [42A] [42B] (Figs. 35-3 and 35-4) . The resultant thrombus that is formed interrupts blood flow and leads to an imbalance between oxygen supply and demand and, if this imbalance is severe and persistent, to myocardial necrosis (Fig. 35-5) .

Figure 35-3 Schematic diagram suggesting probable mechanisms responsible for the conversion from chronic coronary heart disease to acute coronary artery disease syndromes. In this scheme, endothelial injury, usually at sites of atherosclerotic plaques and usually plaque ulceration or fissuring, is associated with platelet adhesion and aggregation and the release or activation of selected mediators, including thromboxane A_2 , serotonin (5HT), adenosine diphosphate (ADP), platelet-activating factor (PAF), thrombin, tissue factor, and oxygen-derived free radicals. The accumulation of these mediators promotes platelet aggregation and mechanical obstruction of the narrowed artery. Thromboxane A_2 , 5HT, thrombin, and PAF are vasoconstrictors at sites of endothelial injury. ADP, 5HT, and tissue factor have mitogenic influences and promote the development of neointimal proliferation. Therefore, the conversion from chronic stable to acute unstable coronary heart disease syndromes is most likely associated with endothelial injury, platelet aggregation, accumulation of platelet and other cell-derived mediators, further platelet aggregation, and vasoconstriction, with consequent dynamic narrowing of the coronary artery lumen. The relative absence of prostacyclin (PGI_2), tissue plasminogen activator (t-PA), and endothelium-derived relaxing factor (EDRF; nitrous oxide) at sites of endothelial injury contributes to the development of thrombosis, vasoconstriction, and neointimal proliferation. There are many different reasons for endothelial injury in addition to atherosclerotic plaque fissuring or ulceration, including flow shear stress, hypertension, immune complex deposition with complement activation, and mechanical injury to the endothelium as it occurs with coronary artery angioplasty, atherectomy, and stent placement and after heart transplantation. *(From Willerson JT, Cohen LS, Maseri A: Pathophysiology and clinical recognition. In Willerson JT, Cohen JN [eds]: Cardiovascular Medicine. New York, Churchill Livingstone,*

1995, p 335.)

COMPOSITION OF PLAQUES.

At autopsy, the atherosclerotic plaque of patients who died of MI is composed primarily of fibrous tissue of varying density and cellularity with superimposed thrombus. Calcium, lipid-laden foam cells, and extracellular lipid each constitute 5 to 10 percent of the remaining area. The atherosclerotic plaques that are associated with thrombosis and a total occlusion, located in infarct-related vessels, are generally more complex and irregular than those in vessels not associated with MI.[43] Histological studies of these lesions often reveal plaque rupture or erosion.[43] Angiographic morphology suggestive of plaque rupture has been identified in the majority of stenoses associated with AMI or abrupt onset of unstable angina.[44] This finding is rare in the non-infarct-related vessels of AMI patients and in the vessels of patients with chronic, stable angina.

Platelet-rich thrombi are often associated with the surface of the most advanced atherosclerotic lesions, called complicated plaques, which are characterized by fibrocalcific degeneration, deposition of lipid, calcium, fibrous tissue, necrotic debris, extravasated blood, and a fibrous cap (see Fig. 35-3) . Impaired endothelial cell function may contribute to atherogenesis through release of growth factors. Luminal narrowing may potentiate platelet activation through augmentation of shear forces.

In patients with MI, coronary thrombi are usually superimposed on or adjacent to atherosclerotic plaques (see Figs. 35-3 and 35-4) .[45] These coronary arterial thrombi, which are approximately 1 cm in length in most cases, adhere to the luminal surface of an artery and are composed of platelets, fibrin, erythrocytes, and leukocytes. The composition of the thrombus may vary at different levels: a white thrombus is composed of platelets, fibrin, or both; and a red thrombus is composed of erythrocytes, fibrin, platelets, and leukocytes.[46] Early thrombi are usually small and nonocclusive and are composed predominantly of platelets.[40A] [47]

PLAQUE FISSURING AND RUPTURE.

The process of plaque fissuring is an area of intense investigation and is likely to be multifactorial in nature (see Fig. 35-3) . In atherosclerotic plaques prone to rupture there is an increased rate of formation of metalloproteinase enzymes such as collagenase, gelatinase, and stromelysin that degrades components of the protective interstitial matrix.[48] These proteinases may be elaborated by activated macrophages and mast cells that have been shown to accumulate in high concentration at the site of atheromatous erosions and plaque rupture in patients who died of AMI.[45] Examination of specimens from atherectomy reveals a much higher content of macrophages and tissue factor in patients with unstable angina or AMI compared with patients with chronic stable angina.[49] In addition to these structural aspects

Figure 35-4 Thrombus propagation. *A,* Left anterior descending coronary artery cut open longitudinally, showing a dark (red) stagnation thrombosis propagating upstream from the initiating rupture/platelet-rich

thrombus at the arrow. In this case, the thrombus has propagated proximally up to the nearest major side branch (the first diagonal branch). *B,* The right coronary artery cut open longitudinally, showing a huge stagnation thrombosis propagating downstream from the initiating rupture/platelet-rich thrombus at the arrow. Unlike upstream thrombus propagation, downstream propagation may, as in this case, occlude major side branches. O = coronary ostium; c = contrast medium injected postmortem. *(From Falk E: Coronary thrombosis: Pathogenesis and clinical manifestations. Am J Cardiol 68:28B, 1991.)*

Figure 35-5 Schematic representation of the progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium (dashed outline) depends on the occluded vessel for perfusion and is the area at risk. Note that a very narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle. *(Redrawn with permission from Schoen FJ: The heart. In Cotran RS, Kumar V, Collins T (eds): Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, p 557.)*

of vulnerable plaques, stresses induced by intraluminal pressure, coronary vasomotor tone, tachycardia (cyclic stretching and compression), and disruption of nutrient vessels combine to produce plaque rupture at the margin of the fibrous cap near an adjacent plaque-free segment of the coronary artery wall (shoulder region of plaque).[41] [43] A number of key physiological variables such as systolic blood pressure, heart rate, blood viscosity, endogenous tissue plasminogen activator (t-PA) activity, plasminogen activator inhibitor-1 (PAI-1) levels, plasma cortisol levels, and plasma epinephrine levels that exhibit circadian and seasonal variations and are increased at times of stress act in concert to produce a heightened propensity for plaque rupture and coronary thrombosis, yielding the clustering of AMI in the early morning hours and especially in the winter and after natural disasters.[50] [51]

Acute Coronary Syndromes

If a sufficient quantity of thrombogenic substances is exposed when plaque rupture occurs, the coronary artery lumen may become obstructed by a combination of fibrin, platelet aggregates, and red blood cells (see Figs. 35-3 and 35-4) .[51A] An adequate collateral network that prevents necrosis from occurring can result in clinically silent episodes of coronary occlusion. The rupture of plaques is now considered to be the common pathophysiological substrate of the *acute coronary syndromes* (see Fig. 35-2) .[5] [42A] [52] [52A] The dynamic process of plaque rupture may evolve to a completely occlusive thrombus, typically producing ST segment elevation on the ECG. Typically, such completely occlusive thrombi lead to a large zone of necrosis involving the full or nearly full thickness of the ventricular wall in the myocardial bed subtended by the affected coronary artery (see Fig. 35-5) . The infarction process alters the sequence of depolarization ultimately reflected as changes in the surface of the QRS complex.[39] The most characteristic change in the QRS complex that develops in about 75 percent of patients initially presenting with ST segment elevation is the evolution of Q waves in the leads overlying the infarct zone, leading to the term "Q-wave infarction" (see Fig. 35-2) .

In about 25 percent of patients presenting with ST segment elevation, no Q waves develop[53] but other abnormalities of the QRS are seen, such as diminution in R wave height and notching or splintering of the QRS complex.

Less obstructive thrombi and/or those that are constituted by less robust fibrin formation and a greater proportion

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of platelet aggregates typically produce ST segment depression and/or T wave inversion on the ECG (see Fig. 35-2) . Relief of transient vasospasm (induced by thromboxane A_2 and serotonin released from activated platelets) (see Fig. 35-3) or spontaneous lysis and restoration of antegrade flow in the culprit coronary vessel in less than 20 minutes usually does not result in histological evidence of necrosis, the release of biochemical markers of necrosis, or persistent changes on the ECG. Episodes of plaque rupture more prolonged and more severe typically result in release of biochemical markers of necrosis but a less extensive pattern of necrosis than found in patients with ST segment elevation MI (STEMI). Patients presenting without ST segment elevation are initially diagnosed as suffering either from a non-ST segment elevation MI (NSTEMI) or unstable angina (see Fig. 35-2) . The distinction between NSTEMI and unstable angina is based on whether a cardiac marker indicative of necrosis is detected in the blood, a finding that is now possible in a greater number of patients using sensitive markers such as cardiac-specific troponin T or I (see p. 1133). The majority of patients presenting with NSTEMI do not develop Q waves on the ECG and are ultimately diagnosed as having had a non-Q-wave MI. However, a minority of patients with NSTEMI develop Q waves and are ultimately diagnosed as having had a Q-wave MI (see Fig. 35-2) .

The acute coronary syndrome spectrum concept, organized around a common pathophysiological substrate, is a useful framework for developing therapeutic strategies.[52A] [54] Patients presenting with persistent ST segment elevation are candidates for reperfusion therapy (either pharmacological or catheter-based) to restore flow in the occluded epicardial infarct-related artery. Patients presenting without ST segment elevation are not candidates for pharmacological reperfusion but should receive vigorous antiischemic therapy (see Chap. 36) . Antithrombin therapy and antiplatelet therapy should be administered to all patients with an acute coronary syndrome regardless of the presence or absence of ST segment elevation. Thus, the 12-lead ECG remains at the center of the decision pathway for management of patients with an acute coronary syndrome to distinguish between presentations with ST segment elevation and those without ST elevation (see Fig. 35-2) .[55] [56] The ECG lacks sufficient sensitivity and specificity to permit reliable distinction of transmural from subendocardial infarcts. Categorization of patients into those with Q-wave and non-Q-wave infarction patterns is best conceived of as only a crude guide to the extent of ventricular damage. Prognostic considerations must take into account other important factors, such as whether the ECG abnormality is due to a first infarct versus subsequent infarct, the location of infarction (anterior vs. inferior), infarct size, and demographic factors such as

patient age.[39]

Some patients with stenotic atherosclerotic lesions experience AMI without evidence of plaque rupture or superimposed thrombosis. AMI occurs in clinical circumstances that produce a marked reduction in myocardial oxygen supply (e.g., prolonged severe vasospasm, as in Prinzmetal's variant angina [see Chap. 37], or associated with a marked increase in myocardial oxygen demand [see later]). These infarcts are located along the least well-perfused inner one third to one half of the ventricular wall and often extend beyond the target territory perfused by a single coronary vessel.[57] The ECG in such patients may show deep T wave inversions or diffuse ST segment depression.

GROSS PATHOLOGICAL CHANGES

The location and extent of AMI can be assessed on pathological examination (Fig. 35-6). On gross inspection, AMI may be divided into two major types: (1) transmural infarcts,

Figure 35-6 Acute myocardial infarct, predominantly of the posterolateral left ventricle, demonstrated histochemically by a lack of staining by the triphenyltetrazolium chloride (TTC) stain in areas of necrosis. The staining defect is due to the enzyme leakage that follows cell death. Note the myocardial hemorrhage at one edge of the infarct that was associated with cardiac rupture (at the 3 o'clock position) and the anterior scar (at the 7 o'clock position), indicative of old infarct. (Specimen oriented with posterior wall at top.) (From Schoen FJ: The heart. *In* Cotran RS, Kumar V, Collins T [eds]: Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, p 559.)

in which myocardial necrosis involves the full thickness (or nearly full thickness) of the ventricular wall, and (2) subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both without extending all the way through the ventricular wall to the epicardium.[57]

An occlusive coronary thrombus appears to be far more common when the infarction is transmural and localized to the distribution of a single coronary artery (see Fig. 35-4) . Nontransmural infarctions, however, frequently occur in the presence of severely narrowed but still patent coronary arteries. Patchy nontransmural infarction may arise from thrombolysis or PTCA of an originally occlusive thrombus with restoration of blood flow *before* the wave front of necrosis has extended from the subendocardium across the full thickness of the ventricular wall (see Fig. 35-5) . The histological pattern of necrosis may differ, with contraction band injury (see later) occurring almost twice as often in nontransmural as in transmural infarction. Paradoxically, before their infarction, patients with nontransmural infarcts have, on average, a more severe stenosis in the infarct-related coronary artery than do patients suffering from transmural infarcts. This finding suggests that a more severe obstruction occurring before infarction protects against the development of transmural infarction, perhaps by fostering the development of collateral circulation. It also accords with the concept that less severely stenotic but lipid-laden plaques with a fragile cap are responsible for the abrupt presentation of ST segment elevation that may evolve into transmural infarctions.

THE FIRST HOURS.

Gross alterations of the myocardium are difficult to identify until at least 6 to 12 hours have elapsed after the onset of necrosis (Fig. 35-7) (Figure Not Available) . However, a variety of histochemical stains can be used to identify zones of necrosis that can be discerned after only 2 to 3 hours. Tissue slices of suspected infarct sites are immersed in a solution of triphenyltetrazolium chloride (TTC), which stains viable myocardium brick red (because of preserved dehydrogenase enzymes that form a red formazan precipitate) and leaves the infarcted region pale as a result of failure of uptake of the vital dye (see Fig. 35-6). The nitroblue tetrazolium (NBT) staining technique can similarly distinguish viable zones of myocardium, which stain dark blue, from necrotic areas of myocardium that therefore remain uncolored and identifiable. Other approaches include autofluorescence staining, immunohistochemical analysis, and, more recently, special DNA staining techniques to identify apoptotic bodies in myocardial sections.[58]

Initially, the myocardium in the affected region may appear pale and slightly swollen. Eighteen to 36 hours after the onset of the infarct, the myocardium is tan or reddish purple (due to trapped erythrocytes), with a serofibrinous exudate evident on the epicardium in transmural infarcts. These changes persist for approximately 48 hours; the infarct then turns gray, and fine yellow lines, secondary to neutrophilic infiltration, appear at its periphery. This zone gradually widens and during the next few days extends throughout the infarct.

THE FIRST DAYS.

Eight to 10 days after infarction the thickness of the cardiac wall in the area of the infarct is reduced as necrotic muscle is removed by mononuclear cells. The cut surface of an infarct of this age is yellow, surrounded by a reddish purple band of granulation tissue that extends through the necrotic tissue by 3 to 4 weeks. Commencing at this time and extending over the next 2 to 3 months, the infarcted area gradually acquires a gelatinous, ground-glass, gray appearance, eventually converting into a shrunken, thin, firm scar that whitens and firms

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Figure 35-7 (Figure Not Available) Temporal sequence of early biochemical, ultrastructural, histochemical, and histological findings after onset of MI. At the top of the figure are schematically shown the time frames for early and late reperfusion of the myocardium supplied by an occluded coronary artery. For approximately one-half hour after the onset of even the most severe ischemia, myocardial injury is potentially reversible; after that there is progressive loss of viability that is complete by 6 to 12 hours. The benefits of reperfusion (both early and late) are greatest when it is achieved early, with progressively smaller benefits occurring as reperfusion is delayed. *(From Schoen FJ: Pathologic considerations of the surgery of adult heart disease. In Edmunds LH [ed]: Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997, p 85.)*

progressively with time[57] (see Fig. 35-6). This process begins at the periphery of the infarct and gradually moves centrally. The endocardium below the infarct increases in thickness and becomes gray and opaque.

Histological and Ultrastructural Changes

ELECTRON MICROSCOPY.

In experimental infarction, the earliest ultrastructural changes in cardiac muscle after ligation of a coronary artery, noted within 20 minutes, consist of reduction in the size and number of glycogen granules, intracellular edema, and swelling and distortion of the transverse tubular system, the sarcoplasmic reticulum, and the mitochondria[58] (see Fig. 35-7) (Figure Not Available) . These early changes are reversible. Changes after 60 minutes of occlusion include myocardial cell swelling, mitochondrial abnormalities such as swelling and internal disruption, development of amorphous, flocculent aggregation and margination of nuclear chromatin, and relaxation of myofibrils. After 20 minutes to 2 hours of ischemia, changes in some cells become irreversible, and there is progression of these alterations; additional changes include indistinct, tight junctions at the intercalated discs, swollen sacs of the sarcoplasmic reticulum at the level of the A band, greatly enlarged mitochondria with few cristae, thinning and fractionation of myofilaments, disappearance of the heterochromatin, rarefaction of the euchromatin and peripheral aggregation of chromatin in the nucleus, disorientation of myofibrils, and clumping of mitochondria. Cells irreversibly damaged by ischemia are usually swollen, with an enlarged sarcoplasmic space; the sarcolemma may peel off the cells, defects in the plasma membrane may appear, and the mitochondria are fragmented. The swollen mitochondria obtained from ischemic myocardium contain deposits of calcium phosphate and amorphous matrix densities. Many of these changes become more intense when blood flow is restored.[57]

LIGHT MICROSCOPY.

It was previously believed that no light microscopic changes could be seen in infarcted myocardium until 8 hours after interruption of blood flow. However, in some infarcts a pattern of wavy myocardial fibers may be seen 1 to 3 hours after onset, especially at the periphery of the infarct (see Figs. 35-7 (Figure Not Available) and 35-8). It is hypothesized that wavy fibers result from the stretching and buckling of noncontractile fibers as forces are transmitted to them from adjacent viable contractile fibers.[57] After 8 hours, edema of the interstitium becomes evident, as do increased fatty deposits in the muscle fibers, along with infiltration of neutrophilic polymorphonuclear leukocytes and red blood cells. Muscle cell nuclei become pyknotic and then undergo karyolysis, and small blood vessels undergo necrosis.

By 24 hours there is clumping of the cytoplasm and loss of cross striations, with appearance of focal hyalinization and irregular cross bands in the involved myocardial fibers. The nuclei become pyknotic and sometimes even disappear. The myocardial capillaries in the involved region dilate, and polymorphonuclear leukocytes accumulate, first at the periphery and then in the center of the infarct. During the first 3 days, the interstitial tissue becomes edematous and red blood cells may extravasate (see Fig.

35-7) (Figure Not Available) . Generally, on about the fourth day after infarction, removal of necrotic fibers by macrophages begins, again commencing at the periphery (see Figs. 35-7 (Figure Not Available) and 35-8). Later, lymphocytes, macrophages, and fibroblasts infiltrate between myocytes, which become fragmented. At 8 days, the necrotic muscle fibers have become dissolved; by about 10 days, the number of poly-morphonuclear

Figure 35-8 Microscopic features of myocardial infraction. *A,* One-day-old infarct showing coagulative necrosis, wavy fibers with elongation, and narrowing, compared with adjacent normal fibers (lower right). Widened spaces between the dead fibers contain edema fluid and scattered neutrophils. *B,* Dense polymorphonuclear leukocytic infiltrate in an area of acute myocardial infarction of 3 to 4 days' duration. *C,* Nearly complete removal of necrotic myocytes by phagocytosis (7 to 10 days). *D,* Granulation tissue with a rich vascular network and early collagen deposition, approximately 3 weeks after infarction. *E,* Well-healed myocardial infarct with replacement of the necrotic fibers by dense collagenous scar. A few residual cardiac muscle cells are present. (In *D* and *E,* collagen is highlighted as blue in this Masson trichrome stain). *F,* Myocardial necrosis with hemorrhage and contraction bands, visible as dark bands spanning some myofibers (arrows). This is the characteristic appearance of markedly ischemic myocardium that has been reper[chfused. (From Schoen FJ: The heart. *In* Cotran RS, Kumar V, Collins T [eds]: Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, pp 560-561.)

leukocytes is reduced and granulation tissue first appears at the periphery (see Figs. 35-7 (Figure Not Available) and 35-8). Ingrowth of blood vessels and fibroblasts continues, along with removal of necrotic muscle cells, until the fourth to sixth week after infarction, by which time much of the necrotic myocardium has been removed. This process continues along with increasing collagenization of the infarcted area. By the sixth week, the infarcted area has usually been converted into a firm connective tissue scar with interspersed, intact muscle fibers (see Figs. 35-7 (Figure Not Available) and 35-8).

PATTERNS OF MYOCARDIAL NECROSIS

COAGULATION NECROSIS.

This results from severe, persistent ischemia and is usually present in the central region of infarcts, which results in the arrest of muscle cells[59] in the relaxed state and the passive stretching of ischemic muscle cells. On light microscopy the myofibrils are stretched, many with nuclear pyknosis, vascular congestion, and healign by phagocytosis of necrotic muscle cells (see Fig. 35-7) (Figure Not Available) . There is evidence of mitochondrial damage with prominent amorphous (flocculent) densities but no calcification.

NECROSIS WITH CONTRACTION BANDS.

This form of myocardial necrosis, also termed "contraction band necrosis" or "coagulative myocytolysis," results primarily from severe ischemia followed by reflow.[57] It is caused by increased calcium ion (Ca^{2+}) influx into dying cells, resulting in the arrest of cells in the contracted state. It is seen in the periphery of large infarcts and is present to a greater extent in nontransmural than in transmural infarcts. The entire infarct may show this form of necrosis when reperfusion occurs experimentally or by surgery[59] (see Figs. 35-8 and 35-9) . Although patches of contraction band necrosis are found after successful reperfusion by thrombolytic therapy, their presence in a large segment of the infarcts of patients who did not receive such therapy suggests that reperfusion through spontaneous thrombolysis or the release of spasm or both have occurred. It is characterized by hypercontracted myofibrils with contraction bands and mitochondrial damage, frequently with calcification, marked vascular congestion, and healign by lysis of muscle cells.

MYOCYTOLYSIS.

Ischemia without necrosis generally causes no acute changes that are visible by light microscopy. However, severe prolonged ischemia can cause myocyte vacuolization, often termed "myocytolysis." Prolonged severe ischemia, which is potentially reversible, causes cloudy swelling, as well as hydropic, vascular, and fatty degeneration. Frequently seen at the borders of an infarct as well as in patchy areas of infarction in patients with chronic ischemic heart disease, myocytolysis is characterized by edema and cell swelling, lysis of myofibrils and nuclei, no neutrophilic response, and healign

Figure 35-9 Several potential outcomes of reversible and irreversible ischemic injury to the myocardium. *(From Schoen FJ: The heart. In Cotran RS, Kumar V, Robbins SL (eds): Pathologic Basis of Disease. 5th ed. Philadelphia, WB Saunders, 1994, p 538.)*

by lysis and phagocytosis of necrotic myocytes and ultimately scar formation.

MODIFICATION OF PATHOLOGICAL CHANGES BY REPERFUSION

Early after the onset of ischemia, contractile dysfunction is observed that is believed to be due in part to shortening of the action potential duration, reduced cytosolic free calcium levels, and intracellular acidosis. When reperfusion of myocardium undergoing the evolutionary changes from ischemia to infarction occurs sufficiently early (i.e., within 15 to 20 minutes), it may successfully prevent necrosis from developing. Beyond such a very early stage, the number of salvaged myocytes and therefore the amount of salvaged myocardial tissue (area of necrosis/area at risk) is directly related to the length of time the coronary artery has been totally occluded, the level of myocardial oxygen consumption, and the collateral blood flow (see Fig. 35-9) . Typical pathological findings

of reperfused infarcts include a histological mixture of necrosis, hemorrhage within zones of irreversibly injured myocytes, coagulative myocytolysis with contraction bands, and distorted architecture of the cells in the reperfused zone[58] (see Fig. 35-9) . After reperfusion, mitochondria in nonviable myocytes develop deposits of calcium phosphate and ultimately a large fraction of the cells may calcify. Reperfusion of infarcted myocardium also accelerates the washout of intracellular proteins ("serum cardiac markers"), producing an exaggerated and early peak value of substances such as the MB isoenzyme of creatine kinase (CK-MB) and cardiac-specific troponin T and I[60] (see p. 1134).

CORONARY ANATOMY AND LOCATION OF INFARCTION

In over 75 percent of patients with MI who come to autopsy, more than one coronary artery is severely narrowed. One third to two thirds of patients with AMI have critical obstruction (to less than 25 percent of luminal area) of all three coronary arteries, whereas the remainder are equally divided between those having one-vessel disease and those having two-vessel disease. Coronary arteriographic studies in surviving patients show that a higher percentage have one-vessel disease. Angiographic studies performed in the earliest hours of AMI in patients presenting with ST segment elevation have revealed approximately a 90 percent incidence of total occlusion of the infarct-related vessel.[61] Recanalization from spontaneous thrombolysis[62] as well as attrition due to some mortality among those patients with total occlusion results in a diminishing incidence of angiographically totally occluded vessels in the period after MI (Fig. 35-10) (Figure Not Available) . Pharmacological thrombolysis markedly increases the proportion of patients with a patent infarct-related artery early after AMI (see Fig. 35-10) (Figure Not Available) . In contrast to patients presenting with ST segment elevation, those patients who present without ST segment elevation have a much lower incidence of complete occlusion of the infarct-related coronary artery.

Thus, transmural infarcts occur distal to an acutely totally occluded coronary artery with thrombus superimposed on a ruptured plaque. However, the converse is not the case, in that chronic total occlusion of a coronary artery is not always associated with myocardial infarction. Collateral blood flow and other factors--such as the level of myocardial metabolism, the presence and location of stenoses

Figure 35-10 (Figure Not Available) Comparison of angiographically documented infarct-related coronary artery patency rates in 10 separate clinical studies and time from MI as modulated by early administration of a thrombolytic agent versus nonthrombolytic (conventional) therapy. The *x* axis is a semilogarithmic scale of time in days from myocardial infarction. Note that the difference in patency rates becomes diminishingly small within the first 2 to 3 weeks after infarction. *(From Rumberg JA, Gersh BJ: Coronary artery patency and left ventricular remodeling after myocardial infarction: mechanisms and mechanics. In Califf RM, Mark DB, Wagner GS [eds]: Acute Coronary Care. St. Louis, Mosby-Year Book, 1995, p 122.)*

in other coronary arteries, the rate of development of the obstruction, and the quantity of myocardium supplied by the obstructed vessel--all influence the viability of myocardial cells distal to the occlusion. In many series of patients studied at necropsy or by coronary arteriography, a small number (5 percent) of patients with AMI are found to have normal coronary vessels. In these patients, an embolus that has lysed, a transiently occlusive platelet aggregate, or a prolonged episode of severe coronary

spasm may have been responsible for the reduction in coronary flow.

Studies of patients who ultimately develop AMI after having undergone coronary angiography at some time before its occurrence have been helpful in clarifying coronary anatomy before infarction. Although high-grade stenoses, when present, more frequently lead to AMI than do less severe lesions, the majority of occlusions actually occur in vessels with a previously identified stenosis of less than 50 percent on angiograms performed months to years earlier. This finding supports the concept that AMI occurs as a result of sudden thrombotic occlusion at the site of rupture of previously nonobstructive but lipid-rich plaques.

Rather frequently, when an area of the ventricle is perfused by collateral vessels, an infarct occurs at a distance from a coronary occlusion. For example, after the gradual obliteration of the lumen of the right coronary artery, the inferior wall of the left ventricle may be maintained viable by collateral vessels arising from the left anterior descending coronary artery. In this circumstance, an occlusion of the left anterior descending artery may cause an infarct of the diaphragmatic wall.

RIGHT VENTRICULAR INFARCTION.

Depending on the criteria used, approximately 50 percent of patients with inferior infarction have some involvement of the right ventricle.[63] [63A] Among these patients, right ventricular infarction occurs exclusively in those with transmural infarction of the inferoposterior wall and the posterior portion of the septum. Right ventricular infarction almost invariably develops in association with infarction of the adjacent septum and left ventricular myocardium, but isolated infarction of the right ventricle is seen in 3 to 5 percent of autopsy-proven cases of MI.

Regardless of whether it is combined with involvement of the left ventricle, right ventricular infarction is generally associated with obstructive lesions of the right coronary artery. However, right ventricular infarction occurs less commonly than would be anticipated from the frequency of atherosclerotic lesions involving the right coronary artery. This discrepancy probably can be explained by the lower oxygen demands of the right ventricle, because right ventricular infarcts occur more commonly in conditions associated with increased right ventricular oxygen needs, such as pulmonary hypertension and right ventricular hypertrophy.[63] Moreover, the intercoronary collateral system of the right ventricle is richer than that of the left, and the thinness of the right ventricular wall allows the chamber to derive some nutrition from the blood within the right ventricular cavity. For the reasons just noted, the right ventricle can sustain long periods of ischemia but still demonstrate excellent recovery of contractile function after reperfusion.[64]

ATRIAL INFARCTION.

This may be seen in up to 10 percent of patients with AMI if PR segment displacement is used as the criterion for atrial infarction. Although isolated atrial infarction may be observed in 3.5 percent of autopsies of patients with AMI, it often occurs in conjunction

with ventricular infarction and can cause rupture of the atrial wall. This type of infarct is more common on the right than the left side, occurs more frequently in the atrial appendages than in the lateral or posterior walls of the atrium, and can result in thrombus formation. The difference in incidence between right and left atrial infarction might be explained by the considerably higher oxygen content of left atrial blood. Atrial infarction is frequently accompanied by atrial arrhythmias.[65] [66] It has also been reported to be associated with reduced secretion of atrial natriuretic peptide and a low cardiac output syndrome when right ventricular infarction coexists.

CORONARY ARTERY SPASM.

In addition to causing AMI in patients with Prinzmetal angina (see p. 1324), coronary artery spasm may also

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cause intimal damage that can initiate formation of an atherosclerotic plaque. Epicardial coronary artery spasm has been identified in patients with fixed atherosclerotic coronary artery stenosis before, during, and after AMI. An association between coronary artery spasm and coronary artery thrombosis has also been documented clinically.

COLLATERAL CIRCULATION IN ACUTE MYOCARDIAL INFARCTION

The coronary collateral circulation is particularly well developed in patients with (1) coronary occlusive disease, especially when it is severe, with the reduction of the luminal cross-sectional area by more than 75 percent in one or more major vessels; (2) chronic hypoxia, as occurs in severe anemia, chronic obstructive pulmonary disease, and cyanotic congenital heart disease; and (3) left ventricular hypertrophy, which intensifies coronary collateral vessels.

The magnitude of coronary collateral flow is one of the principal determinants of infarct size. Indeed, it is rather common for patients with abundant collateral vessels to have totally occluded coronary arteries without evidence of infarction in the distribution of that artery; thus, the survival of the myocardium distal to such occlusions must depend on collateral blood flow. Even if collateral perfusion existing at the time of coronary occlusion is not successful in improving contractile function, it may still exert a beneficial effect by preventing the formation of a left ventricular aneurysm. Some collaterals are seen in nearly 40 percent of patients with an acute total occlusion, and more begin to appear soon after the total occlusion occurs.[61] It is likely that the presence of a high-grade stenosis (90 percent), possibly with periods of intermittent total occlusion, permits the development of collateral vessels that remain only as potential conduits until a total occlusion occurs or recurs. The latter event then brings these channels into full operation.[67]

The incidence of collateral vessels 1 to 2 weeks after AMI varies considerably and may be as high as 75 to 100 percent in patients with persistent occlusion of the infarct vessel

or as low as 17 to 42 percent in patients with subtotal occlusion.

NONATHEROSCLEROTIC CAUSES OF ACUTE MYOCARDIAL INFARCTION

Numerous pathological processes other than atherosclerosis can involve the coronary arteries (see p. 1336) and result in MI (see Table 35-1) . For example, coronary arterial occlusions can be the result of embolization of a coronary artery. Emboli most frequently lodge in the distribution of the left anterior descending coronary artery, commonly in the distal epicardial and intramural branches. The causes of coronary embolism are numerous: infective endocarditis and nonbacterial thrombotic endocarditis (see Chap. 47) , mural thrombi, prosthetic valves, neoplasms, air that is introduced at the time of cardiac surgery, and calcium deposits from manipulation of calcified valves at operation. In situ thrombosis of coronary arteries can occur secondary to chest wall trauma (see Chap. 51) .

VASCULAR INFLAMMATION.

A variety of inflammatory processes can be responsible for coronary artery abnormalities, some of which mimic atherosclerotic disease and may predispose to true atherosclerosis. Epidemiological evidence suggests that viral infections, particularly with Coxsackievirus B, may be an uncommon cause of AMI. Viral illnesses precede AMI occasionally in young persons who are later shown to have normal coronary arteries.

Syphilitic aortitis may produce marked narrowing or occlusion of one or both coronary ostia, whereas Takayasu arteritis may result in obstruction of the coronary arteries (see Chap. 40) . Necrotizing arteritis, polyarteritis nodosa, mucocutaneous lymph node syndrome (Kawasaki disease) (see Chap. 45) , systemic lupus erythematosus (see Chap. 67) , and giant cell arteritis (see Chap. 67) can cause coronary occlusion. Therapeutic levels of mediastinal radiation can cause thickening and hyalinization of the walls of coronary arteries, with subsequent infarction. AMI may also be the result of coronary arterial involvement in amyloidosis (see Chap. 48) , Hurler syndrome, pseudoxanthoma elasticum, and homocystinuria.

COCAINE.

As cocaine abuse has become more common, reports of AMI after the use of cocaine have appeared with increasing frequency. Cocaine may cause AMI in patients with normal coronary arteries, preexisting MI, documented coronary artery disease, or coronary artery spasm.[52] AMI associated with cocaine has also been reported after its topical use in nasal septoplasty and in neonates whose mothers used the drug. Recurrent MI after further cocaine abuse has been reported as well.

Cocaine may cause AMI by at least three mechanisms: (1) increasing myocardial oxygen demand through increases in heart rate and blood pressure, (2) diminishing coronary artery flow resulting from either coronary vasospasm or thrombosis, and (3) active myocarditis (either hypersensitivity or toxicity). In very high doses, cocaine appears to have a direct toxic effect on heart muscle that may produce cardiac failure

and sudden death with extensive myocyte necrosis.

MYOCARDIAL INFARCTION WITH ANGIOGRAPHICALLY NORMAL CORONARY VESSELS

Approximately 6 percent of all patients with AMI and perhaps four times that percentage of patients with this diagnosis younger than the age of 35 years do not have coronary atherosclerosis demonstrated by coronary arteriography or at autopsy.[61] Perhaps half the patients of this group, in turn, have a variety of other lesions involving the coronary vessels or myocardium (see Table 35-1) , whereas the others have no detectable coronary obstructive lesions. Patients with AMI and normal coronary arteries tend to be young and to have relatively few coronary risk factors, except that they often have a history of cigarette smoking. Usually, they have no history of angina pectoris before the infarction. The infarction in these patients is usually not preceded by any prodrome, but the clinical, laboratory, and ECG features of AMI are otherwise indistinguishable from those present in the overwhelming majority of patients with AMI who have classic obstructive atherosclerotic coronary artery disease. In patients who recover, areas of localized dyskinesis and hypokinesis can often be demonstrated by left ventricular angiography. Many of these cases are caused by coronary artery spasm and/or thrombosis, perhaps with underlying endothelial dysfunction or small plaques that are not apparent on coronary angiography. Additional suggested causes include (1) coronary emboli (perhaps from a small mural thrombus, a prolapsed mitral valve, or a myxoma); (2) coronary artery disease in vessels too small to be visualized by coronary arteriography or coronary arterial thrombosis with subsequent recanalization (see Table 35-1) ; (3) a variety of hematological disorders causing in situ thrombosis in the presence of normal coronary arteries (polycythemia vera, cyanotic heart disease with polycythemia, sickle cell anemia, disseminated intravascular coagulation, thrombocytosis, and thrombotic thrombocytopenic purpura); augmented oxygen demand (thyrotoxicosis, amphetamine use); (5) hypotension secondary to sepsis, blood loss, or pharmacological agents; and (6) anatomical variations such as anomalous origin of a coronary artery (see Chap. 44) , coronary arteriovenous fistula (see Chap. 44) , or a myocardial bridge (see Chap. 12) .

PROGNOSIS.

The long-term outlook for patients who have survived an AMI with angiographically normal coronary vessels on arteriography appears to be substantially better than that for patients with MI and obstructive coronary artery disease. After recovery from the initial infarct, recurrent infarction, heart failure, and death are unusual in patients with normal coronary arteries. Indeed, most of these patients have normal exercise ECGs and only a minority develop angina pectoris.

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Pathophysiology

LEFT VENTRICULAR FUNCTION

Systolic Function

On interruption of antegrade flow in an epicardial coronary artery, the zone of myocardium supplied by that vessel immediately loses its ability to shorten and perform contractile work. Four abnormal contraction patterns develop in sequence: (1) dyssynchrony (i.e., dissociation in the time course of contraction of adjacent segments), (2) hypokinesis (reduction in the extent of shortening), (3) akinesis (cessation of shortening), and (4) dyskinesis (paradoxical expansion, systolic bulging).[68] [69] Accompanying dysfunction of the infarcting segment initially is hyperkinesis of the remaining normal myocardium. The early hyperkinesis of the noninfarcted zones is believed to be the result of acute compensatory mechanisms, including increased activity of the sympathetic nervous system and the Frank-Starling mechanism. A portion of this compensatory hyperkinesis is ineffective work because contraction of the noninfarcted segments of myocardium causes dyskinesis of the infarct zone. Increased motion of the noninfarcted region subsides within 2 weeks of infarction, during which time some degree of recovery can be seen in the infarct region as well, particularly if reperfusion of the infarcted area occurs and myocardial stunning diminishes.

Patients with AMI often also show reduced myocardial contractile function in noninfarcted zones. This may result from previous obstruction of the coronary artery

supplying the noninfarcted region of the ventricle and loss of collaterals from the freshly occluded infarct-related vessel, a condition that has been termed "ischemia at a distance."[70] Conversely, the presence of collaterals developing before MI may allow for greater preservation of regional systolic function in an area of distribution of the occluded artery and improvement in left ventricular ejection fraction early after infarction.

If a sufficient quantity of myocardium undergoes ischemic injury, LV pump function becomes depressed; cardiac output, stroke volume, blood pressure, and peak dP/dt are reduced[69] ; and end-systolic volume is increased. The degree to which end-systolic volume increases is perhaps the most powerful predictor of mortality after AMI.[71] Paradoxical systolic expansion of an area of ventricular myocardium further decreases LV stroke volume. As necrotic myocytes slip past each other, the infarct zone thins and elongates, especially in patients with large anterior infarcts, leading to infarct expansion. As the ventricle dilates during the first few hours to days after infarction, regional and global wall stress increases according to Laplace's law. In some patients a vicious cycle of dilatation begetting further dilatation is initiated.[72] [73] The degree of ventricular dilatation, which depends closely on infarct size, patency of the infarct-related artery,[74] and activation of the local renin-angiotensin system in the noninfarcted portion of the ventricle, can be favorably modified by angiotensin-converting enzyme (ACE) inhibition therapy even in the absence of symptomatic LV dysfunction.[75]

With the passage of time, edema, cellular infiltration, and ultimately fibrosis, increase the stiffness of the infarcted myocardium back to and beyond control values. Increasing stiffness in the infarcted zone of myocardium improves LV function because it prevents paradoxical systolic wall motion.

A linear relationship exists between specific parameters of LV function and the likelihood of developing clinical symptoms such as dyspnea and ultimately a shocklike state. The earliest abnormality is a reduction in diastolic compliance (see later), which can be observed with infarcts that involve only 8 percent of the total left ventricle on angiographic examination. When the abnormally contracting segment exceeds 15 percent, the ejection fraction may be reduced and elevations of LV end-diastolic pressure and volume occur. The risk of developing physical signs and symptoms of LV failure also increases proportionally to increasing areas of abnormal left ventricular wall motion.[69] Clinical heart failure accompanies areas of abnormal contraction exceeding 25 percent, and cardiogenic shock, often fatal, accompanies loss of more than 40 percent of the left ventricular myocardium.

Unless infarct extension occurs, some improvement in wall motion takes place during the healign phase, as recovery of function occurs in initially reversibly injured (stunned) myocardium (see Fig. 35-9) . Regardless of the age of the infarct, patients who continue to demonstrate abnormal wall motion of 20 to 25 percent of the left ventricle are likely to manifest hemodynamic signs of LV failure.

Diastolic Function (See Chap. 15)

Left ventricular diastolic properties are altered in infarcted and ischemic myocardium, leading initially to an increase but later to a reduction in LV compliance. These changes

are associated with a decrease in the peak rate of decline in left ventricular pressure (peak [-] dP/dt), an increase in the time constant of the fall in left ventricular pressure, and an initial rise in LV end-diastolic pressure. Over a period of several weeks, end-diastolic volume increases and diastolic pressure begins to fall toward normal. As with impairment of systolic function, the magnitude of the diastolic abnormality appears to be related to the size of the infarct.

CIRCULATORY REGULATION

The abnormality in circulatory regulation that is present in AMI is diagrammed in Figure 35-11 . The process begins with an anatomical or functional obstruction in the coronary vascular bed, which results in regional myocardial ischemia and, if the ischemia persists, in infarction. If the infarct is of sufficient size, it depresses overall left ventricular function so that LV stroke volume falls and filling pressures rise. A marked depression of LV stroke volume ultimately lowers aortic pressure and reduces coronary perfusion pressure; this condition may intensify myocardial ischemia and thereby initiate a vicious cycle (see Fig. 35-11) . The inability of the left ventricle to empty also leads to an increased preload, that is, it dilates the well-perfused, normally functioning portion of the left ventricle. This compensatory mechanism tends to restore stroke volume to normal levels but at the expense of a reduced ejection fraction. However, the dilatation of the left ventricle also elevates ventricular afterload, because Laplace's law dictates that at any given arterial pressure the dilated ventricle must develop a higher wall tension. This increased afterload not only depresses left ventricular stroke volume but also elevates myocardial oxygen consumption, which in turn intensifies myocardial ischemia. When regional myocardial dysfunction is limited and the function of the remainder of the left ventricle is normal, compensatory mechanisms sustain overall LV function. If a large portion of the left ventricle becomes necrotic, pump failure occurs; that is, overall left ventricular function becomes so depressed that the circulation cannot be sustained despite the dilatation of the remaining viable portion of the ventricle.

Figure 35-11 The vicious circle in cardiogenic shock. LVEDP = left ventricular end-diastolic pressure. *(From Hollenberg SM, Kavinsky CJ, Parrillo JE: Cardiogenic shock. Ann Intern Med 131:47-59, 1999.)*

VENTRICULAR REMODELING

As a consequence of MI, the changes in left ventricular size, shape, and thickness involving both the infarcted and the noninfarcted segments of the ventricle just described occur and are collectively referred to as *ventricular remodeling.* This process, in turn, can influence ventricular function and prognosis.[72] A combination of changes in left ventricular dilation and hypertrophy of residual noninfarcted myocardium is responsible for remodeling.[72A] After the size of infarction, the two most important factors driving the process of left ventricular dilatation are ventricular loading conditions and

infarct artery patency[72] [74] [76] (Fig. 35-12) . Elevated ventricular pressure contributes to increased wall stress and the risk of infarct expansion, and a patent infarct artery accelerates myocardial scar formation and increases tissue turgor in the infarct zone, reducing the risk of infarct expansion and ventricular dilatation.

INFARCT EXPANSION.

An increase in the size of the infarcted segment, known as infarct expansion, is defined as "acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis."[77] Infarct expansion appears to be caused by (1) a combination of slippage between muscle bundles, reducing the number of myocytes across the infarct wall; (2) disruption of the normal myocardial cells; and (3) tissue loss within the necrotic zone.[77] It is characterized by disproportionate thinning and dilation of the infarct zone before formation of a firm, fibrotic scar.[72A] The degree of infarct expansion appears to be related to the preinfarction wall thickness, with existing hypertrophy possibly protecting against infarct thinning. The apex is the thinnest region of the ventricle and an area of the heart that is particularly vulnerable to infarct expansion.[78] Infarction of the apex secondary to occlusion of the left anterior descending coronary artery causes the radius of curvature at the apex to increase, exposing this normally thin region to a marked elevation in wall stress.

When it is present, infarct expansion is associated with both a higher mortality and a higher incidence of nonfatal complications, such as heart failure and ventricular aneurysm.[79] Infarct expansion has been noted in more than three fourths of the hearts of patients succumbing to AMI and in one third to one half of all patients with anterior Q-wave infarctions.[79] Infarct expansion is best recognized echocardiographically as elongation of the noncontractile region of the ventricle. When expansion is severe enough to cause symptoms, the most characteristic clinical finding is deterioration of systolic function associated with new or louder gallop sounds and new or worsening pulmonary congestion. Rupture of the ventricle may be considered to be a consequence of extreme infarct expansion.

VENTRICULAR DILATATION.

Although infarct expansion plays an important role in the ventricular remodeling that occurs early after MI, remodeling is also caused by dilatation of the viable portion of the ventricle, commencing immediately after AMI and progressing for months or years thereafter (Fig. 35-12) .[72A] As opposed to distention, dilatation may be accompanied by a shift of the pressure-volume curve of the left ventricle to the right, resulting in a larger left ventricular volume at any given diastolic pressure. This global dilatation of the noninfarct zone may be viewed as a compensatory mechanism that maintains stroke volume in the face of a large infarction. However, ventricular dilatation is also associated with nonuniform repolarization of the myocardium that predisposes the patient to life-threatening ventricular arrhythmias.

After AMI, an extra load is placed on the residual functioning myocardium, a load that presumably is responsible for the compensatory hypertrophy of the uninfarcted

myocardium. This hypertrophy could help to compensate for

Figure 35-12 Therapeutic maneuvers in various stages of ischemia and infarction. Severely ischemic tissue (2) may be reperfused, thereby averting MI (*A*). Infarcting tissue (3) may be reperfused, leading to sparing of myocardial tissue (*B*). If blood flow is restored only in part (*B*), the myocardium may remain noncontractile although viable (i.e., hibernating). After completion of the infarct (4), late reperfusion (*C*) may still be useful. Mechanical reperfusion of moderately ischemic myocardium (*C*) may restore contractility of hibernating myocardium to normal. Ventricular unloading may be useful throughout the preinfarct and postinfarct periods. Unloading may reduce ischemia (D_2), infarct size (D_3), infarct expansion (D_4), and ventricular dilation ($D_{5,6}$). *(From Braunwald E, Pfeffer MA: Ventricular enlargement and remodeling following acute myocardial infarction: Mechanisms and management. Am J Cardiol 68:4D, 1991.)*

Figure 35-13 Flow chart showing postulated sequence of events from an unstable atherosclerotic plaque to death. The original paradigm emphasizing early reperfusion is shown at the left; the expanded paradigm illustrating the benefits of late reperfusion is shown at the right. *(From Kim CB, Braunwald E: Potential benefits of late reperfusion of infarcted myocardium: The open artery hypothesis. Circulation 88:2426, 1993. Copyright 1993, American Heart Association.)*

the functional impairment caused by the infarct and may be responsible for some of the hemodynamic improvement seen in the months after infarction in some patients.[72A]

EFFECTS OF TREATMENT.

Ventricular remodeling after AMI can be affected by several factors, the first of which is infarct size (see Fig. 35-12) . Acute reperfusion and other measures to restrict the extent of myocardial necrosis limit the increase in ventricular volume after AMI, and evidence suggests that an open infarct artery per se achieved even late after coronary occlusion also attenuates ventricular enlargement[72A] [74] (Fig. 35-13) . The second factor is scar formation in the infarct. Glucocorticosteroids and nonsteroidal anti-inflammatory agents given early after MI can cause scar thinning and greater infarct expansion, whereas ACE inhibitors[72] attenuate ventricular enlargement (see p. 1169 and Figs. 35-12 and 35-13) . Additional beneficial consequences of inhibition of angiotensin II that may contribute to myocardial protection include attenuation of endothelial dysfunction and direct antiatherogenic effects.[72A] [80]

PATHOPHYSIOLOGY OF OTHER ORGAN SYSTEMS

PULMONARY FUNCTION

Changes in pulmonary gas exchange, ventilation, and distribution of perfusion all occur

with AMI. Hypoxemia is a frequent consequence, with a severity, in general, proportional to that of left ventricular failure. There is an inverse relation between pulmonary artery diastolic pressure and arterial oxygen tension in patients with AMI. This suggests that increased pulmonary capillary hydrostatic pressure leads to interstitial edema, which results in arteriolar and bronchiolar compression that ultimately causes perfusion of poorly ventilated alveoli with resultant hypoxemia. In addition to hypoxemia, there is a fall in diffusing capacity. Hyperventilation often occurs in patients with AMI and may cause hypocapnia and respiratory alkalosis, particularly in restless, anxious patients with pain. With reversal of heart failure, hypoxemia and intrapulmonary shunting diminish.

INCREASE IN INTERSTITIAL WATER.

A positive correlation has been demonstrated between pulmonary extravascular (interstitial) water content, left ventricular filling pressure, and the clinical signs and symptoms of left ventricular failure. The increase in pulmonary extravascular water may be responsible for the alterations in pulmonary mechanics observed in patients with AMI (i.e., reduction of airway conductance, pulmonary compliance, forced expiratory volume, and midexpiratory flow rate and an increase in closing volume--the last presumably related to the widespread closure of small, dependent airways during the first 3 days after AMI). Ultimately, severe increases in extravascular water may lead to pulmonary edema. Recovery of LV function or diuresis reduces abnormally elevated values for closing volumes (i.e., the lung volume at which airway closure commences) to normal.

The "closing volume" can encroach on and sometimes exceed functional residual volume. This can lead to arterial hypoxemia by the shunting of blood through alveoli that are not well ventilated.

REDUCTION OF VITAL CAPACITY.

Virtually all lung volume indices--total lung capacity, functional residual capacity, and residual volume, as well as vital capacity--fall in the presence of AMI.[81] These reductions correlate with the elevations of left-sided filling pressures and are most probably due to increases in pulmonary extravascular water. Lung volumes, oxygenation, and airway resistance all return toward normal by the time of hospital discharge for most patients.[81] Increased pulmonary venous pressure also results in redistribution of pulmonary blood flow from the bases to the apices of the lung in patients with AMI, altering the relationship between ventilation and perfusion. However, at follow-up examination 3 to 25 weeks after MI, the ventilation-perfusion relationship has usually returned to normal or almost so.

REDUCTION OF AFFINITY OF HEMOGLOBIN FOR OXYGEN.

In patients with MI, particularly when complicated by LV failure or cardiogenic shock, the affinity of hemoglobin for oxygen is reduced (i.e., the P_{50} is increased). The increase in P_{50} results from increased levels of erythrocyte 2,3-diphosphoglycerate (2,3-DPG), which constitutes an important compensatory mechanism, responsible for an estimated

18 percent increase in oxygen release from oxyhemoglobin in patients with cardiogenic shock.

ENDOCRINE FUNCTION

PANCREAS.

Hyperglycemia and impaired glucose tolerance are common in patients with AMI. Although the absolute levels of blood insulin are often in the normal range, they are usually inappropriately low for the level of blood sugar, and there may be relative insulin resistance as well. Stress-induced hyperglycemia in the setting of AMI is associated with an increased risk of mortality even in patients without diabetes mellitus.[81A] Patients with cardiogenic shock often demonstrate marked hyperglycemia and depressed levels of circulating insulin, often with complete suppression of insulin secretion in response to tolbutamide.[82] These abnormalities in insulin secretion and the resultant impaired glucose tolerance appear to be secondary to a reduction in pancreatic blood flow as a consequence of splanchnic vasoconstriction accompanying severe LV failure. In addition, increased activity of the sympathetic nervous system with augmented circulating catecholamines inhibits insulin secretion and augments glycogenolysis, also contributing to the elevation of blood sugar.[83]

Glucose appears to be a more favorable energy source than free fatty acids for the ischemic myocardium by more efficiently replenishing the Krebs cycle and stimulating contractile performance.[84] Because hypoxic heart muscle derives a considerable portion of its energy from the metabolism of glucose (see Chap. 63) and because insulin is essential for the uptake of glucose by the myocardium as well as for myocardial protein synthesis and inhibition of lysosomal activity, the deleterious effects of insulin deficiency are clear. These metabolic considerations, combined with epidemiological observations that diabetic patients have a markedly worse prognosis, have served as the foundation for efforts to more aggressively administer insulin-glucose infusions to diabetics with AMI (see p. 1172).

ADRENAL MEDULLA.

Excessive secretion of catecholamines produces many of the characteristic signs and symptoms of AMI. The plasma and urinary catecholamine levels are highest during the first 24 hours after the onset of chest pain,[83] with the greatest rise in plasma catecholamine secretion occurring during the first hour after the onset of MI. These high levels of circulating catecholamines in patients with AMI correlate with the occurrence of serious arrhythmias and result in an increase in myocardial oxygen consumption, both directly and indirectly, as a consequence of catecholamineinduced elevation of circulating free fatty acids. As might be anticipated, the concentration of circulating catecholamines correlates with the extent of myocardial damage and incidence of cardiogenic shock, as well as both early and late mortality rates.

Circulating catecholamines enhance platelet aggregation; when this occurs in the

coronary microcirculation, the release of the potent

vasoconstrictor thromboxane A_2 may further impair cardiac perfusion. The marked increase in sympathetic activity associated with AMI serves as the foundation for beta-adrenoceptor blocker regimens in the acute phase (see p. 1168).

LOCAL MYOCARDIAL AND SYSTEMIC RENIN-ANGIOTENSIN SYSTEM.

Noninfarcted regions of the myocardium appear to exhibit activation of the tissue renin-angiotensin system with increased angiotensin II production. Both locally and systemically generated angiotensin II may stimulate the production of various growth factors, such as platelet-derived growth factor and transforming growth factor, that promote compensatory hypertrophy in the noninfarcted myocardium as well as control the structure and tone of the infarct-related coronary and other myocardial vessels.[72A] Additional potential actions of angiotensin II that have a more negative impact on the infarction process include release of endothelin, PAI-1, and aldosterone, which may cause vasoconstriction, impaired fibrinolysis, and increased sodium retention, respectively. Inhibition of generation of circulating and tissue angiotensin II is one of the proposed mechanisms of benefit from ACE inhibitors in AMI.

NATRIURETIC PEPTIDES.

The peptides atrial natriuretic factor (ANF) and N-terminal pro-ANF are released from cardiac atria in response to elevation of atrial pressure. In a case-control study from the Thrombolysis in Myocardial Infarction (TIMI) II trial, Hall and colleagues have shown that elevated N-terminal pro-ANF levels within the first 12 hours of AMI are highly predictive of an increased mortality risk in the year after infarction. A novel protein, brain natriuretic peptide (BNP), originally isolated from porcine brain, has been shown to be secreted by human ventricular myocardium. It appears to be released early after AMI, peaking at about 16 hours. Patients with anterior infarction, lower cardiac index, and more significant congestive heart failure after AMI have higher levels of BNP and also show a second peak of BNP release about 5 days after infarction. These intriguing observations suggest that BNP levels may be a marker of the degree of left ventricular dysfunction in AMI and that markedly elevated levels of BNP correlate with a worse prognosis.

ADRENAL CORTEX.

Plasma and urinary 17-hydroxycorticosteroids and ketosteroids, as well as aldosterone, are also markedly elevated in patients with AMI.[83] Their concentrations correlate directly with the peak level of serum creatine kinase, implying that the stress imposed by larger infarcts is associated with greater secretion of adrenal steroids. The magnitude of the elevation of cortisol correlates with infarct size and mortality. Glucocorticosteroids

also contribute to the impairment of glucose tolerance.

THYROID GLAND.

Although patients with AMI are generally euthyroid, evidence indicates a significant transient decrease in serum triiodothyronine (T_3) levels, a fall that is most marked on about the third day after the infarct. This fall in T_3 is usually accompanied by a rise in reverse T_3, with variable changes or no change in thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels. The alteration in peripheral T_4 metabolism appears to correlate with infarct size and may be mediated by the rise in endogenous levels of cortisol that accompanies AMI.

RENAL FUNCTION

Both prerenal azotemia and acute renal failure can complicate the marked reduction of cardiac output that occurs in cardiogenic shock. On the other hand, an increase in circulating atrial natriuretic peptide occurs after AMI, an increase that is correlated with the severity of left ventricular failure. An increase in atrial natriuretic peptide is also found when right ventricular infarction accompanies inferior wall infarction, suggesting that this hormone may play a role in the hemodynamic disturbances that accompany right ventricular infarction.

HEMATOLOGICAL FUNCTION

PLATELETS.

AMI generally occurs in the presence of extensive coronary and systemic atherosclerotic plaques, which may serve as the site for the formation of platelet aggregates, a sequence that has been suggested as the initial step in the process of coronary thrombosis, coronary occlusion, and subsequent MI. Circulating platelets are hyperaggregable in patients with AMI. The role of platelets in AMI is discussed in Chapter 62 . Platelets from AMI patients have an increased propensity for aggregation locally in the area of a disrupted plaque and also release vasoactive substances such as thromboxane A_2 (see Fig. 35-3) .

HEMOSTATIC MARKERS.

Elevated levels of serum fibrinogen degradation products, an end product of thrombosis--as well as release of distinctive proteins when platelets are activated (i.e., platelet factor 4 and beta-thromboglobulin)--have been reported in some patients with AMI. Fibrinopeptide A, a protein released from fibrin by thrombin, is a marker of ongoing thrombosis and is increased during the early hours of AMI. Marked elevation of hemostatic markers such as FPA, TAT, and F1&2 is associated with an increased risk of mortality in AMI patients[85] (see Chap. 62 and Fig. 35-7) (Figure Not Available) . The interpretation of the coagulation tests in patients with AMI may be complicated by elevated blood levels of catecholamines, concomitant shock, and/or pulmonary

embolism, conditions that are all capable of altering various tests of platelet and coagulation function. Thus, it is not yet clear whether the aforementioned changes are the causes or consequences of AMI.

LEUKOCYTES.

An elevated leukocyte count is an epidemiologic marker for coronary heart disease.[86] AMI is usually accompanied by leukocytosis, which is related to the magnitude of the necrotic process, elevated glucocorticoid levels, and possibly inflammation in the coronary arteries. The magnitude of elevation of the leukocyte count is associated with in-hospital mortality after AMI.[87] [87A] Activation of neutrophils may produce important intermedaries, such as leukotriene B_4 and oxygen free radicals, that have important microcirculatory effects.

BLOOD VISCOSITY.

Clinical and epidemiological studies suggest that several hemostatic and hemorheological factors (e.g., fibrinogen, factor VII, plasma viscosity, hematocrit, red blood cell aggregation, total white blood cell count) are involved in the pathophysiology of atherosclerosis and also play an integral role in acute thrombotic events. An increase in blood viscosity also occurs in patients with AMI. During the first few days after infarction, this is mainly attributable to hemoconcentration, but later the increases in plasma viscosity and red cell aggregation correlate with elevated serum concentrations of $alpha_2$ -globulin and fibrinogen, which are nonspecific reactions to tissue necrosis and are also responsible for the elevated sedimentation rate characteristic of AMI. The high values of blood viscosity indices are observed most frequently in patients with complications such as left ventricular failure, cardiogenic shock, and thromboembolism.

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Clinical Features

PREDISPOSING FACTORS

The risk factors for atherosclerosis and coronary artery disease are discussed in Chapter 31 .

In as many as one half of patients with AMI, a precipitating factor or prodromal symptoms can be identified.[88] Evidence suggests that unusually heavy exercise (particularly in fatigued or emotionally stressed, habitually inactive patients) may play a role in precipitating AMI.[89] [90] Such infarctions could be the result of marked increases in myocardial oxygen consumption in the presence of severe coronary arterial narrowing. It has been suggested that unusually heavy exertion or mental stress such as that caused by anger[91] may trigger plaque disruption, leading to AMI. Patients with known coronary artery disease who have been hospitalized for treatment of an acute coronary syndrome-related event and who subsequently report a high level of stress in their life have an increased risk of rehospitalization for cardiovascular reasons and also for "hard" events such as death and MI. Of interest, however, one study has provided evidence that, in a multivariate analysis adjusting for other cardiac risk factors, job strain did not affect the outcome (including nonfatal AMI) in patients with angiographically proven coronary artery disease.[92]

Accelerating angina and rest angina, two patterns of unstable angina (see Chap. 36) , may culminate as AMI (see Fig. 35-2) . [40A] Noncardiac surgical procedures have also been noted as precursors of AMI (see Chap. 61) . Perioperative risk stratification and the use of beta blockers may reduce the likelihood of AMI and cardiac-related mortality.[93] [94] Reduced myocardial perfusion secondary to hypotension (e.g., hemorrhagic or septic shock) and increased myocardial oxygen demands secondary to

aortic stenosis, fever, tachycardia, and agitation can also be responsible for myocardial necrosis. Other factors reported as predisposing to AMI include respiratory infections, hypoxemia of any cause, pulmonary embolism, hypoglycemia, administration of ergot preparations, use of cocaine, sympathomimetics, serum sickness, allergy, and on rare occasion wasp stings. In patients with Prinzmetal's angina (see Chap. 37) , AMI

may develop in the territory of the coronary artery that repeatedly undergoes spasm.[95] Rarely, munitions workers exposed to high concentrations of nitroglycerin may develop MI when they are withdrawn from this exposure, suggesting that it is caused by vasospasm.[96]

Trauma may precipitate an AMI in one of two ways. Myocardial contusion and hemorrhage into the myocardium may actually cause cell necrosis, or the injury may involve a coronary artery, causing occlusion of that vessel with resultant AMI (see Chap. 51) . Neurological disturbances (transient ischemic attacks or strokes) may also precipitate AMI. Concern has been raised on the basis of a case-control study that patients with hypertension who are receiving short-acting calcium antagonists, particularly in high doses, are at increased risk of developing AMI. Because of possible selection bias in the patients who received calcium antagonists, these results must be viewed cautiously and clinicians should await the results of ongoing multicenter trials (e.g., ALLHAT) before withdrawing calcium antagonists from patients who might be benefiting from their antihypertensive effect (reduction of stroke).

CIRCADIAN PERIODICITY.

An analysis of a large number of patients hospitalized with MI, studied as a part of the Multicenter Investigation of Limitation of Infarct Size (MILIS), revealed a pronounced circadian periodicity for the time of onset of AMI, with peak incidence of events between 6 a.m. and 12 p.m. Circadian rhythms affect many physiological and biochemical parameters; the early morning hours are associated with rises in plasma catecholamines and cortisol and increases in platelet aggregability.[97] Interestingly, the characteristic circadian peak was *absent* in patients receiving beta blocker or aspirin therapy before their presentation with AMI. The concept of "triggering" an AMI is a complex one and likely involves the superimposition of multiple factors such as time of day, season, and the stress of natural disasters.[50] [98]

HISTORY

PRODROMAL SYMPTOMS.

Despite recent advances in the laboratory detection of AMI, the history remains of substantial value in establishing a diagnosis. The prodrome is usually characterized by chest discomfort, resembling classic angina pectoris (see Chap. 37) , but it occurs at rest or with less activity than usual and can therefore be classified as unstable angina.

However, the latter is often not disturbing enough to induce patients to seek medical attention; if they do, they may not be hospitalized. Of the patients with AMI presenting with prodromal symptoms of unstable angina, approximately one third have had symptoms from 1 to 4 weeks before hospitalization; in the remaining two thirds, symptoms predated admission by 1 week or less, with one third of these patients (20 percent of all with prodromes) having had symptoms for 24 hours or less. A feeling of general malaise or frank exhaustion often accompanies other symptoms preceding AMI.

NATURE OF THE PAIN.

The pain of AMI is variable in intensity; in most patients it is severe and in some instances intolerable. The pain is prolonged, usually lasting for more than 30 minutes and frequently for a number of hours. The discomfort is described as constricting, crushing, oppressing, or compressing; often the patient complains of a sensation of a heavy weight or a squeezing in the chest. Although the discomfort is typically described as a choking, viselike, or heavy pain, it may also be characterized as a stabbing, knifelike, boring, or burning discomfort. The pain is usually retrosternal in location, spreading frequently to both sides of the anterior chest, with predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm, producing a tingling sensation in the left wrist, hand, and fingers. Some patients note only a dull ache or numbness of the wrists in association with severe substernal or precordial discomfort. In some instances, the pain of AMI may begin in the epigastrium and simulate a variety of abdominal disorders, a fact that often causes MI to be misdiagnosed as "indigestion." In other patients the discomfort of AMI radiates to the shoulders, upper extremities, neck, jaw, and interscapular region, again usually favoring the left side. In patients with preexisting angina pectoris, the pain of infarction usually resembles that of angina with respect to location. However, it is generally much more severe, lasts longer, and is not relieved by rest and nitroglycerin.

In some patients, particularly the elderly, AMI is manifested clinically not by chest pain but rather by symptoms of acute left ventricular failure and chest tightness or by marked weakness or frank syncope.[98A] [98B] These symptoms may be accompanied by diaphoresis, nausea, and vomiting. The pain of AMI may have disappeared by the time the physician first encounters the patient (or the patient reaches the hospital), or it may persist for many hours. Opiates--in particular morphine--usually relieve the pain. Both angina pectoris and the pain of AMI are thought to arise from nerve endings in ischemic or injured, but not necrotic, myocardium. Thus, in MI, stimulation of nerve fibers in an ischemic zone of myocardium surrounding the necrotic central area of infarction probably gives rise to the pain.

Pain often disappears suddenly and completely when blood flow to the infarct territory is restored. In patients in whom reocclusion occurs after thrombolysis, pain recurs if the initial reperfusion has left viable myocardium. Thus, what has previously been thought of as the "pain of infarction," sometimes lasting for many hours, probably represents pain caused by ongoing ischemia. The recognition that pain implies ischemia and not infarction heightens the importance of seeking ways to relieve the ischemia, for which the pain is a marker. This finding suggests that the clinician should not be complacent

about ongoing cardiac pain under any circumstances.

OTHER SYMPTOMS.

Nausea and vomiting occur in more than 50 percent of patients with transmural MI and severe chest pain, presumably owing to activation of the vagal reflex or to stimulation of left ventricular receptors as part of the Bezold-Jarisch reflex. These symptoms occur more commonly in patients with inferior MI than in those with anterior MI. Moreover, nausea and vomiting are common side effects of opiates. When the pain of AMI is epigastric in location and is associated with nausea and vomiting, the clinical picture may easily be confused with that of acute cholecystitis, gastritis, or peptic ulcer. Occasionally, a patient complains of diarrhea or a violent urge to evacuate the bowels during the acute phase of MI. Other symptoms include feelings of profound weakness, dizziness, palpitations, cold perspiration, and a sense of impending doom. On occasion, symptoms arising from an episode of cerebral embolism or other systemic arterial embolism are the first signs of AMI. The aforementioned symptoms may or may not be accompanied by chest pain.

Differential Diagnosis

The pain of AMI may stimulate the pain of acute pericarditis (see Chaps. 3 and 50) , which is usually associated with some pleuritic features; that is, it is aggravated by respiratory movements and coughing and often involves the shoulder, ridge of the trapezius, and neck. An important feature that distinguishes pericardial pain from ischemic discomfort is that ischemic discomfort never radiates to the trapezius ridge, a characteristic site of radiation of pericardial pain.[99] Pleural pain is usually sharp, knifelike, and aggravated in a cyclical fashion by each breath, which distinguishes it from the deep, dull, steady pain of AMI. Pulmonary

embolism (see Chap. 52) generally produces pain laterally in the chest, is often pleuritic, and may be associated with hemoptysis. The pain due to acute dissection of the aorta (see Chap. 40) is usually localized in the center of the chest, is extremely severe and described by the patient as a "ripping" or "tearing" sensation, is at its maximal intensity shortly after onset, persists for many hours, and often radiates to the back or the lower extremities. Often one or more major arterial pulses are absent. Pain arising from the costochondral and chondrosternal articulations may be associated with localized swelling and redness; it is usually sharp and "darting" and is characterized by marked localized tenderness. Episodes of retrosternal discomfort induced by peristalsis in patients with increased esophageal stiffness and also episodes of sustained esophageal contraction can mimic the pain of AMI.[100] [101]

SILENT MI AND ATYPICAL PRESENTATION.

Population studies suggest that between 20 and 60 percent of nonfatal MIs are

unrecognized by the patient and are discovered only on subsequent routine ECG or postmortem examinations. Of these unrecognized infarctions, approximately half are truly silent, with the patients unable to recall any symptoms whatsoever. The other half of patients with so-called silent infarction can recall an event characterized by symptoms compatible with acute infarction when leading questions are posed after the ECG abnormalities are discovered. Unrecognized or silent infarction occurs more commonly in patients without antecedent angina pectoris and in patients with diabetes[98A] and hypertension.[102] Silent MI is often followed by silent ischemia (see p. 1330). The prognoses of patients with silent and symptomatic presentations of AMI appear similar.

Atypical presentations of AMI include the following: (1) congestive heart failure--beginning de novo or worsening of established failure; (2) classic angina pectoris without a particularly severe or prolonged attack; (3) atypical location of the pain; (4) central nervous system manifestations, resembling those of stroke, secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis; (5) apprehension and nervousness; (6) sudden mania or psychosis; (7) syncope; (8) overwhelming weakness; (9) acute indigestion; and (10) peripheral embolization.

PHYSICAL EXAMINATION

GENERAL APPEARANCE.

Patients suffering an AMI often appear anxious and in considerable distress. An anguished facial expression is common, and--in contrast to patients with severe angina pectoris, who often lie, sit, or stand still, recognizing that all forms of activity increase the discomfort--some patients suffering an AMI may be restless and move about in an effort to find a comfortable position. They often massage or clutch their chests and frequently describe their pain with a clenched fist held against the sternum (the "Levine" sign, named after Dr. Samuel A. Levine). In patients with left ventricular failure and sympathetic stimulation, cold perspiration and skin pallor may be evident; they typically sit or are propped up in bed, gasping for breath. Between breaths, they may complain of chest discomfort or a feeling of suffocation. Cough productive of frothy, pink, or blood-streaked sputum is common.

Patients in cardiogenic shock often lie listlessly, making few if any spontaneous movements. The skin is cool and clammy, with a bluish or mottled color over the extremities, and there is marked facial pallor with severe cyanosis of the lips and nailbeds. Depending on the degree of cerebral perfusion, the patient in shock may converse normally or may evidence confusion and disorientation.

HEART RATE.

The heart rate may vary from a marked bradycardia to a rapid regular or irregular tachycardia, depending on the underlying rhythm and the degree of left ventricular failure. Most commonly, the pulse is rapid and regular initially (sinus tachycardia at 100 to 110 beats/min), slowing as the patient's pain and anxiety are relieved; ventricular premature beats (VPBs) are common, occurring in more than 95 percent of patients

evaluated within the first 4 hours after the onset of symptoms.

BLOOD PRESSURE.

The majority of patients with uncomplicated AMI are normotensive, although the reduced stroke volume accompanying the tachycardia may cause declines in systolic and pulse pressures and elevation of diastolic pressure. Among previously normotensive patients, a hypertensive response occasionally is seen during the first few hours, with the arterial pressure exceeding 160/90 mm Hg, presumably as a consequence of adrenergic discharge secondary to pain and agitation. It is common for previously hypertensive patients to become normotensive without treatment after AMI, although many of these previously hypertensive patients eventually regain their elevated levels of blood pressure, generally 3 to 6 months after infarction. In patients with massive infarction, arterial pressure falls acutely, owing to left ventricular dysfunction and venous pooling secondary to administration of morphine or nitrates or both; as recovery occurs, the arterial pressure tends to return to preinfarction levels.

Patients in cardiogenic shock (see p. 1178), by definition, have systolic pressures below 90 mm Hg and evidence of end-organ hypoperfusion. However, hypotension alone does not necessarily signify cardiogenic shock because some patients with inferior infarction in whom the Bezold-Jarisch reflex is activated may also transiently have systolic blood pressure below 90 mm Hg. Their hypotension eventually resolves spontaneously, although the process can be accelerated by intravenous atropine (0.5 to 1.0 mg) and assumption of the Trendelenburg position. Other patients who are initially only slightly hypotensive may demonstrate gradually falling blood pressures with progressive reduction in cardiac output over several hours or days as they develop cardiogenic shock as a consequence of increasing ischemia and extension of infarction (see Fig. 35-11) . Evidence of autonomic hyperactivity is common, varying in type with the location of the infarction. At some time in their initial presentation, more than half of patients with inferior MI have evidence of excess parasympathetic stimulation, with hypotension, bradycardia, or both, whereas about half of patients with anterior MI show signs of sympathetic excess, having hypertension, tachycardia, or both.[103]

TEMPERATURE AND RESPIRATION.

Most patients with extensive AMI develop fever, a nonspecific response to tissue necrosis, within 24 to 48 hours of the onset of infarction. Body temperature often begins to rise within 4 to 8 hours after the onset of infarction, and rectal temperature may reach 101° to 102°F. Fever usually resolves by the fourth or fifth day after infarction.

The respiratory rate may be slightly elevated soon after the development of an AMI; in patients without heart failure, it results from anxiety and pain because it returns to normal with treatment of physical and psychological discomfort. In patients with left ventricular failure, the respiratory rate correlates with the severity of failure; patients with pulmonary edema may have respiratory rates exceeding 40 breaths/min. However, the respiratory rate is not necessarily elevated in patients with cardiogenic shock. Cheyne-Stokes (periodic) respiration (see Chap. 17) may occur in elderly individuals with cardiogenic shock and heart failure, particularly after opiate therapy and in the

presence of cerebrovascular disease.

JUGULAR VENOUS PULSE.

The height and contour of the jugular venous pulse reflect right atrial and right ventricular diastolic pressures (see Chap. 4) . Because these pressures are usually normal or only slightly elevated in patients with AMI (even in the presence of mild to moderate LV failure), it is not surprising that usually the jugular

venous pulse fails to show any abnormalities. The a wave may be prominent in patients with pulmonary hypertension secondary to LV failure or reduced compliance. In contrast, right ventricular infarction (whether or not it accompanies left ventricular infarction) often results in marked jugular venous distention and, when it is complicated by necrosis or ischemia of right ventricular papillary muscles, tall c-v waves of tricuspid regurgitation are evident. In patients with AMI and cardiogenic shock, the jugular venous pressure is usually elevated. In patients with AMI, hypotension, and hypoperfusion (findings that may resemble those of patients with cardiogenic shock) but who have flat neck veins, it is likely that the depression of left ventricular performance may be related, at least in part, to hypovolemia. The differentiation can be made only by assessing left ventricular performance using echocardiography or by measuring left ventricular filling pressure with a pulmonary artery flotation catheter.

CAROTID PULSE.

Palpation of the carotid arterial pulse provides a clue to the left ventricular stroke volume; a small pulse suggests a reduced stroke volume, whereas a sharp, brief upstroke is often observed in patients with mitral regurgitation or ruptured ventricular septum with a left-to-right shunt. Pulsus alternans reflects severe left ventricular dysfunction.

THE CHEST.

Moist rales are audible in patients who develop left ventricular failure and/or a reduction of left ventricular compliance with AMI. Diffuse wheezing may be present in patients with severe left ventricular failure. Cough with hemoptysis, suggesting pulmonary embolism with infarction, may also occur. In 1967 Killip and Kimball proposed a prognostic classification scheme based on the presence and severity of rales detected in patients presenting with AMI.[104] Class I patients are free of rales and a third heart sound (S_3). Class II patients have rales but to only a mild-moderate degree (<50 percent of lung fields) and may or may not have an S_3 . Patients in Class III have rales in more than half of each lung field and frequently have pulmonary edema. Finally, Class IV patients are in cardiogenic shock. Despite overall improvement in mortality in each class, compared with data observed during the original development of the classification scheme, the

latter remains useful today, as evidenced by data from more recently conducted large MI trials.[15] [22]

Cardiac Examination

PALPATION.

Despite severe symptoms and extensive myocardial damage, the findings on examination of the heart may be quite unremarkable in patients with AMI. Palpation of the precordium may yield normal findings, but in patients with transmural AMI it more commonly reveals a presystolic pulsation, synchronous with an audible fourth heart sound (S_4), reflecting a vigorous left atrial contraction filling a ventricle with reduced compliance. In the presence of left ventricular systolic dysfunction, an outward movement of the left ventricle may be palpated in early diastole, coincident with an S_3. When the anterior or lateral portion of the ventricle is dyskinetic, an abnormal systolic pulsation is present in the third, fourth, or fifth intercostal space to the left of the sternum. In some patients, this paradoxical precordial impulse is clearly separable from the point of maximal impulse, which is more lateral and to the left. In other patients, the abnormal impulse is a diffuse, rippling, precordial movement, approximately 5 to 10 cm in diameter, not clearly separable from the point of maximal impulse and can be appreciated near the left anterior axillary line. Patients with long-standing hypertension or previous infarction with left ventricular hypertrophy often demonstrate a laterally displaced, sustained apical impulse.

AUSCULTATION.

The heart sounds, particularly the first sound (S_1), are frequently muffled and occasionally inaudible immediately after the infarct, and their intensity increases during convalescence. A soft S_1 may also reflect prolongation of the PR interval. Patients with marked ventricular dysfunction and/or left bundle branch block may have paradoxical splitting of the second heart sound (S_2) (see Chap. 4) . Patients with postinfarction angina may also develop a transient, paradoxically split S_2 during anginal episodes.

Third and Fourth Heart Sounds.

An S_3 in AMI usually reflects severe left ventricular dysfunction with elevated ventricular filling pressure. It is caused by rapid deceleration of transmitral blood flow during protodiastolic filling of the left ventricle with resultant oscillations of the cardiohemic system (i.e., myocardium and stream of blood flowing from left atrium to left ventricle) and is usually heard in patients with large infarctions. This sound is detected best at the apex, with the patient in the left lateral recumbent position, and is more common in patients with transmural anterior infarctions than in those with inferior or nontransmural infarctions. The mortality of patients who manifest an S_3 during the acute phase of MI is higher than that of patients without such a sound. An S_3 may be caused not only by left ventricular failure but also by increased inflow into the left ventricle, as occurs when

mitral regurgitation or ventricular septal defect complicates AMI. The S_3 and S_4 emanating from the left ventricle are heard best at the apex; in patients with right ventricular infarcts, these sounds may be heard along the left sternal border and are intensified by inspiration.

An S_4 is almost universally present in patients with AMI in sinus rhythm and is usually best heard between the left sternal border and the apex. This sound reflects the atrial contribution to ventricular filling and is particularly prominent in AMI patients due to a reduction in LV compliance and elevation of LV end-diastolic pressure (LV-EDP), even in the absence of left ventricular systolic dysfunction. This finding is of limited diagnostic value because it is commonly audible in most patients with chronic ischemic heart disease and is recordable, although not often audible, in many normal subjects older than 45 years.

Murmurs.

Systolic murmurs, transient or persistent, are commonly audible in patients with AMI and generally result from mitral regurgitation secondary to dysfunction of the mitral valve apparatus (papillary muscle dysfunction, left ventricular dilatation). A new, prominent apical holosystolic murmur, accompanied by a thrill, may represent rupture of a head of a papillary muscle (see p. 1184). The findings in rupture of the interventricular septum are similar, although the murmur and thrill are usually most prominent along the left sternal border and may be audible at the right sternal border as well. The systolic murmur of tricuspid regurgitation (caused by right ventricular failure due to pulmonary hypertension and/or right ventricular infarction or by infarction of a right ventricular papillary muscle) is also heard along the left sternal border. It is characteristically intensified by inspiration and is accompanied by a prominent c-v wave in the jugular venous pulse and a right ventricular S_4 .

Pericardial Friction Rubs.

These may be heard in patients with AMI, especially those sustaining large transmural infarctions.[99] Rubs are notorious for their evanescence and, hence, are probably even more common than reported; frequent auscultation in patients with transmural infarction often results in the discovery of a rub that might otherwise have gone unnoticed. Although friction rubs may be heard within 24 hours or as late as 2 weeks after the onset of infarction, most commonly they are noted on the second or third day.[99] Occasionally, in patients with extensive infarction, a loud rub may be heard for many days. Patients with AMI and a pericardial friction rub may have a pericardial effusion on echocardiographic study, but only rarely are the classic ECG changes of pericarditis (see Chap. 5) seen.[99] Delayed onset of the rub and the associated

discomfort of pericarditis (as late as 3 months' postinfarction) are characteristic of the

now rare post-MI (Dressler) syndrome (see p. 1196).

Pericardial rubs are most readily audible along the left sternal border or just inside the point of maximal impulse. Loud rubs may be audible over the entire precordium and even over the back. Occasionally, only the systolic portion of a rub is heard; it may be confused with a systolic murmur, and the diagnosis of rupture of the ventricular septum or mitral regurgitation may be incorrectly considered.

OTHER FINDINGS

FUNDI.

Hypertension, diabetes, and generalized atherosclerosis commonly accompany AMI, and because these conditions may produce characteristic changes in the fundus, a careful funduscopic examination may provide information concerning the underlying vascular status; this is particularly useful in patients unable to provide a detailed history.

ABDOMEN.

As already noted, in patients with AMI, particularly in an inferior location with diaphragmatic irritation, the pain may be localized to the epigastrium or the right upper quadrant. Pain in the abdomen associated with nausea, vomiting, restlessness, and even abdominal distention is often interpreted by patients as a sign of "indigestion," resulting in self-medication with antacids, and it may suggest an acute abdominal process to the physician. Right-sided heart failure, characterized by hepatomegaly and a positive abdominojugular reflux, is unusual in patients with acute left ventricular infarction but does occur in patients with severe and prolonged left ventricular failure or right ventricular infarction.

EXTREMITIES.

Coronary atherosclerosis is often associated with systemic atherosclerosis, and it is therefore common for patients with AMI to have a history of intermittent claudication and to demonstrate physical findings of peripheral vascular disease. Thus, diminished peripheral arterial pulses, loss of hair, and atrophic skin in the lower extremities are noted frequently in patients with coronary artery disease. Peripheral edema is a manifestation of right ventricular failure and, like congestive hepatomegaly, is unusual in patients with acute left ventricular infarction. Cyanosis of the nailbeds is common in patients with severe left ventricular failure and is particularly striking in patients with cardiogenic shock.

NEUROPSYCHIATRIC FINDINGS.

Except for the altered mental status that occurs in patients with AMI who have a markedly reduced cardiac output and cerebral hypoperfusion, the neurological examination is normal unless the patient has suffered cerebral embolism secondary to a mural thrombus. Indeed, an underlying MI is common in patients with cerebral embolic

stroke. The coincidence between these two conditions may be explained by systemic hypotension due to MI precipitating a cerebral infarction and the converse, as well as by mural emboli from the left ventricle causing cerebral emboli.

Patients with AMI often exhibit alterations of the emotional state, including intense anxiety, denial, and depression. Medical staff caring for AMI patients must be sensitive to changes in the patient's emotional state: a calm, professional atmosphere, with thorough explanations of equipment and prognosis, can help alleviate the distress associated with AMI.

LABORATORY EXAMINATIONS

Markers of Cardiac Damage

The classic World Health Organization (WHO) criteria for the diagnosis of AMI require that at least two of the following three elements be present: (1) a history of ischemic-type chest discomfort, (2) evolutionary changes on serially obtained ECG tracings, and (3) a rise and fall in serum cardiac markers.[105] There is considerable variability in the pattern of presentation of AMI with respect to these three elements, as exemplified by the following statistics. ST segment elevation and Q waves on the ECG, two features that are highly indicative of AMI, are seen in only about half of AMI cases on presentation. Approximately one third of patients with AMI do not present with classic chest pain,[98A] and the event would go unrecognized unless an ECG were recorded fortuitously in temporal proximity to the infarction or permanent pathological Q waves were are seen on later tracings. Nondiagnostic ECGs are recorded in approximately half of patients presenting to emergency departments with chest pain suggestive of MI who ultimately are shown to have an AMI. Among patients admitted to the hospital with a chest pain syndrome, fewer than 20 percent are subsequently diagnosed as having had an AMI. Therefore, in the majority of patients, clinicians must obtain serum cardiac marker measurements at periodic intervals to either establish or exclude the diagnosis of AMI; such measurements may also be useful for a rough quantitation of the size of infarction.[106] The availability of new serum cardiac markers with markedly enhanced sensitivity for myocardial damage enables clinicians to diagnose AMI in about an additional one third of patients who would not have fulfilled criteria for AMI in the past.[107] The increased use of more sensitive biomarkers of AMI combined with more precise imaging techniques has necessitated establishment of new criteria for AMI (Table 35-2) .

As myocytes become necrotic, the integrity of the sarcolemmal membrane is compromised and intracellular macromolecules (serum cardiac markers) begin to diffuse into the cardiac interstitium and ultimately into the microvasculature and lymphatics in the region of the infarct[60] (Fig. 35-14 and Table 35-3) . The rate of appearance of these macromolecules in the peripheral circulation depends on several factors, including intracellular location, molecular weight, local blood and lymphatic flow, and the rate of elimination from the blood.[60] [108] [109]

Given the accelerated pace of decision-making in patients with acute coronary syndromes and emphasis on reduction of length of hospital stay, there is considerable

interest in evaluating new serum cardiac markers,[60] shortening assay time in the central chemistry laboratory,[110] and designing rapid whole blood bedside assays.[111] For optimal specificity, a serum marker of MI should be present in high concentration in the myocardium and be absent from nonmyocardial tissue and serum.[60] [108] For optimal sensitivity it should be rapidly released into the blood after myocardial injury, and there should be a stoichiometric relationship between the plasma level of the marker and the extent of myocardial injury. For ease of clinical use, the marker should persist in blood for an appropriate length of time to provide a convenient diagnostic time window (see Table 35-3) . Finally, the assay methodology should be inexpensive and easy to perform.

CREATINE KINASE (CK).

Serum CK activity exceeds the normal range within 4 to 8 hours after the onset of AMI and declines to normal within 2 to 3 days (see Fig. 35-14) .

TABLE 35-2 -- CRITERIA FOR THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION (AMI)

INCREASED BIOMARKERS PLUS ONE OR MORE OF THE FOLLOWING	PATHOLOGICAL FINDINGS OF AMI	TYPICAL SYMPTOMS OF AMI PLUS ONE OF THE FOLLOWING	PROCEDURAL MYOCARDIAL DAMAGE
Typical symptoms of myocardial ischemia	No other findings required	ST segment elevation in the ECG	Increased levels of cardiac biomarkers to prespecified levels; symptoms may be absent; ECG changes may be absent or nonspecific
Q waves in the ECG		Increased levels of cardiac biomarkers	
ST segment elevation or depression in the ECG			

Modified from Alpert J, Thygesen K, et al: Towards a new definition of myocardial infarction for the 21st century. J Am Coll Cardiol 2000, in press.

Figure 35-14 Plot of the appearance of cardiac markers in blood versus time after onset of symptoms. Peak A, early release of myoglobin or CK-MB isoforms after AMI; peak B, cardiac troponin after AMI; peak C, CK-MB after AMI; peak D, cardiac troponin after unstable angina. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration. *(From Wu AH, Apple FS, Gibler WB, et al: National Academy of Clinical Biochemistry Standards of Laboratory Practice: Recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 45:1104-1121, 1999.)*

Although the peak CK occurs on average at about 24 hours, peak levels occur earlier in patients who have had reperfusion as a result of the administration of thrombolytic therapy or mechanical recanalization (as well as in patients with early spontaneous thrombolysis). Because the time-activity curve of serum CK is influenced by reperfusion, and because reperfusion itself influences infarct size, reperfusion interferes with estimation of infarct size by enzyme analysis.[60] [112]

Although elevation of the serum CK is a sensitive enzymatic detector of AMI that is routinely available in most hospitals,[60] important drawbacks include false-positive results in patients with muscle disease, alcohol intoxication, diabetes mellitus, skeletal muscle trauma, vigorous exercise, convulsions, intramuscular injections, thoracic outlet syndrome, and pulmonary embolism.[60] [109] [113]

CK ISOENZYMES.

Three isoenzymes of CK (MM, BB, and MB) have been identified by electrophoresis. Extracts of brain and kidney contain predominantly the BB isoenzyme, skeletal muscle contains principally MM but does contain some MB (1 to 3 percent), and both MM and MB isoenzymes are present in cardiac muscle. The MB isoenzymes of CK may also be present in minor quantities in the small intestine, tongue, diaphragm, uterus, and prostate. Strenuous exercise, particularly in trained long-distance runners or professional athletes, may cause elevation of both total CK and CK-MB.[114] Because CK-MB can be detected in the blood of healthy subjects, the cutoff value for abnormal elevation of CK-MB is usually set a few units above the end of the reference (normal) range for a given laboratory. Despite the fact that small quantities of CK-MB isoenzyme are found in tissues other than the heart, elevated levels of CK-MB may be considered, for practical purposes, to be the result of AMI (except in the case of trauma or surgery on the aforementioned organs).

Earlier CK-MB assay methods that were in common use included radioimmunoassay and agarose gel electrophoresis techniques; these have now been largely supplanted by highly sensitive and specific enzyme immunoassays that use monoclonal antibodies directed against CK-MB.[115] Mass assays report results in nanograms per milliliter rather than units per milliliter and have been confirmed to be more accurate than CK-MB activity assays, especially in patients presenting within 4 hours of the onset of AMI. It has been

TABLE 35-3 -- MOLECULAR MARKERS USED OR PROPOSED FOR USE IN THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

MARKER	MW (D)	RANGE OF TIMES TO INITIAL ELEVATION (hr)	MEAN TIME TO PEAK ELEVATIONS (NONTHROMBOLYSIS)	TIME TO RETURN TO NORMAL RANGE	MOST COMMON SAMPLING SCHEDULE
hFABP	14,000-15,000	1.5	5-10 hr	24 hr	On presentation, then 4 hr later
Myoglobin	17,800	1-4	6-7 hr	24 hr	Frequent; 1-2 hr after CP
MLC	19,000-27,000	6-12	2-4 d	6-12 d	Once at least 12 hr after CP
cTnI	23,500	3-12	24 hr	5-10 d	Once at least 12 hr after CP
cTnT	33,000	3-12	12 hr-2 d	5-14 d	Once at least 12 hr after CP
MB-CK	86,000	3-12	24 hr	48-72 hr	Every 12 hr×3[*]
MM-CK tissue isoform	86,000	1-6	12 hr	38 hr	60-90 min after CP
MB-CK tissue isoform	86,000	2-6	18 hr	Unknown	60-90 min after CP
Enolase	90,000	6-10	24 hr	48 hr	Every 12 hr×3
LD	135,000	10	24-48 hr	10-14 d	Once at least 24 hr after CP
MHC	400,000	48	5-6 d	14 d	Once at least >2 d after CP

hFABP=heart fatty acid binding proteins; MLC=myosin light chain; cTnI=cardiac troponin I; cTnT=cardiac troponin T; MB-CK=MB isoenzyme of creatinine kinase (CK); MM-CK=MM isoenzyme of CK; LD=lactate dehydrogenase; MHC=myosin heavy chain; CP=chest pain

Modified from Adams J III, Abendschein D, Jaffe A: Biochemical markers of myocardial injury. Is MB creatine kinase the choice for the 1990s? Circulation 88:750, 1993. Copyright 1993, American Heart Association.

*-Increased sensitivity can be achieved with sampling every 6 or 8 hours.

proposed that a ratio (relative index) of CK-MB mass/CK activity of about 2.5 is indicative of a myocardial rather than a skeletal source of the CK-MB elevation. Although this ratio may be satisfied by many patients with AMI, it is inaccurate in several circumstances: (1) when high levels of total CK are present because of skeletal muscle injury (a large quantity of CK-MB must be released from the myocardium to satisfy criteria); (2) chronic skeletal muscle injury releases large amounts of CK-MB; and (3) total CK measurements are within the normal reference range for the laboratory and CK-MB is elevated (possibly indicating that a microinfarction has occurred). Patients with minimally elevated CK-MB and normal CK levels have a prognosis that is generally worse than that for patients with suspected MI but no CK-MB elevation. Elevation of CK-MB after percutaneous coronary artery revascularization is associated with increased late (1-3 years) cardiac mortality.[116]

Clinicians should not rely on measurements of CK and CK-MB at a single point in time but instead should evaluate the temporal rise and fall of serially obtained values; skeletal muscle release of CK-MB generally remains elevated for a longer time than myocardial release of CK-MB and produces a "plateau" pattern of CK-MB values over several days, in contrast to the shorter time course of skeletal muscle CK-MB elevation, as depicted in Figure 35-7 (Figure Not Available) . Of note, since the cardiac-specific troponin I and T (cTnI and cTnT) (see Fig. 35-14 and Tables 35-2 and 35-3) accurately distinguish skeletal from cardiac muscle damage, the troponins are now considered the preferred biomarkers for diagnosing AMI.[117]

In addition to AMI secondary to coronary obstruction, other forms of injury to cardiac muscle--such as those resulting from myocarditis, trauma, cardiac catheterization, shock, and cardiac surgery--may also produce elevated serum CK-MB levels.[114] These latter causes of elevation of serum CK-MB values can usually be readily distinguished from AMI by the clinical setting.

CK ISOFORMS.

Isoforms of the MM and MB isoenzymes have been identified.[118] These are subtypes of the individual isoenzymes and are formed in the circulation when the enzyme carboxypeptidase cleaves lysine residues from the carboxy terminus of the myocardial form of the enzyme (CK-MM3 and CK-MB2), producing isoforms with a different electrophoretic mobility (CK-MM2, CK-MM1, and CK-MB1). Certain isoforms appear to

be released into the blood quite rapidly, perhaps as soon as 1 hour, after the onset of infarction. An absolute level of CK-MB2 isoform greater than 1.0 U/liter or a ratio of CK-MB2/CK-MB1 greater than 2.5 has a sensitivity for diagnosing AMI of 46.4 percent at 4 hours and of 91.5 percent at 6 hours.[119] A rapid high-voltage electrophoretic assay for these isoforms is available, and results in experienced research laboratories suggest it may permit early identification of patients with AMI and early detection of successful reperfusion (peak CK-MB2/CK-MB1 > 3.8 at 2 hours).[120]

MYOGLOBIN.

This low-molecular-weight heme protein is released into the circulation from injured myocardial cells and can be detected within a few hours after the onset of infarction (see Fig. 35-14 and Table 35-3) . Peak levels of serum myoglobin are reached considerably earlier (1 to 4 hours) than peak values of serum CK.[120] Because of its lack of cardiac specificity, an isolated measurement of myoglobin within the first 4 to 8 hours after onset of chest discomfort in patients with a nondiagnostic ECG should not be relied on to make the diagnosis of AMI but should be supplemented by a more cardiac-specific marker such as cTnI or cTnT.[117]

In contrast to CK, myoglobin is readily excreted into the urine. A more rapid rise in serum myoglobin has been observed after reperfusion, and its measurement has been suggested as a useful index of successful reperfusion[120] (Fig. 35-15) and even infarct size. In patients presenting less

Figure 35-15 Receiver operator curves (ROC) of the 60-min value of myoglobin, CK-MB and cardiac troponin-I (cTnI), for noninvasive prediction of occlusion after thrombolysis. Auc=area under curve; Se=sensitivity; Sp=specificity. *(Modified from Tanasijevic MJ, Cannon CP, Antman EM, et al: Am Coll Cardiol 1999;34:739-747.)*

than 6 hours from symptoms and with ST segment elevation where the diagnosis of AMI is not in doubt, an elevated myoglobin level is associated with an increased risk of mortality.[121] The adverse prognostic significance of an elevated myoglobin level at presentation is probably due to a combination of a large amount of myocardial damage and a delay of at least several hours from onset of symptoms to blood sampling.

CARDIAC-SPECIFIC TROPONINS.

The troponin complex consists of three subunits that regulate the calcium-mediated contractile process of striated muscle. These include troponin C, which binds Ca^{2+} ; troponin I (TnI), which binds to actin and inhibits actin-myosin interactions; and troponin T (TnT), which binds to tropomyosin, thereby attaching the troponin complex to the thin filament (see Chap. 14) . Although the majority of TnT is incorporated in the troponin complex, approximately 6 percent is dissolved in the cytosol; about 2 to 3 percent of TnI is found in a cytosolic pool.

Although both TnT and TnI are present in cardiac and skeletal muscle, they are

encoded by different genes and the amino acid sequence differs.[122] This permits the production of antibodies that are specific for the cardiac form (cTnT and cTnI) and has led to the development of quantitative assays for cTnT and cTnI that have been approved by the Food and Drug Administration (FDA) for clinical use[117] (see Fig. 35-14 and Table 35-3) . Several studies have confirmed the reliability of these new quantitative assays for detecting myocardial injury, and measurement of cTnT or cTnI is now at the center of a new diagnostic criterion for AMI.[52] [123] [123A] Qualitative, rapid, bedside assays for cTnT and cTnI have also been approved for diagnosing AMI.[124]

When interpreting the results of assays for cTnT or cTnI, clinicians must be cognizant of several analytical issues.[124A] The first-generation assay for cTnT exhibited some nonspecific binding to skeletal muscle troponin, but this was corrected in subsequent generations of assays. The cTnT assays are produced by a single manufacturer, leading to relative uniformity of cutoffs, whereas multiple manufacturers produce cTnI assays. The majority of cTnI released into the bloodstream in AMI is complexed with cardiac troponin C.[125] Variations in the cutoff concentration for abnormal levels of cTnI in the clinically available immunoassays may be due in part to different specificities of the antibodies used for detecting free and complexed cTnI.[125] Thus, when using the measurement of cTnI for diagnosing AMI, clinicians

should apply the cutoff values for the particular assay used in their laboratory. For both cTnT and cTnI, the definition of an abnormally increased level is a value exceeding that of 99 percent of a reference control group.[123]

Because cTnT or cTnI is not detected in the peripheral circulation under normal circumstances, the cutoff value for these analytes may be set only slightly above the "noise" level of the assay.[109] Furthermore, whereas CK-MB usually increases 10- to 20-fold above the upper limit of the reference range, cTnT and cTnI typically increase more than 20 times above the reference range. These features of the cardiac-specific troponin assays provide an improved signal-to-noise ratio, enabling the detection of even minor degrees of myocardial necrosis.[52A] [111] In patients with AMI, cTnT and cTnI first begin to rise above the upper reference limit by 3 hours from the onset of chest pain. Due to a continuous release from a degenerating contractile apparatus in necrotic myocytes, elevations of cTnI may persist for 7 to 10 days after AMI; elevations of cTnT may persist for up to 10 to 14 days. The prolonged time course of elevation of cTnT and cTnI is advantageous for the late diagnosis of AMI.

Patients with AMI who undergo successful recanalization of the infarct-related artery have a rapid release of cardiac troponins that may be useful as an indicator of reperfusion, although myoglobin appears slightly more efficient in this regard.[126] [127]

Troponins vs. CK-MB.

When comparing the diagnostic efficiency of the cardiac troponins versus CK-MB for

AMI, it is important to bear in mind that the troponin assays are probably capable of detecting episodes of myocardial necrosis that are below the detection limit of the current CK-MB assays, leading to a number of "false-positive" cases of troponin elevations if CK-MB is used as the gold standard.[52A] The somewhat vague terms "*minor myocardial damage*" and "*microinfarction*" have been used to describe the pathological process in patients who have a chest pain syndrome and elevated cardiac troponin but in whom CK-MB is in the normal range.[128] From a clinical perspective, it is desirable to have diagnostic tests for AMI with increased sensitivity to increase the number of AMI cases identified and increased specificity to reduce the number of cases incorrectly diagnosed and treated for AMI. In addition, cardiac troponin measurements have been shown to have prognostic value for identifying patients with an acute coronary syndrome at risk for adverse clinical outcomes and who also exhibit enhanced responsiveness to new therapies such as glycoprotein (GP) IIb/IIIa inhibitors and low-molecular-weight heparins.[129] The prognostic value of the troponins is independent of other risk factors, such as age and ECG abnormalities, as well as the measurement of classic biomarkers such as CK-MB. The exact mechanism(s) by which troponins convey adverse prognostic potential is not clearly established. They may provide a more accurate reflection of the amount of myocardial necrosis sustained by the patient, but they may also reflect an increased propensity for thromboembolization from an unstable coronary plaque.

Interpretation of Elevated Troponin.

Both cTnI and cTnT have been detected in the blood of patient with end-stage heart failure, including those with a nonischemic cardiomyopathy.[130] Observations such as these emphasize that the troponins detect myocyte damage regardless of the cause.

Balanced against the advantages of the troponins for improved detection of AMI and prognostication of risk are the epidemiological, social, and health care delivery implications of assigning a diagnosis of AMI to a larger cohort of patients than was the case in an earlier era (see Table 35-2) . Revised criteria for AMI impact on the ability to monitor trends in the incidence of AMI and draw comparisons with previous observations, the psychological status of the patient, ability to obtain driving and pilot licenses, disability applications, and hospital reimbursement.[123] There is no clear solution to the issues just cited. It has been proposed that two decision limits are needed for optimal interpretation of troponin tests: a low abnormal value indicating myocardial damage and a higher value indicating the diagnosis of AMI according to traditional criteria.[128] There is a quantitative relationship between the amount of cardiac troponin released into the blood and the risk for adverse clinical outcomes.[5] We consider patients without elevation of cTnI or cTnT not to have had an AMI, those with elevated troponin but normal CK-MB to have microinfarction and a slight increase in risk compared with patients without troponin elevations, and those with elevation of both troponin and CK-MB to fulfill the "classic" definition of AMI with a larger amount of myocardial infarction and the greatest risk of adverse outcome.

LACTATE DEHYDROGENASE (LDH).

The activity of this enzyme exceeds the normal range by 24 to 48 hours after the onset

of AMI, reaches a peak 3 to 6 days after the onset of pain, and returns to normal levels 8 to 14 days after the infarction. LDH comprises five isoenzymes, which are numbered in the order of the rapidity of their migration toward the anode of an electrophoretic field. LDH_1 moves most rapidly, whereas LDH_5 is the slowest. Fractionation of the serum LDH into its five isoenzymes increases diagnostic accuracy because the heart contains principally LDH_1 . However, LDH isoenzyme analysis for the diagnosis of AMI is no longer recommended because it has been superseded by newer, more cardiac-specific late markers such as cTnT or cTnI (see Table 35-3) . [117]

OTHER SERUM CARDIAC MARKERS.

Other promising serum cardiac markers that are under development include heart fatty acid binding proteins (hFABP), myosin light chains (MLC), myosin heavy chains (MHC), and glycogen phosphorylase isoenzyme BB (GPBB).[113] These markers offer the potential for earlier diagnosis (hFABP, GPBB) and a longer diagnostic window (MLC, MHC), but their relative roles compared with traditional markers such as CK-MB and newer markers such as CK-MB isoforms, cTnT, or cTnI remain to be defined and we do not recommend their routine use for diagnosing AMI.[117]

RECOMMENDATIONS FOR MEASUREMENT OF SERUM MARKERS.

It seems reasonable for clinicians to measure either cTnT or cTnI in patients with suspected AMI. From a cost-effectiveness perspective, it is unnecessary to measure both a cardiac-specific troponin and CK-MB at all time points.[131] Routine diagnosis of AMI can be accomplished within 12 hours using CK-MB, cTnT, or cTnI by obtaining measurements approximately every 8 to 12 hours (see Table 35-2) . Retrospective diagnosis or diagnosis of AMI in the presence of skeletal muscle injury is more readily accomplished with cTnT or cTnI. Future directions for research with the cardiac troponins involve evaluating their ability to aid in the diagnosis of AMI that occurs after cardiac and noncardiac surgery[132] and interventional catheterization procedures and in identifying myocardial injury from conditions other than AMI, such as myocarditis.

Although serum cardiac markers have been used successfully to stratify patients for risk of cardiac events when the presenting ECG does not show ST segment elevation, bedside assays for troponin or myoglobin either alone or in combination with the ECG also are useful for stratifying risk in patients with STEMI.[121] [133]

OTHER LABORATORY MEASUREMENTS

Numerous nonspecific manifestations may be recognized in patients with AMI. Although they are not generally employed in establishing the diagnosis, awareness of their coexistence with infarction is important to avoid misinterpretation or erroneous diagnosis of other disorders.

SERUM LIPIDS.

These are often determined in patients with AMI. However, the results may be misleading because numerous factors that can alter the values are operating at the time of the patient's admission to the hospital. Serum triglycerides are affected by caloric intake, intravenous glucose, and recumbency.

During the first 24 to 48 hours after admission, total cholesterol and high-density lipoprotein (HDL) cholesterol remain at or near baseline values but generally fall precipitously after that. The fall in HDL cholesterol after AMI is greater than the fall in total cholesterol; thus, the ratio of total cholesterol to HDL cholesterol is no longer useful for risk assessment early after MI. A lipid profile should be obtained

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on all AMI patients who are admitted within 24 to 48 hours of symptoms. Based on the success of lipid-lowering therapy in primary and secondary prevention studies and evidence that hypolipidemic therapy improves endothelial function and inhibits thrombus formation,[134] [135] it has been argued that early management of serum lipids in patients hospitalized for AMI is advisable.[136] For patients admitted beyond 24 to 48 hours, more accurate determinations of serum lipid levels are obtained about 8 weeks after the infarction has occurred.

HEMATOLOGICAL MANIFESTATIONS.

The elevation of the white blood cell count usually develops within 2 hours after the onset of chest pain, reaches a peak 2 to 4 days after infarction, and returns to normal in 1 week; the peak white blood cell count usually ranges between 12 and 15×10^3 /mm^3 but occasionally rises to as high as 20×10^3 /mm^3 in patients with large transmural AMI. Often there is an increase in the percentage of polymorphonuclear leukocytes and a shift of the differential count to band forms.

The erythrocyte sedimentation rate (ESR) is usually normal during the first 1 or 2 days after infarction, even though fever and leukocytosis may be present. It then rises to a peak on the fourth or fifth day and may remain elevated for several weeks. The increase in the ESR is secondary to elevated plasma $alpha_2$ -globulin fibrinogen, but the peak does not correlate well with the size of the infarction or with the prognosis. The hematocrit often increases during the first few days after infarction as a consequence of hemoconcentration.

Electrocardiographic Findings (See also Chap. 5)

In the majority of patients with AMI, some change can be documented when serial ECGs are compared. However, many factors limit the ability of the ECG to diagnose and localize MI: the extent of myocardial injury, the age of the infarct, its location, the presence of conduction defects, the presence of previous infarcts or acute pericarditis,

changes in electrolyte concentrations, and the administration of cardioactive drugs. Changes in the ST segment and T wave are quite nonspecific and may occur in a variety of conditions, including stable and unstable angina pectoris, ventricular hypertrophy, acute and chronic pericarditis, myocarditis, early repolarization, electrolyte imbalance, shock, and metabolic disorders and after the administration of digitalis. Serial ECGs may be of considerable aid in differentiating these conditions from AMI. Transient changes favor angina or electrolyte disturbances, whereas persistent changes argue for infarction if other causes, such as shock, administration of digitalis, and persistent metabolic disorders, can be eliminated. Nevertheless, serial standard 12-lead ECGs remain a potent and extremely clinically useful method for the detection and localization of MI.[55] [137] [138] Analysis of the constellation of ECG leads showing ST segment elevation may also be useful for identifying the site of occlusion in the infarct artery.[139] [140] The extent of ST deviation on the ECG, location of infarction, and QRS duration correlate with risk of adverse outcomes.[56] [141] Even when left bundle branch block is present on the ECG, MI can be diagnosed when striking ST segment deviation is present beyond that which can be explained by the conduction defect.[142] In addition to the diagnostic and prognostic information contained within the 12-lead ECG, it also provides valuable noninvasive information about the success of reperfusion for STEMI.

Although general agreement exists on ECG and vectorcardiographic criteria for the recognition of infarction of the anterior and inferior myocardial walls, less agreement is found on criteria for lateral and posterior infarcts[143] ; here even the terminology may be confusing. It has been reported that patients with an abnormal R wave in V_1 (0.04 second in duration and/or R/S ratio
1 in the absence of preexcitation or right ventricular hypertrophy) with inferior or lateral Q waves have an increased incidence of isolated occlusion of a dominant left circumflex coronary artery without collateral circulation; such patients have a lower ejection fraction, increased end-systolic volume, and higher complication rate than patients with inferior infarction due to isolated occlusion of the right coronary artery.

More sophisticated forms of ECG recordings including high-resolution ECG, body surface potential mapping of ST segments, and continuous vectorcardiography have all been reported in small series of patients to augment the 12-lead ECG in diagnosing AMI, but the lack of ready availability of equipment and the special expertise required limit the use of these techniques.

Although most patients continue to demonstrate the ECG changes from an infarction for the rest of their lives, particularly if they evolve Q waves, in a substantial minority the typical changes disappear, Q waves can regress, and the ECG can even return to normal after a number of years. Under many circumstances Q-wave patterns may simulate MI. Conditions that may mimic the ECG features of MI by producing a pattern of "pseudoinfarction" include ventricular hypertrophy, conduction disturbances, preexcitation, primary myocardial disease, pneumothorax, pulmonary embolus, amyloid heart disease, primary and metastatic tumors of the heart, traumatic heart disease, intracranial hemorrhage, hyperkalemia, pericarditis, early repolarization, and cardiac involvement with sarcoidosis. Normalization of negative T waves on serial ECGs is a useful marker of recovery of regional ventricular function after AMI.[143A]

Q-WAVE AND NON-Q-WAVE INFARCTION.

As noted earlier (see p. 1116), the presence or absence of Q waves on the surface ECG does not reliably predict the distinction between transmural and nontransmural (subendocardial) AMI.[39] Q waves on the ECG signify abnormal electrical activity but are not synonymous with irreversible myocardial damage. Also, the absence of Q waves may simply reflect the insensitivity of the standard 12-lead ECG, especially in the posterior zones of the left ventricle. True pathological subendocardial AMI, as recognized at autopsy, is seen with ST segment depression and/or T wave changes only about 50 percent of the time.[144] Angiographic studies in AMI patients without ST segment elevation show a higher incidence of subtotal occlusion of the culprit coronary vessel and greater collateral flow to the infarct zone. Observational data suggest that AMI without ST segment elevation is seen more commonly in elderly patients and patients with a prior MI.

ISCHEMIA AT A DISTANCE.

Patients with new Q waves and ST segment elevation diagnostic for AMI in one territory often have ST segment depression in other territories. These additional ST segment changes may be caused either by ischemia in a territory other than the area of infarction, termed "ischemia at a distance," or by reciprocal electrical phenomena. A good deal of attention has been directed to associated ST segment depression in the anterior leads when it occurs in patients with acute inferior MI. However, despite the clinical importance of differentiation among causes of anterior ST segment depression in such patients--including anterior ischemia, posterior wall infarction, and true reciprocal changes--such a differentiation cannot be made reliably by ECG or even vectorcardiographic techniques. Although precordial ST segment depression is more commonly associated with extensive infarction of the posterior, lateral, or inferior septal segments--rather than anterior wall subendocardial ischemia--imaging techniques such as two-dimensional echocardiography are necessary to ascertain whether an anterior wall motion abnormality is present.[145] [146] Regardless of whether the anterior ST segment changes reflect anterior wall ischemia or are reciprocal to changes elsewhere, this finding, as with ischemia at a distance, implies a poorer prognosis than if such changes are not present.[147]

RIGHT VENTRICULAR INFARCTION.

ST segment elevation in right precordial leads (V_1 , V_3 R-V_6 R) is a relatively sensitive and specific sign of right ventricular infarction.[63A] [148] Occasionally, ST segment elevation in leads V_2 and V_3 may be due to acute right ventricular infarction; this appears to occur only when the injury to the left inferior wall is minimal.[149]

Usually, the concurrent inferior wall injury suppresses this anterior ST segment elevation resulting from right ventricular injury. Likewise, right ventricular infarction appears to reduce the anterior ST segment depression often observed with inferior wall MI. A QS or QR pattern in leads V_3 R and/or V_4 R also suggests right ventricular myocardial necrosis but has less predictive accuracy than ST segment elevation in these leads.[52]

ATRIAL INFARCTION.

The most common ECG patterns are depression or elevation of the PR segment, alterations in the contour of the P wave, and abnormal atrial rhythms, including atrial flutter, atrial fibrillation, wandering atrial pacemaker, and atrioventricular (AV) nodal rhythm.

Imaging

ROENTGENOGRAPHY.

The initial chest roentgenogram in patients with AMI is almost invariably a portable film obtained in the emergency department or the CCU. When present, prominent pulmonary vascular markings on the roentgenogram reflect elevated left-ventricular end-diastolic pressure, but significant temporal discrepancies may occur because of what have been termed diagnostic lags and post-therapeutic lags. Up to 12 hours may elapse before pulmonary edema accumulates after ventricular filling pressure has become elevated. The posttherapeutic phase lag represents a longer time interval; up to 2 days are required for pulmonary edema to resorb and the radiographic signs of pulmonary congestion to clear after ventricular filling pressure has returned toward normal. The degree of congestion and the size of the left side of the heart on the chest film are useful for defining groups of patients with AMI who are at increased risk of dying after the acute event.[150]

Echocardiography (See Figs. 7-104 , 7-105 , and 7-106)

TWO-DIMENSIONAL ECHOCARDIOGRAPHY.

The relative portability of echocardiographic equipment makes this technique ideal for the assessment of patients with AMI hospitalized in the CCU or even in the emergency department before admission. In patients with chest pain compatible with AMI but with a nondiagnostic ECG, the finding on echocardiography of a distinct region of disordered contraction can be helpful diagnostically because it supports the diagnosis of myocardial ischemia. Echocardiography is also useful in evaluating patients with chest pain and a nondiagnostic ECG who are suspected of having an aortic dissection. The identification of an intimal flap consistent with an aortic dissection is a crucial observation because it represents a major contraindication to thrombolytic therapy (see Chap. 40) .

Areas of abnormal regional wall motion are observed almost universally in patients with AMI, and the degree of wall motion abnormality can be categorized with a

semiquantitative wall motion score index. Of note, abnormal wall motion is less often noted echocardiographically when the infarction is small and the age of regional wall motion abnormality cannot always be determined.[52] Left ventricular function estimated from two-dimensional ECGs correlates well with measurements from angiography and is useful in establishing prognosis after AMI.[145] Furthermore, the early use of echocardiography can aid in the early detection of potentially viable but stunned myocardium (contractile reserve), residual provocable ischemia, patients at risk for the development of congestive heart failure after AMI, and mechanical complications of AMI.[145]

Whereas transthoracic imaging is adequate in most patients, occasional patients have poor echo windows, especially if they are undergoing mechanical ventilation. In such patients transesophageal echocardiography can be safely performed and can be useful in evaluating ventricular septal defects and papillary muscle dysfunction.[146]

DOPPLER ECHOCARDIOGRAPHY (see Fig. 7-28) .

This technique allows for assessment of blood flow in the cardiac chambers and across cardiac valves. Used in conjunction with two-dimensional echocardiography, it is helpful in detecting and assessing the severity of mitral or tricuspid regurgitation after AMI. Identification of the site of acute ventricular septal rupture, as well as quantification of shunt flow across the resulting defect, is also possible.[146]

Other Imaging Modalities

NUCLEAR IMAGING.

Radionuclide angiography, perfusion imaging, infarct-avid scintigraphy, and positron-emission tomography have been used to evaluate patients with AMI. Nuclear cardiac imaging techniques (see Figs. 9-15 and 9-16) can be useful for detecting AMI; assessing infarct size, collateral flow, and jeopardized myocardium; determining the effects of the infarct on ventricular function; and establishing prognosis of patients with AMI.[151] However, the necessity of moving a critically ill patient from the CCU to the nuclear medicine department limits their practical application unless a portable gamma camera is available. Cardiac radionuclide imaging for the diagnosis of MI should be restricted to special, limited situations in which the trial of clinical history, ECG findings, and serum marker measurements is unavailable or unreliable.[52]

COMPUTED TOMOGRAPHY (CT) (see Chap. 10) .

This technique can provide useful cross-sectional information in patients with MI. In addition to the assessment of cavity dimensions and wall thickness, left ventricular aneurysms may be detected and, of particular importance in AMI, intracardiac thrombi can be identified. Although cardiac CT is a less convenient technique, it probably is more sensitive for thrombus detection than is echocardiography.

MAGNETIC RESONANCE IMAGING (MRI) (see Fig. 10-9) .

In addition to localizing and sizing the area of infarction, MRI techniques are capable of early recognition of MI and of providing an assessment of the severity of the ischemic insult.[152] This modality is attractive because of its ability to assess perfusion of infarcted and noninfarcted tissue as well as of reperfused myocardium; to identify areas of jeopardized but not infarcted myocardium; to identify myocardial edema, fibrosis, wall thinning, and hypertrophy; to assess ventricular chamber size and segmental wall motion; and to identify the temporal transition between ischemia and infarction[153] but has limited practical application because of the need to transport patients with AMI to the MRI facility.

ESTIMATION OF INFARCT SIZE

ELECTROCARDIOGRAPHY.

Interest in limiting infarct size, in large part because of the recognition that the quantity of myocardium infarcted has important prognostic implications, has focused attention on the accurate determination of MI size. The sum of ST segment elevations measured from multiple precordial leads correlates with the extent of myocardial injury in patients with anterior MI.[154] QRS scoring systems and planar or vectorcardiographic techniques to estimate infarct size have also been developed. Although they demonstrate good correlations with infarct size at autopsy and with enzymatic estimates, formal sizing of infarcts by ECG technique is not necessary in most patients. Of note, however, there is a relationship between the number of ECG leads showing ST segment elevation and mortality: patients with 8 or 9 of 12 leads with ST segment elevation have three to four times the mortality of those with only 2 or 3 leads with ST segment elevation. The duration of ischemia time as estimated from continuous ST segment monitoring is correlated with infarct size, the ratio of infarct size to area at risk, and the extent of regional wall motion abnormality observed at 7 days and 30 days after AMI.[154]

CARDIAC MARKER METHODS.

To estimate infarct size by analysis of serum cardiac marker levels, it is necessary to account for the quantity of the marker lost from the myocardium, its volume of distribution, and its release ratio.[60] Serial measurements of proteins released by necrotic myocardium are helpful in determining AMI size. Clinically, the peak CK or CK-MB provides an approximate estimate of infarct

size and is widely used prognostically. In the prethrombotic era, quantification of the cumulative release of CK or CK-MB correlated with other techniques for estimating infarct size in vivo as well as with the area of necrosis at autopsy. However, coronary

artery reperfusion dramatically changes the washout kinetics of CK and other markers from myocardium, resulting in early and exaggerated peak levels and limiting the usefulness of such curves as a measure of infarct size.

NONINVASIVE IMAGING TECHNIQUES.

Echocardiography (see Chap. 7) , radionuclide scintigraphy[52] (see Chap. 9) , CT (see Chap. 10) , and MRI (see Chap. 10) have all been used for the clinical and experimental assessment of infarct size. Infarct-avid scintigraphy and myocardial perfusion imaging have been used to quantify infarct size. Estimation of infarct size by quantitative tomographic technetium-99m (^{99m} Tc)-sestamibi imaging appears to be less limited by ventricular geometry and can distinguish small infarcts and ischemia from infarcted myocardium more readily than other noninvasive methods.[155] Tomography has improved on planar techniques employing ^{99m} Tc pyrophosphate to image AMI (see Chap. 9) .[156] Contrast medium-enhanced MRI has been helpful in demonstrating the regional heterogeneity of infarction patterns in patients with persistently occluded infarct arteries versus those with successfully reperfused vessels.

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Management

PREHOSPITAL CARE

The prehospital care of patients with suspected AMI is a crucial element bearing directly on the likelihood of survival. Most deaths associated with AMI occur within the first hour of its onset and are usually due to ventricular fibrillation[157] (see also Chap. 26) . Accordingly, the importance of the immediate implementation of definitive resuscitative efforts and of rapidly transporting the patient to a hospital cannot be overemphasized.[52] Major components of the delay from the onset of symptoms consistent with AMI to reperfusion include the following[157] : (1) the time for the patient to recognize the seriousness of the problem and seek medical attention; (2) prehospital evaluation, treatment, and transportation; (3) the time for diagnostic measures and initiation of treatment in the hospital (e.g., "door-to-needle" time for patients receiving a thrombolytic and "door-to-balloon" time for patients undergoing a catheter-based reperfusion strategy); and (4) the time from initiation of treatment to restoration of flow (Fig. 35-16) (Figure Not Available) .

Patients with previously diagnosed coronary heart disease have the same delay times (median of 2.0 hours) as those without prior AMI or coronary heart disease.[158] [159] Therefore, patients must be educated to seek immediate medical attention should they develop manifestations of AMI. Patient-related factors that correlate with longer decision to seek medical attention include older age; female gender; African-American race; low socioeconomic status; low emotional or somatic awareness; history of angina, diabetes, or both; consulting a spouse or other relative; and consulting a physician.[159] [160]

Health care professionals should heighten the level of awareness of patients at risk for AMI (e.g., those with hypertension, diabetes, history of angina pectoris).[158] They should

review and reinforce with patients and their families the need for seeking urgent medical attention for a

Figure 35-16 (Figure Not Available) Major components of time delay between onset of infarction and restoration of flow in the infarct-related artery. Plotted sequentially from left to right are shown the time for patients to recognize symptoms and seek medical attention, transportation to the hospital, in-hospital decision-making and implementation of reperfusion strategy, and time for restoration of flow once the reperfusion strategy has been initiated. The time to initiate thrombolytic therapy is the "door-to-needle" (D-N) time; this is followed by the period of time required for pharmacological restoration of flow. More time is required to move the patient to the catheterization laboratory for a percutaneous coronary interventional (PCI) procedure, referred to as the "door-to-balloon" (D-B) time, but restoration of flow in the epicardial infarct-related artery occurs promptly after PCI. At the bottom are shown a variety of methods for speeding the time to reperfusion along with the goals for the time intervals for the various components of the time delay. *(Cannon CP, Antman EM, Walls R, Braunwald E: Time as an adjunctive agent to thrombolytic therapy. J Thromb Thrombol 1:27-34, 1994.)*

pattern of symptoms including chest discomfort, extreme fatigue, and dyspnea, especially if accompanied by diaphoresis, lightheadedness, palpitations, or a sense of impending doom[52] (see Fig. 35-16) (Figure Not Available) . Although many patients shun such discussions and tend to minimize the likelihood of ever needing emergency cardiac treatment, emphasis should be placed on the prevention and treatment of potentially fatal arrhythmias as well as salvage of the jeopardized myocardium by reperfusion, for which time is crucial.[161] Patients should also be instructed in the proper use of sublingual nitroglycerin, which should be taken as one tablet at the onset of ischemic-type discomfort and repeated at 5-minute intervals for a total of three doses. If the symptoms have not dissipated within 15 minutes, the patient should be rapidly transported to a medical facility that has the capability of recording and interpreting an ECG, providing advanced cardiac life support and cardiac monitoring, and initiating reperfusion therapy with either thrombolysis or angioplasty if indicated. Primary care physicians play an important role in helping implement strategies to facilitate early treatment. [158]

THE NATIONAL HEART ATTACK ALERT PROGRAM.

This program has stressed the importance of community-wide planning for strategies allowing rapid recognition and triage of patients potentially suffering from AMI[162] (see Fig. 35-16) (Figure Not Available) . Well-equipped ambulances and helicopters staffed by personnel trained in the acute care of the infarction victim (mobile CCUs) allow definitive therapy to commence while the patient is being transported to the hospital[163] (Table 35-4) (Table Not Available) . To be used effectively, they must be placed strategically within a community, and excellent radio communication systems must be available. These units should be equipped with battery-operated monitoring equipment, a direct-current defibrillator, oxygen, endotracheal tubes and suction apparatus, and commonly used cardiovascular drugs. Radiotelemetry systems that allow transmission of the ECG signal to the hospital are highly desirable and are becoming increasingly available in many communities (see Fig. 35-16) (Figure Not Available) . The

effectiveness of such a prehospital system depends on the competency of paramedics,[160] [164] transmission distances, and the availability of expert consultation on the receiving end.[165] Observations of simple variables such as heart rate and blood pressure permit initial classification of patients into high- or low-risk subgroups[166] because those patients initially presenting with hypotension have a mortality in excess of 30 percent, whereas young patients with isolated sinus bradycardia and a normal or elevated blood pressure appear to have a mortality that is under 5 percent.[15]

In addition to prompt defibrillation, the efficacy of prehospital care appears to depend on several factors, including early relief of pain with its deleterious physiological sequelae, reduction of excessive activity of the autonomic nervous system, and abolition of prelethal arrhythmias, such as ventricular tachycardia. However, these efforts must not inhibit rapid transfer to the hospital.[52]

PREHOSPITAL THROMBOLYSIS.

The potential benefits of prehospital thrombolysis have been evaluated in several

TABLE 35-4 -- CHEST PAIN CHECKLIST FOR USE BY EMT/PARAMEDIC FOR DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION AND THROMBOLYTIC THERAPY SCREENING

(Not Available)

Adapted from the Seattle/King County EMS Medical Record. From 1999 Updated ACC/AHA AMI Guideline (Web version), p 16.

randomized trials.[167] Although none of the individual trials showed a significant reduction in mortality with prehospital-initiated thrombolytic therapy, there was a generally consistent observation of benefit from earlier treatment, and meta-analyses of all the available trials demonstrate a significant 17 percent reduction in mortality.[167] [167A]

Several factors must be weighed when communities consider whether their ambulances and emergency transport vehicles should have capabilities of initiating thrombolytic therapy. The greatest reduction in mortality is observed when reperfusion can be initiated within 60 to 90 minutes of the onset of symptoms.[15] [168] It has been suggested that the streamlining of emergency department triage practices so that treatment can be started within 30 minutes, when coupled with the 15- to 30-minute transport time that is common in most urban centers, may be more cost-effective than equipping all ambulances to administer prehospital thrombolytic therapy[52] (see Fig. 35-16) (Figure Not Available) . The latter would require extensive training of personnel (see Table 35-4) (Table Not Available) , installation of computer-assisted electrocardiographs or systems for radio transmission of the ECG signal to a central station, and stocking of medicine kits with the necessary drug supplies[165] [169] [170] [171] (see Fig. 35-16) (Figure Not Available) . However, in selected communities where transport delays may be 60 to 90

minutes or longer and experienced personnel or physicians are available on ambulances, prehospital thrombolytic therapy is probably beneficial.[52] [172] [173]

MANAGEMENT IN THE EMERGENCY DEPARTMENT

Physicians evaluating patients in the emergency department must confront the difficult task of rapidly identifying patients who require urgent reperfusion therapy, triaging lower risk patients to the appropriate facility within the hospital, and not discharging patients home inappropriately while avoiding unnecessary admissions.[157] [168] [174] [174A] [174B] As emphasized in Figure 35-17 , a history of ischemic-type discomfort and the initial 12-lead ECG (Fig. 35-18) are the primary tools for screening patients with acute coronary syndromes in the emergency department. ST segment elevation on the ECG of a patient with a history compatible with AMI is highly suggestive of thrombotic occlusion of an epicardial coronary artery,[61] and its presence should serve as the trigger for a well-rehearsed sequence of rapid assessment of the patient for contraindications to thrombolysis and initiation of a reperfusion strategy[157] [168] [175] [176] [177] (see Fig. 35-17) .

Because lethal arrhythmias can occur suddenly in patients with an acute coronary syndrome, all patients should have a 12-lead ECG performed immediately while a brief targeted history is taken[157] [168] (see Fig. 35-17) . Patients should then be attached to a bedside ECG monitor and intravenous access obtained for infusion of 5 percent dextrose in water. If the initial ECG shows ST segment elevation of 1 mm or more in at least two contiguous leads (see Fig. 35-18) or a new or presumably new bundle branch block, the patient should be screened immediately for any contraindications to thrombolysis (Table 35-5) (Table Not Available) to help facilitate expeditious initiation of reperfusion therapy. [178] The National Heart Attack Alert Program recommends that emergency departments strive for a goal of treating eligible AMI patients with thrombolytic therapy within 30 minutes[157] [168] [177] (see Figs. 35-16 (Figure Not Available) and 35-17) . As door-to-needle times increase beyond 30 minutes, there is a progression in mortality and the likelihood of developing an ejection fraction less than 40 percent.[179] Evidence exists that for patients undergoing primary PTCA for AMI, delays in door-to-balloon times in excess of 2 hours are associated with increased mortality, emphasizing the need for expeditious transfer to the catheterization laboratory if primary PTCA is selected as the reperfusion strategy.[179A]

The available data fail to show a benefit of thrombolysis in AMI patients who do not present with ST segment elevation[15] [180] (see Fig. 35-17) . Patients with an initial ECG that reveals new or presumably new ST segment depression and/or T wave inversion, while not considered candidates for thrombolytic therapy, should be treated as though they are suffering from AMI without ST segment elevation or unstable angina (a distinction to be made subsequently after scrutiny of serial ECGs and cardiac marker measurements) (see Figs. 35-2 and 35-14 and Chap. 36) .

Management of the AMI patient without ST segment elevation is an important problem because 40 to 50 percent of patients with AMI are not considered candidates for thrombolysis on the basis of an initial ECG that does not show ST segment elevation.[5] Some patients without ST segment elevation on the initial ECG may subsequently

experience a worsening of ischemic discomfort, develop ST segment elevation (presumably when a subtotal occlusion of the culprit coronary artery progresses to total occlusion), and become candidates for reperfusion therapy (see Table 35-5) (Table Not Available) . Therefore, patients whose ECG is highly suggestive of myocardial ischemia should be admitted to a hospital unit with facilities for continuous monitoring of the ECG (either the CCU or intermediate care unit) that will alert the staff if arrhythmias or ST segment elevation occurs.[181] [182] Arrangements should be made for 12-lead ECGs to be obtained approximately every 8 hours for the first 24 hours, or more frequently if ischemic discomfort recurs.

Patients with a history suggestive of AMI (see p. 1128) and an initial nondiagnostic ECG (i.e., no obvious ST segment deviation or T wave inversion) should have serial tracings obtained while being evaluated in the emergency department for AMI (see Fig. 35-17) . Emergency department staff may be alerted to the sudden development of ST segment elevation by periodic visual inspection of the bedside ECG monitor, by continuous ST segment recording, or by auditory alarms when the ST segment deviation exceeds programmed limits. Decision aids such as computer-based diagnostic algorithms, identification of high-risk clinical indicators, rapid determination of cardiac serum markers,[111] two-dimensional echocardiographic screening for regional wall motion abnormalities, and myocardial perfusion imaging are of greatest clinical utility when the ECG is nondiagnostic. In an effort to improve the cost-effectiveness of care of patients with a chest pain syndrome, nondiagnostic ECG, and low suspicion of AMI but in whom the diagnosis has not been entirely excluded, many medical centers have developed critical pathways that involve a coronary observation unit with a goal of ruling out AMI in less than 12 hours (see Fig. 35-17) . [183] [184]

General Treatment Measures

ASPIRIN.

This agent is effective across the entire spectrum of acute coronary syndromes (see Fig. 35-2) and now forms part of the initial management strategy of patients with suspected AMI (see Fig. 35-17) . The pharmacology of aspirin is presented in Chapter 62 . The goal of aspirin treatment is to quickly block formation of thromboxane A_2 in platelets by cyclooxygenase inhibition. Because low doses (40 to 80 mg) take several days to achieve full antiplatelet effect, at least 160 to 325 mg should be administered acutely in the emergency department.[52] To achieve therapeutic blood levels rapidly, the patient should chew the tablet, thus promoting buccal absorption rather than absorption through the gastric mucosa.

CONTROL OF CARDIAC PAIN.

Analgesia is an important element of management of AMI patients in the emergency department. Often there is a tendency to underdose the

Figure 35-17 Algorithm for management of patients with suspected acute coronary syndrome in emergency department. All patients with possible ischemic-type discomfort should be rapidly evaluated and have a 12-lead electrocardiogram (ECG) performed. If the ECG is diagnostic of an acute coronary syndrome, patients should receive aspirin (ASA), beta blockers (in the absence of contraindications), and an antithrombin. Patients with ST segment elevation should be considered candidates for reperfusion, whereas those without ST segment elevation whose ECG and clinical history are strongly suspicious for ischemia should be admitted for initiation of antiischemic therapy. Patients with a nondiagnostic ECG should undergo further evaluation in the emergency department or short-term observation unit with ultimate disposition based on the results of serial serum cardiac marker levels and echocardiographic findings. Patients with ST segment elevation treated within 12 hours who are eligible for thrombolytics should expeditiously receive thrombolytic therapy or be considered for primary percutaneous coronary intervention (PCI). Primary PCI should be supported by an intravenous glycoprotein IIb/IIIa inhibitor and stent as needed. Primary PCI is also to be considered when thrombolytic therapy is contraindicated. Individuals treated after 12 hours should receive the initial medical therapy noted earlier and on an individual basis and may be candidates for angiotensin-converting enzyme (ACE) inhibitors (particularly if left ventricular function is impaired). Routine blood tests that should be obtained in all patients admitted by means of the algorithm include a complete blood cell count (CBC), lipid profile, and electrolyte levels. After discharge, all patients should receive aspirin and a beta blocker (in the absence of contraindications). Dietary modifications and, if needed, treatment to reduce low-density lipoprotein cholesterol and elevated high-density lipoprotein cholesterol are strongly encouraged, as is life style modification (including regular physical exercise and cessation of cigarette smoking).

Figure 35-18 This 12-lead ECG was obtained from a middle-aged man admitted with an extensive anterior AMI. (Note pathological Q waves in the precordial leads and marked repolarization abnormalities in the anterior and lateral leads.) A five-beat salvo of nonsustained ventricular tachycardia is seen extending over the transition between leads III and aV_f . *(From Antman EM, Rutherford JD: Coronary Care Medicine. Boston, Martinus Nijhoff Publishing, 1986, p 81.)*

TABLE 35-5 -- CONTRAINDICATIONS AND CAUTIONS FOR THROMBOLYTIC USE IN MYOCARDIAL INFARCTION

(Not Available)
From 1999 Updated ACC/AHA AMI Guideline (Web version), p 38.

patient for fear of obscuring response to antiischemic or reperfusion therapy. This should be avoided because pain contributes to the heightened sympathetic activity that is particularly prominent during the early phase of AMI. Control of cardiac pain is typically accomplished with a combination of nitrates, analgesics (e.g., morphine), oxygen, and beta-adrenoceptor blockers. Similar pharmacological principles apply in the CCU, where many of the therapies discussed in this section are continued after initial

dosing in the emergency department. Because the pain associated with MI is related to ongoing ischemia, many interventions that act to improve the oxygen supply-demand relationship (by either increasing supply or decreasing demand) may lessen the pain associated with AMI.

Analgesics.

Although a wide variety of analgesic agents has been used to treat the pain associated with AMI, including meperidine, pentazocine, and morphine, the last one remains the drug of choice, except in patients with well-documented morphine hypersensitivity. Four to 8 mg of morphine should be administered intravenously and doses of 2 to 8 mg repeated at intervals of 5 to 15 minutes until the pain is relieved or evident toxicity (i.e., hypotension, depression of respiration, or severe vomiting) precludes further administration of the drug. In some patients, remarkably large cumulative doses of morphine (2 to 3 mg/kg) may be required and are usually tolerated.[185]

The reduction of anxiety resulting from morphine diminishes the patient's restlessness and the activity of the autonomic nervous system, with a consequent reduction of the heart's metabolic demands. The beneficial effect of morphine in patients with pulmonary edema is unequivocal and may relate to several factors, including peripheral arterial and venous dilatation (particularly among patients with excessive sympathoadrenal activity), reduction of the work

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of breathing, and slowing of heart rate secondary to combined withdrawal of sympathetic tone and augmentation of vagal tone.[185]

Hypotension after the administration of nitroglycerin and morphine can be minimized by maintaining the patient in a supine position and elevating the lower extremities if systolic arterial pressure declines below 100 mm Hg. Obviously, such positioning is undesirable in the presence of pulmonary edema, but morphine rarely produces hypotension under these circumstances. The concomitant administration of atropine in doses of 0.5 to 1.5 mg intravenously may be helpful in reducing the excessive vagomimetic effects of morphine, particularly when hypotension and bradycardia are present before it is administered.[52] Respiratory depression is an unusual complication of morphine in the presence of severe pain or pulmonary edema, but as the patient's cardiovascular status improves, impairment of ventilation may supervene and should be watched for. It can be treated with naloxone, in doses of 0.1 to 0.2 mg intravenously initially, repeated after 15 minutes if necessary. Nausea and vomiting may be troublesome side effects of large doses of morphine and may be treated with a phenothiazine.

NITRATES.

By virtue of their ability to enhance coronary blood flow by coronary vasodilation and to decrease ventricular preload by increasing venous capacitance, sublingual nitrates are

indicated for most patients with an acute coronary syndrome. At present, the only groups of patients with AMI in whom sublingual nitroglycerin should *not* be given are those with inferior MI and suspected right ventricular infarction[63] [63A] or marked hypotension (systolic pressure < 90 mm Hg), especially if accompanied by bradycardia.

Once it is ascertained that hypotension is not present, a sublingual nitroglycerin tablet should be administered and the patient observed carefully for improvement in symptoms or change in hemodynamics. If an initial dose is well tolerated and appears to be of benefit, further nitrates should be administered, with careful monitoring of the vital signs. Even small doses may produce sudden hypotension and bradycardia, a reaction that can be life threatening but can usually be easily reversed with intravenous atropine if it is recognized quickly. Long-acting oral nitrate preparations should be avoided in the very early course of AMI because of the frequently changing hemodynamic status of the patient. In patients with a prolonged period of waxing and waning chest pain, intravenous nitroglycerin may be of benefit in controlling symptoms and correcting ischemia, but frequent monitoring of blood pressure is required.[185]

BETA-ADRENOCEPTOR BLOCKERS.

These drugs relieve pain, reduce the need for analgesics in many patients, and reduce infarct size.[186] Patients most suited for the use of beta blockers early in the course of AMI are those who also have sinus tachycardia and hypertension because beta blockers lower both the heart rate and arterial blood pressure, thereby lowering myocardial oxygen demand. A popular and relatively safe protocol for the use of a beta blocker in this situation is as follows:

1. Patients with heart failure (rales >10 cm up from diaphragm), hypotension (BP<90 mm Hg), bradycardia (heart rate<60 beats/min), or heart block (PR >0.24 sec) are first excluded.[187]
2. Metoprolol is given in three 5-mg boluses.
3. Patients are observed for 2 to 5 minutes after each bolus, and if the heart rate falls below 60 beats/min or systolic blood pressure falls below 100 mm Hg, no further drug is given; a total of three intravenous doses (15 mg) is administered.
4. If hemodynamic stability continues, 15 minutes after the last intravenous dose, the patient is begun on oral metoprolol, 50 mg every 6 hours for 2 days, then switched to 100 mg twice daily. An infusion of an extremely short-acting beta blocker, esmolol (50 to 250 mg/kg/min), may be useful in patients with relative contraindications to beta blockade in whom heart rate slowing is considered highly desirable.[188]

OXYGEN.

Hypoxemia may occur in patients with AMI and is usually secondary to ventilation-perfusion abnormalities that are sequelae of left ventricular failure; pneumonia and intrinsic pulmonary disease are additional causes of hypoxemia. It is common practice to treat all patients hospitalized with AMI with oxygen for at least 24 to 48 hours, based on the empirical assumption of hypoxia and evidence that increased oxygen in the inspired air may protect ischemic myocardium.[189] However, this practice

may not be cost-effective. Augmentation of the fraction of oxygen in the inspired air does not elevate oxygen delivery significantly in patients who are not hypoxemic. Furthermore, it may increase systemic vascular resistance and arterial pressure and thereby lower cardiac output slightly.

In view of these considerations, arterial oxygen saturation may be estimated by pulse oximetry (an increasingly available technology), and oxygen therapy may be omitted if it is normal. On the other hand, oxygen should be administered to patients with AMI when arterial hypoxemia is clinically evident or can be documented by measurement (e.g., $Sa_{O_2} < 90\%$).[52] In these patients, serial arterial blood gas measurements may be employed to follow the efficacy of oxygen therapy.

In general, the delivery of 2 to 4 liters/min of 100 percent oxygen by mask or nasal prongs for 6 to 12 hours is satisfactory for most patients with mild hypoxemia. If arterial oxygenation is still depressed on this regimen, the flow rate may have to be increased and other causes for hypoxemia should be sought. In patients with pulmonary edema, endotracheal intubation and positive-pressure controlled ventilation may be necessary.

Limitation of Infarct Size

Infarct size is an important determinant of prognosis in patients with AMI. Patients who succumb from cardiogenic shock generally exhibit either a single massive infarct or a small to moderate-sized infarct superimposed on multiple prior infarctions.[190] Survivors with large infarcts frequently exhibit late impairment of ventricular function, and the long-term mortality rate is higher than that for survivors with small infarcts, who tend not to develop cardiac decompensation.[78] [191]

In view of the prognostic importance of infarct size, the concept that modification of infarct size is possible has attracted a great deal of experimental and clinical attention[192] (see Fig. 35-17) . Efforts to limit the size of the infarct have been divided among several different (sometimes overlapping) approaches: (1) early reperfusion,[193] (2) reduction of myocardial energy demands, (3) manipulation of sources of energy production in the myocardium, and (4) prevention of reperfusion injury. Although early reperfusion ("time-dependent effect of reperfusion") has been the major focus of modern management strategies for AMI, it is important to note that in addition to the limitation of infarct size, even late reperfusion of ischemic myocardium conveys several benefits that contribute to mortality reduction ("time-independent effect of reperfusion")[74] (see Fig. 35-17) .

THE DYNAMIC NATURE OF INFARCTION.

AMI is a dynamic process that does not occur instantaneously but evolves over hours (see Fig. 35-5) . The fate of jeopardized, ischemic tissue may be affected favorably by interventions that restore myocardial perfusion, reduce microvascular damage in the infarct zone, reduce myocardial oxygen requirements, inhibit accumulation of or facilitate washout

of noxius metabolites, augment the availability of substrate for anaerobic metabolism,[84] [194] or blunt the effects of mediators of injury (e.g., calcium overload or oxygen free radicals)[84] [194] [195] [196] [197] that compromise the structure and function of intracellular organelles and constituents of cell membranes. Strong evidence in experimental animals and suggestive evidence in patients indicate that ischemic preconditioning, a form of endogenous protection against AMI, before sustained coronary occlusion decreases infarct size and is associated with a more favorable outcome and with decreased risk of extension of infarction and recurrent ischemic events.[198] Brief episodes of ischemia in one coronary vascular bed may precondition myocardium in a remote zone, attenuating the size of infarction in the latter when sustained coronary occlusion occurs.[199] Intriguing data have been reported that the expression of angiogenesis factors early after the onset of AMI may also contribute to the limitation of infarct size by promoting neovascularization in the infarct zone.[199A]

The perfusion of the myocardium in the infarct zone appears to be reduced maximally immediately after coronary occlusion. Up to one third of patients may develop spontaneous recanalization of an occluded infarct-related artery beginning at 12 to 24 hours. This delayed spontaneous reperfusion has been associated with improvement of left ventricular function because it improves healign of infarcted tissue, prevents ventricular remodeling, and reperfuses hibernating myocardium. However, in order to *maximize* the amount of myocardium salvaged by *accelerating* the process of reperfusion and also implementing it in those patients who would otherwise have an occluded infarct-related artery, the strategies of pharmacologically induced and catheter-based reperfusion of the infarct vessel have been developed (see page 1145).

Additional factors that may contribute to limitation of infarct size in association with reperfusion include relief of coronary spasm, prevention of damage to the microvasculature, improved systemic hemodynamics (augmentation of coronary perfusion pressure and reduced LV-EDP), and development of collateral circulation. The prompt implementation of measures designed to protect ischemic myocardium and support myocardial perfusion may provide sufficient time for the development of anatomical and physiological compensatory mechanisms that limit the ultimate extent of infarction (see Figs. 35-10 (Figure Not Available) and 35-12) . It is possible that interventions designed to protect ischemic myocardium during the initial event may also reduce the incidence of extension of infarction or early reinfarction.

ROUTINE MEASURES FOR INFARCT SIZE LIMITATION.

Whereas reperfusion of ischemic myocardium is the most important technique for limiting infarct size, several routine measures to accomplish this goal are applicable to all patients with AMI, whether or not reperfusion therapy is prescribed. The treatment strategies discussed in this section may be initiated in the emergency department (see Fig. 35-17) and then continued in the CCU.

It is important to maintain an optimal balance between myocardial oxygen supply and demand so that as much as possible of the jeopardized zone of the myocardium surrounding the most profoundly ischemic zones of the infarct can be salvaged. During the period before irreversible injury has occurred, myocardial oxygen consumption should be minimized by maintaining the patient at rest, physically and emotionally, and by using mild sedation and a quiet atmosphere, which may lower heart rate, a major determinant of myocardial oxygen consumption. If the patient was receiving a beta-adrenoceptor blocking agent at the time the clinical manifestations of the infarction began, the drug should be continued unless a specific contraindication develops, such as left ventricular systolic failure or bradyarrhythmia. Marked sinus bradycardia (heart rate less than approximately 50 beats/min) and the frequently coexisting hypotension should be treated with postural maneuvers (the Trendelenburg position) to increase central blood volume and atropine and electrical pacing, but not with isoproterenol. On the other hand, the routine administration of atropine, with the resultant increase in heart rate, to patients without serious bradycardia is contraindicated. All forms of tachyarrhythmias require prompt treatment because they increase myocardial oxygen needs.[52]

Congestive heart failure should be treated promptly. Given their multiple beneficial actions in AMI patients, ACE inhibitors are the first line of drugs indicated in the treatment of congestive heart failure associated with AMI unless the patient is hypotensive (see p. 1169).[199B] Drugs such as isoproterenol that increase myocardial oxygen consumption should be avoided.

As discussed earlier, arterial oxygenation should be restored to normal in patients with hypoxemia, such as occurs in patients with chronic pulmonary disease, pneumonia, or left ventricular failure. Oxygen-enriched air should be administered to patients with hypoxemia, and bronchodilators and expectorants should be used when indicated. Severe anemia, which can also extend the area of ischemic injury, should be corrected by the cautious administration of packed red cells, accompanied by a diuretic if there is any evidence of left ventricular failure. Associated conditions, particularly infections and the accompanying tachycardia, fever, and elevated myocardial oxygen needs, require immediate attention.

Systolic arterial pressure should not be allowed to deviate by more than approximately 25 to 30 mm Hg from the patient's usual level unless marked hypertension had been present before the AMI. It is likely that each patient has an optimal range of arterial pressure; as coronary perfusion pressure deviates from this level, the unfavorable balance between oxygen supply (which is related to coronary perfusion pressure) and myocardial oxygen demand (which is related to ventricular wall tension) that ensues increases the extent of ischemic injury.

REPERFUSION OF MYOCARDIAL INFARCTION

GENERAL CONCEPTS.

Although reperfusion occurs spontaneously in some patients, persistent thrombotic

occlusion is present in the majority of patients with STEMI while the myocardium is undergoing necrosis.[62] Timely reperfusion of jeopardized myocardium represents the most effective way of restoring the balance between myocardial oxygen supply and demand. The extent of protection appears to be related directly to the rapidity with which reperfusion is implemented after the onset of coronary occlusion[166] [193] [200] (see Fig. 35-7) (Figure Not Available) . Preliminary data exist suggesting that after thrombolytic therapy more rapid reperfusion (and smaller infarcts) occurs in patients with AMI preceded by unstable angina compared with those without preinfarction angina.[201]

In some patients, particularly those with cardiogenic shock, tissue damage occurs in a "stuttering" manner rather than abruptly, a condition that might more properly be termed subacute infarction. This concept of the nature of the infarction process, as well as the observation that the incidence of complications of AMI in both the early and late postinfarction periods is a function of infarct size, underscores the need for careful history-taking to ascertain whether the patient appears to have had repetitive cycles of spontaneous reperfusion and reocclusion. "Fixing" the time of onset of the infarction process in such patients can be difficult. In such patients with waxing and waning ischemic discomfort, a rigid time interval from the first episode of pain should not be used when determining whether a patient is "outside the window" for benefit from acute reperfusion therapy.

PATHOPHYSIOLOGY OF MYOCARDIAL REPERFUSION.

Prevention of cell death by the restoration of blood flow depends on the severity and duration of preexisting ischemia. Substantial experimental and clinical evidence exists indicating that recovery of left ventricular systolic function, improvement in diastolic function, and reduction in overall mortality are more favorably influenced the earlier that blood flow is restored[15] [193] (see Fig. 35-7) (Figure Not Available) . Collateral coronary vessels also appear to play a role in the successful left ventricular function after reperfusion.[67] They provide sufficient perfusion of myocardium to retard cell death and are probably of greater importance in patients having reperfusion later rather than 1 to 2 hours after coronary occlusion.

Even after successful reperfusion and despite the absence of irreversible myocardial damage, a period of postischemic contractile dysfunction can occur--a phenomenon referred to as *myocardial stunning*[202] (see Chap. 34) . Animal data suggest that selective proteolysis of troponin I may contribute to myocardial stunning.[202A] Periods of myocardial stunning are well described in experimental animals but have also been confirmed in AMI patients by Gerber and coworkers using positron emission tomography after PTCA to measure myocardial blood flow and oxygen consumption.[203]

Reperfusion Injury

The process of reperfusion, although beneficial in terms of myocardial salvage, may

come at a cost owing to a process known as *reperfusion injury*[204] [204A] (see Fig. 35-9) . Kloner and Przyklonk have summarized the data on the four types of reperfusion injury that have been observed in experimental animals.[205] These consist of (1) lethal reperfusion injury--a term referring to reperfusion-induced death of cells that were still viable at the time of restoration of coronary blood flow; (2) vascular reperfusion injury--progressive damage to the microvasculature such that there is an expanding area of no reflow and loss of coronary vasodilatory reserve[206] [207] ; (3) stunned myocardium--salvaged myocytes display a prolonged period of contractile dysfunction after restoration of blood flow owing to abnormalities of intracellular biochemistry leading to reduced energy production[196] (see Chap. 34) (see Fig. 35-9) ; and (4) reperfusion arrhythmias--bursts of ventricular tachycardia and, on occasion, ventricular fibrillation that occur within seconds of reperfusion. The available evidence suggests that vascular reperfusion injury, stunning, and reperfusion arrhythmias can all occur in patients with AMI. The concept of lethal reperfusion injury of potentially salvageable myocardium remains controversial, both in experimental animals and in patients.[57] [205] [208]

Reperfusion increases the cell swelling that occurs with ischemia. Reperfusion of the myocardium in which the microvasculature is damaged leads to the creation of a hemorrhagic infarct (see Fig. 35-9) . Thrombolytic therapy appears more likely to produce hemorrhagic infarction than reperfusion by mechanical means. Although concern has been raised that this hemorrhage may lead to extension of the infarct, this does not appear to be the case. Histological study of patients not surviving in spite of successful reperfusion has revealed hemorrhagic infarcts, but this hemorrhage usually does not extend beyond the area of necrosis.[57]

The loss of magnesium with ischemia, followed during reperfusion by the sudden exposure of severely ischemic cells to both calcium and oxygen on restoration of flow, has been observed to affect the severity of ischemic damage in several animal species.[195] [196] [209] Toxicity from oxygen-derived free radicals mediated at least in part by stimulated leukocytes has attracted considerable attention for its possible role in extending myocardial injury and contributing to calcium overload and inability to regulate cell volume. It has been proposed that necrotic myocytes expose cardiac antigens that lead to T-cell activation and generation of cytokines such as interferon gamma, interleukin-3, and granulocyte-monocyte colony stimulating factor.[210] These cytokines ultimately increase the expression of integrins such as Mac-1 on monocytes promoting adhesion to the endothelium in the ischemic territory and microvascular plugging (i.e., no-reflow phenomenon). Interest has therefore arisen in development of antibodies that interrupt leukocyte-leukocyte and leukocyte-endothelium interactions in patients with AMI.[210] Experimental models of AMI have revealed a consistent message: interventions that attenuate reperfusion injury exert their maximal beneficial effect if blood levels (and presumably myocardial tissue concentrations) are elevated at the time reperfusion occurs.[204A] [211] The effectiveness of agents such as superoxide dismutase and magnesium rapidly declines the later they are administered after reperfusion; eventually no beneficial effect is detectable in animal models after 45 to 60 minutes of reperfusion has elapsed.[208] Drugs such as beta-adrenoceptor blockers, which delay the death of ischemic cells, may, if administered prophylactically to patients at high risk of occlusion (or reocclusion) or in the earliest phases of the development of an AMI, enhance the quantity of myocardium salvaged by early reperfusion.[212] [213]

Ischemic Preconditioning

Brief periods of experimental coronary occlusion and reperfusion before a more sustained period of occlusion result in marked reduction in the amount of necrosis that develops has led to the concept of *ischemic preconditioning*[198] [214] (see Chap. 14) . Data suggest that during the period of brief coronary occlusion adenosine receptors are activated that initiate a cascade of intracellular events culminating in phosphorylation of a membrane protein that is responsible for the protective effect. The leading candidate is the mitochondrial adenosine triphosphate (ATP)-dependent potassium channel that, when activated, causes a decrease in calcium influx, a reduction in contractile force generation, and thereby an energy-sparing effect.[215] The implications of ischemic preconditioning, including a possible modification of the severity of MI, are profound and have stimulated interest in ATP-dependent potassium channel openers such as nicorandil, bimakalim, and other "preconditioning mimetic" agents for potential use in patients with AMI.[198] [216] A second window of protection after preconditioning has been described.[198] It may be mediated by such processes as molecular adaptation leading to the production of heat shock protein or antioxidant enzymes, augmentation of inducible NO synthase, and opening of mitochondrial ATP-sensitive potassium channels.[215] Preconditioning appears to be associated with a more oxidized cellular redox state, which may contribute to protection against subsequent bouts of ischemia. In experimental animals the infarct size-limiting effect of ischemic preconditioning is blunted by hypercholesterolemia but is restored by treatment with pravastatin.[217]

Clinical observations consistent with the concept of ischemic preconditioning include the "warm-up phenomenon" reported by many angina patients (i.e., angina early in exercise necessitating a brief rest period followed by a resumption of exercise without angina) and a lower 30-day cardiac event rate (mortality, recurrent MI, congestive heart failure, or shock) in AMI patients who have a history of angina within the 48-hour period that precedes infarction. [218] A history of preinfarction angina in patients with a first Q-wave MI has been reported to be associated with lower peak CK activity, lower in-hospital incidence of sustained ventricular tachycardia (VT) and ventricular fibrillation, and a lower incidence of pump failure and cardiac mortality. Of interest, in patients with a first anterior MI, a history of preinfarction angina was associated with a

greater degree of recovery of left ventricular function.[219] The greater protective effect of a longer time interval between angina pectoris and AMI suggests that the beneficial effect of prior angina is due to a delayed response to preconditioning.[219]

Reperfusion Arrhythmias

Transient sinus bradycardia occurs in many patients with inferior infarcts at the time of acute reperfusion; it is most often accompanied by some degree of hypotension. This combination of hypotension and bradycardia with a sudden increase in coronary flow

has been ascribed to the activation of the Bezold-Jarisch reflex. Premature ventricular contractions, accelerated idioventricular rhythm, and nonsustained VT are also seen commonly after successful reperfusion. In experimental animals with AMI, ventricular fibrillation occurs shortly after reperfusion, but this arrhythmia is not as frequent in patients as in the experimental setting. Although some investigators have postulated that early afterdepolarizations participate in the genesis of reperfusion ventricular arrhythmias, Vera and colleagues have shown that early afterdepolarizations are present both during ischemia and during reperfusion and are therefore unlikely to be involved in the development of reperfusion VT or ventricular fibrillation.

When present, rhythm disturbances may actually be a marker of successful restoration of coronary flow. However, although reperfusion arrhythmias have a high sensitivity for detecting successful reperfusion, the high incidence of identical rhythm disturbances in patients without successful coronary artery reperfusion limits their specificity for detection of restoration of coronary blood flow. In general, clinical features are poor markers of reperfusion, with no single clinical finding or constellation of findings being reliably predictive of angiographically demonstrated coronary artery patency.[220]

Although reperfusion arrhythmias may show a temporal clustering at the time of restoration of coronary blood flow in patients with successful thrombolysis, the overall incidence of such arrhythmias appears to be similar in patients not receiving a thrombolytic agent who may develop these arrhythmias as a consequence of spontaneous coronary artery reperfusion or the evolution of the infarct process itself. These considerations, as well as the fact that the brief "electrical storm" occurring at the time of reperfusion is generally innocuous, indicate that no prophylactic antiarrhythmic therapy is necessary when thrombolytics are prescribed.[221]

Late Establishment of Patency of the Infarct Vessel

It has been suggested that improved survival and ventricular function after successful reperfusion are not due entirely to limitation of infarct size.[74] [222] Both experimental and clinical evidence indicates that the benefits of a patent artery include a favorable effect on ventricular remodeling (improved healign of infarcted tissue and prevention of infarct expansion),[72] [78] [191] [223] enhancement of collateral flow, improvement in diastolic and systolic function, increased electrical stability, and reduced long-term mortality.[224] [225] Late reperfusion of the artery perfusing an infarction provides a vascular scaffolding in the infarct zone and increases the influx of inflammatory cells that participate in the formation of a mature fibrous scar. The vascular scaffold and firmer myocardial scar prevent infarct segment lengthening and decrease the tendency toward infarct expansion and aneurysm formation.[222] Poorly contracting or noncontracting myocardium in a zone that is supplied by a stenosed infarct-related artery with slow antegrade perfusion may still contain viable myocytes. This situation is referred to as *hibernating* myocardium[204] (see Chap. 37) , and its function can be improved by PTCA to augment flow in the infarct-related artery.[226] Late reperfusion of the infarct-related artery by thrombolysis or late restoration of flow by PTCA enhances the electrical stability of the infarcted zone and is probably related to the reduced incidence of ventricular fibrillation and automatic firing of implantable cardioverter-defibrillator devices.[227] [228] The beneficial effect of late reperfusion of the infarct-related artery is

independent of left ventricular function and other mortality-reducing therapies such as ACE inhibitors.[224] Several clinical trials are under way testing the benefits of late reperfusion of an occluded infarct artery in asymptomatic patients (OAT, ACTOR).

Summary of Effects of Myocardial Reperfusion

As illustrated in Figure 35-13 , rupture of an unstable plaque in the culprit vessel produces complete occlusion of the infarct-related coronary artery. AMI occurs with the ensuing development of left ventricular dilatation and ultimate death through a combination of pump failure and electrical instability. Early reperfusion (i.e., thrombolysis, primary PTCA) shortens the duration of coronary occlusion, minimizes the degree of ultimate LV dysfunction and dilatation, and reduces the probability that the AMI patient will develop pump failure or malignant ventricular tachyarrhythmias. Late reperfusion may favorably affect the process of infarct healign and minimize LV remodeling and the ultimate development of pump dysfunction and electrical instability.

CORONARY THROMBOLYSIS

Many years elapsed between the first report of intracoronary clot lysis in an experimental animal and the widespread use of thrombolytic agents in AMI. With publication of the first Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial of over 11,000 patients in 1986,[229] in which intravenous streptokinase was shown to result in a significant reduction in mortality in patients treated within 6 hours of the onset of symptoms, the routine use of thrombolytic therapy in AMI was established. It is now clear that thrombolysis recanalizes thrombotic occlusion associated with AMI (see Fig. 35-10) (Figure Not Available) and that restoration of coronary flow reduces infarct size and improves myocardial function and survival over both the short and the long term.[230] [231] The majority of the mortality benefit seen at 10-year follow-up in the GISSI trial was obtained before hospital discharge because no survival difference was seen in thrombolysed and control patients discharged alive except for those treated within the first hour after symptoms.[230]

INTRACORONARY THROMBOLYSIS.

Clinical investigation of pharmacological reperfusion of ischemic myocardium initially focused on intracoronary thrombolysis in the early hours of AMI.[193] [232] [233] The fact that viability could be maintained in a portion of the successfully reperfused myocardium was reflected in studies showing the restoration of contractile activity.[234] Most reported experience with intracoronary thrombolysis has not been in randomized controlled trials, largely because it has been thought difficult to withhold thrombolytic therapy once a thrombotic coronary artery occlusion has been visualized angiographically and because it has not been considered ethical to catheterize patients if randomization to no thrombolytic therapy were possible for a portion of the patients. Because of the delay involved in catheterizing patients with AMI, current consensus is that intracoronary administration of thrombolytic therapy should be reserved for patients who develop coronary thrombosis during the course of an angiographic procedure and in whom either a coronary catheter is already in place or such placement is easily and rapidly

achieved.

INTRAVENOUS THROMBOLYSIS.

This form of thrombolytic therapy has several important advantages over intracoronary use. Because only the placement of a peripheral intravenous line is required, therapy may be initiated early, in a variety of locations (home, ambulance, helicopter,

Figure 35-19 Correlation of Thrombolysis in Myocardial Infarction (TIMI) flow grade and mortality. A pooled analysis of data from 5498 patients in several angiographic trials of reperfusion for ST segment elevation MI showed a gradient of mortality when the angiographic findings were stratified by TIMI flow grade. Patients with TIMI 0 or TIMI 1 flow had the highest mortality; TIMI 2 flow was associated with an intermediate mortality; lowest mortality was observed in patients with TIMI 3 flow. *(Personal communication, Dr. Michael Gibson, 2000.)*

emergency department) and at relatively low cost. The subject of intravenous thrombolysis has perhaps been one of the most rapidly evolving areas in the management of patients with AMI, especially over the past decade.

To provide a level of standardization for comparison of the various regimens, most investigators describe the flow in the infarct vessel according to the TIMI grading system:

Grade 0 = complete occlusion of the infarct-related artery.

Grade 1 = some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed.

Grade 2 = perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery.

Grade 3 = full perfusion of the infarct vessel with normal flow.[235] [236]

When evaluating reports of angiographic studies of thrombolytic agents, it must be kept in mind that only in studies in which a pretreatment coronary arteriogram documents occlusion of the culprit vessel can the term *recanalization* be applied if flow is restored. If the status of the culprit vessel is not known before treatment, the only fact that can be stated with certainty is the *patency rate* of the vessel at the moment contrast medium is injected. This snapshot in time does not reflect the fluctuating status of flow in the infarct vessel that characteristically undergoes repeated cycles of patency and reocclusion, as has been documented angiographically and by continuous ST segment monitoring.

Figure 35-20 Relationship between coronary blood flow and mortality in AMI. *(From Gibson CM: Primary angioplasty, rescue angioplasty, and new devices. In Hennekens CH (ed): Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 194.)*

Issues of the fluctuating nature of patency of the infarct-related artery notwithstanding, the majority of angiographic studies of reperfusion regimens for STEMI used an assessment of the TIMI flow grade at 90 minutes as the primary endpoint of the trial. With an increasing number of angiographers being able to perform diagnostic catheterizations in patients with AMI more expeditiously than in the past, investigators have now focused on the TIMI grade flow assessed at 60 minutes. Evidence exists that differences between reperfusion regimens with respect to the rate and extent of thrombolysis can be discriminated better at 60 rather than 90 minutes after initiation of therapy: earlier opening of infarct-related arteries is expected to reduce infarct size further and translate into a reduction in mortality.[237]

Initially, combined TIMI grade 2 and grade 3 flow was lumped into the favorable category of coronary patency that was compared with a combined TIMI grade 0 and grade 1 flow into an unfavorable category of persistent occlusion. However, TIMI grade 2 flow should not be lumped with grade 3 flow because it has been recognized that TIMI grade 3 flow is far superior to grade 2 flow in terms of infarct size reduction and both short-term[238] and long-term [239] mortality benefit. Therefore, TIMI grade 3 flow should be considered to be the goal of reperfusion therapy[240] [241] (Fig. 35-19) . In an effort to provide a more quantitative statement of the briskness of coronary blood flow in the infarct artery and also to account for differences in the size and length of vessels (e.g., left anterior descending artery vs. right coronary artery) and interobserver variability, Gibson and coworkers have developed the *TIMI frame count*--a simple count of the number of angiographic frames elapsed until the contrast medium arrives in the distal bed of the vessel of interest. The TIMI frame count, an objective and quantitative index of coronary blood flow, is an independent predictor of in-hospital mortality from AMI and also discriminates patients with TIMI grade 3 flow into low- and high-risk groups.[242] [243] The TIMI frame count can also be used to quantitate coronary blood flow (milliliters per second) calculated at 21/(observed TIMI frame count) × 1.7 (based on Doppler velocity wire data showing normal flow equals 1.7 cm^3 /sec, which is proportional to 21 frames). The relationship between calculated coronary perfusion and mortality for patients treated with thrombolytics and primary PTCA is illustrated in Figure 35-20 .

MYOCARDIAL PERFUSION.

Despite the intense interest in development of reperfusion regimens that normalize flow in the epicardial infarct-related artery, the real goal of reperfusion in STEMI is to improve myocardial perfusion in the infarct zone. Of course, myocardial perfusion cannot be

improved adequately without restoration of flow in the occluded infarct-related artery (Fig. 35-21) . However, even patients with TIMI grade 3 flow may not achieve adequate myocardial perfusion.[207] [244] The two major impediments to normalization of myocardial perfusion are microvascular damage[245] (see Fig. 35-21) and reperfusion injury. Obstruction of the distal microvasculature in the downstream bed of the infarct-related artery is caused by platelet microemboli and thrombi. Microembolization of platelet aggregates may actually be exacerbated by thrombolysis by means of the exposure of clot-bound thrombin, an extremely potent platelet agonist. Spasm may also occur in the microvasculature owing to the release of substances from activated platelets such as serotonin and thromboxane A_2 (see Fig. 35-3) . Reperfusion injury, discussed earlier (see p. 1144), results in cellular edema, free radical formation, and calcium overload. In addition, cytokine activation leads to neutrophil accumulation and inflammatory mediators that contribute to tissue injury.

Several techniques have been used to evaluate the adequacy of myocardial perfusion. ST segment resolution on the ECG is a strong predictor of outcome in AMI patients (Fig. 35-22) ; its absence is a better predictor of an occluded rather than patent infarct-related artery.[207] [246] [247] [248] [249] [250] Absence of early ST segment resolution after angiographically successful primary PTCA identifies patients with a higher risk of left ventricular dysfunction and mortality, presumably because of microvascular damage in the infarct zone.[251] [252] Thus, the 12-lead ECG can serve as a clinically useful marker of the biological integrity of myocytes in the infarct zone and can reflect inadequate myocardial perfusion even in the presence of TIMI 3 flow.[207] Given the dynamic nature of coronary occlusion, it has been proposed that continuous ST segment monitoring is more informative than static 12-lead ECG recordings, but practical limitations have prevented continuous ST segment monitoring from

Figure 35-21 Patterns of response to thrombolysis. *A,* Failure of epicardial reperfusion can occur owing to failure to induce a lytic state or to mechanical factors at the site of occlusion. Failure of microvascular reperfusion is due to a combination of platelet microthrombi followed by endothelial swelling and myocardial edema ("no reflow"). *B,* Thrombolysis may fail owing to persistent occlusion of the epicardial infarct-related artery (TIMI 0 and 1), patency of an epicardial artery in the presence of impaired (TIMI 2) flow, or microvascular occlusion in the presence of angiographically normal flow (TIMI 3). Successful reperfusion requires a patent artery with an intact microvascular network. Conversely, reperfusion may occur despite an occluded epicardial artery due to the presence of collateral vessels. *(From Davies CH, Ormerod OJ: Failed coronary thrombolysis. Lancet 351:1191-1196, 1998.)*

Figure 35-22 Relationship between ST segment resolution and 30-day mortality. Patients with complete (> 70 percent) ST segment resolution have the lowest 30-day mortality followed by patients with partial (30-70 percent) and no (< 30 percent) ST segment resolution. The gradient of mortality stratified by ST segment resolution is evident at both 90 minutes and 180 minutes after initiation of thrombolytic therapy. *(Adapted from data in Schroder R, et al: Comparison of the predictive value of ST segment elevation resolution at 90 and 180 min after start of streptokinase in acute myocardial infarction: A substudy of the*

Hirudin for Improvement of Thrombolysis [HIT]-4 study. Eur Heart J 20:1563-1571, 1999.

widespread clinical application.[253] [254] Defects in perfusion patterns seen with myocardial contrast echocardiography correlate with regional wall motion abnormalities[255] and lack of myocardial viability on dobutamine stress echocardiography.[256] A practical limitation to myocardial contrast echocardiography is the need for intracoronary injection of echo contrast medium, although this may be circumvented

Figure 35-23 Myocardial perfusion in AMI. *A,* ^{99m} Tc-sestamibi SPECT before reperfusion; vertical long-axis slice; reduced tracer uptake of basal inferior left ventricular myocardium (arrows). *B,* ^{99m} Tc-sestamibi SPECT 7 days after stenting of left circumflex coronary artery; nearly normal tracer uptake of basal inferior left ventricular myocardium. (From Horcher J, et al: Myocardial perfusion in acute coronary syndrome. Circulation 99:e15, 1999. Copyright 1999, American Heart Association.)

by the availability of new echo contrast agents that may be injected intravenously.[257] [257A] Doppler flow wire studies, MRI, and nuclear imaging with positron emission tomography (Fig. 35-23) have also been used to define abnormalities of myocardial perfusion.[245] [258] [259] [260]

A new angiographic method for assessing myocardial perfusion has also been introduced by Gibson and colleagues--the TIMI myocardial perfusion grade (Fig. 35-24) . Abnormalities of increasing myocardial perfusion as assessed by the TIMI myocardial perfusion grade correlate with mortality risk even after adjusting for the presence of TIMI grade 3 flow or a normal TIMI frame count.[261]

A variety of treatments have been tested for increasing myocardial perfusion. A generally consistent theme is that myocardial protective agents should be administered either before or concurrent with efforts at restoration of flow in the epicardial infarct-related artery to minimize damage that may occur as a consequence of reperfusion strategies. Administration of adenosine in the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial was associated with a reduction in infarct size in patients with an anterior wall MI.[262] Efforts to treat vasospasm with vasodilators such as nicorandil, papavarine, verapamil, and trimetazidine have been associated with improvement in myocardial perfusion in several small series.[216] The most promising intervention to date for treating obstruction of the microvasculature is the administration of an intravenous GPIIb/IIIa inhibitor either in conjunction with a reduced dose of thrombolytic or in association with a catheter-based reperfusion strategy.

Figure 35-24 Relationship between TIMI myocardial perfusion grade and mortality. TIMI myocardial perfusion (TMP) grade 0 or no perfusion of the myocardium is associated with the highest mortality. If the stain of the myocardium is present (grade 1), mortality is also high. A reduction in mortality is seen if the dye enters the microvasculature but is still persistent at the end of the washout phase (grade 2). The lowest mortality is observed in those patients with normal perfusion (grade 3) in whom the dye is minimally persistent at the end of the washout phase. *(From Gibson CM, et al: Circulation 101:125-130,*

2000. Copyright 2000, American Heart Association.)

With the exception of intravenous GPIIb/IIIa inhibitors, no intervention can be recommended definitively for the specific purposes of improving myocardial perfusion, although this situation may change as more data become available.

Effect on Mortality

There is no doubt that early intravenous therapy and thrombolytic drugs improve survival in patients with AMI[15] [52] (Fig. 35-25) . Mortality varies considerably depending on patients included for study and adjunctive therapies employed. The benefit of thrombolytic therapy appears to be greatest when agents are administered as early as possible, with the most dramatic results when the drug is given less than 1 to 2 hours after symptoms begin.[166] [263] [264] The Fibrinolytic Therapy Trialists' (FTT) collaborative group has performed a comprehensive overview of nine trials of thrombolytic therapy, each of which enrolled more than 1000 patients[15] (Fig. 35-26) . The data base for the FTT overview consisted of a total of 58,600 patients, including 6,177 (10.5 percent) who died, 564 (1.0 percent) who sustained a stroke, and 436 (0.7 percent) who sustained major noncerebral hemorrhages. The absolute mortality rates for the control and fibrinolytic groups stratified by presenting features are shown in Figure 35-26 . The overall results indicated an 18 percent reduction in short-term mortality, but as much as a 25 percent reduction in mortality for the subset of 45,000 patients with ST segment elevation or bundle branch block. Two trials, Late Assessment

Figure 35-25 Cumulative vascular mortality (deaths from cardiac, cerebral, hemorrhagic, or other known vascular disease, or unknown causes) in days 0 to 35 of the Second International Study of Infarct Survival (ISIS-2). The four curves describe mortality for patients allocated (i) active streptokinase only, (ii) active aspirin only, (iii) both active treatments, and (iv) neither. Note that individually aspirin and streptokinase have a favorable effect of similar magnitudes and together the benefits appear additive. *(From ISIS-2 [Second International Study of Infarct Survival] Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 2:349, 1988.)*

of Thrombolytic Efficacy (LATE) and Estudio Multicentrico Estreptquinasa Republicas de America del Sur (EMERAS), viewed together provide evidence that a mortality reduction may still be observed in patients treated with thrombolytics between 6 and 12 hours from the onset of ischemic symptoms.[265] [266] The data from LATE and EMERAS and the FTT overview form the basis for extending the "window" of treatment with thrombolytics up to 12 hours from the onset of symptoms. Boersma and colleagues pooled the trials in the FTT overview, 2 smaller studies with data on time to randomization, and 11 additional trials of more than 100 patients. Patients were divided into six time categories from symptom onset to randomization. A regression analysis revealed there was a nonlinear relationship of treatment benefit to time.

MORTALITY REDUCTIONS IN SUBGROUPS.

The mortality effect of thrombolytic therapy in elderly patients is of considerable interest and controversy.[23A] [23B] Whereas patients older than the age of 75 were initially excluded from randomized trials of thrombolytic therapy, they now constitute about 15 percent of the patients studied in recent megatrials of thrombolysis and are being analyzed in registries of AMI patients.[19] [267] [268] Barriers to initiation of therapy in older patients with AMI include a protracted period of delay in seeking medical care, a lower incidence of ischemic discomfort and greater incidence of atypical symptoms and concomitant illnesses, and an increased incidence of nondiagnostic ECGs.[158] Younger patients with AMI achieve a slightly greater relative reduction in mortality compared with elderly patients, but the higher absolute mortality in the elderly results in similar absolute mortality reductions. Thus, as seen in Figure 35-26 , there was a 26 percent decrease in mortality in patients who were younger than 55 years of age (11 lives saved per 1000 with thrombolytic therapy) and a 4 percent reduction in mortality in patients older than age 75 (10 lives saved per 1000 treated). Observational data from the Cooperative Cardiovascular Project (CCP) have raised concern about increased mortality in patients over age 75 years.[23A] However, such observations should not be considered definitive given the nonrandomized nature of the dataset.[23B] Nevertheless clinicians should consider the risks of thrombolysis, especially intracranial hemorrhage, when selecting a reperfusion strategy for elderly patients.[23B]

Other important baseline characteristics that have an impact on the mortality effect of thrombolytic therapy include the vital signs at presentation and the presence of diabetes mellitus (see Fig. 35-26) . For example, there was an 18 percent decrease in mortality for patients presenting with a systolic pressure less than 100 mm Hg (62 lives saved per 1000 treated), compared with a 12 percent reduction in mortality for patients with a systolic pressure of 175 mm Hg or more (10 lives saved per 1000 treated). Patients with a history of diabetes mellitus experienced a mortality reduction of 21 percent (37 lives saved per 1000 treated), compared with a mortality reduction of 15 percent (15 lives saved per 1000 treated) in patients without a history of diabetes.

A number of models have been developed to integrate the many clinical variables that affect a patient's mortality risk before administration of thrombolytic therapy. In the TIMI II trial, patients were classified as low risk if they *lacked* any of the following: age of 70 years or older, previous infarction, atrial fibrillation, anterior infarction, rales in more than one third of the lung fields, hypotension and sinus tachycardia, female gender, and diabetes mellitus (see Table 35-4) (Table Not Available) . A more comprehensive, convenient, bedside, simple risk-scoring system for predicting 30-day mortality at presentation for fibrinolytic-eligible patients with ST-elevation MI was developed by Morrow et al using the InTIME-2 trial database[268A] (Fig. 35-27) . However, modeling of mortality risk cannot cover all clinical scenarios and should not substitute for clinical judgment in individual cases. For

Figure 35-26 Mortality differences during days 0 to 35 subdivided by presentation features in a collaborative overview of results from nine trials of thrombolytic therapy. The absolute mortality rates are shown for fibrinolytic and control groups in the center portion of the figure for each of the clinical features at presentation listed on the left side of the figure. The odds ratio for death in the fibrinolytic group to that in the control group is shown for each subdivision (colored square), along with its 99 percent confidence interval (horizontal line). The summary odds ratio at the bottom of the figure corresponds to an 18 percent proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1000 patients treated with thrombolytic agents. *(From Fibrinolytic Therapy Trialists' [FTT] Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 343:311, 1994.)*

example, patients with inferior MI who might otherwise be considered to have a low risk of mortality and for whom many physicians have questioned the benefits of thrombolytic therapy might be in a much higher mortality risk subgroup if their inferior infarction is associated with right ventricular infarction, precordial ST segment depression, or ST segment elevation in the lateral precordial leads. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I investigators developed a regression model to illustrate the relative importance of clinical characteristics on 30-day mortality in contemporary thrombolytic-treated patients.[269] Much greater proportions of the risk of mortality are contributed by the systolic blood pressure and heart rate at presentation than precisely which thrombolytic agent is selected.

CLINICAL BENEFIT.

As a result of greater patency of the infarct vessel in patients treated with thrombolytic agents, the clinical benefits that appear to accrue and contribute to the reduction in mortality include reductions in left ventricular failure, malignant arrhythmias,[270] and serious complications of AMI such as septal rupture and cardiogenic shock.[270] [271] [272] The short-term survival benefit enjoyed by patients who receive thrombolytic therapy is maintained over the 1- to 10-year follow-up that has been reported in a number of studies.[230] However, room for improvement remains, given reports of reocclusion rates of the infarctrelated artery as high as 10 percent in hospital and up to 30 percent by 3 months[273] and reinfarction rates as high as 5 percent in hospital and 7 percent within the first year in thrombolytic-treated patients.

Comparison of Thrombolytic Agents (See also Chap. 62)

There has been considerable controversy regarding the efficacy of various thrombolytic agents[274] (Table 35-6) . In the GUSTO I trial, 41,021 patients were randomized into one of four treatment arms: streptokinase,

Figure 35-27 TIMI Risk Score for STEMI for predicting 30-day mortality. STE=ST elevation; LBBB=left bundle branch block; h/o=history of; HTN=hypertension. *(From Morrow DA, Antman EM, Charlesworth A, et al: The TIMI risk score for ST elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An InTIME II substudy. Circulation, in press.)*

1.5 MU over 60 minutes with immediate intravenous heparin to a target activated partial thromboplastin time of 60 to 85 seconds; accelerated t-PA with immediate intravenous heparin; a combination arm of intravenous t-PA (1 mg/kg over 60 minutes) and streptokinase (1.0 MU over 60 minutes); and streptokinase, 1.5 MU over 60 minutes with subcutaneous heparin. The 30-day mortality for the accelerated t-PA group was 6.3 percent; streptokinase plus subcutaneous heparin, 7.2 percent; streptokinase plus intravenous heparin, 7.4 percent; and streptokinase plus t-PA combination plus intravenous heparin, 7.0 percent.

In the GUSTO angiographic substudy involving 2431 patients, those with TIMI grade 0 or 1 flow had a 30-day mortality of 9.8 percent that was reduced to 7.9 percent in patients with TIMI grade 2 flow and to 4.3 percent in those with TIMI grade 3 flow.[238] The 90-minute patency rates for the infarct-related artery in the four treatment arms were as follows: accelerated t-PA, 81 percent (54 percent grade 3 flow); combination t-PA plus streptokinase, 73 percent (38 percent grade 3 flow); streptokinase plus intravenous heparin, 60 percent (32 percent grade 3 flow); and streptokinase plus subcutaneous heparin, 54 percent (29 percent grade 3 flow). This early gradient in patency rates favoring t-PA was no longer apparent beyond 180 minutes, presumably because of a "catch-up" phenomenon whereby late patency rates with streptokinase approach those of front-loaded t-PA, albeit beyond a time when as much myocardial salvage is possible as with t-PA. A related observation on early arterial patency was made in the TIMI 4 trial that randomized patients with AMI presenting within 6 hours to receive front-loaded t-PA, anistreplase (APSAC, anisoylated plasminogen streptokinase activator complex), or a combination of a reduced dose of both t-PA and anistreplase.[275] The 90-minute patency rate for front-loaded t-PA was 84 percent (60 percent grade 3); anistreplase, 73 percent (43 percent grade 3); and the combination, 68 percent (45 percent grade 3). A mortality trend favoring t-PA compared with both of the other treatment regimens was seen at 1 year.[275]

TISSUE PLASMINOGEN ACTIVATOR.

The t-PA molecule contains the following five domains: finger, epidermal growth factor, kringle 1 and kringle 2, and serum protease[276] (Fig. 35-28) . In the absence of fibrin, t-PA is a weak plasminogen activator; fibrin provides a scaffold on which t-PA and plasminogen are held in such a way that the catalytic efficiency for plasminogen activation of t-PA is increased manyfold. Plasma clearance of t-PA is mediated to a varying degree by residues in each of the domains except the serine protease domain, which is responsible for the enzymatic activity of t-PA. The accelerated dose regimen of

t-PA over 90 minutes produces more rapid thrombolysis than the standard 3-hour infusion of t-PA. A double-bolus regimen of t-PA was not shown to be equivalent to the accelerated dose regimen[277] [278] [279] and was associated with a slightly higher rate of intracranial hemorrhage; the double-bolus regimen has not been recommended for clinical use.

Modifications of the basic t-PA structure have been made to yield a group of third-generation fibrinolytics (see Fig. 35-28 and Table 35-6) . A common feature among the third-generation fibrinolytics is prolonged plasma clearance, allowing them to be administered as a bolus rather than the

TABLE 35-6 -- KEY PROPERTIES OF NEW FIBRINOLYTIC AGENTS AS COMPARED WITH t-PA AND STREPTOKINASE

PROPERTY	SK	t-PA	r-PA	TNK-tPA	SAK
Molecular weight (daltons)	47,000	70,000	39,000	70,000	16,500
Plasma half-life (min)	23-29	4-8	15	±20	6
Fibrin specificity	--	++	+	+++	++++
Plasminogen activation	Indirect	Direct	Direct	Direct	Indirect
Dose*	1.5 MU/60 min	100 mg/90 min	2×10 MU bolus 30 min apart	0.5 mg/kg bolus	20-30 mg/30 min
Antigenic	+	-	-	-	+
Hypotension	+	-	-	-	-
Patency at 90 min	+	+++	++++	+++	+++(+?)
Hemorrhagic stroke	+	++	++	++	?
Mortality reduction	+	++	++	++	?
Cost	+	+++	+++	+++(?)	++(?)
Concomitant heparin	?	+	+	+	+
Bleeding (noncerebral)	+++	++	++	+	?

Modified from White HD, van de Werf F: Thrombolysis for acute myocardial infarction. Circulation 97:1632-1646, 1998. Copyright 1998, American Heart Association.

SK=streptokinase; t-PA=recombinant tissue-type plasminogen activator (alteplase); SAK=recombinant staphylokinase; TNK-tPA=TNK variant of tissue-type plasminogen activator; r-PA=reteplase.

*Most frequently used/tested.

With the exception of SK and t-PA, the need for concomitant heparin has not been formally tested.

Figure 35-28 Molecular structure of alteplase (t-PA), lanoteplase (n-PA), reteplase (r-PA), and tenecteplase. Streptokinase is the least fibrin-specific thrombolytic agent in clinical use; the progressive increase in relative fibrin specificity for the various thrombolytics is shown at the bottom. *(Modified from Brener SJ, Topol EJ: Third-generation thrombolytic agents for acute myocardial infarction. In Topol EJ [ed]: Acute Coronary Syndromes. New &York, Marcel Dekker, Inc., 1998, p. 169.)*

bolus and double infusion technique by which accelerated dose t-PA is administered.[276]

RETEPLASE (rPA).

This is a recombinant deletion mutant form of t-PA lacking the finger, epidermal growth factor, and kringle 1 domains as well as the carbohydrate side chains (see Fig. 35-28 and Table 35-6) . After a series of four phase II angiographic trials were performed (GRECO,[280] GRECO-DB,[281] Recombinant Plasminogen Activator Angiographic Phase II International Dose Finding Study [RAPID]-1,[282] RAPID-2[283]), it was determined that the optimum dose and administration schedule for reteplase was 10 + 10 units delivered as two separate intravenous boluses separated by 30 minutes. The TIMI 3 flow rate with a 10 + 10-unit regimen of reteplase was 51.2 percent at 60 minutes and 59.5 percent at 90 minutes compared with 37.4 percent and 45.2 percent at 60 and 90 minutes, respectively, for 100 mg of accelerated dose t-PA.[283]

The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial was the first equivalence trial in the field of thrombolytic therapy for STEMI.[284] A total of 6010 patients were randomized to a double bolus 10 + 10-unit reteplase regimen given 30 minutes apart or 1.5 million units of streptokinase over 60 minutes. Mortality at 35 days was 9.02 percent in the reteplase group and 9.53 percent in the streptokinase group. The 95 percent confidence intervals of the differences in mortality range from -1.98 percent to 0.96 percent, satisfying the prespecified definition for equivalence between reteplase and streptokinase. The intracranial hemorrhage rate with reteplase was 0.77 percent compared with 0.37 percent for streptokinase.

The GUSTO III trial compared the 10 + 10-unit regimen of reteplase with accelerated t-PA in 15,059 patients.[20] The 30-day mortality rate was 7.47 percent in the reteplase group and 7.24 percent in the t-PA group, corresponding to an absolute difference of 0.23 percent, with a 95 percent confidence interval of -0.66 percent to +1.1 percent (Fig. 35-29) . The results of GUSTO III did not demonstrate superiority of reteplase over t-PA;

using a 1 percent absolute difference as a boundary for equivalence, the mortality results also do not formally demonstrate equivalence. [278] [279] The intracranial hemorrhage rate was 0.91 percent with reteplase and 0.87 percent with t-PA. The secondary composite endpoint of net clinical benefit (death or disabling stroke) was 7.89 percent with reteplase and 7.91 percent with accelerated t-PA.

Although GUSTO III did not fulfill formal criteria for equivalence of reteplase and t-PA, many clinicians consider the two agents to be therapeutically similar and consider the double bolus method of administration of reteplase to be an advantage over t-PA.

LANOTEPLASE.

Lanoteplase (nPA, novel plasminogen activator) is a mutant of t-PA lacking the finger and epidermal growth factor domains and also containing an amino acid substitution in the kringle 1 domain, leading to deletion of a glycosylation site (see Fig. 35-28 and Table 35-6) . The phase II dose-ranging angiographic trial InTIME I suggested that lanoteplase at a dose of 120 kU/kg was superior to accelerated dose t-PA in that the TIMI 3 flow rate at 90 minutes was 57.1 percent with lanoteplase versus 46.4 percent with t-PA.[285] InTIME II was a phase III double-blind equivalence trial in 15,078 patients comparing 120 kU/kg of lanoteplase with 100 mg of accelerated dose t-PA. The 30-day mortality was 6.61 percent in the t-PA group and 6.75 percent in the lanoteplase group[21] (relative risk 1.02; $p = 0.075$ for equivalence) (Fig. 35-29) . The intracranial hemorrhage rate was 0.64 percent for t-PA and 1.12 percent for lanoteplase ($p = 0.004$).

TENECTEPLASE.

Tenecteplase (TNK-t-PA) is a mutant of t-PA with specific amino acid substitutions in the kringle 1 domain and protease domain introduced to decrease plasma clearance, increase fibrin specificity, and reduce sensitivity to PAI-1[286] (see Fig. 35-28 and Table 35-6) . The phase II angiographic dose-ranging studies TIMI 10A and TIMI 10B defined the optimum dose of tenecteplase with respect to efficacy.[287] [288] A single bolus of 40 mg of tenecteplase over 5 to 10 seconds was associated with a 63 percent rate of TIMI 3 flow at 90 minutes; 50 mg of tenecteplase

Figure 35-29 Mortality rates in trials of bolus thrombolytics. A 30-day mortality rate was similar in patients receiving the bolus thrombolytics in the trials shown compared with patients receiving the accelerated dose regimen of tissue plasminogen activator. *(Adapted from data in [1] The Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO III] Investigators. N Engl J Med 337:1118-1123, 1997. [2] Neuhaus KL: InTIME-2 results. Presented at the Scientific Sessions of the American College of Cardiology, New Orleans, March 9, 1999; and [3] Assessment of the Safety and Efficacy of a New Thrombolytic [ASSENT-2] Investigators. Lancet 354:716-722, 1999.)*

produced a 66 percent TIMI 3 flow rate. An analysis comparing the weight-adjusted

dose of tenecteplase compared with TIMI 3 flow indicated that a dose of 0.53 mg/kg was optimal for achieving high rates of TIMI 3 flow.[288]

The safety of tenecteplase was evaluated in both TIMI 10B and another large phase II clinical trial called ASSENT 1.[289] Initially, tenecteplase doses of 30, 40, and 50 mg were tested in ASSENT 1, but the 50-mg dose was discontinued and replaced by the 40-mg dose because of increased bleeding observed in the TIMI 10B study. An overall rate of intracranial hemorrhage of 0.77 percent was observed in the total ASSENT 1 study population. Observations made in the combined data set of TIMI 10B and ASSENT 1 suggested that a reduction in the dose of adjunctive unfractionated heparin was associated with a reduction in the risk of intracranial hemorrhage.

ASSENT 2 was a randomized double-blind phase III equivalence trial comparing single-bolus tenecteplase with accelerated dose t-PA in 16,949 patients.[22] The 30-day mortality rate with tenecteplase was 6.179 percent and with t-PA 6.151 percent (p = 0.0059 for equivalence) (see Fig. 35-29) . The rate of intracranial hemorrhage was 0.93 percent with tenecteplase and 0.94 percent with t-PA. Major bleeding occurred in 4.66 percent of tenecteplase-treated patients compared with 5.94 percent of t-PA-treated patients (peak was 0.0002). There was no specific subgroup of patients in whom tenecteplase or t-PA was significantly better, with the exception of patients treated after 4 hours from the onset of symptoms in whom the mortality rate was 7.0 percent with tenecteplase and 9.2 percent with t-PA (p = 0.018).

OTHER THROMBOLYTIC AGENTS.

SPB, a naturally occurring plasminogen activator, has been undergoing evaluation for treatment of AMI for at least three decades. Although it offers the potential advantage of less antigenicity than that with streptokinase, infarct artery patency rates are about the same as those achieved with streptokinase. Although it is prescribed in an intravenous regimen for AMI in some countries, given its high cost and lack of advantage over streptokinase, its use in the United States is almost exclusively for intracoronary infusion (6000 IU/min to an average cumulative dose of 500,000 IU) to lyse intracoronary thrombi that are believed to be responsible for an evolving AMI. Anistreplase, usually administered in a dose of 30 mg over 2 to 5 minutes intravenously, has a side effect profile similar to that of streptokinase, a patency profile similar to that of conventional-dose t-PA, and a mortality benefit similar to that of streptokinase or t-PA (double-chain form, duteplase). The lack of any compelling advantages (other than bolus administration) and costs higher than streptokinase have relegated anistreplase to an extremely infrequently prescribed drug for AMI in the United States.

SPB (scuPA or prourokinase) has been produced both in nonglycosylated (e.g., saruplase) and glycosylated (e.g., Abbott-74187) forms. Angiographic studies of saruplase (PRIMI,[290] Saruplase and Urokinase in the Treatment of Acute Myocardial Infarction [SUTAMI][291] , Study in Europe with Saruplase and Alteplase in Myocardial Infarction [SESAMI][292]) have shown it to have thrombolytic efficacy similar to streptokinase, urokinase, and a 3-hour infusion of t-PA; and the Practical Applications of Saruplase Study (PASS) suggested it could be administered safely (intracranial hemorrhage rate of 0.5 percent in 1698 patients).[276] [293] In the Comparison Trial of

Saruplase and Streptokinase (COMPASS), the 30-day mortality was 5.8 percent for saruplase versus 6.7 percent for streptokinase; intracranial hemorrhage occurred in 0.9 percent of saruplase patients and 0.3 percent of streptokinase patients.[294] In the Bolus versus Infusion in Rescuepase Development (BIRD) trial, single-bolus administration of saruplase, 80 mg, was found to be similar to a 1 hour infusion.[295]

Staphylokinase.

This is a highly fibrin-specific plasminogen activator that requires priming on the surface of a clot.[296] (see Table 35-6) . Recombinant forms of staphylokinase have shown high degrees of thrombolytic efficiency (STAR trial[297]), and dose-ranging studies are the ongoing Collaborative Angiographic Patency Trial of Recombinant Staphylokinase [CAPTORS].[298] Of concern is the fact that recombinant staphylokinase is highly antigenic, which may limit its use beyond a single administration unless pegilated variants with reduced immunogenicity prove to be clinically safe and effective.

Effect on Left Ventricular Function

Although precise measurements of infarct size would be an ideal endpoint for clinical reperfusion studies, such measures have been found to be impractical. Attempts to use LV ejection fraction as a surrogate for infarct size have not been productive because little difference is seen in ejection fraction between treatment groups that show a significant difference in mortality. Alternative methods of assessing left ventricular function, such as end-systolic volume[299] or quantitative echocardiography,[300] are more revealign because patients with smaller volumes and better-preserved ventricular shape have an improved survival.

As with survival, improvement in global LV function is related to the time of thrombolytic treatment, with greatest improvement occurring with earliest therapy. Greater improvement in left ventricular function has been reported with anterior than with inferior infarcts. Earlier trials failed to demonstrate any difference in global left ventricular function when streptokinase and t-PA were compared.[301] The angiographic substudy in GUSTO I reported detailed regional wall motion analyses stratified by thrombolytic regimen.[238] Patients who received the accelerated t-PA regimen had significantly less depression of regional wall motion in the ischemic zone, as evidenced by fewer abnormal chords when their ventricular silhouettes were subjected to segmental wall motion analysis. In addition, this patient group tended to have a slightly higher global ejection fraction and slightly reduced end-systolic volume index at 90 minutes after initiation of thrombolytic therapy. The totality of the data presented in the GUSTO angiographic substudy[238] is consistent with the hypothesis that more rapid and complete restoration of normal coronary blood flow in the infarct-related artery with t-PA was associated with an improvement in regional and global left ventricular function (presumably through greater myocardial salvage in the ischemic zone) and that this difference in function compared with that obtained with streptokinase may have contributed to the mortality differences observed at 30 days and beyond.

Complications of Thrombolytic Therapy

Recent (< 1 year) exposure to streptococci or streptokinase produces some degree of antibody-mediated resistance to streptokinase (and anistreplase) in most patients. Although this is of clinical consequence only rarely, it is recommended that patients not receive streptokinase for AMI if they have been treated with a streptokinase product within the past year. Bleeding complications are, of course, the most common and potentially the most serious. Most bleeding is relatively minor with all agents, with more serious episodes occurring in patients requiring invasive procedures.[302] [303] Overall, 70 percent of bleeding episodes occur at the site of vascular punctures.[302] [303] [304] Intracranial hemorrhage is the most serious complication of thrombolytic therapy[305] [306] ; its frequency varies with the clinical characteristics of the patient and the thrombolytic prescribed[306] [307] (Table 35-7) .

Collaborators from the European Cooperative Society Group (ECSG) and GISSI, TAMI, TIMI, and ISAM groups pooled their respective data bases on thrombolytic-treated patients with AMI to develop a statistical model for individual risk assessment for intracranial hemorrhage using a case-control format.[307] The following four clinical variables known at hospital admission were shown to predict an increased risk of intracranial hemorrhage: age older than 65 years (odds ratio for intracranial hemorrhage = 2.2), weight less than 70 kg (2.1), hypertension on presentation (2.0), and use of t-PA as opposed to streptokinase (1.6). Assuming an overall incidence of intracranial hemorrhage of 0.75 percent, the expected incidence of intracranial hemorrhage stratified by the number of risk factors would be 0.26 percent for no risk factors, 0.96 percent for one risk factor, 1.32 percent for two risk factors, and 2.17 percent for three risk factors. The incremental incidence of intracranial hemorrhage with thrombolysis appears to be at least partially

TABLE 35-7 -- INTRACRANIAL HEMORRHAGE IN RECENT THROMBOLYTIC TRIALS WITH TISSUE PLASMINOGEN ACTIVATORS

PATIENT CHARACTERISTICS	GUSTO-I	GUSTO-II	COBALT	GUSTO-III	ASSENT-2	IN TIME-II
Number	41,021	3473	7169	15,059	16,950	15,078
Average age (yr)	62	62.5	62.4	63		
>75 yr (%)	10.5	11.8	13.0	13.6		
Female (%)	25.2	22.4	23.4	27.4		
Intracranial hemorrhage rates						

SK	0.51	0.37	Double bolus 1.12	0.87	0.94	0.64
t-PA	0.70	0.72	Accl infusion 0.81			
t-PA				0.91		
TNK-tPA		0.70	0.72		0.94	
nPA						1.13

Accl=accelerated; nPA=lanoteplase; rPA=reteplase; TNK-tPA=a genetically engineered variant of t-PA; t-PA=recombinant tissue-type plasminogen activator; SK=streptokinase.

Modified from Ryan TJ, Antman EM, Brooks NH, et al: 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 100:1016-1030, 1999. Copyright 1999, American Heart Association.

offset by a lower frequency of thrombotic strokes, so that the overall incidence of stroke is usually not much higher in patients receiving thrombolytic therapy than in control patients.[229] [305] [308] Gurwitz and colleagues analyzed 71,073 patients in the National Registry of Myocardial Infarction 2 who had received t-PA for AMI.[309] Multivariable analysis indicated the following patient characteristics were associated with an increased risk of intracranial hemorrhage: older age, female sex, black ethnicity, systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, history of stroke, t-PA dose more than 1.5 mg/kg, and a low body weight (Table 35-8) .

There have been reports of an "early hazard" with thrombolytic therapy, that is, an excess of deaths in the first 24 hours in thrombolytic-treated patients compared with controls (especially in elderly patients treated >12 hours).[15] However, this excess early mortality is more than offset by the deaths prevented beyond the first day, culminating in an 18 percent (13 to 23 percent) reduction in mortality by 35 days.[15] The mechanisms responsible for this early hazard are not clear but probably are multiple, including an increased risk of myocardial rupture (particularly in the elderly), fatal intracranial hemorrhage,[305] inadequate myocardial reperfusion resulting in pump failure and cardiogenic shock,[310] and possible reperfusion injury of reperfused myocardium.[205] Reports of more unusual complications such as splenic rupture, aortic dissection, and cholesterol embolization have also appeared.

Recommendations for Thrombolytic Therapy

NET CLINICAL BENEFIT OF THROMBOLYSIS.

Perhaps one of the most important messages from all of the available evidence is that

thrombolytic therapy is underused in patients with AMI.[311] Hesitancy in prescribing a thrombolytic agent is often the result of uncertainty about the risk of bleeding, and analysis from GUSTO-1 shows that moderate to severe bleeding occurred more often in patients who were older, female, lighter, shorter, and of African ancestry and who underwent an invasive procedure.[312] The specific profile of patients at risk for intracranial hemorrhage was discussed previously. Patients with a higher baseline risk of mortality are more likely to benefit from thrombolytic therapy.

Against the mortality benefit associated with thrombolytic therapy must be weighed the excess risk of stroke. By using the net clinical benefit composite endpoint of 30-day mortality or nonfatal stroke, a small but statistically significant benefit is seen for accelerated dose t-PA compared with streptokinase. Given the data from the GUSTO-3 and Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2 trials, it appears that the net clinical benefit of accelerated dose t-PA is similar to that obtained with reteplase or tenecteplase.[20] [22] Of interest, the rate of noncerebral major bleeding was lower with tenecteplase than t-PA in the ASSENT-2 trial, possibly due to the greater fibrin specificity of tenecteplase.[22]

CHOICE OF AGENT.

Analysis of the net clinical benefit and cost-effectiveness of t-PA versus streptokinase does not easily yield recommendations for treatment because clinicians must weigh the risk of mortality and risk of intracranial hemorrhage when confronting a thrombolytic-eligible patient with AMI; additional considerations may be the constraints placed on physicians' therapeutic decision-making

TABLE 35-8 -- ADJUSTED ODDS RATIOS RELATING PATIENT CHARACTERISTICS TO INTRACRANIAL HEMORRHAGE

CHARACTERISTIC	ADJUSTED ODDS RATIO (95%CI)
Age	
< 65 yr	1.00
65-74 yr	2.71
	4.34
75 yr	
Sex	
Male	1.00
Female	1.59
Ethnicity	
White	1.00
Black	1.70
History of stroke	
No	1.00

Yes	1.90
Systolic blood pressure	
< 140 mm Hg	1.00
140-159 mm Hg	1.33
160 mm Hg	1.48
Diastolic blood pressure	
< 80 mm Hg	1.00
80-99 mm Hg	1.09 (*p*=NS)
100 mm Hg	1.40
Dose of tissue plasminogen activator	
< 1.5 mg/kg	1.00
1.5 mg/kg	1.49

Modified from Gurwitz JF, Gore JM, Goldberg RJ, et al: Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. Participants in the National Registry of Myocardial Infarction 2. Ann Intern Med 129:597-604, 1998.

by the health care system in which they are practicing.[313] We are in agreement with the general recommendations by Martin and Kennedy[193] and Simoons and Arnold[314] that categorize patients into those that are at high risk of death (advanced age, female gender, depressed left ventricular function, anterior MI, bundle branch block, total magnitude of ST segment elevation, diabetes, heart rate greater than 100 beats/min, systolic pressure less than 100 mm Hg, long delay since onset of ischemic discomfort),[193] [314] and high risk of intracranial hemorrhage. In the subgroup of patients presenting within 4 hours of symptom onset, the speed of reperfusion of the infarct vessel is of paramount importance, and a high-intensity thrombolytic regimen such as accelerated t-PA or tenecteplase is the preferred treatment, except in those individuals in whom the risk of death is low (e.g., a young patient with a small inferior MI) and the risk of intracranial hemorrhage is increased (e.g., acute hypertension), in whom streptokinase and accelerated t-PA are approximately equivalent choices. Of note, for those patients presenting between 4 and 12 hours from symptom onset with a low mortality risk but an increased risk of intracranial hemorrhage (e.g., elderly patients with inferior MI, blood pressure greater than 100 mm Hg, and heart rate less than 100 beats/min), streptokinase is probably preferable to t-PA because of cost considerations if thrombolytic therapy is prescribed at all in such a patient.

In those patients considered appropriate candidates for thrombolysis and in whom t-PA would have been selected as the agent of choice in the past, we believe clinicians should now consider using a bolus thrombolytic such as reteplase or tenecteplase. The rationale for this recommendation is that bolus thrombolysis has the advantage of ease of administration and a lower chance of medication errors (and the associated increase in mortality when such medication errors occur) and also offers the potential for prehospital thrombolysis.

LATE THERAPY.

No mortality benefit was demonstrated in the LATE and EMERAS trials when thrombolytics were routinely administered to patients between 12 and 24 hours,[265] [266] although we believe it is still reasonable to consider thrombolytic therapy in appropriately selected patients with persistent symptoms and ST segment elevation on ECG beyond 12 hours (see Fig. 35-17) . Persistent chest pain late after the onset of symptoms correlates with a higher incidence of collateral or antegrade flow in the infarct zone and is therefore a marker for patients with viable myocardium that might be salvaged.[315] Because elderly patients treated with thrombolytics more than 12 hours after the onset of symptoms are at increased risk of cardiac rupture, it is our practice to restrict late thrombolytic administration to younger patients (<65 years) with ongoing ischemia, especially those with large anterior infarctions. The elderly patient with ongoing ischemic symptoms but presenting late (>12 hours) is probably better managed with direct (primary) PTCA (discussed subsequently) than with thrombolytic therapy.

Before the institution of thrombolytic therapy, consideration should be given to the patient's need for intravascular catheterization, as would be required for the placement of an arterial pressure monitoring line, a pulmonary artery catheter for hemodynamic monitoring, or a temporary transvenous pacemaker. If any of these are required, ideally they should be placed as expeditiously as possible *before* infusion of the thrombolytic agent. If such procedures require an additional delay of more than 30 minutes, they should be deferred as long as possible after thrombolytic therapy is begun. In the early hours after institution of thrombolytic therapy, such catheterization should be performed only if crucial to survival, and then sites where excessive bleeding can be controlled should be chosen (e.g., subclavian vein catheterization should be avoided).

As noted earlier, all patients with suspected AMI should receive aspirin (160 to 325 mg) regardless of the thrombolytic agent prescribed. Aspirin should be continued indefinitely. The issues surrounding antithrombin therapy as an adjunct to thrombolysis are complex and are discussed in detail in a subsequent section (see p. 1162).

CATHETER-BASED REPERFUSION (See also Chap. 38)

It is now established that reperfusion can be achieved by emergency percutaneous coronary intervention (PCI). By using a guidewire and balloon catheter, it is technically easier to cross a total occlusion consisting of a fresh thrombus than to cross a long-standing occlusion of a coronary artery. Thus, wire-guided balloon angioplasty can be useful to achieve reperfusion in two quite different circumstances: (1) in lieu of

thrombolytic therapy where it is referred to as *direct* or *primary angioplasty*[316] and (2) as adjunctive therapy with thrombolysis or as a management strategy in the subacute phase of AMI (days 2 to 7) in patients who do not receive thrombolysis. Several clinical scenarios have been described that represent different categories of use of PCI when it is not selected as the primary reperfusion strategy. When thrombolysis has failed to reperfuse the infarct vessel or a severe stenosis is present in the infarct vessel, a *rescue PCI* may be performed as soon as possible. Alternatively, strategies of empirical *immediate* (i.e., performed urgently within a few hours) or *deferred* (i.e., performed within the first week) PCI have been proposed for all patients with residual critical stenosis (> 70 percent of lumen diameter) who receive thrombolysis. Finally, a more conservative approach of *elective* PCI may be used to manage AMI patients only when spontaneous or exercise-provoked ischemia occurs whether or not they have received a previous course of thrombolytic therapy.

Catheter-based strategies for reperfusion of the occluded infarct-related artery in patients with AMI is a rapidly evolving field. Coronary artery stenting, originally introduced for elective percutaneous procedures, was originally withheld in patients with AMI because of concerns over acute stent thrombosis. However, with advances in stent deployment (high pressure inflations, intravascular ultrasound guidance), improvements in antiplatelet therapy (GPIIb/IIIa inhibitors) and operator experience have fueled interest in primary coronary artery stenting as a new catheter-based strategy for reperfusion.[316] [317]

Primary Angioplasty

ADVANTAGES.

An important advantage of primary PCI in AMI is the ability to achieve reperfusion of the infarct vessel without the risk of bleeding associated with thrombolytic therapy. In addition, primary PCI (performed predominantly in experienced centers) as compared with thrombolytic therapy has been shown in several randomized trials and registries to yield higher patency rates of the infarct vessel both at 90 minutes (85 to 90 percent for PCI vs. 65 percent for thrombolysis).[238] [273] [318] Systematic overviews of trials of primary PTCA versus thrombolysis collectively enrolling 2635 patients revealed lower 30-day and 6-month mortality rates for patients treated with primary PTCA versus thrombolysis[319] [320] (Fig. 35-30) . The rate of recurrent infarction was also lower for patients treated with primary PTCA[320] (see Fig. 35-30) . Primary PTCA was also associated with significant reductions in total stroke and hemorrhagic stroke. Thus, primary PCI appears to be superior to thrombolytic therapy when it is performed in experienced

Figure 35-30 Comparison of mortality and reinfarction in AMI patients treated with thrombolysis vs. primary percutaneous transluminal coronary angioplasty (PTCA). Pooled data from 11 randomized trials

revealed significant reductions in the 30-day and 6-month rates of mortality and reinfarction in patients treated with primary PTCA. *(Adapted from Grines CL, Ellis SG, Jones M, et al: Primary coronary angioplasty vs. thrombolytic therapy for acute myocardial infarction (MI): Long term follow-up of ten randomized trials. Circulation [Suppl] I-499, 1999.)*

centers with a well-staffed invasive angiography team. It is also associated with a shorter length of hospital stay and reduced costs because of fewer patients with recurrent ischemia and recurrent MI when treated with primary PCI.[321] [322]

Primary PCI appears to have a particular advantage over thrombolysis for the management of high-risk AMI patients such as diabetics and the elderly.[323] [324] In an analysis of Medicare patients in the Cooperative Cardiovascular Project data base, primary PCI was associated with improved 30-day survival (hazard ratio 0.74, 95 percent confidence interval 0.63-0.88) and also 1-year survival (hazard radio 0.88, 95 percent confidence intervals 0.73-0.94).[325] The benefits of primary PCI in the elderly persisted after stratification by the volume of AMI patients cared for at individual hospitals and the presence of on-site angiography.

Why have these dramatic differences favoring primary PCI over thrombolytic therapy been observed? In addition to the high level of technical expertise in the dedicated centers that have reported promising results with primary PCI, differences in the adequacy of reperfusion and responses of ischemic myocardium to restoration of flow by thrombolysis and mechanical means should be considered. Early patency of the infarct-related artery is higher with direct PCI, full reperfusion (TIMI grade 3 flow) is higher, the degree of residual stenosis is less, reocclusion rates are lower,[273] and collateral flow to non-infarct-related myocardial zones is probably increased--all features that promote better healign in the infarct zone, less left ventricular dilatation, and reduced morbidity and mortality.[326] [327] [328] Mechanical recanalization of the infarct vessel does not produce the interstitial edema, contraction band necrosis, and microvascular hemorrhage seen with thrombolytic therapy (see Figs. 35-8 and 35-9) .

OBSTACLES TO IMPLEMENTATION.

The clinical trial results and intriguing experimental observations cited earlier must be placed in perspective when one considers implementing primary PCI as a treatment strategy for the majority of patients with AMI. Because PCI is performed only in patients with suitable angiographic anatomy, a bias may have been introduced in the available data bases excluding patients at higher risk of events from being treated by PCI.[329] The MITRA Registry of 54 university and community hospitals in Germany found that in clinical practice patients treated with primary PTCA are more often given beta blockers and ACE inhibitors than patients treated with thrombolytics, drug treatment practices that could contribute to a reduction in mortality that is not a direct result of PTCA.[330] Although reports from individual community hospitals replicating the results in randomized trials can be found in the literature, fewer than 20 percent of hospitals in the United States and less than 10 percent of hospitals in Europe can perform primary PCI, and an even smaller proportion are capable of performing it on an emergency basis 24 hours a day, 7 days a week.[331]

It remains to be determined whether lower-volume PCI centers with less-experienced investigators can replicate the encouraging results reported to date. In addition, it is unclear whether on-site cardiac surgical backup is a necessary component of a primary PCI strategy for AMI.[332] The problem of lack of on-site surgical backup is being evaluated in studies such as Air PAMI in which patients who present to a community hospital that does not perform primary PCI and who are thrombolytically eligible with at least one high-risk criterion are randomized to either immediate intravenous thrombolysis or emergency transfer for PCI.[333] The randomized population in Air PAMI will be compared with a separate registry of Air PAMI-eligible patients who have PCI performed in hospitals with catheterization laboratories but no on-site surgery (No S.O.S. Registry).[333] Preliminary results from the No S.O.S. Registry are encouraging in that the in-hospital death rate was 2.7 percent and the stroke rate was 2.7 percent in 500 patients.[332] The PRAGUE study compared the incidence of death/MI/stroke at 30 days in a randomized trial of aspirin plus streptokinase with management in a community hospital (Group A); aspirin plus streptokinase with transfer to a nearby interventional center (Group B); and aspirin plus heparin (10,000 U) with transfer to a nearby interventional center (Group C). All patients received fraxiparine for 3 days and ticlopidine for 1 month.[334] There were no deaths during or within 30 minutes of transport. The primary composite endpoint occurred in 23 percent of group A, 15 percent of group B, and 8 percent of group C patients, respectively ($p < 0.02$), indicating that interhospital transport for primary PCI is feasible and safe and may be associated with a lower event rate after AMI. The potential cost implications of offering primary PCI to all eligible patients with AMI are staggering and have been the subject of considerable ongoing debate in several countries.[316]

Primary Stenting

Although it has been agreed that primary PTCA has an advantage over thrombolysis in AMI patients with a prior CABG, observations from the National Registry of Myocardial Infarction (NRMI)-2 suggest the outcome is similar to the two reperfusion strategies.[335] Interventionalists have begun to embrace new strategies such as stenting and intravenous GPIIb/IIIa inhibitors (see Chap. 38) to improve on results with PTCA in AMI. Experience gained with elective coronary stenting (see Chap. 38) led to a series of reports of implantation of coronary stents in AMI patients.[336] A high procedural success rate was reported and the subacute thrombosis rate was low (< 3 percent), largely due to aggressive use of antiplatelet therapy with aspirin and ticlopidine. Table 35-9 summarizes major randomized trials of primary stenting versus primary PTCA in AMI. In general, the procedural success rate was high with both stenting and PTCA. Of interest, in the largest of the trials, PAMI-STENT, a slightly lower rate of TIMI grade 3 flow was seen with stenting compared with PTCA, raising the possibility of embolization of platelet aggregates at the time of stent deployment.[337] Mortality rates were generally low, with

TABLE 35-9 -- RANDOMIZED TRIALS OF PRIMARY STENT PLACEMENT VS. PRIMARY PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) IN ACUTE MYOCARDIAL INFARCTION

	ESCOBAR	FRESCO	GRAMI	PASTA	PRISAM	PAMI-STENT
No. of patients						
Stent	112	75	52	67	39	452
PTCA	115	75	52	69	49	448
Enrollment criteria	6 hr after symptoms onset; 6-24 hr of persistent symptoms	6 hr after symptoms onset; 6-24 hr of persistent symptoms; ST segment elevation	< 30 min after symptoms onset; ST segment elevation; 24 hr after symptoms onset; 75 years old	12 hr after symptom onset	24 hr after symptom onset	12 hr after symptom onset
Randomization criteria	Lesion suitable for stenting	Optimal PTCA result	Lesion suitable for stenting	Lesion suitable for stenting	Lesion suitable for stenting	Lesion suitable for stenting
Length of follow-up	6 mo	6 mo	1 yr	1 yr	6 mo	30 d
Crossover (bailout), No. (%)	15 (13)	0 (0)	13 (25)			68 (15.1)
TIMI grade 3 flow, %						
Stent		100	98 $p<0.03$			88.9
PTCA			99	83		92.7
Mortality, %[*]						
Stent	2	1	3.8	4.8	0	3.5
PTCA	3	0	7.6	9.1	0	1.8
Target vessel revascularization, %						
Stent	4 $p=0.0016$	7 $p=0.002$	14 p=NS	18.6 $p=0.009$	11 $p=0.01$	0.9 $p=0.006$
PTCA	17	25	21	37.6	36	3.5

From Every NR: Thrombolysis and Interventional Therapy in Acute Myocardial Infarction. Presented at the George Washington University 15th International Workshop on Thrombolysis and Interventional Therapy in Acute Myocardial Infarction, November 6, 1999, Atlanta, GA.

*All differences in mortality are nonsignificant.

slight nonsignificant trends favoring stenting. The major benefit of stenting was seen in a significant reduction in the incidence of the subsequent target vessel revascularization.[337]

Angioplasty as an Adjunct to Thrombolysis

Ellis and associates have summarized the heterogeneous outcomes reported in observational series of *rescue* PTCA after failed thrombolysis. Although procedural success was obtained in about 80 percent of patients, the average rate of reocclusion was 18 percent and the average mortality was 10.6 percent. The RESCUE trial focused on the subset of AMI patients with an anterior infarction and reported a reduction in the composite endpoint of death or congestive heart failure by 30 days in the PTCA group.[338]

After thrombolytic therapy, the majority of patients are found to have a significant residual stenosis.[338A] Even in patients who clinically appear to have reperfused, PTCA, whether applied immediately or deferred, has the theoretical benefit of further opening of a stenosed coronary artery to increase flow, perhaps enhancing myocardial recovery and diminishing the possibility of reocclusion. Several trials have compared immediate, early (within several hours to a few days), or deferred (delayed for 4 days) PTCA versus no PTCA, whereas others have compared immediate versus deferred PTCA or immediate versus deferred versus no PTCA. A summary of the design features and main findings of 16 trials that collectively enrolled about 6200 patients in these categories has been published along with meta-analysis of the mortality results.[339] Although none of the individual comparisons of strategies achieved conventional statistical significance, a consistent theme was observed--the *routine empirical* use of PTCA (either immediate or delayed) after thrombolysis was associated with a trend toward *increased* mortality. [339] In addition, there were higher rates of abrupt reclosure of the infarct-related coronary artery and complications, including reinfarction and the need for urgent CABG while providing no benefit in terms of recovery of ventricular function.[340] [341] Possible explanations for the increased hazard associated with PTCA soon after thrombolysis include exacerbation of platelet activation and thrombosis at the site of plaque rupture and increased bleeding, including hemorrhagic dissections of the target vessel.[212] [340] [342] [343]

There is also no evidence to support *empirically deferred* PCI in patients without evidence of recurrent or provocable ischemia. The TOPS trial randomized patients with a negative exercise test several days after thrombolysis to either medical therapy or medical therapy plus PCI. There was no benefit in terms of rest or exercise ejection fraction, but there were disturbing trends toward a higher rate of abrupt vessel closure and non-Q-wave MI acutely and a lower rate of infarct-free survival at 1-year follow-up in the PTCA-treated patients.

Because many of the previous trials of PCI early after full-dose thrombolytics were undertaken during the thrombolytic infusion or shortly thereafter, which potentially contributed to a lower success rate of PCI, higher bleeding, and a trend toward higher rates of adverse outcomes, the Plasminogen-activator Angioplasty Compatibility Trial (PACT) was undertaken.[344] After aspirin and heparin, 606 AMI patients were randomized within 6 hours of symptoms to a 50-mg bolus of t-PA over 3 minutes or placebo followed by angiography and rescue PTCA for less than TIMI 3 flow. Patency of the infarct artery was 61 percent (TIMI 3 = 33 percent, TIMI 2 = 28 percent) in the t-PA group versus 34 percent (TIMI 3 = 15 percent, TIMI 2 = 19 percent) in the placebo group (p = 0.001) before PCI (median of 98 minutes from pharmacological reperfusion). Rescue PCI was successful in over 90 percent of patients in both groups as was left ventricular ejection fraction at 5 to 7 days. However, left ventricular function was significantly higher in those patients achieving TIMI 3 flow by the time of diagnostic angiography and those patients who had rescue PCI within 1 hour of the bolus of the study drug. The rates of major bleeding and reinfarction were similar in the t-PA and placebo groups. Thus, PACT reaffirmed the time-dependent nature of the open artery hypothesis with greater preservation of left ventricular function in patients with earlier attainment of TIMI 3 flow. This trial also showed that a tailored combination of reduced dose lytic and rescue PCI as needed could be performed safely.[345] However, only 26 percent of patients in PACT underwent stenting, and GPIIb/IIIa inhibitors were used in only 5 percent of patients.[344] [346] Whether the improved equipment available now for PTCA, the use of stents,[347] and modified pharmacological reperfusion regimens such as reduced-dose thrombolytics, intravenous GPIIb/IIIa inhibitors, or the combination of reduced dose thrombolytics and GPIIb/IIIa inhibitors (see p. 1164) would swing the evidence in favor of routine angiography followed by catheter-based reperfusion as needed after MI is an intriguing question that needs to be addressed.

Recommendations for Catheter-Based Reperfusion in AMI

It appears that primary PCI, when carried out by experienced interventional cardiologists in high-volume angiography laboratories, is superior to thrombolytic therapy. It is our practice to refer thrombolytic-ineligible patients to primary PCI and also to select primary PCI as the reperfusion method of choice if the patient is at relatively high risk of intracerebral hemorrhage consequent to thrombolytic therapy (see p. 1153), or if the anticipated time to placement of angioplasty catheters is less than 1 hour from the patient's presentation to the emergency department. In the special circumstances of cardiogenic shock, provided no other life-threatening comorbidities are present, we refer patients for revascularization (see p. 1179).

Patients in whom thrombolytic therapy fails to achieve reperfusion represent candidates for rescue PCI, and in such patients this can usually be safe and effective. The practical issue is the difficulty in reliably identifying patients who fail to reperfuse after thrombolytic therapy using noninvasive indices either alone or in combination.[127] [348] [348A] Therefore, until there are better ways to recognize patients who might benefit from "rescue PCI," the question of optimal treatment of thrombolytic failure remains unresolved. However, we consider patients with evolving chest pain and ST segment elevations that persist for 90 minutes after the onset of administration of a thrombolytic agent to be candidates for emergency catheterization and, if the infarct-related vessel is occluded, for rescue PCI. Elective PCI can be considered for most patients receiving thrombolytic therapy in whom ischemia develops at rest, during ambulation in the hospital, or during a prehospital discharge exercise test.[349] We do not consider it necessary to carry out routine coronary arteriography on asymptomatic patients with negative prehospital discharge exercise tests to identify patients who have severe obstruction in whom PCI can be performed.

Although some reports suggested that prophylactic intraaortic balloon counterpulsation may be useful to maintain vessel patency after PCI, subsequent randomized trials in high-risk patients showed that balloon counterpulsation did not decrease the rates of infarct-related artery reocclusion or reinfarction, promote myocardial recovery, or

improve overall clinical outcome.[350] We believe that intraaortic balloon pumping should be reserved for hemodynamically unstable patients.[351]

SURGICAL REPERFUSION

There have been extensive improvements in intraoperative myocardial preservation with cardioplegia and hypothermia and in surgical techniques. These have allowed surgical reperfusion in patients with AMI to be carried out at quite low short- and long-term mortality rates--approximately 2 percent in hospital and 25 percent 10-year mortality rates in selected centers. This has kept alive the concept of emergency coronary revascularization as a possible measure to protect jeopardized myocardium in patients suffering AMI.[352] As appears to be the case for all methods designed to limit infarct size, salvage of myocardium is most successful if surgery is performed within the first 4 to 6 hours of the onset of the acute event. In the usual patient who develops an AMI outside the hospital, it is logistically almost impossible to bring the patient to the hospital, carry out a clinical evaluation, outline the coronary anatomy by arteriography, assemble the surgical team, commence operation, and place the patient on cardiopulmonary bypass in less than 4 to 6 hours after the onset of the event. It is therefore unlikely that surgical reperfusion can or will be applied in the *routine* treatment of AMI. Indeed, the operation is contraindicated in patients with uncomplicated transmural infarcts more than 6 hours after the onset of the event. When carried out at this time, surgical reperfusion appears to produce marked hemorrhage into the area of

infarction. In some patients with AMI, including some with cardiogenic shock, infarction appears to occur in a stuttering manner over an interval of several days.[353] Revascularization carried out more than 6 hours after the onset of the event might be of benefit in this group, but this has yet to be rigorously established.

Ten to 20 percent of AMI patients are currently referred for CABG for one of the following indications: persistent or recurrent chest pain despite thrombolysis or PCS, high-risk coronary anatomy (e.g., left main artery stenosis) discovered at catheterization, or a complication of AMI such as ventricular septal rupture or severe mitral regurgitation due to papillary muscle dysfunction. Patients with AMI with continued severe ischemic and hemodynamic instability are likely to benefit from emergency revascularization. PCI with stenting as needed is the preferable technique when revascularization is needed in the first 48 to 72 hours after AMI; surgery should be reserved for those in whom PCI has been unsuccessful or whose anatomy dictates the need for CABG, such as patients with left main or extensive multivessel coronary artery disease.

Patients undergoing successful thrombolysis but with important residual stenoses, who on anatomical grounds are more suitable for surgical revascularization than for PCI, have undergone CABG with quite low mortality (about 4 percent) and morbidity *provided* that they are operated on more than 24 hours after AMI; those patients requiring urgent or emergency CABG within 24 to 48 hours of AMI have mortality rates between 15 and 20 percent.[352] When surgery is performed under urgent conditions with active and ongoing ischemia or cardiogenic shock, operative mortality rises steeply. At autopsy, such patients have extensive myocardial necrosis that is often hemorrhagic. Patients who are referred urgently for CABG within 6 to 12 hours of receiving a thrombolytic should receive aprotinin and fresh-frozen plasma to correct their coagulation system deficit and minimize the requirements for blood transfusion (see Chap. 60) . Although postoperative chest tube drainage with relatively minor bleeding occurs more commonly than after elective bypass surgery, this problem is not of major concern.

ANTITHROMBOTIC AND ANTIPLATELET THERAPY (See also Chap. 62)

Antithrombotic Therapy

Despite more than 30 years of active clinical investigation, the use of antithrombotic agents after AMI remains controversial. The rationale for administering heparin acutely in AMI includes prevention of deep venous thrombosis, pulmonary embolism, ventricular thrombus formation, and cerebral embolization. In addition, establishing and maintaining patency of the infarct-related artery, whether or not a patient receives thrombolytic therapy, is another common rationale for heparin therapy in AMI.

EFFECT ON MORTALITY.

Randomized trials in AMI conducted in the prethrombolytic era (between 1969 and 1973) showed that the risks of pulmonary embolism, stroke, and reinfarction were reduced in patients who received intravenous heparin. This formed the basis for the use

of heparin in AMI patients not treated with thrombolytic therapy. With the introduction of the thrombolytic era and importantly after the publication of the Second International Study of Infarct Survival (ISIS-2),[308] the situation became more complicated because of strong evidence of a substantial mortality reduction with aspirin alone and confusing and conflicting data regarding the risk-benefit ratio of heparin used as an adjunct to aspirin or in combination with aspirin and a thrombolytic agent (Table 35-10) .

In the SCATI trial of streptokinase for AMI, in which patients were randomized to receive either delayed subcutaneous heparin or placebo as the *sole* adjunctive therapy (i.e., no aspirin), there was a trend toward lower mortality in the heparin group. In the combined data set of GISSI-2 and ISIS-3 (totalign over 62,000 patients), the 35-day mortality was 10.0 percent in the patients receiving subcutaneous heparin versus 10.2 percent in the patients not receiving any subcutaneous heparin. In addition, in the GUSTO study, no difference was seen in the 35-day mortality rate in patients receiving streptokinase plus subcutaneous heparin (7.2 percent) or intravenous heparin (7.4 percent).[19] Nonrandomized subgroup analyses from the LATE trial of 2821 patients who received t-PA showed a 35-day mortality of 7.6 percent when intravenous heparin was administered, compared with 10.4 percent when no heparin was given.[265] Thus, the available information suggests that intravenous heparin is probably of no benefit in patients receiving streptokinase but may be helpful in patients receiving t-PA.[274] Heparin was administered as adjunctive therapy in randomized trials of reteplase and tenecteplase under the supposition that those agents were more fibrin specific than streptokinase and required concomitant use of heparin.[289] [354]

EFFECT ON PATENCY OF INFARCT ARTERY

A number of angiographic studies have examined the role of heparin in establishing and maintaining patency of the infarct-related artery in patients with AMI. Comparison of these trials is difficult because of potentially important differences in study design, including whether aspirin was administered along with heparin, the thrombolytic agent that was administered, and variations in the time of diagnostic coronary arteriography. The Bleich and coworkers[355] and HART[356] studies showed a higher infarct-related artery patency rate in AMI patients treated with t-PA plus heparin than t-PA plus placebo (71 to 82 percent

TABLE 35-10 -- EFFECTS OF HEPARIN IN THE ABSENCE AND IN THE PRESENCE OF ASPIRIN: OVERVIEW OF 26 RANDOMIZED TRIALS

	TRIALS WITH ROUTINE ASPIRIN (68,000 PATIENTS: 93%ALSO HAD FIBRINOLYTIC AGENT)		
	Aspirin +Heparin (34,053)	**Aspirin Only (34,055)**	**Effect per 1000 Allocated to Aspirin and Heparin**

Death (generally in hospital)	8.6%	9.1%	5±2 less
	2932	3092	(2*p*=0.03)
Reinfarction	3.0%	3.3%	3±less
	1009	1103	(2*p*=0.04)
Stroke	1.2%	1.1%	1±1 more
	397	375	(NS)
Pulmonary embolism	0.3%	0.4%	1±0.4 less
	82	117	(2*p*=0.01)
Major bleed	1.0%	0.7%	3±1 more
	342	234	(2*p*<0.00001)

Modified from Baigent C, Collins R: Aspirin and heparin. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease: Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 60.

vs. 43 to 52 percent infarct-related artery patency at 7 to 72 hours). The European Cooperative Study Group performed angiograms relatively late (i.e., 48 to 120 hours after t-PA) and still showed a somewhat greater patency rate of the infarct-related artery in the heparin-treated patients.[357] The TAMI-3 study suggested that in patients receiving aspirin plus t-PA no patency benefit was achieved by the immediate intravenous administration of heparin and that it could therefore be delayed for at least 60 to 90 minutes after thrombolysis.

Although a slightly better 90-minute infarct-related artery patency rate was observed in the OSIRIS (streptokinase plus aspirin) study in patients who received heparin versus placebo (82 percent patency vs. 72 percent), the GUSTO angiographic substudy[238] showed no benefit of intravenous heparin versus subcutaneous heparin in patients who received streptokinase plus aspirin with respect to 90-minute infarct-related artery patency (60 percent vs. 54 percent). Although preliminary observations suggested that extremely high doses of intravenous unfractionated heparin (300 U/kg) alone were associated with an increase in patency rates of the infarct-related artery, this was not confirmed on follow-up in a larger trial.[358] [359]

EFFECT ON LEFT VENTRICULAR THROMBUS.

Anticoagulant therapy significantly reduces the incidence of echocardiographically documented left ventricular thrombi.[360] These benefits are observed most prominently in patients with anterior MI, particularly those with a large area of wall motion abnormality. In the thrombolytic era, the incidence of left ventricular thrombi is reduced.[361] Although coadministration of heparin does not appear to affect the incidence of left ventricular thrombus formation in patients who receive thrombolytic therapy, the thrombi protrude less into the ventricular cavity when heparin is

administered.

COMPLICATIONS OF ANTITHROMBOTIC THERAPY

Although heparin may induce thrombocytopenia through an immunological mechanism, this is seen only rarely, probably occurring in only 2 to 3 percent of patients.[362] The most serious complication of antithrombotic therapy is bleeding (especially intracranial hemorrhage) when thrombolytic agents are prescribed. Major hemorrhagic events occur more frequently in patients of low body weight, advanced age, female gender, marked prolongation of the activated partial thromboplastin time (> 90 to 100 seconds), and the performance of invasive procedures.[302] [303] [312] [363] Frequent monitoring of the activated partial thromboplastin time (facilitated by use of a bedside testing device) reduces the risk of major hemorrhagic complications in patients treated with heparin. However, during the first 12 hours after thrombolytic therapy, the activated partial thromboplastin time may be elevated from the thrombolytic agent alone (particularly if streptokinase is administered), making it difficult to accurately interpret the effects of a heparin infusion on the patient's coagulation status.

The optimal dose of unfractionated heparin as an adjunct to thrombolysis and its potential causative role in intracranial hemorrhage is unclear. Giugliano and associates examined the data from four sets of trials: (1) TIMI trials studying accelerated t-PA and intravenous heparin, (2) studies with t-PA and intravenous unfractionated heparin in which the heparin regimen was changed during the course of the trial, (3) phase III trials with accelerated dose t-PA and intravenous unfractionated heparin, and (4) trials of new single-bolus thrombolytics.[364] The intracranial hemorrhage rate in the angiographic TIMI trials was nearly double that in the nonangiographic TIMI trials (1.42 percent vs. 0.76 percent). Lower rates of intracranial hemorrhage were observed among studies of t-PA that reduced the dose of unfractionated heparin midtrial (TIMI 9A-9B, 1.87 percent-1.07 percent; GUSTO IIA-IIb, 0.92 percent-0.7 percent; TIMI 10B, 2.80 percent-1.16 percent). The rates of intracranial hemorrhage with accelerated-dose t-PA gradually increased from GUSTO I (0.72 percent) conducted in 1990-1993 to ASSENT 2 (0.94 percent) conducted in 1997-1998. Potential explanations for the increase in intracranial hemorrhage rates over time include enrollment of higher-risk patients and greater ascertainment of intracranial hemorrhage due to increased availability of imaging modalities such as CT and MRI. This trend in intracranial hemorrhage with t-PA was reversed in the InTIME-II trial, which used the lowest dose of heparin and most aggressive activated partial thromboplastin time monitoring and observed an intracranial hemorrhage rate of 0.64 percent. Observations regarding the benefit of a reduction in the dose of intravenous unfractionated heparin with t-PA also were extended to tenecteplase and laneteplase.

NEW ANTITHROMBOTIC AGENTS

Potential disadvantages of unfractionated heparin include dependency on antithrombin III for inhibition of thrombin activity, sensitivity to platelet factor 4, inability to inhibit clot-bound thrombin, marked interpatient variability in therapeutic response, and the need for frequent activated partial thromboplastin time monitoring.[365] In an effort to circumvent these disadvantages of unfractionated heparin, there has been interest in

the development of novel antithrombotic compounds.

HIRUDIN.

The prototypical direct antithrombin hirudin was compared with heparin in several phase III trials: TIMI 9A, GUSTO IIA, and r-Hirudin for Improvement of Thrombolysis (HIT) III.[302] [303] [366] A feature common to all three trials was that they were stopped prematurely because of unacceptable rates of serious bleeding, particularly intracranial hemorrhage. This excessive rate of bleeding appeared to be attributable to high levels of anticoagulation in both the heparin and hirudin groups. Possible explanations for the unexpectedly high rates of bleeding were low estimates of the hemorrhagic risk of the doses of hirudin infused owing to the relatively small number of patients previously evaluated in phase II studies and attempts to push the heparin dose to achieve activated partial thromboplastin time levels in an effort to prevent reocclusion of successfully reperfused vessels.[302] After downward modification of the dose of antithrombins, the TIMI 9B and GUSTO IIb trials were initiated.[354] [367] The results of a prospectively planned meta-analysis of the TIMI 9B and GUSTO IIB data are shown in Table 35-11 . [368] Mortality rates were similar at 30 days in both trials. A generally consistent reduction in the rate of reinfarction was seen in the two trials, but this was of borderline statistical significance in the pooled data set: no statistically significant reduction

TABLE 35-11 -- GUSTO-TIMI METAANALYSIS: EVENTS WITHIN 30 DAYS

GROUP	NO.	MORTALITY		
		Heparin (%)	Hirudin (%)	OR (95% CI)
TIMI 9	3002	5.1	6.1	1.21 (0.88-1.65)
GUSTO II Lytic	3052	6.5	6.0	0.91 (0.68-1.23)
Combined	6054			1.04 (0.84-1.29)
GROUP	**NO.**	**REINFARCTION**		
		Heparin (%)	**Hirudin (%)**	**OR (95% CI)**
TIMI 9	3002	5.2	4.5	0.85 (0.61-1.18)
GUSTO II Lytic	3052	6.8	5.3	0.77 (0.58-1.04)
Combined	6054			0.81 (0.65-1.00)
GROUP	**NO.**	**DEATH+ REINFARCTION**		
		Heparin (%)	**Hirudin (%)**	**OR (95% CI)**
TIMI 9	3002	9.5	9.7	1.02 (0.80-1.31)

GUSTO II Lytic	3052	12.1	10.2	0.84 (0.66-1.03)
Combined	6054			0.91 (0.77-1.08)

Modified from Antman EM, Bittl JA: Direct thrombin inhibitors. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 155.

was seen in the composite endpoint of death and nonfatal reinfarction.

By inhibiting the coagulation cascade upstream from thrombin, heparin has an advantage over the direct antithrombins because of its additional ability to decrease thrombin generation along with its ability to inhibit thrombin activity. Hirudin has a greater ability than heparin to decrease thrombin activity, but once the thrombin inhibitory capacity is exceeded (by virtue of the local concentration of hirudin), free thrombin may be generated in an explosive fashion. The net result of this balance of actions is that use of heparin or the direct antithrombins in a dose that is safe results in an equivalent decrement in thrombus formation in the infarct-related artery.

EFEGATRAN.

Efegatran, another direct antithrombin, was compared with unfractionated heparin as an adjunct to streptokinase in the ESCALAT study.[369] Efegatran was not superior to heparin in achieving coronary patency and was associated with high rates of bleeding.

HIRULOG.

It has been argued by the Hirulog Early Reperfusion/Occlusion (HERO) trial investigators that in order to truly expose the benefits of a direct antithrombin, it must be administered before a thrombolytic.[370] The ongoing HERO II trial is comparing hirulog with unfractionated heparin for reduction in mortality in patients receiving streptokinase.[371]

LOW-MOLECULAR-WEIGHT HEPARINS.

These are formed by controlled enzymatic or chemical depolymerization producing chains of glycosaminoglycans of varying length but with a mean molecular weight of approximately 5000 daltons.[365] Advantages of low-molecular-weight heparins include a stable, reliable anticoagulant effect, high bioavailability permitting administration by means of the subcutaneous route, and a high anti-factor Xa:anti-factor IIa ratio producing blockade of the coagulation cascade in an upstream location resulting in a marked decrement in thrombin generation. Preliminary observations suggest that low-molecular-weight heparins facilitate thrombolysis and prevent recurrent ischemic events.[372] [373] [374] Low-molecular-weight heparin preparations are now being examined in AMI patients both in the presence (AMISK, HART-2, ENTIRE-TIMI 23) and absence (TETAMI) of thrombolytic therapy.

Recommendations for Antithrombin Therapy

Given the pivotal role played by thrombin in the pathogenesis of AMI, antithrombotic therapy remains an important therapeutic intervention. All patients with an acute coronary syndrome should receive antiplatelet therapy (aspirin remains the recommended agent at this time). For patients who do *not* receive thrombolytic therapy, overviews of the available data indicate that heparin reduces mortality and morbidity from serious complications such as reinfarction and thromboembolism.[52] Therefore, in the absence of contraindications to anticoagulation we routinely use antithrombin therapy in *all* AMI patients presenting with ST segment elevation who are not candidates for thrombolysis and also prescribe it for AMI patients presenting without ST segment elevation. Although intravenous unfractionated heparin for 48 to 72 hours is an acceptable choice, given the greater ease of use we prefer subcutaneous injections of a low-molecular-weight heparin instead of either subcutaneous or intravenous unfractionated heparin for such patients.[375] In view of its superiority over unfractionated heparin[376] in patients with an acute coronary syndrome presenting without ST segment elevation, we prefer to prescribe enoxaparin, 1 mg/kg twice daily, for the duration of the hospitalization.[376] In patients at high risk for systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, known left ventricular thrombus), intravenous unfractionated heparin is the preferred form of anticoagulation because of insufficient data to formulate recommendations for treatment with a low-molecular-weight heparin.

For patients receiving thrombolytic therapy with either streptokinase or anistreplase, there is no apparent mortality benefit of immediate intravenous heparin, and we do not recommend its use if those thrombolytics are prescribed. The only exception to this are patients who have another compelling indication for anticoagulation, such as a large anterior MI with a significant wall motion abnormality[360] or atrial fibrillation; in this case we generally use intravenous heparin administered to a target activated partial thromboplastin time of 50 to 70 seconds. The relative benefits of routine use of delayed (4 to 12 hours), high-dose (12,500 IU twice daily) subcutaneous heparin in patients receiving streptokinase remain unresolved.[377]

On the basis of the principle that t-PA is a more fibrin-specific lytic agent and the evidence that infarct-related artery patency rates are higher in patients receiving intravenous heparin adjunctively with t-PA, it is commonly recommended that with t-PA, intravenous heparin should be administered.[360] A similar line of reasoning can be applied to reteplase and tenecteplase. Nevertheless, the dose of heparin in thrombolytic-treated patients remains controversial. Lessons learned from clinical trials over the past 5 to 10 years suggest that the target activated partial thromboplastin time values should be lower than was previous practice; the current recommendation is an activated partial thromboplastin time of 50 to 70 seconds.[312] In addition, unfractionated heparin should be administered using a weight-based regimen with lower total maximum doses than was previous practice. An initial 60-unit/kg bolus (maximum 4000 units) should be followed by a maintenance infusion of 12 units/kg/hr (maximum 1000

units/hr).[52] It is important to emphasize that it is difficult to provide a heparin adjustment nomogram that is universally applicable because of varying responsiveness of the thromboplastin reagent used in local laboratories for measuring the activated partial thromboplastin time. The appropriate therapeutic range must be established for each local laboratory reagent, with nomograms developed corresponding to the defined therapeutic range. Whereas for patients with venous thrombosis or pulmonary embolism, the target activated partial thromboplastin time should be equivalent to a heparin level of 0.3 to 0.7 unit/ml by anti-factor Xa heparin levels, the therapeutic range should be lower in patients receiving thrombolytics and/or GPIIb/IIIa inhibitors. Although no large-scale studies are available, we are in agreement with the recommendation of Hochman and coworkers, who proposed a therapeutic range corresponding to anti-factor Xa levels of 0.14 to 0.34 unit/ml.[378]

Because of concern about the possibility of a rebound increase in thrombin generation and recurrent ischemia after cessation of heparin therapy, some clinicians have suggested a tapering of heparin infusions rather than abrupt discontinuation together with continued aspirin.[379]

Antiplatelet Therapy

As discussed earlier (see p. 1116), platelets play a major role in the thrombotic response to rupture of a coronary artery plaque[380] (see Fig. 35-3) . Platelets are activated in response to thrombolysis and platelet-rich thrombi are also more resistant to thrombolysis than are fibrin and erythrocyte-rich thrombi[381] (Fig. 35-31) . Thus, there is a sound scientific basis for inhibiting platelet aggregation in *all* AMI patients, regardless of whether a thrombolytic agent is prescribed. Comprehensive overviews of randomized trials of antiplatelet therapy have summarized the overwhelming evidence of the benefit of antiplatelet therapy for a wide range of vascular disorders.[14] [382] [383] [384] In patients at risk for AMI, patients with a documented prior AMI, and patients in the acute phase of an AMI, dramatic reductions (between 25 to 50 percent in relative risk) in mortality, nonfatal reduction of recurrent infarction, and nonfatal stroke are achieved by antiplatelet therapy[14] (Fig. 35-32) . Not unexpectedly, the *absolute* benefits are greatest in those patients at highest baseline risk.[14] Although several antiplatelet regimens have been evaluated, the agent most extensively tested has been aspirin, and this also is the drug for which the most compelling evidence of benefit exists.[274]

The ISIS-2 study was the largest trial of aspirin in AMI and provides the single strongest piece of evidence that aspirin reduces mortality in AMI[308] (see Fig. 35-25) . Of interest, in contrast to the observations of a time-dependent mortality effect of thrombolytic therapy, the mortality reduction with aspirin was similar in patients treated within 4 hours (25 percent reduction in mortality), between 5 and 12 hours (21 percent reduction), and between 13 and 24 hours (21 percent reduction). There was an overall 23 percent reduction in mortality from aspirin in ISIS-2 that was largely additive to the 25 percent reduction in mortality from streptokinase, so that patients receiving both therapies experienced a 42 percent reduction in mortality.[308] The mortality reduction was as high as 53 percent in those patients who received both aspirin and streptokinase within 6 hours of symptoms. Of particular interest was the finding that the combination of streptokinase and aspirin reduced mortality from 23.8 to 15.8 percent (34 percent

reduction) *without* increasing the risk of stroke or hemorrhage. Fibrinogen bound to the GPIIb/IIIa receptor on platelets interacts with leukocytes by means of the CD116/CD18 (Mac-1) receptor, providing a link between platelet activation and inflammatory processes in AMI.[385] [386]

Obstructive arterial thrombi that are platelet rich are resistant to thrombolysis and have an increased tendency to produce reocclusion after initial successful reperfusion in patients with ST segment elevation AMI.[47] [51A] [387] Despite the inhibition of cyclooxygenase by aspirin, platelet activation continues to occur through thromboxane A2-independent pathways, leading to platelet aggregation and increased thrombin formation. Activation of platelets by a variety of agonists results in the expression of functional receptors for fibrinogen and other ligands on the platelet surface--the GPIIb/IIIa receptor.[388] GPIIb/IIIa inhibition accelerates thrombolysis and prevents reocclusion in several animal species with experimentally induced platelet-rich coronary thromboses.[237] [389] Potential mechanistic explanations for the beneficial effects of GPIIb/IIIa inhibition when combined with thrombolytics center around important interactions between thrombolytics and platelets (see Fig. 35-31) . Platelets can be stimulated by thrombolytics (e.g., by the exposure of clot-bound thrombin). A narrowed lumen and a highly stenosed infarct-related artery generate high shear forces, a potent stimulus to platelet activation. Activated platelets may inhibit thrombolysis through the release of substances such as PAI-1, $alpha_2$ -plasminogen inhibitor, and factor XIII, which stabilize the clot and also enhance clot retraction, all features that make the clot more resistant to thrombolysis. Observations such as those just noted served as the foundation for testing the hypothesis that GPIIb/IIIa inhibition is a potent and safe addition to thrombolytic regimens and introduced the concept of *combination reperfusion* for STEMI.[390]

GPIIb/IIIa INHIBITION.

Reperfusion in AMI represents a potent stimulus for platelet activation and aggregation as well as activation of the coagulation cascade. Thus, GPIIb/IIIa inhibition has also been used to support PCI and stenting in AMI patients with the hopes of decreasing the risk of acute thrombotic occlusion of the infarct artery and also reducing the risk of death and cardiac ischemic events.[390]

Aspirin only partially inhibits platelet aggregation by inhibiting the thromboxane A_2 pathway. Thienopyridines such as ticlopidine and clopidogrel inhibit binding to the adenosine diphosphate receptor and also block adenosine diphosphate-dependent pathways for platelet activation. Platelet inhibition by aspirin and the thienopyridines blocks only a limited number of the pathways of platelet activation. Irrespective of the stimulus for platelet activation, the final common pathway is expression of the GPIIb/IIIa receptor on the platelet surface.[47] Therefore, direct inhibition of the GPIIb/IIIa receptor with intravenous agents such as abciximab, tirofiban, and eptifibatide has been studied in patients with AMI[391] (see Fig. 35-31) .

Figure 35-31 Pharmacological dissolution of thrombus in infarct-related artery. The three panels shown in this figure are schematic views of a longitudinal section of an infarct-related artery at the level of the obstructive thrombus. *A,* After rupture of a vulnerable plaque (bottom center), the coagulation cascade is activated, ultimately leading to the deposition of fibrin strands (black curvilinear arcs); platelets are activated and begin to aggregate (transition from flat discs representing inactive platelets to spiked ball elements representing activated and aggregating platelets). The mesh of fibrin strands and platelet aggregates obstructs flow (normally moving from left to right) in the infarct-related artery; this would correspond to TIMI grade 0 on angiography. Pharmacological reperfusion is a multipronged approach consisting of thrombolytics that digest fibrin, antithrombins that prevent the formation of thrombin and inhibit the activity of thrombin that is formed, and antiplatelet therapy. *B,* Full-dose thrombolysis results in incomplete reperfusion in about 50 percent of patients because of persistent platelet aggregates and fibrin strands. On angiography, this would correspond to TIMI flow grade 2. *C,* Combination reperfusion therapy with an intravenous glycoprotein IIb/IIIa inhibitor and reduced dose thrombolytic facilitates the rate and extent of thrombolysis. Prevention of platelet aggregates allows deeper penetration of the thrombolytic into the weakened clot structure, and full reperfusion (TIMI flow grade 3) is achieved. *(Courtesy of Luke Welles, The Exeter Group.)*

Figure 35-32 Antiplatelet therapy in myocardial infarction. Pooled data from randomized control trials (RCTs) of acute myocardial infarction indicate reductions in the rate of reinfarction, stroke (cerebrovascular accident [CVA]), and death in patients receiving antiplatelet therapy compared with control. Similarly, reductions in reinfarction, CVA, and death are seen in the pooled data from trials of secondary prevention with antiplatelet therapy after AMI. Based on the absolute event rates and the treatment effect for each endpoint, the benefit per 1000 patients treated with an antiplatelet agent can be calculated. *(Adapted from data in Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy: I. Prevention of death by myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 308:81-106, 1994.)*

Pharmacological Reperfusion with Thrombolytic and GPIIb/IIIa Inhibition

Several clinical studies evaluated the combination of GPIIb/IIIa inhibitors and thrombolytics. The first series of trials combined full doses of thrombolytic agents with GPIIb/IIIa inhibitors. TAMI-8 was a dose-ranging study that demonstrated that 80 percent or more inhibition of platelet aggregation with the murine Fab fragments of a monoclonal antibody against the GPIIb/IIIa receptor (m7E3) could be accomplished safely.[392] TIMI grade 2 or 3 flow was seen in the infarct-related artery at follow-up angiography at day 5 in 56 percent of 9 control patients and 92 percent of 37 patients receiving m7E3 (p = 0.02). The IMPACT AMI trial demonstrated that patients receiving doses of eptifibatide achieving 50 to 60 percent of platelet aggregation in combination with full-dose t-PA showed an increased rate of TIMI grade 3 flow at 90 minutes (66 percent compared with 39 percent in the placebo group).[393] The streptokinase-eptifibatide trial combined full-dose streptokinase with ascending doses of

eptifibatide. Although increased rates of TIMI grade 3 flow were observed in the combination arms, unacceptably high rates of major hemorrhage were also observed, leaving the investigators to conclude that eptifibatide could not be safely combined with full doses of streptokinase.[394] The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) investigators compared different doses of lamifiban with either t-PA or streptokinase at standard doses.[395] Lamifiban was associated with improved ST segment resolution on continuous ECG monitoring, suggesting improved myocardial perfusion.

The combination of a reduced dose thrombolytic agent and GPIIb/IIIa inhibitor was tested in a subsequent series of trials. The TIMI 14 trial demonstrated that abciximab facilitated the rate and extent of thrombolysis, producing early, marked increases in TIMI 3 flow when combined with half the usual dose of t-PA (50 mg) (Fig. 35-33) (Figure Not Available) . [237] The improvement in epicardial reperfusion with reduced-dose t-PA occurred without an increase in major bleeding. Although modest improvements in TIMI 3 flow were seen when abciximab was combined with reduced doses of streptokinase, there was an increased risk of bleeding suggesting that even reduced doses of streptokinase could not be safely combined with a GPIIb/IIIa inhibitor.[237] In multivariate logistic regression analyses, after adjusting for infarct location and time from symptom onset to administration of the reperfusion regimen when compared with a full-dose thrombolytic, use of abciximab with a reduced-dose thrombolytic was associated with a significant increase

Figure 35-33 (Figure Not Available) Abciximab (Abx) facilitates the rate and extent of thrombolysis. Compared with patients receiving full-dose t-PA (100 mg), patients receiving abciximab and reduced-dose t-PA (50 mg) had a significantly higher rate of TIMI grade 3 flow at 60 minutes after initiation of reperfusion therapy. A significantly greater proportion of patients treated with the combination reperfusion regimen had lower frame counts (i.e., faster flow).

Figure 35-34 Improved myocardial perfusion with combination therapy. Abciximab in combination with reduced-dose thrombolytics increased the proportion of patients achieving complete ST segment resolution at 90 minutes and TIMI myocardial perfusion grade 2 or 3 at 90 minutes. TMPG = TIMI myocardial perfusion grade. *(Modified from data in de Lemos JA, Antman EM, Gibson CM, et al: Circulation. 2000;101:239-43 and Antman EM, Gibson CM, de Lemos JA, et al: Combination reperfusion therapy with abciximab and reduced dose reteplase: Results from TIMI 14. Eur Heart J, 2000, in press.)*

in the probability of achieving TIMI 3 flow and complete ST segment resolution at 90 minutes.[396] Improvement in ST segment resolution and TIMI myocardial perfusion grade was observed even among patients with normal epicardial flow, indicating that abciximab improves not only epicardial flow but also myocardial perfusion (Fig. 35-34) . [396A] Combination reperfusion therapy for STEMI is being studied in GUSTO IV, a large phase III trial that will provide data on the impact of abciximab with reduced doses of reteplase on clinical outcome.

The Strategies for Patency Enhancement in the Emergency Department (SPEED) and INTRO-AMI trials evaluated abciximab with low-dose reteplase and eptifibatide with low-dose t-PA, respectively.[397] [398] Both studies showed that combination therapy with intravenous GPIIb/IIIa inhibitors and reduced doses of lytics increased the proportion of patients achieving TIMI 3 flow by 60 to 90 minutes and also facilitated rescue PTCA procedures.

GPIIb/IIIa Inhibition to Support Catheter-Based Reperfusion

Interest in the use of intravenous GPIIb/IIIa inhibitors to support primary PTCA for AMI began with a small series of patients studied by Gold and colleagues and a subset of patients in the EPIC trial.[399] [400] Promising observations included improvements in TIMI 3 flow and a reduction in the primary composite endpoint of death, MI, or urgent revascularization in patients treated with abciximab and primary PTCA. Neumann and colleagues reported that improvement in papaverine-induced peak flow velocities and wall motion indices was seen in patients undergoing stenting for AMI when the procedure was supported by abciximab[260] (Fig. 35-35) . Schomig and associates reported that in patients with AMI, coronary stenting plus abciximab led to a greater degree of myocardial salvage and a better clinical outcome than did fibrinolysis with t-PA.[260A]

Abciximab given in the emergency department in patients awaiting primary angioplasty increases the probability of achieving TIMI grade 3 flow before the procedure. Compared with an 8 percent incidence of TIMI 3 flow in the GUSTO IIB trial in patients receiving heparin and aspirin, a time-dependent increase in the proportion of patients with TIMI 3 flow was seen with 18 percent in the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) trial (45 minutes), 23 percent in the SPEED trial (60 minutes), and 32 percent in TIMI 14 (90 minutes).[401] The ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) was a double-blind comparison of abciximab versus placebo.[402] The composite endpoint of death, MI, or urgent target vessel revascularization was reduced from 17.8 percent in the placebo group to 11.6 percent in the abciximab group, the benefit being driven almost entirely by a 64 percent reduction in the odds of requiring urgent target vessel revascularization when abciximab was used. Major bleeding occurred significantly more frequently in the abciximab group (16.6 percent vs. 9.5 percent, $p = 0.02$) mostly at the arterial access site. The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) investigators randomized AMI patients with 12 hours of symptoms to either abciximab or placebo, which was administered in the ambulance, emergency department, or catheterization

Figure 35-35 Effect of abciximab on myocardial flow and contractile function. *A,* Plot of differences between 14-day follow-up and initial postinterventional study in basal flow velocity and papaverine-induced flow velocity in patients treated with primary percutaneous intervention for acute MI. The columns represent mean differences. *B,* Plot of differences between 14-day follow-up and initial postinterventional study in wall motion index and in number of cords with an infarct region. *(From Neumann FJ, Blasini R, Schmitt C, et al: Effect of glycoprotein IIb/IIIa receptor blockade on recovery of*

coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 98:2695-2701, 1998. Copyright 1998, American Heart Association.)

Figure 35-36 Glycoprotein IIb/IIIa receptor antagonists for failed rescue angioplasty. *A,* Before balloon angioplasty there is acute inferior MI with hampered flow and cardiogenic shock. A thrombus is seen in the middle of the right coronary artery (arrow). *B,* After balloon angioplasty, there is no reflow. Although proximal coronary artery is patent, smaller distal vessels are occluded (arrow). *C,* Approximately 10 minutes after abciximab administration (0.25-mg/kg bolus and a 10-mug/min infusion), coronary artery flow is restored to TIMI 3 flow. *(Reproduced from Ronner E, et al: IIb/IIIa receptor antagonists for failed rescue angioplasty. Circulation 101:214-215, 2000. Copyright 2000, American Heart Association.)*

laboratory as soon as AMI was diagnosed and before sheath insertion. The incidence of death/recurrent MI/urgent target vessel revascularization at 30 days was reduced by 46.5 percent with abciximab from 20.0 percent in the placebo group to 10.7 percent in the abciximab group ($p < 0.03$). [403] As was observed in the RAPPORT trial, the major benefit of abciximab was in reducing urgent target vessel revascularization.

The CADILLAC trial was designed to compare in a 2 × 2 factorial fashion the effects of balloon angioplasty (with or without abciximab) and stenting (with or without abciximab) in AMI patients presenting within 12 hours of symptoms. TIMI 3 flow was obtained after PTCA in about 95 percent of patients both with and without abciximab treatment. There was a slight reduction in the rate of TIMI 3 flow to 92.1 percent in the stent group without abciximab, which rose to 96.7 percent in patients receiving a stent in combination with abciximab. Use of abciximab was associated with reductions in target vessel revascularization and recurrent ischemia both in patients undergoing primary PTCA without stenting and those patients undergoing primary stenting.[404]

Recommendations for Antiplatelet Therapy

Some uncertainty about the optimal dose of aspirin for acute treatment of AMI remains. In general, high doses of aspirin are not more effective than lower doses but are more likely to provoke gastrointestinal side effects. However, adequate cyclooxygenase inhibition (and reduction in thromboxane A_2 production) takes several days to accomplish with less than 75 mg of aspirin, and loading doses of 160 to 325 mg (preferably chewed) are therefore recommended for all AMI patients without a history of aspirin allergy whether they present with ST segment elevation or not and whether they undergo reperfusion with thrombolytics or PTCA or are treated with a more conservative medical regimen (see Fig. 35-17) . Active peptic ulcer disease is a relative contraindication to antiplatelet therapy. For patients with severe nausea and vomiting, aspirin suppositories (325 mg) can be used. Aspirin should be continued indefinitely in patients with AMI.

In patients with AMI who cannot tolerate aspirin, clopidogrel, 75 mg orally, is an

acceptable alternative. Administration of intravenous GPIIb/IIIa inhibitors cannot be recommended as a routine measure after full-dose thrombolytic therapy has been given. However, as reviewed earlier they are useful to support primary PCI (Fig. 35-36) .[405] [406] [407]

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Hospital Management

CORONARY CARE UNITS

Deaths from primary ventricular fibrillation in AMI have been prevented because the CCU allows continuous monitoring of cardiac rhythm by highly trained nurses with the authority to initiate immediate treatment of arrhythmias in the absence of physicians and because of the specialized equipment (defibrillators, pacemakers) and drugs available. Although all of these benefits can be achieved for patients scattered throughout the hospital, the clustering of patients with AMI in the CCU has greatly improved the efficient use of the trained personnel, facilities, and equipment. In recent years, with increasing emphasis on hemodynamic monitoring and treatment of the serious complications of AMI with such modalities as thrombolytic therapy, afterload reduction, and intraaortic balloon counterpulsation, the CCU has assumed even greater importance.[185] Improvements in the 30-day survival of elderly patients with AMI can be traced to advances in therapy delivered in CCUs.[408] As interventional strategies including thrombolytic therapy and acute coronary angioplasty are used more routinely in AMI patients, facilities in which patients may undergo diagnostic and therapeutic angiographic procedures are being integrated into the CCU structure.

At the same time, the value of CCUs for patients with uncomplicated AMI has been questioned and restudied.[185] With increasing attention directed to the limitation of resources and to the economic impact of intensive care, there have been efforts to select patients for whom hospitalization in a CCU would likely be of benefit. The ECG, on presentation, particularly in conjunction with previous tracings[409] and an immediate general clinical assessment, can be useful both for predicting which patients will have the diagnosis of AMI confirmed and identifying low-risk patients who may require less intensive care.[55] Among patients with a history of typical chest pain but with a normal ECG in the emergency department, less than 20 percent ultimately have an AMI on that

admission, and less than 1 percent develop any significant complication. Thus, a patient with a normal ECG may not require admission to a full-fledged CCU. Careful analysis of the quality of pain may help identify such low-risk patients as well. Patients without a history of angina pectoris or MI presenting with pain that is sharp or stabbing and pleuritic, positional, or reproduced by palpation of the chest wall are extremely unlikely to have an AMI. Computer-guided decision protocols are being developed to aid clinicians in identifying those AMI patients who require admission to the CCU as opposed to a less intensive hospital ward.[174]

Contemporary CCUs typically have equipment available

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for noninvasive monitoring of single or multiple ECG leads, cardiac rhythm, ST segment deviation, arterial pressure, and arterial oxygen saturation. Computer algorithms for detection and analysis of arrhythmias are superior to visual surveillance by skilled CCU staff. However, even the most sophisticated ECG monitoring systems are susceptible to artifacts due to patient movement or noise on the signal from poor skin preparation when monitoring electrodes are applied.[185] Noninvasive monitoring of arterial blood pressure using a sphygmomanometric cuff that undergoes cycles of inflation and deflation at programmed intervals is suitable for the majority of patients admitted to a CCU. Invasive arterial monitoring is preferred in patients with a low output syndrome under circumstances in which inotropic therapy is initiated for severe left ventricular failure.[185]

The CCU remains the appropriate hospital unit for patients with complicated infarctions (e.g., hemodynamic instability, recurrent arrhythmias) and those patients requiring intensive nursing care for devices such as an intraaortic balloon pump.[44] For patients with a low risk of mortality from AMI (Fig. 35-27) , the clinician should consider admission to an intermediate care facility (see later) equipped with simple ECG monitoring and resuscitation equipment.[52] This strategy has been shown to be cost-effective and may reduce CCU utilization by one third, shorten hospital stays, and have no deleterious effect on patients' recovery. Intermediate-care units for low-risk AMI patients may also be appealign to patients who stand to gain little benefit from the high staffing, intense activity, and elaborate technology available in current CCUs (with their attendant high costs) and who may be disturbed by that activity and equipment.[410] [411]

RECOMMENDATIONS FOR ADMISSION TO THE CCU.

The following should be considered:

1. Patients with clear-cut AMI, presenting within 12 to 24 hours of symptoms, should, in general, be admitted to a CCU. A possible exception are patients who are taken directly from the emergency department to the catheterization laboratory where they undergo a successful and uncomplicated revascularization procedure. Such patients may be considered for admission to an intermediate-care unit rather than

the CCU.

2. Patients with severe unstable angina should also be admitted to the CCU, particularly if episodes of chest pain occur at rest, high doses of intravenous nitroglycerin (e.g.,
   300 mg/min) are required to relieve chest pain, or frequent adjustments of intravenous nitroglycerin infusions are required because of fluctuating symptoms and hemodynamic status (see Chap. 36) .
3. Once an AMI is ruled out (ideally by 12 hours) and symptoms are controlled with oral or topical pharmacological agents, discharge from the CCU should be considered.
4. AMI patients with an uncomplicated status, such as those without a history of previous infarction, persistent ischemic-type discomfort, congestive heart failure, hypotension, heart block, or hemodynamically compromising ventricular arrhythmias, may be safely transferred out of the CCU within 24 to 36 hours.
5. In patients with a complicated AMI, the duration of the CCU stay should be dictated by the need for "intensive" care, that is, hemodynamic monitoring, close nursing supervision, intravenous vasoactive drugs, and frequent changes in the medical regimen.

General Measures for Management of AMI

The CCU staff must be sensitive to patient concerns about mortality, prognosis, and future productivity. A calm, quiet atmosphere and the "laying on of hands" with a gentle but confident touch help allay anxiety and reduce sympathetic tone, ultimately leading to a reduction in hypertension, tachycardia, and arrhythmias.[185] To reduce the risk of nausea and vomiting early after infarction and to reduce the risk of aspiration, during the first 4 to 12 hours after admission patients should receive either nothing by mouth or a clear liquid diet (Table 35-12) (Table Not Available) . Subsequently, a diet with 50 to 55 percent of calories from complex carbohydrates and up to 30 percent from mono- and unsaturated fats should be given. The diet should be enriched in foods that are high in potassium, magnesium, and fiber but low in sodium (see Table 35-12) (Table Not Available) .

The results of laboratory tests obtained in the CCU should be scrutinized for any derangements potentially contributing to arrhythmias, such as hypoxemia, hypovolemia, disturbances of acid-based balance or of electrolytes, and drug toxicity. Oxazepam, 15 to 30 mg orally four times a day, is useful to allay the anxiety that is common in the first 24 to 48 hours (see Table 35-12) (Table Not Available) . Delirium may be provoked by medications frequently used in the CCU, including antiarrhythmic drugs, histamine-2 blockers, narcotics, and beta blockers. Potentially offending agents should be discontinued in patients with an abnormal mental status. Haloperidol, a butyrophenone, may be used safely in patients with AMI beginning with a dose of 2 mg intravenously for mildly agitated patients and 5 to 10 mg for progressively more agitated patients. Hypnotics, such as temazepam, 15 to 30 mg, or an equivalent, should be provided as needed for sleep. Dioctyl sodium sulfosuccinate, 200 mg daily, or another stool softener should be used to prevent constipation and straining (see Table 35-12) (Table Not Available) .

"Coronary precautions" that do *not* appear to be supported by evidence from clinical research include the avoidance of iced fluids,[412] hot beverages, caffeinated beverages, rectal examinations, back rubs, and assistance with eating.[185]

PHYSICAL ACTIVITY.

In the absence of complications, patients with AMI need not be confined to bed for more than 12 hours and, unless they are hemodynamically compromised, they may use a bedside commode shortly after admission (see Table 35-12) (Table Not Available) . Progression of activity should be individualized depending on the patient's clinical status, age, and physical capacity.

In patients without hemodynamic compromise, early ambulation (including dangling feet on the side of the bed,

TABLE 35-12 -- SAMPLE ADMITTING ORDERS

(Not Available)

From 1999 Updated ACC/AHA AMI Guidelines (Web version), p 54. Severe chronic obstructive pulmonary disease

sitting in a chair, standing, and walking around the bed) does not cause important changes in heart rate, blood pressure, or pulmonary wedge pressure. Although heart rate increases slightly (usually by less than 10 percent), pulmonary wedge pressures fall slightly as the patient assumes the upright posture for activities. Early ambulatory activities are rarely associated with any symptoms; when symptoms do occur, they generally are related to hypotension. Thus, when Levine and Lown proposed the "armchair" treatment of AMI in 1952, they were undoubtedly correct that stress to the myocardium is less in the upright position.[413] As long as blood pressure and heart rate are monitored carefully, early ambulation offers considerable psychological and physical benefit without any clear medical risk.

The Intermediate Coronary Care Unit

AMI patients are at risk for late in-hospital mortality from recurrent ischemia or infarction, hemodynamically significant ventricular arrhythmias, and severe congestive heart failure after discharge from the CCU. Therefore, continued surveillance in intermediate CCUs (also called step-down units) is justifiable. Risk factors for mortality in the hospital after discharge from the CCU include significant congestive heart failure, evidenced by persistent sinus tachycardia for more than 2 days and rales greater than one third of the lung fields; recurrent VT and ventricular fibrillation; atrial fibrillation or flutter while in the CCU; intraventricular conduction delays or heart block; anterior location of infarction;

and recurrent episodes of angina with marked ST segment abnormalities at low activity levels. Although it has not been shown rigorously, it is likely that a reduction in late hospital mortality can be achieved with the use of intermediate CCUs, which permits prolonged continuous monitoring of the ECG and prompt, effective treatment of ventricular fibrillation and other serious arrhythmias.

The availability of intermediate care units may also be helpful in identifying those patients who remain free of complications and are suitable candidates for early discharge from the hospital. Aggressive reperfusion protocols with angioplasty or thrombolytics can reduce length of hospital stay.[322] In patients who are believed to have undergone successful reperfusion, the *absence* of early sustained ventricular tachyarrhythmias, hypotension, or heart failure, coupled with a well-preserved LV ejection fraction, predicts a low risk of late in-hospital complications.[414] Such patients are suitable candidates for discharge from the hospital in less than 5 days from the onset of symptoms,[410] although decisions regarding the length of stay must also factor in the need to optimize medication dosages and the patient's psychological state and support systems at home.[411]

After AMI, patients are often eager for information, in need of reassurance, confused by misinformation and prior impressions, capable of counterproductive denial, and simply frightened.[185] Intermediate care facilities provide ideal settings and ample opportunities to begin the rehabilitation process.[52] [414b] The capacity for the early detection of problems after AMI and the social and educational benefits of grouping such patients together strongly argue for continued utilization of intermediate CCUs. Furthermore, the economic advantage of grouping such patients together for sharing of skilled personnel and resources outweighs any questions raised by the lack of a clear consensus regarding reduced mortality. An additional potential advantage is the facilitation of patient education in a group setting with lectures and audiovisual programs.

PHARMACOLOGICAL THERAPY

The rationale and recommendations for initiation of several pharmacological measures to treat AMI in the emergency department have been reviewed previously (see p. 1139 ; see Fig. 35-18) . The early use of beta blockers, ACE inhibitors, calcium antagonists, nitrates, and other therapies such as magnesium and glucose-insulin-potassium is discussed in this section. Secondary prevention with some of these agents is discussed subsequently (see p. 1203).

Beta Blockers

The effects of beta blockers on AMI can be divided into those that are immediate, when the drug is given very early in the course of infarction, and long term (secondary prevention), when the drug is initiated sometime after infarction. The intravenous administration of beta-adrenoceptor blockers reduces cardiac index, heart rate, and blood pressure.[186] The net effect is a reduction in myocardial oxygen consumption per minute and per beat. Favorable effects of acute intravenous administration of beta-adrenoceptor blockers on the balance of myocardial oxygen supply and demand are reflected in reductions in chest pain, in the proportion of patients with threatened

infarction who actually evolve AMI, and in the development of ventricular arrhythmias.[415] Because beta-adrenoceptor blockade diminishes circulating levels of free fatty acids by antagonizing the lipolytic effects of catecholamines and because elevated levels of fatty acids augment myocardial oxygen consumption and probably increase the incidence of arrhythmias, these metabolic actions of beta-blocking agents may also be beneficial to the ischemic heart.

Objective evidence of beneficial effects of beta blockers in AMI has been reported using the precordial ST segment mapping technique. Acute beta blockade probably reduces infarct size in AMI. Reduction in release of cardiac enzymes with beta blockade[416] is suggestive of a smaller infarct, as is the preservation of R waves and reduction in the development of Q waves.

At least 29 randomized beta blocker trials involving more than 28,970 patients have been undertaken. Intravenous, followed by oral, beta-blocker therapy is associated with about a 13 percent relative reduction in the risk of mortality[417] (Fig. 35-37) . Although antagonism of sympathetic stimulation to the heart might be expected to exacerbate pulmonary edema in patients with occult heart failure, usually only small changes in pulmonary capillary wedge pressure occur when the drug is used in patients with AMI. Thus, in appropriately selected patients (Table 35-13) (Table Not Available) the

Figure 35-37 Effect of beta blockers on mortality in myocardial infarction. The relative risk of mortality is reduced with beta blockers both during the acute phase of treatment and when prescribed as secondary prevention after acute myocardial infarction. *(Adapted from data in Chae CU, Hennekens CH: Beta blockers. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 84.)*

TABLE 35-13 -- CONTRAINDICATIONS TO BETA-ADRENOCEPTOR BLOCKER THERAPY IN ACUTE MYOCARDIAL INFARCTION

(Not Available)
From 1999 Updated ACC/AHA AMI Guidelines (Web version), p 109.

benefits just noted occur at a cost of about a 3 percent incidence of provocation of congestive heart failure or complete heart block and a 2 percent incidence of the development of cardiogenic shock.

Because reduction of infarct size in AMI patients treated with beta blockers is likely to occur only with early treatment (4 hours from the onset of pain), investigators have sought other explanations for the reduction in the mortality in the acute phase that has been observed. Intriguing observations from the ISIS-1 trial raise the possibility that a reduction in the development of cardiac rupture or electromechanical dissociation during

the first day is achieved with early beta blockade.[418]

In the TIMI-II trial the addition of a beta blocker (metoprolol) to thrombolytic therapy was studied.[349] Although recurrent ischemia and reinfarction were reduced by immediate intravenous versus delayed use of metoprolol, mortality was not reduced nor was ventricular function improved. Thus, immediate intravenous beta blockade, although clinically beneficial, may not enhance salvage of myocardium in the setting of early reperfusion but may confer clinical benefit by means of its antiischemic effect.[213]

Substantial proportions of elderly patients who are hospitalized with AMI and are ideal candidates for early beta blocker therapy do not receive this treatment.[419] Compared with elderly patients who receive early beta blockade in AMI, those who do not receive beta blockade are older, more likely to be women, and less likely to be white. Elderly patients who receive early beta-blocker therapy have significantly lower in-hospital mortality rates than those who do not receive beta blockers (5.1 percent compared with 8.1 percent; p 0.001).

RECOMMENDATIONS.

Given the overwhelming evidence of benefits of early blockade in AMI, patients without a contraindication who can be treated within 12 hours of the onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty, should receive beta blockers. We do not draw a distinction between AMI patients presenting with ST segment elevation and those presenting without ST segment elevation and therefore consider early beta blockade applicable across the entire spectrum of acute coronary syndromes. For patients presenting within 12 hours of the onset of symptoms or for those presenting with overactivity of the sympathetic nervous system, we prefer to begin beta-blocker therapy intravenously. For patients presenting after 12 hours, especially if there is little sympathetic overactivity, it is our practice to begin beta-blocker therapy orally. Beta blockers are especially helpful in patients in whom infarction is complicated by persistent or recurrent ischemic pain, by progressive or repetitive serum enzyme elevations suggestive of infarct extension, or by tachyarrhythmias early after the onset of infarction. If adverse effects of beta blockers develop or if patients present with complications of infarction that are contraindications to beta blockade such as heart failure or heart block, the beta blocker should be withheld. Unless there are contraindications (see p. 1243), beta blockade probably should be continued in patients who develop AMI.

Selection of Beta Blocker.

Favorable effects have been reported with atenolol, timolol, and alprenolol; these benefits probably occur with propranolol and with esmolol, an ultra-short-acting agent, as well. In the absence of any favorable evidence supporting the benefit of agents with intrinsic sympathomimetic activity, such as pindolol and oxprenolol, and with some unfavorable evidence for these agents in secondary prevention,[420] beta blockers with intrinsic sympathomimetic activity probably should not be chosen for treatment of AMI. Occasionally, the clinician may wish to proceed with beta-blocker therapy even in the

presence of relative contraindications, such as a history of mild asthma, mild bradycardia, mild heart failure, or first-degree heart block. In this situation, a trial of esmolol may help determine whether the patient can tolerate beta blockade.[188] [420] Because the hemodynamic effects of this drug, with a half-life of 9 minutes, disappear in less than 30 minutes, it offers considerable advantage over longer-acting agents when the risk of a beta blocker complication is relatively high.

ACE Inhibitors

In 1992, with the publication of the Survival and Ventricular Enlargement (SAVE) trial,[421] ACE inhibitors were established as an important addition to the list of treatments for AMI. The rationale for their use includes experimental and clinical evidence of a favorable impact on ventricular remodeling, improvement in hemodynamics, and reductions in congestive heart failure.[78] [191] There is now unequivocal evidence from randomized, placebo-controlled mortality trials that ACE inhibitors reduce death from AMI.[199B] These trials may be grouped into two categories. The first *selected* AMI patients for randomization, based on features indicative of increased mortality such as left ventricular ejection fraction less than 40 percent,[421] clinical signs and symptoms of congestive heart failure,[422] anterior location of infarction,[423] and abnormal wall motion score index[424] (Fig. 35-38) . The second group were *unselective* trials that randomized all patients with AMI provided they had a minimum systolic pressure of approximately 100 mm Hg (ISIS-4,[425] GISSI-3,[426] Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] II,[427] and Chinese Captopril Study[428]) (Fig. 35-39) . With the exception of the Survival

Figure 35-38 Effect of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction: Results from the long-term trials. *(From Flather MD, Pfeffer MA: Angiotensin-converting enzyme inhibitors. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 97.)*

Figure 35-39 Effects of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction: results from the short-term trials. *(From Flather MD, Pfeffer MA: Angiotensin-converting enzyme inhibitors. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 1999, p 101.)*

of Myocardial Infarction Long-term Evaluation (SMILE) trial,[423] all of the selective trials initiated ACE inhibitor therapy between 3 and 16 days after AMI and maintained it for 1 to 4 years, whereas the unselective trials all initiated treatment within the first 24 to 36 hours and maintained it for only 4 to 6 weeks.

A consistent survival benefit was observed in all of the trials already noted, except for

CONSENSUS II, the only study that used an intravenous preparation early in the course of AMI.[427] Estimates of the mortality benefit of ACE inhibitors in the unselective, short duration of therapy trials was 5 per 1000 patients treated.[429] [430] Analysis of these unselective short-term trials indicates that approximately one third of the lives saved occurred within the first 1 to 2 days. Certain subgroups such as those with anterior infarction showed proportionately greater benefit from early administration (11 lives saved/1000) of ACE inhibitors. Not unexpectedly, greater survival benefits of 42 to 76 lives saved per 1000 patients treated were obtained in the *selective,* long duration of therapy trials. Of note, there was generally a 20 percent reduction in the risk of death attributable to ACE inhibitor treatment in the selective trials. The mortality reduction with ACE inhibitors is accompanied by significant reductions in the development of congestive heart failure, supporting the underlying pathophysiological rationale for administering this class of drugs in AMI.[421] [422] [424] [426] In addition, some data suggest that ischemic events, including recurrent infarction and the need for coronary revascularization, can also be reduced by chronic administration of ACE inhibitors after an AMI.[431]

The mortality benefits of ACE inhibitors are additive to those achieved with aspirin and beta blockers.[421] [426] Thus, ACE inhibitors should not be considered a substitute for these other therapies with proven benefit in AMI patients.[199B] The benefits of ACE inhibition appear to be a class effect because mortality and morbidity have been reduced by several agents. However, to replicate these benefits in clinical practice, physicians should select a specific agent and prescribe the drug according to the protocols used in the successful clinical trials reported to date.

The major *contraindications* to the use of ACE inhibitors in AMI include hypotension in the setting of adequate preload, known hypersensitivity, and pregnancy. Adverse reactions include hypotension, especially after the first dose, and intolerable cough with chronic dosing; much less commonly angioedema can occur (see Chap. 18) .

The benefits of an alternative method of pharmacological inhibition of the renin-angiotensin system by angiotensin-II receptor antagonists is being evaluated in the VALIANT[431A] and Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan, (OPTIMAAL) trials.[432]

RECOMMENDATIONS.

After administration of aspirin and initiating reperfusion strategies and, where appropriate, beta blockade, *all* AMI patients should be considered for ACE inhibition therapy. Although there is little disagreement that high-risk AMI patients (elderly, anterior infarction, prior infarction, Killip class II or greater, and asymptomatic patients with evidence of depressed global ventricular function on an imaging study) should receive life-long treatment with ACE inhibitors,[191] [433] therapy to a broader group of patients has also been proposed based on the pooled results of the unselective mortality trials.[425] Considering all the available data, we favor a strategy of an initial trial of oral ACE inhibitors in all AMI patients with congestive heart failure as well as in hemodynamically stable patients with ST segment elevation or left bundle branch block, commencing within the first 24 hours.[430] [434] Recommendations for chronic use of ACE

inhibitors are discussed on p. 1203 .

Nitrates

Sublingual nitroglycerin very rarely opens occluded coronary arteries. However, in patients with AMI the potential for reductions in ventricular filling pressures, wall tension, and cardiac work coupled with improvement in coronary blood flow, especially in ischemic zones, and antiplatelet effects make nitrates a logical and attractive pharmacological intervention in AMI.[435] [436]

In patients with AMI, the administration of nitrates reduces pulmonary capillary wedge pressure and systemic arterial pressure, left ventricular chamber volume, infarct size, and the incidence of mechanical complications. As with other interventions to spare ischemic myocardium in AMI, intravenous nitroglycerin appears to be of greatest benefit in patients treated earliest after the onset of symptoms.

CLINICAL TRIAL RESULTS.

In the prethrombolytic era, 10 randomized trials of acute administration of intravenous nitroglycerin (or nitroprusside, another nitric oxide donor) collectively enrolled 2042 patients. A meta-analysis of these trial results showed a reduction in mortality of 35 percent associated with nitrate therapy.

In the thrombolytic era two megatrials of nitrate therapy have been conducted--GISSI-3[426] and ISIS-4.[425] In GISSI-3, there was no independent effect of nitrates on short-term mortality.[426] Similarly, in ISIS-4, no effect of a mononitrate on 35-day mortality was observed. A pooled analysis of over 80,000 patients treated with nitrate-like preparations intravenously or orally in 22 trials revealed a mortality rate of 7.7 percent in the control group, which was reduced to 7.4 percent in the nitrate group. These data are consistent with a small treatment effect of nitrates on mortality such that three to four fewer deaths would occur for every 1000 patients treated.[425]

NITRATE PREPARATIONS AND MODE OF ADMINISTRATION.

Intravenous nitroglycerin can be administered safely to patients with evolving MI as long as the dose is titrated carefully to avoid induction of reflex tachycardia or systemic arterial hypotension. Patients with inferior wall infarction are particularly sensitive to an excessive fall in preload, particularly if concurrent right ventricular infarction is present.[52] In such cases nitrate-induced venodilatation could impair cardiac output and reduce coronary block flow, thus worsening myocardial oxygenation rather than improving it.

A useful regimen employs an initial infusion rate of 5 to 10 mug/min with increases of 5

to 20 mug/min until the mean arterial blood pressure is reduced by 10 percent of its baseline level in normotensive patients and by 30 percent for hypertensive patients, but in no case below a systolic pressure of 90 mm Hg. Alternatively, nitroglycerin may be administered as a sustained-release oral preparation (30 to 60 mg/d) or as an ointment (1 to 3 inches every 6 to 8 hours for patients with a systolic pressure greater than 120 mm Hg). Nitroglycerin can also be given sublingually at doses of 0.3 to 0.6 mg. This route may be more hazardous because the rate of absorption is difficult to control and arterial pressure may decline precipitously.

ADVERSE EFFECTS.

Clinically significant methemoglobinemia has been reported to occur during administration of intravenous nitroglycerin. Although uncommon, this problem is seen when unusually large doses of nitrates are administered. It is important not only for its potential to cause symptoms of lethargy and headache but also because elevated methemoglobin levels can impair the oxygencarrying capacity of blood, potentially exacerbating ischemia. Dilatation of the pulmonary vasculature supplying poorly ventilated lung segments may produce a ventilation-perfusion mismatch.

Tolerance to intravenous nitroglycerin (as manifested by increasing nitrate requirements) develops in many patients, often as soon as 12 hours after the infusion is started. Despite the theoretical and demonstrated benefit of sulfhydryl agents in diminishing tolerance, their use has not become widespread.

RECOMMENDATIONS.

Nitroglycerin is indicated for the relief of persistent pain and as a vasodilator in patients with infarction associated with left ventricular failure. In the absence of recurrent angina or congestive heart failure, we do not routinely prescribe them in AMI patients. Higher-risk patients such as those with large transmural infarctions, especially of the anterior wall, have the most to gain from nitrates in terms of reduction of ventricular remodeling, and we therefore routinely use intravenous nitrates for 24 to 48 hours in such patients. There is no clear benefit to empirical long-term cutaneous or oral nitrates in the asymptomatic patient, and we therefore do not prescribe nitrates beyond the first 48 hours unless angina or ventricular failure is present.

Calcium Antagonists

Despite sound experimental and clinical evidence of an antiischemic effect, calcium antagonists have *not* been found to be helpful in the acute phase of AMI; concern has been raised in several systematic overviews about an increased risk of mortality when they are prescribed on a routine basis to AMI patients.[186] [437] [438] Perhaps in response to the lack of compelling data showing a beneficial effect and concerns about the risk of excess mortality coupled with more convincing evidence of benefit from aspirin and beta blockers, many clinicians have decreased their use of calcium antagonists in the setting of AMI.[26] [439] A distinction should be made between the dihydropyridine type of calcium antagonists (e.g., nifedipine) and the nondihydropyridine calcium antagonists (e.g.,

verapamil and diltiazem).[437]

NIFEDIPINE.

In multiple trials involving a total of over 5000 patients, the immediate-release preparation of nifedipine has not shown any reduction in infarct size, prevention of progression to infarction, control of recurrent ischemia, or lowering of mortality. When trials of the immediate-release form of nifedipine are pooled in a meta-analysis, evidence suggests a dose-related increased risk of in-hospital mortality (especially above 80 mg of nifedipine),[438] [440] although post-hospital mortality does not appear to be increased in nifedipine-treated patients.[441] Nifedipine does not appear to be helpful in conjunction with either thrombolytic therapy or beta blockade.[442] A potential mechanism by which the immediate-release form of nifedipine may be harmful in AMI is coronary hypoperfusion due to an abrupt fall in systolic pressure from peripheral vasodilatation. The abrupt fall in arterial pressure may also provoke a reflex action of the renin-angiotensin system and sympathetic discharge that produces tachycardia. Thus, we do not recommend use of immediate-release nifedipine early in the treatment of AMI. No trials of the sustained-release preparations of nifedipine in AMI have been reported to date.

VERAPAMIL AND DILTIAZEM.

When administered during the acute phase of AMI, these drugs have not had any demonstrated favorable effect on infarct size or other important endpoints in patients with AMI, with the exception of control of supraventricular arrhythmias.[443] Although the possibility has been raised that verapamil and diltiazem in the first few days after AMI may be helpful in preventing reinfarction in patients with non-Q-wave infarction,[443] [444] [445] the data supporting this contention are not statistically robust and require further evaluation in future studies. Subgroup analyses of the Multicenter Diltiazem Postinfarction Trial (MDPIT) and the Danish Verapamil Infarction Trial (DAVIT)-II with both diltiazem and verapamil have suggested that mortality is reduced in patients free of heart failure in the CCU.[446] [447] These subgroup analyses must be interpreted with caution because in the MDPIT study about 50 percent of patients in the placebo and diltiazem groups were also receiving beta blockers that may have contributed to the observed mortality reduction[446] ; in the DAVIT-II study patients with an indication for beta blockers were excluded from the trial.[447] Furthermore, both the MDPIT and DAVIT-II studies were conducted in an era when aspirin, ACE inhibitors, and early use of coronary angiography for recurrent ischemia were not as common as they are now. The Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (INTERCEPT) trial is testing the hypothesis that sustained-release diltiazem will decrease death and cardiac ischemic events in patients receiving thrombolytic therapy for a first AMI.[448]

RECOMMENDATIONS.

Based on the available data, we do *not* recommend the routine use of either verapamil or diltiazem in AMI regardless of whether it is believed that the patient is suffering from a Q-wave or non-Q-wave infarction.[449] Verapamil and diltiazem may be given for relief of

ongoing ischemia or slowing of a rapid ventricular response in atrial fibrillation in patients for whom beta blockers are ineffective or contraindicated.[52] Their use should be avoided in patients with Killip class II or greater hemodynamic findings.

MAGNESIUM

Patients with AMI may have a total body deficit of magnesium because of a low dietary intake, advanced age, or prior diuretic use. They may also acquire a functional deficit of available magnesium due to trapping of free magnesium in adipocytes, because soaps are formed when free fatty acids are released by catecholamine-induced lipolysis with the onset of infarction. Myocardial and urinary losses of magnesium that occur during AMI may increase a patient's magnesium

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requirement. The magnesium cation serves as a critical cofactor in over 300 intracellular enzymatic processes, including several that are integrally involved in mitochondrial function, energy production, maintenance of trans-sarcolemmal ionic gradients, cell volume control, and resting membrane potential.[450] Experimental models of AMI in at least four different animal species have shown that supplemental administration of magnesium before coronary occlusion, during occlusion, coincident with reperfusion, or for a short time interval (15 to 45 minutes) after reperfusion reduces infarct size and prevents myocardial stunning due to reperfusion injury.[208] However, delayed administration of magnesium beyond a very short interval (15 to 60 minutes) after reperfusion is no longer effective in reducing myocardial damage.[208]

Since 1984, several trials of routine supplemental administration of intravenous magnesium in patients with suspected AMI have been conducted. Synthesis of all the trials published before ISIS-4 suggests that the treatment effect of magnesium is greatest in patients at highest risk of mortality and decreases progressively as the mortality risk in the control population decreases.[208] Despite its large sample size, the negative results for magnesium in ISIS-4 do not conclusively exclude benefits of magnesium in AMI. The control group mortality was 7.2 percent in ISIS-4 compared with 7.6 percent in the magnesium group.[425] Given the low control group mortality rate in ISIS-4, the lack of a beneficial effect of magnesium was not unexpected. In addition, ISIS-4 required that acute phase treatment for MI, including lytic therapy, be administered before randomization and that study drugs such as magnesium be administered beyond the "early" lytic phase (e.g., first hour). Because the time for randomization to actual administration of magnesium was not recorded in ISIS-4, the actual relationship between reperfusion and timing of administration of magnesium cannot be determined with certainty but the available information suggests that magnesium was administered relatively late in ISIS-4--a second feature that may have biased ISIS-4 toward a null effect of magnesium. In contrast, Shechter and associates reported a reduction in mortality with magnesium in a high-risk population of patients who were considered unsuitable for thrombolysis.[451] Because of the trivial cost of magnesium, its ease of administration, widespread availability, and the fact that it has the potential to reduce mortality in high-risk AMI patients, another large-scale

randomized multicenter trial (Magnesium in Coronaries [MAGIC]) is underway to define more explicitly the role of magnesium in AMI.[452]

RECOMMENDATIONS.

Because of the risk of cardiac arrhythmias when electrolyte deficits are present in the early phase of infarction, all patients with AMI should have a serum magnesium measurement on admission. We advocate repleting magnesium deficits to maintain a serum magnesium level of 2.0 mEq/liter or more. In the presence of hypokalemia (< 4.0 mEq/liter) during the course of treatment of AMI, the serum magnesium level should be rechecked and repleted if necessary because it is often difficult to correct a potassium deficit in the presence of a concurrent magnesium deficit. Episodes of torsades de pointes should be treated with 1 to 2 gm of magnesium delivered as a bolus over about 5 minutes. Although routine early (ideally < 6 hours from the onset of chest pain) supplemental magnesium administration may be helpful in certain high-risk patients such as the elderly or those for whom reperfusion therapy is contraindicated,[52] additional data are needed before definite recommendations regarding patient selection and dosing can be made. There does not appear to be any benefit to routine late (> 6 hours) administration of magnesium to patients with uncomplicated AMI who do not have electrolyte deficits.

Because it may cause vasodilation and hypotension, magnesium infusions should not be administered in patients with a systolic pressure less than 80 to 90 mm Hg. Patients with renal failure may not excrete magnesium normally and should not be considered candidates for supplemental magnesium infusions.

Other Approaches

GLUCOSE-INSULIN-POTASSIUM.

Administration of a solution of glucose-insulin-potassium (300 gm of glucose, 50 units of insulin, and 80 mEq of KCl in 1000 ml of water administered at a rate of 1.5 ml/kg/hr) lowers the concentration of plasma free fatty acids and improves ventricular performance, as reflected in systolic arterial pressure, cardiac output, and stroke work at any level of left ventricular filling pressure; also the frequency of VPBs decreases.[453] Fath-Ordoubadi and Beatt reported in a meta-analysis of nine studies conducted between 1965 and 1987 enrolling a cumulative total of 1932 patients that the mortality rate was reduced from 21 percent in the placebo group to 16.1 percent in the glucose-insulin-potassium group (OR 0.72, 95 percent CI 0.57-0.90; $p = 0.004$).[454] Subsequently, the Estudios Cardiologicos Latinoamerica (ECLA) group performed a randomized trial of AMI patients treated within 24 hours of onset of symptoms.[455] Mortality was reduced from 15.2 percent in the control group to 5.2 percent in the glucose-insulin-potassium group for the subset of patients who received thrombolysis (OR 0.34; 95 percent CI 0.15-0.77; $p = 0.01$). The findings from the ECLA study raise the possibility that therapeutic metabolic manipulation in AMI patients may be a fruitful avenue of investigation, particularly in specific patient subgroups such as those with left ventricular hypertrophy and those for whom there is a delay until the performance of a

primary catheter-based reperfusion procedure.[456] [457]

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study reported a significant 30 percent relative decrease in mortality at 1 year in diabetics with AMI who received a strict regimen of an insulin-glucose infusion for 24 hours, followed by 3 months of subcutaneous injections of insulin four times daily as compared with standard therapy[458] (Fig. 35-40) . Thus, "infusions of glucose-insulin-potassium (GIK) may provide necessary metabolic support for the ischemic myocardium; this may be particularly important in patients with large anterior infarcts and cardiogenic shock."[84]

INTRAAORTIC BALLOON COUNTERPULSATION. (See also Chap. 19.)

From a theoretical standpoint, intraaortic balloon counterpulsation might be expected to limit infarct size for several reasons. In experimental animals, intraaortic balloon counterpulsation decreases preload, increases coronary blood flow, and improves cardiac performance. No definitive information is available, indicating that intraaortic balloon counterpulsation alters the prognosis in patients with relatively uncomplicated infarction. The Second Primary Angioplasty in Myocardial Infarction (PAMI-II) investigators randomized high-risk patients undergoing primary PTCA to 36 to 48 hours of intraaortic balloon counterpulsation treatment versus traditional care. There was no significant difference in the predefined composite endpoint of death, reinfarction, infarct-related artery reocclusion, stroke, or new-onset heart failure/hypotension in patients treated with an intraaortic balloon counterpulsation versus those treated conservatively.[350] Intraaortic balloon counterpulsation also did not result in enhanced myocardial recovery after PTCA.

Given the relatively frequent rate of complications after intraaortic balloon insertion and the absence of convincing data for infarct size reduction, intraaortic balloon pumping should be reserved for hemodynamically compromised patients and for those with refractory ischemia. Although noninvasive external forms of counterpulsation have been developed, these approaches have not been rigorously studied in patients with AMI.

OTHER AGENTS.

Oxygen-derived free radicals are abundant in ischemic tissue and may contribute to myocardial injury, particularly after

Figure 35-40 Actuarial mortality curves in patients receiving insulin-glucose infusion and in control subjects of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study during 1 year of follow-up. Numbers below graph indicate the number of patients at different times of observation. Active = patients receiving infusion. *(From Malmberg K, Ryden L, Efendic S, et al: Randomized trial of insulin glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): Effects on mortality at 1 year. J Am Coll Cardiol 26:57, 1995.)*

reperfusion (see Chap. 34) . Although evidence from studies in animals suggested that the extent of myocardial necrosis and postischemic dysfunction can be affected favorably by treatment with oxygen free radical scavengers such as superoxide dismutase,[195] initial results in patients have not been encouraging. Given the important role that nitric oxide (NO) plays in regulating platelet activation, interest has arisen in developing techniques for increasing NO production or providing exogenous NO donors in the setting of AMI other than the nitrates discussed earlier. Adenosine, a widely used pharmacological stress agent for detection of coronary artery disease, has been shown in animal models of reperfusion injury to decrease infarct size. The AMISTAD trial tested the hypothesis that a 3-hour infusion of adenosine as an adjunct to thrombolysis would reduce myocardial infarct size.[262] Although there was a reduction in infarct size as determined by single-photon emission computed tomographic cardiac imaging, this observation was restricted to patients with an anterior infarction. Despite the reduction in left ventricular infarct size in the adenosine group, in-hospital clinical outcomes were similar between the two treatment groups.

Previous studies suggested that poloxamer 188 (RheothRx) reduces infarct size and improves left ventricular function. However, the Collaborative Organization for RheothRx Evaluation (CORE) trial showed no effect on the composite endpoint of mortality, reinfarction, or cardiogenic shock but did increase the risk of renal failure in patients with AMI.[459] The HALT-AMI trial tested whether a humanized IgG4 monoclonal antibody that binds to CD11b/CD18 receptors on leukocytes, would reduce MI size in patients treated with primary angioplasty.[460] Although the study drug was well tolerated when given just before angioplasty, no significant reduction in infarct size or major cardiac adverse events was seen.

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Hemodynamic Disturbances

HEMODYNAMIC ASSESSMENT

In patients with clinically uncomplicated AMI, invasive hemodynamic monitoring is *not* necessary because the status of the circulation can be assessed by careful clinical evaluation. This ordinarily consists of monitoring of heart rate and rhythm, repeated measurement of systemic arterial pressure by cuff, obtaining chest roentgenograms to detect heart failure, careful and repeated auscultation of the lung fields for pulmonary congestion, measurement of urine flow, examination of the skin and mucous membranes for evidence of the adequacy of perfusion, and arterial sampling for P_{O_2}, P_{CO_2}, and pH when hypoxemia or metabolic acidosis is suspected.

In contrast, in patients with AMI whose ventricular contractile performance is not normal, it is important to assess the degree of hemodynamic compromise to initiate therapy with drugs such as vasodilators and diuretics. In the past, central venous or right atrial pressure was used to gauge the degree of left ventricular failure in patients with AMI. However, this technique is fraught with error because central venous pressure actually reflects right rather than left ventricular function. Right ventricular function and therefore systemic venous pressure may be normal or nearly so in patients with significant left ventricular failure. Conversely, patients with right ventricular failure due to right ventricular infarction or pulmonary embolism may exhibit elevated right atrial and central venous pressures despite normal left ventricular function. Low values for right atrial and central venous pressures imply hypovolemia, whereas elevated right atrial pressures usually result from right ventricular failure secondary to left ventricular failure, pulmonary hypertension, or right ventricular infarction or less commonly from tricuspid regurgitation or pericardial tamponade.

Major advances in the management of AMI have resulted from the hemodynamic monitoring that has become widespread in CCUs[461] [462] (Table 35-14) (Table Not Available) . This often consists of both an intraarterial catheter and a pulmonary artery catheter for measurement of pulmonary artery, pulmonary artery occlusive (equivalent to pulmonary wedge) and right atrial pressures, and cardiac output by thermodilution. In patients with hypotension, a Foley catheter provides accurate and continuous measurement of urine output.

NEED FOR INVASIVE MONITORING.

The use of invasive hemodynamic monitoring is based on the following principal factors:

1. Difficulty of interpreting clinical and radiographic findings of pulmonary congestion because of phase lags, such as those occurring after diuretic therapy. Severe depression of cardiac index and/or elevation of left ventricular filling pressure may be unsuspected in as many as 15 percent of patients when estimates are based exclusively on clinical criteria.
2. Need for identifying noncardiac causes of arterial hypotension, particularly hypovolemia.
3. Possible contribution of reduced ventricular compliance to impaired hemodynamics, requiring judicious adjustment of intravascular volume to optimize left ventricular filling pressure.
4. Difficulty in assessing the severity and sometimes even determining the presence of lesions such as mitral regurgitation and ventricular septal defect when the cardiac output or the systemic pressures are depressed.
5. Establishing a baseline of hemodynamic measurements and guiding therapy in patients with clinically apparent pulmonary edema or cardiogenic shock.
6. Underestimation of systemic arterial pressure by the cuff method in patients with intense vasoconstriction.

The prognosis and the clinical status are related to both the cardiac output and the pulmonary artery wedge pressure. Patients with normal cardiac output after AMI have an extremely low expected mortality; prognosis worsens as cardiac output declines. Patients with intraventricular conduction defects, AV block, or both after anterior infarction have lower cardiac indices and higher pulmonary capillary wedge pressures than do patients without these conduction disturbances. On the other hand, patients with these conduction defects and inferior MI usually do not demonstrate such hemodynamic abnormalities.

PULMONARY ARTERY PRESSURE MONITORING.

Patients most likely to benefit from pulmonary artery catheter monitoring

TABLE 35-14 -- INDICATIONS FOR HEMODYNAMIC MONITORING OF ACUTE MYOCARDIAL INFARCTION

(Not Available)

From Gore JM, Zwernet PL: Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS (eds): Modern Coronary Care. Boston, Little, Brown & Co, 1990, p 138.

include those whose AMI is complicated by (1) hypotension that is not easily corrected by fluid administration; (2) hypotension in the presence of congestive heart failure; (3) hemodynamic compromise severe enough to require intravenous vasopressors or vasodilators or intraaortic balloon counterpulsation; (4) mechanical lesions (or suspected ones) such as cardiac tamponade, severe mitral regurgitation, and a ruptured ventricular septum; and (5) right ventricular infarction.[63] Other indications for hemodynamic monitoring include assessment of the effects of mechanical ventilation, differentiating pulmonary disease from left ventricular failure as the cause of hypoxemia, and management of septic shock[185] (see Table 35-14) (Table Not Available) .

Before inserting a pulmonary artery catheter into a patient with an AMI, the physician must decide that the potential benefit of the information to be obtained outweighs any potential risks. Major complications from pulmonary artery catheters are relatively rare (3 to 5 percent of cases), but severe problems can occur, including sepsis, pulmonary infarction, and pulmonary artery rupture. By minimizing the duration of catheterization and by strict adherence to aseptic techniques, risk can be diminished.[462A] Catheter-related bloodstream infections can also be reduced by using antiseptic-impregnated catheters.[463]

Accurate determination of hemodynamics by clinical assessment is difficult in critically ill patients. The use of a pulmonary artery catheter often leads to important changes in therapy that would not have occurred if the hemodynamic information had not been available. Of note, reports exist that complications and mortality may be higher in patients who undergo pulmonary artery catheterization, although such patients are often at higher risk initially. These observations emphasize the importance of patient selection, meticulous technique, and correct interpretation of the data obtained.

Hemodynamic Abnormalities

In 1976, Swan, Forrester, and their associates measured the cardiac output and wedge pressure simultaneously in a large series of patients with AMI and identified four major hemodynamic subsets of patients (Table 35-15) : (1) patients with normal perfusion and without pulmonary congestion (normal cardiac output and normal wedge pressure), (2) patients with normal perfusion and pulmonary congestion (normal cardiac output and elevated wedge pressure), (3) patients with decreased perfusion but without pulmonary congestion (reduced cardiac output and normal wedge pressure), and (4) patients with decreased perfusion and pulmonary congestion (reduced cardiac output and elevated wedge pressure). This classification, which overlaps with a crude clinical classification proposed earlier by Killip and Kimball (see Table 35-15) , has proved to be quite useful, but it should be noted that patients frequently pass from one category to another with

therapy and sometimes apparently even spontaneously.

HEMODYNAMIC SUBSETS.

These are usually reflected in the patient's clinical status. Hypoperfusion usually becomes evident clinically when the cardiac index falls below approximately 2.2 liters/min/m^2 , whereas pulmonary congestion is noted when the wedge pressure exceeds approximately 20 mm Hg. However, approximately 25 percent of patients with cardiac indices less than 2.2 liters/min/m^2 and 15 percent of patients with elevated pulmonary capillary wedge pressures are not recognized clinically. Discrepancies in hemodynamic and clinical classification of patients with AMI arise for a variety of reasons. Patients may exhibit "phase lags" as clinical pulmonary congestion develops or resolves, symptoms secondary to chronic obstructive pulmonary disease may be confused with those resulting from pulmonary congestion, or longstanding left ventricular dysfunction may mask signs of hypoperfusion secondary to compensatory vasoconstriction.[69]

The hemodynamic findings shown in Tables 35-15 and 35-16 allow for rational approaches to therapy. The goals of hemodynamic therapy are to maintain ventricular performance, support blood pressure, and protect jeopardized myocardium. Because these goals occasionally may be at cross-purposes, recognition of the hemodynamic profile, as assessed clinically or as available from hemodynamic monitoring, is required before optimal therapeutic interventions can be designed along the lines discussed here.

Hypotension in the Prehospital Phase

During the prehospital phase of AMI, invasive hemodynamic monitoring is not feasible; during this period, therapy should be guided by frequent clinical assessment and measurement of arterial pressure by cuff, with the recognition that intense vasoconstriction can provide a falsely low pressure measured by this method. Hypotension associated with bradycardia often reflects excessive vagotonia. Relative or absolute hypovolemia is often present when hypotension occurs with a normal or rapid heart rate, particularly among patients receiving diuretics just before the occurrence of infarction. Marked diaphoresis, reduction of fluid intake, or vomiting during the period preceding and accompanying the onset of AMI may all contribute to the development of hypovolemia. Even if the effective vascular volume is normal, relative hypovolemia may be present because ventricular compliance is reduced in AMI and a left ventricular filling pressure as high as 20 mm Hg may be needed to provide an optimal preload.

MANAGEMENT.

In the absence of rales involving more than one third of the lung fields, the patient should be put in the reverse Trendelenburg position, and in those with

TABLE 35-15 -- HEMODYNAMIC CLASSIFICATIONS OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

A. BASED ON CLINICAL EXAMINATION[a]		B. BASED ON INVASIVE MONITORING[b]	
Class	**Definition**	**Subset**	**Definition**
I	Rales and S_3 absent	I	Normal hemodynamics PCWP < 18, CI > 2.2
II	Rales over < 50% of lung	II	Pulmonary congestion PCWP > 18, CI < 2.2
III	Rales over > 50% of lung fields (pulmonary edema)	III	Peripheral hypoperfusion PCWP < 18, CI > 2.2
IV	Shock	IV	Pulmonary congestion and peripheral hypoperfusion PCWP > 18, CI < 2.2

PCWP=pulmonary capillary wedge pressure; CI=cardiac index.

Modified from Killip T, Kimball J: Treatment of myocardial infarction in a coronary care unit: A two year experience with 250 patients. Am J Cardiol 20:457, 1967; and Forrester J, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by the application of hemodynamic subsets. N Engl J Med 295:1356, 1976.
CARDIAC CONDITION 12-20 50-60/12-20 30-40/18-25 12-16
2.5

TABLE 35-16 -- HEMODYNAMIC PATTERNS FOR COMMON CLINICAL CONDITIONS

CARDIAC CONDITION	CHAMBER PRESSURE (mm Hg)				
	RA	**RV**	**PA**	**PCW**	**CI**
Normal	0-6	25/0-6	25/0-12	6-12	2.5
AMI without LVF	0-6	25/0-6	30/12-18	18	2.5
AMI with LVF	0-6	30-40/0-6	30-40/18-25	> 18	> 2.0
Biventricular failure	> 6	50-60/>6	50-60/25	18-25	> 2.0
RVMI	12-20	30/12-20	30/12	12	< 2.0
Cardiac tamponade	12-16	25/12-16	25/12-16	12-16	< 2.0

Pulmonary embolism	12-20	50-60/12-20	50-60/12	< 12	< 2.0

AMI=acute myocardial infarction; CI=cardiac index; LVF=left ventricular failure; PA=pulmonary artery; PCW=pulmonary capillary wedge; RA=right atrium; RV=right ventricle; RVMI=right ventricular myocardial infarction.

From Gore JM, Zwerner PL: Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS (eds): Modern Coronary Care, pp 139-164, 1990.

sinus bradycardia and hypotension, atropine should be administered (0.3 to 0.6 mg intravenously repeated at 3- to 10-minute intervals up to 2.0 mg). If these measures do not correct the hypotension, normal saline should be administered intravenously, beginning with a bolus of 100 ml followed by 50-ml increments every 5 minutes. The patient should be carefully observed and the infusion stopped when the systolic pressure returns to approximately 100 mm Hg, if the patient becomes dyspneic, or if pulmonary rales develop or increase. Because of the poor correlation between LV filling pressure and mean right atrial pressure, assessment of systemic (even central) venous pressure is of limited value as a guide to fluid therapy.

Administration of cardiotonic agents is indicated during the prehospital phase if systemic hypotension persists despite correction of hypovolemia and excessive vagotonia. In the absence of invasive hemodynamic monitoring, assessment of peripheral vascular resistance must be based on clinical observations. If cutaneous vasoconstriction is present, therapy with dobutamine, which stimulates cardiac contractility without unduly accelerating heart rate and which does not increase the impedance to ventricular outflow, may be helpful (see Chap. 18) . In hypotensive patients with AMI with clinical evidence of vasodilatation, an uncommon circumstance, phenylephrine hydrochloride, is preferable, although this agent, which increases coronary as well as peripheral vascular tone, should be used with caution.

Hypovolemic Hypotension

Recognition of hypovolemia is of particular importance in hypotensive patients with AMI because of the hazard it poses and because of the improvement in circulatory dynamics that can be achieved so readily and safely by augmentation of vascular volume. Because hypovolemia is often occult, it is frequently overlooked in the absence of invasive hemodynamic monitoring. Hypovolemia may be absolute, with low LV filling pressure (8 mm Hg), or relative, with normal (8 to 12 mm Hg) or even modestly increased (13 to 18 mm Hg) left ventricular filling pressures. Because of the reduction of left ventricular compliance that occurs with acute ischemia and infarction (see Chap. 34) , LV filling pressures between 13 and 18 mm Hg, although above the upper limits of normal, may actually be suboptimal.

Exclusion of hypovolemia as the cause of hypotension requires the documentation of a reduced cardiac output despite left ventricular filling pressure exceeding 18 mm Hg. If, in a hypotensive patient, the pulmonary capillary wedge pressure (ordinarily measured as the pulmonary artery occlusive pressure) is below this level, fluid challenge should be carried out as described previously. If hypovolemia is documented or suspected, the fluid replaced should resemble the fluid lost. Thus, when a low hematocrit complicates

AMI, infusion of packed red blood cells or whole blood is the treatment of choice. On the other hand, crystalloid or colloid solutions should be administered when the hematocrit is normal or elevated.

Hypotension caused by right ventricular infarction may be confused with that caused by hypovolemia because both are associated with a low, normal, or minimally elevated LV filling pressure. The findings and management of right ventricular infarction are discussed on page 1180 .

The Hyperdynamic State

When infarction is not complicated by hemodynamic impairment, no therapy other than general supportive measures and treatment of arrhythmias is necessary. However, if the hemodynamic profile is of the hyperdynamic state (i.e., elevation of sinus rate, arterial pressure, and cardiac index, occurring singly or together in the presence of a normal or low LV filling pressure) and if other causes of tachycardia such as fever, infection, and pericarditis can be excluded, treatment with beta-adrenoceptor blockers is indicated. Presumably, the increased heart rate and blood pressure are the result of inappropriate activation of the sympathetic nervous system, possibly secondary to augmented release of catecholamines, pain and anxiety, or some combination of these.

LEFT VENTRICULAR FAILURE

Even in the thrombolytic era, left ventricular dysfunction remains the single most important predictor of mortality after AMI (Fig. 35-41) .[20] [22] In patients with AMI, heart failure is characterized either by systolic dysfunction alone or by both systolic and diastolic dysfunction. Left ventricular diastolic dysfunction leads to pulmonary venous hypertension and pulmonary congestion, whereas systolic dysfunction is principally responsible for a depression of cardiac output and of the ejection fraction. Clinical manifestations of left ventricular failure become more common as the extent of the injury to the left ventricle increases. In addition to infarct size, other important predictors of the development of symptomatic left ventricular dysfunction include advanced age and diabetes.[464] Mortality increases in association with the severity of the hemodynamic deficit.[69]

THERAPEUTIC IMPLICATIONS.

Classification of patients with AMI by hemodynamic subsets has therapeutic relevance. As already noted, patients with normal wedge pressures and hypoperfusion often benefit from infusion of fluids, because the peak value of stroke volume is usually not attained until LV filling pressure reaches 18 to 24 mm Hg. However, a low level of left ventricular filling pressure

Figure 35-41 Impact of left ventricular function on survival after myocardial infarction. The curvilinear relationship between left ventricular ejection fraction (LVEF) for patients treated in the thrombolytic era is shown. Among patients with an LVEF below 40 percent, mortality is markedly increased at 6 months. Thus, interventions such as thrombolysis, aspirin, and angiotensin-converting enzyme (ACE) inhibitors should be of considerable benefit in patients with acute myocardial infarction to minimize the amount of left ventricular damage and interrupt the neurohumoral activation seen with congestive heart failure. *(Adapted from Volpi A, De VC, Franzosi MG, et al: Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: Results of the GISSI-2 data base. The Ad Hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. Circulation 88:416-429, 1993. Copyright 1993, American Heart Association.)*

does not imply that left ventricular damage is necessarily slight. Such patients may be relatively hypovolemic and/or may have suffered a right ventricular infarct with or without severe left ventricular damage.

The relation between ventricular filling pressure and cardiac index when preload is increased by an infusion of saline or dextran can provide valuable hemodynamic information, in addition to that obtained from baseline measurements. For example, the ventricular function curve rises steeply (marked increase in cardiac index, small increase in filling pressure) in patients with normal left ventricular function and hypovolemia, whereas the curve rises gradually or remains flat in those patients with a combination of hypovolemia and depressed cardiac function.

Invasive hemodynamic monitoring is essential to guide therapy for patients with severe left ventricular failure (pulmonary capillary wedge pressure > 18 mm Hg *and* cardiac index < 2.5 liters/min/m^2).

AVOIDANCE OF HYPOXEMIA.

Patients whose AMI is complicated by congestive heart failure characteristically develop hypoxemia due to a combination of pulmonary vascular engorgement (and in some cases pulmonary interstitial edema), diminished vital capacity, and respiratory depression from narcotic analgesics. Hypoxemia can impair the function of ischemic tissue at the margin of the infarct and thereby contribute to establishing or perpetuating the vicious circle (see Fig. 35-11) . The ventilation-perfusion mismatch that results in hypoxemia requires careful attention to ventilatory support. Increasing fractions of inspired oxygen (F_{IO_2}) via face mask should be used initially, but if the oxygen saturation of the patient's blood cannot be maintained above 85 to 90 percent on 100 percent F_{IO_2} , strong consideration should be given to endotracheal intubation with positive-pressure ventilation. The improvement of arterial oxygenation and hence myocardial oxygen supply may help to restore ventricular performance. Positive end-expiratory pressure (PEEP) may diminish systemic venous return and reduce effective left ventricular filling pressure. This may require reduction in the amount of PEEP, normal saline infusions to maintain LV filling pressure, adjustment of the rate of infusion of vasodilators such as nitroglycerin, or some combination. Because myocardial ischemia frequently occurs during the return to unsupported spontaneous breathing, the

weaning process should be accompanied by observation for signs of ischemia and is potentially facilitated by a period of intermittent mandatory ventilation or pressure support ventilation before extubation. Continuous ST segment monitoring has been recommended for these patients.

When wheezing complicates pulmonary congestion, bronchodilators that act primarily on $beta_2$ -adrenoceptors, such as metaproterenol, given as an aerosol, or terbutaline, are more desirable than conventional bronchodilators such as isoproterenol or epinephrine. The latter act primarily on $beta_1$ -receptors, which, by increasing myocardial oxygen consumption, can increase ischemia. Racemic $beta_2$ agonists are composed of a 50:50 mixture of R and S isomers. The R isomers exhibit virtually all the bronchodilation, whereas the S isomers enhance bronchial reactivity to methacholine, eosinophil activation, and histamine-induced influx of fluid, proteins, and neutrophils into the airspaces. As suggested by Handley, use of pure R isomers of $beta_2$ -adrenoceptor agonists may permit bronchodilation with few beta-adrenoceptor-mediated side effects.[465]

Although positive inotropic agents may be useful, they do not represent the initial therapy of choice in patients with AMI. Instead, heart failure is managed most effectively first by reduction of ventricular preload and then, if possible, by lowering afterload. Arrhythmias may contribute to hemodynamic compromise and should be treated promptly in patients with left ventricular failure.

DIURETICS. (See also Chap. 18.)

Mild heart failure in patients with AMI frequently responds well to diuretics such as furosemide, administered intravenously in doses of 10 to 40 mg, repeated at 3- to 4-hour intervals if necessary. The resultant reduction of pulmonary capillary pressure reduces dyspnea, and the lowering of LV wall tension that accompanies the reduction of LV diastolic volume diminishes myocardial oxygen requirements and may lead to improvement of contractility and augmentation of the ejection fraction, stroke volume, and cardiac output. The reduction of elevated LV filling pressure may also enhance myocardial oxygen delivery by diminishing the impedance to coronary perfusion attributable to elevated ventricular wall tension. It may also improve arterial oxygenation by reducing pulmonary vascular congestion.

The intravenous administration of furosemide reduces pulmonary vascular congestion and pulmonary venous pressure within 15 minutes, before renal excretion of sodium and water has occurred; presumably this action results from a direct dilating effect of this drug on the systemic arterial bed. It is important not to reduce left ventricular filling pressure much below 18 mm Hg, the lower range associated with optimal left ventricular performance in AMI, because this may reduce cardiac output further and cause arterial hypotension. Excessive diuresis may also result in hypokalemia, with its attendant risk of digitalis intoxication.

AFTERLOAD REDUCTION. (See also Chap. 18.)

Myocardial oxygen requirements depend on LV wall stress, which in turn is proportional to the product of peak developed left ventricular pressure, volume, and wall thickness. Vasodilator therapy is recommended in patients with AMI complicated by (1) heart failure unresponsive to treatment with diuretics, (2) hypertension, (3) mitral regurgitation, or (4) ventricular septal defect. In these patients, treatment with vasodilator agents increases stroke volume and may reduce myocardial oxygen requirements and thereby lessen ischemia. Hemodynamic monitoring of systemic arterial and, in many cases, pulmonary capillary wedge (or at least pulmonary artery) pressure and cardiac output in patients treated with these agents is important. Improvement of cardiac performance

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and energetics requires three simultaneous effects: (1) reduction of LV afterload, (2) avoidance of excessive systemic arterial hypotension in order to maintain effective coronary perfusion pressure, and (3) avoidance of excessive reduction of ventricular filling pressure with consequent diminution of cardiac output. In general, pulmonary capillary wedge pressure should be maintained at approximately 20 mm Hg and arterial pressure above 90/60 mm Hg in patients who were normotensive before developing the AMI.

Vasodilator therapy is particularly useful when AMI is complicated by mitral regurgitation or rupture of the ventricular septum. In such patients, vasodilators alone or in combination with intraaortic balloon counterpulsation can sometimes serve as a "holding maneuver" and provide hemodynamic stabilization to permit definitive catheterization and angiographic studies to be carried out and to prepare the patient for early surgical intervention. Because of the precarious state of patients with complicated infarction and the need for meticulous adjustment of dosage, therapy is best initiated with agents that can be administered intravenously and that have a short duration of action, such as nitroprusside, nitroglycerin, or isosorbide dinitrate. After initial stabilization, the medication of choice is generally an ACE inhibitor, but long-acting nitrates given by mouth, sublingually, or by ointment may also be useful.

Nitroglycerin. (See also Chap. 36.)

This drug has been shown in animal experiments to be less likely than nitroprusside to produce a "coronary steal" (i.e., to divert blood flow from the ischemic to the nonischemic zone). Therefore, apart from consideration of its routine use in AMI patients discussed earlier (see p. 1170), it may be a particularly useful vasodilator in patients with AMI complicated by left ventricular failure. Ten to 15 mug/min is infused, and the dose is increased by 10 mug/min every 5 minutes until (1) the desired effect (improvement of hemodynamics or relief of ischemic chest pain) is achieved or (2) a decline in systolic arterial pressure to 90 mm Hg, or by more than 15 mm Hg, has occurred. Although both nitroglycerin and nitroprusside lower systemic arterial pressure, systemic vascular resistance, and the heart rate/systolic blood pressure product, the reduction of LV filling pressure is more prominent with nitroglycerin because of its

relatively greater effect than nitroprusside on venous capacitance vessels. Nevertheless, in patients with severe left ventricular failure, cardiac output often increases despite the reduction in LV filling pressure produced by nitroglycerin.

Oral Vasodilators.

The use of oral vasodilators in the treatment of chronic congestive heart failure is discussed in Chapter 21 . In patients with AMI and persistent heart failure, long-term treatment with a converting enzyme inhibitor should be carried out. This reduced ventricular load decreases the remodeling of the left ventricle that occurs commonly in the period after MI and thereby reduces the development of heart failure and risk of death.[72]

DIGITALIS. (See also Chap. 18.)

Although digitalis increases the contractility and the oxygen consumption of normal hearts, when heart failure is present the diminution of heart size and wall tension frequently results in a net reduction of myocardial oxygen requirements. In animal experiments it fails to improve ventricular performance immediately after experimental coronary occlusion, but salutary effects are elicited when it is administered several days later. The absence of early beneficial effects may be due to the inability of ischemic tissue to respond to digitalis or the already maximal stimulation of contractility of the normal heart by circulating and neuronally released catecholamines.

Although the issue is still controversial, arrhythmias may be increased by digitalis glycosides when they are given to patients in the first few hours after the onset of MI, particularly in the absence of hypokalemia. Also, undesirable peripheral systemic and coronary vasoconstriction may result from the rapid intravenous administration of rapidly acting glycosides such as ouabain.

Administration of digitalis to patients with AMI in the hospital phase should generally be reserved for the management of supraventricular tachyarrhythmias such as atrial flutter and fibrillation and of heart failure that persists despite treatment with diuretics, vasodilators, and beta-adrenoceptor agonists. There is no indication for its use as an inotropic agent in patients without clinical evidence of left ventricular dysfunction, and it is too weak an inotropic agent to be relied on as the principal cardiac stimulant in patients with overt pulmonary edema or cardiogenic shock. It may, however, be useful as a supplement to vasodilator agents and in the maintenance phase of treatment for persistent or recurrent left ventricular failure.[466]

Cardiac glycosides appear to become progressively more effective in the treatment of heart failure as the interval from onset of infarction lengthens; that is, they are more effective in the treatment of chronic than of acute heart failure secondary to ischemic heart disease. Of note, in a direct comparison of captopril versus digoxin for prevention of left ventricular remodeling and dysfunction after AMI, patients in whom captopril therapy was initiated 7 to 10 days after onset of infarction had less left ventricular remodeling and better preserved global left ventricular function than patients receiving

digitalis. In addition, the possibility that continued administration of digitalis might contribute to late mortality in the 2 years after AMI has been raised[467] [468] [469] and debated.[470] [471] Although it is clear that mortality is greater in patients treated with digoxin after AMI, it is not clear that this increase in mortality is due to digoxin itself or to confounding variables that correlate with use of digoxin.[471] At this time, digoxin appears to be indicated in AMI patients only if they exhibit supraventricular tachyarrhythmias or overt heart failure that is not adequately controlled by ACE inhibitors and diuretics.

BETA-ADRENOCEPTOR AGONISTS.

When left ventricular failure is severe, as manifested by marked reduction of cardiac index (< 2 liters/min/m^2), and pulmonary capillary wedge pressure is at optimal (18 to 24 mm Hg) or excessive (> 24 mm Hg) levels despite therapy with diuretics, beta-adrenoceptor agonists are indicated. Although isoproterenol is a potent cardiac stimulant and improves ventricular performance, it should be avoided in AMI patients. It also causes tachycardia and augments myocardial oxygen consumption and lactate production; in addition, it reduces coronary perfusion pressure by causing systemic vasodilation and in animal experiments it increases the extent of experimentally induced infarction. Norepinephrine also increases myocardial oxygen consumption because of its peripheral vasoconstrictor as well as positive inotropic actions.

Dopamine and dobutamine (see Chap. 18) may be particularly useful in patients with AMI and reduced cardiac output, increased left ventricular filling pressure, pulmonary vascular congestion, and hypotension. Fortunately, the potentially deleterious alpha-adrenergic vasoconstrictor effects exerted by dopamine occur only at higher doses than those required to increase contractility. Its vasodilating actions on renal and splanchnic vessels and its positive inotropic effects generally improve hemodynamics and renal function. In patients with AMI and severe left ventricular failure, this drug should be administered at a dose of 3 mug/kg/min while monitoring pulmonary capillary wedge and systemic arterial pressures as well as cardiac output. The dose may be increased stepwise to 20 mug/kg/min, to reduce pulmonary capillary wedge pressure to approximately 20 mm Hg and elevate cardiac index to exceed 2 liters/min/m^2 . However, it must be recognized that doses exceeding 5 mug/kg/min activate peripheral alpha receptors and cause vasoconstriction.

Dobutamine has a positive inotropic action comparable to that of dopamine but a slightly less positive chronotropic effect and less vasoconstrictor activity. In patients with AMI, dobutamine improves left ventricular performance without augmenting enzymatically estimated infarct size.[472] It may be administered in a starting dose of 2.5 mug/kg/min and increased stepwise to a maximum of 30 mug/kg/min. Both dopamine and dobutamine must be given carefully and with constant monitoring of the ECG, systemic arterial pressure, and pulmonary artery or pulmonary artery occlusive pressure and, if possible, with frequent measurements of cardiac output. The dose must be reduced if the heart rate exceeds 100 to 110 beats/min, if supraventricular or ventricular

tachyarrhythmias are precipitated, or if ST segment changes increase.

OTHER POSITIVE INOTROPIC AGENTS.

Milrinone is a noncatecholamine, nonglycoside, phosphodiesterase inhibitor with inotropic and vasodilating action (see Chap. 18) . It is useful in selected patients whose heart failure persists despite treatment with diuretics, who are not hypotensive, and who are likely to benefit from both an enhancement in contractility and afterload reduction. Milrinone should be given as a loading dose of 50 mug/kg over 10 minutes, followed by a maintenance infusion of 0.375 to 0.75 mug/kg/min.

CARDIOGENIC SHOCK

This severest clinical expression of left ventricular failure is associated with extensive damage to the left ventricular myocardium (about 40 percent) in more than 80 percent of AMI patients in whom it occurs; the remainder have a mechanical defect such as ventricular septal or papillary muscle rupture or predominant right ventricular infarction.[473] [473A] In the past, cardiogenic shock has been reported to occur in up to 20 percent of patients with AMI,[474] but estimates from recent large randomized trials of thrombolytic therapy and observational data bases report an incidence rate in the range of 7 percent.[192] [475] About 10 percent of patients with cardiogenic shock present with this condition at the time of admission, whereas 90 percent develop it during hospitalization. This low-output state is characterized by elevated ventricular filling pressures, low cardiac output, systemic hypotension, and evidence of vital organ hypoperfusion (e.g., clouded sensorium, cool extremities, oliguria, acidosis).[190] Patients with cardiogenic shock due to AMI are more likely to be older, to have a history of a prior MI or congestive heart failure, and to have sustained an anterior infarction at the time of development of shock.[190] [475A] Of note, although the incidence of cardiogenic shock in AMI has been relatively stable since the mid 1970s, the short-term mortality decreased from 70 to 80 percent in the 1970s to 50 to 60 percent in the 1990s.[475] Cardiogenic shock is the cause of mortality in about 60 percent of patients dying after thrombolysis for AMI.[476]

PATHOLOGICAL FINDINGS.

At autopsy, more than two thirds of patients with cardiogenic shock demonstrate stenosis of 75 percent or more of the luminal diameter of all three major coronary vessels, usually including the left anterior descending coronary artery. Almost all patients with cardiogenic shock are found to have thrombotic occlusion of the artery supplying the major region of recent infarction with loss of about 40 percent of the left ventricular mass.[473] Other causes of cardiogenic shock in AMI include mechanical defects such as rupture of the ventricular septum, a papillary muscle, or a free wall with tamponade; right ventricular infarction[473] ; or marked reduction of preload due to conditions such as hypovolemia.[477]

Patients who die as a consequence of cardiogenic shock often have "piecemeal" necrosis, that is, progressive myocardial necrosis from marginal extension of their

infarct into an ischemic zone bordering on the infarction. This is generally associated with persistent elevation of CK-MB. Early deterioration in left ventricular function secondary to apparent extension of infarction may, in some cases, result from expansion of the necrotic zone of myocardium without actual extension of the necrotic process (Fig. 35-42) . Shear forces that develop during ventricular systole can disrupt necrotic myocardial muscle bundles, with resultant expansion and thinning of the akinetic zone of myocardium, which in turn results in deterioration of overall left ventricular function.

At autopsy, patients with cardiogenic shock consistently demonstrate marginal extension of recent areas of infarction. Additionally, focal areas of necrosis are frequently found in regions of the left and right ventricles that are not adjacent to the major area of recent infarction. Such extensions and focal lesions are probably in part the result of the shock state itself, because they can also be found in the hearts of patients dying of noncardiogenic shock. Infarction of the ischemic periinfarction zone can be precipitated by a number of factors that adversely affect the supply of oxygen or the metabolic demand in this zone of myocardium. These include a reduction of coronary perfusion pressure that causes impaired myocardial perfusion in the presence of atherosclerotic obstructions of the nonculprit artery. An augmentation of myocardial oxygen demand resulting from the local release of catecholamines from ischemic adrenergic nerve endings in the heart as well as from circulating

Figure 35-42 Infarct expansion after transmural anterior myocardial infarction. *(From Tice FD, Kisslo J: Echocardiographic assessment and monitoring of the patient with AMI: Prospects for the thrombolytic era. In Califf RM, Mark DB, Wagner GS (eds): Acute Coronary Care. St. Louis, Mosby-Year Book, 1995, p 496.)*

endogenous or infused catecholamines may also play a role. Patients with shock due to a mechanical defect often have smaller infarcts than do those with cardiogenic shock secondary to ventricular failure without a mechanical lesion. The prognosis is better in such patients because the smaller infarct allows their left ventricle to support the circulation if the mechanical defect has been corrected surgically.

PATHOPHYSIOLOGY.

The shock state in patients with AMI appears to be the result of a vicious circle, demonstrated in Figure 35-11 (see p. 1124).[190] According to this formulation, coronary obstruction leads to myocardial ischemia, which impairs myocardial contractility and ventricular performance. This, in turn, reduces arterial pressure and therefore coronary perfusion pressure, leading to further ischemia and extension of necrosis until the left ventricle has insufficient contracting myocardium to sustain life. The progressive nature of the myocardial insult in this syndrome is reflected in the stuttering and progressive evolution of elevations in the plasma enzyme-time activity curves of markers specific for

myocardial injury. Consideration of the vicious circle also points to the hazard of hypovolemic hypotension in patients with AMI but without cardiogenic shock. Hypotension, whatever its cause, reduces coronary perfusion, especially of myocardium in the territory of obstructive arteries, and thereby may enhance necrosis.

DIAGNOSIS.

Cardiogenic shock is characterized by marked and persistent (>30 min) hypotension with systolic arterial pressure less than 80 mm Hg and a marked reduction of cardiac index (generally<1.8 liters/mm/m^2) in the face of elevated LV filling pressure (pulmonary capillary wedge pressure>18 mm Hg). Spurious estimates of LV filling pressure based on measurements of the pulmonary artery wedge pressure can occur in the presence of marked mitral regurgitation, in which the tall v wave in the left atrial (and pulmonary artery wedge) pressure tracing elevates the mean pressure above LV end-diastolic pressure. Accordingly, mitral regurgitation and other mechanical lesions, such as ventricular septal defect, ventricular aneurysm, and pseudoaneurysm, must be excluded before the diagnosis of cardiogenic shock due to impairment of left ventricular function can be established. Mechanical complications should be suspected in any patient with AMI in whom circulatory collapse occurs.[190] Immediate hemodynamic, angiographic, and echocardiographic evaluations are necessary in patients with cardiogenic shock. It is important to exclude mechanical complications because primary therapy of such lesions usually requires immediate operative treatment with intervening support of the circulation by intraaortic balloon counterpulsation.

Medical Management

When the aforementioned mechanical complications are not present, cardiogenic shock is due to impairment of left ventricular function. Although dopamine or dobutamine usually improves the hemodynamics in these patients, unfortunately neither appears to improve hospital survival significantly. Similarly, vasodilators have been used in an effort to elevate cardiac output and to reduce left ventricular filling pressure. However, by lowering the already markedly reduced coronary perfusion pressure, myocardial perfusion can be compromised further, accelerating the vicious circle illustrated in Figure 35-11 . Vasodilators may nonetheless be used in conjunction with intraaortic balloon counterpulsation and inotropic agents in an effort to increase cardiac output while sustaining or elevating coronary perfusion pressure.[190]

The systemic vascular resistance is usually elevated in patients with cardiogenic shock, but occasionally resistance is normal and in a few cases vasodilation actually predominates. When systemic vascular resistance is not elevated (i.e., <1800 dyne-sec/cm^5) in patients with cardiogenic shock, norepinephrine, which has both alpha- and beta-adrenoceptor agonist properties (in doses ranging from 2 to 10 g/min), may be employed to increase diastolic arterial pressure, maintain coronary perfusion, and improve contractility. Norepinephrine should be used only when other means, including balloon counterpulsation, fail to maintain arterial diastolic pressure above 50 to 60 mm Hg in a previously normotensive patient. The use of alpha-adrenoceptor agents such as phenylephrine and methoxamine is contraindicated in patients with cardiogenic

shock (unless systemic vascular resistance is inordinately low).

Intraaortic Balloon Counterpulsation (See also Chap. 19)

INDICATIONS.

Intraaortic balloon counterpulsation is used in the treatment of AMI in three groups of patients[478] : (1) those whose conditions are hemodynamically unstable and in whom support of the circulation is required for the performance of cardiac catheterization and angiography carried out to assess lesions that are potentially correctable surgically or by angioplasty; (2) those with cardiogenic shock that is unresponsive to medical management; and (3) rarely, those with persistent ischemic pain that is unresponsive to treatment with inhalation of 100 percent oxygen, beta-adrenoceptor blockade, and nitrates. Unfortunately, among patients with cardiogenic shock, improvement is often only temporary and "balloon dependence" commonly develops. Patients with cardiogenic shock treated with this modality can be successfully weaned from the supporting system only occasionally. Counterpulsation alone does not improve overall survival in patients either with or without a surgically remediable mechanical lesion.

COMPLICATIONS.

These occur infrequently but include damage to or perforation of the aortic wall, ischemia distal to the site of insertion of the balloon in the femoral artery, thrombocytopenia, hemolysis, renal emboli, and mechanical failure such as rupture of the balloon. Those at highest risk include patients with peripheral vascular disease, the elderly, and women, particularly if they are small. These factors should be taken into consideration before an attempt is made to institute intraaortic balloon counterpulsation. Because of the potential for vascular bleeding complications, there has been reluctance to use intraaortic pumps in patients who have undergone thrombolytic therapy. However, despite the increased bleeding risk, because of the poor outcome among patients with shock after thrombolysis (usually ineffective thrombolysis), this modality should be considered in selected patients who are candidates for an aggressive approach to revascularization.

Revascularization

Reversal of cardiogenic shock by acute reperfusion has been reported, usually with thrombolytic therapy, emergency PTCA, or a combination of these measures.[190] In uncontrolled reports, the mortality of patients with cardiogenic shock appears to have been reduced by about 30 percent by early angioplasty or coronary artery bypass surgery.[479] Encouraging evidence favoring early angiography and revascularization has been reported in a cardiogenic shock registry. Another small retrospective series reported that patients with cardiogenic shock who underwent a successful angioplasty had a better 1-year survival than either those who did not undergo a successful angioplasty or those who received only medical therapy. These promising results must be interpreted cautiously because selection bias due to exclusion of elderly and

moribund patients may have inflated the estimate of the beneficial effect of angioplasty.

Of the five therapies frequently used to treat patients with cardiogenic shock (vasopressors, intraaortic balloon counterpulsation, thrombolysis, angioplasty, and CABG), the first two are useful temporizing maneuvers. Surgical

Figure 35-43 (Figure Not Available) Effect of early revascularization in cardiogenic shock. The 6-month mortality is lower in patients with cardiogenic shock from myocardial infarction who were randomized to early revascularization in the SHOCK trial. Subgroups of patients that showed a particular benefit from early revascularization include those patients younger than age 75, a history of prior myocardial infarction, and randomization in less than 6 hours from the onset of symptoms. *(Adapted from data in Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 341:625-634, 1999.)*

treatment in cardiogenic shock (aside from correcting mechanical abnormalities) may involve bypassing occluded as well as severely obstructed nonoccluded vessels. Occlusion of one major vessel may cause left ventricular dysfunction and hypotension, which can then lead to hypoperfusion and ischemia of myocardium subserved by the other diseased vessels. Left ventricular function may be improved by relief of this ischemia with revascularization.

The SHOCK study evaluated early revascularization for the treatment of patients with AMI complicated by cardiogenic shock. Patients with shock due to left ventricular failure complicating MI were randomized to emergency revascularization (n = 152), accomplished by either CABG or angioplasty, or initial medical stabilization (n = 150). In 86 percent of patients in both groups, intraaortic balloon counterpulsation was performed. The primary endpoint was all-cause mortality at 30 days; a secondary endpoint was mortality at 6 months. At 30 days, overall mortality was 46.7 percent in the revascularization group, not significantly different from the 56.0 percent mortality rate observed in the medical-therapy group ($p = 0.11$). However, 6-month mortality was significantly lower in the revascularization group than in the medical-therapy group, with rates of 50.3 percent versus 63.1 percent, respectively ($p = 0.027$). [480] Subgroups of patients in the SHOCK trial that showed particular benefit from the early revascularization strategy (i.e., reduced 6-month mortality) were those who were younger than 75 years of age, had a prior AMI, and were randomized in less than 6 hours from onset of infarction (see Fig. 35-43) (Figure Not Available) .

RECOMMENDATIONS.

We recommend assessment of patients on an individualized basis to determine their desire for aggressive care and overall candidacy for further treatment (e.g., age, mental status, comorbidities). Patients who are potential candidates for revascularization should then rapidly receive intraaortic balloon counterpulsation and be referred for coronary arteriography. Those with suitable anatomy should be revascularized with

angioplasty or CABG. In appropriately selected patients, emergency cardiac transplantation has also been used successfully to manage cardiogenic shock.

RIGHT VENTRICULAR INFARCTION

A characteristic hemodynamic pattern (Table 35-17) has been observed in patients with right ventricular infarction, which frequently accompanies inferior left ventricular infarction or rarely occurs in isolated form. Right-sided heart filling pressures (central venous, right atrial, and right ventricular end-diastolic pressures) are elevated, whereas left ventricular filling pressure is normal or only slightly raised; right ventricular systolic and pulse pressures are decreased, and cardiac output is often markedly depressed. Rarely,

TABLE 35-17 -- FEATURES OF RIGHT VENTRICULAR MYOCARDIAL INFARCTION

Clinical Findings
Normal or depressed right ventricular function
Shock
Tricuspid regurgitation
Ruptured ventricular septum
Hemodynamic Measurements
Abnormally elevated right atrial pressure
Normal right ventricular and pulmonary artery systolic pressures
Increased ratio of right ventricular to left ventricular filling presure
Depressed right ventricular function curve
Scintigraphy
Uptake in right ventricular free wall
Increased right ventricular dimensions and decreased wall motion
Echocardiography
Increased right ventricular dimension
Absence of pericardial effusion
Cardiac Enzymes
Increased magnitude of enzyme values relative to degree of left ventricular dysfunction
Cardiac Catheterization
Involvement of right (usually) or left (rarely) circumflex coronary arteries
Right ventricular akinesis
Differential Diagnosis

Hypotension with acute myocardial infarction
Pericardial tamponade
Constrictive pericarditis
Pulmonary embolus
Modified from Rackley CE, Russell RO Jr, Mantle JA, et al: Right ventricular infarction and function. Am Heart J 101:215, 1981.

this disproportionate elevation of right-sided filling pressure causes right-to-left shunting through a patent foramen ovale. This possibility should be considered in patients with right ventricular infarction who have unexplained systemic hypoxemia. The finding of an elevation in atrial natriuretic factor in this condition has led to the suggestion that abnormally high levels of this peptide might be in part responsible for the hypotension seen in right ventricular infarction. Of note, the same protective effect of ischemic preconditioning that has been described in infarction of the left ventricle has also been reported in patients with infarction of the right ventricle.[481] [482]

Diagnosis

Right ventricular infarction is common among patients with inferior left ventricular infarction. Therefore, otherwise unexplained systemic arterial hypotension or diminished cardiac output or marked hypotension in response to small doses of nitroglycerin in patients with inferior infarction should lead to the prompt consideration of this diagnosis.

Many patients with the combination of normal left ventricular filling pressure and depressed cardiac index have right ventricular infarcts (with accompanying inferior left ventricular infarcts). The hemodynamic picture may superficially resemble that seen in patients with acute pericarditis (see Chap. 50) . It includes elevated right ventricular filling pressure; steep, right atrial *y* descent; and an early diastolic drop and plateau (square root sign) in the right ventricular pressure tracing. Moreover, Kussmaul's sign (an increase in jugular venous pressure with inspiration, see Chap. 4) and pulsus paradoxus (a fall in systolic pressure of greater than 10 mm Hg with inspiration, see Chap. 4) may be present in patients with right ventricular infarction.[52] In fact, Kussmaul's sign in the setting of inferior wall AMI is highly predictive of right ventricular involvement.

ELECTROCARDIOGRAPHY.

The ECG may provide the first clue that right ventricular involvement is present in the patient with inferior wall MI (see Chap. 5) . Most patients with right ventricular infarction have ST segment elevation in lead V_4 R (right precordial lead in V_4 position). [63A] [482] Transient elevation of the ST segment in any of the right precordial leads may occur

with right ventricular MI, and the presence of ST segment elevation of 0.1 mV or more in any one or combination of leads V_4 R, V_5 R, and V_6 R in patients with the clinical picture of acute MI is highly sensitive and specific for the diagnosis of right ventricular MI.[483] Wellens has emphasized that, in addition, noting the presence or absence of convex upward ST segment elevation in V_4 R, clinicians should determine if the T wave is positive or negative; such distinctions help distinguish proximal versus distal occlusion of the right coronary artery versus occlusion of the left circumflex artery[140] (Fig. 35-44) . Elevation of the ST segments in leads V_1 through V_4 due to right ventricular infarction can be confused with that due to anteroseptal infarction. Although the elevated ST segments are oriented anteriorly in both cases, it is the frontal plane that provides important clues--the ST segments are oriented to the right in right ventricular infarction (e.g. +120 degrees) whereas they are oriented to the left in anteroseptal infarction (e.g. -30 degrees).[484]

ECHOCARDIOGRAPHY AND RADIONUCLIDE ANGIOGRAPHY.

Echocardiography is helpful in the differential diagnosis because in right ventricular infarction, in contrast to pericardial tamponade, no significant quantities of pericardial fluid are seen. On two-dimensional echocardiography, abnormal wall motion of the right ventricle as well as right ventricular dilatation and depression of right ventricular ejection fraction are noted.[52] Gated equilibrium radionuclide angiography is also useful for recognizing right ventricular MI. Serial studies have shown that some degree of recovery of an initially depressed right ventricular ejection fraction is the rule with right ventricular MI,[424] whereas this is less apparent in left ventricular ejection fraction.

HEMODYNAMICS.

Loss of atrial transport in patients with right ventricular infarction can result in marked reductions in stroke volume and arterial blood pressure. As already noted, disproportionate elevation of the right-sided filling pressure is the hemodynamic hallmark of right ventricular infarction. Therefore, ventricular pacing may fail to increase cardiac output, and atrioventricular sequential pacing may be required.

Management

Because of their ability to reduce preload, medications routinely prescribed for left ventricular infarction may produce profound hypotension in patients with right ventricular in

Figure 35-44 ST segment and T wave configurations in lead V_4 R in inferoposterior myocardial infarction. Proximal occlusion of the right coronary artery is characterized by ST segment elevation of at least 1 mm and a positive T wave. Distal occlusion of the right coronary artery is characterized by a positive T wave but no ST segment elevation. Occlusion of the circumflex coronary artery is characterized by a negative T wave and ST segment depression of at least 1 mm. *(Reproduced with permission from Wellens HJ: The value of the right precordial leads of the electrocardiogram. N Engl J Med 340:381-383,*

1999.)

farction.[52]

TABLE 35-18 -- TREATMENT STRATEGY FOR RIGHT VENTRICULAR ISCHEMIA/INFARCTION

(Not Available) *From 1999 Updated ACC/AHA AMI Guidelines (Web version), p 66.* *Echocardiographic findings Oxygen step-up in RV May have pericardial effusion* *Prominent v wave in PCW tracing*

In patients with hypotension due to right ventricular MI, hemodynamics may be improved by a combination of expanding plasma volume to augment right ventricular preload and cardiac output and, when left ventricular failure is present, arterial vasodilators[63] (Table 35-18) (Table Not Available) . The initial therapy for hypotension in patients with right ventricular infarction should almost always be volume expansion. However, if hypotension has not been corrected after one or more liters of fluid has been administered briskly, consideration should be given to hemodynamic monitoring with a pulmonary artery catheter, because further volume infusion may be of little use and may produce pulmonary congestion.[485] Vasodilators reduce the impedance to left ventricular outflow and, in turn, left ventricular diastolic, left atrial, and pulmonary (arterial) pressures, thereby lowering the impedance to right ventricular outflow and enhancing right ventricular output (see Table 35-18) (Table Not Available) .

In view of the importance of atrial transport, patients requiring pacing should have atrial or AV sequential pacing. Successful reperfusion of the right coronary artery significantly improves right ventricular mechanical function and lowers in-hospital mortality in patients with right ventricular infarction.[64] Replacement of the tricuspid valve and repair of the valve with annuloplasty rings have been carried out in the treatment of severe tricuspid regurgitation secondary to right ventricular infarction.

MECHANICAL CAUSES OF HEART FAILURE

Free Wall Rupture

The most dramatic complications of AMI are those that involve tearing or rupture of acutely infarcted tissue[486] (Fig. 35-45). The clinical characteristics of these lesions vary considerably and depend on the site of rupture, which may involve the papillary muscles, the interventricular septum, or the free wall of either ventricle. The overall incidence of these complications is hard to assess because clinical and autopsy series differ considerably.[487] [488] However, as a group they are probably responsible for about 15 percent of all deaths from AMI.[486] [489] In general, patients with rupture of a cardiac structure during AMI have a greater delay to hospital admission and are more likely to

have engaged in sustained physical activity after the onset of AMI compared

Figure 35-45 Cardiac rupture syndromes complicating acute myocardial infarction. *A,* Anterior myocardial rupture in an acute infarct (arrow). *B,* Rupture of the ventricular septum (arrow). *C,* Complete rupture of a necrotic papillary muscle. (From Schoen FJ: The heart. *In* Cotran RS, Kumar V, Collins T [eds]: Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, p 562.)

with those AMI patients who do not experience cardiac rupture.[490] The comparative clinical profile of these complications, as gathered from different studies, is shown in Table 35-19 . The incidence of myocardial rupture has increased since the late 1960s.[487] The prior use of corticosteroids or nonsteroidal antiinflammatory agents has been implicated as predisposing to rupture as a result of impaired healign. Controversy remains about the actual relationship between the use of such agents and the frequency of rupture, with several series suggesting a correlation of rupture with their use[491] and others not.[488] Conversely, the early use of thrombolytic therapy appears to reduce the incidence of cardiac rupture, an effect that is responsible in part for improved survival with effective thrombolysis. Late thrombolytic therapy may actually *increase* the risk of cardiac rupture despite improving overall survival.

Rupture of the free wall of the infarcted ventricle (see Fig. 35-45) occurs in up to 10 percent of patients dying in the hospital of AMI.[486] Thinness of the apical wall, marked intensity of necrosis at the terminal end of the blood supply, poor collateral flow, the shearing effect of muscular contraction against an inert and stiffened necrotic area, and aging of the myocardium with laceration of the myocardial microstructure have all been proposed as the local factors that lead to rupture.

CLINICAL FEATURES.

The following are some features that characterize this serious complication of AMI:

1. It occurs more frequently in the elderly and possibly more frequently in women than in men with infarction.[492]
2. It appears to be more common in hypertensive than in normotensive patients.
3. It occurs more frequently in the left than the right ventricle and seldom occurs in the atria.
4. It usually involves the anterior or lateral walls[486] of the ventricle in the area of the terminal distribution of the left anterior descending coronary artery.
5. It is usually associated with a relatively large transmural infarction involving at least 20 percent of the left ventricle.
6. It occurs between 1 day and 3 weeks, but most commonly 1 to 4 days, after infarction.
7. It is usually preceded by infarct expansion (i.e., thinning and a disproportionate dilatation within the softened necrotic zone).
8. Most commonly it results from a distinct tear in the myocardial wall or a dissecting hematoma that perforates a necrotic area of myocardium (see Fig. 35-45).
9. It usually occurs near the junction of the infarct and the normal muscle.

10. It occurs less frequently in the center of the infarct, but when rupture occurs here, it is usually during the second rather than the first week following the infarct.
11. It rarely occurs in a greatly thickened ventricle or in an area of extensive collateral vessels.
12. It most often occurs in patients *without* previous infarction.[488]
13. There is no evidence that the intensity of anticoagulation influences the occurrence of rupture.[492]

Rupture of the free wall of the left ventricle usually leads to hemopericardium and death from cardiac tamponade. Occasionally, rupture of the free wall of the ventricle occurs as the first clinical manifestation in patients with undetected or silent MI, and then it may be considered a form of "sudden cardiac death."

TABLE 35-19 -- CLINICAL PROFILE OF MECHANICAL COMPLICATIONS OF MYOCARDIAL INFARCTION

VARIABLE	VENTRICULAR SEPTAL DEFECT	FREE WALL RUPTURE	PAPILLARY MUSCLE RUPTURE
Age (mean, years)	63	69	65
Days post-MI	3-5	3-6	3-5
Anterior MI	66%	50%	25%
New murmur	90%	25%	50%
Palpable thrill	Yes	No	Rare
Previous MI	25%	25%	30%
Echocardiographic findings			
Two-dimensional	Visualize defect	May have pericardial effusion	Flail or prolapsing leaflet
Doppler	Detect shunt		Regurgitant jet in LA
PA catheterization	Oxygen step-up in RV	Equalization of diastolic pressure	Prominent *c-v* wave in PCW tracing
Mortality			
Medical	90%	90%	90%
Surgical	50%	Case reports	40-90%

MI=myocardial infarction; LA=left atrium; PA=pulmonary artery; RV=right ventricle; PCW=pulmonary capillary wedge.

Modified from Labovitz AJ, et al: Mechanical complications of acute myocardial infarction. Cardiovasc Rev Rep 5:948, 1984.

The course of rupture varies from catastrophic, with an acute tear leading to immediate death, to subacute, with nausea, hypotension, and pericardial type of discomfort being the major clinical clues to its presence.[486] Survival depends on the recognition of this complication, on hemodynamic stabilization of the patient (usually with inotropic agents and/or intraaortic balloon pump), and, most importantly, on prompt surgical repair.

PSEUDOANEURYSM.

Incomplete rupture of the heart may occur when organizing thrombus and hematoma, together with pericardium, seal a rupture of the left ventricle and thus prevent the development of hemopericardium (Fig. 35-46) . With time, this area of organized thrombus and pericardium can become a pseudoaneurysm (false aneurysm) that maintains communication with the cavity of the left ventricle. In contrast to true aneurysms, which always contain some myocardial elements in their walls, the walls of pseudoaneurysms are composed of organized hematoma and pericardium and lack any elements of the original myocardial wall. Pseudoaneurysms can become quite large, even equalign the true ventricular cavity in size, and they communicate with the left ventricular cavity through a narrow neck. Frequently, pseudoaneurysms contain significant quantities of old and recent thrombus, superficial portions of which can cause arterial emboli. Pseudoaneurysms can drain off a portion of each ventricular stroke volume exactly as do true aneurysms. The diagnosis of pseudoaneurysm can usually be made by two-dimensional echocardiography (see Chap. 7) and contrast angiography, although at times differentiation between true aneurysm and pseudoaneurysm may be difficult by any imaging technique.

DIAGNOSIS.

The rupture usually is first suggested by the development of sudden profound shock, often rapidly leading to electromechanical dissociation due to pericardial tamponade. Immediate pericardiocentesis confirms the diagnosis and relieves the pericardial tamponade, at least momentarily. If the patient's condition is relatively stable, echocardiography may help in establishing the diagnosis of tamponade.[52] Under the most favorable conditions, cardiac catheterization can be carried out, not necessarily to confirm the diagnosis of rupture but to delineate the coronary anatomy. This is helpful so that, in addition to ventricular repair, CABG can be performed in patients in whom high-grade obstructive lesions are present. In patients in whom hemodynamics are critically compromised, establishment of the diagnosis should be followed immediately by surgical resection of the necrotic and ruptured myocardium with primary reconstruction (Fig. 35-47) . When rupture is subacute and a pseudoaneurysm is suspected or present, prompt elective surgery is indicated because rupture of the

pseudoaneurysm occurs relatively frequently.

Rupture of the Interventricular Septum

Although rupture of the interventricular septum previously was reported in up to 11 percent of autopsied cases and 2 percent of AMI patients in the prethrombolytic era, it occurs in 0.2 percent of patients in recent thrombolytic trials.[486] [493] [494] Clinical features associated with an increased risk of rupture of the interventricular septum include lack of development of a collateral network, advanced age, hypertension, anterior location of infarction, and possibly thrombolysis.[493] [494] Patients who develop a rupture of the

Figure 35-46 Differences between a pseudoaneurysm and a true aneurysm. *(From Shah PK: Complications of acute myocardial infarction. In Parmley W, Chatterjee K [eds]: Cardiology. Philadelphia, JB Lippincott, 1987.)*

Figure 35-47 Management of free wall rupture. Typically, the rupture site is within a larger area of necrotic muscle *(A).* After debridement, pledgeted sutures are placed inside the ventricle and through a tailored prosthetic patch *(B).* The patch is then secured to the free wall *(C).(Courtesy of Dr. David Adams, Division of Cardiac Surgery, Brigham and Women's Hospital.)*

interventricular septum after AMI have a higher 30-day mortality (74 percent) compared with those patients who do not develop this complication (7 percent).[493]

The perforation may range in length from one to several centimeters (see Fig. 35-45). It may be a direct through-and-through opening, or it may be more irregular and serpiginous. The size of the defect determines the magnitude of the left-to-right shunt and the extent of hemodynamic deterioration, which in turn affects the likelihood of survival.[486] As in rupture of the free wall of the ventricle, transmural infarction underlies rupture of the ventricular septum. Rupture of the septum with an anterior infarction tends to be apical in location, whereas inferior infarctions are associated with perforation of the basal septum and with a worse prognosis than those in an anterior location. In contrast to rupture of the free wall, rupture of the ventricular septum is more likely (20 to 30 percent of cases) to be associated with complete heart block, right bundle branch block, and atrial fibrillation.[495] Virtually all patients have multivessel coronary artery disease, with the majority exhibiting lesions in all of the major vessels. The likelihood of survival depends on the degree of impairment of ventricular function and the size of the defect.[496]

A ruptured interventricular septum is characterized by the appearance of a new harsh, loud holosystolic murmur that is heard best at the lower left sternal border and that is usually accompanied by a thrill.[52] Biventricular failure generally ensues within hours to

days. The defect can also be recognized by two-dimensional echocardiography with color flow Doppler imaging or insertion of a pulmonary artery balloon catheter to document the left-to-right shunt. Catheter placement of an umbrella-shaped device within the ruptured septum has been reported to stabilize the conditions of critically ill patients with acute septal rupture after AMI.

Papillary Muscle Rupture

Partial or total rupture of a papillary muscle is a rare but often fatal complication of transmural MI[486] (see Fig. 35-45). Inferior wall infarction can lead to rupture of the posteromedial papillary muscle,[497] which occurs more commonly than rupture of the anterolateral muscle, a consequence of anterolateral MI. Rupture of a right ventricular papillary muscle is rare but can cause massive tricuspid regurgitation and right ventricular failure. Complete transection of a left ventricular papillary muscle is incompatible with life because the sudden massive mitral regurgitation that develops cannot be tolerated. Rupture of a portion of a papillary muscle, usually the tip or head of the muscle, resulting in severe, although not necessarily overwhelming, mitral regurgitation, is much more frequent and is not immediately fatal. Unlike rupture of the ventricular septum, which occurs with large infarcts, papillary muscle rupture occurs with a relatively small infarction in approximately one half of the cases seen. The extent of coronary artery disease in these patients sometimes is modest as well.

In a small number of patients, rupture of more than one cardiac structure is noted clinically or at postmortem examination; all possible combinations of rupture of the free left ventricular wall, the interventricular septum, and the papillary muscles have been described.[495]

Figure 35-48 Surgical management of mitral regurgitation due to ruptured papillary muscle. Acute papillary muscle rupture results in severe mitral regurgitation due to leaflet and commissural prolapse *(A).* Mitral valve replacement is usually necessary. Mitral debridement with retention of the unruptured commissural and leaflet segment is performed to preserve partial annular papillary continuity *(B).* Mitral valve replacement is then performed *(C).* Occasionally, mitral valve repair can be performed by transfer of a papillary head to a nonrupture segment *(D).(Courtesy of Dr. David Adams, Division of Cardiac Surgery, Brigham and Women's Hospital.)*

As with patients who have a ruptured ventricular septal defect, those with papillary muscle rupture manifest a new holosystolic murmur and develop increasingly severe heart failure. In both conditions the murmur may become softer or disappear as arterial pressure falls. Mitral regurgitation due to partial or complete rupture of a papillary muscle may be promptly recognized echocardiographically.[498] Color flow Doppler imaging is particularly helpful in distinguishing acute mitral regurgitation from a ventricular septal defect in the setting of AMI (Table 35-19) .[499] Therefore, an echocardiogram should be obtained immediately on any patient in whom the diagnosis

is suspected, because hemodynamic deterioration can ensue rapidly. Echocardiography also often permits differentiation of papillary muscle rupture from other, generally less severe forms of mitral regurgitation that occur with AMI.

Differentiation Between Ventricular Septal Rupture and Mitral Regurgitation

It may be difficult, on clinical grounds, to distinguish between acute mitral regurgitation and rupture of the ventricular septum in patients with AMI who suddenly develop a loud systolic murmur. This differentiation can be made most readily by color flow Doppler echocardiography. In addition, a right-heart catheterization with a balloon-tipped catheter can readily distinguish between these two complications. As already noted, patients with ventricular septal rupture demonstrate a "step-up" in oxygen saturation in blood samples from the right ventricle and pulmonary artery compared with those from the right atrium. Patients with acute mitral regurgitation lack this step-up; they may demonstrate tall c-v waves in both the pulmonary capillary wedge and pulmonary arterial pressure tracings.

Invasive monitoring, which is essential in these patients, also allows for the critically important assessment of ventricular function.[52] Right and left ventricular filling pressures (right atrial pressure and pulmonary capillary wedge pressure) dictate fluid administration or the use of diuretics, whereas measurements of cardiac output and mean arterial pressure are obtained for calculation of systemic vascular resistance as a guide for vasodilator therapy. Unless systolic pressure is below 90 mm Hg, this therapy, generally using nitroglycerin or nitroprusside, should be instituted as soon as possible once hemodynamic monitoring is available. This may be critically important for stabilizing the patient's condition in preparation for further diagnostic studies and surgical repair. If vasodilator therapy is not tolerated or if it fails to achieve hemodynamic stability, intraaortic balloon counterpulsation should be rapidly instituted.

Surgical Treatment

Operative intervention is most successful in patients with AMI and circulatory collapse when a surgically correctable mechanical lesion such as ventricular septal defect or mitral regurgitation can be identified and repaired.[493] In such

Figure 35-49 Repair of ischemic ventricular septal defect. The infarct typically involves a free wall and septum (*A* and *B*). Repair of the defect is performed through an incision in the ventricular wall infarct. The septal defect is closed with a prosthetic patch, and a second patch is used to close the incision in the free wall *(C).(Courtesy of Dr. David Adams, Division of Cardiac Surgery, Brigham and Women's Hospital.)*

patients the circulation should at first be supported by intraaortic balloon pulsation and a positive inotropic agent such as dopamine or dobutamine in combination with a vasodilator, unless the patient is hypotensive. Operation should not be delayed in patients with a correctable lesion who agree to an aggressive management strategy and require pharmacological and/or mechanical (counterpulsation) support.[494] Such patients frequently develop a serious complication (infection, adult respiratory distress

syndrome, extension of the infarct, or renal failure) if operation is delayed. Surgical survival is predicted by early operation, short duration of shock, and mild degrees of right and left ventricular impairment.[494] When the hemodynamic status of a patient with one of these mechanical lesions complicating an AMI remains stable after the patient has been weaned from pharmacological and/or mechanical support, it may be possible to postpone operation for 2 to 4 weeks to allow some healign of the infarct to occur. Surgical repair may involve correction of mitral regurgitation, insertion of a prosthetic mitral valve repair, or closure of a ventricular septal defect, usually accompanied by coronary revascularization (Figs. 35-48 and 35-49) .[52]

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Arrhythmias

The genesis, diagnosis, and treatment of cardiac arrhythmias are presented in Chapters 22 to 26 . The role of arrhythmias in complicating the course of patients with AMI and the prevention and treatment of these arrhythmias in this setting are discussed here and summarized in Table 35-20 .

The incidence of arrhythmias is higher in those patients seen earlier after the onset of symptoms. Many serious arrhythmias develop before hospitalization, even before the patient is monitored.[500] Some abnormality of cardiac rhythm also occurs in the majority of patients with AMI treated in CCUs.[501] When patients are seen very early during the course of MI, they almost invariably exhibit evidence of increased activity of the autonomic nervous system. Thus, sinus bradycardia, sometimes associated with AV block, and hypotension reflect augmented vagal activity.

MECHANISM OF ARRHYTHMIAS IN MYOCARDIAL INFARCTION.

Owing to the difficulty of studying cardiac arrhythmias

TABLE 35-20 -- CARDIAC ARRHYTHMIAS AND THEIR MANAGEMENT DURING ACUTE MYOCARDIAL INFARCTION

CATEGORY	ARRHYTHMIA	OBJECTIVE OF TREATMENT	THERAPEUTIC OPTIONS
1. Electrical instability	Ventricular premature beats	Correction of electrolyte deficits and increased sympathetic tone	Potassium and magnesium solutions, beta blocker
	Ventricular tachycardia	Prophylaxis against ventricular fibrillation, restoration of hemodynamic stability	Antiarrhythmic agents; cardioversion/defibrillation
	Ventricular fibrillation	Urgent reversion to sinus rhythm	Defibrillation; bretylium tosylate
	Accelerated idioventricular rhythm	Observation unless hemodynamic function is compromised	Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents
	Nonparoxysmal atrioventricular junctional tachycardia	Search for precipitating causes (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication present
2. Pump failure/excessive sympathetic stimulation	Sinus tachycardia	Reduce heart rate to diminish myocardial oxygen demands	Antipyretics; analgesics; consider beta blocker unless congestive heart failure present; treat latter if present with anticongestive measures (diuretics, afterload reduction)
	Atrial fibrillation and/or atrial flutter	Reduce ventricular rate; restore sinus rhythm	Verapamil, digitalis glycosides; anticongestive measures (diuretics, afterload reduction); cardioversion; rapid atrial pacing (for atrial flutter)

	Paroxysmal supraventricular tachycardia	Reduce ventricular rate; restore sinus rhythm	Vagal maneuvers; verapamil, cardiac glycosides, beta-adrenergic blockers; cardioversion; rapid atrial pacing
3. Bradyarrhythmias and conduction disturbances	Sinus bradycardia	Acceleration of heart rate only if hemodynamic function is compromised	Atropine; atrial pacing
	Junctional escape rhythm	Acceleration of sinus rate only if loss of atrial "kick" causes hemodynamic compromise	Atropine; atrial pacing
	Atrioventricular block and intraventricular block		Insertion of pacemaker

Modified from Antman EM, Rutherford JD (eds): Coronary Care Medicine: A Practical Approach. Boston, Martinus Nijhoff Publishing, 1986, p 78.

in patients with acute myocardial ischemia and infarction, investigators have resorted to animal models of coronary occlusion and release in an attempt to elucidate the causes of arrhythmias in the clinical setting and identify potential therapeutic targets.[502] [503] Animal models have generally been divided into arrhythmias occurring during the early phase of MI (first 30 minutes after coronary occlusion) and arrhythmias occurring during later phases in the infarction process (occurring hours to days and even weeks after infarction).[504] When interpreting animal models to draw correlations to clinical arrhythmias, several factors must be considered: the mode of coronary artery occlusion (thrombotic occlusion versus coronary ligation), number of successive coronary occlusions (e.g., preconditioning), the size of the myocardial ischemic zone, the level of activity of the autonomic nervous system, and the presence or absence of collateral vessels.[505] Electrophysiological disturbances during the acute phase of coronary occlusion in experimental animals that are probably relevant in patients with AMI include a loss of transmembrane resting potential, alterations in refractoriness and excitability, slowing of conduction, and the emergence of abnormal mechanisms of automatic impulse formation. A leading hypothesis for a major mechanism of arrhythmias in the acute phase of coronary occlusion is micro-reentry due to inhomogeneity of the electrical characteristics of ischemic myocardium. Cells at the center of the ischemic zone have a relatively uniform increase in extracellular potassium concentration, whereas cells in the border zone between the ischemic region and normal myocardium are only partially depolarized and therefore have action potentials with a larger amplitude. Slowing of impulse conduction and block occurs in markedly depressed areas leading to arrhythmias such as polymorphic VT and ventricular fibrillation.[506]

The cellular electrophysiological mechanisms for reperfusion arrhythmias appear to include washout of various ions such as lactate and potassium and toxic metabolic substances that have accumulated in the ischemic zone. Cells in reperfused myocardial zones can exhibit action potentials of the slow response type.[504] In animal models in which reperfusion does not take place and a permanent occlusion of the infarct artery occurs, delayed afterdepolarizations and triggered automaticity have been demonstrated. It is unclear whether such phenomena also occur in patients with AMI.

The treatment of tachyarrhythmias involves not only the use of antiarrhythmic drugs but also correction of abnormalities of plasma electrolyte concentrations, acid-base balance disturbances, hypoxemia, anemia, and digitalis intoxication. In addition, it is essential to treat pericarditis, pulmonary emboli, and pneumonia or other infections, which may give rise to sinus tachycardia or other supraventricular tachyarrhythmias.

Arrhythmias occurring in patients with AMI require aggressive treatment when they (1) impair hemodynamics, (2) compromise myocardial viability by augmenting myocardial

oxygen requirements, or (3) predispose to malignant ventricular arrhythmias (i.e., VT, ventricular fibrillation, or asystole). Evidence indicates that both the diminished threshold to ventricular fibrillation[507] and the incidence of malignant ventricular arrhythmias associated with infarction are affected by the extent of the underlying infarction.[508]

HEMODYNAMIC CONSEQUENCES.

Patients with significant left ventricular dysfunction have a relatively fixed stroke volume and depend on changes in heart rate to alter cardiac output. However, there is a narrow range of heart rate over which the cardiac output is maximal, with significant reductions occurring at both faster and slower rates. Thus, all forms of bradycardia and tachycardia may depress the cardiac output in patients with AMI. Although the optimal rate insofar as cardiac output is concerned may exceed 100 beats/min, it is important to consider that heart rate is one of the major determinants of myocardial oxygen consumption and that at more rapid heart rates myocardial energy needs can be elevated to levels that adversely affect ischemic myocardium. Therefore, in patients with AMI, the optimal rate is usually lower, in the range of 60 to 80 beats/min.

A second factor to consider in assessing the hemodynamic consequences of a particular arrhythmia is the loss of the atrial contribution to ventricular preload. Studies in patients without AMI have demonstrated that loss of atrial transport decreases left ventricular output by 15 to 20 percent.[509] However, in patients with reduced diastolic left ventricular compliance of any cause (including AMI), atrial systole is of greater importance for left ventricular filling. In patients with AMI, atrial systole boosts end-diastolic volume by 15 percent, end-diastolic pressure by 29 percent, and stroke

volume by 35 percent.

VENTRICULAR ARRHYTHMIAS (See also Chap. 25)

Ventricular Premature Beats

Before the widespread use of reperfusion therapy, aspirin, beta blockers, and intravenous nitrates in the management of AMI, it was believed that frequent VPB (more than five per minute), VPBs with multiform configuration, early coupling (the "R-on-T" phenomenon), and repetitive patterns in the form of couples or salvos presaged ventricular fibrillation. However, it is now clear that such "warning arrhythmias" are present in as many patients who do not develop fibrillation as those who do. Several reports have shown that primary ventricular fibrillation (see later) occurs without antecedent warning arrhythmias and may even develop in spite of suppression of warning arrhythmias. [510] On the other hand, frequent and complex VPBs and R-on-T beats are commonly observed in patients with AMI who never develop ventricular fibrillation.[510] Both primary ventricular fibrillation and VPBs, especially R-on-T beats, occur during the early phase of AMI when considerable heterogeneity of electrical activity is present. Although R-on-T beats expose this heterogeneity and can precipitate ventricular fibrillation in a small minority of patients, the ubiquitous nature of VPBs in AMI and the extremely infrequent nature of ventricular fibrillation in the current era of AMI management produce unacceptably low sensitivity and specificity of ECG patterns observed on monitoring systems for identifying patients at risk of ventricular fibrillation.

MANAGEMENT.

Because the incidence of ventricular fibrillation in AMI seen in CCUs over the past three decades appears to be declining, the prior practice of prophylactic suppression of VPBs with antiarrhythmic drugs is no longer necessary and there is the possibility that its use may actually be associated with an increased risk of fatal bradycardic and asystolic events.[511] [512] [513] [514] [515] Therefore, we pursue a conservative course when VPBs are observed in AMI and do not routinely prescribe antiarrhythmic drugs but instead determine whether recurrent ischemia or electrolyte (Fig. 35-50) or metabolic disturbances are present.[510]

When, at the very inception of an infarction, VPBs are encountered in the presence of sinus tachycardia, augmented sympathoadrenal stimulation is often a contributing factor and may be treated by beta-adrenoceptor blockade. In fact, early administration of an intravenous beta blocker is effective in reducing the incidence of ventricular fibrillation in evolving MI.[516] [517]

Accelerated Idioventricular Rhythm

Commonly defined as a ventricular rhythm with a rate of 60 to 125 beats/min, and frequently called "slow ventricular tachycardia," this arrhythmia is seen in up to 20 percent of patients with AMI. It occurs frequently during the first 2 days, with about equal frequency in anterior and inferior infarctions, and probably results from enhanced

automaticity of Purkinje fibers. Most episodes are of short duration, and the arrhythmia may terminate abruptly, slow gradually before termination, or be overdriven by acceleration of the basic cardiac rhythm. Variation of the rate is common.

Accelerated idioventricular rhythm is often observed shortly after successful reperfusion has been established.[518] However, the frequent occurrence of these rhythms in patients without reperfusion limits their reliability as markers of restoration of patency of the infarct-related coronary artery.[519] In contrast to rapid ventricular tachycardia, accelerated idioventricular rhythms are thought not to affect prognosis. There is no definitive evidence that this arrhythmia, when left untreated, increases the incidence of either ventricular fibrillation or death. Therefore, we do not routinely treat accelerated idioventricular rhythms. In the rare patient with clear-cut hemodynamic compromise or recurrent angina related to accelerated idioventricular rhythms, we attempt to accelerate the sinus rate with atropine or atrial pacing; suppressive antiarrhythmic therapy with lidocaine or procainamide is usually not used unless there is unequivocal precipitation of more serious ventricular tachyarrhythmias.

Ventricular Tachycardia

Nonsustained ventricular tachycardia (VT) is usually defined as three or more consecutive ventricular ectopic beats (at a rate > 100 beats/min and lasting < 30 seconds; see Fig. 35-18); sustained VT refers to similar rhythms that last longer than 30 seconds or cause hemodynamic compromise *that requires intervention.* (Although most brief runs of VT

Figure 35-50 Importance of electrolyte deficits, as shown in this study in which the risk for ventricular fibrillation was strikingly increased in patients who presented to the critical care unit (CCU) with hypokalemia. *(From Nordrehaug JE, van der Lippe G: Hypokalemia and ventricular fibrillation in acute myocardial infarction. Br Heart J 50:525, 1983.)*

cause some reduction in blood pressure that is observed on arterial line pressure tracings, the majority of such episodes are not recognized by the patient). Additional descriptive features of note for sustained VT are whether the ECG appearance is monomorphic or polymorphic.[520] This may be of importance because the former is more likely to be due to a myocardial scar and require aggressive strategies to prevent its recurrence and the latter may be more responsive to measures directed against ischemia. When continuous ECG recordings during the first 12 hours of AMI are analyzed, nonsustained paroxysms of monomorphic or polymorphic VT may be seen in up to 67 percent of patients.[521] These *nonsustained* runs of ventricular tachycardia do not appear to be associated with an increased mortality risk, either during hospitalization or over the first year. Data from the GUSTO-I trial indicate that in the thrombolytic era, sustained VT occurs in 3.5 percent of patients, ventricular fibrillation in 4.1 percent of patients, and a combination of sustained VT and ventricular fibrillation in 2.7 percent of

patients.[522] Patients who experience sustained VT either in isolation or in combination with ventricular fibrillation have larger infarcts than patients who do not experience sustained VT or ventricular fibrillation. Not unexpectedly, the larger infarcts in patients with sustained VT are associated with a significantly higher risk of congestive heart failure, cardiogenic shock, and atrial fibrillation. The in-hospital mortality rate for patients experiencing only sustained VT is 18.6 percent, whereas those experiencing both sustained VT and ventricular fibrillation have a 44 percent in-hospital mortality.[522] Patients with sustained VT or both VT and ventricular fibrillation who survive to 30 days have a higher 1-year mortality rate (approximately 7 percent) compared with patients who do not experience either arrhythmia (approximately 3 percent).[522]

VT occurring late in the course of AMI is more common in patients with transmural infarction and left ventricular dysfunction, is likely to be sustained, usually induces marked hemodynamic deterioration, and is associated with both an increased hospital mortality and long-term mortality.

MANAGEMENT.

Because hypokalemia may increase the risk of developing VT,[523] low serum potassium levels should be identified quickly after a patient's admission for AMI and should be treated promptly. The serum potassium level should be maintained above 4.5 mEq/liter, and the serum magnesium level should be above 2 mEq/liter.[185]

Rapid abolition of sustained VT in patients with AMI is mandatory because of its deleterious effect on pump function and because it frequently deteriorates into ventricular fibrillation. When the ventricular rate is rapid (150 beats/min) and/or there is a decline in arterial pressure, a single attempt at "thumpversion" (i.e., striking a sharp blow to the precordium) is indicated. Rapid polymorphic VT should be managed similar to ventricular fibrillation, with an unsynchronized discharge of 200 J, whereas monomorphic VT should be treated with a synchronized discharge of 50 to 100 J.[52] Occasionally, lower-energy (10 to 20 J) synchronized discharges can terminate monomorphic VT.

When the ventricular rate is slower than approximately 150 beats/min and the arrhythmia is well tolerated hemodynamically, antiarrhythmic therapy with one of the following regimens should be attempted[52] :

1. *Lidocaine*--initial bolus of 1.0 to 1.5 mg/kg followed by supplemental boluses of 0.5 to 0.75 mg/kg every 5 to 10 minutes as needed to a maximum of 3 mg/kg. A maintenance infusion of 20 to 50 mug/kg/min (1 to 4 mg/min) may then be started. The metabolism of lidocaine is slowed not only in patients with heart failure or hypotension but also in those with diminution of hepatic blood flow due to effects of pharmacological agents such as propranolol. The rate of infusion should be lower in patients with renal failure. Therefore, careful titration is needed to avoid toxicity, manifested primarily by central nervous system hyperactivity, as well as by depression of intraventricular and atrioventricular conduction and cardiac contractility. Saturation of an extravascular pool normally occurs after a continuous infusion of approximately 3 hours, at which time blood levels increase despite

maintenance of a constant infusion rate. At this time, it may be desirable to reduce the rate of administration by about 25 percent.

2. *Procainamide*--loading infusion of 12 to 17 mg/kg over about 20 to 30 minutes, followed by a maintenance infusion of 1 to 4 mg/min (see also Chap. 23) .
3. *Amiodarone*--loading infusion of 150 mg, followed by a constant infusion of 1.0 mg/min for up to 6 hours and then a maintenance infusion at 0.5 mg/min (see also Chap. 23) .

After reversion to sinus rhythm, every effort should be made to correct underlying abnormalities such as hypoxia, hypotension, acid-base or electrolyte disturbances, and digitalis excess. Although no definitive data are available, it is a common clinical practice to continue maintenance infusions of antiarrhythmic drugs for several days after an index episode of VT and to discontinue the drug and either observe the patient for recurrence or perform a diagnostic electrophysiology study. Patients with recurrent or refractory VT should be considered for specialized procedures such as implantation of antitachycardia devices or surgery (see Chap. 24) . Occasionally, urgent attempts at revascularization with angioplasty or CABG may help control refractory VT.[520]

Ventricular Fibrillation

This arrhythmia may occur in three settings in hospitalized patients with AMI. (Its occurrence as a mechanism of sudden death is discussed in Chapter 26.) *Primary* ventricular fibrillation occurs suddenly and unexpectedly in patients with no or few signs or symptoms of left ventricular failure.[520A] Although primary ventricular fibrillation occurred in up to 10 percent of patients hospitalized with AMI several decades ago, analyses suggest that its incidence has declined.[511] [524] Approximately 60 percent of episodes occur within 4 hours and 80 percent within 12 hours of the onset of symptoms.[521] *Secondary* ventricular fibrillation, on the other hand, is often the final event of a progressive downhill course with left ventricular failure and cardiogenic shock. So-called *late* ventricular fibrillation develops more than 48 hours after AMI and frequently but not exclusively occurs in patients with large infarcts and ventricular dysfunction. Patients with intraventricular conduction defects and anterior wall infarction, patients with persistent sinus tachycardia, atrial flutter, or fibrillation early in the clinical course, and those with right ventricular infarction who require ventricular pacing are at higher risk for suffering late in-hospital ventricular fibrillation than are patients without these features.

PROGNOSIS.

The effect of primary ventricular fibrillation on prognosis continues to be debated.[515] The MILIS study, conducted in the prethrombolytic era, suggested that it does not have an adverse effect on hospital mortality, whereas the GISSI investigators, reporting observations in large cohorts of thrombolytic-treated patients, suggest that there is an excess mortality due to primary ventricular fibrillation during the hospital phase but not thereafter.[525] Observations from the GUSTO I trial indicate that the in-hospital mortality of patients with early (within the first 48 hours) ventricular fibrillation is 19.8 percent but survivors to 30 days have a 1-year mortality of 2.7 percent, similar to the 1-year mortality of 30-day survivors who do not experience ventricular fibrillation or VT during

the initial hospitalization for AMI.[522] On the other hand, secondary ventricular fibrillation occurring in association with marked left ventricular

failure or cardiogenic shock, an arrhythmia that typically occurs late (>48 hours) after presentation with AMI, entails a poor prognosis, with an in-hospital mortality rate of 40 to 60 percent.[521] [526] With the availability of amiodarone and new antitachycardia devices, the prognosis of late ventricular fibrillation is improving and is probably driven more by residual ventricular function and recurrent ischemia than the arrhythmic risk per se.[510]

PROPHYLAXIS.

In the early years of MI care in CCUs, concern about the risk of primary ventricular fibrillation led to aggressive monitoring for "warning" ventricular arrhythmias and the initiation of antiarrhythmic therapy when they appeared. Later, when it was shown that warning arrhythmias could not be relied on to predict the risk of ventricular fibrillation, arrhythmia prophylaxis became routine.[527] [528] Lidocaine has been studied most extensively in this regard and has been shown to reduce the incidence of ventricular fibrillation,[529] leading to its widespread routine use in CCUs in patients with known or suspected AMI. However, we no longer endorse that CCU practice for the following reasons:

1. As already noted, the incidence of ventricular fibrillation in patients hospitalized for AMI is decreasing so that the risk for the arrhythmia is now much lower than it was several decades ago (probably under 5 percent). The reasons for this reduction in ventricular fibrillation are not clear but probably include general improvements in the care of AMI patients, greater use of beta blockers, aggressive repletion of electrolytes, prompt treatment of ischemia and congestive heart failure, and reduction in infarct size from reperfusion strategies.[511]
2. There is no evidence that prophylaxis with lidocaine actually reduces mortality in hospitalized patients with AMI because they can almost always be promptly defibrillated.[515] Furthermore, there appear to be trends to excess mortality risk when lidocaine is used on a routine prophylactic basis.[512] [513] [514] [529]
3. Beta-adrenoceptor blockers, which should be administered promptly to the majority of patients with AMI (see p. 1168), have been shown to reduce not only ventricular fibrillation[517] but also mortality from AMI.[510] [530]
4. There is an association between hypokalemia and the risk of ventricular fibrillation in the CCU.[531] [532] (see Fig. 35-50)

Although it has not been conclusively shown that correction of hypokalemia to a level of 4.5 mEq/liter actually reduces the incidence of ventricular fibrillation, our experience suggests that this probably is protective and of little risk. The data on magnesium and the risk of ventricular fibrillation are incomplete at present. Despite the fact that no consistent relationship between hypomagnesemia and ventricular fibrillation has been observed,[532] magnesium deficits may still be involved in the risk of ventricular fibrillation

because intracellular magnesium levels are reduced in AMI and are not adequately reflected by serum measurements. For these reasons, plus the fact that it is often difficult to repair a potassium deficit without administering supplemental magnesium, we routinely replete magnesium to a level of 2 mEq/liter.

The only situation in which we might consider prophylactic lidocaine (bolus of 1.5 mg/kg followed by 20 to 50 mug/kg/min) would be the unusual circumstance in which a patient within the first 12 hours of an AMI must be managed in a facility where cardiac monitoring is not available and equipment for prompt defibrillation is not readily accessible.

MANAGEMENT. (See also Chap. 25.)

The likelihood of successful restoration of an effective cardiac rhythm declines rapidly with time after the onset of uncorrected ventricular fibrillation. Irreversible brain damage may occur within 1 to 2 minutes, particularly in elderly patients. The treatment of ventricular fibrillation is an unsynchronized electrical countershock with at least 200 to 300 J, implemented as rapidly as possible.[52] This interrupts fibrillation and restores an effective cardiac rhythm in patients under direct medical observation in the CCU. When ventricular fibrillation occurs outside an intensive care unit, resuscitative efforts are much less likely to be successful, primarily because the time interval between the onset of the episode and the institution of definitive therapy tends to be prolonged. Because closed-chest cardiopulmonary resuscitation with external cardiac compression provides only a marginal cardiac output even under optimal circumstances, countershock could be implemented as soon as possible after the detection of ventricular fibrillation rather than deferred under the mistaken impression that adequate circulatory and respiratory support can be maintained in the interim. Failure of electrical countershock to restore an effective cardiac rhythm is due almost always to rapidly recurrent VT or ventricular fibrillation, to electromechanical dissociation, or, very rarely, to electrical asystole.

Ventricular fibrillation often recurs rapidly and repeatedly when the metabolic milieu of the heart has been compromised by severe or prolonged hypoxemia, acidosis, electrolyte abnormalities, or digitalis intoxication. Under these conditions, continued cardiopulmonary resuscitation, prompt implementation of pharmacological and ventilatory maneuvers designed to correct these abnormalities, and rapidly repeated attempts with electrical countershock may be effective. Even though repeated shocks with excessive energy may damage the myocardium and elicit arrhythmias, speed is essential and prompt efforts with high-intensity shocks (generally 300 to 400 watt-seconds) are justified. When ventricular fibrillation persists without documented interruption by electrical countershock, administration of epinephrine either by the intracardiac route (up to 10 ml of a 1:10,000 concentration) or intravenous route (1 mg initially) may facilitate a subsequent defibrillation attempt.

Successful interruption of ventricular fibrillation or prevention of refractory recurrent episodes may also be facilitated by administration of bretylium tosylate, 5 mg/kg intravenously, repeated 5 to 20 minutes later if necessary, or amiodarone (75 to 150 mg bolus). When synchronous cardiac electrical activity is restored by countershock but contraction is ineffective (i.e., during electromechanical dissociation), the usual

underlying cause is very extensive myocardial ischemia or necrosis or rupture of the ventricular free wall or septum. If rupture has not occurred, intracardiac administration of calcium gluconate or epinephrine may promote restoration of an effective heartbeat. We do *not* usually administer bicarbonate injections to correct acidosis because of the high osmotic load they impose and the fact that hyperventilation of the patient is probably a more suitable means of clearing the acidosis.

BRADYARRHYTHMIAS

Sinus Bradycardia

Sinus bradycardia is a common arrhythmia occurring during the early phases of AMI, and it is particularly frequent in patients with inferior and posterior infarction.[52] Observations in mobile CCUs indicate that 25 to 40 percent of patients with AMI have ECG evidence of sinus bradycardia within the first hour after the onset of symptoms; however, 4 hours after infarction commences the incidence of sinus bradycardia has declined to 15 to 20 percent.[500] Stimulation of cardiac vagal afferent receptors (which are more common in the inferoposterior than the anterior or lateral portions of the left ventricle), with resulting efferent cholinergic stimulation of the heart, produces vagotonia with resultant bradycardia and hypotension. This is a manifestation of the

Bezold-Jarisch reflex[533] that is mediated by the vagus nerves and occurs during reperfusion, particularly of the right coronary artery.[277] [308] [534] Often sinus bradycardia is a component of vasovagal or vasodepressor response, which may be intensified by severe pain as well as by morphine, and may be related to vasovagal syncope (see Chap. 27) . [535]

On the basis of data obtained in experimental infarction and from some clinical observations, it appears that the increased vagal tone that produces sinus bradycardia during the early phase of AMI may actually be protective, perhaps because it reduces myocardial oxygen demands.[536] Thus, the acute mortality rate appears to be as low in patients with sinus bradycardia as in patients without this arrhythmia.

MANAGEMENT.

Isolated sinus bradycardia, unaccompanied by hypotension or ventricular ectopy, should be observed rather than treated initially. In the first 4 to 6 hours after infarction, if the sinus rate is extremely slow (under 40 to 50 beats/min), administration of intravenous atropine in aliquots of 0.3 to 0.6 mg every 3 to 10 minutes (with a total dose not exceeding 2 mg) to bring heart rate up to approximately 60 beats/min often abolishes the VPBs commonly associated with this degree of sinus bradycardia.[537] Atropine often contributes to restoration of arterial pressure and hence coronary perfusion and should be employed if hypotension accompanying any degree of sinus bradycardia is present. The favorable effects of atropine may be accompanied by regression of ST segment

elevation. Elevation of the lower extremities also often elevates arterial pressure by redistributing blood from the systemic venous bed to the thorax, thereby augmenting ventricular preload, cardiac output, and arterial pressure.

Sinus bradycardia occurring more than 6 hours after the onset of the AMI is often transitory, is caused by sinus node dysfunction or atrial ischemia rather than vagal hyperactivity, is usually not accompanied by hypotension, and does not usually predispose to ventricular arrhythmias. Treatment is not required unless ventricular performance is compromised or the administration of a beta-adrenoceptor blocker or high doses of antiarrhythmic drugs (which may slow the sinus rate further) is planned. When atropine is ineffective and the patient is symptomatic and/or hypotensive, electrical pacing is indicated.[52] In patients with depressed ventricular performance, who require the atrial contribution to ventricular filling, atrial pacing or atrioventricular sequential pacing is superior to simple ventricular pacing.

Atrioventricular and Intraventricular Block

Ischemic injury can produce conduction block at any level of the AV or intraventricular conduction system. Such blocks may occur in the AV node and the bundle of His, producing various grades of AV block; in either main bundle branch, producing right or left bundle branch block; and in the anterior and posterior divisions of the left bundle branch, producing left anterior or left posterior (fascicular) divisional blocks.[538] Disturbances of conduction can, of course, occur in various combinations. The mechanisms and recognition of intraventricular and AV conduction disturbances are discussed in Chapter 22 .

First-Degree AV Block

First-degree AV block occurs in less than 15 percent of patients with AMI admitted to CCUs. His bundle ECG studies have shown that almost all patients with first-degree AV block have disturbances in conduction above the bundle of His (i.e., intranodal). The localization of the site of block is important because development of complete heart block and ventricular asystole is restricted almost exclusively to those patients with first-degree block in whom the conduction disturbance is *below* the bundle of His; this occurs more commonly in patients with anterior infarction and those with associated bifascicular block.

First-degree AV block generally does not require specific treatment. However, if digitalis intoxication is suspected as the cause, this drug should be discontinued. Beta blockers and calcium antagonists (other than nifedipine) prolong AV conduction and may be responsible for first-degree AV block as well. However, discontinuation of these drugs in the setting of AMI has the potential to increase ischemia and ischemic injury. Therefore, it is our practice not to decrease the dosage of these drugs unless the PR interval is greater than 0.24 second. Only if higher-degree block or hemodynamic impairment occurs should these agents be stopped. If the block is a manifestation of excessive vagotonia and is associated with sinus bradycardia and hypotension, administration of atropine, as already outlined, may be helpful. Continued ECG monitoring is important in

such patients in view of the possibility of progression to higher degrees of block.

Second-Degree AV Block

MOBITZ TYPE I OR WENCKEBACH AV BLOCK.

Mobitz type I block occurs in up to 10 percent of patients with AMI admitted to CCUs and accounts for about 90 percent of all patients with AMI and second-degree AV block. This type of block (1) generally occurs within the AV node, (2) is usually associated with narrow QRS complexes, (3) is presumably secondary to ischemic injury, (4) occurs more commonly in patients with inferior than anterior MI, (5) is usually transient and does not persist for more than 72 hours after infarction, (6) may be intermittent, and (7) rarely progresses to complete AV block (Table 35-21) . First-degree and type I second-degree AV blocks do not appear to affect survival, are most commonly associated with occlusion of the right coronary artery, and are caused by ischemia of the AV node.

Specific therapy is not required in patients with second-degree AV block of the Mobitz type I variety when the ventricular rate exceeds 50 beats/min and ventricular irritability, heart failure, and bundle branch block are absent. However, if these complications develop or if the heart rate falls below approximately 50 beats/min and the patient is symptomatic, immediate treatment with atropine (0.3 to 0.6 mg) is indicated; temporary pacing systems are almost never needed in the management of this arrhythmia.

MOBITZ TYPE II AV BLOCK.

This is a rare conduction defect after AMI, occurring in only 10 percent of all cases of second-degree block. Thus, the overall incidence of Mobitz type II block after infarction is less than 1 percent. In contrast to Mobitz type I block, type II second-degree block (1) usually originates from a lesion in the conduction system below the bundle of His, (2) is associated with a wide QRS complex, (3) often but not invariably reflects trifascicular block with impaired conduction distal to the bundle of His, (4) often progresses suddenly to complete AV block, and (5) is almost always associated with anterior rather than inferior infarction (see Table 35-21) .

Because of its potential for progression to complete heart block, Mobitz type II second-degree AV block should be treated with a temporary external or transvenous demand pacemaker with the rate set at approximately 60 beats/min.[52]

Complete (Third-Degree) AV Block

The AV conduction system has a dual blood supply: the AV branch of the right coronary artery and the septal perforating branch from the left anterior descending coronary artery. Therefore, complete AV block can occur in patients

TABLE 35-21 -- ATRIOVENTRICULAR (AV) CONDUCTION DISTURBANCES IN ACUTE MYOCARDIAL INFARCTION

	LOCATION OF AV CONDUCTION DISTURBANCE	
	Proximal	**Distal**
Site of block	Intranodal	Infranodal
Site of infarction	Inferoposterior	Anteroseptal
Compromised arterial supply	RCA (90%), LCX (10%)	Septal perforators of LAD
Pathogenesis	Ischemia, necrosis, hydropic cell swelling, excess parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
Predominant type of AV nodal block	First-degree (PR>200 msec)	Mobitz type II second-degree
	Mobitz type I second-degree	Third-degree
Common premonitory features of third-degree AV block	(a) First-second-degree AV block	(a) Intraventricular conduction block
	(b) Mobitz I pattern	(b) Mobitz II pattern
Features of escape rhythm following third-degree block		
(a) Location	(a) Proximal conduction system (His bundle)	(a) Distal conduction system (bundle branches)
(b) QRS width	(b) < 0.12/sec-*	(b) > 0.12/sec
(c) Rate	(c) 45-60/min but may be as low as 30/min	(c) Often < 30/min
(d) Stability of escape rhythm	(d) Rate usually stable; asystole uncommon	(d) Rate often unstable with moderate to high risk of ventricular asystole
Duration of high-grade AV block	Usually transient (2-3 days)	Usually transient but some form of AV conduction disturbance and/or intraventricular defect may persist

Associated mortality rate	Low unless associated with hypotension and/or congestive heart failure	High because of extensive infarction associated with power failure or ventricular arrhythmias
Pacemaker therapy		
(a) Temporary	(a) Rarely required; may be considered for bradycardia associated with left ventricular power failure, syncope, or angina	(a) Should be considered in patients with anteroseptal infarction and acute bifascicular block
(b) Permanent	(b) Almost never indicated because conduction defect is usually transient	(b) Indicated for patients with high-grade AV block with block in His-Purkinje system and those with transient advanced AV block and associated bundle branch block

RCA=right coronary artery; LCX=left circumflex coronary artery; LAD= left anterior descending coronary artery.

Modified from Antman EM, Rutherford JD: Coronary Care Medicine: A Practical Approach. Boston, Martinus Nijhoff, 1986; Dreifus LS, et al: Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. J Am Coll Cardiol 18:1, 1991. Reprinted with permission from the American College of Cardiology.

*Some studies suggest that a wide QRS escape rhythm (>0.12 sec) following high-grade AV block in inferior infarction is associated with a worse prognosis.

with either anterior or inferior infarction. Complete AV block occurs in about 5 percent of patients in the thrombolytic era, although the incidence may be higher in patients with right ventricular infarction.[63] [539] [540] As with other forms of AV block, the prognosis depends on the anatomical location of the block in the conduction system and the size of the infarction.[541]

Complete heart block in patients with inferior infarction usually results from an intranodal or supranodal lesion[542] and develops gradually, often progressing from first-degree or type I second-degree block (see Table 35-21) . The escape rhythm is usually stable without asystole and often junctional, with a rate exceeding 40 beats/min and a narrow QRS complex in 70 percent of cases and a slower rate and wide QRS in the others. This form of complete AV block is often transient, may be responsive to pharmacological antagonism of adenosine with methylxanthines,[543] [544] and resolves in the majority of patients within a few days. The mortality may approach 15 percent unless right ventricular infarction is present, in which case the mortality associated with complete AV block may be more than doubled.

In patients with anterior infarction, third-degree AV block often occurs suddenly, 12 to 24 hours after the onset of infarction, although it is usually preceded by intraventricular

block and often Mobitz type II (not first-degree or Mobitz type I) AV block (see Table 35-20) . Such patients have unstable escape rhythms with wide QRS complexes and rates less than 40 beats/min; ventricular systole may occur quite suddenly. The mortality in this group of patients is extremely high, 70 to 80 percent.

PROGNOSIS.

This depends on the extent and secondarily on the anatomical site of the myocardial injury.[539] [545] Patients with inferior infarction often have concomitant ischemia or infarction of the AV node secondary to hypoperfusion of the AV nodal artery. However, the His-Purkinje system usually escapes injury in such individuals. Patients with inferior MI who develop AV block usually have lesions in both the right and left anterior descending coronary arteries. Likewise, patients with inferior MI and AV block have larger infarcts and more depressed right ventricular and left ventricular function than do patients with inferior infarct and no AV block. As already noted, junctional escape rhythms with narrow QRS complexes occur commonly in this setting. In patients with anterior infarction, AV block usually develops as a result of extensive septal necrosis that involves the bundle branches. The high mortality in this group of patients with slow idioventricular rhythm and wide QRS complexes is the consequence of extensive myocardial necrosis resulting in severe left ventricular failure and often shock.

Although data suggest that complete AV block is *not* an independent risk factor for mortality, whether temporary transvenous pacing per se improves survival of patients with anterior AMI remains controversial. Some investigators contend that ventricular pacing is useless when employed to correct complete AV block in patients with anterior infarction in view of the poor prognosis in this group

regardless of therapy. However, pacing may protect against transient hypotension with its attendant risks of extending infarction and precipitating malignant ventricular tachyarrhythmias. Also, pacing protects against asystole, a particular hazard in patients with anterior infarction and infranodal block. Improved survival with pacing probably occurs in only a small fraction of patients with complete AV block and anterior wall infarcts because the extensive destruction of the myocardium that almost invariably accompanies this condition results in a very high mortality rate, even in paced patients. Given these considerations, an extremely large series of patients would be required to demonstrate the small reduction of mortality that might be achieved by pacing. The absence of data supporting such an effect, however, by no means excludes the possibility that it may be present.

Pacing is not usually needed in patients with inferior wall infarction and complete AV block that is often transient in nature, but it is indicated if the ventricular rate is very slow (< 40 to 50 beats/min), if ventricular irritability or hypotension is present, or if pump failure develops; atropine is only rarely of value in these patients. Only when complete heart block develops in less than 6 hours after the onset of symptoms is atropine likely

to abolish the AV block or cause acceleration of the escape rhythm. In such cases the AV block is more likely to be transient and related to increases in vagal tone than the more persistent block seen later in the course of MI, which generally requires cardiac pacing.

Intraventricular Block

In the prethrombolytic era, studies of intraventricular conduction disturbances, such as a block within one or more of the three subdivisions (fascicles) of the His-Purkinje system (the anterior and posterior divisions of the left bundle and the right bundle), had been reported to occur in 5 to 10 percent of patients with AMI.[532] [546] [547] Several series in the thrombolytic era suggest that intraventricular blocks occur in 2 to 5 percent of patients with AMI.[540] [548] The right bundle branch and the left posterior division have a dual blood supply from the left anterior descending and right coronary arteries, whereas the left anterior division is supplied by septal perforators originating from the left anterior descending coronary artery. Not all conduction blocks observed in patients with AMI can be considered to be complications of infarcts because almost half are already present at the time the first ECG is recorded, and they may represent antecedent disease of the conduction system.[547] [549] Compared with patients without conduction defects, AMI patients with bundle branch blocks have more comorbid conditions; are less likely to receive therapies such as thrombolytics, aspirin, and beta blockers; and have an increased in-hospital mortality rate.[550]

ISOLATED FASCICULAR BLOCKS.

Isolated left anterior divisional block is unlikely to progress to complete AV block.[546] [551] [552] Mortality is increased in these patients, although not as much as in patients with other forms of conduction block. The posterior fascicle is larger than the anterior fascicle, and, in general, a larger infarct is required to block it. As a consequence, mortality is markedly increased. Complete AV block is not a frequent complication of either form of isolated divisional block.[546] [551] [552]

RIGHT BUNDLE BRANCH BLOCK.

This defect alone occurs in approximately 2 percent of patients with AMI and may lead to AV block because it is often a new lesion, associated with anteroseptal infarction.[547] Isolated right bundle branch block is associated with an increased mortality risk in patients with anterior MI even if complete AV block does not occur, but this appears to be the case only if it is accompanied by congestive heart failure.[547] [551] [553]

BIFASCICULAR BLOCK.

The combination of right bundle branch block with either left anterior or posterior divisional block or the combination of left anterior and posterior divisional blocks (i.e., left bundle branch block) is known as bidivisional or bifascicular block. If a new block occurs in two of the three divisions of the conduction system, the risk of developing complete AV block is quite high. Mortality is also high because of the occurrence of

severe pump failure secondary to the extensive myocardial necrosis required to produce such an extensive intraventricular block.[548] [552] Left bundle branch block occurs in 2 to 5 percent of patients with AMI. Although the latter defect progresses to complete AV block only half as frequently as does right bundle branch block, it is associated with as high a mortality as right bundle branch block and the other two forms of bifascicular block[551] and with a high late mortality. Patients with intraventricular conduction defects, particularly right bundle branch block, account for the majority of patients who develop ventricular fibrillation late in their hospital stay. However, the high mortality in these patients occurs even in the absence of high-grade AV block and appears to be related to cardiac failure and massive infarction rather than to the conduction disturbance.[550]

Preexisting bundle branch block or divisional block is less often associated with the development of complete heart block in patients with AMI than are conduction defects acquired during the course of the infarct.[551] Bidivisional block in the presence of prolongation of the PR interval (first-degree AV block) may indicate disease of the third subdivision rather than of the AV node. In such cases, termed "trifascicular block," nearly 40 percent progress to complete heart block, a risk that is considerably greater than the risk of complete heart block without first-degree AV block.[546]

Complete bundle branch block (either left or right), the combination of right bundle branch block and left anterior divisional (fascicular) block, and any of the various forms of trifascicular block are all more often associated with anterior than inferoposterior infarction. All these forms are more frequent with large infarcts and in older patients and have a higher incidence of other accompanying arrhythmias than is seen in patients without bundle branch block.

Asystole

This arrhythmia has been reported to occur in 1 to 14 percent of patients with AMI admitted to CCUs. This wide variation in incidence reflects differences in the definition of this event. The lower incidence rates include only patients who develop asystole either as a primary event or after abnormalities of AV or intraventricular conduction, whereas the higher rates include patients who develop asystole as a terminal complication. In either event, the mortality is very high.

The presence of apparent ventricular asystole on monitor displays of continuously recorded ECGs may be misleading, because the mechanism may in fact be fine ventricular fibrillation. Because of the predominance of ventricular fibrillation as the cause of cardiac arrest in this setting, initial therapy should include electrical countershock, even if definitive ECG documentation of this arrhythmia is not available. In the rare instance in which asystole can be documented to be the responsible electrophysiological disturbance, immediate transcutaneous pacing (or stimulation with a transvenous pacemaker if one is already in place) is indicated.[52]

Use of Pacemakers in AMI (See also Chap. 24)

TEMPORARY PACING.

Just as is the case for complete AV block, transvenous ventricular pacing has not resulted in statistically demonstrable improvement in prognosis among patients with AMI who develop intraventricular

conduction defects. However, temporary pacing is advisable in some of these patients because of the high risk of developing complete AV block. This includes patients with new bilateral (bifascicular) bundle branch block (i.e., right bundle branch block with left anterior or posterior divisional block and alternating right and left bundle branch block); first-degree AV block adds to this risk. Isolated new block in only one of the three fascicles even with PR interval prolongation and preexisting bifascicular block and normal PR interval poses somewhat less risk; these patients should be monitored closely, with insertion of a temporary pacemaker deferred unless higher-degree AV block occurs.

It has been proposed on the basis of results of an analysis of several large series of well-characterized patients that the risk of developing complete heart block after AMI can be predicted.[552] The presence (new or preexisting) of any of the following conduction disturbances is considered a risk factor: first-degree AV block, Mobitz type I second-degree AV block, Mobitz type II second-degree AV block, left anterior hemiblock, left posterior hemiblock, right bundle branch block, and left bundle branch block. Each risk factor was assigned a score of 1, and the risk score was calculated as the sum of these ECG risk factors. The incidence of complete heart block occurred as follows: risk score 0, 1.2 to 6.8 percent incidence; risk score 1, 7.8 to 10.4 percent incidence; risk score 2, 25.0 to 30.1 percent incidence; and risk score 3, 36 percent or greater incidence.[552] Some authorities have pointed out deficiencies in this scoring system in that Mobitz type II AV block is assigned a score of only 1 point but appears to carry more significance; also there is no differentiation between preexisting and newly appearing bundle branch block.

We believe that failure to demonstrate improved prognosis statistically does not belie the potential value of pacemaker therapy; it probably reflects the overriding impact on mortality of the extensive infarction responsible for the development of the conduction abnormality and the large number of patients required to permit statistical documentation of reduction of mortality.

In assessing the need for temporary pacing (see Table 35-21) , the clinician must keep in mind that between 10 and 20 percent of patients develop pacemaker-related complications. A pericardial friction rub develops in approximately 5 percent of patients but does not necessarily indicate cardiac perforation, nor is such a finding an indication for withdrawal of the pacemaker electrode. Arrhythmias requiring cardioversion, right ventricular perforation, and local infectious complications occur in 1 to 3 percent of

cases. Pacemaker malfunction also occurs rather frequently and is, in part, related to the experience of the clinical team in managing the device and its insertion.

Although external temporary cardiac pacing was introduced in 1952, its widespread clinical use did not occur until relatively recently owing to technical refinements making the technique safe, quickly applicable, and relatively well tolerated. Noninvasive external temporary cardiac pacing is now possible routinely in conscious patients and is acceptable to many but not all patients because of the discomfort.[554] Used in a standby mode, it is virtually free of complications and contraindications and provides an important alternative to transvenous endocardial pacing.[52] Once it is clinically evident that continuous pacing is required, external pacing, which is generally not well tolerated for more than minutes to hours, should be replaced by a temporary transvenous pacemaker.

PERMANENT PACING.

The question of permanent pacing in survivors of AMI associated with conduction defects is still controversial (see Table 35-21) . Patients with inferior infarction with transient type II second-degree block or complete AV block without an associated intraventricular conduction defect do not appear to require permanent pacing. Some contend that prophylactic pacing makes little difference in the long-term survival of patients with AMI and bundle branch block complicated by transient high-degree block. On the other hand, in a retrospective multicenter study, survivors of AMI and bundle branch block who experienced transient high-degree (Mobitz type II second-degree or third-degree) block had a high incidence of recurrent high-degree AV block and sudden death, and this incidence was reduced by insertion of a permanent demand pacemaker.[546] [551] Thus, these findings suggest a role for prophylactic permanent pacing in patients with AMI and bundle branch block with transient high-degree AV block.

The question of the advisability of permanent pacemaker insertion is complicated by the fact that not all sudden deaths in this population are due to recurrent high-degree block. A high incidence of late in-hospital ventricular fibrillation occurs in CCU survivors with anteroseptal MI complicated by either right or left bundle branch block. If the propensity for this arrhythmia continued, ventricular fibrillation rather than asystole due to failure of AV conduction and of the infranodal pacemaker could be responsible for late sudden death.

Long-term pacing is often helpful when complete heart block persists throughout the hospital phase in a patient with AMI, when sinus node function is markedly impaired, or when Mobitz II second- or third-degree block occurs intermittently.[52] When high-grade AV block is associated with newly acquired bundle branch block or other criteria of impairment of conduction system function, prophylactic long-term pacing may be justified as well. Thus, despite the difficulty of proving that long-term pacing improves survival after MI because of the high mortality associated with extensive infarction frequently responsible for high degrees of heart block, prophylactic long-term pacing is prudent.

SUPRAVENTRICULAR TACHYARRHYTHMIAS (See also Chap. 25)

SINUS TACHYCARDIA.

This arrhythmia is typically associated with augmented sympathetic activity and may provoke transient hypertension or hypotension. Common causes are anxiety, persistent pain, left ventricular failure, fever, pericarditis, hypovolemia, pulmonary embolism, and the administration of cardioaccelerator drugs such as atropine, epinephrine, or dopamine; rarely it occurs in patients with atrial infarction. Sinus tachycardia is particularly common in patients with anterior infarction, especially if there is significant accompanying left ventricular dysfunction. It is an undesirable rhythm in patients with AMI because it results in an augmentation of myocardial oxygen consumption, as well as a reduction in the time available for coronary perfusion, thereby intensifying myocardial ischemia and/or external myocardial necrosis. Persistent sinus tachycardia may signify persistent heart failure and under these circumstances is a poor prognostic sign associated with an excess mortality.[52] An underlying cause should be sought and appropriate treatment instituted (e.g., analgesics for pain, diuretics for heart failure, oxygen, beta blockers and nitroglycerin for ischemia, and aspirin for fever or pericarditis.

Administration of beta-adrenoceptor blocking agents, may be helpful in the treatment of sinus tachycardia, particularly when this arrhythmia is a manifestation of hyperdynamic circulation, which is seen particularly in young patients with an initial MI without extensive cardiac damage. However, beta blockade is contraindicated in patients in whom the sinus tachycardia is a manifestation of hypovolemia or of pump failure, the latter reflected by a systolic arterial pressure below 100 mm Hg, rales involving more than one third of the lung fields, a pulmonary capillary wedge pressure exceeding 20 to 25 mm Hg, or a cardiac index below approximately 2.2 liters/min/m^2 . A possible exception to this is a patient in whom persistent ischemia is believed to be the cause or the result of tachycardia: cautious administration of an ultrashort-acting beta-adrenoceptor blocker such as esmolol (25 to 200 mug/kg/min) may be tried to ascertain the patient's response to slowing of the heart rate.[188]

ATRIAL PREMATURE CONTRACTIONS.

Atrial premature contractions, and the atrial tachyarrhythmias (paroxysmal supraventricular tachycardia, atrial flutter, and atrial fibrillation) that they often herald, may be caused by atrial distention secondary to increases in left ventricular diastolic pressure, by pericarditis with its associated atrial epicarditis, or, less commonly, by ischemic injury to the atria and sinus node. Atrial premature beats per se are not associated with an increase in

mortality, and cardiac output is unaffected. No specific therapy is needed, but it should be kept in mind that these beats may indicate excessive autonomic stimulation or the

presence of overt or occult heart failure--conditions that may be assessed by physical examination, chest roentgenography, and echocardiography.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA.

This arrhythmia occurs in less than 10 percent of patients with AMI but requires aggressive management because of the rapid ventricular rate.[462] Augmentation of vagal tone by manual carotid sinus stimulation may restore sinus rhythm. The drug of choice for paroxysmal supraventricular tachycardia in the non-AMI patient is adenosine (6 to 12 mg).[462] Few data exist to guide therapy with adenosine in the AMI patient, but we believe that it can be used safely provided that hypotension (systolic pressure 100 mm Hg) is not present before its administration. Intravenous verapamil (5 to 10 mg), diltiazem (15 to 20 mg), and metoprolol (5 to 15 mg) are suitable alternatives in patients without significant left ventricular dysfunction. In the presence of congestive heart failure or hypotension, direct-current countershock or rapid atrial stimulation via a transvenous intraatrial electrode should be used. Although digitalis glycosides may be useful in augmenting vagal tone, thereby terminating the arrhythmia, their effect is often delayed.

ATRIAL FLUTTER AND FIBRILLATION.

Atrial flutter is the least common major atrial arrhythmia associated with AMI. Atrial flutter is usually transient, and in AMI it is typically a consequence of augmented sympathetic stimulation of the atria, often occurring in patients with left ventricular failure or pulmonary emboli in whom the arrhythmia intensifies hemodynamic deterioration.[500] [555]

Atrial fibrillation is far more common than flutter, occurring in 10 to 20 percent of patients with AMI.[556] [557] As with atrial premature contractions and atrial flutter, fibrillation is usually transient and tends to occur in patients with left ventricular failure but is also observed in patients with pericarditis and ischemic injury to the atria and right ventricular infarction.[63] [558] The increased ventricular rate and the loss of the atrial contribution to left ventricular filling result in a significant reduction in cardiac output. Atrial fibrillation during AMI is associated with increased mortality and stroke, particularly in patients with anterior wall infarction.[557] [559] However, because it is more common in patients with clinical and hemodynamic manifestations of extensive infarction and a poor prognosis, atrial fibrillation is probably a marker of poor prognosis, with only a small independent contribution to increased mortality.

Management.

Atrial flutter and fibrillation in patients with AMI are treated in a manner similar to these conditions in other settings (see Chap. 23) . Because of the possibility that the rapid ventricular rate and hypotension associated with these arrhythmias can increase infarct size and because of the important role played by atrial contraction in the support of cardiac output in patients with AMI, treatment must be prompt, especially when the ventricular rate exceeds 100 beats/min. When hemodynamic decompensation is prominent, electrical cardioversion is indicated, beginning with 25 to 50 J for atrial flutter

and 50 to 100 J for atrial fibrillation, with gradual increase if the initial shock is not successful. For patients without hemodynamic compromise, the first maneuver should be to slow the ventricular rate. Ideally, a beta-adrenoceptor blocker (e.g., metoprolol in 5-mg intravenous boluses every 5 to 10 minutes to a total dose of 15 to 20 mg, followed by 25 to 50 mg orally every 6 hours) should be used because of the combined effects of ischemia and sympathetic tone that are usually present in patients with atrial fibrillation. If there is concern about the patient's ability to tolerate beta blockade, esmolol may be used. Intravenous doses of verapamil or diltiazem are attractive alternatives because of their ability to slow the ventricular rate promptly, but they should be used with caution if at all in patients with pulmonary congestion. In patients with congestive heart failure, digitalis is the principal agent used to slow the ventricular response, although the onset of its effect may be delayed for several hours. Digitalis may be supplemented by small intravenous doses of a beta blocker, which also prolongs the AV nodal refractory period: 1 to 4 mg of propranolol in divided doses is often quite effective in reducing the ventricular rate and is well tolerated, even in patients with mild heart failure and a rapid ventricular rate. An additional important option for the treatment of atrial flutter is the use of rapid atrial stimulation through a transvenous intraatrial electrode. Because of the increased risk of embolism in atrial fibrillation, intravenous anticoagulation with heparin should be instituted in the absence of any contraindications.

Attention should be directed to the management of the underlying cause (usually heart failure), and then a decision must be made about the advisability of antiarrhythmic therapy to restore and maintain sinus rhythm. In patients who have acute atrial flutter or fibrillation without a history of atrial fibrillation and in whom congestive symptoms are either absent or easily controlled, we usually administer intravenous procainamide (2 to 4 mg/min) for 24 to 48 hours. The goal is to achieve pharmacological cardioversion or secondarily to establish a therapeutic concentration of the drug in preparation for direct-current cardioversion.

In view of the mounting evidence of an increased risk of proarrhythmia from antiarrhythmic drugs prescribed for atrial fibrillation, as well as an adverse interaction between recurrent ischemia and antiarrhythmic drugs, we are reluctant to prescribe type I antiarrhythmic agents over the intermediate or long term in patients with AMI.[510] [560] Amiodarone appears to be an increasingly attractive antiarrhythmic drug for suppression of recurrences of atrial fibrillation. This drug is also useful for prevention of ventricular arrhythmias and can block the AV node should atrial fibrillation recur, both desirable features after AMI. It may be prescribed in a low dose (200 mg/d), thereby reducing the risk of toxicity. Although experience is limited, we believe that amiodarone is a logical choice for suppression of atrial fibrillation after AMI; often only a short course of treatment (6 weeks) is needed because the risk of atrial fibrillation decreases as time passes after infarction.

Patients with recurrent episodes of atrial fibrillation should be treated with oral anticoagulants (to reduce the risk of stroke), even if sinus rhythm is present at the time of hospital discharge, because no antiarrhythmic regimen can be relied on to be completely effective in suppressing atrial fibrillation. In the absence of contraindications, the majority of patients should receive a beta blocker after AMI; in addition to their several other beneficial effects in MI and post-MI patients, these agents are helpful in

slowing the ventricular rate should atrial fibrillation recur.

JUNCTIONAL RHYTHMS.

These arrhythmias are often transient, occur during the first 48 hours of the infarction, typically develop and terminate gradually, and are characterized by QRS complexes that resemble those of normally conducted beats. Retrograde P waves may be evident, or AV dissociation may occur, with the junctional rate slightly in excess of the underlying sinus rate. Junctional rhythms fall into two categories:

1. AV junctional rhythm at a rate of 35 to 60 beats/min in which the AV junctional tissue simply assumes the role of the dominant pacemaker when the sinus node is depressed. This arrhythmia is generally a benign protective escape rhythm that is commonly seen among patients with a slow sinus rate in the presence of inferior MI. When there is hemodynamic impairment, transvenous sequential AV pacing may be required to facilitate ventricular performance and maintain adequate peripheral perfusion.
2. Accelerated junctional rhythm (nonparoxysmal junctional tachycardia) is less common and occurs when there is increased automaticity of the junctional tissue, which

usurps the role of pacemaker, usually appearing at a rate of 70 to 130 beats/min. This arrhythmia is seen more commonly with inferior than anterior AMI and may also appear in patients with digitalis intoxication. In studies conducted during the prethrombolytic era, the appearance of accelerated junctional rhythm in the setting of anterior infarction was associated with a poor prognosis, but this was not observed when it occurred in patients with inferior infarction.

OTHER COMPLICATIONS

Recurrent Chest Discomfort

Evaluation of postinfarction chest discomfort may be complicated by previous abnormalities on the ECG and a vague description of the discomfort by the patient who either may be exquisitely sensitive to fleeting discomfort or may deny a potential recrudescence of symptoms. The critical task for clinicians is to distinguish recurrent angina or infarction from nonischemic causes of discomfort that might be caused by infarct expansion, pericarditis, pulmonary embolism, and noncardiac conditions. Important diagnostic maneuvers include a repeat physical examination, repeat ECG, and assessment of the response to sublingual nitroglycerin, 0.4 mg. (The use of noninvasive diagnostic evaluation for recurrent ischemia in patients whose symptoms only appear with moderate levels of exertion is discussed on page 1199 .)

RECURRENT ISCHEMIA AND INFARCTION.

The incidence of postinfarction angina without reinfarction is between 20 and 30 percent.[349] It does not appear to be reduced by the use of thrombolytic therapy as the management strategy during the acute phase[19] but has been reported to be lower in patients who undergo primary PTCA for AMI, especially if stents are used.[337] When accompanied by ST segment and T wave changes in the same leads where Q waves have appeared, it may be due to occlusion of an initially patent vessel, reocclusion of an initially recanalized vessel, or coronary spasm.

Extension of the original zone of necrosis or *reinfarction* in a separate myocardial zone can be a difficult diagnosis, especially within the first 24 hours after the index event.[79] It is more convenient to refer to both extension and reinfarction collectively under the more general term *recurrent infarction.* Circulating cardiac markers may still be elevated from the initial infarction, and it may not be possible to distinguish the ECG changes that are part of the normal evolution after the index infarction from those due to recurrent infarction. Because the cardiac-specific troponins (see p. 1134) remain elevated for more than 1 week after the index event, they are of less value for diagnosing recurrent infarction than are more rapidly rising and falling markers such as CK-MB. Within the first 18 to 24 hours after the initial infarction, when serum cardiac markers may not have returned to the normal range, recurrent infarction should be strongly considered when there is repeat ST segment elevation on the ECG. Although pericarditis remains a possibility in such patients, the two can usually be distinguished by the presence of a rub and the lack of responsiveness to nitroglycerin in patients with pericardial discomfort.

Beyond the first 24 hours, cardiac markers such as CK-MB have usually returned to the normal range; thus, recurrent infarction may be diagnosed either by reelevation of the CK-MB above the upper limit of normal and increased by at least 50 percent of the previous value or by the appearance of new Q waves on the ECG.[52] Because of variations in patient populations and definitions of recurrent infarction, estimates of the incidence of this complication vary; recent large thrombolytic trials report reinfarction rates of 5 to 6 percent.[20] [22] Reinfarction is more common in patients with diabetes mellitus and those with a previous MI, but it cannot be predicted reliably from the angiographic appearance of the coronary artery early after infarction, at least when thrombolytic therapy has been given.

Regardless of whether postinfarction angina is persistent or limited, its presence is important because short-term morbidity is higher among such patients; mortality may be increased if the recurrent ischemia is accompanied by ECG changes and hemodynamic compromise.[52] [561] Recurrent infarction (due in many cases to reocclusion of the infarct-related coronary artery) carries serious adverse prognostic information because it is associated with a twofold to fourfold higher rate of in-hospital complications (congestive heart failure, heart block) and mortality. The mortality rate at 1 to 3 years after the initial infarction is higher in those patients who suffered from recurrent infarction during their index hospitalization.[562] Presumably, the higher mortality is

related to the larger mass of myocardium whose function becomes compromised.

Of the standard therapies that are routinely prescribed during the acute phase of AMI, aspirin and beta blockers have been associated with a reduction in the incidence of recurrent infarction.[52] [349] [563] The data on heparin are less convincing.

Management.

As with the acute phase of treatment of AMI, algorithms for management of patients with recurrent ischemic discomfort at rest center on the 12-lead ECG (Fig. 35-51) . Those patients with ST segment reelevation should either receive repeat thrombolysis[52] [564] or be referred for urgent catheterization and PTCA. Insertion of an intraaortic balloon pump may help stabilize the patient while other procedures are being arranged. For patients believed to have recurrent ischemia who do not have evidence of hemodynamic compromise, an attempt should be made to control symptoms with sublingual or intravenous nitroglycerin and intravenous beta blockade to slow the heart rate to 60 beats/min. When hypotension, congestive heart failure, or ventricular arrhythmias develop during recurrent ischemia, urgent catheterization and revascularization are indicated.

Pericardial Effusion and Pericarditis (See also Chap. 50.)

PERICARDIAL EFFUSION.

Effusions are generally detected echocardiographically, and their incidence varies with technique, criteria, and laboratory expertise. Effusions are more common in patients with anterior MI and with larger infarcts and when congestive heart failure is present.[565] The majority of pericardial effusions that are

Figure 35-51 Treatment of recurrent ischemic events. *(From Cannon CP, Ganz LI, Stone PH: Complicated myocardial infarction. In Rippe JM, Irwin RS, Fink MP, Cerra FB [eds]: Intensive Care Medicine. 3rd ed. Boston, Little, Brown & Co, 1995.)*

seen after AMI do not cause hemodynamic compromise; when tamponade occurs, it is usually due to ventricular rupture or hemorrhagic pericarditis.[99]

The reabsorption rate of a postinfarction pericardial effusion is slow, with resolution often taking several months. The presence of an effusion does not indicate that pericarditis is present; although they may occur together, the majority of effusions occur without other evidence of pericarditis.

PERICARDITIS.

When secondary to transmural AMI, pericarditis may produce pain as early as the first day and as late as 6 weeks after MI. The pain of pericarditis may be confused with that resulting from postinfarction angina, recurrent infarction, or both. An important distinguishing feature is the radiation of the pain to either trapezius ridge, a finding that is nearly pathognomonic of pericarditis and rarely seen with ischemic discomfort.[99] Transmural MI, by definition, extends to the epicardial surface and is responsible for local pericardial inflammation. An acute fibrinous pericarditis (pericarditis epistenocardica) occurs commonly after transmural infarction, but the majority of patients do not report any symptoms from this process.[99] Although transient pericardial friction rubs are relatively common among patients with transmural infarction within the first 48 hours, pain or ECG changes occur much less often. However, the development of a pericardial rub appears to be correlated with a larger infarct and greater hemodynamic compromise. The discomfort of pericarditis usually becomes worse during a deep inspiration, but it may be relieved or diminished when the patient sits up and leans forward.

Although anticoagulation clearly increases the risk for hemorrhagic pericarditis early after MI, this complication has not been reported with sufficient frequency during heparinization or after thrombolytic therapy to warrant absolute prohibition of such agents when a rub is present, but the detection of a pericardial effusion on an echocardiogram is usually an indication for discontinuation of anticoagulation.[99] In patients in whom continuation or initiation of anticoagulant therapy is strongly indicated (such as during cardiac catheterization or after coronary angioplasty), heightened monitoring of clotting parameters and observation for clinical signs of possible tamponade are needed. Late pericardial constriction due to anticoagulant-induced hemopericardium has been reported.

Treatment of pericardial discomfort consists of aspirin, but usually in higher doses than prescribed routinely after infarction: doses of 650 mg orally every 4 to 6 hours may be needed. Nonsteroidal antiinflammatory agents and corticosteroids should be avoided because they may interfere with myocardial scar formation.[566]

DRESSLER SYNDROME.

Also known as the postmyocardial infarction syndrome,[567] Dressler syndrome usually occurs 1 to 8 weeks after infarction. Its incidence is difficult to define because it often blends imperceptibly with the more common early post-MI pericarditis. Dressler cited an incidence of 3 to 4 percent of all AMI patients in 1957, but the incidence has decreased dramatically since that time. Clinically, patients with Dressler syndrome present with malaise, fever, pericardial discomfort, leukocytosis, an elevated ESR, and a pericardial effusion. At autopsy, patients with this syndrome usually demonstrate localized fibrinous pericarditis containing polymorphonuclear leukocytes.[567] The cause of this syndrome is not clearly established, although the detection of antibodies to cardiac tissue has raised the notion of an immunopathological process. Treatment is with aspirin, 650 mg, as often as every 4 hours. Glucocorticosteroids or nonsteroidal antiinflammatory agents are

best avoided in patients with Dressler syndrome within 4 weeks of AMI because of their potential to impair infarct healign, to cause ventricular rupture,[568] and to increase coronary vascular resistance. Aspirin in large doses is effective. Four weeks after AMI, nonsteroidal antiinflammatory agents and in occasional patients corticosteroids are necessary to control what may be severe, recurrent symptoms.

Venous Thrombosis and Pulmonary Embolism

Almost all pulmonary emboli originate from thrombi in the veins of the lower extremities (see Chap. 52) ; much less commonly, they originate from mural thrombi overlying an area of right ventricular infarction. Bed rest and heart failure predispose to venous thrombosis and subsequent pulmonary embolism, and both of these factors occur commonly in patients with AMI, particularly those with large infarcts. Several decades ago, at a time when patients with AMI were routinely subjected to prolonged periods of bed rest, significant pulmonary embolism was found in more than 20 percent of patients with MI coming to autopsy, and massive pulmonary embolism accounted for 10 percent of deaths from AMI.[569] In recent years, with early mobilization and the widespread use of low-dose anticoagulant prophylaxis, especially using low-molecular-weight heparins, pulmonary embolism has become an uncommon cause of death in this condition. When pulmonary embolism does occur in patients with AMI, management is generally along the lines described for noninfarction patients.

Left Ventricular Aneurysm

The term *left ventricular aneurysm* (often termed *true aneurysm*) is generally reserved for a discrete, dyskinetic area of the left ventricular wall with a broad neck (to differentiate it from pseudoaneurysm due to a contained myocardial rupture). True left ventricular aneurysms probably develop in less than 5 to 10 percent of all patients with AMI and perhaps somewhat more frequently in patients with transmural infarction (especially anterior).[57] The wall of the true aneurysm is thinner than the rest of the left ventricle (Fig. 35-46) , and it is usually composed of fibrous tissue as well as necrotic muscle, occasionally mixed with viable myocardium. Aneurysm formation presumably occurs when intraventricular tension stretches the noncontracting infarcted heart muscle, thus producing infarct expansion; a relatively weak, thin layer of necrotic muscle; and fibrous tissue that bulges with each cardiac contraction. With the passage of time, the wall of the aneurysm becomes more densely fibrotic, but it continues to bulge with systole, causing some of the left ventricular stroke volume during each systole to be ineffective.

When an aneurysm is present after anterior MI, there is generally a total occlusion of a poorly collateralized left anterior descending coronary artery. An aneurysm is rarely seen with multivessel disease when there are either extensive collaterals or a nonoccluded left anterior descending artery. Aneurysms usually range from 1 to 8 cm in diameter. They occur approximately four times more often at the apex and in the anterior wall than in the inferoposterior wall. The overlying pericardium is usually densely adherent to the wall of the aneurysm, which may even become partially calcified after several years. True left ventricular aneurysms (in contrast to pseudoaneurysms) rarely rupture soon after development. Late rupture, when the true

aneurysm has become stabilized by the formation of dense fibrous tissue in its wall, almost never occurs.

Mortality in patients with a left ventricular aneurysm is up to six times higher than in patients without aneurysms, even when compared with that in patients with comparable left ventricular ejection fraction.[570] Death in these patients is often sudden and presumably related to the high incidence of ventricular tachyarrhythmias that occur with aneurysms.[510]

The presence of persistent ST segment elevation in an ECG area of infarction, classically thought to suggest aneurysm formation, actually indicates a large infarct but does not necessarily imply an aneurysm. The diagnosis of aneurysm is best made noninvasively by an echocardiographic study by radionuclide ventriculography or at the time of cardiac catheterization by left ventriculography. With the loss of shortening from the area of the aneurysm, the remainder of the ventricle must be hyperkinetic in order to compensate. With relatively large aneurysms, complete compensation is impossible. The stroke volume falls or, if maintained, it is at the expense of an increase in end-diastolic volume, which in turn leads to increased wall

tension and myocardial oxygen demand. Heart failure may ensue, and angina may appear or worsen.

TREATMENT.

Aggressive management of AMI, including coronary thrombolysis, may diminish the incidence of ventricular aneurysms. Surgical aneurysmectomy (Fig. 35-52) generally is successful only if there is relative preservation of contractile performance in the nonaneurysmal portion of the left ventricle. In such circumstances, when the operation is performed for worsening heart failure or angina, operative mortality is relatively low and clinical improvement can be expected.[571]

Left Ventricular Thrombus and Arterial Embolism

Mural thrombi occur in approximately 20 percent of patients with AMI who do not receive anticoagulant therapy; the incidence rises to 40 percent with anterior infarction and to as high as 60 percent in patients with large anterior infarcts that involve the apex of the left ventricle.[346] The most convenient and accurate method for diagnosing left ventricular thrombosis is two-dimensional echocardiography (see Chap. 7) . It is hypothesized that endocardial inflammation during the acute phase of infarction provides a thrombogenic surface for clots to form in the left ventricle. With extensive transmural infarction of the septum, however, mural thrombi may overlie infarcted myocardium in both ventricles. Prospective studies have suggested that patients who develop a mural thrombus early (within 48 to 72 hours of infarction) have an extremely poor early prognosis,[494] with a high mortality from the complications of a large infarction

(shock, reinfarction, rupture, and ventricular tachyarrhythmia), rather than emboli from the left ventricular thrombus.

Although a mural thrombus adheres to the endocardium overlying the infarcted myocardium, superficial portions of it can become detached and produce systemic arterial emboli. Although estimates vary based on patient selection, about 10 percent of mural thrombi result in systemic embolization.[346] Echocardiographically detectable features that suggest a given thrombus is more likely to embolize include increased mobility and protrusion into the ventricular chamber, visualization in multiple views, and contiguous zones of akinesis and hyperkinesis.

MANAGEMENT.

Over the past decade six randomized trials involving only 560 patients tested whether anticoagulant therapy reduced the incidence of *left ventricular thrombus formation.* [572] [573] Collectively, these smaller trials showed that anticoagulation (intravenous heparin or high-dose subcutaneous heparin) reduced the development of *thrombi* by 50 percent, but, because of the low event rate, it was not possible to demonstrate a reduction in the incidence of *systemic embolism.* Additional data from thrombolytic trials suggest that thrombolysis reduces the rate of thrombus formation and the character of the thrombi so that they are less protuberant. Of note, however, the data from thrombolytic trials are difficult to interpret because of the confounding effect of antithrombotic therapy with heparin.[573] Recommendations for anticoagulation vary considerably,[574] [575]

Figure 35-52 Surgical repair of ventricular aneurysm. In this case the aneurysm is located at the apex (*A*). The aneurysmal segment is resected, and felt pledget strips are used to reinforce interrupted suture closure of the apex (*B*). Completed repair partially restores apical geometry (*C*). *(Courtesy of Dr. David Adams, Division of Cardiac Surgery, Brigham and Women's Hospital.)*

and thrombolysis has precipitated fatal embolization. Nevertheless, anticoagulation for 3 to 6 months with warfarin is advocated for many patients with demonstrable mural thrombi.

Based on the available data, it is our practice to recommend anticoagulation (intravenous heparin to elevate the activated partial thromboplastin time one and one-half to two times control, followed by a minimum of 3 to 6 months of warfarin) in the following clinical situations: (1) an embolic event has already occurred or (2) the patient has a large anterior infarction whether or not a thrombus is visualized echocardiographically. We are also inclined to follow the same anticoagulation practice in patients with infarctions other than those in the anterior distribution if a thrombus or large wall motion abnormality is detected.

Aspirin, although probably not capable of affecting thrombus size in most patients, may prevent further platelet deposition on existing thrombi and also is protective against recurrent ischemic events. It should be prescribed in conjunction with warfarin to patients who are candidates for long-term anticoagulation therapy based on the

indications discussed earlier.

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Convalescence, Discharge, and Post-Myocardial Infarction Care

Prolonged hospitalization and enforced bed rest for any illness may lead to complications (particularly in elderly patients) such as constipation, decubitus ulcers, excessive resorption of bone with formation of renal calculi, atelectasis, thrombophlebitis, pulmonary emboli, urinary retention, mild anemia due to repetitive blood sampling for diagnostic tests, impaired oral intake of fluids, bleeding from the gastrointestinal tract due to stress ulcers, and deconditioning of cardiovascular reflex responses to postural changes. Because of the precarious status of the heart recovering from AMI, avoidance of such complications is of primary importance. For example, constipation may lead to straining,

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transitory reduction of venous return and diminution of cardiac output, impaired coronary perfusion, and ventricular arrhythmias, occasionally culminating in ventricular fibrillation. Early use of a bedside commode, stool softeners, and a bed-chair regimen appear to be useful in avoiding many of the difficulties encountered previously among patients with AMI confined to bed for several weeks.

Although concern has been raised from studies in animals that early physical activity might unfavorably influence ventricular remodeling, perhaps by causing infarct extension, no evidence indicates that this concern is relevant to patients, and early mobilization appears to be warranted in most stable AMI patients. For the patient with an uncomplicated AMI, washing and personal care may begin within the first 12 to 24 hours. If the convalescence continues uneventfully, limited ambulation within the room can be begun on the second or third day (see Table 35-12) (Table Not Available) . Once

early ambulatory activities are begun, advancement in the activity should depend on the patient's condition. A shower may be allowed some time after the third day.

TIMING OF HOSPITAL DISCHARGE.

The time of discharge from the hospital is variable. Patients who have undergone aggressive reperfusion protocols and have no significant ventricular arrhythmias, recurrent ischemia, or congestive heart failure have been safely discharged in less than 5 days. More commonly, discharge occurs 5 or 6 days after admission for patients who experience no complications, who can be followed readily at home, and whose family setting is conducive to convalescence. Most complications that would preclude early discharge occur within the first day or two of admission; therefore, patients suitable for early discharge can be identified early during the hospitalization. [410] [576] However, as noted previously, even if no complications have occurred by hospital day 3, many clinicians find it useful to keep the patient hospitalized for another 1 to 2 days to finalize the discharge prescriptions, provide additional patient education, and confirm the adequacy of the patient's support systems at home.[411]

For patients who have experienced a complication, discharge is deferred until their condition has been stable for several days and it is clear that they are responding appropriately to necessary medications such as antiarrhythmic agents, vasodilators, or positive inotropic agents or that they have undergone the appropriate work-up for recurrent ischemia.

COUNSELING.

Before discharge from the hospital, all patients should receive detailed instruction concerning physical activity. Initially, this should consist of ambulation at home but avoidance of isometric exercise such as lifting; several rest periods should be taken daily. In addition, the patient should be given fresh nitroglycerin tablets and instructed in their use and should receive careful instructions about the use of any other medications prescribed. As convalescence progresses, graded resumption of activity should be encouraged. Many approaches have been used, ranging from formal rigid guidelines to general advice advocating moderation and avoidance of any activity that evokes symptoms. Sexual counseling is often overlooked during recovery from MI and should also be included as part of the educational process. Such counseling should begin early after AMI and should include the recommendation that sexual activity be resumed after successful completion of either early submaximal or later symptom-limited exercise stress testing.[52]

Some evidence indicates that behavioral alteration is possible after recovery from MI and that this may improve prognosis. A cardiac rehabilitation program with supervised physical exercise and an educational component has been recommended for most MI patients after discharge. Although the overall clinical benefit of such programs continues to be debated, there is little question that most people derive considerable knowledge and psychological security from such interventions and they continue to be endorsed by experienced clinicians.[52] Meta-analyses of randomized trials of medically supervised rehabilitation programs versus usual care that were conducted in an era before the

widespread use of beta-adrenoceptor blockers and thrombolytics have shown a reduction in cardiovascular death but no change in the incidence of nonfatal reinfarction.[577] Given the relationship between a history of depression and risk for AMI,[578] interest has arisen in psychosocial intervention programs in the convalescent phase of AMI.[579] [580] Psychosocial intervention programs alone have not been proven to be helpful, but they are a useful adjunct to standard cardiac rehabilitation programs after AMI.[581] [581A] More detailed information on physical and psychological aspects of rehabilitation of patients convalescing from AMI is discussed in Chapter 38 .

RISK STRATIFICATION

The process of risk stratification after AMI occurs in several stages: initial presentation, in-hospital course (CCU, intermediate care unit), and at the time of hospital discharge. The tools used to form an integrated assessment of the patient consist of baseline demographic information,[268A] serial ECGs and serum cardiac marker measurements, hemodynamic monitoring data, a variety of noninvasive tests, and, if performed, the findings at cardiac catheterization.[414] [582]

INITIAL PRESENTATION.

Certain demographic and historical factors are associated with a poor prognosis in patients with AMI, including female gender, age older than 70 years, a history of diabetes mellitus, prior angina pectoris, and previous MI.[414] Diabetes mellitus, in particular, appears to confer a threefold to fourfold increase in risk. Whether this is due to accelerated atherosclerosis or some other characteristic induced by the diabetic state (such as a larger infarct size) is unclear. (Surviving diabetic patients also experience a more complicated post-MI course, including a greater incidence of postinfarction angina, infarct extension, and heart failure.)[52]

In addition to playing a central role in the decision pathway for management of patients with AMI based on the presence or absence of ST segment elevation, the 12-lead ECG carries important prognostic information. Mortality is greater in patients experiencing anterior wall MI than after inferior MI, even when corrected for infarct size.[52] Patients with right ventricular infarction complicating inferior infarction, as suggested by ST segment elevation in V_4 R, have a greater mortality rate than patients sustaining an inferior infarction without right ventricular involvement.[63] Patients with multiple leads showing ST segment elevation and those with a high sum of ST segment elevation have an increased mortality, especially if their infarct is anterior.[582] Patients whose ECG demonstrates persistent advanced heart block (e.g., Mobitz type II, second-degree, or third-degree AV block) or new intraventricular conduction abnormalities (bifascicular or trifascicular) in the course of an AMI have a worse prognosis than do patients without these abnormalities. The influence of high degrees of heart block is particularly important in patients with right ventricular infarction, for such patients have a markedly increased mortality. Other ECG findings that augur poorly are persistent horizontal or downsloping ST segment depression, Q waves in multiple leads, evidence of right ventricular infarction accompanying inferior infarction,[63] ST segment depressions in anterior leads in patients with inferior infarction,[583] and atrial arrhythmias (especially

atrial fibrillation).

Data from the thrombolytic era have confirmed that important determinants of short- and long-term prognosis appear

to be similar in patients who have received thrombolytic therapy compared with those who have not.[414] A constellation of clinical factors can be detected at the time of presentation to help select patients at particularly high risk of death in the first 4 to 6 weeks after AMI (see Fig. 35-27, p. 1151).

HOSPITAL COURSE.

Soon after CCUs were instituted, it became apparent that left ventricular function is an important early determinant of survival. Hospital mortality from AMI depends directly on the severity of left ventricular dysfunction.[414] Risk stratification by means of clinical findings, estimation of infarct size, and, in appropriate patients, invasive hemodynamic monitoring in the CCU (see p. 1174) provides an assessment of the likelihood of a complicated hospital course[584] and may also identify important abnormalities such as hemodynamically significant mitral regurgitation that convey an adverse long-term prognosis.

Recurrent ischemia and infarction after AMI, either in the same location as the index infarction or "at a distance," influence prognosis adversely. Poor prognosis comes from the loss of viable myocardium, with the resulting larger area of infarction creating a greater compromise in ventricular function. Postinfarction angina generally connotes a less favorable prognosis because it indicates the presence of jeopardized myocardium.[582] In the current era of aggressive revascularization, early postinfarction angina often leads to early interventions that tend to improve outcome, diminishing the long-term impact and significance of angina early after AMI.[585]

Assessment at Hospital Discharge

Both short-term and long-term survival after AMI depend on three factors: (1) resting left ventricular function, (2) residual potentially ischemic myocardium, and (3) susceptibility to serious ventricular arrhythmias. The most important of these factors is the state of left ventricular function[586] (see Fig. 35-41) . The second most important factor is how the severity and extent of the obstructive lesions in the coronary vascular bed perfusing residual viable myocardium impacts the risk of recurrent infarction, additional myocardial damage, and serious ventricular arrhythmias.[582] Thus, survival relates to the quantity of myocardium that has become necrotic and the quantity at risk of becoming necrotic. At one extreme, the prognosis is best for the patient with normal intrinsic coronary vessels whose completed infarction constitutes a small fraction (5 percent) of the left ventricle as a consequence of a coronary embolus and who has no jeopardized myocardium. At the other extreme is the patient with a massive infarct with left ventricular failure whose

residual viable myocardium is perfused by markedly obstructed vessels. Obviously, progression of atherosclerosis or lowering of perfusion pressure in these vessels impairs the function and viability of the residual myocardium on which left ventricular function depends. The situation may not be hopeless even in such a patient, however, because revascularization may reduce the threat to the jeopardized myocardium. The third risk factor, the susceptibility to serious arrhythmias, is reflected in ventricular ectopic activity and other indicators of electrical instability such as reduced heart rate variability or baroreflex sensitivity and an abnormal signal-averaged ECG. All of these identify patients at increased risk of death.

In addition, as noted earlier, patients with an occluded infarct-related artery late (e.g., 1 to 2 weeks) after AMI have a higher long-term mortality.[74] Persistent occlusion of the culprit artery is associated with an increased incidence of abnormal late potentials on the ECG[587] and appears to have an adverse prognostic effect independent of the level of ventricular function (Fig. 35-53) .[224]

ASSESSMENT OF LEFT VENTRICULAR FUNCTION.

Left ventricular ejection fraction may be the most easily assessed

Figure 35-53 Impact of patency of the infarct-related artery on long-term mortality. In patients with a patent infarct-related coronary artery at 2 weeks after infarction, the long-term mortality is significantly reduced compared with that of patients with an occluded infarct-related vessel. The beneficial effect of infarct-related artery patency was independent of the number of obstructed coronary arteries or of left ventricular function. *(From Lamas GA, Flaker GC, Mitchell G, et al: Effect of infarct artery patency on prognosis after acute myocardial infarction. Circulation 92:1101, 1995. Copyright 1995, American Heart Association.)*

measurement of left ventricular function, and this measurement is extremely useful for risk stratification (see Fig. 35-41) . However, imaging of the left ventricle at rest may not distinguish adequately between infarcted, irreversibly damaged myocardium and stunned or hibernating myocardium. To circumvent this difficulty, a variety of techniques has been investigated to assess the extent of residual viable myocardium, including exercise and pharmacological stress echocardiography, stress radionuclide ventricular angiography, perfusion imaging in conjunction with pharmacological stress, and positron emission tomography (see Chap. 13) . All of these techniques can be performed safely in postinfarction patients. Because no study has clearly shown one imaging modality to be superior to others, clinicians should be guided in their selection of ventricular imaging technique by the availability and level of expertise with a given modality at their local institution.[414]

In patients with low left ventricular ejection fraction, the measurement of exercise capacity is useful for further identifying those patients at particularly high risk and also for establishing safe exercise limits after discharge.[588] Patients with a good exercise capacity despite a reduced ejection fraction have a better long-term outcome than those who cannot perform more than modest exercise.

ASSESSMENT OF MYOCARDIAL ISCHEMIA.

Because of the potent adverse consequences of recurrent MI after AMI,[562] it is important to assess a patient's risk for future ischemia and infarction. Given the increasing array of pharmacological, interventional catheterization, and surgical options available to modify the likelihood of developing recurrent episodes of myocardial ischemia, most clinicians find it helpful to identify patients at risk for provocable myocardial ischemia before discharge. A predischarge evaluation for ischemia allows clinicians to select patients who might benefit from catheterization and revascularization after

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AMI and to assess the adequacy of medical therapy for those patients who are suitable for a more conservative management strategy. Although it may be argued that coronary arteriography for risk stratification after AMI has the advantage of permitting simultaneous identification and treatment (angioplasty) of coronary obstructions, important limitations of this strategy should be noted.[589] As discussed previously (see p. 1116), the coronary artery plaques that are most likely to rupture (and produce future events) are those that are lipid laden and have a thin fibrous cap. These plaques cannot be adequately identified with arteriography because they may be associated with less than a 75 percent stenosis of the coronary artery lumen at the time of angiography after an index AMI. Furthermore, coronary arteriography does not provide information on the functional significance of coronary lesions. Previous studies comparing routine use of coronary angiography versus selected use only in patients with spontaneous or provoked ischemia showed no advantage to the routine catheterization strategy with respect to 6-week mortality and reinfarction.[52] [589]

An exercise test also offers the clinician an opportunity to formulate a more precise exercise prescription and is helpful in boosting patients' confidence in their ability to conduct their daily activities after discharge. Patients who are unable to exercise may be evaluated using a pharmacological stress protocol such as an infusion of dobutamine or dipyridamole with echocardiography or perfusion imaging.

Treadmill exercise testing after AMI has traditionally used a submaximal protocol that requires the patient to exercise until symptoms of angina appear, ECG evidence of ischemia is seen, or a target workload (approximately 5 METS) has been reached (see Chap. 6) . It has been proposed that symptom-limited exercise tests may be safely performed before discharge in patients with an uncomplicated postinfarction course in hospital.[590] Variables derived from exercise tests after AMI that have been evaluated for their ability to predict the occurrence of death or recurrent nonfatal infarction include the development and magnitude of ST segment depression, the development of angina, exercise capacity, and the systolic blood pressure response during exercise.[586]

Myocardial perfusion with ^{99m} Tc sestamibi during exercise or pharmacological (e.g.,

dipyridamole, adenosine, or dobutamine) stress increases the sensitivity for detection of patients at risk for death or recurrent infarction (see Chap. 9) . Similar results have been reported for dipyridamole stress echocardiography. Although perfusion imaging may be helpful for risk stratification in patients with uninterpretable ECGs or the inability to exercise, the regular use of these more expensive procedures in patients with interpretable ECGs and the ability to exercise has been questioned.[414] [591] An increasing number of patients are treated with thrombolysis, angioplasty, or surgery and have a more favorable natural history than that reported in patients who have not undergone aggressive reperfusion and revascularization for AMI.[591] Until clinical trials relating the findings of a postinfarction perfusion imaging test to long-term outcome in cohorts of patients receiving contemporary therapy for AMI are available, we do not advocate the *routine* use of perfusion imaging for risk stratification after AMI. At present its use should be restricted to patients who are candidates for further revascularization procedures and have physical limitations preventing them from exercising to an adequate workload or those with conduction abnormalities, significant resting ST segment and T wave abnormalities, or repolarization abnormalities on the ECG due to ventricular hypertrophy or digitalis therapy.[592] We have also used perfusion imaging studies when a conventional exercise ECG is mildly abnormal and there is uncertainty about the significance of the finding or uncertainty about the potential culprit vessel or vessels. In such cases perfusion imaging may help guide decisions after catheterization if multiple coronary vessels have important stenoses.

The Danish Trial in Acute MI (DANAMI) investigators reported that when patients with provokable ischemia after infarction were randomized to catheterization and revascularization versus conservative medical therapy, they experienced a lower requirement for antianginal medications, less unstable angina, and fewer nonfatal infarctions.[585]

ASSESSMENT FOR ELECTRICAL INSTABILITY.

After AMI, patients are at greatest risk for the development of sudden cardiac death due to malignant ventricular arrhythmias over the course of the first 1 to 2 years.[593] [594] Several techniques have been devised to stratify patients into those who are at increased risk of sudden death after AMI: measurement of QT interval dispersion (variability of QT intervals between ECG leads), ambulatory ECG recordings for detection of ventricular arrhythmias (Holter monitoring; see Chap. 22) , invasive electrophysiological testing, recording a signal-averaged ECG (a measure of delayed, fragmented conduction in the infarct zone), and measuring heart rate variability (beat-to-beat variability in RR intervals) or baroreflex sensitivity (slope of a line relating beat-to-beat change in sinus rate in response to alteration of blood pressure).[510]

Given the risks associated with routine use of type I antiarrhythmics prescribed to suppress VPBs that are detected on ambulatory ECG recordings, we do not recommend routine Holter monitoring to determine which patients should receive antiarrhythmic therapy after AMI. The value of empirical administration of the type III antiarrhythmic drug amiodarone after infarction is discussed on p. 1204 .

A variety of noninvasive tests have been used to assess patients for electrical instability

after AMI.[510] The presence of a filtered QRS complex duration greater than 120 milliseconds and abnormal late potentials recorded on a signal-averaged ECG after AMI have a positive predictive value between 8 and 27 percent and a negative predictive value of over 95 percent for serious arrhythmic events. When viewed in isolation, the signal-averaged ECG suffers from a high false-positive rate, which may be improved by combining it with other variables, such as left ventricular ejection fraction. Electrophysiological testing also appears to suffer from a high false-positive rate and has the additional disadvantage of being invasive. The ability of electrophysiological testing to identify patients at risk for arrhythmic events after AMI appears to be improved if it is performed in patients who also have an ejection fraction less than 40 percent, an abnormal signal-averaged ECG, and VPBs. Depressed heart rate variability (HRV) is an independent predictor of mortality and arrhythmic complications after AMI, especially if cutoffs of standard deviation of the average interval between normal beats below 50 milliseconds and HRV triangular index (a geometric method for integrating the distribution of intervals between normal beats) less than 15 are used. A depressed baroreflex sensitivity value (3.0 msec/mm Hg) is associated with about a threefold increase in the risk of mortality.[595]

Despite the increased risk of arrhythmic events after AMI in patients who are found to have abnormal results on one or more of the noninvasive tests described earlier, several points should be emphasized. The low positive predictive value (<30 percent) for the noninvasive screening tests limits their usefulness when viewed in isolation. Although the predictive value of screening tests can be improved by combining several of them together, the therapeutic implications of an increased risk profile for arrhythmic events have not been established. The mortality reductions achievable with the general use of beta blockers, ACE inhibitors, aspirin, and revascularization when appropriate after infarction, coupled with concerns about efficacy and safety of antiarrhythmic drugs and cost of implanted defibrillators, leave considerable uncertainty about the therapeutic implications of an abnormal noninvasive test for

electrical instability in an asymptomatic patient. Additional data on patient outcomes when clinicians act on the results of an abnormal finding are required before definitive recommendations can be made for asymptomatic patients.[52] The management of patients with sustained, hemodynamically compromising arrhythmias is discussed in Chapter 23 .

Recommendations for Predischarge Management

An algorithm for predischarge management of patients at varying levels of risk after infarction is outlined in Figure 35-54 . Initially, a judgment is made as to the presence of clinical variables indicative of high risk for future cardiac events. Patients with spontaneous episodes of ischemia or depressed left ventricular function who are considered suitable candidates for revascularization based on their overall medical condition should be referred for cardiac catheterization (Fig. 35-54) . The former group of patients is at increased risk of recurrent infarction (and subsequent increased

mortality risk[562]), whereas the latter group may benefit from revascularization surgery if multivessel coronary artery disease is identified at catheterization (see Chap. 37) . [562A] Patients with sustained VT or ventricular fibrillation that occurs more than 48 hours after the acute event (see Fig. 35-54) are at increased risk of sudden cardiac death and should be considered for diagnostic electrophysiology study and treatment as outlined in Chapter 25 .

In the absence of high-risk clinical indicators, two management strategies are possible; the choice between them may be influenced by patient and physician preferences and the availability of resources in the patient's local community for the necessary follow-up procedures (see Fig. 35-54) . Initial exercise testing can use conventional ECG with supplementation by a perfusion imaging study for patients with uninterpretable resting ECGs or an equivocal (i.e., mildly abnormal) initial ECG result. Submaximal exercise testing can be performed before discharge to triage patients to an early catheterization strategy or medical therapy strategy. Plans for a follow-up symptom-limited exercise test in patients without clear indications for catheterization are formulated based on the patient's life style and occupation. Patients who undergo aggressive reperfusion therapy and have an uncomplicated course in the CCU may be suitable candidates for early hospital discharge with plans for a symptom-limited exercise test 2 to 3 weeks later. Subsequent decisions about continued medical therapy or referral for cardiac catheterization can then be made as outlined in Figure 35-54 .

SECONDARY PREVENTION OF RECURRENT ACUTE MYOCARDIAL INFARCTION

The concept of secondary prevention of reinfarction and death after recovery from an AMI has been investigated actively for several decades. Problems in proving the efficacy of various interventions have been related both to the ineffectiveness of certain strategies and to the difficulty in proving a benefit as mortality and morbidity have improved after AMI. Nevertheless, patients who survive the initial course of AMI are at increased risk because of coronary artery disease and its complications; therefore, it is imperative that efforts be made to reduce this risk. Although secondary prevention drug trials generally have tested one form of therapy against placebo in an attempt to demonstrate a benefit of that therapy, the physician must remember that disciplined clinical care of the individual patient is far more important than rote use of an agent found beneficial in the latest drug trial.[17] [596]

LIFE STYLE MODIFICATION.

Efforts to improve survival and the quality of life after MI that relate to life style modification of known risk factors are considered in Chapter 36 . Of these, cessation of smoking and control of hypertension are probably most important. It has been shown that within 2 years of quitting smoking, the risk of a nonfatal MI in these former smokers falls to a level similar to that in patients who never smoked. Being hospitalized for an AMI is a powerful motivation for patients to cease cigarette smoking, and this is an ideal time to encourage that clearly beneficial and highly cost-effective life style change.[597] It is also an ideal time to begin to treat hypertension, to counsel patients to achieve optimal body weight, and to consider various strategies to improve the patient's lipid

profile (see later).

Physicians caring for patients after an AMI need to be sensitive to the fact that some patients experience major depression after infarction, and the development of this problem is an independent risk factor for mortality.[598] In addition, lack of an emotionally supportive network in the patient's environment after discharge is associated with an increased risk of mortality and recurrent cardiac events.[599] The precise mechanisms relating depression and lack of social support to worse prognosis after AMI are not clear, but one possibility is lack of adherence to prescribed treatments, a behavior that has been shown to be associated with increased risk of mortality after infarction.[600] Evidence exists that a comprehensive rehabilitation program using primary health care personnel who counsel patients and make home visits favorably impacts the clinical course of patients after infarction and reduces the rate of rehospitalization for recurrent ischemia and infarction. A supportive physician attitude can also have a positive impact on the rate of return to work after AMI.

MODIFICATION OF LIPID PROFILE.

Compelling evidence now exists that an increased cholesterol level, and most importantly an increased low-density lipoprotein (LDL) cholesterol level, is associated with an increased risk of coronary heart disease (see Chap. 33) . Based on this observation and the finding that lowering cholesterol reduces the risk of coronary heart disease,[601] [602] a target LDL cholesterol level of less than 100 mg/dl has been recommended in patients with clinically evident coronary heart disease.[603] This recommendation clearly applies to patients with AMI, and it is therefore important to obtain a lipid profile on admission in all patients admitted with acute infarction. (It should be recalled that cholesterol levels may fall 24 to 48 hours after infarction.) In addition to lowering LDL cholesterol, therapy with statins reduces levels of C-reactive protein, suggesting an antiinflammatory effect.[604]

Surveys of physician practice in the past have revealed a disappointingly low rate of treatment of hypercholesterolemia in patients with proven coronary artery disease, indicating considerable room for improvement in this aspect of secondary prevention after AMI.[603]

Recommendations.

All patients recovering from AMI should be considered potential candidates for modification of their lipid profile. Initial therapy should consist of an AHA Step II diet (<7 percent of total calories as saturated fat and cholesterol <200 mg/d). Patients with an LDL cholesterol level greater than 125 mg/dl despite the AHA Step II diet should be placed on drug therapy to reduce the LDL cholesterol level to less than 100 mg/dl.[52] Our preference at present is to prescribe an HMG-CoA reductase inhibitor before hospital discharge in patients with an LDL cholesterol level greater than 130 mg/dl on admission.[605] For many patients recovering from AMI, a low HDL cholesterol level is their primary lipid abnormality. Gemfibrozil (1200 mg/d) reduces the risk of death,

reinfarction, and stroke in such patients.[606]

ANTIPLATELET AGENTS.

On the basis of 11 randomized trials in 20,000 patients with a prior infarction, the Antiplatelet Trialists' Collaboration reported a 25 percent reduction in the risk of recurrent infarction, stroke, or vascular

Figure 35-54 Management algorithm for risk stratification after acute myocardial infarction. Patients with clinical indicators of high risk at hospital discharge such as recurrent ischemia at rest or depressed left ventricular function should be considered candidates for revascularization and referral to cardiac catheterization for ultimate triage to either angioplasty/coronary artery bypass surgery or medical therapy and risk factor reduction (strategy I). Patients with life-threatening arrhythmias such as sustained ventricular tachycardia or ventricular fibrillation should be considered for diagnostic cardiac catheterization, electrophysiology study, and management with implantation of a cardioverter-defibrillator either alone or in conjunction with Amiodarone (strategy I). Patients without indicators of high risk at hospital discharge can be evaluated with either a symptom-limited exercise test at 14 to 21 days (strategy II) or a submaximal exercise test before discharge (strategy III). Patients with either a markedly abnormal exercise test or evidence of reversible ischemia on an exercise imaging study in strategy II or III should be referred for cardiac catheterization. Patients with a negative exercise test or no evidence of reversible ischemia on an exercise imaging study can be managed with medical therapy and risk factor reduction. *(From Ryan TJ, Antman EM, Brooks NH, et al: 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Acute Myocardial Infarction]. Circulation 100:1016-1030, 1999.)*

death in patients receiving prolonged antiplatelet therapy (36 fewer events for every 1000 patients treated).[14] No antiplatelet therapy proved superior to aspirin, and daily doses of aspirin between 80 and 325 mg appear to be effective.[607] Data from the Worcester Heart Attack Study suggest that when an AMI occurs in chronic users of aspirin, it is likely to be smaller and non-Q wave in nature.[608] Experimental data on late reperfusion in a rat model of coronary occlusion suggest that aspirin treatment after AMI increases the patency of the microvasculature in the infarcted area, resulting in less infarct expansion and thicker myocardial walls in the infarct zone.[609] The compelling arguments cited earlier serve as the basis for the recommendation that all patients recovering from AMI should, in the absence of contraindications, remain on aspirin for an indefinite period.[596] [610] Patients with true aspirin allergy may be treated with sulfinpyrazone (400 mg twice daily), ticlopidine (250 mg twice daily),[14] or clopidogrel (75 mg once daily),[611] although the data indicating that these agents reduce mortality after AMI are not nearly as robust as those for aspirin.

ACE INHIBITORS.

The rationale for the acute use of ACE inhibitors after AMI has been discussed earlier (see p. 1169). To prevent late remodeling of the left ventricle and also to decrease the likelihood of recurrent ischemic events,[421] [431] we advocate indefinite therapy with an ACE inhibitor to all patients with clinically evident congestive heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality, even in the face of a normal global ejection fraction.[52] A decision-analytic model that tested strategy of prescription of ACE inhibitors to hypothetical 50- to 80-year-old patients with an ejection fraction of 40 percent or less after AMI reported incremental cost-effectiveness ratios of $4,000 to $10,000 per quality-adjusted life-year (QALY). These calculations compare quite favorably with the costs of other commonly accepted medical procedures such as angioplasty for one- or two-vessel coronary artery disease ($8,000 to $111,000 per QALY).

The optimum duration of therapy with ACE inhibitors after AMI is an intriguing question. Evidence exists that long-term (at least 3 to 5 years) treatment with ACE inhibitors in patients with severely reduced left ventricular function after AMI prolongs survival,[612] [613] especially in diabetic patients.[614] Although the benefit of ACE inhibitors in patients with symptomatic congestive heart failure is greater with higher doses, some protection against death and hospitalization for heart failure is obtained even if lower doses of ACE inhibitors are used.[615] Finally, ACE inhibitors are associated with a reduction in sudden death after AMI,[616] profession of renal failure in insulin-dependent diabetics,[617] and prevention of death, AMI, and stroke when used for primary prevention in patients at high risk for cardiovascular events but without left ventricular dysfunction or heart failure.[618] The observations cited earlier along with data suggesting that ACE inhibitors have direct antiatherosclerotic effects and favorably influence remodeling of vascular walls pose a persuasive argument for a more widespread use of ACE inhibitors for all patients after AMI.

BETA-ADRENOCEPTOR BLOCKERS.

Meta-analyses of trials from the prethrombolytic era involving over 24,000 patients who received beta-adrenoceptor blockers in the convalescent phase of AMI have shown a 23 percent reduction in long-term mortality[417] (see Fig. 35-37) . When beta blockade is initiated early (6 hours) in the acute phase of infarction and continued in the chronic phase of treatment, some of the benefit may result from a reduction in infarct size. However, in the majority of patients who have beta blockade initiated during the convalescent phase of AMI, reduction in long-term mortality is probably due to a combination of an antiarrhythmic effect (prevention of sudden death) and prevention of reinfarction.[417]

Overviews of the results of trials of beta-adrenoceptor blockers with agonist activity have not shown a beneficial effect on mortality compared with more convincing evidence of a beneficial effect and little evidence of harm for trials of beta blockers without agonist activity (odds ratio 0.69 [0.61-0.79]). [186] No differences are seen when cardioselective and noncardioselective agents are compared. The greatest mortality

benefit from chronic beta blockade after AMI is seen in patients with the greatest baseline risk--those with compromised ventricular function and ventricular arrhythmias. The results of the Beta-Blocker Pooling Project, in which data were examined from nine separate studies involving more than 10,000 patients, suggest a highly significant reduction in overall mortality among treated patients with pump failure.[619] Treatment with beta blockers after AMI is particularly helpful for reducing mortality in patients who do not undergo revascularization.[620] Mortality is reduced even in patients who receive less than 50 percent of the dosage found to be effective in preventing cardiac death in large randomized trials.[621]

Recommendations.

Given the well-documented benefits of beta-adrenoceptor blockade, it is disturbing that this form of therapy continues to be underused, especially in high-risk groups such as the elderly.[622] We are in agreement with the "Quality Care Alert" issued jointly by several authoritative bodies that beta-adrenoceptor blockers be prescribed to all high-risk patients regardless of whether the event was a Q-wave or non-Q-wave AMI, as long as no contraindications are present.[623] Patients with a relative contraindication to beta blockade (moderate heart failure, bradyarrhythmias) should undergo a monitored trial of therapy in the hospital. The dosage should be sufficient to blunt the heart rate response to stress or exercise. Much of the impact of beta blockers in preventing mortality occurs in the first weeks; treatment should commence as soon as possible. Evidence exists that programs providing physician feedback improve adherence to guidelines such as those noted earlier for prescription of beta-adrenoceptor blockers after AMI.[624]

Some controversy exists as to how long patients should be treated.[625] The collective data from five trials providing information on long-term follow-up of beta-adrenoceptor blockers after infarction suggest that therapy should be continued for at least 2 to 3 years.[626] [627] At that time, if the beta blocker is well tolerated and if there is no reason to discontinue therapy, such therapy probably should be continued in most patients.[628]

Not all patients derive the same benefit from beta-blocker therapy. The cost-effectiveness of treatment in medium- or high-risk persons compares very favorably with that of many other accepted interventions such as coronary bypass surgery, angioplasty, and lipid-lowering therapy.[625] In patients with an extremely good prognosis (first AMI, good ventricular function, no angina, negative stress test, and no complex ventricular ectopy) in whom a mortality rate of approximately 1 percent per year can be anticipated, beta blockers would have a smaller impact on survival. However, it is our preference to prescribe beta blockers to such patients for whatever postinfarction benefit is achieved and also to have them as part of the patient's usual regimen should AMI recur at an unpredictable time in the future.

NITRATES.

Although these agents are suitable for management of specific conditions after AMI such as recurrent angina or as part of a treatment regimen for congestive heart failure, little evidence indicates that they reduce mortality over the long term when prescribed

on a routine basis to all patients with infarction.[425] [426]

ANTICOAGULANTS. (See also Chap. 62.)

At least three theoretical reasons exist for anticipating that anticoagulants might be beneficial in the long-term management of patients after AMI.

1. Because the coronary occlusion responsible for the AMI is often due to a thrombus, anticoagulants might be expected to halt, slow progression, or prevent the development of new thrombi elsewhere in the coronary arterial tree.
2. Anticoagulants might be expected to diminish the formation of mural thrombi and resultant systemic embolization.
3. Anticoagulants might be expected to reduce the incidence of venous thrombosis and pulmonary embolization.

After several decades of evaluation, the weight of evidence now suggests that anticoagulants have a favorable effect on late mortality, stroke, and reinfarction among patients hospitalized with AMI.[13] [629] Long-term anticoagulant therapy has also been shown to be a cost-effective intervention after AMI, with the major cost savings coming from reductions in the rate of recurrent infarction and related interventions.[630]

Previous small trials of aspirin versus oral anticoagulation have led to conflicting results, with no clear consensus regarding superiority of either antithrombotic strategy. The APRICOT investigators reported that after initially successful thrombolysis, aspirin-treated patients had lower rates of reinfarction, need for revascularization, and mortality than did warfarin-treated patients.[273] As expected, cost-effectiveness calculations show that aspirin is associated with a very favorable economic profile, but its true efficacy compared with or combined with oral anticoagulation remains unknown. The Coumadin Aspirin Reinfarction Study (CARS) was discontinued prematurely owing to lack of evidence of benefit of reduced-dose aspirin (80 mg/d) with either 1 or 3 mg of warfarin daily compared with aspirin 160 mg alone daily.[631] The Combination Hemotherapy and Mortality Prevention (CHAMP) study found no benefit of using warfarin (to an international normalized ratio of 1.5-2.5) plus aspirin 81 mg/d versus aspirin 162 mg/d with respect to total mortality, cardiovascular mortality, stroke, and nonfatal MI (mean follow-up 2.7 years) after an index AMI.[632]

Therefore, at present we recommend routine use of aspirin in all AMI patients without contraindications and add warfarin only to patients with clear indications for anticoagulation such as deep vein thrombosis, pulmonary embolism, mural thrombus seen at echocardiography, a large regional wall motion abnormality (especially anterior) seen at echocardiography even in the absence of a visualized thrombus, atrial fibrillation, and a history of embolic cerebrovascular accident.

CALCIUM ANTAGONISTS.

At present we do *not* recommend the routine use of calcium antagonists for secondary prevention of infarction. A possible exception is a patient who cannot tolerate a beta-adrenoceptor blocker because of adverse effects on bronchospastic lung disease but who has well-preserved left ventricular function; such patients may be candidates for a rate-slowing calcium antagonist such as diltiazem or verapamil.

ANTIARRHYTHMICS.

Although it has been recognized for decades that antiarrhythmic therapy can control atrial and ventricular arrhythmias effectively in many patients, careful reviews of clinical trials after AMI have reported an increased risk of mortality with type I drugs[633] [634] (Table 35-22) . The most notable postinfarction trial in this area was the Cardiac Arrhythmia Suppression Trial (CAST), which tested whether encainide, flecainide, or moricizine for suppression of ventricular arrhythmias detected on ambulatory ECG monitoring would reduce the risk of cardiac arrest and death over the long term. Both the first phase of the trial (encainide or flecainide vs. placebo) and the second phase of the trial (moricizine vs. placebo) were stopped prematurely because of increased mortality in the active treatment groups.[634] [635] [636] The mechanism of the increased risk after AMI remains a subject of investigation, but one hypothesis that has been put forth is an adverse interaction between recurrent ischemia and the presence of an antiarrhythmic drug because the risk of death or cardiac arrest was greater in patients with non-Q-wave AMI than with Q-wave AMI.[637] Sodium channel blockade by antiarrhythmics may exacerbate electrophysiological differences between subepicardial and subendocardial zones of myocardium, rendering the latter more susceptible to ischemic injury.[638]

Subsequent to CAST, another postinfarction prophylactic antiarrhythmic drug trial was undertaken with oral d-sotalol (Survival With ORal D-sotalol = SWORD). This trial was designed to test the hypothesis that prophylactic administration of d-sotalol to patients with depressed left ventricular function (ejection fraction = 40 percent) and either a recent (6 to 42 days) or remote (42 days) AMI would reduce total mortality. SWORD also was stopped prematurely after enrollment of only 3121 of a planned 6400 patients because statistical evidence of increased mortality emerged in the active treatment group[639] (Fig. 35-55) .

The Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) showed that amiodarone reduced ventricular premature depolarization frequency in patients with recent MI; this correlated with a reduction in arrhythmic death or resuscitation from ventricular fibrillation[640] (see Fig. 35-55) . However, 42 percent of patients discontinued amiodarone during maintenance therapy in CAMIAT because of intolerable side effects. The European Amiodarone Myocardial Infarction Trial (EMIAT) showed a reduction in arrhythmic death after MI in patients with depressed left ventricular function, but there was no reduction in total mortality or other cardiovascular-related mortality[641] (see Fig.

35-55) .

At the present time, the *routine* use of antiarrhythmic agents (including amiodarone) cannot be recommended.[641A] Given the data cited earlier on the protective effects of beta-adrenoceptor blockers against sudden death (see p. 1203) and the ability of aspirin to reduce the risk of reinfarction (see p. 1201), it is unclear whether additional mortality reductions would be achieved by the empirical addition of amiodarone in the patient who is convalescing from an AMI and is free of symptomatic sustained ventricular arrhythmias. Although several trials that included postinfarction patients in the study population have shown mortality reductions in patients randomized to implantable cardioverter-defibrillator implantation versus antiarrhythmic therapy, the profound financial and societal implications have prevented adoption of widespread implantable cardioverterdefibrillator implantation to asymptomatic patients recovering from AMI but with an abnormal noninvasive test (e.g., ejection fraction < 40 percent, frequent ventricular premature depolarizations).[570] [642] [643] [644] Whether subgroups of patients with indicators of high risk of sudden death, such as abnormal heart rate variability or reduced baroreflex sensitivity, should be treated and, if so, by what strategy remains to be determined.

HORMONE REPLACEMENT THERAPY. (See also Chap. 58.)

Estrogen replacement therapy has been reported to possibly be helpful in the primary prevention of coronary heart disease, improves the coronary artery disease risk factor profile in postmenopausal women,[645] and appears to reduce mortality in women with moderate coronary heart disease. However, the decision to prescribe hormone replacement therapy is often a complex one that involves weighing risks of breast and endometrial cancer versus modification of a coronary artery disease risk factor profile.[646] Of note, despite improvement in lipid profiles, hormone replacement therapy with estrogen plus progestin to postmenopausal women with established coronary heart disease in the Heart and Estrogen/Progestin Replacement Study (HERS) did not prevent recurrent coronary events and was associated with significantly increased risk of venous thromboembolic

TABLE 35-22 -- IMPORTANT ARRHYTHMIA TRIALS IN PATIENTS AFTER ACUTE MYOCARDI INFARCTION

TRIAL	OBJECTIVE	NO. OF PATIENTS	ENTRY CRITERIA	TREATMENT ARMS	MAIN RESULTS	

CAST	To test whether PVC suppression (asymptomatic or mildly symptomatic) reduced arrhythmia-related mortality.	2309	6 d to 2 yr post-MI 6 PVCs/hr LVEF 40% if MI 90 d to 2 yr	1) Open-label titration during which three drugs (encainide, flecainide, and moricizine) at two doses were tested	1) 7.7% mortality in encainide/flecainide group vs. 3% in placebo group (p=0.0004).
				2) Titration phase terminated when PVCs suppressed	2) Arrhythmic death was more common in the encainide/flecainide group vs. placebo (4.5% vs. 1.2%, p=0.0004).
				3) Patients excluded if intolerant or arrhythmia worsened	
				4) Patients assigned to active drug that suppressed arrhythmia, or placebo	
CAST II	To test whether PVC suppression (asymptomatic or mildly symptomatic) by moricizine reduced mortality.	1325	6-90 days post-MI 6 PVCs/hr	Two blinded randomized phases:	CAST II was stopped early because of increased mortality in the early 14-d phase.
				1) Early phase to assess risk of starting moricizine post-MI (200 mg tid×14 d vs. placebo)	

			LVEF 55% if MI within 90 d		
			LVEF 40% if MI 90 d to 2 yr	2) Long-term phase evaluated the effect of moricizine on survival in patients whose PVCs were suppressed	
SWORD	To test whether a pure potassium channel blocker without beta blocking activity reduced mortality	3121	LVEF 40% and either recent (6-42 days) MI or symptomatic heart failure with a remote (242 days) MI	d-sotalol vs. placebo	SWORD was stopped prematurely due to higher mortality in d-sotalol (5% vs. 3.1%; *p*=0.006).
CAMIAT	To evaluate the efficacy of amiodarone in reducing arrhythmic death.	1202	6-45 days post-MI > 10 PVCs/hr or any run 3 beats VT > 100 beats/min	Amiodarone vs. placebo	1) Amiodarone did not affect total cardiac mortality but reduced SD or recurrent VF ($p < 0.05$)
					2) There was concordance between PVC suppression and reduced SD and recurrent VF.

					3) Early discontinuation of amiodarone for side effects was common (42.3%).
EMIAT	To assess the efficacy of prophylactic antiarrhythmic therapy in patients with asymptomatic complex ventricular ectopy.	1486	5-21 d post-MI LVEF 40% 18-75 yr 24-hr ambulatory monitoring before entry but not used as part of inclusion criteria	Amiodarone vs. placebo	1) No difference in overall mortality. 2) Reduction in arrhythmic death in the amiodarone group (p=0.052). 3) Drug discontinuation due to side effects or intolerance was high in the amiodarone group (45% by 2 yr).

PVC=premature ventricular contraction; LVEF=left ventricular ejection fraction; VT=ventricular tachyc
VF=ventricular fibrillation; SD=sudden death.

Modified from Tracy CM: Current review of arrhythmia trials. Cardiology Special Edition 5(1):17-23, 19

Figure 35-55 Effect of type III antiarrhythmic drugs after acute myocardial infarction. The results of the

SWORD, EMIAT, and CAMIAT trials are shown with total mortality plotted in the top panels and arrhythmic deaths plotted in the bottom panels. The SWORD trial was stopped prematurely owing to increased total mortality in patients receiving *d*-sotalol compared with placebo; arrhythmic mortality was also significantly increased. Both the EMIAT and CAMIAT trials showed no significant reduction in total mortality with amiodarone, but there was a reduction in arrhythmic deaths in patients receiving amiodarone. However, the rate of discontinuation due to intolerable side effects was high with amiodarone in both the EMIAT and CAMIAT trials. *(Adapted from Waldo AL, Camm AJ, deRuyter H, et al: Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet 348:7-12, 1996; Julian DG, Camm AJ, Frangin G, et al: Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 349:667-674, 1997; and Cairns JA, Connolly SJ, Roberts R, Gent M: Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet 349:675-682, 1997.)*

events and a trend toward an early (year 1) increase in coronary events.[647] At present, we recommend continuing hormone replacement therapy in postmenopausal women after AMI but not starting it in women who have not been on hormone replacement previously until more data are available and longer-term follow-up in HERS has been reported.

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GUIDELINES DIAGNOSIS AND MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

Thomas H. Lee

Key guidelines for the diagnosis and management of acute myocardial infarction (AMI) have been published by the American College of Emergency Physicians (ACEP)[1] and by an ACC/AHA Committee.[2] Additional influential guidelines on management of patients with acute ischemic heart disease syndromes have been published by the National Heart Attack Alert Program (NHAAP),[3] the Agency for Health Care Policy and Research (AHCPR),[4] and an ACC/AHA task force on unstable angina.[5]

Evaluation of Patients with Acute Chest Pain (Table 35-G-1)

In all of these guidelines, the recommended actions in response to the data that are collected during this evaluation are intended to lead to timely care for patients with AMI, unstable angina, aortic dissection, and pulmonary embolus. The ACC/AHA guidelines on unstable angina and non-ST segment elevation MI emphasize that patients with possible acute coronary syndromes should be evaluated at a facility at which a 12-lead electrocardiogram (ECG) can be performed (as opposed to over the telephone).[5] According to these guidelines, patients with suspected acute coronary syndromes of symptom duration of more than 20 minutes, hemodynamic instability, or recent syncope or presyncope are most appropriately seen in an emergency department or specialized chest pain unit. Emergency transport services should be used when available for such patients; private vehicles are acceptable alternatives only if waiting for an emergency

vehicle would impose a long delay.

The ACEP statement on the initial evaluation of patients with acute chest pain[1] include "rules" and "guidelines" about the data that should be recorded and the actions that should follow from certain findings. In these guidelines, "rules" are actions that are general principles of good practice; deviation from a "rule" should generally be justified in the record. "Guidelines" are actions that should be considered, but failure to follow a "guideline" does not necessarily imply that care was improper. The ACEP policy statement includes in its appendix forms that can be used to assess compliance with their "rules" and to remind clinicians of their content.

The ACEP statement indicates that the routine evaluation of nontraumatic chest pain should include a history that obtains data on the

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TABLE 35--G-1 -- EVALUATION OF ACUTE CHEST PAIN: EXCERPTS FROM THE CLINICAL POLICY OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS (ACEP) (1995)

Variable	Finding	Rule*	Guideline

Pain	Ongoing and severe and crushing and substernal or same as previous pain diagnosed as MI	Intravenous access	Serum cardiac markers
		Supplemental oxygen	CXR
		Cardiac monitor	Anticoagulation
		ECG	
		Aspirin	
		Nitrates	
		Management of ongoing pain	
		Admit	
	Severe or pressure or substernal or exertional or radiating to jaw, neck, shoulder, or arm	ECG	Intravenous access
			Supplemental oxygen
			Cardiac monitor
			Serum cardiac markers
			CXR
			Nitrates
			Management of ongoing pain
			Admit
	Tearing, severe, and radiating to back	Large-bore intravenous access	Differential upper extremity blood pressures
		Supplemental oxygen	
		Cardiac monitor	Aortic imaging
		CXR, ECG	Management of ongoing pain
			Admit
	Similar to that of previous pulmonary embolus	Intravenous access	CXR
		Supplemental O_2	Admit
		Cardiac monitor	
		ABG/oximetry	
		Anticoagulation/pulmonary vascular imaging	
		ECG	
	Indigestion or burning	None	ECG

	Indigestion or burning epigastric	None	ECG
	Pleuritic	None	CXR
			ECG
Associated symptoms	Syncope or near-syncope	ECG	Cardiac monitor
			Hematocrit
	Shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, or orthopnea	ECG	ABG/oximetry
			CXR
Past medical history	Previous MI, coronary artery bypass graft, angioplasty, cocaine use within past 96 hours, previous positive cardiac diagnostic studies	ECG	
	Major risk factors for coronary artery disease		ECG

CXR=chest radiograph; ECG=electrocardiogram; ABG=arterial blood gas analysis.

From American College of Emergency Physicians: Clinical policy for the initial approach to adults presenting with a chief complaint of chest pain, with no history of trauma. Ann Emerg Med 25:274-299, 1995.

*Rule: An action reflecting principles of good practice in most situations. There may be circumstances when a rule need not or cannot be followed; in these situations, it is advisable that deviation from the rule be justified in writing. Inability to comply with rules should be incorporated in institutional policies.

Guideline: An action that may be considered, depending on the patient, the circumstances, or other factors. Thus, guidelines are not always followed, and there is no implication that failure to follow a guideline is improper.

character of pain, age, associated symptoms, and past history. The physical examination should include vital signs, a cardiovascular examination, and a pulmonary examination. The performance of an ECG is a "rule" in all but atypical chest pain syndromes. The ACEP statement emphasizes that the decision to admit the patient must be based primarily on clinical judgment.

The NHAAP report also includes guidelines for specific functions related to evaluation and treatment of patients with chest pain aimed at improving the speed with which patients with AMI are identified and treated,[3] including recommendations for which patient subsets should be placed on the AMI protocol. For registration staff, the NHAAP guidelines recommend that patients older than age 30 with the following chief complaints receive immediate assessment by the triage nurse and be referred for

further evaluation:

- Chest pain, pressure, tightness, or heaviness; radiating pain in neck, jaw, shoulders, back, or one or both arms
- Indigestion or "heartburn"/nausea and/or vomiting
- Persistent shortness of breath
- Weakness/dizziness/lightheadedness/loss of consciousness

The triage nurse should immediately assess patients for initiation of the AMI protocol and obtain an ECG if they have any of the following:

- Chest pain
- Associated dyspnea
- Associated nausea/vomiting
- Associated diaphoresis

For physicians, the NHAAP guidelines offer several clinical recommendations

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and explicitly note that the use of a so-called GI cocktail (usually including an antacid) as a diagnostic test to differentiate between gastrointestinal and cardiac causes of the patient's symptoms is inappropriate because it frequently leads to erroneous conclusions.

ECG and aspirin are strongly recommended for patients with new-onset angina that is exertional, but admission is not considered mandatory in the ACEP policy statement. The AHCPR guidelines also indicate that not all patients with unstable angina require admission but recommend that patients with unstable angina be monitored electrocardiographically during their initial evaluation and that those with ongoing rest pain should be placed at bed rest during the initial phase of stabilization.[4]

EARLY RISK STRATIFICATION.

The ACC/AHA guidelines for management of unstable angina emphasize the importance of a search for noncoronary causes that might explain the patient's symptoms but recommend that biochemical cardiac markers be performed for all patients with suspected acute coronary syndromes.[5] This recommendation does not

mandate the performance of markers in patients with a very low probability of acute coronary syndromes, for whom discharge without such testing is appropriate.[6] The ACC/AHA task force supports the use of cardiac troponins as a preferred marker for acute ischemic injury (Table 36-G-2) .

Specific recommendations for the care of patients with unstable angina are included in the guidelines in Chapter 36 .

Urgent Care of AMI (Table 35-G-2)

The 1999 ACC/AHA update of guidelines on AMI[2] seek to ensure timely revascularization of patients who present early in the course of their infarction by setting a goal for timely evaluations of patients with acute chest pain, including performance of an ECG within 10 minutes and administration of thrombolytic therapy for appropriate patients within 30 minutes. To achieve this goal, the NHAAP guidelines[3] recommend measuring the time at which four specific events occur for patients with AMI:

1. Presentation to the emergency department
2. Performance of the ECG
3. Decision of whether to administer thrombolytic therapy
4. Actual infusion of the thrombolytic agent

Specific time goals can be set for the interval between these events (e.g., 10 minutes). Another critical issue is who gives the order to administer thrombolytic therapy. ACEP guidelines recommend that emergency department physicians be given the authority to administer thrombolytic therapy.[1]

In the ACC/AHA guidelines,[2] thrombolytic therapy is considered appropriate (Class I) for up to 12 hours after the onset of symptoms for patients younger than age 75 years and presenting with ST segment elevation or bundle branch block. The ACC/AHA task force considered the weight of evidence in favor of extending the same approach to patients older than 75. Primary intervention with percutaneous transluminal coronary angioplasty (PTCA) was considered an appropriate (Class I) alternative to thrombolytic therapy within the first 12 hours of infarction and beyond for patients with persisting ischemic symptoms. The ACC/AHA guidelines also define goals for speed and volume for operators and institutions performing primary PTCA. Primary PTCA is also endorsed as a strategy for patients with cardiogenic shock due to MI.

The ACC/AHA guidelines do *not* support routine use of angiography

TABLE 35--G-2 -- ACC/AHA GUIDELINES FOR INITIAL MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI) AND ISCHEMIC COMPLICATIONS

Indication	Class I	Class IIa	Class IIb	Class III

Telephone triage[5]	Patients with symptoms suggesting possible ACS should be evaluated by a medical practitioner in a facility equipped to record a 12-lead ECG and not over the telephone.			
Emergency department or outpatient facility presentation [5]	Patients with suspected ACS with symptom duration > 20 minutes, hemodynamic instability, or recent syncope or presyncope should be referred to an emergency department or specialized chest pain unit. Other patients with suspected ACS may be seen initially either in an emergency department, chest pain unit, or an outpatient facility.			

Early risk stratification[5]	Patients presenting with chest pain should undergo early risk stratification focusing on anginal symptoms, the presence or absence of traditional risk factors for coronary artery disease, physical findings, and ECG. A 12-lead ECG should be obtained immediately in patients with ongoing chest pain and within 10 minutes of presentation in patients with a history of chest pain consistent with ACS but has resolved by the time of evaluation.	An acceptable but less preferable marker is CK-MB. Mass assays for CK-MB are preferred over activity assays for CK-MB.		Total CK activity, AST, and/or LDH as the serum markers for detecting MI in patients with chest pain suggestive of ACS.

	Serum cardiac markers should be measured in all patients presenting with chest pain consistent with ACS. A cardiac-specific troponin is the preferred marker and if available should be measured in all patients. For patients presenting within 6 hours of the onset of symptoms, an early marker, myoglobin, should be measured in addition to a cardiac troponin. In patients with negative serum markers within 6 hours of the onset of pain, another determination should be made at 9 hours.		
Oxygen	Overt pulmonary congestion Arterial oxygen desaturation (Sa_{O_2} < 90%)	Routine administration to all patients with uncomplicated MI during the first 2 to 3 hours	Routine administration of supplemental O_2 to patients with uncomplicated MI beyond 3 to 6 hours

Intravenous nitroglycerin	For the first 24 to 48 hours in patients with AMI and CHF, large anterior infarction, persistent ischemia, or hypertension Continued use (beyond 48 hours) in patients with recurrent angina or persistent pulmonary congestion		For the first 24 to 48 hours in all patients with AMI who do not have hypotension, bradycardia, or tachycardia. Continued use (beyond 48 hours) in patients with a large or complicated infarction. (Oral or topical preparations may be substituted.)	Patients with systolic blood pressure < 90 mm Hg or severe bradycardia (< 50/min)
Aspirin	160 to 325 mg on day 1 of AMI and continued indefinitely on a daily basis.		Other antiplatelet agents, such as dipyridamole, ticlopidine, or clopidogrel, may be substituted if true aspirin allergy is present or if the patient is unresponsive to aspirin.	

Atropine	Sinus bradycardia with evidence of low cardiac output and peripheral hypoperfusion or frequent PVCs at onset of symptoms of AMI Acute inferior infarction with type I second- or third-degree AV block associated with symptoms of hypotension, ischemic discomfort, or ventricular arrhythmias Sustained bradycardia and hypotension after administration of nitroglycerin For nausea and vomiting associated with administration of morphine Ventricular asystole	Symptomatic patients with inferior infarction and type I second- or third-degree heart block at the level of the AV node	Administration concomitant with administration of morphine in the presence of sinus bradycardia Asymptomatic patients with inferior infarction and type I second-degree heart block or third-degree heart block at the level of the AV node. Second- or third-degree AV block of uncertain mechanism when pacing is not available.	Sinus bradycardia > 40 beats/min without signs or symptoms of hypoperfusion or frequent PVCs. Type II AV block and third-degree AV block and third-degree AV block with new wide QRS complex presumed due to AMI.

Thrombolysis	ST segment elevation (> 0.1 mV, two or more contiguous leads), time to therapy 12 hr, age < 75 yr BBB (obscuring ST segment analysis) and history suggesting AMI	ST segment elevation, age 75 yr	ST segment elevation, time to therapy>12 to 24 hr Blood pressure on presentation>180 mm Hg systolic and/or > 110 mm Hg diastolic associated with high-risk MI.	ST segment elevation, time to therapy greater than 24 hours, ischemic pain resolved ST segment depression only
Primary percutaneous transluminal coronary angioplasty	As an alternative to thrombolytic therapy in patients with AMI and ST segment elevation or new or presumed new left BBB (LBBB) who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist, and performed in a timely fashion* by persons skilled in the procedure and supported by experienced personnel in an appropriate laboratory environment. In patients who are within 36	As a reperfusion strategy in candidates for reperfusion who have a contraindication to thrombolytic therapy	In patients with AMI who do not present with ST segment elevation but who have reduced (< TIMI grade 2) flow in the infarct-related artery and when PTCA can be performed within 12 hours of onset of symptoms.	Patients with AMI who: 1. Undergo elective PTCA of a non-infarct-related artery at the time of AMI 2. Are beyond 12 hours after onset of symptoms and have no evidence of myocardial ischemia 3. Have received thrombolytic therapy and have no symptoms of myocardial ischemia 4. Are eligible for thrombolysis and are undergoing primary angioplasty performed by a low-volume operator in a laboratory without surgical

	appropriate laboratory environment. In patients who are within 36 hours of an acute ST segment elevation/Q wave or new LBBB MI who develop cardiogenic shock, are < 75 years old, and in whom revascularization can be performed within 18 hours of onset of shock.			angioplasty performed by a low-volume operator in a laboratory without surgical backup
Early coronary angiography in the ST segment elevation or BBB cohort not undergoing primary PTCA		Patients with cardiogenic shock or persistent hemodynamic instability	Patients with evolving large or anterior infarcts treated with thrombolytic agents in whom it is believed that the artery is not patent and adjuvant PTCA is planned	Routine use of angiography and subsequent PTCA within 24 hours of administration of thrombolytic agents

Emergency or urgent coronary artery bypass graft surgery	Failed PTCA with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery AMI with persistent or recurrent ischemia refractory to medical therapy in patients with coronary anatomy suitable for surgery who are not candidates for PCI. At the time of surgical repair of postinfarction ventricular septal defect or mitral regurgitation	Cardiogenic shock with coronary anatomy suitable for surgery	Failed PTCA and small area of myocardium at risk; hemodynamically stable	When the expected surgical mortality rate equals or exceeds the mortality rate associated with appropriate medical therapy

Early coronary angiography and/or interventional therapy in non-ST segment elevation MI	Patients with persistent or recurrent (stuttering) episodes of symptomatic ischemia, spontaneous or induced, with or without associated ECG changes Presence of shock, severe pulmonary congestion, or continuing hypotension			
Glycoprotein IIb/IIIa inhibitors		Patients experiencing an MI without ST segment elevation who have some high-risk features and/or refractory ischemia, provided they do not have a major contraindication due to a bleeding risk		

For definition of classes see p. 1353 .

ACS=acute coronary syndrome; ECG=electrocardiogram; CK=creatine kinase; CK-MB=MB isoenzyme of creatine kinase; AST=aspartate transaminase; LDH=lactate dehydrogenase; CHF=congestive heart failure; BBB=bundle branch block; PVCs=premature ventricular contractions; AV=atrioventricular; PTCA = percutaneous transluminal coronary angioplasty; PCI=percutaneous coronary intervention

Unless otherwise specified, data from Ryan TJ, Antman EM, Brooks NH, et al: 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: Executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 100:1016-1030, 1999. Copyright 1999, American Heart Association.

*Performance standard: balloon inflation within 90 (±30) minutes of admission.

Individuals who perform > 75 PTCA procedures per year.

Centers that perform > 200 PTCA procedures per year and have cardiac surgical capability.

TABLE 35--G-3 -- ACC/AHA GUIDELINES FOR HEMODYNAMIC MONITORING IN ACUTE MYOCARDIAL INFARCTION (AMI)

Indication	Class I	Class IIa	Class IIb	Class III
Balloon flotation right-sided heart catheter monitoring	Severe or progressive CHF or pulmonary edema Cardiogenic shock or progressive hypotension Suspected mechanical complications of AMI (i.e., VSD, papillary muscle rupture, or pericardial tamponade)	Hypotension that does not respond promptly to fluid administration in a patient without pulmonary congestion		Patients with AMI without cardiac or pulmonary complications
Intraarterial pressure monitoring	Patients with severe hypotension (systolic arterial pressure < 80 mm Hg and/or cardiogenic shock Patients receiving vasopressor agents	Patients receiving intravenous sodium nitroprusside or other potent vasodilators	Hemodynamically stable patients receiving intravenous nitroglycerin for myocardial ischemia Patients receiving intravenous inotropic agents	Patients with acute infarction who are hemodynamically stable

Intraaortic balloon counterpulsation	Cardiogenic shock not quickly reversed with pharmacological therapy as a stabilizing measure for angiography and prompt revascularization Acute MR or VSD complicating MI as a stabilizing therapy for angiography and repair/revascularization Recurrent intractable ventricular arrhythmias with hemodynamic instability Refractory post-MI angina as a bridge to angiography and revascularization	Signs of hemodynamic instability, poor left ventricular function, or persistent ischemia in patients with large areas of myocardium at risk.	In patients with successful PTCA after failed thrombolysis or those with three-vessel coronary disease to prevent reocclusion In patients known to have large areas of myocardium at risk with or without active ischemia

CHF=congestive heart failure; VSD=ventricular septal defect; MR=mitral regurgitation; PTCA=percutaneous transluminal coronary angioplasty.

For definition of classes see p. 1353 .

and subsequent PTCA within 24 hours after administration of a thrombolytic agent. Emergency or urgent coronary artery bypass graft (CABG) is endorsed only when patients have severe, persistent ischemia that cannot be addressed by medical therapy and/or PTCA or as part of an effort to correct mechanical complications of MI. Such surgery along with correction of the latter is considered appropriate when these complications cause severe hemodynamic compromise.

For patients with AMI without ST segment elevation, the ACC/AHA guidelines consider early coronary angiography appropriate if they have recurrent ischemia, spontaneous or induced, with or without associated ECG changes. In these patients, glycoprotein IIb/IIIa inhibitors are usually appropriate (Class IIa), assuming that patients do not have major contraindications to these agents. (See guidelines in Chapter 36 for more detail.)

Oxygen therapy is recommended for patients even in the absence of complications in the first 2 to 3 hours, but the evidence was considered weak for this intervention after 3

to 6 hours. Similarly, routine use of intravenous nitroglycerin in patients with uncomplicated courses is not generally advised (Class IIb).

HEMODYNAMIC MONITORING (Table 35-G-3)

Routine use of right-sided heart catheterization or intraarterial pressure monitoring in the absence of cardiac or pulmonary complications is considered inappropriate by the ACC/AHA guidelines. These interventions are considered clearly appropriate (Class I) in patients who have severe hemodynamic derangements or who require vasopressor agents. Intraaortic balloon counterpulsation is endorsed for patients with cardiogenic shock or other major hemodynamic instability and as a bridge to angiography and revascularization in patients with refractory post-MI angina.

Management of Arrhythmias (Table 35-G-4)

The ACC/AHA guidelines recommend a rapid response to the development of atrial fibrillation, including prompt electrical cardioversion for

TABLE 35--G-4 -- ACC/AHA GUIDELINES FOR MANAGEMENT OF ARRHYTHMIAS IN ACUTE MYOCARDIAL INFARCTION (AMI)

Indication	Class I	Class IIa	Class IIb	Class III
Atrial fibrillation	Electrical cardioversion for patients with severe hemodynamic compromise or intractable ischemia Rapid digitalization to slow a rapid ventricular response and improve LV function Intravenous beta adrenoceptor blockers to slow a rapid ventricular response in patients without clinical LV dysfunction, bronchospastic	Either diltiazem or verapamil intravenously to slow a rapid ventricular response if beta-adrenoceptor blocking agents are contraindicated or ineffective		

	rapid ventricular response in patients without clinical LV dysfunction, bronchospastic disease, or AV block			
Ventricular tachycardia (VT)/ventricular fibrillation (VF)	VF should be treated with an electric shock with an initial energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J Sustained (> 30 seconds or causing hemodynamic collapse) polymorphic VT should be treated with an unsynchronized electric shock using an initial energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J. Episodes of sustained monomorphic VT associated with angina, pulmonary edema, or hypotension (systolic pressure < 90 mm Hg) should be treated with a synchronized electric shock of 100 J initial	Infusions of antiarrhythmic drugs may be used after an episode of VT/VF but should be discontinued after 6 to 24 hours and the need for further arrhythmia management assessed Electrolyte and acid-base disturbances should be corrected to prevent recurrent episodes of VF when an initial episode of VF has been treated.	Drug-refractory polymorphic VT should be managed by aggressive attempts to reduce myocardial ischemia, including therapies such as beta-adrenoceptor blockade, intraaortic balloon pumping, and emergency PTCA/CABG surgery. Amiodarone, 150 mg infused over 10 minutes followed by a constant infusion of 1.0 mg/min for up to 6 hours and then a maintenance infusion of 0.5 mg/min.	Treatment of isolated VPBs, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT Prophylactic administration of antiarrhythmic therapy when using thrombolytic agents.

(systolic pressure < 90 mm Hg) should be treated with a synchronized electric shock of 100 J initial energy. Increasing energies may be used if not initially successful.

Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (systolic pressure < 90 mm Hg) should be treated with one of the following regimens:

1. Lidocaine: bolus 1.0 to 1.5 mg/kg. Supplemental boluses of 0.5 to 0.75 mg/kg every 5 to 10 minutes to a maximum of 3 mg/kg total loading dose may be given as needed. Loading is followed by infusion of 2 to 4 mg/min (30 to 50 mug/kg/min).
2. Procainamide: 20 to 30 mg/min loading infusion, up to 12 to 17 mg/kg. This

	e: 20 to 30 mg/min loading infusion, up to 12 to 17 mg/kg. This may be followed by an infusion of 1 to 4 mg/min. 3. Amiodarone: 150 mg infused over 10 minutes followed by a constant infusion of 1.0 mg/min for 6 hours and then a maintenance infusion of 0.5 mg/min. 4. Synchronized electrical cardioversion starting at 50 J (brief anesthesia is necessary).			

Atropine	Symptomatic sinus bradycardia (generally, heart rate < 50 beats/min associated with hypotension, ischemia, or escape ventricular arrhythmia). Ventricular asystole Symptomatic AV block occurring at the AV nodal level (second-degree type I or third-degree with a narrow-complex escape rhythm)			AV block occurring at an infranodal level (usually associated with anterior MI with a wide-complex escape rhythm). Asymptomatic sinus bradycardia
Temporary pacing: placement of transcutaneous patches and active (demand) transcutaneous pacing	Sinus bradycardia (rate less than 50 beats/min) with hypotension (systolic pressure < 80 mm Hg) unresponsive to drug therapy. Mobitz type II second-degree AV block Third-degree heart block Bilateral BBB (alternating BBB, or RBBB) and alternating LAFB, LPFB (irrespective of time of onset) Newly acquired or age-indeterminate LBBB, LBBB and LAFB, RBBB, and	Stable bradycardia (systolic pressure > 90 mm Hg, no hemodynamic compromise, or compromise responsive to initial drug therapy) Newly acquired or age-indeterminate RBBB	Newly acquired or age-indeterminate first-degree AV block	Uncomplicated AMI without evidence of conduction system disease

	(irrespective of time of onset) Newly acquired or age-indeterminate LBBB, LBBB and LAFB, RBBB, and LPFB RBBB or LBBB and first-degree AV block			
Temporary transvenous pacing	Asystole Symptomatic bradycardia (includes sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine) Bilateral BBB (alternating BBB or RBBB with alternating LAFB/LPFB) (any age) New or indeterminate-age bifascicular block (RBBB with LAFB or LPFB, or LBBB) with first-degree AV block Mobitz type II second-degree AV block	RBBB and LAFB or LPFB (new or indeterminate) RBBB with first-degree AV block LBBB, new or indeterminate Incessant VT, for atrial or ventricular overdrive pacing Recurrent sinus pauses (greater than 3 seconds) not responsive to atropine	Bifascicular block of indeterminate age New or age-indeterminate isolated RBBB	First-degree AV block Type I second-degree AV block with normal hemodynamics Accelerated idioventricular rhythm BBB or fascicular block known to exist before AMI

Permanent pacing after AMI	Persistent second-degree AV block in the His-Purkinje system with bilateral BBB or complete AV block after AMI Transient advanced (second- or third-degree) AV block and associated BBB Symptomatic AV block at any level		Persistent advanced (second- or third-degree) block at the AV node level	Transient AV conduction disturbances in the absence of intraventricular conduction defects Transient AV block in the presence of isolated LAFB Acquired LAFB in the absence of AV block Persistent first-degree AV block in the presence of BBB that is old or age indeterminate

LV = left ventricular; AV = atrioventricular; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; BBB = bundle branch block; RBBB and LBBB = right and left bundle branch block; LAFB and LPFB = left anterior and posterior fascicular block.

For definition of classes see p. 1253 .

patients who develop hemodynamic compromise or intractable ischemia with this arrhythmia. Intravenous beta blockers are considered appropriate agents to slow a rapid ventricular response in the absence of contraindications.

The guidelines do *not* recommend routine administration of antiarrhythmic therapy for nonsustained ventricular tachycardia or less severe ventricular arrhythmias, nor do they support prophylactic antiarrhythmic therapy for patients receiving thrombolytic agents. Intravenous amiodarone is considered an appropriate agent in patients with sustained monomorphic ventricular tachycardia.

The ACC/AHA guidelines consider temporary pacemaker placement appropriate in patients with second-degree Mobitz type II or third-degree atrioventricular block, as well as various configurations of bifascicular and potentially trifascicular block. Permanent pacemaker placement is supported for symptomatic atrioventricular block at any level but not for uncomplicated unifascicular block.

Pharmacotherapy (Table 35-G-5)

Intravenous heparin therapy is considered clearly appropriate (Class I) for patients undergoing revascularization and probably appropriate (Class IIa) for patients receiving intravenous alteplase therapy or with non-ST segment elevation MI (Table 35-G-5) . Intravenous heparin is also recommended for patients at high risk for embolic events, such as those with large or anterior MIs.

The ACC/AHA guidelines support a low threshold for initiation of beta-adrenoceptor blocker therapy within 12 hours of the onset of MI in patients without contraindications. Early administration of angiotensin-converting enzyme inhibitors is recommended for patients with ST segment elevation in anterior leads. Initiation of this therapy is considered clearly (Class I) or probably indicated (Class IIa) in broad classes of patients without contraindications.

In contrast, the use of calcium channel blockers is discouraged. Exceptions include the use of verapamil or diltiazem for patients in whom beta blockers cannot be used or are ineffective for management of arrhythmia or ischemia. The ACC/AHA task force considered diltiazem only marginally appropriate (Class IIb) in the first 24 hours for patients with non-ST segment elevation infarction without left ventricular dysfunction, pulmonary congestion, or congestive heart failure.

The role of intravenous magnesium therapy was considered unestablished, although evidence supported its use in patients with documented magnesium deficits or episodes of *torsades de pointes type* ventricular tachycardia.

Discharge from Hospital (Table 35-G-6)

The ACC/AHA guidelines strongly support performance of noninvasive risk stratification using exercise or pharmacological stress testing. The guidelines indicate that the lowest cost alternative--exercise electrocardiography--is an appropriate first-line test. Imaging and pharmacological stress testing are recommended when clinical or electrocardiographic findings compromise the reliability of exercise electrocardiography. The ACC/AHA task force concluded that there was not strong evidence to support *routine* use of ambulatory (Holter) monitoring or analyses of heart rate variability (Class IIb).

Routine use of coronary angiography and revascularization in patients without evidence of ongoing ischemia was also considered inappropriate (Class III) or weakly supported by evidence (Class IIb). However, invasive evaluation and treatment was recommended (Class I or IIa) when patients had spontaneous or induced evidence

TABLE 35--G-5 -- ACC/AHA GUIDELINES FOR PHARMACOTHERAPY IN ACUTE MYOCARDIAL INFARCTION (AMI)

Indication	Class I	Class IIa	Class IIb	Class III
Heparin	Patients undergoing percutaneous or surgical revascularization	Intravenously in patients undergoing reperfusion therapy with alteplase Intravenous UFH or LMWH subcutaneously for patients with non-ST segment elevation MI. Subcutaneous UFH (e.g., 7500 U b.i.d.) or LMWH (e.g., enoxaparin 1 mg/kg b.i.d.) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin. In patients who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus), intravenous heparin is preferred. Intravenously in patients treated with nonselective thrombolytic	Patients treated with nonselective thrombolytic agents, not at high risk, subcutaneous heparin, 7500 U to 12,500 U twice a day until completely ambulatory	Routine intravenous heparin within 6 hours to patients receiving a nonselective fibrinolytic agent (streptokinase, anistreplase, urokinase) who are not at high risk for systemic embolism

		preferred. Intravenously in patients treated with nonselective thrombolytic agents (streptokinase, anistreplase, urokinase) who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus)		
Beta-adrenoceptor blocking agents: early therapy	Patients without a contraindication to beta-adrenoceptor blocker therapy who can be treated < 12 hours of onset of AMI, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty Patients with continuing or recurrent ischemic pain Patients with tachyarrhythmias, such as AF with a rapid ventricular response Non-ST segment elevation MI		Patients with moderate LV failure (the presence of bibasilar rales without evidence of low cardiac output) or other relative contraindications to beta-adrenoceptor blocker therapy, provided patients can be monitored closely	Patients with severe LV failure

Angiotensin-converting enzyme (ACE) inhibitors	Patients within the first 24 hours of a suspected AMI with ST segment elevation in > 2 anterior precordial leads or with clinical heart failure in the absence of hypotension (systolic BP < 100 mm Hg) or known contraindications to use of ACE inhibitors Patients with MI and LV ejection fraction < 40% or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from AMI	All other patients within the first 24 hours of a suspected or established AMI, provided significant hypotension or other clear-cut contraindications are absent Asymptomatic patients with mildly impaired LV function (ejection fraction 40% to 50%) and a history of old MI	Patients who have recently recovered from MI but have normal or mildly abnormal global LV function

Calcium channel blockers		Verapamil or diltiazem in patients in whom beta-adrenoceptor blockers are ineffective or contraindicated (i.e., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with AF after AMI in the absence of CHF, LV dysfunction, or AV block	In non-ST segment elevation infarction, diltiazem may be given to patients without LV dysfunction, pulmonary congestion, or CHF. It may be added to standard therapy after the first 24 hours and continued for 1 year.	Nifedipine (short acting) is generally contraindicated in routine treatment of AMI because of its negative inotropic effects and the reflex sympathetic activation, tachycardia, and hypotension associated with its use. Diltiazem and verapamil are contraindicated in patients with AMI and associated LV dysfunction or CHF.

Magnesium		Correction of documented magnesium (and/or potassium) deficits, especially in patients receiving diuretics before onset of infarction Episodes of torsades de pointes-type VT associated with a prolonged QT interval should be treated with 1 to 2 gm of magnesium administered as a bolus over 5 minutes.	Magnesium bolus and infusion in high-risk patients such as the elderly and/or those for whom reperfusion therapy is not suitable	

UFH = unfractionated heparin; LMWH = low molecular weight heparin; AF = atrial fibrillation; LV = left ventricular; BP = blood pressure; VT = ventricular tachycardia; AV = atrioventricular; CHF = congestive heart failure.

For definition of classes see p. 1253 .

TABLE 35--G-6 -- ACC/AHA GUIDELINES FOR PREPARATION FOR DISCHARGE FROM HOSPITAL AFTER ACUTE MYOCARDIAL INFARCTION (AMI)

Indication	Class I	Class IIa	Class IIb	Class III

Noninvasive evaluation of low-risk patients	Stress ECG Before discharge for prognostic assessment or functional capacity (submaximal at 4 to 6 days or symptom limited at 10 to 14 days) Early after discharge for prognostic assessment and functional capacity (14 to 21 days) Late after discharge (3 to 6 weeks) for functional capacity and prognosis if early stress was submaximal Exercise, vasodilator stress nuclear scintigraphy, or exercise stress echocardiography when baseline abnormalities of the ECG compromise interpretation	Dipyridamole or adenosine stress perfusion nuclear scintigraphy or dobutamine echocardiography before discharge for prognostic assessment in patients judged to be unable to exercise Exercise two-dimensional echocardiography or nuclear scintigraphy (before or early after discharge for prognostic assessment)	Stress testing within 2 to 3 days of AMI Either exercise or pharmacological stress testing at any time to evaluate patients with unstable postinfarction angina pectoris At any time to evaluate patients with AMI who have uncompensated CHF, cardiac arrhythmia, or noncardiac conditions that severely limit their ability to exercise. Before discharge to evaluate patients who have already been selected for cardiac catheterization

Assessment of ventricular arrhythmia--routine testing			Ambulatory (Holter) monitoring, signal-averaged ECG, heart rate variability, baroreflex sensitivity monitoring, alone or in combination for risk assessment after MI, especially in patients at higher perceived risk, when findings might influence management issues, or for clinical research purposes	
Coronary angiography and possible PTCA	Patients with spontaneous episodes of myocardial ischemia or episodes of myocardial ischemia provoked by minimal exertion during recovery from AMI Before definitive therapy of a mechanical complication of infarction such as acute MR, VSD, pseudoaneurysm, or LV aneurysm Patients with persistent hemodynamic instability	When MI is suspected to have occurred by a mechanism other than thrombotic occlusion at an atherosclerotic plaque. This would include coronary embolism, certain metabolic or hematological diseases, or coronary artery spasm Survivors of AMI with depressed LV systolic function (LV ejection fraction less than or equal to 40%), CHF, prior revascularization,	Coronary angiography performed in all patients after infarction to find persistently occluded infarct-related arteries in an attempt to revascularize the artery or to identify patients with three-vessel disease All patients after a non-Q-wave MI Recurrent VT or VF or both, despite antiarrhythmic therapy in patients without	Routine use of coronary angiography and subsequent PTCA of the infarct-related artery within days after receiving thrombolytic therapy Survivors of MI who are thought not to be candidates for coronary revascularization

	or LV aneurysm Patients with persistent hemodynamic instability	LV systolic function (LV ejection fraction less than or equal to 40%), CHF, prior revascularization, or malignant ventricular arrhythmias Survivors of AMI who had clinical heart failure during the acute episode but subsequently demonstrated well-preserved LV function	Recurrent VT or VF or both, despite antiarrhythmic therapy in patients without evidence of ongoing myocardial ischemia	
Routine coronary angiography and PTCA after successful thrombolytic therapy				Routine PTCA of the stenotic infarct-related artery immediately after thrombolytic therapy PTCA of the stenotic infarct-related artery within 48 hours of receiving a thrombolytic agent in asymptomatic patients without evidence of ischemia

ECG = electrocardiogram; CHF = congestive heart failure; MR = mitral regurgitation; VSD = ventricular septal defect; LV = left ventricular; VT = ventricular tachycardia; VF= ventricular fibrillation; PTCA = percutaneous transluminal coronary angioplasty.

For definition of classes see p. 1253 .

TABLE 35--G-7 -- SECONDARY PREVENTION

Indication	Class I	Class IIa	Class IIb	Class III

Management of lipids	The AHA step II diet, which is low in saturated fat and cholesterol in all patients after recovery from AMI Patients with LDLC > 125 mg/dl despite the AHA step II diet should be placed on drug therapy, with the goal of reducing LDLC to < 100 mg/dl Patients with normal plasma cholesterol levels with HDLC < 35 mg/dl should receive nonpharmacological therapy (e.g., exercise) designed to raise it	Drug therapy added to diet in patients with LDLC levels < 130 mg/dl but > 100 mg/dl after an appropriate trial of the AHA step II diet Patients with normal total cholesterol levels but HDLC < 35 mg/dl despite diet and other nonpharmacological therapy may be started on drugs such as niacin to raise HDL levels.	Drug therapy with either niacin or gemfibrozil added to diet regardless of LDLC and HDLC when triglyceride levels are > 200 mg/dl.
Long-term beta-adrenoceptor blocker therapy in survivors of myocardial infarction	All but low-risk patients without a clear contraindication to beta-adrenoceptor blocker therapy. Treatment should begin within a few days of the event (if not initiated acutely) and continue indefinitely.	Low-risk patients without a clear contraindication to beta-adrenoceptor blocker therapy. Survivors of non-ST segment elevation MI.	Patients with moderate or severe LV failure or other relative contraindications to beta-adrenoceptor blocker therapy, provided patients can be monitored closely
Long-term anticoagulation	Post-MI patients unable to take daily aspirin Post-MI patients in persistent AF Patients with LV thrombus	Post-MI patients with extensive wall motion abnormalities Patients with paroxysmal AF.	Post-MI patients with severe LV systolic dysfunction with or without CHF

Estrogen replacement therapy and myocardial infarction		HRT with estrogen plus progestin for secondary prevention of coronary events should not be given de novo to postmenopausal women after AMI. Postmenopausal women who are already taking HRT with estrogen plus progestin at the time of AMI can continue this therapy.		

LDLC and HDLC = low- and high-density lipoprotein cholesterol; LV = left ventricular; CHF = congestive heart failure; AF = atrial fibrillation.
For definition of classes see p. 1253 .

of myocardial ischemia or other complications of ischemic heart disease.

Secondary Prevention (Table 35-G-7)

The ACC/AHA guidelines strongly endorse pharmacological and aggressive dietary interventions to reduce low-density lipoprotein (LDL) cholesterol after acute myocardial infarction. An AHA Step II diet is considered appropriate for all patients after recovery from AMI, and initiation for drug therapy is considered clearly appropriate (Class I) if LDL cholesterol is greater than 125 mg/dl despite this diet. The use of a lower LDL cholesterol threshold (100-125 mg/dl) for initiation of drug therapy was considered to be less clearly established (Class IIa). Exercise and other efforts to raise high-density lipoprotein cholesterol are also recommended.

The guidelines reflect enthusiasm for the benefits of beta blockers for all but low-risk patients if there are no contraindications to these agents. Anticoagulation with warfarin is considered appropriate for patients unable to take daily aspirin or for patients who have atrial fibrillation or left ventricular thrombus. The guidelines are somewhat supportive (Class IIa) of anticoagulation in patients with extensive wall motion abnormalities or paroxysmal atrial fibrillation but not for all patients with severe left ventricular dysfunction.

The guidelines do not support initiation of hormone replacement therapy in postmenopausal patients with the goal of preventing coronary events after AMI but did not oppose their continuation.

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Chapter 36 - Unstable Angina

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Unstable angina lies in the center of the spectrum of clinical conditions caused by myocardial ischemia. These range from chronic stable angina pectoris (see Chap. 37) to the acute coronary syndromes. The latter, in turn, consist of acute myocardial infarction (MI) associated with electrocardiographic ST segment elevation (STEMI) (see Chap. 35) and unstable angina/non-ST segment elevation MI (UA/NSTEMI). The former is most commonly caused by acute total coronary occlusion,[1] [2] and urgent reperfusion is the mainstay of therapy, whereas UA/NSTEMI is usually associated with severe coronary obstruction but not total occlusion of the culprit coronary artery.[3] [4] If the myocardial ischemia that results from the coronary obstruction is long in duration and/or great in severity, myocardial necrosis occurs,[5] and the patient is classified as having a non-Q-wave MI or, now more aptly termed, NSTEMI (see Fig. 35-2) .

Although, with the advent of thrombolysis and other emergency reperfusion therapies, a great deal of attention has focused on acute MI with ST segment elevation, UA/NSTEMI (the focus of this chapter) occurs with much greater frequency. Every year in the United States, approximately 1.3 million patients are admitted to the hospital with unstable

angina or NSTEMI compared with approximately 350,000 patients with acute STEMI.[6]

DEFINITION AND CLASSIFICATION

DEFINITION.

This is largely based on the clinical presentation[7] (see p. 1235). *Stable* angina pectoris is characterized by a deep, poorly localized chest or arm discomfort (rarely described as pain) that is reproducibly associated with physical exertion or emotional stress and relieved within 5 to 15 minutes by rest and/or sublingual nitroglycerin. *Unstable* angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features: (1) it occurs at rest (or with minimal exertion) usually lasting more than 20 minutes (if not interrupted by nitroglycerin); (2) it is severe and described as frank pain and of new onset (i.e., within 1 month); and (3) it occurs with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously). Some patients with this pattern of ischemic discomfort, especially those with prolonged rest pain,[5] develop evidence of myocardial necrosis on the basis of the release of cardiac markers and thus have a diagnosis of NSTEMI. Traditionally, this diagnosis has been based on elevation of serum creatine kinase (CK)-MB, but recently troponin T and I assays have been used to define ischemic myocardial damage based on their higher sensitivity for myocardial necrosis and powerful prognostic ability (see pp. 1236 , 1237 , and 1240).

CLASSIFICATION.

Because unstable angina comprises such a heterogeneous group of patients, classification schemes based on clinical features have been proposed.[7] [8] [9] [10] A clinical classification of unstable angina, presented by one of the authors (Table 36-1) ,[8] has been found to be a useful means of stratifying risk.[11] [12] [13] [14] [15] Patients are divided into three groups according to the clinical circumstances of the acute ischemic episode: primary unstable angina, secondary unstable angina (i.e., with unstable angina related to obvious precipitating noncoronary factors such as anemia, infection, or cardiac arrhythmias), and post-MI angina. Patients are also classified according to the severity of the ischemia (acute rest pain, subacute rest pain, or new-onset severe angina)[8] (see Table 36-1) . This classification has been shown to be predictive of plaques with thrombus at angiography[11] [16] [17] or in atherectomy specimens[18] and in risk stratification (see p. 1234).[12] [13] [14]

Because unstable angina is a clinical syndrome rather than a specific disease (much like hypertension rather than pneumococcal pneumonia), and because it has many potential causes, an etiological approach has been proposed.[10] Five pathophysiological processes that may contribute to the development of unstable angina have been identified (Fig. 36-1) :

1. Plaque rupture with superimposed nonocclusive thrombus
2. Dynamic obstruction (i.e., coronary spasm of an epicardial artery, as in Prinzmetal angina [see Chap. 37] or constriction of the small muscular coronary arteries)
3. Progressive mechanical obstruction

4. Inflammation and/or infection
5. Secondary unstable angina, precipitated by increased myocardial oxygen demand or decreased supply (e.g., thyrotoxicosis or anemia)

Individual patients may have several of these processes coexisting as the cause of their episode of unstable angina. Use of this etiological approach will refine the diagnostic approach and help target therapeutic strategies to treat the underlying disease that precipitated the episode of unstable angina.

TABLE 36-1 -- BRAUNWALD CLINICAL CLASSIFICATION OF UNSTABLE ANGINA

CLASS	DEFINITION	DEATH OR MYOCARDIAL INFARCTION TO 1 YEAR*
Severity		
Class I	New onset of severe angina or accelerated angina; no rest pain	7.3%
Class II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	10.3%
Class III	Angina at rest within 48 hr (angina at rest, subacute)	10.8%
Clinical Circumstances		
A (secondary angina)	Develops in the presence of extracardiac condition that intensifies myocardial ischemia	14.1%
B (primary angina)	Develops in the absence of extracardiac condition	8.5%
C (postinfarction angina)	Develops within 2 weeks after acute myocardial infarction	18.5% $p<0.001$
Intensity of treatment	Patients with unstable angina may also be divided into three groups depending on whether unstable angina occurs (1) in the absence of treatment for chronic stable angina, (2) during treatment for chronic stable angina, or (3) despite maximal antiischemic drug therapy. The three groups may be designated subscripts 1, 2, or 3, respectively.	

Electrocardiographic changes	Patients with unstable angina may be further divided into those with or without transient ST-T wave changes during pain.	

From Braunwald E. Unstable angina: A classification. Circulation 80:410-414, 1989. Copyright 1989, American Heart Association.

*Data from TIMI III Registry: Cannon CP, McCabe CH, Stone PH, et al: Prospective validation of the Braunwald classification of unstable angina: Results from the Thrombolysis in Myocardial Ischemia (TIMI) III Registry (abstract). Circulation 92(Suppl I):1-19, 1995. Copyright 1995, American Heart Association.

p=0.057

PATHOPHYSIOLOGY

The majority of patients with unstable angina have significant obstructive coronary atherosclerosis (see Chap. 30) . Episodes of ischemia can be provoked by an increase in myocardial oxygen demand (e.g., precipitated by tachycardia or hypertension) and/or by a reduction in supply (e.g., due to reduction in coronary lumen diameter by platelet-rich thrombi or vasospasm). Rapid progression of the underlying coronary artery disease has been documented.[19] [20] A sequence of events can be documented in unstable angina in which there is first a reduction in coronary sinus oxygen saturation (signifying a reduction in coronary blood flow), then ST segment depression, followed by chest discomfort.[21] Elevations in blood pressure and/or heart rate sometimes ensue.[21] A patient might have both a small increase in myocardial oxygen demand, in conjunction with a reduction in coronary blood flow, leading to the episode of ischemia. The five major causes of these two broad precipitants of unstable angina are reviewed next.

PLAQUE RUPTURE, FISSURE, OR EROSION.

Rupture or erosion of an atherosclerotic plaque with superimposed nonocclusive thrombus is by far the most common cause of UA/NSTEMI. The type of plaque that ruptures, the so-called vulnerable plaques, are usually lesions with less than 50 percent stenosis.[22] [23] [24] [224A] Plaque rupture can be precipitated by multiple factors, including high plaque lipid content,[25] local inflammation causing breakdown of the thin shoulder of the plaque,[26] coronary artery constriction at the site of the plaque, local shear stress forces, platelet activation,[27] [28]

Figure 36-1 Schematic representation of the causes of unstable angina. Each of the five bars represents one of the etiologic mechanisms, and the red portion of the bar represents the extent to which the mechanism is operative. *A,* Most common form of unstable angina in which atherosclerotic plaque causes moderate (60 percent diameter) obstruction and acute thrombus overlying plaque causes very severe (90 percent diameter) narrowing. *B,* Mild coronary obstruction, adjacent to which there is intense (90 percent diameter) vasoconstriction. (From Braunwald E: Unstable angina: An etiologic approach to management

[editorial]. Circulation 98:2219-2222, 1998. Copyright 1998, American Heart Association.)

and the status of the coagulation system (i.e., a potentially prothrombotic state),[29] [30] all of which culminate in the formation of platelet-rich thrombi at the site of the plaque rupture or erosion and the resultant acute coronary syndrome (see also Chaps. 30 and 35) . [31] [32] [33] Circadian variation with a morning increase in the onset of UA/NSTEMI has been reported[34] and likely relates to similar factors as in MI, including morning elevations in platelet aggregability[35] [36] and in myocardial oxygen demand with increases in blood pressure, heart rate, emotional stress, and physical exertion.[37]

INFLAMMATION AND/OR INFECTION.

Recent evidence has also pointed to a role for inflammation, which appears to play a key role in the development of atherosclerosis (see Chaps. 30 and 31) , [38] [39] and in the development and recurrence of unstable angina.[40] [41] [42] [43] Infectious agents, notably *Chlamydia pneumoniae,* appear to be one of the underlying causes of diffuse inflammation in the pathogenesis of coronary artery disease.[44] [45] [46] Others for which there is some, albeit less strong, evidence include *Helicobacter pylori* and cytomegalovirus.[44] An etiological relationship between these infectious agents to the development of unstable angina (or MI) has not been definitively established.[46] [47] [48] On the other hand, evidence from several animal models,[49] [50] [51] and pilot treatment trials in patients, [52] [53] [54] suggests that *Chlamydia pneumoniae* may be an important and *potentially treatable* cause of unstable angina or MI, and larger trials are ongoing.

THROMBOSIS

(see also Chap. 62) . The central role of coronary artery thrombosis in the pathogenesis of unstable angina is supported by a substantial body of evidence.[4] [31] [32] [55] [56] [57] Six sets of observations contribute to this concept:

1. At autopsy, thrombi can usually be identified at the site of a ruptured plaque[31] [32] [58] or a coronary erosion.[59]
2. Coronary atherectomy specimens obtained from patients with unstable angina demonstrate a high incidence of thrombotic lesions, as compared with those obtained from stable angina patients.[18] [57] [60] [61]
3. Coronary angioscopic observations in unstable angina indicate that thrombus is frequently present.[55] [56] [62] [63] [64]
4. Coronary angiography has demonstrated ulceration or irregularities suggesting a ruptured plaque[22] [65] and/or thrombus in many patients (Fig. 36-2). In the Thrombosis in Myocardial Infarction (TIMI) IIIA trial of patients with UA/NSTEMI, 35 percent of patients had definite thrombus and an additional 40 percent had possible thrombus at angiography.[4]
5. Evidence of ongoing thrombosis has been noted with elevation of several markers of platelet activity and fibrin formation.[66] [67] [68] [69] [70]

6. The clinical outcome of patients with acute coronary syndromes improves with antithrombotic therapy with aspirin,[71] [72] [73] [74] heparin, [73] [74] [75] [76] [77] low-molecular-weight heparin,[78] [79] [80] and platelet glycoprotein IIb/IIIa inhibitors. [81] [82] [83]

PLATELET AGGREGATION

(see also Chap. 62) . Platelets play a key role in the transformation of a stable atherosclerotic plaque to an unstable lesion (Fig. 36-3) . With rupture or ulceration of an atherosclerotic plaque, the subendothelial matrix (e.g., collagen and tissue factor) is exposed to the circulating blood. The first step is *platelet adhesion* by means of the platelet glycoprotein Ib receptor through its interaction with endothelial von Willebrand factor. This is followed by *platelet activation*, which leads to (1) a shape change in the platelet (from a smooth discoid shape to a spiculated form, which increases the surface area upon which thrombin generation can occur); (2) degranulation of the alpha and dense granules, thereby releasing thromboxane A_2 , serotonin, and other platelet aggregatory and chemoattractant agents; and (3) expression of

Figure 36-2 Coronary artery thrombus in a patient with unstable angina. A 60-year-old man presented with prolonged rest pain and transient anterior ST segment elevations. Coronary angiography shows an irregular hazy filling defect in the left anterior descending artery at the level of the second diagonal branch (arrow). Contrast medium surrounds the globular thrombus, which extends into the diagonal branch.

glycoprotein IIb/IIIa receptors on the platelet surface with activation of the receptor so that it can bind fibrinogen. The final step is *platelet aggregation*, that is, the formation of the platelet plug. Fibrinogen (or von Willebrand factor) binds to the activated glycoprotein IIb/IIIa receptors of two platelets, thereby creating a growing platelet aggregate. Antiplatelet therapy is one of the cornerstones of therapy in unstable angina (see p. 1243) and is directed at decreasing the formation of thromboxane A_2 (aspirin), inhibiting the adenosine diphosphate (ADP) pathway of platelet activation (ticlopidine and clopidogrel), and directly inhibiting platelet aggregation (glycoprotein IIb/IIIa inhibitors) (see Fig. 36-3) .

SECONDARY HEMOSTASIS.

Simultaneously with formation of the platelet plug, the plasma coagulation system is activated. Release of tissue factor appears to be the predominant mechanism of initiating hemostasis during plaque rupture and coronary thrombosis (see Chap. 62) . [84] [85] [86] Ultimately, factor X is activated (to factor Xa), leading to the generation of thrombin, which plays a central role in arterial thrombosis. Thrombin has several actions: (1) it converts fibrinogen to fibrin in the final common pathway for clot formation; (2) it is a powerful stimulus for platelet aggregation; and (3) it activates factor XIII, which leads to cross-linking and stabilization of the fibrin clot. Thrombin molecules are incorporated into coronary thrombi and can form the nidus of rethrombosis (i.e., reocclusion or reinfarction) as the thrombus undergoes spontaneous or pharmacologically induced fibrinolysis. Accordingly, effective inhibition of thrombin and

factor Xa plays an important part of the therapy of unstable angina (see later).

CORONARY VASOCONSTRICTION.

There are three settings in which the process of dynamic coronary obstruction is identified:

1. Prinzmetal variant angina, with intense *focal* spasm of a segment of an epicardial coronary artery, is the prototypical example (see also Chap. 37) .[87] This can occur in patients without coronary atherosclerosis or in patients with a nonobstructive atheromatous plaque. The vasospastic angina appears to be due to hypercontractility of vascular smooth muscle and endothelial dysfunction occurring in the region of spasm.[88] Such patients typically present with rest pain accompanied by transient ST segment elevation.

2. Coronary vasoconstriction causing "microcirculatory angina" results from constriction of the small intramural coronary resistance vessels.[89] Although there are no epicardial coronary artery stenoses, coronary flow is usually slowed (see Chap. 37) .
3. Probably the most common setting in which vasoconstriction occurs is in the presence of coronary atherosclerotic plaques.

Vasoconstriction can occur as the result of local vasoconstrictors released from platelets, such as serotonin and thromboxane A_2 ,[66] [69] as well as those present within the thrombus, such as thrombin.[90] A dysfunctional coronary endothelium, with reduced production of nitric oxide and increased release of endothelin (see Chap. 34) , can also lead to vasoconstriction. Adrenergic stimuli, cold immersion,[91] cocaine,[92] [93] or mental stress[94] can also cause coronary vasoconstriction.

Figure 36-3 Primary hemostasis: process of platelet adhesion (a), activation (b), and aggregation (c). Platelets initiate thrombosis at the site of a ruptured plaque: the first step is *platelet adhesion* (1) via the glycoprotein Ib receptor in conjunction with von Willebrand factor. This is followed by *platelet activation* (2), which leads to a shape change in the platelet, degranulation of the alpha and dense granules, and expression of glycoprotein IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is *platelet aggregation* (3), in which fibrinogen (or von Willebrand factor) binds to the activated glycoprotein IIb/IIIa receptors of two platelets. Aspirin (ASA) and clopidogrel act to decrease platelet activation (see text for details), whereas the glycoprotein IIb/IIIa inhibitors inhibit the final step of platelet aggregation.

PROGRESSIVE MECHANICAL OBSTRUCTION.

The fourth etiology of unstable angina results from progressive luminal narrowing. This is most commonly seen in the setting of restenosis after percutaneous coronary intervention (PCI) (see Chap. 38) . However, angiographic[20] and atherectomy studies[60] [95] have demonstrated that many patients without previous intracoronary procedures

have shown progressive luminal narrowing of the culprit vessel that is related to rapid cellular proliferation in the period preceding the onset of unstable angina.

SECONDARY UNSTABLE ANGINA.

This form of unstable angina is precipitated by an imbalance in myocardial oxygen supply and demand caused by conditions extrinsic to the coronary arteries in patients with prior coronary stenosis and chronic stable angina.[8] This could occur by either an increased myocardial oxygen demand, a reduction in coronary blood flow, or both. Conditions that increase oxygen demand include tachycardia (e.g., supraventricular tachycardia or new-onset atrial fibrillation with rapid ventricular response), fever, thyrotoxicosis, hyperadrenergic states, and elevations of left ventricular afterload such as hypertension or aortic stenosis. Secondary unstable angina can also occur due to impaired oxygen delivery, as occurs in anemia, hypoxemia (e.g., due to pneumonia or congestive heart failure), and hyperviscosity states or hypotension. Secondary angina appears to have a worse prognosis than primary unstable angina (see Table 36-1) .[14]

CLINICAL PRESENTATION

The clinical profile of patients presenting with unstable angina differs from that of acute ST elevation MI. Unstable angina occurs more frequently in women, who comprise 30 to 45 percent of patients in studies of unstable angina,[96] [97] [98] compared with 25 to 30 percent of patients with NSTEMI and 20 percent of patients with STEMI.[96] [97] [99] In comparison to the latter, patients with unstable angina also have higher rates of prior MI, angina, previous coronary revascularization, and extracardiac vascular disease.[97] [99] Indeed, approximately 80 percent of patients with unstable angina have a prior history of coronary artery disease.

HISTORY AND PHYSICAL EXAMINATION.

A description of "ischemic pain" is the hallmark of unstable angina (see Chap. 3) . Chronic stable angina is usually described as a discomfort or pressure but rarely as a pain; it is usually located in the substernal region, but sometimes is near the epigastrium, and it frequently radiates to the anterior neck, left shoulder and left arm (see Chap. 37) . In unstable angina, the discomfort, occurring either on exertion or at rest, is usually severe enough to be considered painful. The physical examination may be unremarkable or may support the diagnosis of cardiac ischemia (see Chap. 4) Signs that suggest unstable angina (or MI) with ischemia involving a larger fraction of the left ventricle are transient diaphoresis, pale cool skin, sinus tachycardia, a third or fourth heart sound, and basilar rales on lung examination. Rarely, the severity of left ventricular dysfunction causes hypotension.

ELECTROCARDIOGRAM (ECG).

In unstable angina, ST segment depression (or transient ST segment elevation) and T wave changes occur in up to 50 percent of patients.[83] [100] [101] Three analyses have shown that in patients with the clinical presentation of unstable angina, *new* ST segment

deviation, even of only 0.05 mV, is a specific and important measure of ischemia and prognosis.[100] [102] [103] T wave changes are sensitive but nonspecific of acute ischemia,

Figure 36-4 Electrocardiogram showing deep symmetrical anterolateral T wave inversion without ST segment deviation. Such findings are frequently associated with critical stenosis of the left anterior descending coronary artery and are a useful marker of a patient at high risk of subsequent death or myocardial infarction. (From Haines DE, Raabe DS, Gundel WD, Wackers FJ: Anatomic and prognostic significance of new T-wave inversion in unstable angina. Am J Cardiol 52:14-18, 1983.)

unless they are marked. Thus, transient, deep T wave inversions (0.3 mV) are considered to be relatively specific for acute ischemia, like ST segment deviations, and to signify high risk[7] [83] (Fig. 36-4). On the other hand, the presence of T wave inversions of 0.1 mV in patients with unstable angina may add little to the clinical history.[100] [103]

CONTINUOUS ECG MONITORING.

Continuous ECG monitoring can be used for two purposes in unstable angina: (1) to detect arrhythmias in association with the acute episode and (2) to monitor the ST segments for evidence of recurrent ischemia.[7] Although life-threatening arrhythmias are rare in unstable angina, they may be more common among NSTEMI patients. Guidelines generally recommend continuous monitoring for at least 24 hours in patients hospitalized for UA/NSTEMI.[104] [105] When screening for ischemia, ST segment monitoring appears to be more sensitive than patient's symptoms, and it is a strong marker of adverse short- and long-term outcome.[21] [106] [107] [108] [109] [110] Evidence has shown that continuous 12-lead ST segment monitoring provides independent prognostic information even when it is used in conjunction with troponins and clinical variables.[110] Silent ischemia was more frequent and prolonged in patients with NSTEMI compared with those with unstable angina.[111]

CARDIAC MARKERS.

Among patients presenting with symptoms consistent with unstable angina, the diagnosis of NSTEMI is made if there is biochemical evidence of myocardial necrosis, that is, positive CK-MB, troponin T or I, or potentially other markers of injury[7] [112] (see also Chap. 35) .

The issue of what "cut point" to use for a positive troponin assay is currently being debated. One group has proposed two cut points: one "diagnostic" cut point to define myocardial infarction (derived from a comparison with CK-MB-defined MI) and a second, lower, "prognostic" cut point, generally the upper detectable limit of the assay or more specifically the 97.5th percentile of a normal population of subjects.[113] Each assay

may have different cut points. As an example, at Brigham and Women's Hospital for the Dimension R×L assay for troponin I (Dade-Behring), the cut points are more than 1.5 ng/dl for the diagnosis of MI and 0.1 ng/dl or more for prognosis. Cut points are different for troponin T, and, to date, a cut point of 0.1 ng/dl or more has been used for both diagnosis and prognosis[114] [115] ; however, a cut point for prognosis of as low as 0.01 ng/dl or more is being explored as the prognostic cut point with the third-generation assay.[116]

In patients with UA/NSTEMI, values greater than the upper (diagnostic) cut point indicate evidence of NSTEMI. Smaller elevations in troponin are believed also to signify evidence of myocardial damage, although the extent of myocardial damage has not been documented in patients with the small elevations. The damage is believed to result from obstruction of small, distal coronary vessels, caused by microemboli of thrombus or of plaque debris from a more proximal lesion.[117] Smaller elevations in troponin values (e.g., troponin I between 0.1 and 1.5 ng/dl) have been shown to be of important prognostic value (see Diagnosis, p. 1237, and Risk Stratification, p. 1239) and may assist in the diagnosis of unstable angina when used in conjunction with the clinical history and ECG. Bedside tests can have either a positive versus negative result or provide a quantitative result. However, because each assay is different, each hospital needs to review the specific cut points defined by that assay.

CORONARY ARTERIOGRAPHIC FINDINGS.

The extent of coronary artery disease among patients with UA/NSTEMI enrolled in TIMI IIIB was 15 percent with critical obstruction (> 60 percent luminal diameter stenosis) of three vessels, 30 percent with two-vessel disease, 40 percent with single-vessel disease, and 20 percent with no significant coronary stenosis.[101] Five to 10 percent of patients had left main stem stenosis greater than 50 percent.[100] [101] [118] Similar findings have been reported from registries of unselected UA/NSTEMI patients.[100] [118] Women and nonwhites with UA/NSTEMI have less extensive coronary disease than their counterparts,[96] [97] [98] [118] [119] whereas patients with NSTEMI have more extensive disease than those who present with unstable angina.[97]

Fifteen to 30 percent of patients who present with symptoms of unstable angina will have no significant coronary stenosis on coronary angiography.[96] [97] [100] [101] [118] [119] [120] Women and nonwhites comprise a larger proportion of such patients without epicardial coronary disease,[96] [97] [118] [119] [120] suggesting a difficulty in making a firm diagnosis of unstable angina in these groups and/or a different pathophysiological mechanism for their clinical presentation. Approximately one third of patients with unstable angina without a critical epicardial obstruction will have impaired coronary flow, suggesting a pathophysiological role for coronary microvascular dysfunction.[120] The short-term prognosis is excellent in this group of patients.

The culprit lesion in unstable angina typically exhibits an eccentric stenosis with scalloped or overhanging edges and a narrow neck.[4] [22] [65] These angiographic findings may represent disrupted atherosclerotic plaque, thrombus, or a combination.[121] Features suggesting thrombus include globular intraluminal masses with a rounded or polypoid shape[4] (see Fig. 36-2) . "Haziness" of a lesion has been used as an

angiographic marker of possible thrombus, but this finding is less specific. Patients with angiographically visualized thrombus have impaired coronary flow and worse clinical outcomes, compared with those without thrombus.[122] [123] Of interest, however, is that angiographically documented thrombus is present in only 20 to 40 percent of patients using a rigorous definition.[4] [123] [124] It is likely that the frequency is much greater and that angiography simply is not sensitive enough to detect all but the largest thrombi.

ANGIOSCOPY AND INTRAVASCULAR ULTRASOUND.

Greater definition of the culprit lesion has been possible using angioscopy, where "white" (platelet-rich) thrombi are frequently observed as opposed to "red" thrombi, which are more often seen in patients with acute STEMI.[55] [56] [62] [64] Intravascular ultrasound examination identified more soft "echolucent" plaques and fewer calcified lesions among patients with unstable versus stable angina.[17]

OTHER LABORATORY TESTS.

A chest roentgenogram may be useful in identifying pulmonary congestion or edema, which would be more likely in patients with NSTEMI involving a significant proportion of the left ventricle or in those with prior known left ventricular dysfunction.[7]

The presence of congestion has been shown to confer an adverse prognosis.[125] [126]

Obtaining a serum cholesterol level is useful in identifying an important, treatable cause of coronary atherosclerosis. Because serum cholesterol levels begin to fall 24 hours after acute MI or unstable angina, it should be measured at the time of hospital admission. If only a later sample is obtained, but the value falls into a range that warrants long-term treatment (see Chap. 39) appropriate therapy can be initiated,[127] [128] [129] although the optimal timing of initiation of cholesterol-lowering therapy is being studied. Other circulating markers of increased risk are discussed later (see p. 1240). Evaluation for other secondary causes of unstable angina[8] may also be appropriate in selected patients (e.g., checking thyroid function in a patient who presents with unstable angina and a persistent tachycardia).

DIAGNOSIS OF UA/NSTEMI

The diagnosis of unstable angina is a clinical one, based on the patient's description of symptoms, as described earlier. A diagnosis of NSTEMI is made on the basis of a clinical history consistent with UA/NSTEMI and positive circulating cardiac markers[7] (see p. 1240 and Chap. 35) . However, in the United States 6 to 7 million persons per year present to an emergency department (ED) with a complaint of chest pain or other symptoms suggestive of possible acute coronary syndrome, of whom only 20 to 25

percent have a final diagnosis of unstable angina or MI.[130] [131]

ASSESSING LIKELIHOOD OF CORONARY ARTERY DISEASE.

Thus, the key first step in evaluation of patients with possible UA/NSTEMI is to determine the *likelihood* that coronary artery disease is the cause of the presenting symptoms.[7] From several large studies of patients presenting with chest pain to an ED,[100] [112] [130] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141] [142] [143] [144] [145] certain features portend a higher likelihood that the patient actually has unstable angina (Table 36-2) . High likelihood exists among patients with prior coronary disease and/or with symptoms

TABLE 36-2 -- FEATURES ASSOCIATED WITH HIGHER LIKELIHOOD OF CORONARY ARTERY DISEASE AMONG PATIENTS PRESENTING WITH SYMPTOMS SUGGESTIVE OF UNSTABLE ANGINA

History
Chest pain as chief complaint similar to prior ACS symptoms
Known history of coronary artery disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft
History of angina
Age>60
Male gender
More than two major cardiac risk factors
Diabetes
Extracardiac vascular disease (carotid or peripheral)
Physical Examination
Pulmonary rales, hypotension
Transient mitral regurgitation
Diaphoresis
Electrocardiogram
New/presumably new ST deviation >0.05 mV
T wave inversion
0.1 mV
Q waves, left bundle branch block
Cardiac Markers
Elevated CK-MB, troponin I or T
Data supporting these factors come from references [100] [130] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141] [142] [143] [144] [145] and [412] .

that are similar to a prior episode of MI or unstable angina.[130] [132] [133] [134] [136] [137] Elevation of cardiac markers or evidence of congestive heart failure or hemodynamic compromise also increase the likelihood of UA/NSTEMI.

CLINICAL AND ECG PREDICTOR RULES.

Several groups have developed predictor rules to enhance clinical assessment of patients presenting with chest pain to the ED.[132] [133] [134] [135] [136] [137] [138] [139] These "predictor rules" use clinical variables as well as ECG findings to define either MI,[132] [133] [135] any acute coronary syndrome (UA, NSTEMI, or STEMI),[134] [137] [138] [139] or subsequent cardiac complications regardless of initial diagnosis.[136] In general, all of these prediction rules can assist the clinician in assessing the likelihood of unstable angina or MI, but because of the numerous questions that are part of the assessment they are not often used in clinical practice. One algorithm, the Acute Cardiac Ischemia--Time Insensitive Prediction Instrument (ACI-TIPI) has been integrated into ECG devices and provides a likelihood of the patient having unstable angina or MI.[137] [139] This device evaluates the ECG for the presence of ST segment deviation, Q waves, and T wave inversion; and the operator enters into the computer the patient's age and gender and whether the patient's primary symptom was chest/left arm pain. The ACI-TIPI algorithm then computes a probability that the patient has an acute coronary syndrome, which is printed with the computer's standard interpretation of the ECG. This device was shown in a randomized trial to reduce unnecessary hospital and coronary care unit admissions and thus provide more cost-effective triage of patients.[139]

CARDIAC-SPECIFIC TROPONINS.

The troponins can be used in two ways in the ED to evaluate patients with possible UA/NSTEMI: (1) to diagnose NSTEMI and (2) to define prognosis (i.e., the risk of developing recurrent cardiac ischemic events, including death, recurrent infarction, and recurrent severe ischemia requiring rehospitalization or urgent revascularization). In numerous studies, in patients admitted to the hospital with unstable angina[115] [141] [142] [143] [144] [145] [146] [147] [148] [149] [150] [151] [152] [153] [154] [155] (see p. 1240) as well as in the broad group of patients presenting to the ED with chest pain,[141] [143] [144] elevations of either troponin T or I have been shown to be very strong predictors of subsequent cardiac events.

However, "false-positive" troponin tests have been noted among series of patients presenting to the ED with chest pain.[156] [157] [158] In patients presenting to the ED with a complaint of chest pain, the clinical suspicion (and prevalence) of coronary artery disease is lower than it is in patients who are admitted to the hospital with unstable angina.[141] [143] Thus, the use of cardiac markers in the ED setting should be integrated with the clinical history and the ECG to arrive at an overall assessment of the likelihood of the patient having unstable angina.[141] [143] [159]

The timing of when blood samples should be obtained during initial evaluation of UA/NSTEMI has been examined in several studies. Most have included a "baseline" sample,[115] [146] [148] [149] which in studies conducted within clinical trials of unstable angina was at the time of randomization (i.e., at least several hours after the patient had presented to the ED). Recent large studies, in which the first blood sample is taken at the time of the patient's initial evaluation in the ED, have shown elevations of troponin T or I to be strongly predictive of subsequent cardiac complications.[141] [144] However,

several recent studies have found incremental benefit by adding an additional one or two samples (generally 4, 8, or 16 hours later), with the second or third sample identifying a progressively greater number of patients who are positive and who are found to be high risk.[141] [143] [146] [151] [153]

Serial measurements are definitely needed among patients who present to the hospital within 6 hours from the onset of pain (which comprise the majority of patients[133] [141]) because of the release kinetics of troponins and CK-MB (see Chap. 35) . In this early time window, myoglobin or CK-MB isoforms may be useful markers.[112] [160] [161] However,

owing to low specificity of myoglobin for myocardial tissue, it should not be used in isolation but rather confirmed with a later sample analyzed for a more cardiac-specific marker (e.g., troponin or CK-MB).[7]

Emergency Department Chest Pain Pathways

The current approach to evaluating patients with chest pain (or related symptoms suggestive of UA/NSTEMI) incorporates four major diagnostic tools--clinical history, ECG, cardiac markers and provocative stress testing. They have three major objectives: (1) to diagnose infarction (using cardiac markers), (2) to evaluate for evidence of ischemia at rest (using symptoms, ECG, and/or continuous ECG monitoring), and (3) to evaluate for significant coronary artery disease (provocative stress testing).

Most pathways, including that shown in Figure 36-5 , begin with a clinical assessment of the likelihood of the presenting symptoms being angina.[7] Patients with intermediate or high likelihood of ischemia (i.e., those with any feature shown in Table 36-2) are admitted to the hospital and treated with appropriate therapy for UA/NSTEMI (see p. 1241). On the other hand, patients, with atypical pain, not suggestive of ischemia, are discharged home with follow-up to their primary physicians. The remaining patients with a low likelihood of ischemia (i.e., without any of the factors shown in Table 36-2) are observed in the ED (or chest pain unit or related facility)[162] [163] with a standardized protocol.[164] [165]

These patients are monitored for recurrent rest pain and have a panel of markers (currently CK-MB, troponin I, and myoglobin) at arrival and 6 hours later. If the onset of pain was more than 6 hours before arrival, the baseline sample is frequently considered sufficient to "rule out" MI. If cardiac markers are positive or if the patient develops recurrent pain with ECG changes, the patient is admitted to the hospital and treated for UA/NSTEMI. If the patient remains pain free and the markers are negative, the patient goes on to exercise stress testing. For most patients, ECG stress testing is used, but for patients with fixed ECG abnormalities (e.g., left bundle branch block [LBBB]) perfusion imaging is employed and for those who cannot walk, pharmacological stress testing is used. If the clinical history suggests a very low likelihood of acute ischemia, patients are discharged home with subsequent outpatient stress testing. The goal is to carry out the

testing and discharge (or admit) patients within 6 to 9 hours from ED arrival with follow-up to their primary physicians.

The safety of early exercise stress testing in patients presenting to the ED with chest pain was initially questioned, but several recent studies have demonstrated no adverse outcomes when applied to appropriately selected patients (as described earlier).[166] [167] [168]

CARDIAC IMAGING: SESTAMIBI PERFUSION IMAGING AND ECHOCARDIOGRAPHY.

The use of additional imaging techniques is taking on increasing importance in the early diagnosis of patients presenting with suspected unstable angina and MI, especially when the ECG findings are obscured by LBBB or a paced rhythm. Sestamibi (see Chap. 9) has been useful for patients presenting with chest pain in the ED without diagnostic ECG, to discriminate patients with coronary artery disease (in whom perfusion defects are observed) from those with noncardiac chest pain (with normal perfusion scans).[169] [170] Sestamibi scanning (and echocardiography) also can provide information about left ventricular ejection fraction and wall motion that may be useful in triage decisions of the patients.

Some centers have utilized stress echocardiography in evaluating chest pain patients.[171] [172] [173] However, in two studies, little additional information was obtained in the *routine* use of echocardiography in all chest pain patients.[162] [174] Echocardiography performed while the patient is at rest in the ED has been used to evaluate whether a wall motion

Figure 36-5 Brigham and Women's Hospital Emergency Department "Rule Out Myocardial Infarction (MI)" critical pathway. The approach to patients presenting with acute chest pain or other symptoms suggestive of possible UA/NSTEMI is first to assess the likelihood of coronary artery disease (CAD). Patients with high or intermediate likelihood are admitted to the hospital and treated according to the UA/NSTEMI pathway. Those with clearly atypical chest pain are discharged home. Patients with a low likelihood enter the pathway and are observed in a monitored bed in the emergency department (ED) observation unit over a period of 6 hours, and 12-lead electrocardiograms (ECGs) are performed if the patient has recurrent chest discomfort. A panel of cardiac markers (e.g., troponin I, CK-MB, and myoglobin) are drawn at baseline and 6 hours later. If the patient develops recurrent pain, has ST segment or T wave changes, or has positive cardiac markers, he or she is admitted to the hospital and treated for UA/NSTEMI. If the patient has negative markers and no recurrence of pain, he or she is sent for exercise treadmill testing (ETT), with imaging reserved for patients with abnormal baseline ECGs (e.g., left bundle branch block or left ventricular hypertrophy with ST-T wave abnormalities). If the test is positive in a patient presenting with acute chest pain, the patient is admitted; if the test is negative, the patient is discharged home with follow-up to his or her primary physician.

abnormality is present, to help in establishing (or excluding) the diagnosis of ischemic heart disease,[175] and in determining prognosis.[176] However, cost issues have

precluded widespread *routine* use of echocardiography, but most centers use echocardiography selectively (i.e., in patients with LBBB or paced rhythms or in patients with suspected valvular disease and/or aortic dissection, especially transesophageal echocardiography for the latter).[177] [178] [179]

One study found improved sensitivity of perfusion imaging compared with stress echocardiography or ECG stress testing,[180] whereas another study found similar overall diagnostic capabilities of the two imaging modalities[181] (see also Chap. 13) . Both of these modalities can assess global left ventricular function, a powerful determinant of subsequent prognosis after MI[182] [183] (and presumably after unstable angina as well), and this may be important in triaging medical therapy among patients with confirmed MI or unstable angina (e.g., angiotensin-converting enzyme [ACE] inhibitors).[184] However, because most patients presenting to EDs do not have coronary artery disease,[130] [131] such widespread assessment of left ventricular function would likely not be cost effective.

CHEST PAIN CENTERS.

Many hospitals have developed "chest pain centers" within or closely related to the ED in which patients with suspected acute coronary syndromes can be triaged. Standardized protocols for acute STEMI can be implemented, thereby reducing door-to-needle time[185] (see Chap. 35) , and rapid "rule out MI" protocols for low-risk patients with chest pain can be carried out.[165] [186] Use of such chest pain centers or specialized ED units can reduce by 20 to 30 percent the number of patients who require admission to the hospitals[162] [163] [170] [174] [187] and randomized trials.[163] [174] One multicenter study found that the implementation of a chest pain unit significantly decreased the rate of hospital admission and overall costs, despite an overall increase in the number of patients who underwent "rule-out MI" evaluation instead of being discharged home directly.[187] Thus, there is emerging evidence that chest pain centers or specific protocols/critical pathways in the ED can improve the efficiency of health care for this large population of patients.

Natural History

The outcome of patients with UA/NSTEMI is generally favorable when compared with acute STEMI,[96] [97] [99] although there are several subgroups of patients who can have *higher* mortality (see later). In the TIMI III Registry of patients with UA/NSTEMI, 21 percent "ruled in" for an NSTEMI at the time of admission; 62 percent underwent cardiac catheterization, 22 percent angioplasty, and 13 percent coronary bypass surgery. By 42 days, mortality was 2.4 percent and a new or recurrent MI occurred in 2.9 percent of patients. Within clinical trials, in which inclusion criteria select higher risk patients (see later), rates of death by 30 days ranged from 3.5 to 4.5 percent and rates of new or recurrent MI ranged from 6 to 12 percent.[80] [81] [83]

RISK STRATIFICATION

As already noted, unstable angina is a heterogeneous condition that ranges from one

with an excellent outcome with modest adjustments in therapeutic regimen to one in which the risk of death or MI is high and intensive (and expensive) treatment is needed. Evidence is available from recent large clinical trials for important subgroups of patients who are at higher risk of adverse outcomes (Table 36-3) .[7] Furthermore, these groups appear to derive greater benefit from more aggressive antithrombotic therapy (see p. 1246). Clinical predictors can be also used to assist in triage of unstable angina patients to the coronary care unit versus a monitored

TABLE 36-3 -- INDICATORS OF INCREASED RISK IN UNSTABLE ANGINA

History
Advanced age (>65 years)
Diabetes mellitus
Post-myocardial infarction angina
Prior peripheral vascular disease
Prior cerebrovascular disease
Clinical Presentation
Braunwald Class II or III (acute or subacute rest pain)
Braunwald Class B (secondary unstable angina)
Heart failure/hypotension
Electrocardiogram
New/ST segment deviation
0.05 mV
New T wave inversion
0.3 mV
Left bundle branch block
Cardiac Markers
Increased troponin T or I or CK-MB
Increased C-reactive protein (CRP)
Angiogram
Thrombus

bed.[5] [7] [104] Patients determined to be at high risk should be admitted to the coronary care unit, whereas those with intermediate or lower risk could be admitted to a monitored bed on a cardiac step-down unit.

CLINICAL VARIABLES.

The Braunwald classification of unstable angina [8] (see Table 36-1) has been shown in several studies to be useful in identifying high-risk patients.[12] [13] [14] In the multicenter TIMI III Registry, which included 3318 consecutive patients with UA/NSTEMI, this classification was an important predictor of rate of death or MI to 1 year--both by the severity of the unstable angina and by the clinical circumstances in which it occurred (see Table 36-1) . High-risk groups of patients with unstable angina are those with acute

rest pain, those with post-MI unstable angina, and those with secondary unstable angina.[14]

HIGH-RISK SUBGROUPS.

Increasing age has been shown to be associated with a significant increase in adverse outcomes in patients with UA/NSTEMI.[100] [188] Diabetic patients with UA/NSTEMI are at approximately 50 percent higher risk than nondiabetics (see Chap. 63) .[189] [190] Patients with extracardiac vascular disease (i.e., those with either cerebrovascular disease or peripheral arterial vascular disease) also appear to have approximately 50 percent higher rates of death or recurrent ischemic events compared with patients without previous peripheral or cerebrovascular disease, even after controlling for other differences in baseline characteristics.[191] Patients who present with evidence of congestive heart failure (Killip Class > II) have increased risk of death in the setting of unstable angina.[126] [192] In addition, patients who develop recurrent ischemia after initial presentation have also been found to be at increased risk.[83] [193]

PRIOR ASPIRIN THERAPY.

Another group of patients with UA/NSTEMI that has been identified as high risk are those who present with acute ischemia despite chronic aspirin therapy. These patients are sometimes termed "aspirin failures," and a subset of these patients may actually represent "aspirin resistance"[194] ; however, the pathophysiology of this observation is not fully defined and is actively being studied.[195] This group represents an increasing proportion of patients (from 60 to 80 percent of patients in recent trials) and, among patients not randomized to a glycoprotein IIb/IIIa inhibitor, their subsequent rate of death or MI was 50 percent higher than those not previously taking aspirin.[196] [197] Treatment with a glycoprotein IIb/IIIa inhibitor

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appeared to decrease this risk (see p. 1246). In the OPUS-TIMI 16 trial, higher event rates were again observed in prior aspirin users, but this was not an independent predictor of mortality or recurrent cardiac events.[198] Thus, the development of UA/NSTEMI despite aspirin therapy is a useful clinical marker of high risk.

RISK ASSESSMENT BY ECG.

The admission ECG is very useful in predicting long-term adverse outcomes. In the TIMI III Registry of patients with UA/NSTEMI, independent predictors of 1-year death or MI included LBBB (risk ratio 2.8) and ST segment deviation of 0.05 mV or greater (risk ratio 2.45) (both $p<0.001$).[100] The presence of 0.05 mV or more ST segment depression on the admission ECG has also been reported to be an independent determinant of 4-year mortality, with a gradient of increasing risk with increasing ST segment depression.[103] In contrast, the presence of T wave changes of 0.1 mV or more was associated with a modest[103] or no increase in subsequent death or MI compared with patients without ST

or T wave changes.[100] Similar findings were observed in predicting 30-day and 6-month outcomes in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb study, in which the presence of ST segment deviation greater than 0.5 mm confers a worse prognosis than T wave changes.[102]

CK-MB AND THE TROPONINS.

Patients with NSTEMI have a worse long-term prognosis than those with unstable angina.[73] [101] [199] [200] [201] [202] [203] [204] However, the high-risk population extends beyond those who have positive CK-MB fractions, the traditional definition of MI. Studies have found that patients with "microinfarction"[205] or "minor myocardial damage"[206] [207] (i.e., those not meeting usual criteria for MI of elevated CK and CK-MB but with elevated troponin T,[115] [144] [146] [147] [149] [151] [154] [155] [208] troponin I,[148] [150] [152] [155] [209] myosin light chains,[147] or mildly elevated CK-MB[210] [211]) are a high-risk population.

Patients with elevated troponin values are at much higher risk of subsequent cardiac complications, including mortality[115] [144] [146] [147] [148] [149] [150] [151] [152] [153] [154] [155] [208] (Fig. 36-6) . This has been observed even in patients without CK-MB elevation.[146] [148] [153] [212] Beyond just a positive versus negative test result, there is a linear relationship between the level of troponin T or I in the blood and subsequent risk of death--the higher the troponin, the higher the mortality risk (see Fig. 36-6 *B*). Similar results have been obtained using a bedside rapid assay for troponin T, in which time to positivity is a semi-quantitative measure of serum troponin T and related to increased mortality.[144] [212] Thus, troponin T and I are very useful not only in diagnosing infarction[205] (see p. 1237 and Chap. 35) but also in risk assessment in patients presenting with acute UA/NSTEMI and in "targeting" therapies to high-risk patients (see p. 1241).

C-REACTIVE PROTEIN.

Additional markers also appear to be useful in assessing patients with UA/NSTEMI, among which C-reactive protein (CRP) is very promising. Elevated CRP has been related to increased risk of death, MI, and/or need for urgent revascularization.[40] [41] [42] [43] [213] [214] [215] [216] In TIMI 11A, 14-day mortality for patients with an elevated CRP (1.55 mg/dl, the 99th percentile of normal subjects) was 5.6 percent compared with 0.3 percent for patients without an elevated CRP (Fig. 36-7 *A*).[43] Even among patients with negative troponin T at baseline, who had a 14-day mortality of 1.5 percent overall, CRP was able to discriminate a high- and low-risk group: mortality for patients with an elevated CRP was 5.8 percent versus 0.4 percent for patients without elevated CRP (see Fig. 36-7 *A*). [43] When using both CRP and troponin T, mortality could be stratified from 0.4 percent for patients with both markers negative, to 4.7 percent if either CRP or troponin were positive, to 9.1 percent if both were positive (see Fig. 36-7 *B*). [43] Thus, the combination of a necrosis marker (troponin T or I) and an inflammatory marker (CRP) provides independent and powerful prognostic information in patients with acute coronary syndromes.[43] [214] [216]

Figure 36-6 TIMI IIIB. *A,* The relationship of a positive versus negative troponin I versus 42-day mortality

in the total group (left) and those with negative creatine kinase (CK)-MB (right). *B,* A direct relationship was observed between increasing levels of troponin I and a higher 42-day mortality. cTnI=cardiac specific troponin I; Neg=negative. (Adapted from Antman EM, Tanasijevic MJ, Thompson B, et al: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 335:1342-1349, 1996, with permission of the New England Journal of Medicine.)

In another recent study, CRP was not predictive of in-hospital events but was a powerful predictor of 30-day and 6-month events.[215]

CRP measured at the time of hospital discharge has been found to be a very strong predictor of outcome to 3 to 12 months.[217] [218] Other inflammatory markers have offered consistent evidence of an association between systemic inflammation and recurrent adverse events, including serum amyloid A,[219] interleukin-6,[220] CD40 ligand,[221] $CD4^{+}$ $CD28^{null}$.[222] These studies indicate that inflammation is related to the instability of patients and an increased risk of recurrent cardiac events.

COMBINED RISK ASSESSMENT SCORES.

An emerging approach to unstable angina is to use a comprehensive approach to risk assessment. As illustrated in Figure 36-8 , patients with symptoms of unstable angina fall on a spectrum. ST segment deviation or deep T wave inversion defines high-risk patients. CK-MB can be used to define NSTEMI. Troponins are more sensitive markers of necrosis and extend the population that is identified as high risk. Finally, even among patients who are troponin negative, CRP can further identify high-risk patients.

By integrating this approach, comprehensive risk scores

Figure 36-7 TIMI 11A. *A,* Relationship of C-reactive protein (CRP) vs. 14-day mortality in all patients with UA/NSTEMI (left) and those with negative baseline troponin T (right). *B,* Use of both troponin T and CRP to predict mortality. (An "early positive" rapid bedside troponin T assay [RTnT] was defined as positive 10 minutes.) These data demonstrate that an elevated CRP (the high-sensitivity assay was used in this study) is a potent predictor of increased mortality and extends beyond the prognostic information that troponin provides. CRP is a marker of inflammation, whereas the troponins are markers of myocardial necrosis, and these data demonstrate the complementary information provided by these two markers in patients with UA/NSTEMI. Early+= early positive; neg=negative. (From Morrow DA, Rifai N, Antman EM, et al: C-reactive protein is a potent predictor of mortality independently and in combination with troponin T in acute coronary syndromes: A TIMI 11A substudy. J Am Coll Cardiol 31:1460-1465, 1998.)

can be developed using both clinical variables, as well as variables from the ECG and initial serum cardiac markers. One such analysis used three simple markers: age 65 years or older, ST segment deviation of 0.5 mm or more, and positive serum cardiac markers (either CK-MB or troponin). When these three parameters were used, the risk of death, MI, or urgent revascularization at 43 days rose from 14.5 percent for none or one of these risks to 19.3 percent and 27.3 percent for patients with one, two or all three

factors (p<0.0001). [223] The more detailed TIMI risk score was developed using multivariate analysis, which identified

Figure 36-8 Risk stratification across the spectrum of acute coronary syndromes (ACS). Positive tests identify higher risk patients. This summary of the risk stratification tools currently available shows that among the broad spectrum of patients with ischemic heart disease, the electrocardiogram (ECG), cardiac markers creatine kinase (CK-MB) and troponin, and C-reactive protein (CRP) can identify increasing proportions of the overall group as being at high risk of recurrent cardiac events or death. For the ECG, markers of high risk include ST depression of 0.05 mV or more. The newer markers troponins and CRP identify a higher percentage of patients than did CK-MB, the only marker used in the mid 1990s.

seven independent risk factors: age 65 years or older; more than three risk factors for coronary artery disease; documented coronary artery disease at catheterization; ST segment deviation of 0.5 mm or more, more than two episodes of angina in the last 24 hours, aspirin within prior week, and elevated cardiac markers. Use of this scoring system was able to risk-stratify patients across a 10-fold gradient of risk, from 4.7 to 40.9 percent (p<0.001). [224]

MEDICAL THERAPY

TREATMENT GOALS.

The treatment objectives for patients with UA/NSTEMI are focused on stabilizing and "passivating" the acute coronary lesion, treatment of residual ischemia, and long-term secondary prevention. Antithrombotic therapy (e.g., aspirin, low or unfractionated molecular weight heparin, glycoprotein IIb/IIIa inhibitors, and clopidogrel) is used to prevent further thrombosis and allow endogenous fibrinolysis to dissolve the thrombus and reduce the degree of coronary stenosis. Antithrombotic therapy is continued long term to reduce the risk of developing future events and/or to prevent progression to complete occlusion of the coronary artery. Antiischemic therapies (e.g., beta blockers, nitrates, and/or calcium antagonists) are used primarily to reduce myocardial oxygen demand. Coronary revascularization is frequently needed to treat recurrent or residual ischemia that occurs despite the medical therapy. After the acute event is stabilized, the many factors that led up to the event need to be reversed (i.e., treatment of atherosclerotic risk factors such as hypercholesterolemia, hypertension, and cessation of smoking, each of which contributes to stabilization of the cholesterol-laden plaque and healing of the endothelium).

General Measures

The approach to the patient with UA/NSTEMI generally includes admission to a monitored bed. In these settings, continuous ECG monitoring (i.e., telemetry) is used to evaluate

for cardiac arrhythmias and potentially for new asymptomatic ST deviations as markers of ischemia.[7]

Bed rest is usually prescribed initially for patients with UA/NSTEMI.[7] Ambulation as tolerated is permitted if the patient has been stable hemodynamically without recurrent chest discomfort for at least 12 to 24 hours. Means of improving the physical and emotional surroundings for the patient, such as placing the patient in a quiet atmosphere, away from any emotionally taxing arguments, and offering physician's reassurance and/or mild sedation may act to reduce sympathetic drive and thereby reduce ischemia.[7] Supplemental oxygen is frequently administered to patients with UA/NSTEMI, but there are no studies to demonstrate its usefulness. It is advisable to provide supplemental oxygen only to patients with cyanosis, extensive rales, and documented hypoxemia. Oxygen saturation determined by oximetry is useful with supplemental oxygen administered if the arterial oxygen saturation declines below 92 percent.[7]

Relief of chest pain is an initial goal of treatment. In patients with persistent pain despite therapy with nitrates and beta blockers (see later), morphine sulfate, 1 to 5 mg intravenously, is recommended. Contraindications include hypotension or prior allergy (meperidine can be substituted for the patients who are allergic to morphine). With careful blood pressure monitoring, repeat doses can be administered every 5 to 30 minutes. Morphine may act both as an analgesic and anxiolytic, but its venodilatory effects may produce beneficial hemodynamic effects by reducing preload. The latter is especially useful in the setting of acute pulmonary edema. If hypotension develops after administration of morphine, supine positioning or intravenous saline should restore blood pressure and pressors are rarely needed. If respiratory depression develops, naloxone (0.4 to 2.0 mg) may be given.

Nitrates (see also Chap. 37)

Nitrates are endothelium-independent vasodilators that both increase myocardial blood flow by coronary vasodilatation and reduce myocardial oxygen demand. The latter effect is produced by venodilation leading to reduced myocardial preload and reduction in ventricular wall stress, thereby reducing myocardial oxygen demand. Nitrates should initially be given sublingually or by buccal spray (0.3 to 0.6 mg) if the patient is experiencing ischemic pain. If pain persists after three sublingual tablets (or buccal sprays) each 5 minutes apart and initiation of beta blockade, intravenous nitroglycerin (5 to 10 mug/min using nonabsorbing tubing) is recommended.[7] The rate of the infusion may be increased by 10 mug/min every 3 to 5 minutes until symptoms are relieved or systolic blood pressure falls by more than 30 mm Hg or to below 100 mm Hg. Although there is no absolute maximum dose, a dose of 200 mug/min is generally used as a ceiling. Contraindications to use of nitrates are hypotension or the use of sildenafil (Viagra) within the previous 24 hours.[225]

Topical or oral nitrates can be used if the episode of pain has resolved, or they may replace intravenous nitroglycerin if the patient has been pain free for 12 to 24 hours.[7] Dosing of nitrates depends on the formulation (see Table 37-4) , but dosing should attempt to have an 8- to 10-hour nitrate-free interval to avoid the development of tolerance.

The effect of nitrates on mortality was evaluated in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3 and International Study of Infarct Survival (ISIS)-4 trials for patients with suspected MI (both STEMI and NSTEMI).[226] [227] No benefit on mortality was observed in the overall population or in the subgroup of patients with NSTEMI. Consequently, the goal of nitrate therapy is relief of pain; chronic nitrate therapy can frequently be tapered off in the long-term management of patients, with primary therapy being aspirin and beta blockers and sublingual or buccal nitroglycerin given as needed for new episodes of pain.

Beta Blockers (see also Chap. 37)

Several placebo-controlled trials in UA/NSTEMI have shown benefit of beta blockers in reducing subsequent MI and/or recurrent ischemia.[228] [229] [230] [231] [232] [233] In patients with acute MI (in studies which included patients with both STEMI and NSTEMI in the prethrombolytic era), beta blockers were shown to reduce infarct size, reinfarction, and mortality (see Chap. 35) . [234] [235] [236] [237] In addition, in subgroup analyses of patients with NSTEMI in three trials, the benefits of beta blockers (intravenous followed by oral) have been observed.[237] [238] [239] [240]

Thus, beta blockers are recommended for patients with UA/NSTEMI who do not have contraindications to these agents (e.g., bradycardia, advanced atrioventricular block, persistent hypotension, pulmonary edema, history of bronchospasm).[104] [105] A reduced ejection fraction is no longer a contradiction to beta blockade, and, indeed, such patients may derive added benefit given the benefits on mortality seen with long-term beta blockade in patients with congestive heart failure (see also Chaps. 18 and 21) . [241] [242] [243] If ischemia and chest pain is ongoing, early intravenous beta blockade should be used, followed by oral beta blockade. The choice of which beta blocker to use can be individualized based on the drug's pharmacokinetics, cost, and physician familiarity (Table 37-6) . However, those with intrinsic sympathomimetic activity (ISA), such as pindolol, should not be selected. Examples of doses tested in large trials include atenolol (5-10 mg intravenous bolus followed by 100 mg orally daily)[237] and metoprolol (5 mg intravenous boluses, three given 2 to 5 minutes apart, followed by 50 mg orally twice daily titrated up to 100 mg twice daily).[244] Commencing therapy with intravenous esmolol could be considered in patients with possible contraindications (e.g., a history of possible asthma) with an initial loading dose of 0.5 mg/kg/min over 1 minute, followed by a 0.05 mg/kg/min infusion, with repeat loading doses and increases in the infusion of 0.05 mg/kg/min to achieve the desired heart rate.[245]

Calcium Channel Blockers (see also Chap. 37)

These drugs have vasodilatory effects and lower blood pressure, and some also slow heart rate (Table 37-8) . They may be used in patients who have persistent or recurrent symptoms but are currently recommended only in patients who have persistent ischemia after treatment with full-dose nitrates and beta blockers have been used or in patients with contraindications to beta blockade.[7] Such patients should be treated with heart rate-slowing calcium channel blockers (e.g., diltiazem or verapamil).[104] [105] Oral doses of diltiazem and verapamil range from 30 to 90 mg four times daily to 360 mg once daily of the long-acting preparations.

In the Diltiazem Reinfarction Study, involving 576 patients with non-Q-wave MI, diltiazem reduced recurrent MI from 9.3 percent on placebo to 5.2 percent on diltiazem.[201] A more recent pilot study using intravenous diltiazem[246] and a larger clinical trial using long-acting diltiazam[247] [248] in patients after thrombolytic therapy found trends toward benefit of diltiazem versus placebo. In the Danish Study Group on Verapamil in Myocardial Infarction (DAVIT) II trial of patients with suspected MI or unstable angina, of whom nearly half did not have confirmed MI, verapamil tended to reduce recurrent MI or death.[249] However, meta-analyses have found no beneficial effect of the calcium antagonist drugs as a class in reducing mortality or subsequent infarction.[229] [250] [251] One overview did suggest benefit of verapamil alone.[252]

Importantly, in patients with acute MI with left ventricular dysfunction or congestive heart failure, a harmful effect of diltiazem has been observed.[253] Nifedipine, which does not lower heart rate, has been shown to increase the incidence

of adverse events in patients with acute MI when not coadministered with a beta blocker.[254] [255] In contrast, no harm was observed in one study with verapamil in patients with congestive heart failure, all of whom were treated with ACE inhibitors.[256] Similarly, no harm with long-term treatment with amlodipine[257] or felodipine [258] was observed in patients with documented left ventricular dysfunction and coronary artery disease, indicating that these vasoselective calcium antagonists may be safely used in patients with unstable angina with left ventricular dysfunction.

In summary, calcium antagonists should be used in patients with UA/NSTEMI if needed for recurrent ischemia despite beta blockade or in patients in whom beta blockade is contraindicated (e.g., bronchospasm);[7] diltiazem should be avoided in patients with left ventricular dysfunction and/or congestive heart failure.

Angiotensin-Converting Enzyme Inhibitors (see also Chap. 29)

ACE inhibitors have been shown to be beneficial in many settings, including patients *post* MI who have demonstrated either impaired left ventricular function (ejection fraction<40 percent)[184] or congestive heart failure.[259] The GISSI-3, ISIS-4, and Chinese Captopril trials showed a 0.5 percent absolute mortality benefit of early (initiated within

24 hours) ACE inhibition in patients with acute MI.[226] [227] [260] However, in the ISIS-4 study, no benefit was observed in patients without ST segment elevation. Thus, *short-term* ACE inhibition does not appear to confer any benefit for patients with unstable angina or NSTEMI without impaired left ventricular function.

On the other hand, *long-term* use of ACE inhibition is applicable to several groups of patients: those with (1) left ventricular dysfunction,[184] (2) congestive heart failure,[259] and (3) based on recent evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial, it may apply to most patients with all forms of ischemic heart disease, including UA/NSTEMI.[261] Recurrent MI and the need for revascularization were reduced with ACE inhibitors in the Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) trials, suggesting an antiischemic effect of this class of agents,[262] [263] which was confirmed in the HOPE trial (see also Chap. 39) .

Lipid-Lowering Therapy (see also Chap. 33)

Long-term treatment with lipid-lowering therapy, especially with statins, has been shown to be beneficial in patients after acute MI and unstable angina[127] [128] [129] (see also Chap. 39) . In the Scandinavian Simvastatin Survival Study (4S), carried out in hypercholesterolemic patients with a history of MI *or* unstable angina, mortality was reduced by 30 percent (p=0.0003) and coronary deaths were significantly reduced by 42 percent.[128] In addition, recurrent MI was significantly reduced by 37 percent (p<0.001), coronary revascularization by 37 percent (p<0.0001), and rehospitalization for acute cardiovascular disease by 26 percent (p<0.001).[128] [264] The cost savings of these reductions offset nearly all the cost of the simvastatin therapy. Thus, the cost-effectiveness is very favorable: cost per year of life saved ranged from $3,800 for 70-year-old men with a cholesterol level of 309 mg/dl to $27,400 for 35-year-old women with a cholesterol level of 213 mg/dl.[265]

The Cholesterol and Recurrent Events (CARE) and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies extended these benefits to patients with average cholesterol levels (i.e., <240 mg/dl), which constitute the majority of patients with acute coronary syndromes. In CARE, treatment with pravastatin for an average of 5 years led to a 24 percent reduction in cardiovascular death or MI (p=0.003), with similar reductions in need for revascularization and stroke.[127] Interestingly, no benefit was observed in the subgroup of patients with a baseline low-density lipoprotein (LDL) of less than 125 mg/dl. The LIPID trial enrolled more than 9000 patients with a history (at least 3 months prior) of MI or unstable angina. In the prespecified subgroup of more than 3200 patients with unstable angina, pravastatin therapy led to a significant 26 percent reduction in total mortality (p=0.004).[129]

Thus, long-term cholesterol lowering has been shown to have dramatic benefits in secondary prevention after infarction[266] [267] [268] and is very cost effective. For patients with UA/NSTEMI, testing the cholesterol level is critical. To ensure that all patients would benefit from cholesterol lowering, as demonstrated in these three trials, the total cholesterol and LDL cholesterol levels (calculated or direct measurement) should be obtained and treatment initiated with a statin drug if the LDL is more than 125 mg/dl (as suggested by the CARE and LIPID results). The National Cholesterol Education Panel

recommends diet therapy if the LDL is higher than 100 mg/dl and drug therapy if the LDL is 130 mg/dl or more, with a target of reducing LDL to 100 mg/dl or less.[267] The timing of the blood sample is ideally in the first 24 hours after admission, because cholesterol levels fall with acute illness. However, cholesterol should be measured at some time during admission, because if it is high, therapy is warranted. Because treatment with statin drugs was associated with the previously mentioned benefits on mortality and cardiovascular morbidity, these are the current first-line lipid-lowering drugs. Additional or alternate therapy is also warranted according to the National Cholesterol Education Program (see also Chap. 39) .[267]

Antithrombotic Therapy in UA/NSTEMI

Aspirin (see also Chap. 62)

Several trials have demonstrated clear beneficial effects of aspirin in patients with UA/NSTEMI, with a more than 50 percent reduction in the risk of death or MI[71] [72] [73] [74] (Fig. 36-9). Thus, aspirin has a dramatic effect in reducing adverse clinical events both early and late in the course of treatment of UA/NSTEMI and is primary therapy for these patients (see Chap. 64) .

The dose of aspirin in the four randomized trials (Fig. 36-9) ranged from 75 mg to 1300 mg/d, and each trial showed a roughly 50 percent reduction in death or MI.[71] [72] [73] [74] Thus, there does not appear to be a dose response in efficacy of aspirin. In the International Study of Infarct Survival (ISIS)-2, a dose of 160 mg/d was shown to be associated with a mortality benefit, so this dose is the minimum initial dose recommended.[269] For safety (e.g., gastrointestinal bleeding), the rate of bleeding appears to be slightly higher with higher doses, and thus a dose of 75 to 81 mg/d could be an appropriate dose for long-term therapy, although major bleeding is relatively rare (<1 percent) even at a dose of 325 mg/d.[270]

Absolute contraindications for aspirin therapy are few but include documented aspirin allergy (e.g., asthma), active bleeding, or a known platelet disorder. In patients who had reported dyspepsia or other gastrointestinal symptoms with long-term aspirin therapy (i.e., intolerance), this would not be expected to be an acute problem of in-hospital treatment, and aspirin therapy is recommended, at least for the short term.

Clopidogrel and Ticlopidine (see also Chap. 62)

Clopidogrel, like its sister drug ticlopidine, is a thienopyridine derivative that inhibits platelet aggregation, increases bleeding time, and reduces blood viscosity by inhibiting ADP action on platelet receptors. *Ticlopidine* was studied in a randomized trial of patients with unstable angina involving 652 patients. The control group did not receive aspirin because at the time of protocol design it was not routinely used to treat unstable angina. At 6-month follow-up,

Figure 36-9 Four randomized trials showing the benefit of aspirin (ASA) in UA/NSTEMI. In UA/NSTEMI, the incidence of death or myocardial infarction was reduced by over 50 percent in each of the four trials. The doses of aspirin in the four trials were 325 mg, 1300 mg, 650 mg, and 75 daily, respectively, indicating no difference in efficacy for aspirin across these doses. (Data from Lewis HD, Davis JW, Archibald DG, et al: Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. N Engl J Med 309:396-403, 1983; Cairns JA, Gent M, Singer J, et al: Aspirin, sulfinpyrazone, or both in unstable angina. N Engl J Med 313:1369-1375, 1985; Theroux P, Ouimet H, McCans J, et al: Aspirin, heparin or both to treat unstable angina. N Engl J Med 319:1105-1111, 1988; and The RISC Group: Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 336:827-830, 1990.)

ticlopidine led to a significant 46 percent reduction in vascular death or nonfatal MI.[271] Of note, there was no difference in the number of events over the first 10 days, consistent with the delayed onset of the antiplatelet effect of ticlopidine. Thus, ticlopidine appears to be comparable to aspirin for secondary prevention of events post UA/NSTEMI. Ticlopidine has also been demonstrated to be effective in combination with aspirin for prevention of thrombosis and recurrent ischemic events in patients undergoing coronary stent implantation, a portion of whom have recently suffered UA/NSTEMI (see also Chap. 38) .[272] [273] [274] However, ticlopidine is associated with neutropenia and thrombocytopenia in approximately 1 percent of patients, and quite rarely with thrombotic thrombocytopenic purpura, which can be fatal in 25 to 40 percent of cases.[275] [276] Thus, if ticlopidine is used, short courses (2-3 weeks) and biweekly monitoring of complete blood cell count are generally recommended.

Clopidogrel has been tested for secondary prevention in a broad population of patients with atherosclerosis in the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial. An 8.7 percent reduction relative to aspirin in the combined endpoint of ischemic stroke, MI, or vascular death during long-term follow-up was reported (see also Chap. 37) .[270] When added to aspirin, clopidogrel also appears to be as effective as ticlopidine in preventing stent thrombosis,[277] [278] [279] [280] especially when using a loading dose of 300 mg, which achieves effective platelet inhibition within 2 to 5 hours.[281] Clopidogrel is not associated with neutropenia and an extremely low rate of (approximately four cases per million) thrombotic thrombocytopenic purpura. It was associated with a lower rate of gastrointestinal bleeding compared with aspirin.[270] These data support the use of clopidogrel in patients with unstable angina who cannot take aspirin (e.g., a true aspirin allergy). Trials are in progress for patients with UA/NSTEMI testing the combination of clopidogrel plus aspirin versus aspirin alone.

Heparin (see also Chap. 62)

Heparin also appears to be beneficial in UA/NSTEMI: Several randomized trials suggest that unfractionated heparin (UFH) can improve clinical outcome compared with aspirin alone (see Chap. 62) .[73] [74] [75] [76] The greatest benefit was observed during the period of intravenous therapy, with "rebound" in recurrent events after stopping UFH observed

in one study.[282] A meta-analysis showed a 33 percent reduction in death or MI at 2 to 12 weeks follow-up when comparing UFH plus aspirin versus aspirin alone, although this reduction was of borderline statistical significance (Fig. 36-10) . [77]

HEPARIN RESISTANCE.

Variability in the anticoagulant effects of UFH, so-called heparin resistance,[283] [284] is thought to be due to the heterogeneity of heparin and to the neutralization of heparin by circulating plasma factors and by proteins released by activated platelets.[285] [286] Clinically, frequent monitoring of the anticoagulant response using activated partial thromboplastin time (APTT) is recommended, with titrations made according to a standardized nomogram (Table 36-4) . [104] The latter minimizes the variability in the dosing adjustments given by various physicians and has been shown to improve the achievement of a target APTT.[287] [288]

THERAPEUTIC RANGE.

The exact level of anticoagulation that constitutes the "therapeutic range" is not yet firmly established. Small studies in unstable angina[289] and acute MI[290] [291] [292] [293] have suggested that lower APTT values may be related to recurrent ischemic events, suggesting that the lower limit of the target range of APTT is at least 1.5 times control. On the upper boundary of the target range, higher APTT values are associated with an increased risk of hemorrhage.[294] The lowest rate of bleeding (and mortality) in

Figure 36-10 Meta-analysis of six randomized trials comparing unfractionated heparin plus aspirin (ASA) vs. ASA alone, showing benefit of the combination therapy. The rate of death or myocardial infarction during follow-up (2-12 weeks in these trials) tended to be reduced in patients randomized to aspirin plus heparin. (Adapted from Oler A, Whooley MA, Oler J, Grady D: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: A meta-analysis. JAMA 276:811-815, 1996. Copyright 1996, American Medical Association.)

TABLE 36-4 -- STANDARDIZED NOMOGRAM FOR TITRATION OF HEPARIN

Initial Dose: 60 U/kg bolus and 12 U/kg/hr infusion
Activated partial thromboplastin time (APTT) should be checked and infusion adjusted at 6, 12, and 24 hours after initiation of heparin, daily thereafter, and 4 to 6 hours after any adjustment in dose.

APTT (secs)	CHANGE	IV INFUSION (U/kg/hr)
<35	70 U/kg bolus	+3
35-49	35 U/kg bolus	+2

50-70	0	+0
71-90	0	-2
>100	Hold infusion for 30 min	-3

From Becker RC, Ball SP, Eisenberg P, et al: A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. Am Heart J 137:59-71, 1999.

patients with STEMI treated with thrombolytic therapy was when the 12-hour APTT was between 50 and 70 seconds.[293] Furthermore, in TIMI IIIB, there appeared to be no advantage of higher levels of anticoagulation in reducing ischemic events.[295]

DOSING.

Dosing of UFH has traditionally used a 5000-U bolus followed by a 1000-U/hr infusion, which is then titrated according to the APTT.[285] The use of weight-adjusted UFH has been suggested as a means of improving APTT control and safety.[296] Three randomized trials of weight-adjusted UFH in unstable angina have been conducted. In one trial, there was a high percentage of patients who "overshot" in the initial APTT at 6 hours (median 150 seconds).[297] A more recent study examined a 60-U/kg bolus and 12-U/kg/hr infusion and found a higher percentage of patients within range without a large number of APTTs above range at 6 hours.[297a] The third trial tested standard dosing versus weight-adjusted dosing (70-U/kg bolus and 15-U/kg/hr initial infusion), and found no significant difference in control of APTT with weight-adjusted dosing.[298] Another approach uses "on-line" feedback of APTT data to a computer algorithm using a pharmacodynamic model of heparin response in the individual patient, with promising results in an initial pilot trial.[299]

CURRENT RECOMMENDATIONS.

Based on available data, the current optimal regimen appears to be a weight-adjusted dose of UFH (60 U/kg bolus and 12 U/kg/hr infusion), frequent monitoring of APTT (every 6 hours until in the target range and every 12 to 24 hours thereafter), and titration of UFH using a standardized nomogram (see Table 36-4) with a target range of APTT between one and one-half to two times control or approximately 50 and 70 seconds.[7]

Low-Molecular-Weight Heparins (see also Chap. 62)

A major advance in the use of heparin has been in the development of low-molecular-weight heparins (LMWH), which *combine* factor IIa and factor Xa inhibition. Thus, they inhibit both the action (anti-IIa action) and generation (anti-Xa action) of thrombin. LMWH are obtained by depolymerization of standard UFH and selecting those with lower molecular weight.[285] [300] As compared with UFH that has nearly equal anti-IIa (thrombin) and anti-Xa activity, LMWH have increased ratios of anti-Xa to anti-IIa activity of either 2:1 (e.g., dalteparin) or 3.8:1 (e.g., enoxaparin) (see

Chap. 62) .

LMWH have several potential advantages over UFH. First, their greater anti-factor Xa activity inhibits thrombin generation more effectively.[300] LMWH also induce a greater release of tissue factor pathway inhibitor than does UFH, and they are not neutralized by platelet factor 4.[285] LMWH have been found to have a lower rate of thrombocytopenia compared with UFH.[301] Their high bioavailability allows for subcutaneous administration, which provides a long duration of systemic anticoagulation, so that dosing can be administered twice daily. Finally, LMWH have less binding to plasma proteins (e.g., acute phase reactant proteins) and thus have a more consistent anticoagulant effect in relation to the dose administered. Accordingly, monitoring of the level of anticoagulation (as is necessary using APTT for UFH) is not necessary. These final two differences make LMWH a much simpler anticoagulant to administer than UFH. However, LMWH are more affected by renal dysfunction than UFH, and a reduced dose should be considered in patients with creatinine clearance less than 30 mL/min.

CLINICAL TRIALS.

Five trials have compared LMWH with aspirin, [78] or with UFH plus aspirin.[79] [80] [302] [303] In the Fragmin during Instablity in Coronary Artery Disease (FRISC) study, dalteparin plus aspirin was found to reduce death or MI over the first 6 days compared with aspirin alone (1.8 percent vs. 4.8 percent, p=0.001). [78] However, in the Fragmin in Unstable Coronary Artery Disease (FRIC) trial, no difference was observed between intravenous UFH and dalteparin.[302] Similarly, no benefit was seen when nadroparin was compared with UFH in the Fraxiparine in Ischaemic Syndrome (FRAXIS) trial.[303]

On the other hand, in two trials, Evaluation of the Safety and Efficacy of Enoxaparin in Non-ST Elevation Coronary Events (ESSENCE) and TIMI 11B, enoxaparin was found to confer a significant benefit in reducing death, MI, or recurrent ischemia compared with UFH. In ESSENCE, death, MI, or recurrent ischemia at 14 days was significantly lower (16.6 percent vs. 19.8 percent for UFH, p=0.019). [79] The rates of this endpoint at 30 days were 19.8 percent vs. 23.3 percent (p=0.016). Death or MI at 30 days also favored enoxaparin (6.2 percent vs. 7.7 percent).[79] The rates of catheterization (43 percent vs. 46 percent for enoxaparin vs. UFH) and PCI (13 percent vs. 17 percent, respectively) were lower in patients treated with enoxaparin than UFH.[79] A subsequent cost-effectiveness analysis found that there was a minimal increase in the cost for the drug (enoxaparin vs. UFH with APTT measurements) ($75); but with lower rates of catheterization and revascularization, treatment with enoxaparin led to a savings of $1172 per patient treated.[304] Thus, both improved outcomes and lower costs were observed with enoxaparin versus UFH.

The TIMI 11B trial studied high-risk patients with UA/NSTEMI. Death, MI, or severe recurrent ischemia requiring urgent revascularization through day 8 occurred in 12.4 percent of patients treated with enoxaparin versus 14.5 percent of patients treated with UFH (p=0.048), a 15 percent relative risk reduction.[80] Parallel reductions in death and MI were also observed. No additional benefit of continuing enoxaparin beyond hospital

discharge was observed.

A meta-analysis of the TIMI 11B and ESSENCE trials showed a consistent 20 percent reduction in both the composite endpoint of death, MI, or urgent revascularization and of death or MI that occurred at 8, 14, and 43 days (Fig. 36-11) .[305] Enoxaparin reduced the rate of death, MI, or urgent revascularization from 18.7 to 15.6 percent (p=0.0006).[305] Death or MI at 43 days was reduced from 8.6 to 7.1 percent (p=0.02) (see Fig. 36-11) . Thus, in two large randomized trials enoxaparin has been shown to be superior to UFH for the treatment of UA/NSTEMI, a benefit that has not been demonstrated yet for the other LMWH. It is not clear whether these differences in clinical results are related to the patients enrolled in the trials, the trial design, or the specific characteristics of the LMWH.

The effects of prolonged administration of LMWH after hospital discharge have been examined in several of the trials with mixed results. No benefit of 6 weeks of therapy was observed with dalteparin therapy in the FRIC trial,[302] of enoxaparin in the TIMI 11B trial,[80] or of 14 days of

Figure 36-11 TIMI 11B/ESSENCE meta-analysis: Data from over 7000 patients randomized in these two trials show a consistent and significant 20 percent reduction in the rate of death or myocardial infarction at each of the four time points in patients treated with enoxaparin (ENOX) vs. unfractionated heparin (UFH). (Adapted from Antman EM, Cohen M, Radley D, et al: Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. Circulation 100:1602-1608, 1999. Copyright 1999, American Heart Association.)

therapy with nadroparin in the FRAXIS trial.[303] On the other hand, in FRISC II, there was a lower rate of death or MI at 1 month but not at 3 or 6 months in patients treated with a 90-day course of dalteparin.[306] This early benefit was present only in patients randomized to the conservative strategy arm.[307] Thus, the FRISC II Investigators proposed a potential role for continued LMWH therapy after hospital discharge in selected higher-risk patients who are managed conservatively or in patients awaiting angiography and revascularization.[306] All four trials found higher rates of bleeding in patients receiving LMWH after hospital discharge. Thus, the *routine* use of prolonged LWMH therapy is not indicated, but it may be applicable to selected, conservatively managed patients.

Direct Thrombin Inhibitors

Direct thrombin inhibitors have also undergone extensive evaluation. The prototypic agent is hirudin, a naturally occurring anticoagulant from the medicinal leech. Hirudin, which is made by recombinant DNA technology, is a 65 amino acid polypeptide that binds directly to thrombin, independent of antithrombin. The hirudin desirudin was tested in the GUSTO IIb trial involving 12,142 patients with UA/NSTEMI and STEMI. In the

entire cohort, the 30-day rate of death or MI tended to be lower, 8.9 percent versus 9.8 percent (p=0.06),[99] with no difference in mortality and a modest reduction in reinfarction (5.4 percent vs. 6.3 percent for heparin, p=0.04). In the 8011 patients with UA/NSTEMI, 30-day death or MI was not significantly reduced (8.3 percent vs. 9.1 percent, p=0.22).[99]

The Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial[308] compared lepirudin to UFH: cardiovascular death or MI at 7 days tended to be lower (3.6 percent vs. 4.2 percent, respectively, p=0.08). Major bleeding requiring transfusion was rare but more frequent with lepirudin (1.2 percent vs. 0.7 percent for heparin, p=0.01). A meta-analysis of all hirudin trials showed a modest 10 percent benefit favoring hirudin, which was not statistically significant for patients with UA/NSTEMI. Other synthetic direct thrombin inhibitors have also been tested (e.g., argatroban and bivalirudin [Hirulog]), and, again, only modest or no improvements were observed compared with heparin,[309] [310] [311] although lower rates of bleeding have been observed with bivalirudin.[311] The direct thrombin inhibitors have been shown to provide a very stable level of anticoagulation, as measured by APTT,[99] [312] [313] and no episodes of thrombocytopenia were reported for the hirudin class. Of note, lepirudin is approved by the U.S. Food and Drug Administration for use as an anticoagulant in patients with heparin-induced thrombocytopenia and associated thromboembolic disease. Additional trials with this class of drugs are ongoing.

Oral Anticoagulation (see also Chap. 62)

Oral anticoagulation with warfarin has been examined in several recent trials, with the rationale that prolonged treatment might extend the benefit of early anticoagulation with an antithrombin agent (e.g., UFH, LMWH). Although pilot trials suggested benefit of a strategy of initial UFH followed by warfarin,[76] [314] [315] [316] two larger trials have failed to show a significant benefit of long-term warfarin plus aspirin versus aspirin alone. In the OASIS-2 trial of patients with UA/NSTEMI, the rate of cardiovascular death, MI, or stroke at 5 months was 7.4 percent for those receiving warfarin plus aspirin versus 8.2 percent for those receiving aspirin alone (p=NS). Similarly, in the Combination Hemotherapy and Mortality Prevention (CHAMP) trial of survivors of MI, there was no difference in the rate of all-cause mortality over an average 2.7-year follow-up between the combination of warfarin plus aspirin versus aspirin alone but there was a higher rate of major bleeding.[317] In addition, fixed-dose warfarin plus aspirin was not better than aspirin alone in the Coumadin Aspirin Reinfarction Study (CARS) trial.[318] Of note, however, a post-hoc analysis of OASIS-2 suggested that if compliance is excellent, a benefit might be observed with the combination of aspirin plus warfarin.[319]

One primary prevention trial in high-risk patients was a 2×2 factorial design of aspirin versus placebo and warfarin adjusted to an international normalized ratio of 1.5 and placebo found a significant reduction in coronary death or MI of the combination of warfarin plus aspirin (8.7 percent vs. 13.3 percent for placebo) but not significantly better than aspirin alone (10.2 percent) or warfarin alone (10.3 percent).[320] In this trial, however, there was an increase in hemorrhagic strokes among patients treated with the combination: 0.9 percent vs. 0.1 percent for warfarin alone, 0.2 percent for aspirin alone, and 0 percent for placebo (p=0.009).[320] Thus, the *routine* use of the combination of

warfarin plus aspirin cannot be recommended.

Warfarin therapy (without aspirin) has been shown to be superior to placebo after MI (both STEMI and NSTEMI)[321] [322] [323] and could be considered a suitable *alternative* to aspirin. Furthermore, warfarin is indicated in patients with atrial fibrillation[324] [325] or severe left ventricular dysfunction who are at high risk of systemic embolization (see Chap. 62) .[326]

Glycoprotein IIb/IIIa Inhibitors (See also Chap. 62)

Because plaque rupture in a coronary artery is followed by platelet aggregation and thrombosis and given the dramatic clinical benefits of the relatively weak antiplatelet agent aspirin,[327] attention has focused on the new class of drugs that inhibit platelet aggregation by binding to the platelet glycoprotein IIb/IIIa receptor. By preventing the final common pathway of platelet aggregation (i.e., fibrinogen mediated cross-linkage of platelets by means of the glycoprotein IIb/IIIa receptor) (see Fig. 36-3) , these agents are potent inhibitors of platelet aggregation from all types of stimuli (e.g., thrombin, ADP, collagen, serotonin). Three agents are now available for use in UA/NSTEMI--abciximab, tirofiban, and eptifibatide--with the former currently approved only in patients undergoing PCI. Abciximab is a Fab fragment of a monoclonal antibody directed at the glycoprotein IIb/IIIa receptor. Eptifibatide, a synthetic heptapeptide, and tirofiban, a nonpeptide molecule, are antagonists of the glycoprotein IIb/IIIa receptor whose structure mimics the arginine-glycine-aspartic

acid (abbreviated RGD) amino acid sequence by which fibrinogen binds to the glycoprotein IIb/IIIa receptor (see Chap. 62) .

Several trials have shown benefit of glycoprotein IIb/IIIa inhibition in UA/NSTEMI either in patients managed predominantly with medical management,[82] with early interventional management,[328] or with both.[81] [83] [329] [330] [331] In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, tirofiban plus heparin and aspirin significantly reduced the rate of death, MI, or refractory ischemia at 7 days compared with heparin plus aspirin.[83] Death or MI at 30 days was also significantly reduced by 30 percent, from 11.9 percent to 8.7 percent, with improvements generally consistent across all subgroups and management strategies (i.e., medical therapy [25 percent reduction], percutaneous transluminal coronary angioplasty [PTCA, 35 percent reduction], and coronary artery bypass grafting [CABG, 30 percent reduction].[332] In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integfrilin Therapy (PURSUIT) trial, involving 10,948 patients, eptifibatide also significantly reduced the rate of death or MI at 30 days.[81] In this trial, a greater benefit of eptifibatide was observed in patients undergoing early angioplasty compared with other treatment strategies.[81] Meta-analyses involving over 30,000 patients found that treatment with a glycoprotein

IIb/IIIa inhibitor led to a 21 percent reduction in death or MI at 30 days.[330] [331]

The relative benefits of IIb/IIIa inhibition relative to medical versus interventional treatment have been examined more closely. The PRISM trial, involving patients managed medically for the first 48 hours, found a significant 32 percent reduction in death, MI, or refractory ischemia at 48 hours, suggesting a significant clinical benefit during medical treatment alone.[82] In a recent pooling of data from PRISM-PLUS, PURSUIT, and the Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment (CAPTURE) trials involving 12,296 patients, there was a 34 percent relative reduction in death or MI during a period of 24 to 72 hours of medical management only (3.8 percent vs. 2.5 percent, p=0.001) (Fig. 36-12) .[333] These findings support the use of glycoprotein IIb/IIIa inhibition in the medical management of patients with UA/NSTEMI.[7] However, in the recently reported GUSTO-IV ACS trial, conducted in a relatively low-risk unstable angina population in whom the use of early PCI was discouraged,

Figure 36-12 Pooled data from CAPTURE, PRISM-PLUS, and PURSUIT trials of unstable angina, showing benefit of glycoprotein IIb/IIIa inhibition during medical therapy only (left panel), during, and immediately after percutaneous coronary intervention (PCI, right panel). (From Boersma E, Akkerhuis KM, Theroux P, et al: Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: Early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 100:2045-2048, 1999. Copyright 1999, American Heart Association.)

no clinical benefit was demonstrated when abciximab was added to aspirin and heparin.[333A]

On the other hand, among patients with unstable angina who undergo PCI (i.e., those managed with an early invasive strategy), glycoprotein IIb/IIIa inhibition appears to be beneficial both *before* intervention and especially *during* the intervention. This was first demonstrated in CAPTURE, in which abciximab was shown to reduce death, MI, or the need for urgent revascularization significantly.[328] In the meta-analysis, a significant benefit was seen when the agents are continued during angioplasty (death or MI was reduced from 8.0 to 4.9 percent (see Fig. 36-12) . A broader overview of patients with UA/NSTEMI who underwent PCI can be obtained by including patients enrolled in PCI trials (Fig. 36-13) .[7] In this overview, the benefit of IIb/IIIa inhibition is quite dramatic, with reductions of death or MI seen ranging from 30 to 70 percent. Thus, glycoprotein IIb/IIIa inhibition appears to have an additional benefit in patients in whom the drug is continued through PCI.[7]

NEED FOR INTRAVENOUS HEPARIN.

The long-term effects of glycoprotein IIb/IIIa inhibition appear to be greater when used in conjunction with heparin, as was done in the majority of patients in the PRISM-PLUS and PURSUIT trials.[82] [83] [334] It is not clear whether even greater benefits can be safely achieved when combining glycoprotein IIb/IIIa inhibitors with LMWH. This question is

being addressed in several ongoing clinical trials.

SAFETY.

The rate of major hemorrhage was slightly higher for patients treated with glycoprotein IIb/IIIa inhibitors than for those receiving aspirin and heparin alone. For example, in the PRISM-PLUS trial, major bleeding occurred in 4.0 percent of patients treated with tirofiban plus heparin plus aspirin versus 3.0 percent for heparin plus aspirin *(p*=NS). [83] For eptifibatide, the rates of severe or moderate bleeding for eptifibatide versus placebo were 12.8 percent versus 9.9 percent (*p*<0.001).[81]

Thrombocytopenia is an uncommon but important complication of glycoprotein IIb/IIIa inhibitors: For tirofiban in PRISM-PLUS, the rate of severe thrombocytopenia (<50,000 cells/mm[3]) was 0.5 percent versus 0.3 percent for heparin (*p*=NS)[83] ; in the PURSUIT trial, thrombocytopenia (<20,000 cells/mm[3]) occurred in 0.2 percent versus less than 0.1 percent for heparin.[81] Thrombocytopenia is associated with increased bleeding and, in a smaller proportion of patients, with recurrent thrombotic events.[335] [336] This syndrome bears resemblance to heparin-induced thrombocytopenia and indicates a need to monitor platelet count daily during the glycoprotein IIb/IIIa infusion.

ORAL GLYCOPROTEIN IIb/IIIa INHIBITION.

Because the benefit of the small molecule intravenous glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) occurs only during the infusion, whereas abciximab's action dissipates 12 to 48 hours after cessation of the infusion, it has been hoped that prolonged glycoprotein IIb/IIIa inhibition using oral agents might lead to further, and continued, reduction in recurrent events. Unfortunately, four large trials, one in patients with acute coronary syndromes, OPUS-TIMI 16,[337] two in stabilized patients after an acute coronary syndrome, SYMPHONY,[338] [338A] and one in patients undergoing PCI, EXCITE,[339] all failed to show any benefit of the oral glycoprotein IIb/IIIa inhibitors orbofiban, sibrafiban, and xemilofiban, respectively. A higher degree of variability in the drug level and of the degree of platelet inhibition achieved with oral as compared with intravenous drugs is one potential explanation of the difference in outcomes between the two types of IIb/IIIa inhibitors.[340] It also appears that some of the agents may have intrinsic proaggregatory effects.[341] Trials are continuing to evaluate "second generation" oral glycoprotein IIb/IIIa inhibitors, which have longer half-lives and tighter binding to the glycoprotein IIb/IIIa receptor similar to that of abciximab.[342]

MECHANISM OF BENEFIT.

Three new concepts are emerging on the benefit of glycoprotein IIb/IIIa inhibitors in

Figure 36-13 Benefit of glycoprotein IIb/IIIa inhibition among patients with UA/NSTEMI treated with percutaneous coronary intervention across all large trials. As shown, both the relative benefit and the absolute benefit are quite substantial, ranging from 50 to 100 deaths or myocardial infarctions prevented for every 1000 patients treated. (Adapted from Braunwald E, Antman EM, et al: ACC/AHA guidelines for the management of patients with unstable angina/non-ST segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on the Management of Unstable Angina and Non-ST Segment Elevation Myocardial Infarction]. J Am Coll Cardiol 36:970-1062, 2000, with data for ESPRIT provided by Tcheng JE.)

UA/NSTEMI. First, angiographic data from two trials have shown that the IIb/IIIa inhibitors lead to greater resolution of thrombus and improved coronary flow compared with aspirin and heparin alone.[123] [343] In PRISM-PLUS, for example, tirofiban led to a 35 percent overall improvement in TIMI flow grade (p=0.002).[123] Together these data establish the pathophysiological link between the potent platelet inhibition achieved by glycoprotein IIb/IIIa inhibition, a reduction in thrombus, improvement in coronary blood flow, and consequent improvement in clinical outcome.[344]

A second new concept based on evidence from two trials is that glycoprotein IIb/IIIa inhibitors can reduce the size of an evolving NSTEMI (Fig. 36-14) .[345] [346] It was observed in the PURSUIT trial that the size of the MI, either index or recurrent, measured by peak CK-MB was significantly smaller in patients treated with eptifibatide. Similarly, in the PRISM-PLUS troponin substudy, those randomized to tirofiban plus heparin had a significantly lower peak troponin (see Fig. 36-14) .[346]

The third new concept is that there appears to be a greater benefit of treatment when administered earlier relative to the onset of pain. In an analysis from PURSUIT, the absolute reduction in death or MI with eptifibatide was 2.8 percent for patients treated within 6 hours from the onset of pain and was less for those treated between 6 and 12 and 12 and 24 hours after onset of pain. No benefit was observed in patients treated 24 hours after the onset of pain (Fig. 36-15) . Similar data have been observed in PRISM-PLUS (unpublished data).

COST BENEFIT OF GLYCOPROTEIN IIb/IIIa INHIBITION.

Thus, intravenous glycoprotein IIb/IIIa inhibition has been shown to be beneficial in patients at intermediate to high risk, on the basis of rest pain and either ECG changes or positive cardiac markers.[81] [82] [83] Although these agents add to the expense of therapy, this cost is balanced by a reduction in recurrent cardiac events. A cost-effectiveness analysis from PURSUIT found that the cost per year of life saved was approximately $16,000, well within the generally acceptable range for medical interventions.[346A] As noted later (see p. 1253), benefit of glycoprotein IIb/IIIa inhibition appears to be greatest in patients at higher risk, as evidence by those who have a positive troponin at baseline,[154] [155] those with diabetes,[189] those with recurrent angina,[83] [193] or those with prior aspirin use.[196] In these high-risk subgroups of patients, the absolute benefit is greater and the therapy is even more cost effective.

In conclusion, it appears reasonable to use an intravenous glycoprotein IIb/IIIa inhibitor

with aspirin and UFH as antithrombotic therapy in patients who have UA/NSTEMI with high-risk features (see Table 36-3) , especially those with a positive troponin value.

Thrombolytic Therapy

Because thrombolytic therapy is beneficial in the treatment of patients with acute STEMI, it was thought that it might also be effective in the other acute coronary syndromes in which thrombosis plays a role. In TIMI IIIB, 1473 patients

Figure 36-14 PRISM-PLUS troponin substudy: Peak levels of troponin I (TnI) were reduced in patients treated with the glycoprotein IIb/IIIa inhibitor tirofiban compared with aspirin and heparin in the trial. These data demonstrate that early treatment (within 12 hours from the onset of chest pain in this study) led to a reduced infarct size among patients with UA/NSTEMI. (Data from Januzzi JL, Hahn SS, et al: Reduction of troponin I levels in patients with acute coronary syndromes by glycoprotein IIb/IIIa inhibition with tirofiban. Am J Cardiol [in press].)

Figure 36-15 PURSUIT: Evidence showing greater benefit of glycoprotein IIb/IIIa inhibition with more rapid time to treatment. The absolute reduction in death or myocardial infarction to 30 days in patients treated with eptifibatide versus placebo was greatest for patients treated within 6 hours from the onset of chest pain, with lower benefit as time from onset of pain increased. These data underscore the importance of treating patients with UA/NSTEMI rapidly, preferably in the emergency department, with IIb/IIIa inhibitors. (Data from Bhatt, et al: Circulation 98[Suppl. I]:I-561, 1998. Copyright 1998, American Heart Association.)

with UA/NSTEMI were treated with aspirin, UFH, and antiischemic therapy and were randomized to receive either tissue plasminogen activator (t-PA) or placebo. No differences were observed in the incidence of death, postrandomization MI, or recurrent, objectively documented ischemia through 6 weeks.[101] Fatal and nonfatal MI after randomization actually occurred *more frequently* in t-PA-treated patients (7.4 percent) than in placebo-treated patients (4.9 percent) (p=0.04). In addition, t-PA was associated with a 0.6 percent rate of intracranial hemorrhage compared with 0 percent for UFH alone (p=0.06).

The TIMI IIIB results are corroborated by a meta-analysis of all previous smaller trials of thrombolytic therapy in UA/NSTEMI, in which no benefit of thrombolytic therapy was observed.[104] In both ISIS-2 and the Fibrinolytic Therapy Trialists' overview, patients with suspected MI and ST segment depression had a *higher* mortality with thrombolytic therapy compared with placebo.[269] [347] Accordingly,routine thrombolytic therapy *is not indicated* in UA/NSTEMI.[7]

The proposed mechanism for adverse effect of thrombolysis in UA/NSTEMI is a prothrombotic effect of thrombolysis. Thrombolysis is known to activate platelets[348] and

increase fibrinopeptide A,[349] and the dissolution of the fibrin clot exposes clot-bound thrombin, which is enzymatically active and can lead to clot formation.[350] Because most patients with UA/NSTEMI have a patent culprit artery, these prothrombotic forces can lead to progression of the thrombus to total occlusion, thereby causing an MI (as was observed in TIMI IIIB).[101] In STEMI, in contrast, the culprit vessel is occluded at baseline and can only improve with successful thrombolysis.

Registry Experience with Compliance

A major problem recently identified in current practice is that a large proportion of patients do not receive guideline-recommended therapies.[98] [100] [118] [351] [352] For example, in the first National Registry of Myocardial Infarction (NRMI) conducted in 1990 to 1993, only 63 percent of patients with NSTEMI received aspirin.[353] In the TIMI III Registry of UA/NSTEMI conducted in 1992 to 1993, 80 percent of patients received aspirin,[98] [100] and in the Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) registry conducted in 1996, 83 percent of patients received aspirin.[118] [354] [355] This slight improvement suggests a possible benefit of the widespread dissemination and education after the publication of the Unstable Angina Guideline in 1994.[104] However, despite the overwhelming benefits of aspirin (arguably the best studied and most beneficial medication in cardiovascular medicine),[327] significant proportions of patients do not receive this drug. The American Heart Association published a scientific statement strongly urging physicians to use aspirin in appropriate patients,[356] which includes all UA/NSTEMI patients without contraindications. Similar findings have been observed for beta blockers and UFH,[98] [100] [118] [352] [355] with the latter used in only 57 percent of patients in the TIMI III Registry and in 67 percent of patients in the GUARANTEE Registry.[100] [118] [355] Importantly, recent evidence has suggested that if patients are treated according to the Unstable Angina Guideline recommendations, their adjusted 1-year mortality is lower compared with patients who do not receive all guideline-recommended therapies.[357] Thus, a major focus for physicians, hospitals, and health care systems is to improve the use of aspirin, and other important medications, using critical pathways and other methods (see p. 1254).

TREATMENT STRATEGIES AND INTERVENTIONS

Two general approaches to the use of cardiac catheterization and revascularization in UA/NSTEMI exist: (1) an "early invasive" strategy, involving routine early cardiac catheterization and revascularization with PCI or bypass surgery depending on the coronary anatomy, and (2) a more "conservative" approach with initial medical management, with catheterization and revascularization only for recurrent ischemia either at rest or on a noninvasive stress test. The latter has also been termed an "ischemia-guided" strategy.

Four randomized trials have assessed these two general strategies (Fig. 36-16). In the TIMI IIIB trial, 1473 patients were randomized in a 2×2 factorial design to receive either t-PA or its placebo and follow either an early invasive strategy with routine angiography 18 to 48 hours after randomization with revascularization as appropriate or an early conservative strategy with angiography and revascularization performed only for recurrent ischemia. All patients received intravenous heparin, aspirin, beta blockers,

nitrates, and calcium antagonists as clinically indicated.

There was no difference between the early invasive and conservative strategies in the rate of death, postrandomization MI, or a strongly positive exercise test at 6 weeks (16.2 percent vs. 18.1 percent, *p*=NS). [101] Similarly, there was no difference in the incidence of death or MI at 6 weeks or 1 year (10.8 percent vs. 12.2 percent, *p*=NS)[199] (see Fig. 36-16). It is worth noting that the conservative strategy was truly an "ischemia-guided" strategy, with the indications for catheterization based on very careful assessment for recurrent ischemia (i.e., ischemia at rest with ECG changes, ST segment depression on a Holter monitor, a "high risk" exercise thallium stress test). However, despite this requirement for objective evidence of recurrent ischemia, 49 percent of patients in the conservative arm subsequently required revascularization, evenly split between PTCA and CABG.[101] The results of TIMI IIIB were nearly duplicated in the smaller Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial[358] (see Fig. 36-16) .

The Veterans Administration Non-Q-Wave Infarction Strategies in-Hospital (VANQWISH) trial compared invasive

Figure 36-16 Results from the four randomized trials of invasive (Inv) vs. conservative (Cons) strategies in UA/NSTEMI. The duration of follow-up is shown for each trial at the top, and the number of patients is shown at the bottom. In addition, the rate of cardiac catheterization (Cath) during the initial hospitalization, as well as the rates of revascularization (revasc) with PCI or CABG are shown. **p*=0.05, *p*=0.025, +*p*=0.031. (Data from Anderson, et al. [199] ; Boden, et al.[359] ; McCollough, et al.[358] ; and the Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators.[307])

and conservative strategies in 920 patients with non-Q-wave MI (not unstable angina, and including 15 percent STEMI). There was no significant difference in the primary endpoint of death or nonfatal MI during follow-up (approximately 2 years): 26.9 percent in the invasive arm versus 29.9 percent in the conservative arm.[359] However, there were significantly more deaths in patients assigned to the invasive compared with the conservative strategy at hospital discharge (4.5 percent vs. 1.3 percent), a difference that remained significant at 1 year. Of the 21 in-hospital deaths in the invasive group, 11 followed within 30 days of coronary bypass surgery, indicating a 11.6 percent perioperative mortality in the invasive group, which explains some of the early hazard of the early invasive group. Of note, the peri-CABG mortality in patients in the conservative arm was only 3.4 percent, with a more delayed CABG (median 24 days, versus 8 days in the invasive group).

Most recently, the FRISC II trial of 2457 patients with UA/NSTEMI found a significant *benefit* of a delayed invasive strategy.[307] Patients with chest pain within 48 hours with either ST-T wave changes or positive serum markers were enrolled and received subcutaneous dalteparin in hospital. They were then randomized to an invasive versus conservative strategy. In the invasive arm, cardiac catheterization and revascularization

were carried out within 3 and 7 days of randomization, respectively, and thus this invasive strategy could be considered a "delayed" invasive strategy. Criteria for catheterization in the conservative strategy were strict and required refractory angina despite maximal medical treatment or a positive ECG exercise test with 0.3 mV or more ST segment depression. Thallium imaging was not performed with the stress testing. With this conservative strategy, only 9 percent of patients underwent revascularization during the first 7 days.[307]

The primary endpoint, death or MI at 6 months, was significantly lower in the invasive versus conservative

group (9.4 percent vs. 12.1 percent, p=0.031).[307] Preliminary 1-year results show a significant reduction in *mortality* in the invasive versus conservative groups (2.2 percent vs. 4.0 percent, respectively, p=0.018) and of death or MI (10.5 percent vs. 14.2 percent, respectively, p=0.007).[360] Additional analyses showed greater benefit of the invasive strategy in higher risk groups identified by age >65 years, ST segment depression on the admission ECG or troponin T of 0.01 ng/dl or more.[116] [361] Of note, the 30-day mortality following CABG was less than 2 percent in this study.[307]

A recent meta-analysis of these four studies has shown that there is an early hazard with an invasive strategy, but that this is balanced by later benefit in the invasive group making overall odds ratio of death or MI 0.94 (95% CI 0.78-1.13).[362] This early hazard was also observed in the Kaplan-Meier event rate curves from the TIMI IIIB and FRISC II trials.[199] [307] One randomized trial of CABG versus medical therapy in patients with unstable angina conducted in the 1980s found no overall difference in mortality at 2 years but a survival benefit in patients with left ventricular dysfunction.[204] [363]

Indications for Invasive Versus Conservative Management Strategies

Thus, balancing the current evidence, either an early conservative or early invasive strategy appears to be appropriate for patients with UA/NSTEMI.[7] However, it may be possible to individualize the approach based on the patient population and the success rates of the coronary interventions. For patients managed in a conservative fashion, indications for coronary angiography are (1) recurrent ischemia at rest or with low-level activity accompanied by ECG changes, (2) congestive heart failure, (3) evidence of ischemia on stress testing,[364] (4) when hemodynamic instability is present,[365] and (5) evidence of sustained ventricular arrhythmias.[7] With regard to the exact criteria for "significant" ischemia on stress testing, the relatively worse outcome of the conservative strategy (with strict criteria) in FRISC II as compared with the invasive group, in contrast to the equal outcomes between invasive versus conservative strategies (with moderately stringent criteria in TIMI IIIB), suggest that criteria for proceeding to angiography in a conservative strategy should not be *too* stringent.

An early invasive strategy can be considered appropriate and more expeditious than an

early conservative strategy, and it appears to be *beneficial* in higher risk patients (see Table 36-3) . As noted earlier, a significant benefit of an early invasive strategy was observed in FRISC II in patients with ST segment depression on the admission ECG[307] [361] in patients older than 65 years of age.[199] [307] An early invasive approach appears warranted in those with hemodynamic instability, based on studies in acute MI.[365] [366] In addition, an early invasive strategy in those who present with UA/NSTEMI within 6 months of a prior PCI, in whom restenosis may be frequent, may be a more expeditious strategy.

On the other hand, for the very high-risk patients with NSTEMI and multivessel disease requiring bypass surgery (similar to patients in the VANQWISH trial), and/or at hospitals where intervention complication rates are higher, an *initial* more conservative approach may be most appropriate.[7] For such patients, one might pursue a delayed invasive strategy, based on the lower perioperative mortality in the VANQWISH trial comparing patients who underwent delayed versus early CABG.[359] Results from additional trials such as Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18, conducted in the current era of glycoprotein IIb/IIIa inhibition and coronary stenting, should provide additional perspective on the issue of invasive versus conservative strategies in UA/NSTEMI, including a cost-benefit analysis.[367] [368]

Noninvasive Testing

In the management of unstable angina, noninvasive testing is used (1) at presentation, usually in the ED to diagnose the presence or absence of coronary artery disease (in patients with low likelihood of coronary disease) (see p. 1234); (2) after hospitalization and medical therapy has been carried out, to evaluate the extent of residual ischemia to guide further therapy, especially an "ischemia-guided" strategy; (3) to evaluate left ventricular function; and (4) to estimate prognosis (i.e., risk stratification).

The results from noninvasive tests that portend high risk of future cardiac events are shown in Table 36-5 (see also Chaps. 7 , 9 , and 37) . These results are derived from studies involving patients with UA, MI, and stable coronary artery disease. The markers of high risk are either evidence of ischemia on stress testing or left ventricular dysfunction (either at rest or stress induced).[369] [370] [371] [372] [373]

The need for angiography and revascularization for patients who had a positive stress test (i.e., evidence of ischemia) has long been assumed and has been used in the "conservative" arms of most randomized trials.[101] [244] [307] [359] This benefit of revascularization for provokable ischemia has been documented in patients with a positive ECG stress test following thrombolytic therapy of STEMI.[364]

The safety of early stress testing in patients with UA/NSTEMI has been debated, but evidence from several trials has suggested that pharmacological,[374] or symptom-limited stress testing,[375] is safe after at least 24 to 48 hours of stabilization without recurrent ischemia in patients with UA/NSTEMI. Contraindications to stress testing are a recent recurrence of rest pain, especially if associated with ECG changes or other signs of

instability (hemodynamic or significant arrhythmias).

The merits of various modalities of stress testing have been compared in relatively small series of patients (see also Chaps. 6 , 7 , and 9) . Stress myocardial perfusion imaging with sestamibi and stress echocardiographic imaging are slightly more sensitive than ECG stress testing alone and have shown greater prognostic value.[180] [376] [377] [378] An overview has suggested that the perfusion imaging tests are

TABLE 36-5 -- NONINVASIVE TEST RESULTS PREDICTING HIGH RISK FOR ADVERSE OUTCOMES IN PATIENTS WITHUNSTABLE ANGINA

EXERCISE ECG TESTING
Abnormal horizontal or downsloping ST segment depression with
Onset at heart rate <120 beats/min or 6.5 METS
Magnitude 2.0 mm
Postexercise duration of 6 minutes
Depression in multiple leads
Abnormal systolic blood pressure response
With sustained decrease of >10 mm Hg or flat blood pressure response 130 mm Hg, associated with abnormal electrocardiogram
Other
Exercise-induced ST segment elevation
Ventricular tachycardia
RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING
Abnormal myocardial tracer distribution in more than one coronary artery region at rest or with stress or an anterior defect that reperfuses
Abnormal myocardial distribution with increased lung uptake
Cardiac enlargement
LEFT VENTRICULAR IMAGING
Stress Radionuclide Ventriculography
Exercise EF of 50%
Rest EF 35%
Fall in EF of 10% with exercise
Stress Echocardiography
Rest EF 35%
Wall motion score index >1

EF=ejection fraction; METS=metabolic equivalents

Data from Schlant RC, Blomqvist CG, Brandenburg RO et al: Guidelines for exercise testing: A report of the Joint American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Exercise Testing). Circulation 1986;74:653A-667A, 1986; *O'Rourke RA, Challerjee K, Dodge HT et al. Guidelines for clinical use of cardiac radionuclide imaging, December 1986: A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 8:1471-1483, 1986*; and *Cheitlin MD, Alpert JS, Armstrong WF et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1997;95:1686-1744, 1997*.

more sensitive for ischemia than ECG-only stress testing and that such testing is generally cost effective in higher risk patients.[379] A recommended approach is to individualize the choice based on patient characteristics, local availability, and expertise in interpretation.[7] For most patients, ECG stress testing is recommended if the ECG is without significant ST segment abnormalities.[7] If ST segment abnormalities exist, then perfusion or echocardiographic imaging is recommended. Exercise testing is generally recommended unless the patient cannot walk sufficiently to achieve a significant workload, in which case pharmacological stress testing is recommended.[7]

Intraaortic Balloon Counterpulsation

Intraaortic balloon counterpulsation (IABP) is a very effective means of increasing diastolic coronary blood flow and reducing left ventricular afterload, which act in concert to reduce ischemia (see Chap. 19) . IABP is usually reserved for patients with UA/NSTEMI who are refractory to maximal medical therapy and those with hemodynamic compromise who are awaiting cardiac catheterization or for those identified to have very high risk coronary anatomy (e.g., left main stenosis) as a bridge to coronary angioplasty or bypass surgery.[7] In the TIMI III Registry, only 1 percent of patients required IABP during hospitalization.[98] [100] No randomized

trials are available to document its benefit, but this method is very effective in stabilizing patients with refractory ischemia. However, vascular access site complications are relatively common in the elderly, women, and diabetics.[380] [381]

Revascularization (see also Chap. 38)

PERCUTANEOUS CORONARY INTERVENTION.

PCI is an effective means of reducing coronary obstruction, improving acute ischemia, and improving regional and global left ventricular function in patients with UA/NSTEMI.[382] Current angiographic success rates are high, generally more than 95

percent[383] (see also Chap. 38) , although the presence of unstable angina or visualized thrombus has been associated with increased risk of acute complications such as abrupt closure or MI (as compared with patients with stable angina or those without visualized thrombus).[123] [384] Thus, use of glycoprotein IIb/IIIa inhibitors in such patients is associated with improved PCI outcomes (Fig. 36-13 , p. 1248).

The TIMI III investigators reported a favorable experience with balloon angioplasty in patients with a UA/NSTEMI with a periprocedural MI rate of 2.7 percent, an emergency bypass surgery rate of 1.4 percent, and a mortality of 0.5 percent. Since that time, the advent of coronary stenting has reduced the rate of emergency bypass surgery and the increasing use of glycoprotein IIb/IIIa inhibitors has reduced the rates of death and MI.[81] [328] [385] [386] [387] [388] [389] [390] [390A] [391] When CK-MB is measured serially during the 24 hours after a procedure, the rates of MI are higher: 5 to 8 percent among patients treated with aspirin and heparin. These rates are markedly reduced when IIb/IIIa inhibitors are used during the PCI.[81] [328] [387] [388] [389] [390] [390A] [391] (see Fig. 36-13) (see also Chap. 38) .

PCI VERSUS CABG.

When revascularization is required in patients with UA/NSTEMI, the choice is between PCI and CABG. Five trials have compared PTCA and CABG in patients with ischemic heart disease, many of whom had unstable angina.[392] [393] [394] [395] [396] The results of these trials are reviewed in Chapters 37 and 38 . Based on the results of these trials, and those of previous trials of CABG versus medical therapy,[397] [398] [399] [400] and more recent observational data,[401] CABG is recommended for patients with disease of the left main coronary artery, multivessel disease involving the proximal left anterior descending artery, or multivessel disease and impaired left ventricular function or diabetes.[402] For other patients, either PCI or CABG may be suitable: PCI is associated with a slightly lower initial morbidity and mortality than CABG but a higher rate of repeat procedures, whereas CABG is associated with more effective relief from angina.

TARGETING OF NEW THERAPIES TO SPECIFIC SUBGROUPS

With the large array of new therapies and interventions now available for the treatment of patients with UA/NSTEMI, and in light of the limited resources available for health care, there has been a desire to apply the newer (and generally more expensive) therapies to those who will benefit most. Although it had long been assumed that patients at highest risk would benefit most from more aggressive therapy,[7] [104] there is now a growing body of evidence from large randomized trials to support this hypothesis. Early risk assessment (especially using troponins, but also clinical variables) has been useful in predicting which patients will derive the greatest benefit from newer and more potent antithrombotic therapies such as LMWH and glycoprotein IIb/IIIa inhibitors[153] [154] [155] [224] [403] [404] and from an early invasive strategy.[116] [199] [307] [361] Because the high-risk subgroups have a higher event rate, even a similar *relative* benefit translates into a *greater absolute* number of cardiac events prevented. In addition, there appears to be an *increasing relative* benefit of some of the therapies[80] [405] that would extend further the incremental value of these drugs.

ELDERLY PATIENTS.

Outcomes in elderly patients are worse than in younger patients; and, disappointingly, some therapies, notably thrombolysis for STEMI, appear to have *less* relative benefit than in younger patients.[347] In contrast, in UA/NSTEMI, the elderly appear to derive *greater* relative and absolute benefit from the newer more potent antithrombotic therapies. In both the ESSENCE and TIMI 11B trials, the LMWH enoxaparin, compared with UFH, appeared to exert a greater relative and absolute benefit in patients older than 65 years as compared with younger patients.[80] [405] For the glycoprotein IIb/IIIa inhibitors, an equivalent relative benefit has been observed that translated into a greater *absolute* benefit in older versus younger patients.[81] [82] [83]

With regard to an invasive versus conservative management strategy, in the FRISC II trial, the benefit of an early invasive strategy was confined to patients older than age 65 years with no difference in outcome by strategy in younger patients.[307] A similar trend was observed in the TIMI IIIB trial.[199] Thus, in unstable angina, elderly patients are at higher risk and appear to derive particular *benefit* from more aggressive antithrombotic or interventional therapy.

CLINICAL SUBGROUPS.

Diabetics are known to be at high risk, and there is now evidence of a greater *relative* benefit of intravenous glycoprotein IIb/IIIa inhibition in diabetic patients with UA/NSTEMI, with a dramatic 72 percent risk reduction in 30-day death or MI (15.5 percent for heparin alone vs. 4.7 percent for tirofiban plus heparin), as compared with 13 percent reduction in nondiabetics.[189] Similarly, for patients presenting with unstable angina while already taking aspirin, there was a trend for greater benefit from eptifibatide or enoxaparin in the PURSUIT and TIMI 11B trials, respectively, compared with non-prior-aspirin users.[196] [197] In addition, patients who develop recurrent angina after initial presentation to the hospital are at high risk and derive greater benefit from glycoprotein IIb/IIIa inhibitors.[83] [193]

ELECTROCARDIOGRAPHY.

In both the ESSENCE and TIMI 11B trials, patients with ST segment deviation exhibited a significant reduction in cardiac events from enoxaparin compared with UFH, whereas those without ST segment deviation did not.[80] [405] For glycoprotein IIb/IIIa inhibitors, the greatest benefit has been observed in patients with transient ST segment elevation, followed by ST segment depression, with an absolute benefit two to three times greater than for patients without ST segment changes.[83] Evidence from the FRISC II trial of invasive versus conservative strategies found particular benefit of an invasive strategy in patients with ST segment depression at presentation.[361] Thus, ST segment deviation is a marker of increased risk but also of greater benefit from aggressive antithrombotic and interventional therapy.

CARDIAC MARKERS.

Elevated circulating cardiac markers have been shown to correlate with a higher rate of thrombus at angiography. This has been demonstrated with both CK-MB[4] [123] and troponin T and I.[124] [154] It has been proposed that minor myocardial damaged as assessed by troponin is a marker of microemboli from coronary thrombi.[117] A greater antithrombotic effect has been observed in patients with positive markers: for example, the degree of resolution of thrombus after 24 hours of therapy with abciximab in the CAPTURE trial was greater in patients who were troponin T positive versus troponin T negative.[154]

Clinical benefits have followed the same pattern: When treating with the IIb/IIIa inhibitor abciximab there was a 68

Figure 36-17 *Left,* Benefit of abciximab in the CAPTURE trial of patients with refractory unstable angina treated with angioplasty in those with positive versus negative troponin T values at study entry. *Right,* Greater benefit of tirofiban versus heparin in patients with UA/NSTEMI was also seen in those with positive troponin I values in the PRISM trial, with a nearly 70 percent reduction in death or myocardial infarction at 30 days with the IIb/IIIa inhibitor. (Data from Hamm CW, Heeschen C, Goldmann B, et al: Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. N Engl J Med 340:1623-1629, 1999; and Heeschen C, Hamm CW, Goldmann B, et al: Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 354:1757-1762, 1999.)

percent reduction in death or MI at 6 months in the CAPTURE trial in those who were troponin T positive versus no significant benefit for those who were troponin T negative (p<0.001) [154] (Fig. 36-17) . These findings have recently been essentially duplicated with tirofiban versus heparin in the PRISM trial (see Fig. 36-17) .[155] However, a benefit of abciximab was not observed in GUSTO IV ACS in troponin-positive patients.[333A] In the TIMI 11B trial, even among patients who were CK-MB negative, those with elevations of troponin I derived a significantly greater benefit from the LMWH enoxaparin versus UFH compared with those with negative troponins.[153] Similar findings may also be emerging for selecting patients for an invasive versus conservative strategy: In the FRISC II study, the majority of the benefit of invasive therapy at 1 year was obtained in patients with an elevated troponin T level, using an ultra low threshold of 0.01 ng/dl or more, whereas no benefit was observed in patients with troponin T of less than 0.01 ng/dl.[116]

Thus, there is now evidence from several trials that use of troponins can assist in both risk stratification and in determining which patients should be treated with the newer antithrombotic agents, such as LMWH or glycoprotein IIb/IIIa inhibitors, and potentially

with an invasive management strategy.[7]

C-REACTIVE PROTEIN.

One small study of patients with unstable angina found that a glycoprotein IIb/IIIa inhibitor attenuated the increase in CRP levels as compared with placebo.[406] During long-term treatment of patients after MI, pravastatin has been shown to reduce CRP,[407] and a greater

Figure 36-18 TIMI 11B: Use of a simple, but comprehensive clinical risk stratification score to identify (1) increasing risk of death, myocardial infarction, or urgent revascularization to day 14, and (2) increasing benefit of enoxaparin versus unfractionated heparin (UFH). The risk factors are age 65 years or older, more than three risk factors for coronary artery disease, documented coronary artery disease at catheterization, ST segment deviation of 0.5 mm or more, more than two episodes of angina in last 24 hours, aspirin within prior week, and elevated cardiac markers. (Adapted from Antman EM, Cohen M, Bernink PJLM, et al: The TIMI Risk Score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 284:835-842, 2000.)

TABLE 36-6 -- FACTORS ASSOCIATED WITH FAILURE OF INITIAL MEDICAL THERAPY IN PATIENTS WITH UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION FROM THE TIMI IIIB TRIAL

FACTOR	DEATH, MYOCARDIAL INFARCTION, RECURRENT ISCHEMIA (ODDS RATIO)	DEATH, MYOCARDIAL INFARCTION, RECURRENT ISCHEMIA, MARKEDLY POSITIVE TEST (ODDS RATIO)
ST segment depression	2.6*p<0.01	3.2 p<0.0001
History of angina	1.8	1.9p<0.01
Heparin use	1.7p<0.01	1.3
Aspirin use	1.4p<0.01.	1.3
Age (per 10 years)	1.3p<0.01.	1.2
Family history of coronary artery disease	1.2	1.2

Markedly positive test was defined as: 20 minutes of ST depression
0.1 mV on a Holter monitor, a "high risk" exercise test (ischemic discomfort before end of stage II, ST depression
0.2 mV, or fall in systolic blood pressure >10 mm Hg on two determinations), a "high risk" thallium perfusion imaging with
2 regions of reversible hypoperfusion or increased lung uptake and one region of reversible hypoperfusion. From Stone PH, et al. Factors associated with failure of medical therapy in patients with unstable angina and non-Q wave myocardial infarction: A TIMI-IIIB database study. Eur Heart J 20:1084-1093, 1999.

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relative benefit of this therapy was observed in patients with elevated baseline levels of CRP compared with patients with normal baseline levels of CRP.[38] [408] Additional studies are ongoing to examine the usefulness of CRP in targeting acute therapies for unstable angina.

COMBINED RISK ASSESSMENT SCORES.

Risk scores combining clinical factors have been used to identify patients who derived the greatest benefit from enoxaparin versus UFH (Fig. 36-18) [223] [224] or GP IIb/IIIa inhibitors (Reference Sabative 2000).[224A] Another use of clinical risk stratification score is to predict not just mortality or recurrent MI, but also failure of medical therapy (i.e., recurrent ischemia--either spontaneous or on a provocative test despite therapy). Such an analysis was carried out in the patients randomized to the conservative treatment strategy of the TIMI IIIB trial to identify patients with a high likelihood of failing medical therapy in whom an early invasive strategy might be advisable. Several predictors emerged, including ST segment deviation, history of prior angina, family history of coronary disease, prior use of heparin or aspirin, and advanced age (Table 36-6) . By combining these baseline risk characteristics, the likelihood of developing death, MI, recurrent rest ischemia, or a strongly positive test for ischemia ranged from 8 percent if none was present to 63 percent if all six were present.[409] It seems reasonable that if three or more of these risk factors are present, patients could be referred for early coronary angiography, because it will ultimately be required in the majority, whereas if fewer than three were present, a conservative approach is more likely to be successful, without recurrent ischemia. Such a "risk-based" triage approach could be useful in selecting an appropriate management strategy (see Table 36-6) .

A proposed treatment algorithm integrating the risk assessment and the targeting of therapy is illustrated in Figure 36-19 . Risk assessment based on the clinical history, ECG, and serum markers identifies patients with medium to high risk who are appropriate candidates for aggressive antithrombotic therapy. For patients with uncertain history and negative ECG and markers, a rapid "rule-out MI" pathway is appropriate.

CRITICAL PATHWAYS.

With rising restraints on health care costs, there has been increasing focus on the creation and implementation of "critical pathways," with an initial goal to reduce length of

stay. However, several other goals are appropriate: (1) improving the use of appropriate medications (e.g., aspirin, beta blockers), (2) improving triage of the patient to the appropriate level of care,[164] [410] and (3) reducing the number of unnecessary tests that are performed (e.g., laboratory blood tests, echocardiography). With regard to triage, coronary care unit admission was standard practice for patients with all forms of acute coronary syndromes in the past. However, at present, coronary care unit admission is generally reserved for STEMI patients and those with hemodynamic compromise or other complications.

The pathway for management of UA/NSTEMI at Brigham and Women's Hospital[411] emphasizes (1) early relief of ischemic pain, which has been found to be a determinant of development of NSTEMI among patients presenting with symptoms of acute ischemia[5] ; (2) administration of antithrombotic and antiischemic therapy as outlined earlier; (3) reminders of eligibility criteria of ongoing clinical trials; (4) detailed list of suggested blood and laboratory tests in an effort to reduce unnecessary tests; and (5) choice of either an early conservative strategy or an early invasive strategy, as used in TIMI IIIB.[164] Initial experience with this pathway has shown a reduction in hospital length of stay from a median of 5 days before the pathway to 2 days, as well as an improvement in the use of appropriate medications. As institutions gain experience with implementation of critical pathways, their impact on coronary care will be able to be assessed more clearly.

"CARDIAC CHECKLIST".

One simple method of ensuring better compliance with recommended therapies is to use a checklist of the medications when first treating patients with UA/NSTEMI.[411] Indeed, checklists currently are used for preadmission testing and procedures, and thus this notion can be extended to treatments. Table 36-7 (Table Not Available) shows a proposed "cardiac checklist" for patients with UA/NSTEMI, which includes aspirin, heparin or LMWH, glycoprotein IIb/IIIa inhibition, beta blockers, heart-rate-lowering calcium antagonists (in the absence of congestive heart failure

TABLE 36-7 -- CARDIAC CHECKLIST FOR UNSTABLE ANGINA/NON-ST ELEVATION MYOCARDIAL INFARCTION

(Not Available)

Adapted from Cannon CP: Optimizing the medical management of acute coronary syndromes. J Thromb Thrombolysis 7:171-189, 1999.

Figure 36-19 Algorithm for risk stratification and treatment of patients with UA/NSTEMI. Using the clinical history of the type of pain and prior medical history, the electrocardiogram (ECG), and cardiac markers, one can identify patients who have a low likelihood of UA/NSTEMI, for whom a diagnostic "rule-out" myocardial infarction (MI) or acute coronary syndrome (ACS) is warranted. If this is negative the patient is

discharged home; and if it is positive, the patient is admitted and treated for UA/NSTEMI. On the other end of the spectrum patients with acute ongoing pain and ST segment elevation are treated with thrombolysis or percutaneous coronary intervention (PCI) (see Chap. 35) . For those with UA/NSTEMI, all patients are given standard treatment with aspirin (ASA), unfractionated or low-molecular-weight heparin [LMWH], and antiischemic therapy with beta blockers and nitrates. Risk stratification is used to identify patients at medium to high risk, for whom aggressive treatment with glycoprotein IIb/IIIa inhibition and an early invasive strategy is warranted. (Data on the safety and efficacy of the combination of LMWH and glycoprotein IIb/IIIa inhibition are still emerging at the time of this writing.) For patients at low risk, standard treatment is likely sufficient, and a more conservative approach could be expected to be equivalent in outcomes to a more invasive one. DM=diabetes mellitus; Rx=treatment; STEMI=ST elevation myocardial infarction.

or left ventricular dysfunction), cholesterol lowering, and other risk factor modifications. This "cardiac checklist" could be used in two ways: (1) physicians who encounter these patients frequently could keep a copy on a small index card in their pocket and run down the list when writing admission orders for patients or (2) it could be used in developing standard orders for unstable angina (either printed order sheets or computerized orders).

Therapy at Hospital Discharge

After the acute treatment of patients with acute coronary syndromes, the focus turns to preventing recurrent ischemic events (i.e., secondary prevention). The drugs that have been proven to be of benefit in long-term treatment are aspirin or clopidogrel as antiplatelet therapy, beta blockers, ACE inhibitors, and statin therapy. Efforts should be undertaken to ensure that patients receive such therapies to ensure optimal outcomes during long-term treatment (see Chap. 39) . In patients who have managed on a conservative strategy, a maximal exercise stress test 2 to 6 weeks after discharge is indicated to identify high-risk patients who may benefit from coronary revascularization and who should therefore undergo coronary angiography.

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TARGETING NEW THERAPIES

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GUIDELINES
MANAGEMENT OF UNSTABLE ANGINA/NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

Thomas H. Lee

Key guidelines for management of unstable angina and non-ST segment elevation myocardial infarction (UA/NSTEMI) were issued by an American College of Cardiology/American Heart Association (ACC/AHA) task force in 2000.[1] These guidelines updated and extended recommendations published in 1994 by the Agency for Health Care Policy and Research (AHCPR) and the National Heart, Lung and Blood Institute.[2] Other guidelines relevant to the diagnosis and management of this population have been issued by the American College of Emergency Physicians and other ACC/AHA task forces and are described in the Guidelines to Chapter 35 .

The ACC/AHA guidelines on UA/NSTEMI used the customary ACC/AHA classification system to provide recommendations for the appropriateness of indications, described in Chapter 37 .

In addition, these ACC/AHA guidelines adapted the AHCPR approach of grading the strength of evidence used to develop these recommendations. The weight of evidence was ranked highest (A) if the data were derived from multiple randomized trials involving large numbers of patients. An intermediate rank (B) was assigned if the data were derived from a limited number of randomized trials with small numbers of patients or from careful analysis of nonrandomized studies or observational data bases. A lower rank of "C" was assigned when the basis of the recommendation was expert consensus.

These guidelines focus on the care of patients with *acute coronary syndrome* (ACS),

which includes acute myocardial infarction and UA. UA and NSTEMI are considered closely related conditions that differ primarily in severity. Excluded is the care of patients with acute myocardial infarction and ST segment elevation, who would be eligible for acute reperfusion (see Chap. 35) .

Initial Evaluation and Management (Fig. 36-G-1)

The guidelines emphasize the importance of prompt evaluation of patients with acute chest pain in settings in which a 12-lead electrocardiogram (ECG) can be performed, as opposed to over the telephone. Patients with prolonged (>20 minutes) chest pain or symptoms suggesting hemodynamic instability or arrhythmia should be triaged to an emergency department or chest pain unit; transport should ideally occur by emergency medical vehicles. Patients with*possible ACS* should have a 12-lead ECG and undergo observation with serial measurement of cardiac markers. Cardiac-specific troponins are identified as preferred markers, while creatine kinase MB isoenzyme (CK-MB) is considered a less preferable but acceptable marker.

Immediate Management (Table 36-G-1)

After identifying and appropriately treating patients with reperfusion-eligible acute myocardial infarction (see Chap. 35) , as well as others with cardiac conditions that are not due to ACS, the clinical findings should be used to assign the remaining patients with chest pain to one of four categories (see Table 36-G-1) :

1. A noncardiac diagnosis
2. Chronic stable angina
3. Possible ACS
4. Definite ACS

Management of patients with chronic stable angina is expected to be according to ACC/AHA guidelines on this topic, as summarized in the Guidelines to Chapter 37 .

For patients with possible ACS who have no recurrent chest discomfort over a 4- to 8-hour period and have normal results of follow-up 12-lead ECGs and biochemical cardiac markers, stress testing is considered appropriate (Table 36-G-1) . Patients with negative stress tests can be discharged for further management as outpatients. Patients with strongly positive stress tests are considered to be at high risk (Table 36-G-2) and should be admitted to the hospital. Management of patients with intermediate test results must be determined by clinical judgment. The ACC/AHA guidelines indicate that exercise ECG is an appropriate first-line test for risk stratification.

Hospital Care (Table 36-G-2 , Fig. 36-G-2)

The guidelines recommend that patients with recurrent symptoms, ECG ST segment deviations, positive cardiac markers (CK-MB or troponin), or hemodynamic instability be

admitted to an inpatient unit with continuous rhythm monitoring. For this population, observation in such facilities for at least 24 hours without any recurrence of ischemia or major complications is recommended before considering transfer to a lower level of care. Factors that suggest triage to a coronary care unit (as opposed to a unit with a lower nurse/patient ratio) are elevated serum markers or hemodynamic instability.

TABLE 36--G-1 -- INITIAL EVALUATION AND MANAGEMENT

Issue	Class	Recommendation	Level of Evidence
Immediate management	I	The history, physical examination, 12-lead ECG, and initial serum marker tests should be integrated to assign patients with chest pain to 1 of 4 categories: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS	C
		Patients whose symptoms are suggestive of ACS or are believed to be consistent with definite ACS but whose initial 12-lead ECG and serum cardiac marker levels are normal should be observed in a facility with cardiac monitoring (e.g., chest pain unit),and a repeat ECG and serum marker measurement should be obtained 4-8 hr later	C C
		If the follow-up 12-lead ECG and cardiac marker measurements are normal, a stress test to provoke ischemia may be performed. Patients with a negative stress test can be managed as outpatients. Patients with a strongly positive stress test are considered to have myocardial ischemia and, in the presence of a clinical picture of acute ischemia, should be admitted to the hospital for further management. The stress test can be conducted on an outpatient basis in low-risk patients with unstable angina/non-ST segment elevation myocardial infarction	C C
		Patients who are unable to exercise or who have an abnormal resting ECG should have stress myocardial perfusion imaging	
		Patients believed to have an ACS with an abnormal initial 12-lead ECG should be managed according to the findings of the 12-lead ECG. Patients with ST elevation should be evaluated for immediate reperfusion therapy. Patients with new ST depression and/or T wave abnormalities should be admitted to the hospital for further management	C C

ACS=acute coronary syndrome; ECG=electrocardiogram.

Figure 36-36-G-1 Algorithm for evaluation and management of patients suspected of having acute coronary syndrome (ACS). ACP=American College of Physicians; ECG=electrocardiogram; LV=left ventricular. (From Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guidelines for the management of patients with unstable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol, 36:970-1062, 2000.)

TABLE 36--G-2 -- HOSPITAL CARE

Issue	Class	Recommendation	Level of Evidence
Antiischemic therapy	I	Bed rest with continuous ECG monitoring for ischemia and arrhythmia detection in patients with ongoing pain at rest	C
		NTG, sublingual tablet or spray or IV, for immediate relief of ischemia and associated symptoms	C
		Supplemental oxygen for patients with cyanosis, respiratory distress, or high-risk features. Finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (Sa_{O_2} >92%) and continued need for supplemental oxygen in the presence of hypoxemia	C
		Morphine sulfate IV when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation is present	C
		A beta blocker, oral or IV, in the absence of contraindications	B
		In patients with continuing or frequently recurring ischemia in whom beta blockers are either contraindicated or fully deployed, a nondihydropyridine calcium antagonist (e.g., diltiazem or verapamil), oral and/or IV, as initial therapy in the absence of severe LV dysfunction or other contraindications	B
		Intraaortic balloon pump counterpulsation for	C

	Intraaortic balloon pump counterpulsation for patients with either ischemia that is continuing or recurs frequently despite intensive medical therapy or hemodynamic instability	C
	An ACE inhibitor when hypertension persists despite treatment with NTG and a beta blocker and in patients with LV systolic dysfunction	B
IIa	Nondihydropyridine calcium antagonist (diltiazem or verapamil), oral and/or IV, as initial therapy in the absence of severe LV dysfunction or other contraindications	B
	Oral long-acting dihydropyridine calcium antagonists in the absence of contraindications for recurrent ischemia when beta blockers and nitrates are fully deployed	C
	An ACE inhibitor for diabetic patients	B
IIb	Long-acting nondihydropyridine calcium antagonists instead of a beta blocker	B
	Immediate-release dihydropyridine calcium antagonists in the presence of a beta blocker	B
III	NTG or other nitrate within 24 hr of sildenafil (Viagra) use	C
	Immediate-release dihydropyridine calcium antagonists in the absence of a beta blocker	B

Antiplatelet and anticoagulation therapy	I	Antiplatelet therapy should be initiated promptly. ASA is the first choice and is administered as soon as possible after arrival and then continued indefinitely	A
		Patients unable to take ASA because of hypersensitivity or major GI intolerance should receive an ADP receptor antagonist as a substitute	B
		Ticlopidine has been found effective	B
		Clopidogrel may be preferred because of safety	
		Parenteral anticoagulation with IV unfractionated heparin or with subcutaneous low-molecular-weight heparin should be added to antiplatelet therapy	A
		A platelet GP IIb-IIIa receptor antagonist should be administered, in addition to ASA and heparin, to patients with unstable angina with continuing ischemia or with other high-risk features. Eptifibatide and tirofiban are approved for this use. Abciximab can also be used for 12-24 hr in patients with UA/NSTEMI in whom an interventional procedure within the following 24 hr is planned	A
	III	IV thrombolytic therapy in patients without acute ST segment elevation of a presumably new left bundle branch block	A

Risk stratification	I	Noninvasive stress testing in patients who have been free of angina at rest or with low-level activity and CHF for a minimum of 24-28 hr and who are not otherwise considered high risk	C
		Choice of stress test is based on the resting ECG, ability to perform exercise, local expertise, and technologies available. Treadmill exercise is suitable in patients able to exercise in whom the ECG is free of baseline ST segment abnormalities, left bundle branch block, LV hypertrophy, intraventricular conduction defect, preexcitation, or digoxin effect	C
		In patients with resting ST segment depression (1 mm), LV hypertrophy, left bundle branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise, an imaging modality is added	C
		Pharmacological stress testing with imaging when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe COPD, general debility) preclude exercise	B
		Choice among different imaging modalities used with stress testing should be based primarily on local expertise	C
		A noninvasive test (echocardiogram, radionuclide angiogram) to evaluate LV function in patients with definite ACS	C
		Prompt angiography without noninvasive risk stratification for failure of stabilization with medical treatment	B
	III	Noninvasive stress testing or coronary angiography in patients with extensive comorbidity in whom revascularization is contraindicated	C

Early conservative vs. invasive strategies	I	An early invasive strategy involving prompt coronary angiography to evaluate for revascularization in patients with any of the following high-risk indicators: Patients receiving intensive antiischemic therapy with recurrent angina/ischemia at rest or with low-level activities or accompanied by CHF symptoms, and S_3 gallop, or new or worsening MR High-risk findings on noninvasive stress testing (see Table G-3) Depressed LV systolic function (EF <0.4) by noninvasive study) Hemodynamic instability Sustained ventricular tachycardia Prior revascularization (PCI or CABG)	C
	IIa	In the absence of findings in Class I, either an early conservative or early invasive strategy may be performed in hospitalized patients without contraindications for revascularization	C
		An early invasive strategy in patients who prefer and have no contraindications to revascularization	C
		Repeated attacks of ACS without evidence for ischemia or high risk	
	III	Coronary angiography in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer) in whom the risks of revascularization are not likely to outweigh the benefits	

Coronary revascularization using PCI and CABG in patients with UA/NSTEMI	I	CABG for patients with significant left main CAD, as well as in patients with severe multivessel CAD or two-vessel disease involving the proximal LAD and depressed LV systolic function	A A A
		PCI or CABG for nondiabetic patients with multivessel CAD. PCI for patients with coronary anatomy suitable for catheter-based therapy and preserved LV function.	A
		Platelet GP IIb-IIIa receptor inhibitor in UA/NSTEMI patients undergoing percutaneous revascularization	
	IIa	CABG for patients with multivessel disease and diabetes mellitus	B
		PCI or CABG for patients with 2-vessel disease not involving the proximal LAD	B
		PCI or CABG for patients with single-vessel, proximal LAD disease	B
	IIb	PCI for patients with multivessel disease and diabetes of LV dysfunction	B
		PCI for patients with significant left main disease in whom CABG cannot be carried out	C

ACE=angiotensin-converting enzyme; ACS=acute coronary syndrome; ADP=adenosine diphosphate; ASA=acetylsalicylic acid; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EF=ejection fraction; GI=gastrointestinal; GP=glycoprotein; LAD=left anterior descending artery; LV=left ventricular; MR=mitral regurgitation; NTG=nitroglycerin; PCI=percutaneous coronary intervention; UA/NSTEMI=unstable angina/non-ST segment elevation myocardial infarction.

ANTIISCHEMIC THERAPY.

Early initiation of beta blocker therapy in the absence of contraindications is recommended. Calcium antagonists are considered useful primarily for symptom control and appropriate for second or third choices following initiation of nitrates and beta blockers. For agents that slow the heart rate (verapamil and diltiazem), early use is more appropriate because of the lack of controlled trial evidence of harm, and some trends suggest potential benefit. The guidelines consider the use of immediate-release dihydropyridine calcium antagonists in the absence of a beta blocker to be *inappropriate*

(Class III).

ANTIPLATELET AND ANTICOAGULATION THERAPY.

The guidelines encourage prompt initiation of an array of agents to impede thrombus formation. Antiplatelet therapy should begin immediately, ideally with acetylsalicylic acid (ASA), but with newer agents (clopidogrel or ticlopidine) if the use of ASA is contraindicated. The guidelines also support a low threshold for anticoagulation with intravenous heparin or with subcutaneous low-molecular-weight heparin for patients with ACS. High-risk patients should also be considered for therapy with a platelet glycoprotein (GP) IIb-IIIa receptor antagonist.

Intravenous thrombolytic therapy in the absence of acute ST segment elevation or a presumably new left bundle branch block is considered inappropriate (Class III).

RISK STRATIFICATION (see Table 36-G-2) .

Early use of noninvasive tests for risk stratification after patients have been free of angina at rest or during low-level activity, heart failure, or other major complications for 24 to 48 hours is recommended. As noted above, an exercise ECG is considered the most appropriate first-line test for patients with adequate functional capacity and appropriate rest ECGs. This recommendation is based on its "simplicity, lower cost, and widespread familiarity with performance and interpretation." For other patients, choices among different imaging modalities should be based on local expertise. Findings on noninvasive testing that predict a high risk for adverse outcomes are shown in Table 36-G-3 .

For patients with definite ACS, left ventricular function should be assessed to help guide long-term management strategies. If medical treatment is not able to control symptoms of ischemia, patients should undergo prompt coronary angiography, as long as other considerations (e.g., extensive comorbidity) would not preclude coronary revascularization.

Early Conservative Versus Invasive Strategies (see Table 36-G-2)

Two strategies for coronary angiography were discussed. In the *early conservative strategy*, patients routinely undergo noninvasive risk stratification, and coronary angiography is reserved for patients identified as being at high risk for adverse outcomes based on their clinical courses or noninvasive test results. In the *early invasive strategy*, patients without obvious contraindications to coronary revascularization are routinely recommended for coronary angiography followed by revascularization, if possible.

A clearly appropriate (Class I) assessment was given to the use of an early invasive

strategy for patients with high-risk indicators, including

Figure 36-36-G-2 Acute ischemia pathway. EF=ejection fraction; GP=glycoprotein; LV=left ventricular. *(From Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guidelines for the management of patients with unstable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on the Management of Patients with Unstable Angina]. J Am Coll Cardiol, 36:970-1062, 2000.)*

recurrent ischemia, markedly abnormal noninvasive test results (see Table 36-G-2) , a history of prior revascularization, depressed left ventricular function, hemodynamic instability, or sustained ventricular tachycardia. In other patients, either strategy is acceptable (Class I). The early invasive approach was considered reasonably appropriate (Class IIa) for patients who prefer revascularization to medical therapy and for patients who have repeated attacks of suspected ACS without evidence of ischemia or increased risk.

CORONARY REVASCULARIZATION.

The indications for revascularization in patients with UA/NSTEMI are similar to those for patients with chronic stable angina (see Guidelines to Chap. 37). These guidelines reflect the growing experience with percutaneous coronary interventions (PCIs) and the benefit of platelet GP IIb-IIIa receptor inhibitors in high-risk patients. Coronary artery bypass graft (CABG) surgery remains the appropriate intervention for patients with left main disease, for patients with severe multivessel disease and depressed left ventricular function, and for patients with two-vessel disease that includes the proximal left anterior descending coronary artery (LAD) with depressed left ventricular function (see Table 36-G-2) . In addition, the guidelines consider CABG surgery most appropriate for patients with multivessel disease and diabetes (Class IIa). Either CABG or PCI may be used in patients with one- or two-vessel disease without significant proximal LAD obstruction. However, PCI is considered appropriate (Class I) for nondiabetic patients with single or multivessel disease if the coronary anatomy is suitable for such procedures. Use of platelet GP IIb-IIIa receptor inhibitors for patients with UA/NSTEMI who are undergoing PCI is also endorsed by these guidelines.

Hospital Discharge And Post-Hospital Discharge Care (Table 36-G-4)

Long-term medical treatment of patients who have been stabilized with medical therapy or revascularization should include, in the absence of contraindications, ASA and beta blockers. Dietary interventions should be used if low-density lipoprotein (LDL) cholesterol is greater than 100 mg/dl; 3-hydroxy-3-methylglutaryl coenzyme A

(HMG-CoA) reductase inhibitors should be started if LDL cholesterol is 125 mg/dl or higher. Angiotensin-converting enzyme inhibitors should be considered, especially in patients with evidence of left ventricular dysfunction.

The ACC/AHA guidelines emphasize the importance of careful follow-up within a few weeks after discharge. Recurrent unstable angina should lead to consideration of coronary revascularization. Explicit recommendations on appropriate educational messages for patients and families are provided (see Table 36-G-4) . These discussions should include information about resumption of sexual activity. The guidelines also recommend control of other risk factors besides elevated LDL cholesterol, including consideration of referral of patients who are smokers to a smoking cessation program.

Special Patient Populations (Table 36-G-5)

The guidelines conclude that women with ACS should be managed in a manner similar to men--that is, no evidence supports the use of different management strategies or indications for procedures. They also recommend similar management strategies for patients with diabetes

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TABLE 36--G-3 -- NONINVASIVE TEST RESULTS PREDICTING HIGH RISK FOR AN ADVERSE OUTCOME

Exercise ECG Testing
Abnormal horizontal or down-sloping ST segment depression with
Onset at heart rate <120/min or 6.5 METS Magnitude 2.0 mm Postexercise duration 6 min Depression in multiple leads
Abnormal systolic blood pressure response--with a sustained decrease of >10 mm Hg or a flat blood pressure response (130 mm Hg), associated with abnormal ECG findings
Other
Exercise-induced ST segment elevation Ventricular tachycardia
Stress Radionuclide Myocardial Perfusion Imaging

Abnormal myocardial tracer distribution in more than one coronary artery region at rest or with stress or a large anterior defect that reperfuses
Abnormal myocardial distribution with increased lung uptake
Cardiac enlargement

Stress Radionuclide Ventriculography

Exercise EF of
0.50
Rest EF
0.35
Fall in EF of
0.10

Stress Echocardiography

Rest EF
0.35Wall motion score index >1

ECG=electrocardiogram; EF=ejection fraction.
Adapted from Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guidelines for the management of patients with unstable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol, 36:970-1062, 2000. Reprinted with permission from the American College of Cardiology.)

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mellitus, while emphasizing the importance of diabetes as a risk factor for cardiovascular complications and the importance of glucose control as an approach to minimizing the effects of this condition. If revascularization is needed for patients with diabetes mellitus and multivessel disease, CABG (with particular attention to the use of internal mammary grafts) is preferred over PCI.

In patients who have previously undergone CABG, decisions about medical treatment or the use of revascularization should be similar to those used in other patients with UA/NSTEMI. The ACC/AHA guidelines considered the use of imaging technologies with stress testing appropriate (Class IIa) in this population. The task force also thought that a lower threshold for angiography may be appropriate in post-CABG patients because of the multiple potential causes of ischemia.

The ACC/AHA guidelines do not suggest qualitatively different strategies for the management of elderly patients with UA/NSTEMI but encourage greater attention to the impact of comorbidities, life expectancy, and the pharmacokinetics and side effects of drugs. Since the survival benefit of interventions may not be similar to those demonstrated in randomized trials involving younger patients, clinicians should give particular emphasis to the impact of interventions on quality of life.

For patients with chest pain after cocaine use, the guidelines support the use of nitroglycerin and calcium channel blockers if they have ST segment deviations. Coronary arteriography or thrombolytic therapy should be used for patients with ST

segment elevation that persists despite these interventions.

Coronary arteriography, nitrates, and calcium channel blockers are also considered appropriate for patients with demonstrated coronary spasm (Prinzmetal's angina). The guidelines discourage provocative testing for spasm without coronary arteriography.

For patients with syndrome X (angina or angina-like discomfort with exercise, ST segment depression on treadmill testing, and normal or nonobstructed coronary arteries by arteriography), the guidelines recommend reassurance in view of the excellent long-term prognosis for these patients. To help relieve symptoms, the task force recommends medical therapy with antianginal agents, as well as risk factor reduction to help prevent the development of atherosclerotic coronary artery disease.

TABLE 36--G-4 -- HOSPITAL DISCHARGE AND POSTDISCHARGE CARE

Issue	Class	Recommendation	Level of Evidence
Hospital discharge and postdischarge care	I	Patients who do not undergo coronary revascularization, patients with unsuccessful revascularization, or patients with recurrent symptoms following revascularization should continue taking the regimen required in the hospital to control ischemia after hospital discharge	C
		Postdischarge antianginal therapy is not required for patients with successful revascularization and recurrent ischemia	C
		All patients should be given sublingual NTG and instructed in its use	C
Long-term medical therapy	I	ASA 75-160 mg/d in the absence of contraindications	A
		Beta blockers in the absence of contraindications in patients with prior MI	A
		Beta blockers in the absence of contraindications in patients without prior MI	B
		Lipid-lowering agents and diet in patients with LDL cholesterol >125 mg/dl, including after revascularization	A
		Diet for LDL >100 mg/dl	C
		Angiotensin-converting enzyme inhibitors, especially if LV dysfunction, <40% EF, or CHF is present	A
		HMG-CoA reductase inhibitors for LDL >125 mg/dl	A

Postdischarge follow-up	I	Discharge instructions should include a follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2-6 wk and higher-risk patients in 1-2 wk	C
		Patients managed initially with a conservative strategy who experience recurrent UA or severe (Canadian class III) chronic stable angina despite medical management should be considered for coronary arteriography if they are suitable for revascularization	B
		Patients who have tolerable stable angina or no anginal symptoms at follow-up visits should be managed with long-term medical therapy for stable CAD	C
Use of medication	I	Prior to hospital discharge, patients and/or designated responsible caregivers should be provided with instruction with respect to medication type, purpose, dose, frequency, and pertinent side effects that are well understood	All C
		Anginal discomfort lasting more than 2 or 3 min should prompt the patient to discontinue the activity or remove himself/herself from the stressful event. If pain does not subside immediately, the patient should be instructed to take NTG. If the first tablet or spray does not provide relief within 5 min, a second and third dose, at 5-min intervals, should be taken. Pain lasting longer than 15-20 min and persistent pain despite 3 NTG doses should prompt the patient to seek immediate medical attention by going to the nearest hospital ED, preferably by ambulance or the quickest available alternative	
		If the pattern of anginal symptoms changes (e.g., pain more frequent or severe, precipitated by less effort, or now occurring at rest), the patient should contact his/her physician to determine the need for additional treatment or testing	

Risk factor modification	I	Specific instructions should be given on	
		Smoking cessation, achievement or maintenance of optimal weight, daily exercise, and diet	B
		Cholesterol-lowering medications for LDL >125 mg/dl	A
		Diet for LDL >100 mg/dl	C
		Hypertension control	B
		Tight control of hyperglycemia in diabetics	B
		Consider referral of patients who are smokers to a smoking cessation program or clinic and/or an outpatient cardiac rehabilitation program	B
Life style issues	I	Health care providers should discuss the safety and timing of resumption of sexual activity (e.g., 1-2 wk for low-risk patients, 4 wk for post-CABG surgery patients)	C
		Beyond the instructions for daily exercise, patients require specific instructions on activities (e.g., heavy lifting, climbing stairs, yard work, household activities) that are permissible and those that should be avoided. Specific mention should be made about when they can resume driving and return to work	C

ASA=acetylsalicylic acid; CAD=coronary artery disease; CHF=congestive heart failure; ED=emergency department; EF=ejection fraction; HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A; LDL=low-density lipoprotein; LV=left ventricular; MI=myocardial infarction; NTG=nitroglycerin; UA=unstable angina.

TABLE 36--G-5 -- MANAGEMENT OF SPECIAL POPULATIONS

Issue	**Class**	**Recommendation**	**Level of Evidence**

Patients with chest pain after cocaine use	I	NTG and calcium channel blockers for patients with ST segment elevation or depression	B
		Immediate coronary arteriography, if possible, in patients whose ST segments remain elevated after NTG and calcium channel blockers. Thrombolysis (with or without PCI) if thrombus is detected	C
	IIa	IV calcium channel blockers for patients with ST segment elevation or depression	B
		Beta blockers for hypertensive patients (systolic B: >150 mm Hg) or those with sinus tachycardia (pulse >100/min)	C
		Thrombolytic therapy if ST segments remain elevated despite NTG and calcium blockers and if coronary angiography is not possible	C
		Coronary arteriography, if available, for patients with ST depression or isolated T wave changes not known to be old and who are unresponsive to NTG and calcium channel blockers	C
	III	Coronary arteriography in patients with chest pain without ST-T wave changes	C
Variant (Prinzmetal) angina	I	Coronary arteriography in patients with episodic chest pain and ST segment elevation that resolves with NTG and/or calcium channel blockers	B
		Treatment with nitrates and calcium channel blockers in patients whose coronary arteriogram is normal or shows only nonobstructive lesions	B
	IIa	In the absence of significant CAD on coronary arteriography, provocative testing with methylergonovine, acetylcholine, or methacholine when coronary spasm is suspected but there is no ECG evidence of transient ST segment elevation	B
	IIb	Provocative testing in patients with a nonobstructive lesion on coronary arteriography, a clinical picture of coronary spasm, and evidence of transient ST segment elevation	B
		Provocative testing in patients with nonobstructive lesions on coronary arteriography and a clinical picture of coronary spasm and transient ST segment depression	B
	III	Provocative testing carried out without coronary arteriography	C

	III	Provocative testing carried out without coronary arteriography	C
		Provocative testing in patients with high-grade obstructive lesions on coronary arteriography	B
Syndrome X	I	Reassurance and medical therapy with nitrates, beta blockers, and calcium channel blockers alone or in combination	B
		Risk factor reduction	C
	IIb	Intracoronary ultrasound to rule out missed obstructive lesions	B
		If no ECGs are available during chest pain and coronary spasm cannot be ruled out, coronary arteriography and provocative testing using methylergonovine, acetylcholine, or methacholine should be carried out	C
		Hormone replacement in postmenopausal women unless contraindicated	C
		Imipramine for continued pain despite Class I measures	C

BP=blood pressure; CAD=coronary artery disease; ECG=electrocardiogram; NTG=nitroglycerin; PCI=percutaneous coronary intervention.

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Chapter 37 - Chronic Coronary Artery Disease

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Chronic coronary artery disease (CAD) is most commonly due to obstruction of the coronary arteries by atheromatous plaque[1] (the pathogenesis of atherosclerosis is described in Chapter 30) . Factors that predispose to this condition are discussed in Chapter 31 , the control of coronary blood flow in Chapter 34 , acute myocardial infarction in Chapter 35 , and unstable angina in Chapter 36 ; sudden cardiac death, another significant consequence of CAD, is presented in Chapter 26 .

No uniform syndrome of signs and symptoms is initially seen in patients with CAD. Chest discomfort is usually the predominant symptom in chronic (stable) angina (see p. 1273), unstable angina (see Chap. 36) , Prinzmetal (variant) angina (p. 1324), microvascular angina (p. 1329), and acute myocardial infarction (Chap. 35) . However, syndromes of CAD also occur in which ischemic chest discomfort is absent or not prominent, such as asymptomatic (silent) myocardial ischemia (see p. 1330), congestive heart failure, cardiac arrhythmias, and sudden death (Chap. 26) . Obstructive CAD also has many nonatherosclerotic causes, including congenital abnormalities of the coronary arteries, myocardial bridging, coronary arteritis in

association with the systemic vasculitides, and radiation-induced coronary disease.[2] [3] Whether coronary ectasia is a cause of angina pectoris in the absence of coronary artery obstruction remains to be clarified.[4] Myocardial ischemia and angina pectoris may also occur in the *absence* of obstructive CAD, as in the case of aortic valve disease (see Chap. 46) , hypertrophic cardiomyopathy (Chap. 48) , and idiopathic dilated cardiomyopathy (Chap. 48) . Moreover, CAD may coexist with these other forms of heart disease.

THE MAGNITUDE OF THE PROBLEM

The importance of CAD in contemporary society is attested to by the almost epidemic number of persons afflicted--especially when this number is compared with the anecdotal reports of its occurrence in the medical literature before this century. Moreover, as the challenges posed by infectious, parasitic, and nutritional disorders and perinatal mortality are overcome, particularly in the developing world, a global epidemic of CAD looms large on the horizon (see Chap. 1) . It is estimated that 12,200,000 Americans have CAD, 6,300,000 of whom have angina pectoris and 7,200,000 have had myocardial infarction.[5] [6] The economic cost of CAD and stroke in the United States in 2000 is estimated at $326.6 billion ($118.2 billion for CAD).[5] Given the current magnitude of the problem and the increasing prevalence of CAD that is anticipated because of aging of the population, recognition, management, and prevention of CAD are of major public health importance.[5] [6]

CAD mortality rates vary widely among countries and even within a country. Recent 10-year data from the World Health Organization Monitoring of Trials and Determinants in Cardiovascular Disease (MONICA) Project in 37 different populations demonstrated a reduction in CAD events and mortality rates in most countries, but with contradictory results for a few countries, mostly in central and eastern Europe and Asia.[7] Within the United States, death rates from cardiovascular disease among black males and females are substantially higher than those among whites.[5] Among American Indians, not only do rates of CAD exceed those reported for other U.S. populations, but the disease is more often fatal.[8] However, there is encouraging evidence that in the last three decades the age-adjusted death rate from CAD, which had reached pandemic proportions in industrial countries during the middle years of the 20th century, has decreased.[9] For example, between 1961 and 1991, the age-adjusted death rate for CAD declined by 52 percent, more so in men than women.[5] Similar trends have been observed in many industrialized nations with different health care systems. Multiple causes may have contributed to this favorable trend, including a reduction in risk factors (see Chap. 31) , improvements in socioeconomic circumstances such as enhanced access to care, and new methods of diagnosis and treatment. In the United States, it has been estimated that approximately 50 percent of the decrease in CAD mortality during the last decade has resulted from reductions in primary and secondary risk factors, but the contributions from new methods of treatment are also considered substantial.[10]

Stable Angina Pectoris

CLINICAL MANIFESTATIONS

CHARACTERISTICS OF ANGINA (see also Chap. 3) .

Angina pectoris is a discomfort in the chest or adjacent areas caused by myocardial ischemia. It is usually brought on by exertion and associated with a disturbance in myocardial function, but without myocardial necrosis.[11] Heberden's initial description of the chest discomfort as conveying a sense of "strangling and anxiety" is still remarkably pertinent, although adjectives frequently used to describe this distress include "viselike," "constricting," "suffocating," "crushing," "heavy," and "squeezing." In other patients, the quality of the sensation is more vague and described as a mild pressure-like discomfort**,** an uncomfortable numb sensation, or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and usually occurs down the ulnar surface of the left arm; the right arm and the outer surfaces of both arms may also be involved[11] (see Fig. 3-2) . Epigastric discomfort alone or in association with chest pressure is not uncommon. Anginal discomfort above the mandible, below the epigastrium, or confined to the ear is rare. Anginal "equivalents" (i.e., symptoms of myocardial ischemia other than angina), such as dyspnea, faintness, fatigue, and eructations, are common, particularly in the elderly. A history of abnormal exertional dyspnea may be an early indicator of CAD even when angina is absent or no electrocardiographic (ECG) evidence of ischemic heart disease can be found.[12] Dyspnea at rest or with exertion may be a manifestation of severe ischemia and lead to increases in left ventricular filling pressure. Nocturnal angina should raise the suspicion of sleep apnea.[13]

A careful clinical history is key to making the correct diagnosis and is particularly important in this era of cost-conscious practice of medicine because it may obviate more expensive testing. If the quality of the pain and its duration, precipitating factors, and associated symptoms are taken into consideration, it is usually possible to arrive at a correct diagnosis (see Table 3-4) . The typical episode of angina pectoris usually begins gradually and reaches its maximum intensity over a period of minutes before dissipating. It is unusual for angina pectoris to reach its maximum severity within seconds, and it is characteristic that patients with angina usually prefer to rest, sit, or stop walking during episodes.[11] Chest discomfort while walking in the cold, uphill, or after a meal is suggestive of angina. Features suggesting the *absence* of angina pectoris include pleuritic pain, pain localized to the tip of one finger, pain reproduced by movement or palpation of the chest wall or arms, and constant pain lasting many hours or, alternatively, very brief episodes of pain lasting seconds. Pain radiating into the lower extremities is also a highly unusual manifestation of angina pectoris.

Typical angina pectoris is relieved within minutes by rest or by the use of nitroglycerin. The response to the latter is often a useful diagnostic tool, although it should be remembered that esophageal pain and other syndromes may also respond to nitroglycerin. A delay of more than 5 to 10 minutes before relief is obtained by rest and nitroglycerin suggests that the symptoms are either not due to ischemia or, alternatively, are due to severe ischemia, i.e., acute myocardial infarction or unstable angina. The

phenomenon of "first effort" or "warm-up" angina is used to describe the ability of some patients in whom angina develops with exertion to subsequently continue at the same level of exertion without symptoms after an intervening period of rest. This attenuation of myocardial ischemia observed with repeated exertion has been postulated to be due to ischemic preconditioning.[14]

An important component of the history is to assess the degree of cardiovascular disability caused by angina pectoris. Such assessment is a crucial part of the evaluation for coronary revascularization. Although several classifications for assessing cardiovascular disability are available,[15] the Canadian Cardiovascular Society Functional Classification System (see Table 3-11) is most widely used.[16]

MECHANISMS.

The mechanisms of cardiac pain and the neural pathways involved are poorly understood.[1] It is presumed that angina pectoris results from ischemic episodes that excite chemosensitive and mechanoreceptive receptors in the heart. Stimulation of these receptors results in the release of adenosine, bradykinin, and other substances that excite the sensory ends of the sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. Impulses are transmitted by the spinal cord to the thalamus and hence to the neocortex. Within the spinal cord, cardiac sympathetic afferent impulses may converge with impulses from somatic thoracic structures, which may be the basis for referred cardiac pain, for example, to the chest. In comparison, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to excite the upper cervical spinothalamic tract cells, which may contribute to the anginal pain experienced in the neck and jaw.[17] On the basis of positron-emission tomographic (PET) findings on changes in regional cerebral blood flow associated with angina pectoris, it has been proposed that cortical activation is necessary for pain sensation and the thalamus acts as a gate for afferent pain signals.[18]

Differential Diagnosis of Chest Pain (see Fig. 3-3 (Figure Not Available) and Table 3-4)

Differentiation of various disorders from CAD is challenging because the severity of the chest pain and the seriousness of the underlying disorder are not necessarily related. Compounding the difficulty in differential diagnosis is the common myth that pain in the left arm or left side of the chest is an ominous sign signifying the presence of CAD. However, a host of other disorders can also cause discomfort in these locations.

ESOPHAGEAL DISORDERS.

The common esophageal disorders that may simulate or coexist with angina pectoris are gastroesophageal reflux and disorders of esophageal motility, including diffuse spasm as well as "nutcracker" esophagus, which is characterized by high-amplitude peristaltic contractions and vigorous achalasia.[19] Symptomatic esophageal reflux is common and estimated to occur in 7 to 14 percent of an otherwise "healthy" U.S.

population. In a comparative study of patients with chest pain and normal coronary angiograms and controls with confirmed CAD, esophageal function testing (including manometry, provocation tests, and 24-hour ambulatory pH monitoring) commonly implicated the esophagus as a cause of pain in patients with normal coronary angiograms. Nonetheless, a similar high frequency of esophageal abnormalities among patients with angina pectoris suggests that the esophagus may be an unrecognized source of pain in both groups of patients.[19] Further evidence of a relationship between esophageal abnormalities and angina pectoris was provided by a prospective study demonstrating that esophageal acid stimulation can cause anginal attacks in association with a significant reduction in coronary blood flow in patients with CAD.[20] A lack of any significant effect in this study in heart transplant recipients with cardiac denervation suggests a neural origin.

The classic manifestation of esophageal pain is "heartburn," particularly in connection with changes in posture and meals and in association with dysphagia. Esophageal spasm may also cause constant retrosternal discomfort of uniform intensity or severe spasmodic pain during or after

swallowing. To further compound the difficulty in distinguishing between angina and esophageal pain, both may be relieved by nitroglycerin. However, esophageal pain is often relieved by milk, antacids, foods, or, occasionally, warm liquids.

GASTROESOPHAGEAL REFLUX.

The esophageal acid perfusion, or Bernstein, test may be helpful in its use of alternate infusions of dilute acid and normal saline by a nasal gastric catheter with the tip placed at the level of the midesophagus.[19] Infusion of acid produces pain in over 90 percent of patients with subjective and objective evidence of gastroesophageal acid reflux, but it is particularly useful if the patient's symptoms are reproduced. Acid reflux into the esophagus can also be recognized by recording the pH from an electrode at the tip of a catheter inserted into the distal portion of the esophagus.

ESOPHAGEAL MOTILITY DISORDERS.

Esophageal motility disorders are not uncommon in patients with retrosternal chest pain of unclear cause and should be specifically excluded or confirmed, if possible.[21] In addition to chest pain, the majority of such patients have dysphagia. Although barium studies may reveal motility problems, esophageal manometry may show diffuse esophageal spasm, increased pressure at the lower esophageal sphincter, and other motility disorders. Provocative pharmacological agents such as methacholine may provoke esophageal pain and manometric signs of spasm.

A more complex problem is determining whether part or all of the symptoms in patients with *known* CAD are due to esophageal disease. Both CAD and esophageal disease

are common clinical entities that may coexist. Diagnostic evaluation for an esophageal disorder may be indicated in patients with CAD who have a poor symptomatic response to antianginal therapy in the absence of documentation of severe ischemia or in patients with persistent symptoms despite adequate coronary revascularization.

BILIARY COLIC.

Although visceral symptoms are a common association of myocardial ischemia (particularly acute inferior myocardial infarction [see Chap. 35]), cholecystitis and related hepatobiliary disorders may also mimic ischemia and should always be considered in patients with atypical chest discomfort, particularly those with diabetes.[22] The pain is steady, usually lasts 2 to 4 hours, and subsides spontaneously without any symptoms between attacks. It is generally most intense in the right upper abdominal area but may also be felt in the epigastrium or precordium. This discomfort is often referred to the scapula, may radiate around the costal margin to the back, or may in rare cases be felt in the shoulder and suggest diaphragmatic irritation. Ultrasonography is accurate in diagnosing gallstones and allows determination of gallbladder size and thickness and whether the bile ducts are dilated.

COSTOSTERNAL SYNDROME.

In 1921, Tietze first described a syndrome of local pain and tenderness, usually limited to the anterior chest wall and associated with swelling of costal cartilage. This condition causes pain that can resemble angina pectoris. The full-blown Tietze syndrome, i.e., pain associated with tender *swelling* of the costochondral junctions, is uncommon, whereas costochondritis causing tenderness of the costochondral junctions (without swelling) is relatively common.[23] Pain on palpation of these joints is a useful clinical sign. Local pressure should be applied routinely to the anterior chest wall during examination of a patient with suspected angina pectoris. In addition, costochondritis is usually well localized. Although palpation of the chest wall often reproduces pain in patients with various musculoskeletal conditions, it should be appreciated that chest wall tenderness may also be associated with and does not exclude symptomatic CAD.[24]

OTHER MUSCULOSKELETAL DISORDERS.

Cervical radiculitis may be confused with angina. This condition may occur as a constant ache, sometimes resulting in a sensory deficit. The pain may be related to motion of the neck, just as motion of the shoulder triggers attacks of pain from bursitis. A hyperalgesic area noted by running the finger down the back and exerting pressure may lead to a suspicion of thoracic root pain. Occasionally, pain mimicking angina can be due to compression of the brachial plexus by the cervical ribs**,** and tendinitis or bursitis involving the left shoulder may also cause angina-like pain. Physical examination may also detect pain brought about by movement of an arthritic shoulder or a calcified shoulder tendon.

OTHER CAUSES OF ANGINA-LIKE PAIN.

Acute myocardial infarction is usually associated with prolonged (>30 minutes), severe pain occurring at rest that apart from duration and intensity, may be similar to angina pectoris. It is associated with characteristic ECG changes and the release of cardiac markers (see Chap. 35) . Unstable angina is a severe form of angina that may also occur at rest and may not be relieved by nitroglycerin (see Chap. 36) .

The classic symptom of *dissecting aortic aneurysm* is a severe, often sharp pain that radiates to the back (see Chap. 40) . Although aortic dissection is generally part of the differential diagnosis of acute myocardial infarction, the syndrome may be chronic in some patients. The pain is often described as sharp, but its pleuropericarditic quality is usually helpful in the differential diagnosis.

Severe pulmonary hypertension may be associated with exertional chest pain with the characteristics of angina pectoris, and indeed, this pain is thought to be due to right ventricular ischemia that develops during exertion (see Chap. 53) . Other associated symptoms include exertional dyspnea, dizziness, and syncope. Associated findings on physical examination, such as parasternal lift, a palpable and loud pulmonary component of the second sound, and right ventricular hypertrophy on the ECG, are usually readily recognized.

Pulmonary embolism is initially characterized by dyspnea as the cardinal symptom, but chest pain may also be present (see Chap. 52) . Pleuritic pain suggests pulmonary infarction, and a history of exacerbation of the pain with inspiration, along with a pleural friction rub, usually helps distinguish it from angina pectoris.

The pain of *acute pericarditis* (see Chap. 50) may at times be difficult to distinguish from angina pectoris. However, pericarditis tends to occur in younger patients than does angina, and the diagnosis depends on the combination of chest pain not relieved by rest or nitroglycerin, a pericardial friction rub, and ECG changes.

Chronic CAD can and frequently does coexist with any of the other disorders mentioned above, and noncardiac disease can trigger a true angina attack in a patient with CAD. An additional component of the history is an evaluation of risk factors for CAD because such risk factors in turn have an effect on both the probability of significant obstructive CAD and the overall prognosis.[25]

Physical Examination

GENERAL EXAMINATION.

Inspection of the eyes may reveal a *corneal arcus*, and examination of the skin may show xanthomas (see Fig. 4-2) . Among patients with heterozygous familial hypercholesterolemia (in whom CAD is common), the presence of a corneal arcus increases with age and, in some studies, correlates positively with levels of cholesterol and low-density lipoprotein (LDL) and also with the prognosis.[26] [27] *Xanthelasma*, in which lipid deposits are intracellular, appears to be promoted by increased levels of

triglycerides and a relative deficiency of high-density lipoprotein (HDL). The presence of xanthelasma is a strong marker of dyslipidemia and, often, a family history of cardiovascular disease, and should provide a strong impetus for performing a comprehensive lipid profile.[28] Retinal arteriolar changes are common in patients with CAD and diabetes mellitus or hypertension. Moreover, diabetes-associated visual impairments, including retinopathy, are independent predictors of increased mortality from all causes, including CAD.[29]

Some correlation has been noted between CAD and a *diagonal earlobe crease* (except in American Indians and Asians). A unilateral diagonal earlobe crease is often present in younger persons with CAD and becomes bilateral with advancing age.[30] A hospital-based, case-control study of men admitted with a first nonfatal myocardial infarction demonstrated that the presence of a diagonal earlobe crease was associated with a relative risk of 1.37 for myocardial infarction; the risk is similarly increased in the presence of baldness and thoracic hairiness.[31]

Blood pressure may be chronically elevated or may rise acutely (along with the heart rate) during an angina attack. Changes in blood pressure may precede (and precipitate) or follow (and be caused by) angina.

Other important features of the general physical examination are abnormalities in arterial pulses and the venous system. A rapid pulse may be a clue to cardiac decompensation

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or to a systemic condition such as thyrotoxicosis or anemia, which can exacerbate angina pectoris. The association between peripheral vascular disease and CAD is strong and well documented.[32] [33] This association is not confined to patients with symptomatic or clinically overt peripheral vascular disease or CAD but is also seen in asymptomatic subjects with a reduced ankle-brachial blood pressure index or evidence of early carotid disease on ultrasonography.[34] The presence of carotid and peripheral arterial disease on palpation and auscultation increases the likelihood that chest discomfort of unclear origin is caused by CAD. Evaluation of the patient's venous system, particularly in the legs, may have an important bearing on the type of grafting procedure used in subsequent coronary bypass surgery.

CARDIAC EXAMINATION.

The physical findings of hypertrophic cardiomyopathy (see Chap. 48) or aortic valve disease (Chap. 46) suggest that angina may be due to conditions other than (or in addition to) CAD. It is often helpful to examine the heart *during* an episode of pain because ischemia may produce transient left ventricular dysfunction with a third heart sound and pulmonary rales detectable on physical examination.[35] If massage of the carotid sinus produces pain relief in a patient without a carotid bruit, the pain is probably anginal. Softening of the mitral component of the first heart sound as a result of

ischemic left ventricular dysfunction may also be demonstrated during angina. Paradoxical splitting of the second heart sound (see Chap. 4) may occur transiently during angina and appears to be related to asynergy and prolongation of left ventricular contraction, which results in delayed closure of the aortic valve. If other obvious cardiac diseases are absent, a third or loud fourth heart sound suggests ischemia as the basis for the chest pain. These sounds are common in patients with angina at rest, and their frequency is increased during handgrip exercise,[36] even if the latter does not precipitate angina pectoris. A sustained apical cardiac impulse is common in patients with moderate or severe left ventricular dysfunction. A displaced ventricular impulse, particularly if dyskinetic, is a sign of significant left ventricular systolic dysfunction, especially in a patient who previously had a myocardial infarction.

Transient apical systolic murmurs are quite common in CAD and have been attributed to reversible papillary muscle dysfunction secondary to transient myocardial ischemia. When persistent, such murmurs may be due to papillary muscle fibrosis, which is often a manifestation of subendocardial infarction or a regional wall motion abnormality altering the alignment of the papillary muscles in relation to other components of the mitral valve apparatus. These murmurs are more prevalent in patients with extensive CAD, especially those with prior myocardial infarction and left ventricular dysfunction, and may indicate an adverse prognosis.[37] Systolic murmurs may assume a variety of configurations (early, late, or holosystolic) and may be accentuated by exertion or during angina. A midsystolic click, often followed by a late systolic murmur produced by mitral valve prolapse (see Chap. 46) , also occurs in patients with CAD. A diastolic murmur or a continuous murmur is a rare finding in CAD and has been attributed to turbulent flow across a proximal coronary artery stenosis.[38]

PATHOPHYSIOLOGY

Angina pectoris results from myocardial ischemia, which is caused by an imbalance between myocardial O_2 requirements and myocardial O_2 supply.[1] The former may be elevated by increases in heart rate, left ventricular wall stress, and contractility (see Chap. 34) ; the latter is determined by coronary blood flow and coronary arterial O_2 content (Fig. 37-1) .

ANGINA CAUSED BY INCREASED MYOCARDIAL C_2 REQUIREMENTS.

In this condition, sometimes termed "demand angina," the myocardial O_2 requirement increases in the face of a constant and usually restricted O_2 supply. The increased requirement commonly stems from norepinephrine release by adrenergic nerve endings in the heart and vascular bed, a physiological response to exertion, emotion, or mental stress. Of great importance to the myocardial O_2 requirement is the *rate* at which any task is carried out. Hurrying is particularly likely to precipitate angina, as are efforts involving motion of the hands over the head. Mental stress may also precipitate angina, presumably by increased hemodynamic and catecholamine responses to stress, increased adrenergic tone, and reduced vagal activity.[39] [40]

Figure 37-1 Factors influencing the balance between myocardial O_2 requirements *(left)* and supply *(right)*. Arrows indicate effects of nitrates. In relieving angina pectoris, nitrates exert favorable effects by reducing O_2 requirements and increasing supply. Although a reflex increase in heart rate would tend to reduce the time for coronary flow, dilation of collaterals and enhancement of the pressure gradient for flow to occur as the left ventricular end-diastolic pressure (LVEDP) falls tend to increase coronary flow. A_o P=aortic pressure; NC=no change. *(From Frishman WH: Pharmacology of the nitrates in angina pectoris. Am J Cardiol 56:8I, 1985. By permission of Excerpta Medica.)*

The combination of physical exertion and emotion in association with sexual activity commonly precipitates angina pectoris, but sexual activity seldom triggers myocardial infarction.[41] Anger may produce constriction of coronary arteries with preexisting narrowing without necessarily affecting O_2 demand. Other factors causing angina secondary to an increase in myocardial O_2 requirement in patients with obstructive CAD include physical exertion after a heavy meal and the excessive metabolic demands imposed by chills, fever, thyrotoxicosis, tachycardia from any cause, and hypoglycemia. Among patients with stable, fixed obstructive CAD, several studies using ambulatory ECG monitoring have documented the importance of increases in myocardial O_2 requirement and, in particular, tachycardia as a precipitant of ischemia. [42]

In all these conditions, underlying coronary artery obstruction is usually present, and the other factors (e.g., exertion, emotion, or fever) precipitate ischemia and chest discomfort by stimulating myocardial O_2 need in the presence of a relatively fixed and limited myocardial O_2 supply.

ANGINA CAUSED BY TRANSIENTLY DECREASED C_2 SUPPLY.

Increasing evidence suggests that not only unstable angina but also chronic stable angina may be caused by transient reductions in O_2 supply as a consequence of coronary vasoconstriction, [1] [43] a condition that is sometimes termed "supply angina" and due to the entity of "dynamic stenosis." [44] The coronary arterial bed is well innervated, and a variety of stimuli alter coronary tone (see Chap. 34) . Two main explanations have been offered for the association between coronary vasoconstriction and spasm in the presence of organic stenoses. First, platelet thrombi and leukocytes may elaborate vasoconstrictor substances such as serotonin and thromboxane A_2 . Second, endothelial damage in atherosclerotic coronary arteries may result in decreased production of vasodilator substances and an abnormal vasoconstrictor response to exercise and other stimuli. A variable threshold of myocardial ischemia in patients with chronic stable angina may be due to dynamic changes in peristenotic smooth muscle tone and also to constriction of arteries distal to the stenosis.[45] In this setting, calcium antagonists and nitrates are less effective than in patients with variant angina, perhaps because of the nature of the constricting stimuli and the site of

constriction.[45]

Patients with angina precipitated by a transient reduction in myocardial O_2 supply may have a spectrum of signs and symptoms that depend on the severity of the underlying fixed defect and the degree of the dynamic change in coronary arterial tone. In a typical patient with chronic stable angina, the degree of fixed obstruction is sufficient to result in an inadequate coronary flow rate to cope with the increased O_2 demands of exercise. However, episodes of transient coronary vasoconstriction may be superimposed on this inadequate flow rate and cause additional limitations to coronary flow reserve in many patients.

In rare patients without organic obstructing lesions, severe dynamic obstruction occurring at rest alone can cause myocardial ischemia and result in angina (see Prinzmetal [Variant] Angina, p. 1324). On the other hand, in patients with severe fixed obstruction to coronary blood flow, only a minor increase in dynamic obstruction is necessary for blood flow to fall below a critical level and cause myocardial ischemia.

FIXED COMPARED WITH VARIABLE-THRESHOLD ANGINA.

The threshold for angina differs widely among patients with chronic angina. In patients with fixed-threshold angina precipitated by increased O_2 demands with few if any dynamic (vasoconstrictor) components, the level of physical activity required to precipitate angina is relatively constant. Characteristically, these patients can predict the amount of physical activity that will precipitate angina, e.g., walking up exactly two flights of stairs at a customary pace. When these patients are tested on a treadmill or bicycle, the pressure-rate product (the so-called double product, a correlate of the myocardial O_2 requirement) that elicits angina and/or ECG evidence of ischemia is relatively constant.

In patients with fixed-threshold, demand angina, the specific threshold at which ischemia develops (as reflected in angina and/or ST segment depression) is a function of the myocardial O_2 requirement. As the activity of the left ventricle (and therefore its O_2 requirement) increases, a point is reached at which perfusion distal to a critical coronary arterial obstruction cannot supply sufficient O_2 to myocardium perfused by the obstructed artery; ischemia and angina ensue. This relationship is, however, modified by the effects of coronary vasomotor tone on myocardial O_2 supply.[46] Coronary vascular reserve (or coronary vasodilator or flow reserve) is impaired in patients with significant obstructive CAD and also in those with microvascular disease or endothelial damage from conditions such as hypertension.[47]

The majority of patients with variable-threshold angina have atherosclerotic coronary arterial narrowing, but dynamic obstruction caused by vasoconstriction plays an important role in causing myocardial ischemia. These patients typically have "good days," when they are capable of substantial physical activity, as well as "bad days," when even minimal activity can cause clinical and/or ECG evidence of myocardial ischemia or angina at rest. Often, even in the course of a single day, they may be

capable of substantial physical activity at one time while minimal activity results in angina at another. Patients with variable-threshold angina often complain of a circadian variation in angina that is more common in the morning. Angina on exertion and sometimes even at rest may be precipitated by cold temperature,[48] emotion, and mental stress.[49] A cold environment has been shown to increase peripheral resistance, both at rest and during exercise.[50] The rise in arterial pressure, by augmenting myocardial O_2 requirements, lowers the threshold for the development of angina. An alternative or additional explanation is the development of cold-induced coronary vasoconstriction via activation of peripheral and reflex mechanisms.[50]

The entity of postprandial angina has been recognized for about two centuries and may be a marker of severe multivessel CAD.[51] The mechanism has not been explained, but it may be due to redistribution of coronary blood flow away from the territory supplied by severely stenosed vessels.[52] Some evidence indicates that this phenomenon is more prominent after high-carbohydrate than high-fat meals.[51]

MIXED ANGINA.

The term *mixed angina* has been proposed by Maseri and colleagues to describe the many patients who fall between the two extremes of fixed-threshold and variable-threshold angina.[53] The pathophysiological and clinical correlations of ischemia in patients with stable CAD may have important implications for the selection of antiischemic agents, as well as for their timing. The greater the contribution from increased myocardial O_2 requirements to the imbalance between supply and demand, the greater the likelihood that beta-blocking agents will be effective, whereas nitrates and calcium channel blocking agents, at least on theoretical grounds, are likely to be especially effective in episodes caused primarily by coronary vasoconstriction. The finding that in most patients with chronic stable angina an increase in myocardial O_2 requirement precedes episodes of ischemia, i.e., that they have demand angina, argues in favor of beta blockers as essential therapeutic agents.[54]

GRADING OF ANGINA PECTORIS.

A system of grading the severity of angina pectoris proposed by the Canadian Cardiovascular Society has gained widespread acceptance[16] (see Table 3-11) . The system is a modification of the New York Heart Association functional classification but allows patients to be categorized in more specific terms. Other grading systems include a specific activity scale developed by Goldman and associates[15] and an anginal "score" developed by Califf and colleagues.[55] The Goldman scale is based on the metabolic cost of specific activities and appears to be valid when used by both physicians and nonphysicians. The anginal score of Califf and coworkers integrates the clinical features and "tempo" of angina together with ECG ST and T wave changes and offers independent prognostic information above that provided by age, gender, left ventricular function, and coronary angiographic anatomy. A limitation of all these grading systems is their dependence on accurate patient observation and patients' widely varying tolerance for symptoms. Prospective evaluation of the reproducibility of the New York Heart Association estimates of functional class made by two physicians demonstrated a

reproducibility of only 56 percent, and only 51 percent of the estimates agreed with treadmill exercise performance. Functional estimates based on the Canadian Cardiovascular Society criteria were more reproducible (73 percent) but still did not correlate well with objective measures of exercise performance.[15]

TABLE 37-1 -- PRETEST LIKELIHOOD OF CORONARY ARTERY DISEASE IN SYMPTOMATIC PATIENTS ACCORDING TO AGE AND SEX*

AGE (yr)	NONANGINAL CHEST PAIN		ATYPICAL ANGINA		TYPICAL ANGINA	
	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

From Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). J Am Coll Cardiol 33:2092, 1999. By permission of The American College of Cardiology and The American Heart Association.

*Each value represents the percentage with significant coronary artery disease on catheterization (combined data from Diamond and Forrester[56] and Chaitman et al. [59]).

CORRELATION BETWEEN HISTORICAL FEATURES AND CORONARY ANGIOGRAPHY.

An important objective of the history and physical examination is to acquire information that can be used to estimate the probability of the presence of obstructive CAD. The importance of this point is emphasized by the impact of the pretest likelihood of CAD on the performance of a standard exercise test.[35] The ability to predict the probability of CAD with reasonable accuracy from the history and physical examination was demonstrated originally by Diamond and Forrester and expanded on by other studies in both men and women referred for cardiac catheterization or stress testing.[56] [57] [58] The inclusion of such risk factors as cigarette smoking, hyperlipidemia, and diabetes mellitus strengthens the predictability of these models, as do certain changes on the ECG.[57] Subsequently, the Diamond and Forrester model was shown to be in strong agreement with the findings of the Coronary Artery Surgery Study (CASS).[59] The joint American College of Cardiology and American Heart Association (ACC/AHA) Guidelines

Committee[35] combined data from both studies to illustrate the pretest likelihood of CAD in men and women stratified by age and nature of the chest pain (Table 37-1) .

Although the clinical manifestations of CAD, including rest angina and nocturnal and postprandial angina, tend to be more severe in patients with multivessel than single-vessel disease, neither the severity, duration, or nature of the pain nor its precipitating factors correlate with the extent of disease at angiography. Perhaps the most striking example of the lack of historical-arteriographic correlation is in two subgroups of patients--those with advanced obstructive CAD who are asymptomatic with "silent ischemia" (see p. 1330 and those with Prinzmetal, or variant, angina, who may have episodes of very severe anginal discomfort, yet have minimal or no underlying coronary atherosclerosis (see p. 1324).

NONINVASIVE TESTING

Biochemical Tests

In patients with chronic stable angina, metabolic abnormalities that are risk factors for the development of CAD are frequently detected. These abnormalities include hypercholesterolemia and other dyslipidemias (see Chap. 31) , carbohydrate intolerance, and insulin resistance.[60] [61] All patients with established or suspected CAD warrant biochemical evaluation of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and fasting blood glucose.[62] New biochemical markers, such as C-reactive protein, lipoprotein Lp(a), and homocysteine, have been shown to increase the likelihood of future cardiovascular events,[63] [64] [65] especially in patients with hypercholesterolemia, but no consensus has been reached regarding routine measurement of these markers, and measuring them is not generally recommended.[66]

Serum levels of cardiac markers are normal in patients with chronic stable angina, which serves to differentiate them from patients with acute myocardial infarction.

Resting Electrocardiogram (see also Chap. 5)

The resting ECG is normal in approximately half of patients with chronic stable angina pectoris, and even patients with severe CAD may have a normal tracing at rest. A normal resting ECG suggests the presence of normal resting left ventricular function[67] and is an unusual finding in a patient with an extensive previous infarction. The most common ECG abnormalities in patients with chronic CAD are nonspecific ST-T wave changes with or without abnormal Q waves. Numerous pitfalls must be avoided when using the *resting* ECG for the diagnosis of myocardial ischemia. In addition to myocardial ischemia, other conditions that can produce ST-T wave abnormalities include left ventricular hypertrophy and dilatation, electrolyte abnormalities, neurogenic effects, and antiarrhythmic drugs.[68] In patients with known CAD, however, the occurrence of ST-T wave abnormalities on the resting ECG may correlate with the severity of the underlying heart disease, including the number of vessels involved and the presence of left ventricular dysfunction.[69] This association may explain the adverse impact of ST-T wave changes on prognosis in these patients. In contrast, a normal

resting ECG is a more favorable long-term prognostic sign in patients with suspected or definite CAD.[35] [70]

Interval ECGs may reveal the development of Q wave infarctions that have gone unrecognized clinically. Various conduction disturbances, most frequently left bundle branch block and left anterior fascicular block, may occur in patients with chronic stable angina, and they are often associated with impairment of left ventricular function[71] and reflect multivessel disease and previous myocardial damage. Hence, such conduction disturbances are an indicator of a relatively poor prognosis.[35] In patients with chronic stable angina, abnormal Q waves are relatively specific, but insensitive indicators of previous myocardial infarction. Various arrhythmias, especially ventricular premature beats, may be present on the ECG, but they too have low sensitivity and specificity for CAD.

Ambulatory ECG monitoring has shown that many patients with symptomatic myocardial ischemia also have episodes of silent ischemia that would otherwise go unrecognized during normal daily activities (see p. 1330). Although this form of ECG testing provides a quantitative estimate of the frequency and duration of ischemic episodes during routine activities, its sensitivity for detecting CAD is less than that of exercise ECG.

Left ventricular hypertrophy on the ECG is a poor prognostic factor in patients with chronic stable angina. This finding should suggest the presence of underlying hypertension, aortic stenosis, or hypertrophic cardiomyopathy and warrants further evaluation, such as echocardiography to assess left ventricular size, wall thickness, and function.

During an episode of angina pectoris, the ECG becomes abnormal in 50 percent or more of patients with normal resting ECGs. The most common finding is ST segment depression, although ST segment elevation and normalization of previous resting ST-T wave depression or inversion ("pseudonormalization") may develop.

Noninvasive Stress Testing (see also Chap. 13)

Noninvasive stress testing can provide useful and often indispensable information to establish the diagnosis and estimate the prognosis in patients with chronic stable angina.[35] [72] However, several studies have emphasized that the indiscriminate use of such tests may provide limited *incremental* information over and above that provided by the physician's detailed and thoughtful clinical assessment.[35] [57] [73] [74] [75] [76] Appropriate application of noninvasive tests requires consideration of Bayesian principles (see Chap. 6) . These principles state that the reliability and predictive accuracy of any test is defined not only by its sensitivity and specificity but also by the prevalence of disease (or pretest probability) in the population under study.

In an era of emphasis on cost-effectiveness, optimal utilization of testing requires an

assessment of the *incremental* amount of information provided by a test, over and above what can be obtained from standard clinical variables alone. Noninvasive testing should be performed only if the test result will alter the planned management strategy. The value of noninvasive stress testing is greatest when the pretest likelihood is intermediate because the test result will have the greatest effect on the posttest probability of CAD and, hence, on clinical decision-making in this group of patients.

Exercise Electrocardiography (see also Chap. 6)

DIAGNOSIS OF CORONARY ARTERY DISEASE.

As a screening test for CAD, the exercise ECG is useful in that it is relatively simple and inexpensive. It is particularly helpful in patients with chest pain syndromes who are considered to have a moderate probability of CAD and in whom the resting ECG is normal, provided that they are capable of achieving an adequate workload.[77] Although the incremental diagnostic value of exercise testing is limited in patients in whom the estimated prevalence of CAD is either high or low, the test provides useful, additional information about the degree of functional limitation in both groups of patients and about the severity of ischemia and prognosis in patients with a high pretest probability of CAD.[35] [78] [79]

The exercise ECG variable most useful for the detection of CAD and, in particular, multivessel disease is the ST segment shift during exercise and recovery.[78] [80] The sensitivity of the ST segment response increases with age, with the severity of CAD, and with the magnitude of the ST segment change itself (see Fig. 6-7) .[35] The predictive value for the detection of CAD is 90 percent if typical chest discomfort occurs during exercise along with horizontal or downward-sloping ST segment depression of 1 mm or more. ST segment depression of 2 mm or more accompanied by typical chest discomfort is virtually diagnostic of significant CAD.[80] In the absence of typical angina pectoris, downsloping or horizontal ST segment depression of 1 mm or more has a predictive value of 70 percent for the detection of significant coronary stenosis, but the predictive value increases to 90 percent with ST segment depression of 2 mm or more. The early onset of ST segment depression during exercise, its long persistence following discontinuation of exercise, a downsloping or horizontal depression, and a low work capacity or exercise duration are all strongly associated with multivessel disease. Exercise-induced QRS prolongation also appears to be a function of exercise-induced ischemia[81] and is related to the extent of exercise-induced segmental contraction abnormalities.

A meta-analysis of 147 published studies involving more than 24,000 patients was performed in the process of establishing the ACC/AHA Guidelines on Exercise Testing.[78] Wide variability in sensitivity and specificity was reported, with a mean sensitivity of 68 percent and mean specificity of 77. The results of stress testing often influence the subsequent decision for angiography and create a posttest referral bias that tends to inflate sensitivity and decrease specificity.[82] When meta-analyses are restricted to studies designed to avoid such work-up bias, the sensitivity is only 45 to 50 percent but the specificity is 85 to 90 percent.[78]

A major factor contributing to the low sensitivity of exercise ECG is that many patients are incapable of reaching the level of exercise required for near-maximal effort (85 percent or more of the maximal predicted heart rate), particularly those receiving beta-adrenergic blockers, those in whom fatigue, leg cramps, or dyspnea develops, and those with musculoskeletal symptoms. ST segment changes have low specificity in patients taking digitalis and those with left ventricular hypertrophy and repolarization abnormalities. ST segment changes cannot be interpreted when patients have left bundle branch block, Wolff-Parkinson-White syndrome, or an artificial pacemaker. In these subsets of patients, noninvasive *imaging* with exercise or pharmacological stress testing or diagnostic coronary angiography may be indicated.

INFLUENCE OF ANTIANGINAL THERAPY.

Antianginal pharmacological therapy reduces the sensitivity of exercise testing as a screening tool. Beta blockade increases the exercise duration and suppresses, diminishes, or delays the appearance of ST segment depression and thus obscures the diagnostic interpretation of exercise testing.[78] [83] Because beta blockade reduces the sensitivity of the test, a negative exercise test in patients receiving antianginal drugs does not exclude significant and possibly life-threatening myocardial ischemia.

Therefore, if the purpose of the exercise test is to diagnose ischemia, it should be performed, if possible, in the absence of antianginal medications. However, the advisability of withholding medications in an individual patient before exercise testing is a matter of judgment. Two or 3 days are required for patients receiving long-acting beta blockers. Unless the patient has severe angina, sublingual nitroglycerin for 1 or 2 days is likely to be sufficient to control symptoms if other therapy is withdrawn. For long-acting nitrates, calcium antagonists, and short-acting beta blockers, discontinuing use of the medications the day before testing usually suffices. If the purpose of the exercise test is to identify safe levels of daily activity or the extent of functional disability, the test should be performed while the patient is taking the usual medications.

Nuclear Cardiology Techniques (see Chap. 9)

STRESS MYOCARDIAL PERFUSION IMAGING.

Exercise perfusion imaging incorporates all the components of the exercise ECG with images of myocardial blood flow by using either thallium-201 or a technetium-99m (^{99m}Tc)-based perfusion tracer. [84] The radionuclide is injected intravenously at peak exercise or at a symptom-limited endpoint, such as angina pectoris or dyspnea; the patient is encouraged to exercise for another 30 to 45 seconds to ensure that initial myocardial uptake of the tracer reflects the perfusion pattern at peak stress. Acquisition of the stress images is performed several minutes later when the patient is at rest. A separate image acquisition is obtained at rest to compare the stress images with images of resting perfusion. Reversible perfusion defects between stress and rest indicate exercise-induced ischemia, whereas irreversible defects usually represent regions of myocardial fibrosis (see Fig. 9-12) . In the case of thallium-201, a stress-redistribution

protocol is usually followed, in which rest images are obtained 3 to 4 hours after the stress test without a second injection of tracer. More rapid washout rates of thallium from normal versus ischemic myocardium produce apparent filling in of perfusion defects caused by reversible ischemia, a process termed "redistribution." With ^{99m} Tc perfusion tracers, which do not redistribute appreciably, two separate injections are required, one during stress and the other at rest. This technique can be accomplished by using either 1-day or 2-day imaging protocols.[84] [85]

A hybrid dual-isotope protocol has evolved in which both thallium and a ^{99m} Tc tracer are used. [86] [87] The lower-energy thallium is injected at rest and imaged, followed immediately by stress imaging with the higher-energy, ^{99m} Tc-labeled compound. This latter procedure can be accomplished within 90 minutes and has the advantage of requiring a much shorter time for completing the study than with standard thallium stress-redistribution or ^{99m} Tc stress-rest imaging protocols.

Exercise perfusion imaging with simultaneous ECG is

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superior to exercise ECG alone in detecting CAD, in identifying multivessel disease, in localizing diseased vessels, and in determining the magnitude of ischemic and infarcted myocardium (see also Chap. 13) . The published results of exercise single-proton emission computed tomographic (SPECT) imaging involving more than 5200 patients with angiographic documentation of the presence or absence of CAD yield an average sensitivity and specificity of 89 and 76 percent, respectively (range, 71 to 98 percent and 43 to 92 percent, respectively).[35] Referral bias may account, in part, for the low specificity of many studies, and the few studies that adjusted for referral bias report a specificity higher than 90 percent.[35] The results with thallium-201 are comparable to those obtained with ^{99m} Tc-sestamibi or ^{99m} Tc-tetrofosmin, so these agents can in general be used interchangeably for the diagnosis of CAD.

Perfusion imaging is valuable for detecting myocardial viability in patients with regional or global left ventricular dysfunction, with or without Q waves[88] [89] (see Chap. 13) . Stress perfusion imaging also provides important information in regard to prognosis.[74] [75] [90] [91]

Stress myocardial scintigraphy is particularly helpful in the diagnosis of CAD in patients with abnormal resting ECGs and those in whom ST segment responses cannot be interpreted accurately, such as patients with left ventricular hypertrophy and repolarization abnormalities, those with left bundle branch block, and those receiving digitalis. Because stress myocardial perfusion imaging is a relatively expensive test (three to four times the cost of an exercise ECG), certain issues should be considered: (1) a regular exercise ECG should always be considered first in patients with chest pain and a normal resting ECG for screening and detection of CAD[35] [78] ; (2) stress myocardial perfusion scintigraphy should *not* be used as a screening test in patients in whom the prevalence of CAD is low because the majority of abnormal tests will be

false-positive results; (3) stress perfusion imaging is more sensitive in detecting CAD, especially in patients with single-vessel CAD, than exercise ECG[35] [84] ; (4) perfusion imaging is more accurate in patients with resting ECG abnormalities and those receiving digitalis; and (5) perfusion imaging is more accurate in localizing and quantifying regions of myocardial ischemia, which is of particular importance in patients who previously had revascularization, and in determining the extent of viable myocardium in patients with left ventricular dysfunction.

PHARMACOLOGICAL NUCLEAR STRESS TESTING.

For patients unable to exercise adequately, especially the elderly and patients with peripheral vascular disease, pulmonary disease, arthritis, or a previous stroke, pharmacological vasodilator stress with dipyridamole or adenosine may be used.[84] [92] [93] In most nuclear cardiology laboratories, such patients account for approximately 40 percent of those referred for perfusion imaging. A comparison of 2000 patients undergoing adenosine and dipyridamole pharmacological stress testing demonstrated that adverse effects occurred less often with dipyridamole than with adenosine.[94] However, the effects of adenosine are very brief, whereas those associated with dipyridamole are more difficult to manage and necessitate longer monitoring time, as well as fairly frequent intravenous administration of aminophylline for reversal. In patients with asthma, dobutamine stress perfusion imaging is a useful and safe alternative to vasodilator stress imaging,[95] but adenosine and dipyridamole are more sensitive for detecting CAD because they produce a greater increase in coronary blood flow.[96] Although the diagnostic accuracy of pharmacological vasodilator stress perfusion imaging is comparable to that achieved with exercise perfusion imaging,[97] treadmill testing is preferred for patients who are capable of exercising because the exercise component of the test provides additional diagnostic information about ST segment changes, effort tolerance and symptomatic response, and heart rate and blood pressure response.

EXERCISE RADIONUCLIDE ANGIOGRAPHY.

The use of radionuclide angiography for detecting and estimating prognosis in CAD has been supplanted largely by exercise echocardiography. Although radionuclide angiography is more accurate than echocardiography in measuring the ejection fraction, failure to augment the ejection fraction with exercise is a nonspecific finding that is influenced by age, gender, and the presence of hypertension. The addition of radionuclide ventriculography in patients with a normal ECG at rest adds little to the diagnostic information provided by clinical and other exercise variables.[84] Echocardiography provides a more accurate assessment of exercise-induced changes in regional wall motion and systolic wall thickening, which are more specific markers of reversible ischemia than are changes in ejection fraction.

Stress Echocardiography (see also Chap. 7)

EXERCISE ECHOCARDIOGRAPHY.

Two-dimensional echocardiography is useful in the evaluation of patients with chronic CAD because it can assess global and regional left ventricular function in the absence and presence of ischemia, as well as detect left ventricular hypertrophy and associated valve disease. Echocardiography is relatively inexpensive and safe. Stress echocardiography, in which imaging is performed at rest and immediately after exercise, allows the detection of regional ischemia by identifying new areas of wall motion disorders. Adequate images can be obtained in more than 85 percent of patients, and the test is highly reproducible. The inability to image at peak exercise is only a minor disadvantage because most wall motion abnormalities do not normalize immediately upon cessation of exercise.

Detection of ischemic myocardium has been enhanced with the development of systems that allow simultaneous side-by-side display of rest and postexercise images. Numerous studies have shown that exercise echocardiography can detect the presence of CAD with an accuracy that is similar to that of stress myocardial perfusion imaging and superior to exercise ECG alone.[35] [98] [99] Stress echocardiography is also valuable in localizing and quantifying ischemic myocardium. Published results in more than 3200 patients with angiographic confirmation of the presence or absence of CAD yield an average sensitivity of 85 percent and specificity of 86 percent.[35] As with perfusion imaging, stress echocardiography also provides important prognostic information in patients with known or suspected CAD.[35]

Indications for stress echocardiography are similar to those discussed above for stress myocardial perfusion imaging. Stress echocardiography is an excellent alternative to nuclear cardiology procedures. Although less expensive than nuclear perfusion imaging, stress echocardiography is more expensive and less available than exercise ECG, and a regular exercise ECG should always be considered first for screening and detection of CAD in patients with a normal resting ECG who are capable of performing treadmill exercise.[35] [78]

PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY.

In patients unable to exercise, those unable to achieve adequate heart rates with exercise, and those in whom the quality of the echocardiographic images during or immediately after exercise is poor, alternative approaches are available. The most well studied and clinically available method is dobutamine stress echocardiography,[35] [100] [101] in which constant echocardiographic imaging is performed during the infusion of dobutamine beginning at 5 to 10 mug/kg/min with graded increases to a maximum of 40 to 45 mug/kg/min. Dobutamine increases both the heart rate and contractility and produces diagnostic changes in regional wall motion and systolic wall thickening as ischemia develops. Low-dose dobutamine infusion (5 to 10 mug/kg/min) is also valuable for assessing contractile reserve in regions with hypokinetic or akinetic wall motion at rest, as a means of identifying viable myocardium that may improve in function after revascularization[89] [102] [103] (see Chap. 13) . Atropine increases the accuracy of dobutamine stress echocardiography in patients with inadequate heart rate responses,[104] especially

those taking beta blockers and those in whom second-degree heart block develops at higher atrial rates. Dobutamine stress imaging achieves diagnostic accuracy comparable to that of exercise echocardiography,[35] [100] [101] but as with myocardial perfusion imaging, exercise stress imaging is preferable in patients capable of performing adequate exercise. An exception to this general policy is a patient with left ventricular dysfunction who is undergoing dobutamine echocardiography to assess myocardial viability. Dobutamine stimulation is safe, especially if the test is terminated at the onset of the first ischemic regional wall motion abnormalities.

An alternative form of pharmacological stress echocardiography is the use of high-dose dipyridamole infusion[105] or adenosine infusion, but exercise and dobutamine stress appear to have greater sensitivity than vasodilator stress in detecting CAD[100] [101] and are superior in assessing the extent of CAD.[100] All forms of stress echocardiography have similar high specificity because a new wall motion abnormality in a patient with normal resting left ventricular function is a highly specific finding for reversible ischemia.

Transesophageal dobutamine stress echocardiography has been shown to be feasible, safe, and accurate for the detection of myocardial ischemia. Although not a readily available technique for large numbers of patients, it may allow extension of dobutamine stress testing to patients with inadequate transthoracic echocardiographic imaging.[106]

STRESS ECHOCARDIOGRAPHY VERSUS STRESS NUCLEAR PERFUSION IMAGING (see also Chap. 13) .

The two stress imaging methods in general provide similar accuracy in detecting CAD. In studies in which the same patients were studied with both techniques and with coronary angiography, nuclear myocardial perfusion imaging had slightly greater sensitivity and stress echocardiography had greater specificity.[107] The potential advantage of stress echocardiography in terms of enhanced specificity has also been demonstrated in meta-analyses (which did not account for possible posttest referral bias).[99] Stress echocardiography is also associated with lower cost and easier implementation in the physician's office. The choice of diagnostic test to perform, however, depends on several additional factors, including local expertise and available facilities.

CONTRAST ECHOCARDIOGRAPHY (see also Chap. 7) .

Contrast echocardiography is a rapidly evolving field in noninvasive testing for the diagnosis and assessment of CAD.[108] A major objective is the development of intravenous ultrasonic contrast agents for noninvasive myocardial perfusion imaging. With greater spatial resolution than nuclear perfusion imaging, echocardiography has the potential for evaluating transmural distribution of flow heterogeneity and detecting changes in subendocardial perfusion. Although this goal has not been fully realized with the intravenous administration of ultrasonic contrast agents, early work is promising.[109] An outgrowth of this research is two developments that have improved wall motion

assessment during standard stress echocardiography. The first is blood pool opacification with intravenous injection of a contrast agent, which has improved delineation of the left ventricular endocardial surface.[110] The second is the use of harmonic imaging, which can be used even without administration of a contrast agent and, in addition, enhances definition of the endocardial border.[111] Poor visualization of endocardial borders in a sizable subset of patients has been a limitation of stress echocardiography for many years, and these two new developments have significantly improved endocardial border definition, with the potential for enhanced detection of ischemic myocardium.

Clinical Application of Noninvasive Testing

GENDER DIFFERENCES IN THE DIAGNOSIS OF CAD (see also Chap. 58) .

On the basis of earlier studies that indicated a much higher frequency of false-positive stress test results in women than in men, it is generally accepted that ECG stress testing is not as reliable in women. However, the prevalence of CAD among women in the patient populations under study was low, and the lower positive predictive value of exercise ECG in women can be accounted for, in large part, on the basis of Bayesian principles (Table 37-1) .[112] Once men and women are stratified appropriately according to the pretest prevalence of disease, the results of stress testing are similar.[78] [113]

Exercise imaging modalities have greater diagnostic accuracy than exercise ECG in both men and women.[35] [78] Although soft tissue attenuation artifacts, especially those caused by breast tissue, may reduce the specificity of myocardial perfusion imaging in women, these artifacts can usually be identified by experienced observers without a substantial reduction in diagnostic accuracy, and risk assessment by nuclear perfusion imaging is not diminished in women compared with men.[114] In addition, the use of gated SPECT imaging has greatly improved identification of these artifacts by demonstrating that regions with apparently irreversible perfusion defects have normal wall motion, thereby enhancing diagnostic accuracy.[115] Among women without a history of myocardial infarction, exercise echocardiography was superior to exercise ECG in the detection of CAD.[116] [117]

IDENTIFICATION OF PATIENTS AT HIGH RISK.

When applying noninvasive tests to the diagnosis and management of CAD, it is useful to grade the results as "negative"; "indeterminate"; "positive, not high risk"; and "positive, high risk." The criteria for high-risk findings on stress ECG, myocardial perfusion imaging, and stress echocardiography are listed in Table 37-2 .

Regardless of the severity of symptoms, patients with high-risk noninvasive test results have a very high likelihood of CAD and, if they have no obvious contraindications to revascularization, should undergo coronary arteriography. Such patients, even if asymptomatic, are at risk for left main or three-vessel CAD, and many will have impaired left ventricular function. Hence, they are at high risk for experiencing coronary events. The prognosis in these patients may often be improved by coronary bypass surgery. In contrast, patients with clearly negative exercise tests, regardless of

symptoms, have an excellent prognosis that cannot usually be improved by revascularization. If they do not have serious symptoms, they generally do not require coronary arteriography.

ASYMPTOMATIC PERSONS.

In asymptomatic persons or in those with chest pain not likely to be angina, the pretest likelihood of CAD is low (<15 percent). In such patients, a negative exercise ECG, for practical purposes, excludes ischemic heart disease. However, if such a patient has an abnormal exercise ST segment response, several alternatives exist. If the ST segment is abnormal but not high risk (<2-mm depression) and the patient demonstrates excellent exercise capacity (i.e., to stage IV of a Bruce protocol or the

TABLE 37-2 -- HIGH-RISK FINDINGS ON NONINVASIVE STRESS TESTING

EXERCISE ELECTROCARDIOGRAPHY
2.0-mm or greater ST segment depression
1.0-mm or greater ST segment depression in stage I
ST segment depression for longer than 5 min during the recovery period
Achievement of a workload of less than 4 METs or a low exercise maximal heart rate
Abnormal blood pressure response
Ventricular tachyarrhythmias
MYOCARDIAL PERFUSION IMAGING
Multiple perfusion defects (total plus reversible defects) in more than one vascular supply region (e.g., defects in coronary supply regions of the left anterior descending and left circumflex vessels)
Large and severe perfusion defects (high semiquantitative defect score)
Increased lung thallium-201 uptake reflecting execise-induced left ventricular dysfunction
Postexercise transient left ventricular cavity dilatation
Left ventricular dysfunction on gated single-photon emission computed tomography
STRESS ECHOCARDIOGRAPHY
Multiple reversible wall motion abnormalities
Severity and extent of these abnormalities (high global wall motion score) Severe reversible cavity dilation
Left ventricular systolic dysfunction at rest

equivalent), the likelihood of left main CAD or multivessel CAD is low, the prognosis is favorable, and the patient may usually be observed without further testing. If, however, such a patient has a high-risk positive exercise ECG, coronary angiography is usually indicated to determine whether left main CAD or severe multivessel disease with left ventricular dysfunction is present. If the patient falls into an intermediate category (a positive but not high-risk exercise test result), a stress imaging study (echocardiography or perfusion scintigraphy) may provide further information. If both studies are abnormal but not high risk, the likelihood of CAD approaches 90 percent.

PATIENTS WITH ATYPICAL ANGINA.

In these patients, the pretest probability of CAD is approximately 50 percent. If two noninvasive tests are abnormal, the likelihood of CAD exceeds 95 percent; if both tests are normal, it falls below 5 percent. When test results are discordant, they should be evaluated in light of the exercise level achieved, the presence of accompanying symptoms, and whether one of the tests is positive with high risk. Thus, for example, a patient who has atypical angina and a normal exercise ECG with multiple large perfusion defects on a stress thallium-201 scintigram at a heart rate of 130 beats/min has a much greater likelihood of having CAD than one who has a normal exercise ECG and a single small perfusion defect without chest pain at a heart rate of 185 beats/min. Although the indications for performing a stress imaging test directly in such a patient without an initial exercise ECG are controversial, such an approach is reasonable if the patient with atypical angina also has multiple cardiovascular risk factors, such as smoking, hypercholesterolemia, or a positive family history of premature CAD.

PATIENTS WITH TYPICAL ANGINA.

In patients with a high pretest likelihood of disease of approximately 90 percent, noninvasive testing is most valuable for estimating the extent and severity of CAD and thereby the prognosis. The development of a high-risk positive stress test points to multivessel disease and a high risk of subsequent coronary events, and unless the patient has contraindications to revascularization, coronary angiography is indicated.

Chest Roentgenogram

The chest roentgenogram is usually within normal limits in patients with chronic stable angina, particularly if they have a normal resting ECG and have not experienced a myocardial infarction. If cardiomegaly is present, it is indicative of severe CAD with previous myocardial infarction, preexisting hypertension, concomitant valvular heart disease, or an associated nonischemic condition such as cardiomyopathy.

ELECTRON BEAM COMPUTED TOMOGRAPHY (see also Figs. 10-40 , 10-41 , and 10-42)

Noninvasive detection of coronary artery calcification has long been possible with fluoroscopy. Such calcific deposits are diagnostic of coronary atherosclerosis.[118] Electron beam cardiac computed tomography (CT) has emerged as a highly sensitive method for detecting coronary calcification and is being used at several centers as a

screening technique for CAD. The calcium score is a quantitative index of total coronary artery calcium detected by CT, and this score has been shown to be a good marker of the total coronary atherosclerotic burden.[119] However, the relationship of the coronary calcium score to subsequent cardiac events in asymptomatic persons has not been fully established.[97] [120] Several other uncertainties persist as well, including (1) the value of coronary calcium screening in comparison to multiple risk factor assessment, (2) whether coronary calcium scores add incremental value beyond the standard risk factors, and (3) whether coronary calcium screening is more accurate and cost-effective in asymptomatic persons than are other new methods that assess atherosclerotic burden, such as the ankle-brachial index and ultrasonic carotid intimal-medial thickening.[121] [122]

The *absence* of calcium on CT imaging is predictive of the absence of significant atherosclerotic disease in older persons,[119] but it is possible for young people (men younger than 45 years, women younger than 55) to have obstructive CAD and, hence, a risk for future cardiac events in the absence of detectable calcification or with a low calcium score.[123] Although coronary calcification is a highly sensitive finding in patients who have CAD and the presence of coronary calcification is an accurate marker of coronary atherosclerosis, the specificity of this finding for identifying patients with obstructive CAD is very low.[124] Thus, in patients with known or suspected CAD, exercise testing is preferable to electron beam CT imaging for determining the extent of CAD and the indications for coronary angiography.[124] An analysis by a committee of the AHA on the potential value of electron beam CT and more recent consensus statements of the ACC and AHA[66] [124] concluded that whereas the technique is highly predictive for the presence of atherosclerosis, the degree of atherosclerosis cannot be predicted and the prognostic importance has not been established. Although this modality was considered to have great potential, it was not recommended for routine screening of patients.[66] [124] The results of several ongoing studies will probably provide important information in regard to defining the role of this promising technique in the future.

MAGNETIC RESONANCE IMAGING (see Chap. 10)

Magnetic resonance imaging is emerging as a versatile noninvasive imaging modality with high spatial resolution that will have many applications for patients with CAD. The potential of this technique for detecting regional myocardial ischemia with dobutamine stress[125] and for identifying viable myocardium in patients with left ventricular dysfunction has been demonstrated.[126] Exciting new developments on the horizon include contrast agents for myocardial perfusion imaging and, ultimately, noninvasive magnetic resonance coronary angiography.[127]

CATHETERIZATION, ANGIOGRAPHY, AND CORONARY ARTERIOGRAPHY

The clinical examination and noninvasive techniques described above are extremely valuable in establishing the diagnosis of CAD and are indispensable to an overall assessment of patients with this condition. However, definitive diagnosis of CAD and precise assessment of its anatomical severity and its effects on cardiac performance still require cardiac catheterization, coronary arteriography, and left ventricular angiography[128] (see Chaps. 11 and 12) . Among patients with chronic stable angina

pectoris referred for coronary arteriography, approximately 25 percent each have one-, two-, or three-vessel disease (i.e., >70 percent luminal diameter narrowing). Five to 10 percent have obstruction of the left main coronary artery, and in approximately 15 percent no critical obstruction is detectable. Coronary angiographic findings differ between patients with an initial attack of acute myocardial infarction and those with chronic stable angina. Patients with unheralded myocardial infarction have fewer diseased vessels, fewer stenoses and chronic occlusions, and less diffuse disease than do chronic stable angina patients, thus suggesting that the pathophysiological substrate and the propensity for thrombosis differ between these two groups of patients.[129] In patients with chronic angina who have a history of prior infarction, total occlusion of at least one major coronary artery is more common than in those without such a history.

CORONARY ARTERY ECTASIA AND ANEURYSMS.

Patulous, aneurysmal dilatation involving most of the length of a major epicardial coronary artery is present in approximately 1 to 3 percent of patients with obstructive CAD at autopsy or angiography. This angiographic lesion does not appear to affect symptoms, survival, or the incidence of myocardial infarction.[130] [131] Most coronary artery ectasia and/or aneurysms are due to coronary atherosclerosis (50 percent), and the rest are due to congenital anomalies and inflammatory diseases such as Kawasaki disease. Despite the absence of overt obstruction, 70 percent of patients with multivessel fusiform coronary artery ectasia/aneurysms demonstrated evidence of cardiac ischemia based on cardiac lactate levels during ergometry and atrial pacing. Moreover, nitroglycerin was of no benefit.[132]

Coronary ectasia should be distinguished from discrete *coronary artery aneurysms*, which are almost never found in arteries without severe stenosis, are most common in the left anterior descending coronary artery, and are usually associated with extensive CAD.[133] These discrete atherosclerotic coronary artery aneurysms do not appear to rupture, and resection of them is not warranted.

CORONARY COLLATERAL VESSELS (see Fig. 12-29) (Figure Not Available) .

Provided that they are of adequate size, collaterals may protect against myocardial infarction when total occlusion occurs.[134] In patients with abundant collateral vessels, myocardial infarct size is smaller than in patients

without collaterals, and total occlusion of a major epicardial artery may not lead to left ventricular dysfunction.[135] In patients with chronic occlusion of a major coronary artery but without infarction, collateral-dependent myocardial segments show nearly normal baseline blood flow and O_2 consumption but severely limited flow reserve. This finding provides an explanation for the ability of collaterals to protect against resting ischemia but not exercise-induced angina.[136]

MYOCARDIAL BRIDGING.

Bridging of coronary arteries (see Chap. 12) is observed in angiographically normal coronary arteries and ordinarily does not constitute a hazard. Occasionally, compression of a portion of a coronary artery by a myocardial bridge can be associated with clinical manifestations of myocardial ischemia during strenuous physical activity and may even initiate malignant ventricular arrhythmias.[137]

LEFT VENTRICULAR FUNCTION.

Ventricular relaxation, as reflected in the early diastolic ventricular filling rate, may be impaired at rest in patients with chronic CAD. Diastolic filling becomes even more abnormal (slowed) during exercise, when ischemia intensifies. In patients with chronic stable angina, the frequency of elevated left ventricular end-diastolic pressure and reduced cardiac output at rest, generally attributed to abnormal left ventricular dynamics, increases with the number of vessels exhibiting critical narrowing and with the number of prior infarctions.[138] However, a great deal of overlap is seen in individual patients, so the severity of coronary arterial disease cannot be predicted from these measurements. Left ventricular end-diastolic pressure may be elevated secondary to reduced ventricular compliance, left ventricular systolic failure, or a combination of these two processes.[139] Both impaired systolic and impaired diastolic function may occur as a consequence of acute, reversible ischemia and/or chronic scar formation. In many patients with normal hemodynamics in the resting state, abnormalities of left ventricular function can be elicited by dynamic or isometric exercise. Elevations of left ventricular end-diastolic pressure usually occur *before* angina develops and before ECG ST segment depression occurs.

Left ventricular function can be assessed by means of biplane contrast ventriculography (see Chap. 15) . Global abnormalities of left ventricular function are reflected by elevations in left ventricular end-diastolic and end-systolic volume and depression of the ejection fraction. These changes are, however, quite nonspecific and can occur in many forms of heart disease. Abnormalities of *regional* wall motion (hypokinesis, akinesia, or dyskinesia) are more characteristic of CAD because the latter is usually regional in distribution. Also, hyperkinetic contraction of nonischemic myocardium, detected by left ventriculography, may compensate for hypokinetic or akinetic ischemic or necrotic myocardium, thereby maintaining normal or nearly normal global left ventricular function despite marked depression of function in one region of the ventricle.

Left ventricular function (global or regional) may be normal at rest in patients with chronic CAD without previous myocardial infarction but may become abnormal during or after stress. Abnormalities of left ventricular function detected angiographically may signify irreversible damage, i.e., prior infarction, or they may indicate acute ischemia or chronic hypoperfusion sufficient to maintain viability, but not contractility of the myocardium, i.e., "myocardial hibernation" [140] [141] [142] (see Chaps. 13 , 14 , and 34 and also Chap. 37 , p. 1316). Reversibility of this form of left ventricular dysfunction in patients with CAD and chronic stable angina is reflected by improved contraction assessed angiographically after an inotropic stimulus (postextrasystolic potentiation or

the infusion of a sympathomimetic amine[102] [103] [143]) or by long-term improvement after myocardial revascularization.

In addition to demonstrating areas of asynergy, left ventriculography may also show mitral valve prolapse, which occurs in approximately 20 percent of patients with obstructive CAD[144] and probably results from impaired contractility of the ventricular myocardium and papillary muscles. Mitral regurgitation secondary to left ventricular dilatation may be observed in patients with chronic stable angina and ischemic cardiomyopathy.

CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM.

Cardiac catheterization can also document abnormal myocardial metabolism in patients with chronic stable angina. With a catheter in the coronary sinus, arterial and coronary venous lactate measurements are obtained at rest and after suitable stress, such as the infusion of isoproterenol[145] or pacing-induced tachycardia. [146] Because lactate is a byproduct of anaerobic glycolysis, its production by the heart and subsequent appearance in coronary sinus blood is a reliable sign of myocardial ischemia. When combined with coronary arteriography, this technique may be helpful in localizing significant coronary obstructive lesions and myocardial ischemia.[147]

Studies of coronary flow reserve (maximum flow divided by resting flow) and endothelial function are frequently abnormal in patients with CAD and chronic stable angina. They are discussed in Chapter 34 .

MEDICAL MANAGEMENT

Comprehensive management of chronic stable angina has five aspects: (1) identification and treatment of associated diseases that can precipitate or worsen angina; (2) reduction of coronary risk factors; (3) application of general and nonpharmacological methods, with particular attention toward adjustments in life style; (4) pharmacological management; and (5) revascularization by percutaneous catheter-based techniques or by coronary bypass surgery. Although discussed individually, all five of these approaches must be considered, often simultaneously, in each patient. Among the medical therapies, only two (aspirin and effective lipid lowering) have been convincingly shown to reduce mortality and morbidity in patients with chronic stable angina and preserved left ventricular function. A single large multicenter randomized trial has provided strong evidence that angiotensin-converting enzyme (ACE) inhibitors may also reduce mortality and ischemic events in such patients. Other therapies such as nitrates, beta blockers, and calcium antagonists have been shown to improve symptomatology and exercise performance, but their effect, if any, on survival has not been demonstrated.

In stable patients with left ventricular dysfunction following myocardial infarction, data consistently indicate that ACE inhibitors and beta blockers reduce both mortality and the risk of repeat infarction, and these agents are recommended in such patients, along with

aspirin and lipid-lowering drugs.

TREATMENT OF ASSOCIATED DISEASES.

Several common medical conditions that can increase myocardial O_2 demand or reduce O_2 delivery may contribute to the onset of new angina pectoris or the exacerbation of previously stable angina. These conditions include anemia, marked weight gain, occult thyrotoxicosis, fever, infections, and tachycardia. Drugs such as amphetamines and isoproterenol all increase myocardial O_2 demand, as do other agents that stimulate the sympathetic nervous system. Cocaine, which can cause acute coronary spasm and myocardial infarction, is discussed in Chapter 48 . Congestive heart failure, by causing cardiac dilatation, mitral regurgitation, or tachyarrhythmias, including sinus tachycardia, can increase myocardial O_2 need, along with an increase in the frequency and severity of angina. Identification and treatment of these conditions are critical to the management of chronic stable angina.

Reduction of Coronary Risk Factors

HYPERTENSION (see also Chaps. 28 and 29) .

Epidemiological links between increased blood pressure and CAD severity and mortality are well established.[62] [148] [149] Hypertension predisposes to vascular injury, accelerates the development of atherosclerosis, increases myocardial O_2 demand, and intensifies ischemia in patients with preexisting obstructive coronary vascular disease. Although the relationship between hypertension and CAD is linear,[150] left ventricular hypertrophy is a stronger predictor of myocardial infarction and CAD death than is the actual degree of

increase in blood pressure.[151] A meta-analysis of clinical trials of treatment of mild to moderate hypertension showed a statistically significant 16 percent reduction in CAD events and mortality in patients receiving antihypertensive therapy.[152] This treatment effect is nearly twice as great in older than younger persons.[153] It is logical to extend these observations on the benefits of antihypertensive therapy on mortality and ischemic events to patients with established CAD. Therefore, blood pressure control is an essential aspect of the management of patients with chronic stable angina.

Dietary and Life Style Modification.

Alterations in life style and dietary treatment should be initiated in conjunction with antihypertensive therapy. Attainment of ideal body weight is particularly important in obese patients, in whom weight reduction, in addition to assisting in blood pressure control, greatly aids in control of lipid abnormalities, diabetes, and hyperinsulinemia,

which otherwise increase the risk of ischemic events.[62] [154] More directly, weight loss increases the threshold for and may even abolish angina pectoris.

CIGARETTE SMOKING.

Smoking remains one of the most powerful risk factors for the development of CAD in all age groups (see Chap. 31) , and cardiac events occur at a younger age in smokers, especially among women.[61] [150] [155] Postmortem data suggest that smoking predisposes to atherosclerotic plaque erosion and acute thrombosis,[156] which is consistent with the known effects of smoking on fibrinogen and platelet adhesion.[157] Smoking also aggravates other CAD risk factors. Among patients with angiographically documented CAD, cigarette smokers have a higher 5-year mortality and relative risk of infarction or sudden death than do those who have stopped smoking,[158] and smoking cessation lessens the risk of adverse coronary events in patients with established CAD.[159] In patients who have undergone coronary bypass surgery, cessation of cigarette smoking has been shown to decrease both morbidity and mortality substantially.[160] [161]

Cigarette smoking may be responsible for aggravating angina pectoris other than through the progression of atherosclerosis. It may increase myocardial O_2 demand and reduce coronary blood flow by means of an alpha-adrenergically mediated increase in coronary artery tone and thereby cause acute ischemia.[162] Cigarette smoking also appears to reduce the efficacy of antianginal drugs.[163] Smoking cessation is one of the most effective and certainly the least expensive approach to the prevention of disease progression in native vessels and bypass grafts. Techniques for smoking cessation are discussed in Chapter 39 .

Passive cigarette smoking, air pollution, and ascent to high altitude all lower the threshold for angina, and their avoidance represents an important aspect of therapy.

MANAGEMENT OF DYSLIPIDEMIA (see also Chap. 33) .

The beneficial effect of reducing serum cholesterol in patients with hypercholesterolemia is incontrovertible. Cholesterol lowering by diet and drugs has been shown to reduce the incidence of clinical CAD events in primary prevention trials. Among men with moderate hypercholesterolemia in the West of Scotland trial, treatment with pravastatin significantly reduced the incidence of myocardial infarction and death without adversely affecting the risk of death from noncardiovascular causes.[164] Similarly, lovastatin reduced fatal and nonfatal coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), which enrolled both men and women with average levels of total cholesterol and LDL cholesterol for age and gender and low levels of HDL cholesterol.[165] In view of the low-risk characteristics of the population, no significant effect of therapy on mortality alone was observed.

In patients with established CAD, clinical trials have demonstrated a significant reduction in disease progression and subsequent cardiovascular events in patients with a wide range of serum cholesterol and LDL cholesterol levels who are treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins).[166]

[167] [168] [169] [170] [171] Angiographic trials of cholesterol lowering in patients with chronic CAD, many of whom had chronic stable angina, have shown that the effects on coronary obstruction are modest whereas the reduction in cardiovascular events is quite impressive. Several studies have shown that statins significantly improve endothelium-mediated responses in the coronary and systemic arteries of patients with hypercholesterolemia or known atherosclerosis.[172] [173] [174] In addition, pravastatin has been shown to reduce circulating levels of C-reactive protein[175] and decrease thrombogenicity [176] ; these effects do not appear to correlate well with the change in serum LDL cholesterol and suggest antiatherothrombotic properties of this and possibly other statin agents.[175] [176] [177] These findings may explain the improvement in blood flow,[47] [178] the reduction in inducible myocardial ischemia, [179] and the disproportionate reduction in coronary events in patients treated with statins despite very small degrees of anatomical regression of atherosclerotic stenoses.

Results from the three secondary prevention trials of patients with a history of angina, unstable angina, or previous myocardial infarction provide convincing evidence that effective lipid-lowering therapy significantly improves overall survival and reduces cardiovascular mortality in patients with coronary heart disease[168] [170] [171] (see Chap. 33) . These effects have been demonstrated in both men and women and in the elderly[180] [181] [182] and provide a cost-effective approach to the management of large numbers of patients with chronic CAD.[183] [184]

The National Cholesterol Education Program Guidelines advocate cholesterol-lowering therapy for all patients with coronary heart disease or extracardiac atherosclerosis to LDL levels below 100 mg/dl, and these guidelines have been adopted by the AHA and ACC.[35]

Low HDL Cholesterol.

Patients with low levels of HDL cholesterol represent a subgroup with considerable risk for future coronary events.[61] [185] Low HDL levels are often associated with obesity, hypertriglyceridemia, and insulin resistance[61] [186] [187] and often signify the presence of small lipoprotein remnants and small dense LDL particles that are thought to be particularly atherogenic.[188] Therapy has focused on diet and exercise, as well as LDL cholesterol reduction in patients with a concomitant increase in LDL cholesterol.[61] [189] The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) Study Group has demonstrated the efficacy of gemfibrozil treatment in patients with low HDL cholesterol (
40 mg/dl) without elevations in LDL cholesterol (
140 mg/dl) or triglycerides (mean, 160 mg/dl).[190] Gemfibrozil resulted in a 6 percent increase in HDL cholesterol and a 31 percent decrease in triglycerides, and these changes were associated with a 24 percent reduction in death, nonfatal myocardial infarction, and stroke (p=0.006). The 22 percent reduction in cardiac death achieved only borderline statistical significance (p=0.07).

DYSLIPIDEMIA AFTER MYOCARDIAL REVASCULARIZATION.

In patients who have undergone coronary artery bypass surgery (CABG), elevation of

LDL cholesterol is a risk factor for the development of saphenous vein graft occlusive disease, as well as progression of atherosclerosis in the native coronary arteries.[191] [192] In the Post Coronary Artery Bypass Graft Clinical Trial, patients randomly assigned to receive treatment with lovastatin and the addition of cholestyramine as necessary to achieve an LDL cholesterol level less than 100 mg/dl had a 31% reduction in saphenous vein occlusive disease at a mean of 4.3 years in comparison to patients randomly assigned to receive placebo.[191] This effect was observed in both men and women and in both young and old patients.[193] In patients with low HDL cholesterol after bypass surgery, similar benefits have been obtained with gemfibrozil.[194] Lipid-lowering therapy reduces mortality and acute coronary

events in patients who have undergone either surgical or percutaneous revascularization,[195] and therapy for dyslipidemia should be given to these patients, as to all patients with chronic CAD. However, lipid-lowering strategies do not have an effect on restenosis at the site of angioplasty.[196]

ESTROGEN REPLACEMENT (see also Chaps. 32 and 58) .

Male gender and, in women, the postmenopausal state are risk factors for the development and progression of CAD. Epidemiological studies have shown that the favorable cardiovascular risk profile in premenopausal women changes after menopause--the levels of total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides all increase and HDL cholesterol levels decrease slightly or are unchanged.[197] Several long-term studies have identified reduced HDL cholesterol and increased triglyceride levels as powerful predictors of CAD risk among postmenopausal women,[198] and several large cross-sectional studies[199] and a randomized trial[200] have indicated that hormone replacement therapy with estrogens, alone or in combination with medroxyprogesterone acetate, has a favorable effect on the cardiovascular risk factor lipid profile. These changes are similar to, but less pronounced than, those achieved with therapy with statin agents.[201]

The potential beneficial effect of estrogen replacement therapy is probably not limited to altering the lipid profile favorably. Estrogens have multiple complex and interrelated beneficial effects on vascular structure and function,[202] [203] including immediate, short-term, and long-term effects. The principal short-term pharmacological effect is vasodilatation mediated directly via stimulation of estrogen receptors and indirectly through elaboration of nitric oxide (NO). The long-term effects, mediated via genetic signaling, include a reduction in vascular inflammation and injury, delay in lipid accumulation and LDL oxidation, enhanced function of the vascular endothelium to promote vasodilatation and reduce thrombosis, and reduction in vascular smooth muscle proliferation.

A large data base derived from observational studies suggests an important protective effect of hormone replacement therapy for postmenopausal women, with a 30 to 50

percent reduction in overall mortality from cardiovascular disease.[204] [205] Most of these studies evaluated the effects of estrogen alone, primarily in healthy women. Several randomized primary and secondary prevention trials investigating hormone replacement therapy are under way. The only completed randomized trial to date is the Heart and Estrogen/Progestin Replacement Study (HERS),[206] which randomly assigned postmenopausal women (mean age, 68 years) with established CAD to receive conjugated estrogen plus medroxyprogesterone or placebo, with a follow-up period of 4 years. No difference was seen in cumulative cardiac mortality or total cardiovascular events between the two groups despite a greater decrease in LDL cholesterol and increase in HDL cholesterol in the treatment group. This result has generated considerable discussion and controversy about the efficacy or lack of efficacy as well as the safety of hormone replacement therapy. Most endpoints took place in the first year, when more events occurred in the group randomly assigned to receive hormone therapy. This finding raises the possibility that the potential long-term beneficial antiatherogenic efficacy of therapy is offset by a short-term risk, perhaps related to increased thrombogenicity. This limitation is supported by the finding of greater venous thrombosis in the first year in the treatment group in HERS[206] and other patients who have received hormone replacement therapy.[207] Because of the specific progestin used in HERS, the question has also been raised about a less favorable reduction in lipids than might have occurred with estrogen alone.

In light of the HERS results, the case for estrogen replacement therapy as secondary prevention of CAD is now less strong. The other ongoing secondary prevention trials will help clarify this issue. The HERS findings may not be representative of the effects of estrogen or estrogen-progestin replacement when used as primary prevention in younger women, and this point will also be clarified by current and future trials. While awaiting these results and in view of the increased risk of estrogen alone and estrogen-progesterone combinations on the development of breast cancer and the increased risk of "unopposed estrogen" on uterine cancer, it is *not* advised that hormone replacement therapy be *commenced* in women with CAD. However, such therapy may be continued in women who are already receiving it, once CAD is discovered.

ANTIOXIDANTS (see also Chap. 32)

Oxidized LDL particles are strongly linked to the pathophysiology of atherogenesis, and descriptive, prospective cohort, and case-control studies suggest that a high dietary intake of antioxidant vitamins (A, C, and beta-carotene) and flavonoids (polyphenolic antioxidants), naturally present in vegetables, fruits, tea, and wine, is associated with a decrease in coronary heart disease events.[208]

RANDOMIZED TRIALS.

All three primary prevention trials, each involving between 18,000 and 29,000 subjects monitored from 4 to 12 years, failed to demonstrate a positive effect of beta-carotene on major cardiac events.[209] [210] [211] The single trial that also studied vitamin E showed no cardiovascular benefit but rather an increased risk of death from hemorrhagic stroke in subjects receiving vitamin E.[209] The Cambridge Heart Antioxidant Study (CHAOS)

investigators studied 2002 patients with angiographic evidence of CAD who were randomly assigned to receive alpha-tocopherol, 400 and 800 mg daily, versus placebo.[212] During the brief follow-up period (mean, 510 days), patients receiving alpha-tocopherol had a 77 percent reduction in myocardial infarction and a 47 percent reduction in all cardiovascular events. No effect on cardiac mortality was demonstrated. Similar, but less impressive results were obtained in a secondary analysis of 1862 patients with previous myocardial infarction in the Alpha-Tocopherol and Beta-Carotene (ATBC) study, in which vitamin E treatment was associated with a 38 percent reduction in recurrent myocardial infarction.[213] In a third nonrandomized study, analysis of patients who had undergone previous coronary bypass surgery indicated less angiographic progression of CAD in subjects with a supplementary vitamin E intake of 100 IU/d or more than in those with lower intake.[213A] However, the largest trial to date with the longest duration of study has shown no benefit of vitamin E supplementation. The Heart Outcomes Prevention Evaluation (HOPE) investigators randomly assigned more than 9200 patients with known atherosclerotic vascular disease or diabetes and another CAD risk factor to receive vitamin E or placebo and demonstrated no effect of vitamin E supplementation on cardiovascular death, myocardial infarction, or stroke over the course of 5 years.[214]

Taken together, current data bases indicate that beta-carotene, vitamin C, and vitamin E have little cardiovascular benefit and do not support the case for antioxidant vitamin supplementation to reduce cardiovascular events. The use of vitamin E supplementation must be balanced against the potential for increased risk of bleeding, especially in patients who are taking aspirin. Unless new clinical trials in this area provide more positive information, *there is no basis for recommending antioxidant vitamins to patients with chronic CAD*.[215] [216]

However, another possible role for antioxidant therapy is in prevention of restenosis after percutaneous coronary intervention. Two studies have demonstrated that probucol (a lipid-lowering agent with potent additional antioxidant properties) significantly reduces restenosis when administered 1 month before and continued for 6 months after the procedure.[217] [218]

EXERCISE (see also Chap. 39)

The conditioning effect of exercise on skeletal muscles allows a greater workload at any level of total-body O_2 consumption. By decreasing the heart rate at any level of exertion, a higher cardiac output can be achieved at any level of myocardial O_2 consumption. The combination of these two effects of exercise conditioning permits patients with chronic stable angina to increase physical performance substantially following institution of a continuing exercise program.[219]

Most of the information about the physiological effects of exercise and their effect on prognosis in patients with CAD comes from studies on patients entered into cardiac rehabilitation programs,[219] [220] many of whom previously sustained a myocardial infarction. Less information is available on the benefits of exercise in patients with chronic stable CAD, but nine small randomized studies with a total of 980 patients have

consistently demonstrated improved effort tolerance, O_2 consumption, and quality of life in patients undergoing exercise training.[35] Six studies have shown a consistent reduction in indexes of myocardial ischemia during the course of conditioning,[35] [221] [222] and a seventh study has demonstrated a striking and direct relationship between the intensity of exercise and favorable changes in the morphology of obstructive lesions on angiography.[223] The question of

whether exercise accelerates the development of collateral vessels in patients with chronic CAD remains unsettled.

Exercise is safe if begun under supervision,[219] and if survivors of myocardial infarction can be used as a yardstick, it is probably cost-effective.[224] The psychological benefits of exercise are difficult to evaluate. However, a single nonrandomized study demonstrated significant improvement in well-being scores and positive effect scores, as well as a reduction in disability scores, in patients in a structured exercise program.[225] In addition, exercise conditioning programs may be quite helpful in increasing the self-confidence of patients with chronic CAD (as they are in patients recovering from acute myocardial infarction). Patients who are involved in exercise programs are also more likely to be health conscious, to pay attention to diet and weight, and to discontinue cigarette smoking. Thus, in addition to a conditioning effect on skeletal and cardiac muscle, regular dynamic exercise provides the patient with a feeling of well-being, an important consideration in the management of any chronic disease.

For all the aforementioned reasons, patients should be urged to participate in regular exercise programs--usually walking (see below)--in conjunction with their drug therapy.[35]

ASPIRIN (see also Chaps. 32 and 62) .

A meta-analysis of 140,000 patients in 300 studies confirmed the prophylactic benefit of aspirin in both men and women with angina pectoris, previous myocardial infarction or stroke, and after bypass surgery.[226] In a Swedish trial of both men and women with chronic stable angina, 75 mg daily of aspirin in conjunction with the beta blocker sotalol caused a 34 percent reduction in acute myocardial infarction and sudden death.[227] In a smaller study confined to men with chronic stable angina but without a history of myocardial infarction, 325 mg of aspirin on alternate days reduced the risk of myocardial infarction during 5 years of follow-up by 87 percent.[228] Therefore, 75 to 325 mg of aspirin daily is advisable in patients with chronic stable angina but without contraindications to this drug.[229]

Two other orally acting drugs that block platelet aggregation are the thienopyridine derivatives ticlopidine and clopidogrel,[230] and they may be substituted for aspirin in patients with aspirin hypersensitivity or those who cannot tolerate this drug (see Chap.

36) .

In addition to its antithrombotic effects, aspirin may be beneficial in reducing cardiovascular events in patients with chronic CAD via its antiinflammatory effects, properties not shared by ticlopidine or clopidogrel. Aspirin reduces the risk of subsequent myocardial infarction in healthy men with increased levels of C-reactive protein,[63] and in patients with established CAD and inducible myocardial ischemia, aspirin reduces circulating levels of C-reactive protein, macrophage colony-stimulating factor, and interleukin-6.[231] Aspirin also improves endothelial function in patients with atherosclerosis through a mechanism that may involve blockade of cyclooxygenase-dependent release of endothelium-derived constricting factors.[232]

Although warfarin has proved beneficial in postinfarct patients, no data support the use of chronic anticoagulation in patients with stable angina. However, a single large randomized trial in patients with risk factors for atherosclerosis but without symptoms of angina has shown that low doses of warfarin (achieving a mean international normalized ratio [INR] of 1.47) combined with aspirin decrease the risk of coronary death and myocardial infarction when used for primary prevention in high-risk groups.[233] Any benefit of this combination must be balanced against the potential for increased bleeding, which was also noted in this study.

INTERACTION WITH ACE INHIBITORS.

With the increasing use of ACE inhibitors in patients with cardiovascular disease, concern has arisen about a possible adverse interaction between aspirin and these drugs. Aspirin has the potential to inhibit prostaglandin-mediated pathways of ACE inhibition, and evidence of such antagonism has been demonstrated in patients with hypertension and heart failure.[234] [235] In the Second Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) of survival after myocardial infarction, evidence for such an interaction was observed.[234] Patients taking aspirin had less benefit of enalapril on survival than did those not taking aspirin, and the enalapril-aspirin interaction term was a significant predictor of mortality (p=0.047). Such an effect has not been reported in patients with chronic stable CAD, and evidence demonstrating no such effect was reported by the Bezafibrate Infarction Prevention Trial investigators.[236] Among 1247 patients with established CAD treated with ACE inhibitors, 618 (50 percent) were also treated with aspirin. Five-year mortality was significantly lower among patients taking ACE inhibitors and aspirin than those taking ACE inhibitors alone (19 vs. 27 percent, p0.001). The beneficial effect of aspirin was even more marked in patients with symptomatic heart failure. These data are supported by findings of the HOPE Study investigators, who reported no difference in the cardiovascular benefits of ramipril in patients with or without concomitant aspirin therapy (Fig. 37-2) .[214] Thus, current evidence supports aspirin therapy for all patients with CAD, including those taking ACE inhibitors. Ongoing clinical trials in this area will provide additional information.

BETA BLOCKERS.

The value of beta blockers in reducing death and recurrent myocardial infarction in

patients who have experienced a myocardial infarction is well established[237] [238] (see Chap. 35) , as is their usefulness in the treatment of angina (see p. 1290). Whether these drugs are also of value in preventing infarction and sudden death in patients with chronic stable angina is uncertain. However, there is no reason to assume that the favorable effects of beta blockers on ischemia and perhaps on arrhythmias should not apply to patients with chronic stable angina pectoris. Therefore, it is sensible to use these drugs when angina, hypertension, or both are present in patients with chronic CAD and when these drugs are well tolerated.

ANGIOTENSIN CONVERTING-ENZYME (ACE) INHIBITORS.

Studies of the effect of ACE inhibitors on the severity of angina pectoris and ischemia are limited by small sample size and brief duration of therapy. ACE inhibitors are not indicated for the treatment of angina. However, ACE inhibitors appear to have important benefits in reducing the risk of future ischemic events.

An unexpected and far-reaching finding from recent randomized trials of ACE inhibitors in postinfarct and other patients with ischemic and nonischemic causes of left ventricular dysfunction is the striking reduction in incidence of subsequent ischemic events such as myocardial infarction, unstable angina, and the need for coronary revascularization procedures.[239] [240] [241] [242] [243] Data from four trials including approximately 11,000 patients demonstrated a statistically significant risk reduction in myocardial infarction of 21 percent and in subsequent unstable angina of 15 percent.[243] The potentially beneficial effects of ACE inhibitors include a reduction in left ventricular hypertrophy, vascular hypertrophy, progression of atherosclerosis, plaque rupture, and thrombosis, in addition to a potentially favorable influence on myocardial O_2 supply/demand relationships and cardiac hemodynamics and a reduction in sympathetic activity.[243] Recent evidence also indicates that ACE inhibitors enhance coronary endothelial vasomotor function in patients with CAD,[244] which may contribute to enhanced myocardial blood flow during increases in myocardial demand.[245]

These beneficial effects of ACE inhibitors on vascular structure and function should in theory extend beyond patients with left ventricular dysfunction to a much wider range of patients with CAD, including those with normal left ventricular function. This is the subject of several ongoing randomized multicenter trials. The first of these trials to be completed has provided strong evidence supporting the therapeutic benefit of ACE inhibitors. The HOPE Study enrolled 9297 patients with atherosclerotic vascular disease or diabetes and at least one other CAD risk factor and randomly assigned them to receive ramipril (10 mg daily) or placebo; the mean follow-up was 5 years (Fig. 37-2) .[214] Eighty percent of patients had CAD, only 12 percent of whom had a myocardial infarction within 1 year after enrollment. No patient had heart failure symptoms on study entry, and echocardiograms (available for 5183 patients) demonstrated preserved left ventricular function (ejection fraction
40%) in 92 percent of patients. Ramipril significantly decreased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, and stroke from 17.7 to 14.1 percent (relative risk reduction of

Figure 37-2 Kaplan-Meier estimates of the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes in the ramipril group and the placebo group (Heart Outcomes Prevention Evaluation [HOPE] Study). The relative risk of the composite outcome in the ramipril group versus the placebo group was 0.78 (95 percent confidence interval, 0.70 to 0.86). *(From Yusuf S, Dagenais G, Pogue J, et al: Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342:154, 2000. By permission of the Massachusetts Medical Society.)*

22 percent, *p*0.001). The relative decreases in cardiovascular death, myocardial infarction, and stroke were 25, 20, and 31 percent, respectively. Ramipril also reduced secondary endpoints such as myocardial revascularization and all-cause mortality. The results were similar when examined in patient subsets defined by age, sex, known CAD, hypertension, diabetes, left ventricular function, or previous myocardial infarction. Beneficial effects were also similar in patients who were or were not taking aspirin.

The results of the HOPE Study have wide-reaching implications and suggest that all patients with stable CAD should be receiving ACE inhibitor therapy. Although these results were obtained from a large and well-designed and well-executed clinical trial, they represent the results of only a single trial. Definite recommendations should await the findings of two other ongoing randomized trials: Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) and the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) in patients with stable CAD, which will also clarify whether the benefits in patients with preserved left ventricular function are unique to ramipril (Fig. 37-2) .

Counseling and Changes in Life Style

The psychosocial issues faced by a patient with chronic stable angina for the first time are similar to, although usually less intense than, those experienced by a patient with an acute myocardial infarction. Many patients have an unrealistically gloomy perception of their prognosis; they should be offered a realistic appraisal, together with an understandable explanation of the pertinent clinical features of the disease.

An important aspect of the physician's role is to counsel patients in the kinds of work they can do and in their leisure activities, eating habits, vacation plans, and the like.[246] Certain changes in life style may be helpful, such as modifying strenuous activities if they constantly and repeatedly produce angina. These changes may be minor in many instances. For example, golfing could be modified to include the use of a golf cart instead of walking. A history of CAD and stable angina is not inconsistent with the ability to continue to perform vigorous exertion, which is important not only in regard to recreational activities and life style but also for patients in whom some physical exertion is required in their employment. However, isometric activities such as weight lifting[247] and other activities such as snow shoveling, which involves an energy expenditure

between 60 and 65 percent of peak oxygen consumption,[248] and cross-country or downhill skiing[249] are undesirable. In addition, some activities expose the individual to the detrimental effects of cold on the O_2 demand/supply relationship,[50] [250] and these activities should also be avoided if possible.

Thoughtful counseling, which may include supervised exercise sessions simulating the particular activity in question, can play a vital role in maintaining a productive and enjoyable life style in patients with chronic stable angina. Many activities, such as shopping or climbing stairs, need not be discontinued by patients with chronic angina; often, it is necessary merely to perform them more slowly or pause intermittently for brief periods of rest. Patients with chronic stable angina should avoid excessive fatigue and exhaustion. Although it is desirable to minimize the number of bouts of angina, an occasional episode is not to be feared. Indeed, unless patients occasionally reach their angina threshold, they may not appreciate the extent of their exercise capacity. Most patients with chronic stable angina should not be treated as invalids. Often, the propensity for angina actually declines with time, perhaps as a result of the development of collaterals and/or because of training effects.

Eliminating or reducing the factors that precipitate anginal episodes is of obvious importance. Patients learn their usual threshold by trial and error. Because many anginal episodes are precipitated by increases in mechanical activity of the heart (because of increases in myocardial O_2 requirements), patients should avoid *sudden* bursts of activity, particularly after long periods of rest or after meals and in cold weather. Both chronic angina and unstable angina exhibit a circadian rhythm characterized by a lower angina threshold shortly after arising.[251] Therefore, morning activities such as showering, shaving, and dressing should be done at a slower pace and, if necessary, with the use of prophylactic nitroglycerin. The stress of sexual intercourse is approximately equal to that of climbing one flight of stairs at a normal pace or any activity that induces a heart rate of approximately 120 beats/min. With proper precautions, i.e., commencing more than 2 hours postprandially and taking an additional dose of a short-acting beta blocker 1 hour before and nitroglycerin 15 minutes before, the majority of patients with chronic stable angina are able to continue satisfactory sexual activity.

Just as exercise has a role in the management of CAD, so too rest has a role, especially when angina has become frequent or severe. Marked restriction in activity or even complete bed rest, in addition to drug therapy, may occasionally

be necessary to control symptoms. In less critical situations, merely reducing the amount of time spent working or increasing the rest periods has a beneficial effect. For example, a long lunch break that includes a short nap may be beneficial. It may be helpful for the patient to use a face mask or scarf to cover the mouth or nose in cold weather. A hot, humid environment may also precipitate angina, and air conditioning may be a necessity rather than a luxury for patients with chronic angina. Large meals

can have a similar effect if they are followed by exertion. An effort should be made to minimize emotional outbursts because they too increase myocardial O_2 requirements and sometimes induce coronary vasoconstriction. Occasionally, antianxiety drugs and sedatives or relaxation techniques using biofeedback mechanisms may be helpful. Hostility is an adverse risk factor in CAD.

PHARMACOLOGICAL MANAGEMENT

Nitrates

MECHANISM OF ACTION.

Even though the clinical effectiveness of amyl nitrite in angina pectoris was first described in 1867 by Brunton, organic nitrates are still the drugs most commonly used in the treatment of patients with this condition. The action of these agents is to relax vascular smooth muscle.[252] The vasodilator effects of nitrates are evident in both systemic (including coronary) arteries and veins in normal subjects and in patients with ischemic heart disease, but they appear to be predominant in the venous circulation. The venodilator effect reduces ventricular preload,[253] which in turn reduces myocardial wall tension and O_2 requirements. The action of nitrates in reducing both preload and afterload makes them useful in the treatment of heart failure (see Fig. 37-1) , as well as angina pectoris.

Posture is important in evaluating the hemodynamic effects of nitrates. In a supine patient, venous return is normally greater and exercise tolerance and the angina threshold are lower than in the upright position. The hemodynamic and angina-relieving effects of nitrates are most marked when patients are sitting or standing, i.e., when the preload-reducing effects of these drugs are most prominent. By reducing the heart's mechanical activity, volume, and O_2 consumption, nitrates increase exercise capacity in patients with ischemic heart disease, thereby allowing a greater total-body workload to be achieved before the angina threshold is reached.

EFFECTS ON THE CORONARY CIRCULATION

Conductance Vessels (see Table 37-3) .

Quantitative, computer-assisted measurements of coronary arterial diameter have been used to show that nitroglycerin causes dilatation of epicardial stenoses. These stenoses are often eccentric lesions, and nitroglycerin causes relaxation of the smooth muscle in the wall of the coronary artery that is not encompassed by plaque. Even a small increase in a narrowed arterial lumen can produce a significant reduction in resistance to blood flow across obstructed regions[254] (see Fig. 34-21) . Nitrates may also exert a beneficial effect in patients with impaired coronary flow reserve by alleviating the vasoconstriction caused by endothelial dysfunction.[255]

REDISTRIBUTION OF MYOCARDIAL BLOOD FLOW.

Studies in experimental animals with coronary obstruction have shown that nitroglycerin causes redistribution of blood flow from normally perfused to ischemic areas, particularly in the subendocardium.[256] This redistribution may be mediated in part by an increase in collateral blood flow and in part by lowering of ventricular diastolic pressure, thereby reducing subendocardial compression. In patients with chronic stable angina responsive to nitroglycerin, topical nitroglycerin under resting conditions alters myocardial perfusion by preferentially increasing flow to areas of reduced perfusion with little or no change in global myocardial perfusion.[257]

The results of studies of nitroglycerin on coronary blood flow in patients have been conflicting. Some studies have reported increased blood flow after sublingual or intravenous nitroglycerin,[257] but most report no change or reduced flow.[258] However, because myocardial O_2 demand fell, the net effect on O_2 balance became favorable in the latter studies. Intracoronary injection of xenon-133 (as well as retrograde perfusion during coronary bypass surgery) has been used to demonstrate that blood flow in regions of myocardium perfused by stenotic coronary arteries rises after the administration of nitroglycerin when well-developed collaterals supplying those regions are present. In patients with chronic stable angina, topical nitroglycerin alters myocardial perfusion by preferentially increasing flow to areas of reduced perfusion with little or no change in global myocardial perfusion.[257]

The presence of well-developed collaterals may be an important determinant of a good therapeutic response to nitrates.[259] After systemic nitroglycerin, the heart can be paced to higher rates before

TABLE 37-3 -- EFFECTS OF ANTIANGINAL AGENTS ON INDICES OF MYOCARDIAL OXYGEN SUPPLY AND DEMAND*

INDEX	NITRATES	BETA-ADRENOCEPTOR BLOCKERS				CALCIUM ANTAGONISTS	
		ISA		Cardioselective			
		No	*Yes*	*No*	*Yes*	Nifedipine	Verapamil
SUPPLY							
Coronary resistance							
Vascular tone			0		0		

Intramyocardial diastolic tension			0				0
Coronary collateral circulation		0	0	0	0		0
Duration of diastole	0( )		0			0 ( )	( )
DEMAND							
Intramyocardial systolic tension							
Preload			0			0	0
Afterload (peripheral vascular resistance)							
Contractility	0( )					( )	( )*
Heart rate	0( )		0			0( )	( )

ISA=intrinsic sympathomimetic activity.

From Shub C, Vlietstra RE, McGoon MD: Selection of optimal drug therapy for the patient with angina pectoris. Mayo Clin Proc 60:539, 1985. By permission of the Mayo Foundation.

*

=Increase;
=decrease; 0=little or no definite effect. The number of arrows represents the relative intensity of effect. Symbols in parentheses indicate reflex-mediated effects.

Effect of calcium entry on left ventricular *contractility,* as assessed in the intact animal model. The net effect on *left ventricular performance* is variable since it is influenced by alterations in afterload, reflex cardiac stimulation, and the underlying state of the myocardium.

Figure 37-3 Mechanisms of the effects of nitrates in the generation of nitric oxide (NO) and stimulation of guanylate cyclase cyclic guanosine monophosphate (GMP), which mediates vasodilation. Sulfhydryl (SH) groups are required for the formation of NO and stimulation of guanylate cyclase. Isosorbide dinitrate is metabolized by the liver, whereas the liver is bypassed by mononitrates. GTP=guanosine triphosphate. *(Redrawn from Opie LH: Drugs for the Heart. 4th ed. Philadelphia, WB Saunders, 1995, p 33. By permission.)*

angina occurs. However, such is not the case after intracoronary administration, which implies that the systemic effects of nitrates may predominate in patients with pure effort angina.[258] Nitrates have also been shown to improve ventricular wall motion in patients with CAD, as demonstrated by contrast ventriculography, echocardiography, and radionuclide ventriculography, both at rest and during exercise. They also reduce the extent of myocardial ischemia, as reflected in exercise-thallium tomographic perfusion defect severity.[260]

ANTITHROMBOTIC EFFECTS.

Stimulation of guanylate cyclase by NO results in inhibitory action on platelets in addition to vasodilation. Although the antithrombotic effects of intravenous nitroglycerin have been demonstrated both in patients with unstable angina and in those with chronic stable angina,[261] the clinical significance of these actions is not clear.

CELLULAR MECHANISM OF ACTION.

Nitrates have the ability to cause vasodilation regardless of whether the endothelium is intact. After entering the vascular smooth muscle cell, nitrates are converted to reactive oxygen species, such as nitric oxide (NO) or *S*-nitrosothiols, which activate intracellular guanylate cyclase to produce cyclic guanosine monophosphate,[262] which in turn triggers smooth muscle relaxation and antiplatelet aggregatory effects (Fig. 37-3) . Sulfhydryl (SH) groups are required for both formation of NO and stimulation of guanylate cyclase, and nitroglycerin-induced vasodilation can be enhanced by prior administration of *N*-acetylcysteine, an agent that increases the availability of SH groups.[263] This action of *N*-acetylcysteine potentiates peripheral hemodynamic responses[263] and the coronary vasodilator effect of nitroglycerin[264] and reverses the partial tolerance to the coronary vasodilator effect of nitroglycerin.

Types of Preparations and Routes of Administration (see Table 37-4)

Nitroglycerin administered sublingually remains the drug of choice for the treatment of acute angina episodes and for the prevention of angina. Because sublingual administration avoids first-pass hepatic metabolism, a transient but effective

concentration of the drug rapidly appears in the circulation. The half-life of nitroglycerin itself is brief, and it is rapidly converted to two inactive metabolites, both of which are found in the urine. The liver possesses large amounts of hepatic glutathione organic nitrate reductase, the enzyme that breaks down nitroglycerin, but there is also evidence that blood vessels (veins and arteries) may metabolize nitrates directly. Within 30 to 60 minutes, hepatic breakdown has abolished the hemodynamic and clinical effects.

The usual sublingual dose is 0.3 to 0.6 mg, and most patients respond within 5 minutes to one or two 0.3-mg tablets. If symptoms are not relieved by a single dose, additional doses of 0.3 mg may be taken at 5-minute intervals, but no more than 1.2 mg should be used within a 15-minute period. The development of tolerance (see below) is rarely a problem with intermittent use. Sublingual nitroglycerin

TABLE 37-4 -- RECOMMENDED DOSING REGIMENS FOR LONG-TERM NITRATE THERAPY

PREPARATION OF AGENT	DOSE	SCHEDULE
NITROGLYCERIN*		
Ointment	0.5-2 inches	2-3 times daily
Buccal or transmucosal	1-3 mg	3 times daily
Transdermal patch	0.2-0.8 mg/hr	q24hr; remove at bedtime for 12-14 hr
Sublingual tablet	0.3-0.6 mg	As needed up to 3 doses 5 min apart
Spray	1-2 sprays	As needed up to 3 doses 5 min apart
Oral sustained release	2.5-6.5 mg	2-3 times daily
ISOSORBIDE DINITRATE*		
Oral	10-40 mg	2-3 times daily
Oral sustained release	80-120 mg	1-2 times daily (eccentric schedule)
ISOSORBIDE 5-MONONITRATE		
Oral	20 mg	2 times daily (given 7-8 hr apart)
Oral sustained release	30-240 mg	Once daily

*A 10- to 12-hour nitrate-free interval is recommended.

Very limited data available on efficacy.

is especially useful when it is taken prophylactically shortly before undertaking physical activities that are likely to cause angina. When used for this purpose, it may prevent

angina for up to 40 minutes.

ADVERSE REACTIONS.

Adverse reactions are common and include headache, flushing, and hypotension. The latter is rarely severe, but in some patients with volume depletion and in an upright posture, nitrate-induced hypotension is accompanied by a paradoxical bradycardia, consistent with a vasovagal or vasodepressor response. This reaction is more common in the elderly, who are less able to tolerate hypovolemia. Administration of nitrates before a meal, particularly in patients with a tendency toward postprandial hypotension, may enhance venous pooling, preload reduction, and the extent of the fall in blood pressure after the meal.[265] In addition, the partial pressure of O_2 in arterial blood may fall after large doses of nitroglycerin because of a ventilation-perfusion imbalance caused by inability of the pulmonary vascular bed to constrict in areas of alveolar hypoxia, thereby leading to perfusion of less hypoxic tissues.[266] Methemoglobinemia is a rare complication of very large doses of nitrates; commonly used doses of nitrates cause small elevations of methemoglobin that are probably not of clinical significance.

PREPARATIONS (see Table 37-4)

Nitroglycerin Tablets.

Nitroglycerin tablets tend to lose their potency, especially if exposed to light, and should thus be kept in dark containers. Other nitrate preparations are available in sublingual, buccal, oral, spray, and ointment forms. An oral nitroglycerin spray that dispenses metered, aerosolized doses of 0.4 mg may be better absorbed than the sublingual form in patients with dry mucosal membranes.[267] It can also be quickly sprayed onto or under the tongue. For prophylaxis, the spray should be used 5 to 10 minutes before angina-provoking activities.

Isosorbide Dinitrate.

This drug is an effective antianginal agent but has low bioavailability after oral administration. It undergoes hepatic metabolism rapidly, and marked variation in plasma concentrations may be seen after oral administration. It has two metabolites (one has potent vasodilator action) that are cleared less rapidly than the parent drug and excreted unchanged in the urine. It is available in tablets for sublingual use, in chewable form, in tablets for oral use, and in sustained-release capsules.

Partial or complete nitrate tolerance (see below) develops with regimens of isosorbide dinitrate when it is administered as 30 mg three or four times daily.[268] A dosage schedule should be adopted that allows a 10- to 12-hour nitrate-free interval. If the drug is administered on a three-times-daily schedule (e.g., at 8 A.M., 1 P.M., and 6 P.M.), the antianginal benefit lasts for approximately 6 hours, and the magnitude of the antianginal benefit decreases with each successive dose.[268]

Isosorbide 5-Mononitrate.

This active metabolite of the dinitrate is completely bioavailable with oral administration because it does not undergo first-pass hepatic metabolism,[269] and it is efficacious in the treatment of chronic stable angina.[270] Plasma levels of isosorbide 5-mononitrate reach their peak between 30 minutes and 2 hours after ingestion, and the drug has a plasma half-life of 4 to 6 hours. A single 20-mg tablet still exhibits activity 8 hours after administration. Tolerance has not been demonstrated with once-a-day or eccentric dosing intervals but does occur with a twice-daily dosing regimen at 12-hour intervals. The only sustained-release preparation of isosorbide 5-mononitrate is Imdur, which is given once daily in a dose of 30 to 240 mg. Presumably, this preparation avoids tolerance by either providing a sufficiently low nitrate level or a duration of activity of 12 hours or less.

Topical Nitroglycerin

Ointment.

Nitroglycerin ointment (15 mg/inch) is efficacious when applied (most commonly to the chest) in strips of 0.5 to 2.0 inches. The delay in onset of action is approximately 30 minutes. Because this form of the drug is effective for 4 to 6 hours, it is particularly useful in patients with severe angina or unstable angina who are confined to bed and chair. Nitroglycerin ointment may also be used prophylactically after retiring by patients with nocturnal angina. Skin permeability increases with increased hydration, and absorption is also enhanced if the paste is covered with plastic whose edges are taped to the skin.

Transdermal Patches.

Application of silicone gel or polymer matrix impregnated with nitroglycerin results in absorption for 24 to 48 hours at a rate determined by various methods of preparation of the patch, including a semipermeable membrane placed between the drug reservoir and the skin (usually 7.5 to 10 mg/12 hr patch, to remove after 12 hrs, and 15 mg for the phasic nitroglycerin patch). The release rate of the patches varies from 2.5 to 15 mg per 24 hours. Relatively low doses (2.5 to 5 mg per 24 hours) may not produce sufficient plasma and tissue concentrations to sustain consistent, effective antianginal effects. Transdermal nitroglycerin therapy has been shown to increase exercise duration and maintain antiischemic effects for 12 hours after patch application throughout 30 days of therapy without significant evidence of nitrate tolerance or rebound phenomena,[271] provided that the patch is not applied for more than 12 out of 24 hours.

NITRATE TOLERANCE

A major problem with the use of nitrates is the development of nitrate tolerance, which has been demonstrated with all forms of nitrate administration delivering continuous, relatively stable blood levels of the drug.[253] [268] [271] [272] Although nitrate tolerance is rapid in onset, renewed responsiveness is easily established after a short nitrate-free interval. The problem of tolerance applies to all nitrate preparations and is particularly important in patients with chronic stable angina pectoris, as opposed to those receiving short-acting courses of nitrates (e.g., unstable angina and myocardial infarction). Nitrate tolerance appears to be limited to the capacitance and resistance vessels and has not been noted in the large conductance vessels, including the epicardial coronary arteries and radial arteries, despite continuous administration of nitroglycerin for 48 hours.[273]

A meta-analysis of randomized clinical trials of nitroglycerin patches suggested that in doses of 5 to 10 mg, exercise duration was improved early after administration but, by 24 hours, the effect of nitroglycerin on exercise performance was attenuated by the development of nitrate tolerance. However, a regimen in which transdermal nitroglycerin was applied for 12 hours and removed for 12 hours improved exercise performance for 8 to 12 hours after application of the patch. After 1 month of such therapy, responsiveness to transdermal nitroglycerin remained virtually unchanged. Therefore, after application of a transdermal nitroglycerin patch, one can expect therapeutic efficacy (improved exercise performance) for 8 to 12 hours. Provided that patients have a substantial nitrate-free interval (10 to 12 hours) every 24-hour period, sustained improvement in exercise performance may be maintained. If a state of tolerance is induced, a nitrate-free interval restores responsiveness. If large intermittent doses of transdermal or oral nitrates are used (equivalent to 20 mg per 24 hours of a transdermal patch), rebound angina may occur during the nitrate-free period.

MECHANISMS (Fig. 37-3) .

Several mechanisms of nitrate tolerance have been proposed,[253] but their relative importance has not been defined.

Depletion of Sulfhydryl Groups.

The most widely accepted and most extensively studied explanation of nitrate tolerance is that intracellular SH co-factors are depleted and that they are a crucial component of the metabolic conversion of nitroglycerin to NO or *S*-nitrosothiols, a conversion necessary for activation of guanylate cyclase.[274]

Neurohormonal Activation.

Nonspecific activation of neurohormonal mechanisms may occur in response to the hypotensive effects of nitrates, with a resultant increase in plasma catecholamines, plasma renin activity, and arginine vasopressin causing sodium retention and weight gain.[275] [276] It has been suggested that ACE inhibitors modify nitrate tolerance by blunting the neurohormonal response to nitrate therapy.[277]

Plasma Volume Expansion.

Plasma volume expansion occurs during continuous nitrate administration,[275] even in the absence of neurohormonally mediated sodium retention. It may be the result of a fluid shift from the extravascular to the intravascular space in response to the vasodilating or hemodynamic actions of nitrates. However, diuretic therapy appears to have no effect on nitrate tolerance in patients with chronic CAD.[278]

Downregulation of Nitrate Receptors.

It has been proposed that high-affinity receptors, which respond to low concentrations of nitrates,

are downregulated during the development of tolerance. The activity of low-affinity receptors is maintained, and these continue to respond but require increasing concentrations of nitrate.[279]

Free Radical Generation.

A novel mechanism that may contribute to nitrate tolerance is the production of superoxide anions and other free radicals by the endothelium.[280] This mechanism is supported by two small clinical studies reporting positive results of antioxidant vitamin supplements in reducing tolerance in patients with chronic CAD.[281] [282] The mechanism of nitrate-induced free radical generation is uncertain but may involve endothelin and angiotensin II.[283]

MANAGEMENT.

The only practical strategy to manage nitrate tolerance is to prevent it by providing a "nitrate-free" interval. The optimal interval is unknown, but with patches or ointment of nitroglycerin or preparations of isosorbide dinitrate or isosorbide 5-mononitrate, a 12-hour off period is recommended.[269] The timing of administration should be adapted to the pattern of symptoms, e.g., whether angina is predominantly exercise related during the day or nocturnal. Moreover, nitroglycerin administered by the sublingual route does not result in tolerance, and even after 2 weeks of therapy, efficacy is not reduced when sublingual nitroglycerin is administered two or three times daily.[284] The use of supplemental antioxidant vitamins to attenuate nitrate tolerance is attractive, but larger-scale studies are needed to confirm the current preliminary findings.

NITRATE WITHDRAWAL.

A common form of nitrate withdrawal (rebound) is observed in patients whose angina is intensified after discontinuation of large doses of long-acting nitrates.[285] In this situation, patients may also have heightened sensitivity to constrictor stimuli.[276] [277] The potential for rebound can be modified by adjusting the dose and timing of administration in addition to the use of other antianginal drugs.

Because of the possibility of nitrate dependence, nitrate therapy should be withdrawn carefully. In persons exposed to industrial doses of nitroglycerin, nitrate tolerance, nitrate dependence, and withdrawal symptoms may cause serious problems. During the manufacture of dynamite, substantial levels of nitrates are often present in the atmosphere and can be absorbed through the skin and lungs. After an acute response of headache, hypotension, palpitations, and gastrointestinal disturbances, adaptation occurs.[286] Withdrawal from this environment may result in angina unrelated to exertion or emotion. In fact, spontaneous coronary vasospasm and acute myocardial infarction have been documented during a period of withdrawal.

INTERACTION WITH SILDENAFIL.

The combination of nitrates and sildenafil may cause serious, prolonged, and potentially life-threatening hypotension.[287] Nitrate therapy is an absolute contraindication to the use of sildenafil and vice versa. Patients who wish to take sildenafil should be aware of the serious nature of this adverse drug interaction and be warned about taking sildenafil within 24 hours of any nitrate preparation, including short-acting sublingual nitroglycerin tablets.

Beta-Adrenoceptor Blocking Agents

Beta-adrenoceptor blocking drugs (beta blockers) constitute a cornerstone of therapy for angina pectoris. In addition to their antiischemic properties, beta blockers are effective antihypertensives (see Chap. 29) and antiarrhythmics (Chap. 23) . They have also been shown to reduce mortality and reinfarction in patients after myocardial infarction (see Chap. 35) and reduce mortality in patients with heart failure (Chap. 18) . This combination of actions makes them extremely useful in the management of chronic stable angina. A number of studies have shown that beta blockers, in doses that are generally well tolerated, reduce the frequency of anginal episodes and raise the anginal threshold, both when given alone and when added to other antianginal agents.

The salutary action of these drugs (which have a chemical structure resembling that of beta-adrenoceptor agonists) depends on their ability to cause competitive inhibition of the effects of neuronally released and circulating catecholamines on beta adrenoceptors[288] (Table 37-5) . Beta blockade reduces myocardial O_2 requirements, primarily by slowing the heart rate; the slower heart rate in turn increases the fraction of the cardiac cycle occupied by diastole, with a corresponding increase in the time available for coronary perfusion (Fig. 37-4 and Table 37-6 ; see also Table 37-3) . These drugs also reduce exercise-induced increases in blood pressure and limit exercise-induced increases in contractility. Thus, beta blockers reduce myocardial O_2

demand primarily during activity or excitement, when surges of increased sympathetic activity occur.[54] Thus, in the face of impaired myocardial perfusion, the effects of beta blockers on myocardial O_2 demand may critically and favorably alter the imbalance between supply and demand, thereby resulting in the elimination of ischemia.

Beta blockers may reduce blood flow to most organs by means of the combination of unopposed alpha-adrenergic vasoconstriction and $beta_2$ receptor blockade. Complications are relatively minor, but in patients with peripheral vascular disease, the reduction in blood flow to skeletal muscles with the use of nonselective beta blockers may reduce maximal exercise capacity. In patients with preexisting left ventricular dysfunction, beta blockade may increase ventricular volume and thereby enhance O_2 demand.

Characteristics of Different Beta Blockers (see Table 37-6)

SELECTIVITY.

Two major subtypes of beta receptors, designated $beta_1$ and $beta_2$, are present in different proportions in different tissues. $Beta_1$ receptors predominate in the heart, and stimulation of these receptors leads to an increase in heart rate, atrioventricular (AV) conduction, and contractility; release of renin from juxtaglomerular cells in the kidneys; and lipolysis in adipocytes. $Beta_2$ stimulation causes bronchodilation, vasodilation, and glycogenolysis. Nonselective beta-blocking drugs (propranolol, nadolol,

TABLE 37-5 -- PHYSIOLOGICAL ACTIONS OF BETA-ADRENERGIC RECEPTORS

ORGAN	RECEPTOR TYPE	RESPONSE TO STIMULUS
HEART		
SA node	$Beta_1$	Increased heart rate
Atria	$Beta_1$	Increased contractility and conduction velocity
AV node	$Beta_1$	Increased automaticity and conduction velocity
His-Purkinje system	$Beta_1$	Increased automaticity and conduction velocity
Ventricles	$Beta_1$	Decreased automaticity, contractility, and conduction velocity
ARTERIES		
Peripheral	$Beta_2$	Dilatation
Coronary	$Beta_2$	Dilatation
Carotid	$Beta_2$	Dilatation

OTHER	$Beta_1$	Increased insulin release
		Increased liver and muscle glycogenolysis
LUNGS	$Beta_2$	Dilatation of bronchi
UTERUS	$Beta_2$	Smooth muscle relaxation

AV=atrioventricular; SA=sinoatrial.

From Abrams J: Medical therapy of stable angina pectoris. In Beller G, Braunwald E (eds): Chronic Ischemic Heart Disease. Atlas of Heart Disease. Vol 5. Philadelphia, Mosby, 1995, p 7.19. By permission of Current Medicine.

Figure 37-4 Effects of beta blockade on the ischemic heart. Beta blockade has a beneficial effect on ischemic myocardium unless (1) the preload rises substantially as in left-sided heart failure or (2) vasospastic angina is present, in which case spasm may be promoted in some patients. Note the recent proposal that beta blockade diminishes exercise-induced vasoconstriction. *(Redrawn from Opie LH: Drugs for the Heart. 4th ed. Philadelphia, WB Saunders, 1995. Figure copyright L.H. Opie.)*

penbutolol, pindolol, sotalol, timolol, carteolol) block both $beta_1$ and $beta_2$ receptors, whereas cardioselective beta blockers (acebutolol, atenolol, betaxolol, bisoprolol, esmolol, and metoprolol) block $beta_1$ receptors while having less effect on $beta_2$ receptors. Thus, cardioselective beta blockers reduce myocardial O_2 requirements while tending to not block bronchodilation, vasodilation, or glycogenolysis. However, as the doses of these drugs are increased, this cardioselectivity diminishes. Because cardioselectivity is only relative, the use of cardioselective beta blockers in doses sufficient to control angina may still cause bronchoconstriction in some susceptible patients.

Some beta blockers also cause vasodilatation. Such drugs include labetalol (an alpha-adrenergic blocking agent and $beta_2$ agonist, see Chap. 29) , carvedilol (with alpha- and $beta_1$ -blocking activity), and bucindolol (a nonselective beta blocker that causes direct [non-alpha-adrenergic-mediated] vasodilation).[289]

ANTIARRHYTHMIC ACTIONS (see also Chap. 23) .

Beta blockers have antiarrhythmic properties as a direct effect of their ability to block sympathoadrenal myocardial stimulation, which in certain situations may be arrhythmogenic.[290] Sotalol has combined class II (beta blocking) and class III antiarrhythmic activities; it is an attractive drug when it is desired to treat angina and suppress ventricular tachyarrhythmias.[291]

MEMBRANE-STABILIZING ACTIVITY.

This property refers to the "quinidine-like" effect of certain beta blockers in reducing the rate of rise in cardiac action potential. The clinical relevance of this effect is negligible (except perhaps in cases of overdose) because it is observed only at concentrations far exceeding therapeutic levels.[292]

INTRINSIC SYMPATHOMIMETIC ACTIVITY.

Beta blockers with intrinsic sympathomimetic activity (ISA), such as acebutolol, carteolol, celiprolol, penbutolol, and pindolol, are partial beta agonists that also produce blockade by shielding beta receptors from more potent beta agonists. Pindolol and acebutolol produce low-grade beta stimulation when sympathetic activity is low (at rest), whereas these partial agonists behave more like conventional beta blockers when sympathetic activity is high. Agents with ISA may not be as effective as those without this property in reducing the heart rate or the frequency, duration, and magnitude of ambulatory ST segment changes or in increasing the duration of exercise in patients with severe angina.[293]

POTENCY.

Potency can be measured by the ability of beta blockers to inhibit the tachycardia produced by isoproterenol. All drugs are considered in reference to propranolol, which is given a value of 1.0 (see Table 37-6) . Timolol and pindolol are the most potent agents, and acebutolol and labetalol are the least potent.

LIPID SOLUBILITY.

The hydrophilicity or lipid solubility of beta blockers is a major determinant of their absorption and metabolism. The lipid-soluble (lipophilic) beta blockers propranolol, metoprolol, and pindolol are readily absorbed from the gastrointestinal tract, are metabolized predominantly by the liver, have a relatively short half-life, and usually require administration twice or more daily to achieve continuing pharmacological effects. The water-soluble (hydrophilic) beta blockers (atenolol, sotalol, and nadolol) are not as readily absorbed from the gastrointestinal tract, are not as extensively metabolized, have relatively long plasma half-lives, and can be administered once daily. If either metoprolol or propranolol is administered intravenously, a much higher concentration reaches the bloodstream, and therefore intravenous dosing has much greater potency than oral dosing.

ALPHA ADRENOCEPTOR BLOCKING ACTIVITY.

The alpha-blocking potency of labetalol is approximately 20 percent of its beta-blocking potency, and it is also one of the weaker beta blockers in comparison with propranolol,[294] although it possesses significant ISA (see Table 37-6) . Labetalol's

combined alpha- and beta-blocking effects make it a particularly useful antihypertensive agent (see Chap. 29) , and it is especially so in patients with hypertension and angina. The major side effects of labetalol are postural hypotension and retrograde ejaculation.

OXIDATION PHENOTYPE.

Metoprolol and propranolol are lipid-soluble beta blockers noted for the variability of their pharmacokinetics, drug metabolism, and pharmacodynamics. The oxidative metabolism of metoprolol exhibits the debrisoquin type of genetic polymorphism; poor hydroxylators or metabolizers (up to 10 percent of whites) have significant prolongation of the elimination half-life of the drug in comparison to extensive hydroxylators or metabolizers. Thus, angina might be controlled by a single daily dose of metoprolol in poor metabolizers, whereas extensive metabolizers require the same dose two or three times a day.[295] If a patient exhibits an exaggerated clinical response (e.g., extreme bradycardia) following the administration of metoprolol, propranolol, or other lipid-soluble beta blockers, it may be the result of prolongation of the elimination half-life because of slow oxidative metabolism.

EFFECTS ON SERUM LIPIDS.

Beta blocker therapy (with agents lacking ISA) usually causes no significant changes in total or LDL cholesterol but increases triglycerides and reduces HDL cholesterol.[296] The most commonly studied drug has been propranolol, which can increase plasma triglyceride concentrations by up to 50 percent and reduce HDL cholesterol by approximately 15 percent. Adverse effects on the lipid profile may be more frequent with nonselective than with $beta_1$ -selective blockers. Two drugs possessing ISA--acebutolol and pindolol--do not significantly change total cholesterol, triglycerides, or LDL cholesterol, and pindolol increases serum HDL cholesterol. The effects of these changes in serum lipids by long-term administration of beta blockers must be considered when this therapy is begun or maintained for either hypertension or angina.[296]

DOSAGE.

For optimal results, the dosage of a beta blocker should be carefully adjusted. In the case of propranolol, it is usual to start with a dose of 80 mg daily (20 mg four times a day); other beta blockers should be started

TABLE 37-6 -- PHARMACOKIN

CHARACTERISTIC	ATENOLOL	METOPROLOL/XL	NADOLOL	PINDOLOL	PROPRANOLOL/

Extent of absorption (%)	50	>95	30	>90	>90
Extent of bioavailability (% of dose)	40	50/77	30	90	30/20
Beta-blocking plasma concentration	0.2-0.5 mug/ml	50-100 ng/ml	50-100 ng/ml	50-100 ng/ml	50-100 ng/ml
Protein binding (%)	<5	12	30	57	93
Lipophilicity[*]	Low	Moderate	Low	Moderate	High
Elimination half-life (hr)	6-9	3-7	14-25	3-4	3.5 to 6/8-11
Drug accumulation in renal disease	Yes	No	Yes	No	No
Route of elimination	RE (mostly unchanged)	HM	RE	RE (40% unchanged and HM)	HM
Beta-blocker potency ratio (propranolol=1)	1.0	1	1.0	6.0	1
Adrenergic receptor blocking activity	$beta_1$ [¶]	$beta_1$ [¶]	$beta_1$ /$beta_2$	$beta_1$ /$beta_2$	$beta_1$ /$beta_2$
Intrinsic sympathetic activity	0	0	0	+	0
Membrane-stabilizing activity	0	0	0	+	++
Usual maintenance dose	50-100 mg/d	50-100 mg b.i.d.-q.i.d./50-400 mg/d	40-80 mg/d	10-40 mg/d (b.i.d.-t.i.d.)	80-320 mg/d (b.i.d.-t.i.d.)/80-160 mg/d
FDA-approved indications		XL			LA
Hypertension	Yes	Yes Yes	Yes	Yes	Yes Yes
Angina	Yes	Yes Yes	Yes	No	Yes Yes
Postmyocardial infarction	Yes	Yes No	No	No	Yes No

FDA=Food and Drug Administration; HM=hepatic metabolism; ND=no data; RE=renal excretion.

*Determined by the distribution ratio between octanol and water.

Half-life of the active metabolite, diacetolol, is 12 to 15 hours.

Acebutolol is mainly eliminated by the liver, but its major metabolite, diacetolol, is excreted by the kidney.
§Rapid metabolism by esterases in the cytosol of red blood cells.
¶Beta$_1$ selectivity is maintained at lower doses, but beta$_2$ receptors are inhibited at higher doses.

at comparable doses. Twenty-four to 48 hours is required for the drug to achieve an antianginal effect. Efficacy is determined by its effect on the heart rate and symptoms, and when these are unclear, its effect on exercise performance can be evaluated by treadmill exercise testing. The resting heart rate should be reduced to between 50 and 60 beats/min, and an increase of less than 20 beats/min should occur with modest exercise[297] (e.g., climbing one flight of stairs). The usual dosage of propranolol ranges from 80 to 320 mg/day, but some patients require (and tolerate) much higher doses. Therapy needs to be individualized and requires repeated clinical evaluation during the initial period of drug administration.

ADVERSE EFFECTS AND CONTRAINDICATIONS.

Most of the adverse effects of beta blockers occur as a consequence of the known properties of these drugs and include cardiac effects (severe sinus bradycardia, sinus arrest, AV block, reduced left ventricular contractility), bronchoconstriction, fatigue, mental depression, nightmares, gastrointestinal upset, sexual dysfunction, intensification of insulin-induced hypoglycemia, and cutaneous reactions (Table 37-7) . Lethargy, weakness, and fatigue may be caused by reduced cardiac output or may arise from a direct effect on the central nervous system. Bronchoconstriction results from blockade of beta$_2$ receptors in the tracheobronchial tree. As a consequence, asthma and chronic obstructive lung disease are contraindications to beta blockers, even to beta$_1$ -selective agents.[298]

In patients who already have impaired left ventricular function, congestive heart failure may be intensified, an effect that can be counteracted in part by the use of digitalis or diuretics. Beginning therapy with a very low dose (e.g., metoprolol, 12.5 mg daily, for the first week) and then gradually increasing the dose over the course of several weeks has been shown to be beneficial in patients with idiopathic dilated cardiomyopathy and those with heart failure caused by ischemic heart disease (see Chap. 18) .

Beta blockers should be prescribed with great caution in patients with cardiac conduction disease involving either the sinus node or the AV conduction system. In patients with symptomatic conduction disease, beta blockers are contraindicated unless a pacemaker is in place. In patients with asymptomatic sinus node dysfunction or first-degree AV block, beta blockers may be tolerated, but their administration

TABLE 37-7 -- CANDIDATES FOR USE OF BETA-BLOCKING AGENTS FOR ANGINA

Ideal Candidates
Prominent relationship of physical activity to attacks of angina
Coexistent hypertension
History of supraventricular or ventricular arrhythmias
Previous myocardial infarction
Left ventricular systolic dysfunction
Mild to moderate heart failure symptoms (NYHA functional Class II-III)
Prominent anxiety state
Poor Candidates
Asthma or reversible airway component in chronic lung disease patients
Severe left ventricular dysfunction with severe heart failure symptoms (NYHA functional Class IV)
History of severe depression
Raynaud's phenomenon
Symptomatic peripheral vascular disease
Severe bradycardia or heart block
Brittle diabetes
NYHA=New York Heart Association.
Modified from Abrams JA: Medical therapy of stable angina pectoris. In Beller G: Chronic Ischemic Heart Disease. In Braunwald E (ed): Atlas of Heart Disease. Vol 5. Philadelphia, Mosby, 1995, p 7.22. By permission of Current Medicine.

requires careful observation. Pindolol, because of its ISA activity, may be preferable in this situation. Blockade of noncardiac $beta_2$ receptors inhibits catecholamine-induced glycogenolysis, so noncardioselective beta blockers can impair the defense to insulin-induced hypoglycemia. Blockade of $beta_2$ receptors also inhibits the vasodilating effects of catecholamines in peripheral blood vessels and leaves the constrictor (alpha-adrenergic) receptors unopposed, thereby enhancing vasoconstriction. Noncardioselective beta blockers may precipitate episodes of Raynaud's phenomenon in patients with this condition and may cause uncomfortable coldness in the distal extremities. Reduced flow to the limbs may occur in patients with peripheral vascular disease.[299]

Abrupt withdrawal of beta-adrenoceptor blocking agents after prolonged administration can result in increased total ischemic activity in patients with chronic stable angina. This increased ischemia may be caused by a return to the previously high levels of myocardial O_2 demand while the underlying atherosclerotic process has progressed.[300] Occasionally, such withdrawal can precipitate unstable angina and may in rare cases

even provoke myocardial infarction. Chronic beta blocker therapy can be safely discontinued by slowly withdrawing the drug in a stepwise manner over the course of 2 to 3 weeks. If abrupt withdrawal of beta blockers is required, patients should be instructed to reduce exertion and manage angina episodes with sublingual nitroglycerin and/or substitute a calcium antagonist.

Calcium Antagonists (see also Chap. 29)

The critical role of calcium ions in the normal contraction of cardiac and vascular smooth muscle is discussed in Chapter 14 . Calcium antagonists are a heterogeneous group of compounds that inhibit calcium ion movement through slow channels in cardiac and smooth muscle membranes by noncompetitive blockade of voltage-sensitive L-type calcium channels[301] [302] [303] [303A] (see Fig. 14-14) . The three major classes of calcium antagonists are the dihydropyridines (nifedipine is the prototype), the phenylalkylamines (verapamil is the prototype), and the modified benzothiazepines (diltiazem is the prototype). The two predominant effects of calcium antagonists result from blocking the entry of calcium ions and slowing recovery of the channel.[303A] Phenylalkylamines have a marked effect on recovery of the channel and thereby exert depressant effects on cardiac pacemakers and conduction, whereas dihydropyridines, which do not impair channel recovery, have little effect on the conduction system.

MECHANISM OF ACTION.

The efficacy of calcium antagonists in patients with angina pectoris is related to the reduction in myocardial O_2 demand and the increase in O_2 supply that they induce[303A] (see Table 37-3) . The latter effect is particularly important in patients with conditions in which a prominent vasospastic or vasoconstrictor component may be present, such as Prinzmetal (variant) angina (see p. 1324), variable-threshold angina (p. 1276), and angina related to impaired vasodilator reserve of small coronary arteries.[304] Calcium antagonists may be effective on their own or in combination with beta-adrenoceptor blockers and nitrates in patients with chronic stable angina.[301] [305] [306]

Several calcium antagonists are effective for the treatment of angina pectoris (Table 37-8) . Each of these agents is effective in causing relaxation of vascular smooth muscle in both the systemic arterial and coronary arterial beds. In addition, blockade of the entry of calcium into myocytes results in a negative inotropic effect, which is counteracted to some extent by peripheral vascular dilation and by activation of the sympathetic nervous system in response to drug-induced hypotension.[302] However, the negative inotropic effect must be taken into consideration in patients with significant left ventricular dysfunction.

TABLE 37-8 -- PHARMACOKINETICS OF CALCIUM ANTAGONISTS USED C

CHARACTERISTIC	DILTIAZEM/SR	NICARDIPINE	NIFEDIPINE/SR	VERAPAMIL/SR
Usual adult dose	IV: 0.25-mg/kg bolus, then 5-15 mg/hr	IV: 3-15 mg/hr	Oral: 10-30 mg t.i.d.	IV: 0.075-0.15 mg/kg
	Oral: 30-90 mg t.i.d.-q.i.d.	Oral: 20-40 mg t.i.d.	SR: 90 mg/d	Oral: 80-120 mg t.i.d.-q.i.d.
	SR: 60-180 mg b.i.d.	SR: 30-60 mg b.i.d.		SR: 180-480 mg/d
	CD: 120-480 mg/d			
Extent of absorption (%)	80-90	100	90	90
Extent of bioavailability (%)	40-70	30	65-75/86	20-35
Onset of action	IV: 3 min	IV: 1 min	20 min	IV: 2-5 min
	Oral: 30-60 min	Oral: 20 min		Oral: 30 min
Time to peak serum concentration (hr)	2-3/6-11	0.5-2.0	0.5/6	IV: 3-5 min
				Oral: 1-2
				SR: 7-9
Therapeutic serum levels (ng/ml)	50-200	30-50	25-100	80-300
Elimination half-life (hr)	3.5/5-7	2.0-4.0	2.0-5.0	3.0-7.0*
Elimination	60% metabolized by liver; remainder excreted by kidneys	High first-pass hepatic metabolism	High first-pass hepatic metabolism	85% eliminated by first-pass hepatic metabolism
Heart rate				
Peripheral vascular resistance				
FDA-approved indications	IR SR		IR SR	IR SR
Hypertension	No Yes	Yes	No Yes	Yes Yes

Angina	Yes No	Yes	Yes Yes	Yes No
Coronary spasm	Yes No	No	Yes Yes	Yes No

CD=combination drug; CR=controlled release; FDA=Food and Drug Administration; IR=immediate rel

*Half-life of 4.5 to 12 hours with multiple dosing; may be prolonged in the elderly.

The sustained-release formulation may be preferred for hypertension.

With a rapid onset of action and metabolism by the liver, calcium antagonists have a limited bioavailability of between 13 and 52 percent and a half-life of between 3 and 12 hours. Amlodipine and bepridil are exceptions in that both drugs have long half-lives and may be administered once daily. In the case of some of the other calcium antagonists, sustained-release preparations have been shown to be effective.

ANTIATHEROGENIC ACTION.

Studies in experimental animals, both primates and nonprimates, have suggested that calcium antagonists might have an antiatherogenic effect, and human studies support this conclusion.[307] [308] In multicenter randomized trials using quantitative coronary arteriography, significantly fewer new lesions developed in patients showing mild CAD and taking nifedipine than in patients taking placebo. However, preexisting lesions did not appear to be affected. Prolonged follow-up is necessary to determine whether these angiographic observations are accompanied by clinical benefit. In patients undergoing cardiac transplantation, diltiazem has been reported to be beneficial in reducing the frequency and severity of coronary arteriopathy in the transplanted heart.[309]

First-Generation Calcium Antagonists

NIFEDIPINE.

This dihydropyridine is a particularly effective dilator of vascular smooth muscle and is a more potent vasodilator than either diltiazem or verapamil. Although its in vitro actions on myocardium and specialized cardiac tissue are similar to those of other agents, the concentration required to reproduce effects on these tissues is not reached in vivo because of the early appearance of its powerful vasodilating effects. Thus, in clinical practice, the potential negative chronotropic, inotropic, and dromotropic (on AV conduction) effects of nifedipine are seldom a problem, although even nifedipine can worsen heart failure in patients with preexisting chronic congestive heart failure.[310]

In contrast to beta blockers, which decrease the heart rate and the rate-pressure product at rest and during exercise, nifedipine reduces only systolic pressure.[311] Thus,

the beneficial effects of nifedipine in the treatment of angina result from its capacity to reduce myocardial O_2 requirements because of its afterload-reducing effect and to increase myocardial O_2 delivery as a result of its dilating action on the coronary vascular bed (see Table 37-3) . In patients without heart failure, nifedipine causes modest reflex increases in the ejection fraction, velocity of circumferential fiber shortening, heart rate, and cardiac index; these increases can be blocked by beta-adrenoceptor blockade.

The initial dose is 10 mg orally every 8 hours, increased stepwise to 20 mg every 6 hours guided by the blood pressure response, to a maximal daily dose of 160 mg. An extended-release formulation using the gastrointestinal therapeutic system (GITS) of drug delivery (see Table 37-8) is designed to deliver 30, 60, or 90 mg of nifedipine in a single daily dose at a relatively constant rate over a 24-hour period and is useful for the treatment of chronic stable angina, Prinzmetal angina, and hypertension. [312] The efficacy of the extended-release preparation, either alone or in conjunction with beta blockers, in reducing episodes of angina and ischemia on ambulatory monitoring has been documented.[313]

Adverse Effects.

Adverse effects occur in 15 to 20 percent of patients and require discontinuation of medication in about 5 percent. Most adverse effects are related to systemic vasodilation and include headache, dizziness, palpitations, flushing, hypotension, and leg edema (unrelated to heart failure). Gastrointestinal side effects, including nausea, epigastric pressure, and vomiting, are noted in approximately 5 percent of patients. In rare instances, in patients with extremely severe, fixed coronary obstructions, nifedipine aggravates angina, presumably by lowering arterial pressure excessively, with subsequent reflex tachycardia. For this reason, combined treatment of angina with nifedipine and a beta blocker is particularly effective and superior to nifedipine alone.[306] [311] Most of the adverse effects are reduced by the use of extended-release preparations.

Several clinical case-control studies of hypertension and associated reviews have suggested that *short-acting nifedipine* may cause an increase in mortality.[314] [315] [316] [317] These findings have not been confirmed by other case-control studies,[318] [319] and these conclusions have not been accepted universally. No firm data indicate that this risk applies to extended-release nifedipine or to other calcium antagonists.[320] [321] Although insufficient data are available to assess the long-term risks (if any) of calcium antagonists in chronic CAD, *long-acting nifedipine* should be considered an effective and safe antianginal drug for the treatment of symptomatic patients with chronic CAD who are already receiving beta blockers, with or without nitrates. Shortacting nifedipine should ordinarily be avoided.

Because of its potent vasodilator effects, nifedipine is contraindicated in patients who are hypotensive or have severe aortic valve stenosis and in patients with unstable angina who are not simultaneously receiving a beta blocker and in whom reflex-mediated increases in the heart rate may be harmful. Nifedipine (or one of the second-generation dihydropyridines) is the calcium antagonist of choice in patients with mild left ventricular dysfunction, sinus bradycardia, sick sinus syndrome, or AV block

(particularly if a beta-adrenoceptor blocking agent is administered concurrently and additional drug therapy for angina is indicated).[306] This recommendation is based on nifedipine having fewer negative effects on myocardial contractility, heart rate, and AV conduction than seen with verapamil or diltiazem in doses used clinically. Nonetheless, in patients with more serious left ventricular dysfunction, all calcium antagonists--even nifedipine--can precipitate heart failure.[310]

Nifedipine interacts significantly with prazosin (resulting in excessive hypotension), cimetidine, and phenytoin (resulting in increased bioavailability of nifedipine and increased quinidine clearance). Nifedipine increases blood levels of propranolol, and use of the two drugs together poses the risk of an added negative inotropic and hypotensive effect.[311] In patients with Prinzmetal angina, abrupt cessation of nifedipine therapy may result in a rebound increase in the frequency and duration of attacks.

VERAPAMIL (see also Chap. 23) .

Verapamil dilates systemic and coronary resistance vessels and large coronary conductance vessels. It slows the heart rate and reduces myocardial contractility. This combination of actions results in a reduction in myocardial O_2 requirement, which is the basis for the drug's efficacy in the management of chronic stable angina. Thrombus formation and thrombin-mediated platelet aggregation are decreased by verapamil,[322] effects also observed with transdermal nitroglycerin. To what extent the clinical benefits of verapamil and nitrates are related to their effects on platelet aggregation and thrombus formation is uncertain.

Verapamil reduces the frequency of angina and prolongs exercise tolerance in patients with symptomatic chronic CAD, and the combination of verapamil and a beta blocker provides clinical benefit that is additive.[323] Despite the marked negative inotropic effects of verapamil in isolated cardiac muscle preparations, changes in contractility are modest in patients with normal cardiac function. However, in patients with cardiac dysfunction, verapamil, like beta blockers, may reduce cardiac output, increase left ventricular filling pressure, and cause clinical heart failure. In clinically useful doses, verapamil inhibits calcium influx into specialized cardiac cells, sometimes causing slowing of the heart rate and AV conduction. Therefore, it is contraindicated in patients with preexisting AV nodal disease or sick sinus syndrome, congestive heart failure, and suspected digitalis or quinidine toxicity.

The usual starting dose of verapamil for oral administration is 40 to 80 mg three times daily to a maximal dose of 480 mg/d (see Table 37-8) . Sustained-release capsules of verapamil are available (60, 90, and 120 mg), and starting doses are 60 to 120 mg twice daily with a usual optimal dose range of 240 to 360 mg/d.

Verapamil interacts significantly with several other drugs. Intravenous verapamil should not be used together with a beta blocker (given intravenously or orally), nor should a beta blocker be administered intravenously in patients

receiving oral verapamil. The bioavailability of verapamil is increased by cimetidine and carbamazepine, whereas verapamil may increase plasma levels of cyclosporine and digoxin and may be associated with excessive hypotension in patients receiving quinidine or prazosin. Hepatic enzyme inducers such as phenobarbital may reduce the effects of verapamil.

Adverse effects of verapamil are noted in approximately 10 percent of patients and relate to systemic dilation (hypotension and facial flushing), gastrointestinal symptoms (constipation and nausea), and central nervous system reactions such as headache and dizziness. A rare side effect is gingival hyperplasia, which appears after 1 to 9 months of therapy.

DILTIAZEM.

Diltiazem's actions are intermediate between those of nifedipine and verapamil. In clinically useful doses, its vasodilator effects are less profound than nifedipine's, and its cardiac depressant action (on the sinoatrial and AV nodes and myocardium) is less than that of verapamil. This profile may explain the remarkably low incidence of adverse effects of diltiazem. This drug is a systemic vasodilator that lowers arterial pressure at rest and during exertion and increases the workload required to produce myocardial ischemia, but it may also increase myocardial O_2 delivery. Although diltiazem causes little vasodilation of epicardial coronary arteries under basal conditions, it may enhance perfusion of the subendocardium distal to a flow-limiting coronary stenosis[324] ; it also blocks exercise-induced coronary vasoconstriction. In patients with chronic stable angina receiving maximally tolerated doses of diltiazem, the heart rate is significantly reduced at rest, but no effect on peak blood pressure is achieved during exercise, and the duration of symptom-limited treadmill exercise is prolonged.

The dose of diltiazem is 30 to 60 mg four times daily, although higher doses are sometimes needed. Several sustained-release formulations have been approved and are available for once-daily treatment of systemic hypertension and angina pectoris.[325]

Diltiazem is a highly effective antianginal agent. Atenolol and diltiazem have similar efficacy in increasing nonischemic exercise duration in patients with variable-threshold angina and act primarily by slowing the resting heart rate.[326] High doses (mean dose, 340 mg) have been shown to be a relatively safe addition to maximally tolerated doses of isosorbide dinitrate and a beta blocker and cause increases in exercise tolerance and resting and exercise left ventricular ejection fraction.[325] Major side effects are similar to those of the other calcium channel blockers and are related to vasodilation, but they are relatively infrequent, particularly if the dose does not exceed 240 mg/d. As is the case with verapamil, diltiazem should be prescribed with caution for patients with sick sinus syndrome or AV block. In patients with preexisting left ventricular dysfunction, diltiazem may exacerbate or precipitate heart failure.

Diltiazem interacts with other drugs, including beta-adrenergic blocking agents (causing enhanced negative inotropic, chronotropic, and dromotropic effects), flecainide, and cimetidine (which increases the bioavailability of diltiazem), and diltiazem has been associated with increased plasma levels of cyclosporine, carbamazepine, and lithium carbonate. Diltiazem may cause excessive sinus node depression if administered with disopyramide and may reduce digoxin clearance, especially in patients with renal failure.[327]

Second-Generation Calcium Antagonists

The second-generation calcium antagonists (nicardipine, isradipine, amlodipine, and felodipine) are mainly dihydropyridine derivatives, with nifedipine being the prototypical agent. Considerable experience has also accumulated with nimodipine, nisoldipine, and nitrendipine. These agents differ in potency, tissue specificity, and pharmacokinetics and, in general, are potent vasodilators because of greater vascular selectivity than seen with the first-generation antagonists, i.e., verapamil, nifedipine, and diltiazem.

AMLODIPINE.

This agent, which is less lipid soluble than nifedipine, has a slow, smooth onset and ultra-long duration of action (plasma half-life of 36 hours). It causes marked coronary and peripheral dilatation and may be useful in the treatment of patients with angina accompanied by hypertension. It may be used as a once-daily hypotensive or antianginal agent.[328] In a series of randomized placebo-controlled studies in patients with stable exercise-induced angina pectoris, amlodipine was shown to be effective and well tolerated.[329] It has little, if any, negative inotropic action and may be especially useful in patients with chronic angina and left ventricular dysfunction. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) investigators enrolled 1153 patients with New York Heart Association Class III to IV failure and a mean ejection fraction of 21 percent.[330] When amlodipine versus placebo was added to a full regimen of digoxin, diuretic, and ACE inhibitor therapy, no significant difference in survival was observed in patients with ischemic cardiomyopathy. Although amlodipine did not have a beneficial effect on mortality, these data suggest that in patients with congestive heart failure caused by severe CAD, amlodipine may be safely added for control of hypertension or angina, without an adverse effect on survival.[330]

NICARDIPINE.

This drug has a similar half-life to that of nifedipine (2 to 4 hours), but it appears to have greater vascular selectivity. Nicardipine may be used as an antianginal and antihypertensive agent and requires three-times-daily administration, although a sustained-release formulation is available for twice-daily dosing in hypertension. For chronic stable angina pectoris, it appears to be as effective as verapamil or diltiazem, and its efficacy is enhanced when combined with a beta blocker.

FELODIPINE AND ISRADIPINE.

In the United States, both drugs are approved by the Food and Drug Administration (FDA) for the treatment of hypertension but not for angina pectoris. A recent study documented similar efficacy between felodipine and nifedipine in patients with chronic stable angina.[331] Felodipine has also been reported to be more vascular selective than nifedipine and to have a mild positive inotropic effect as a result of calcium channel agonist properties. Isradipine has a longer half-life than nifedipine and demonstrates greater vascular sensitivity.

BEPRIDIL.

This calcium antagonist interacts with dihydropyridine-binding sites and also has a sodium channel blocking effect. It markedly prolongs the atrial refractory period and may be useful in the treatment of patients with angina and arrhythmias. However, it is also arrhythmogenic and causes QT prolongation and torsades de pointes.[332] Although chemically unrelated to the other calcium channel blockers, bepridil has been shown to be an effective antianginal agent. Nonetheless, because of its potential to prolong the QT interval and to cause torsades de pointes, the drug should be reserved only for patients in whom other antianginal drugs have failed. Interactions with antiarrhythmic agents, tricyclic antidepressants, and cardiac glycosides are potentially hazardous.

Medical Management of Angina Pectoris

RELATIVE ADVANTAGES OF BETA BLOCKERS AND CALCIUM ANTAGONISTS (seeTable 37-9) .

The choice between a beta blocker and a calcium channel antagonist as initial therapy in patients with chronic stable angina is controversial because both classes of agents are effective in relieving symptoms and reducing ischemia.[333] Trials comparing beta blockers and calcium antagonists have not shown any difference

TABLE 37-9 -- RECOMMENDED DRUG THERAPY (CALCIUM ANTAGONIST VS. BETA BLOCKER) IN PATIENTS WHO HAVE ANGINA IN CONJUNCTION WITH OTHER MEDICAL CONDITIONS

CLINICAL CONDITION	RECOMMENDED DRUG
CARDIAC ARRHYTHMIA OR CONDUCTION DISTURBANCE	
Sinus bradycardia	Nifedipine or amlodipine
Sinus tachycardia (not caused by cardiac failure)	Beta blocker

Supraventricular tachycardia	Beta blocker (verapamil)
Atrioventricular block	Nifedipine or amlodipine
Rapid atrial fibrillation (with digitalis)	Verapamil or beta blocker
Ventricular arrhythmia	Beta blocker
LEFT VENTRICULAR DYSFUNCTION	
Heart failure	Beta blocker
MISCELLANEOUS MEDICAL CONDITIONS	
Systemic hypertension	Beta blocker (calcium antagonist)
Severe preexisting headaches	Beta blocker (verapamil or diltiazem)
COPD with bronchospasm or asthma	Nifedipine, amlodipine, verapamil, or diltiazem
Hyperthyroidism	Beta blocker
Raynaud's syndrome	Nifedipine or amlodipine
Claudication	Calcium antagonist
Severe depression	Calcium antagonist
COPD=chronic obstructive pulmonary disease. (alternatives in parentheses)	

in the rate of death or myocardial infarction,[334] [335] [336] [337] although in some studies beta blockers appeared to have greater clinical efficacy.[334] [336] [337] Because long-term administration of beta blockers has been demonstrated to prolong life in patients after acute myocardial infarction and in the treatment of hypertension, it is reasonable to consider beta blockers over calcium antagonists as the agents of choice in treating patients with chronic stable angina. However, it must be recognized that beta blockers (without ISA) increase serum triglycerides and decrease HDL cholesterol with uncertain long-term consequences.[296] In addition, these drugs may produce fatigue, depression, and sexual dysfunction. In contrast, long-term administration of calcium antagonists has not been shown to improve long-term survival after acute myocardial infarction,[338] although diltiazem is apparently effective in preventing severe angina and early reinfarction after non-Q-wave infarction[339] and verapamil reduces reinfarction rates,[340] whereas nifedipine has been associated with the development of fewer new coronary artery lesions[307] in patients with established CAD.

The choice of drug with which to initiate therapy is influenced by a number of clinical factors (see Table 37-9) .

1. Calcium antagonists are the preferred agents in patients with a history of asthma, chronic obstructive lung disease, and/or wheezing on clinical examination, in whom beta blockers, even relatively selective agents, are contraindicated.
2. Nifedipine (long acting), amlodipine, and nicardipine are the calcium antagonists of choice in patients with chronic stable angina and sick sinus syndrome, sinus bradycardia, or significant AV conduction disturbances, whereas beta blockers and verapamil should be used only with great caution in such patients. In patients

with symptomatic conduction disease, neither a beta blocker nor a calcium channel blocker should be used unless a pacemaker is in place. If a beta blocker is required in patients with asymptomatic evidence of conduction disease, pindolol, which has the greatest ISA, is useful. In the case of calcium channel blockers, nifedipine or nicardipine is preferable to verapamil and diltiazem, but careful observation for deterioration of conduction is mandatory.

3. Calcium antagonists are clearly preferred in patients with suspected Prinzmetal (variant) angina; beta blockers may even aggravate angina under these circumstances.
4. Calcium antagonists may be preferred over beta blockers in patients with significant symptomatic peripheral arterial disease because the latter may cause peripheral vasoconstriction.
5. Beta blockers should usually be avoided in patients with a history of significant depressive illness and should be prescribed cautiously for patients with sexual dysfunction, sleep disturbance, nightmares, fatigue, or lethargy.
6. The presence of moderate to severe left ventricular dysfunction in patients with angina limits the therapeutic options. The beneficial effects of beta blockers on survival in patients with left ventricular dysfunction after myocardial infarction,[237] [238] coupled with their beneficial effects on survival and left ventricular performance in patients with heart failure,[341] [342] has established beta blockers as the drug class of choice for the treatment of angina in patients with left ventricular dysfunction, with or without symptoms of heart failure, together with ACE inhibitors, digitalis, and diuretics. If angina persists despite beta blockade and nitrates, amlodipine can be administered.[330] Verapamil, nifedipine, and diltiazem should be avoided.
7. Short-acting nifedipine should not be used as the initial and only agent in patients with unstable angina (see Chap. 36) because the reflex-mediated tachycardia may aggravate unstable angina.[343] However, long-acting nifedipine may be helpful if symptoms persist despite therapy with a beta blocker, aspirin, nitrates, and antithrombotic agents.
8. Hypertensive patients with angina pectoris do well with either beta blockers or calcium antagonists because both agents have antihypertensive effects. However, beta blockers are the preferred initial agent for treating angina in such patients, as noted above, and an ACE inhibitor should be strongly considered for all patients with CAD who have hypertension.[214]

COMBINATION THERAPY.

The combination of a beta blocker, calcium antagonist, and long-acting nitrate is widely used in the management of chronic stable angina.[337] When adrenergic blockers and calcium antagonists are used together in the treatment of angina pectoris, several issues should be considered:

1. The addition of a beta blocker enhances the clinical effect of nifedipine and other dihydropyridines.
2. In patients with moderate or severe left ventricular dysfunction, sinus bradycardia, or AV conduction disturbances, combination therapy with calcium antagonists and beta blockers either should be avoided or should be initiated with caution. In patients with AV conduction system

disease, the preferred combination is long-acting nifedipine or another dihydropyridine and a beta blocker. The negative inotropic effects of calcium antagonists are not usually a problem in combined therapy with low doses of beta blockers but can become significant with higher doses. With such doses, amlodipine is the calcium antagonist of choice, but it should be used cautiously.
3. The combination of a dihydropyridine and a long-acting nitrate (without a beta blocker) is not an optimal combination because both are vasodilators.

Approach to Patients with Chronic Stable Angina

1. Identify and treat precipitating factors, such as anemia, uncontrolled hypertension, thyrotoxicosis, tachyarrhythmias, uncontrolled congestive heart failure, and concomitant valvular heart disease.
2. Initiate risk factor modification, physical exercise, diet, and life style counseling. Initiate therapy with an HMG-CoA reductase inhibitor, as needed, to reduce LDL cholesterol below 100 mg/dl.
3. Initiate pharmacotherapy with aspirin and a beta blocker. Strongly consider an ACE inhibitor as first-line therapy in all patients with chronic CAD.
4. Use sublingual nitroglycerin for alleviation of symptoms and prophylactically.
5. If episodes occur more than two or three times per week, the next step is addition of a calcium antagonist or a long-acting nitrate via eccentric dosing schedules to prevent nitrate tolerance. The decision to add a calcium antagonist or a long-acting nitrate is not based entirely on the frequency and severity of symptoms. The need to treat concomitant hypertension or the presence of left ventricular dysfunction and symptoms of heart failure may be an indication for the use of one of these agents, even in patients in whom episodes of symptomatic angina are infrequent.
6. If angina persists despite two antianginal agents (a beta blocker with either a long-acting nitrate preparation or a calcium antagonist), add the third antianginal agent.
7. Coronary angiography, with a view to considering coronary revascularization, is indicated in patients with refractory symptoms or ischemia despite optimal medical therapy; it should also be carried out in patients with "high-risk" noninvasive test results (see Table 37-2) and in those with occupations or life styles that require a more aggressive approach.

OTHER THERAPIES

An option for patients with refractory angina who are not candidates for coronary revascularization is spinal cord stimulation using a specially designed electrode inserted into the epidural space. The beneficial effects of neuromodulation via this technique on pain are based on the gate theory, in which stimulation of axons in the spinal cord that do not transmit pain to the brain will reduce input to the brain from axons that do so. Irrespective of the mechanism, several observation studies have reported success rates

of up to 80 percent in terms of the frequency and severity of angina.[344] What is less easily explained is the apparent antiischemic effect of this technique. Randomized placebo-controlled trials are impossible to perform, and this approach should be reserved for patients in whom all other treatment options have been exhausted.[345]

The use of enhanced external counterpulsation (EECP) is another promising alternative to treatment of refractory angina. The mechanisms underlying the effects of EECP are currently under evaluation and include (1) hemodynamic changes that reduce myocardial O_2 demand in addition to the potential for increased transmyocardial pressure to open collaterals and (2) the possibility that exposure of the arterial bed to the augmented blood flow produced by EECP could lead to the elaboration of various substances that improve endothelial function and vascular remodeling.[346] Irrespective of the mechanism, in a recent multicenter prospective trial in which active counterpulsation was compared with "inactive counterpulsation," the former reduced angina and extended the time to exercise-induced ischemia over a 4- to 7-week period in patients with symptomatic CAD. Moreover, the treatment was relatively well tolerated, so this modality warrants further investigation.[347]

Translaser myocardial revascularization techniques are addressed on p. 1305 .

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Percutaneous Coronary Interventions (see also Chap. 38)

Percutaneous coronary interventions (PCIs), which include percutaneous transluminal coronary angioplasty (PTCA), stenting, and related techniques, represent a major therapeutic advance in the management of chronic stable angina.[348] Their importance to the management of CAD in the United States is reflected by the performance of approximately 447,000 procedures in 1997 (52 percent of which were performed on persons younger than 65 years). This figure represents an increase of 190 percent from 1987 to 1997. The dramatic growth in the use of PCI has not eliminated growth in the use of coronary bypass surgery, and in 1997, the latter procedures were performed on 366,000 patients, which reflects an increase of 227 percent in the number of patients treated from 1979 to 1997. The practice of interventional cardiology has changed radically during the last 5 years following the widespread use of stents, the introduction of new platelet inhibitors, and the development of other devices that have a niche in the context of specific technical issues, e.g., rotablator and atherectomy.[349]

PATIENT SELECTION.

Improved technology and increasing operator experience have continued to expand the pool of patients with both single-vessel and multivessel disease who are candidates for PCI (and other catheter-based techniques for revascularization). Factors that need to be considered in patient selection include the following:

1. The need for revascularization (surgical or catheter based) as opposed to medical therapy, including stringent risk factor modification.
2. The likelihood of successful catheter-based revascularization based on the angiographic characteristics of the lesion-type A, B, or C lesions,[350] which characterize complexity as mild, moderate, or severe, respectively (see Chap. 38)

. Equally important are factors such as vessel size, extent of calcification, tortuosity, and relationships to sidebranches.
3. The risk and potential consequences of acute failure of PCI, which are a function, in part, of the coronary artery anatomy and underlying left ventricular function.
4. The likelihood of restenosis.
5. The need for complete revascularization based on the extent of CAD, the severity of ischemia, and the presence or absence of left ventricular dysfunction.
6. The presence of comorbid conditions and the suitability of the patient for surgery.
7. Patient preference.

The patient with chronic stable angina who is ideal for PCI, i.e., who is at low risk for complications and in whom the likelihood of technical success is high, is a male with

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chronic stable angina who is younger than 70 years and has single-vessel and single-lesion CAD, the anatomical characteristics of a type A lesion with less than 90 percent stenosis, no history of congestive heart failure, and an ejection fraction greater than 40 percent. Although these characteristics define the ideal candidate, excellent technical and clinical results can still be obtained in many patients who do not fulfill these ideal criteria.

Features associated with an increased risk for PCI failure include advanced age, female gender, unstable angina, congestive heart failure, left main coronary artery-equivalent disease, multivessel multi-lesion CAD, and probably recent thrombolytic therapy.[351] Diabetes mellitus in patients with multivessel disease has been associated with increased periprocedural ischemic complications and late mortality in comparison with patients without diabetes. Patients with impaired renal function, particularly those with diabetes, are also at increased risk for periprocedural morbidity and, in particular, contrast agent nephropathy.[351] [352]

The original ACC/AHA criteria for PTCA success based on lesion morphology suggested that the outcome was poorer with type B or C lesions. These data, validated in the early 1990s,[353] were examined more recently in the setting of better guidewires, new devices, and perfusion balloons.[354] In this large study of patients treated between 1994 and 1996, success rates were not shown to differ among patients with A, B1, or B2 lesions, but each was accompanied by higher success rates than seen with type C lesions. Independent predictors of procedural failure were the presence of total occlusion and vessel tortuosity. Predictors of complications were bifurcation lesions, the presence of thrombus, the inability to protect a sidebranch, and degenerative vein graft lesions. The presence of the aforementioned features does not necessarily contraindicate PCI but should certainly raise the threshold for performing the procedure. However, it would appear that in the current era, lesion morphology may be a less powerful predictor of complications than was previously the case.

EARLY OUTCOME.

Continued improvement in the technical aspects of PCI, as well as increasing operator experience, has had a favorable impact on the rate of primary success (usually defined as an increase in diameter of >20 percent and a final diameter obstruction <50 percent) and the rate of reductions in complications, i.e., death, myocardial infarction, and emergency coronary bypass surgery.[355] These improvements have occurred despite broadening of the selection criteria for PCI to include older and sicker patients with more complex anatomy.[349] [351] Current expectations for PCI, particularly with the widespread use of coronary stents, are an overall procedural success rate of at least 90 percent with a mortality of less than 1 percent, rate of Q wave myocardial infarction of less than 1.5 percent, and rate of emergency bypass surgery of 1 to 2 percent.

ABRUPT CLOSURE.

This complication after initially successful PCI has been defined as total or subtotal occlusion of the target lesion, and it is usually recognized before the patient leaves the laboratory. The entity of "threatened" vessel closure is defined by recurrent stenosis of less than 50 percent and Thrombosis in Myocardial Infarction (TIMI) flow less than grade 3.[356]

The treatment objectives of abrupt closure are to establish adequate coronary perfusion as a bridge to coronary bypass surgery or, in some patients, as a definitive strategy.

LONG-TERM OUTCOME.

For the majority of patients undergoing PCI, the intermediate and late outcomes can be characterized by a low mortality or nonfatal myocardial infarction rate.[357] Several recent studies provide reassuring data on the long-term results of PTCA. The 10-year follow-up of the first series of patients undergoing PTCA performed by Gruentzig demonstrated a survival rate of 95 percent in patients with single-vessel disease and 81 percent in those with multivessel disease.[358] In the National Heart, Lung, and Blood Institute (NHLBI) Registry, 5-year survival rates were 93.2, 88.8, and 86 percent in patients with single-, double-, and triple-vessel disease, respectively.[357] Five-year survival rates from 1980 to 1990 in the Emory University data base of over 10,000 patients were 88 and 93 percent, respectively, for patients with and those without diabetes mellitus.[359] Independent correlates of late survival were younger age, preserved left ventricular ejection fraction, and absence of congestive heart failure, multivessel disease, and diabetes.

Restenosis, the Achilles heel of angioplasty, continues to have a major impact on long-term outcome. Also, angina frequently recurs.[349] [357] [360] [361] [362] [363] Restenosis and, to a lesser extent, progression of disease are the major reasons for repeat revascularization procedures, which in the randomized trials were performed in 30 to 40 percent of patients at 1 to 2 years and, in the Bypass Angioplasty Revascularization Investigation (BARI), in 60 percent of patients at 5 years.[352] Approximately 50 percent of all repeat revascularization procedures are repeat PCIs, with the rest being coronary

artery bypass procedures.[352] [364] [365] What is reassuring is that the need for repeat revascularization tapers off rapidly after the second year.

STENTS.

Since their entry into clinical practice in the early 1990s, stents have had an effect on both the early and late results of PCI. In regard to the former, stents have produced a marked reduction in the need for emergency bypass surgery, and in comparison with PTCA, stents have been associated with a significant reduction in the incidence of major cardiac events after discharge.[366] However, these results are not due to any reduction in death or myocardial infarction, but almost entirely to a reduction in the need for and performance of target vessel repeat revascularization, which in turn reflects a reduction in clinical restenosis. The development of newer techniques such as intravascular brachytherapy,[367] techniques for local drug delivery, and new stent coatings may result in a further improvement in long-term results.

COMPARISONS BETWEEN PTCA AND MEDICAL THERAPY.

Only four trials have compared PTCA with medical therapy.[183] [368] [369] [370] The first major randomized trial involving PTCA was the Veterans Administration Comparison of Angioplasty with Medical Therapy in the treatment of single-vessel CAD, reported in 1992.[371] PTCA was distinctly superior to medical therapy in the relief of angina and in improvement in exercise tolerance, although repeat PTCA or CABG surgery was required in 15 percent of patients by 6 months. A conclusion that can be drawn from this study is that a trial of medical therapy followed by PCI in the event of treatment failure is a reasonable initial strategy for patients with stable angina and single-vessel disease. Nonetheless, indices of quality of life, including functional capacity and the patient's perception of well-being, were significantly better among patients treated with PTCA.[372] At 2 to 3 years, although some of the early benefits of PTCA on exercise tolerance and symptoms were sustained, the subsequent use of CABG and PTCA in the two groups was no different.

Another small randomized trial from Brazil, the Medicine Angioplasty or Surgery Study (MASS), compared PTCA with medical therapy and CABG for patients with proximal stenosis of the left anterior descending coronary artery. After 3 years, no difference was seen between medical therapy and PTCA in the combined endpoints of cardiac death, myocardial infarction, and refractory angina requiring revascularization, but the surgical arm was superior to the two other modalities (3 percent incidence in the surgical arm vs. 24 percent after PTCA and 17 percent with medical therapy). Nonetheless, both revascularization arms were superior to medical therapy for the relief of symptoms and reduction in exercise-induced ischemia. At 5 years of follow-up, surgery using the internal mammary artery (IMA) in all patients was superior to PTCA and medical therapy for the combined endpoints of death, myocardial infarction, unstable angina, and treatment failure requiring revascularization, and the only significant difference

between PTCA and medical therapy was in the severity of angina, which was significantly less in the PTCA arm.[369]

The most recent trial of PTCA versus medical therapy and the most relevant to contemporary clinical practice is the Atorvastatin Versus Revascularization Treatment Trial (AVERT).[183] Patients with one- or two-vessel disease who were asymptomatic or had chronic mild to moderate stable angina were randomly assigned to atorvastatin (80 mg/d) or PTCA, followed by usual care, including lipid-lowering therapy in some patients, but this therapy was protocol mandated. The serum LDL cholesterol in the atorvastatin arm exhibited a 46 percent decrease versus an 18 percent decrease in the angioplasty arm. At 18 months, the incidence of ischemic events was 21 percent in the PTCA group in comparison with 13 percent in the atorvastatin group (p=0.024), and among patients with exercise-induced ST segment depression at baseline, the rate of ischemic events was 19 percent versus 8.6 percent in the atorvastatin arm.[183]

The U.K. trial Randomized Intervention Treatment of Angina-2 (RITA-2) enrolled 1018 patients who were generally at low risk in that 80 percent of them had Class 0 to 2 stable angina (patients with unstable angina were excluded), 60 percent had single-vessel disease, 33 percent had double-vessel disease, and only 6 percent had significant left ventricular dysfunction.[370] The rate of death and nonfatal myocardial infarction was 6.3 percent in the PTCA group and 3.3 percent in the medical therapy group (p=NS). The difference was attributable primarily to an excess of periprocedural myocardial infarctions in the PTCA group. The benefits of PTCA over medical therapy in the relief of symptoms occurred primarily in patients who at baseline had much more severe symptoms. The results of this trial are consistent with those of other trials comparing PTCA with medical therapy, which have demonstrated that PTCA is more effective in the relief of symptoms but does not produce any apparent reduction in mortality or late myocardial infarction.

The Duke University data base provides important information on the relative benefits of CABG, PTCA, and medical therapy on survival in 9263 patients referred for cardiac catheterization between 1984 and 1990. Adjusted 5-year survival rates for patients with single-vessel disease were similar--95 percent with PTCA and 94 percent with medical therapy; in patients with two-vessel disease, the rates were 91 and 86 percent, respectively, and in patients with three-vessel disease, they were 81 and 72 percent. These trends suggest that PTCA is superior to medical management in patients with multivessel disease (Fig. 37-5) .

PCI IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION.

Several studies of PCI in patients with left ventricular dysfunction have documented a high initial procedural success rate with successful dilatation of at least one lesion in 88 percent and all lesions in 76 percent. Nonetheless, successful dilatation of all lesions is less than the rate in patients with well-preserved ventricular function, probably a

reflection of more extensive CAD and total occlusion,[360] and the long-term results are less favorable. Two-year survival rate among patients with an ejection fraction of 0.40 or less and multivessel disease was only approximately 75 percent.[373] In another series, 23 percent of patients with an ejection fraction less than 0.35 died during mean follow-up period of 21 months.[374] In a 1985-1986 report from the NHLBI Registry, the 4-year survival rate for patients with very poor left ventricular function (ejection fraction <25 percent) was only 45 percent.[360] Nonetheless, 87 percent of patients with a mean ejection fraction of 39.6 percent were alive at the latest follow-up, and 77 percent were alive and free of recurrent myocardial infarction or the necessity for bypass surgery.[360] Another study demonstrated similar results with 3-year survival rates of 83 and 92 percent in patients with ejection fractions of 0.31 to 0.35 and 0.36 to 0.40, respectively, but only 69 percent in patients with an ejection fraction of 0.30 or less.[375] To achieve a good outcome in patients with multivessel disease and left ventricular dysfunction, particularly if angina or ischemia is severe, revascularization should be complete. Complete revascularization, however, is often difficult to achieve with PCI, particularly in the presence of chronic total occlusions, which are not infrequent in these patients. This limitation of PCI in the achievement of complete revascularization is an important factor contributing to its relatively disappointing results in patients with significant left ventricular dysfunction and multivessel disease. It is likely that stents and other devices that have the potential to restore and maintain the patency of vessels with chronic total occlusion will expand the pool of patients with multivessel disease which is amenable to complete revascularization, with the potential for better long-term results.

RESTENOSIS (see also Chap. 38)

Although striking improvement has occurred in the initial results of PTCA during the last 20 years, restenosis continues to dominate late events. The most frequently used definition is greater than 50 percent diameter stenosis and/or greater than 50 percent late loss of the acute luminal gain, but no clear consensus has been reached regarding the optimal angiographic definition.[361] From a clinical perspective, restenosis is considered a recurrent ischemic event, usually angina, but restenosis may be clinically silent in approximately 30 percent of patients.[361] Before the introduction of stents, the incidence was 30 to 50 percent.

MECHANISMS OF AND RISK FACTORS FOR RESTENOSIS.

The pathogenesis of restenosis in response to mechanical injury is incompletely understood and multifactorial. Traditionally, restenosis has been considered to be due to the development of neointimal thickening as a result of migration and stimulation of smooth muscle by growth factors. The elastic properties of the vessel undergoing PTCA and its recoil in the development of restenosis have also received attention (Fig. 37-6) . Recent concepts of restenosis suggest that intimal proliferation may account for only about 30 percent of the late loss in lumen diameter 6 months after PTCA. The major mechanism appears

Figure 37-5 Hazard ratios for percutaneous transluminal coronary angioplasty (PTCA) versus medicine

calculated from the Cox regression model to evaluate relative survival differences. Points indicate hazard ratios for each level of the coronary artery disease index; bars indicate 99 percent confidence intervals. The horizontal line at ratio 1.0 indicates the point of prognostic equivalence between treatments. Hazard ratios below the line favor PTCA; those above the line favor medicine. Prox LAD=proximal left anterior descending coronary artery; VD=vessel disease. *(From Mark DB, Nelson CL, Califf RM, et al: Continuing evolution of therapy for coronary artery disease: Initial results from the era of coronary angioplasty. Circulation 89:2015, 1994. By permission of the American Heart Association, Inc.)*

Figure 37-6 Possible mechanisms of restenosis after percutaneous transluminal coronary angioplasty (PTCA) and coronary stenting. Serial intravascular ultrasonographic studies suggest that PTCA almost always disrupts plaque without reducing the total intimal area, frequently causes dissections that penetrate into the tunica media through the internal elastic lamina, and transiently enlarges the vessel, measured as the cross-sectional area subtended by the external elastic lamina. Restenosis is caused by pathological arterial remodeling characterized by shrinkage of the area circumscribed by the external elastic lamina and, to a lesser extent, by neointimal thickening. Coronary stenting also enlarges the cross-sectional area of the vessel. The radial force of the stent prevents vessel shrinkage, but neointimal proliferation can be excessive. *(From Bittl JA: Advances in coronary angioplasty. N Engl J Med 335:1290, 1996. By permission of the Massachusetts Medical Society.)*

to be shrinkage of the dilated segment--a maladaptive form of arterial remodeling.[349] [362] This mechanism would explain why stenting, which produces a larger luminal area, is so effective in decreasing the incidence of restenosis. In contrast to the mechanisms of restenosis in native vessels, stent restenosis is accounted for primarily by neointimal proliferation through the stent.[349] Clinical variables that appear to be associated with increased rates of restenosis include diabetes, severe angina, male sex, smoking, and older age. *Anatomical* factors include total occlusion, left anterior descending coronary artery location, saphenous vein graft lesions, long lesions, and multivessel or multilesion PTCA. *Procedural* variables include greater residual stenosis following PTCA, severe dissection, the absence of an intimal tear, the use of inappropriately sized balloons, and the presence of thrombus.

PREVENTION OF RESTENOSIS.

The single major advance in the reduction of restenosis has been the development of stents. In the Belgium Netherlands Stent (BENESTENT) Trial, restenosis rates were 22 percent in the stent group versus 32 percent in the group receiving PTCA alone. This improvement was accompanied by a reduction in clinical events.[376] In the Stent Restenosis Study (STRESS), restenosis rates were 32 and 42 percent in the stent and PTCA groups, respectively. Intracoronary radiation therapy using beta and gamma emitters shows promise in preventing restenosis.[377] [378] Many issues need to be resolved, including cost and logistics, long-term safety, and the potential incidence of "late" restenosis or subacute reocclusion.

MANAGEMENT OF RESTENOSIS.

The incidence of restenosis peaks between 3 and 6 months, and this interval is the period of maximal vigilance for detecting restenosis in asymptomatic patients. The role of "routine" cardiac stress testing, particularly in asymptomatic patients, has not been clarified. Angiography after PTCA should be confined to patients with symptoms or abnormal functional studies because angiographic as opposed to clinical follow-up is associated with a marked increase in repeat revascularization procedures.[379]

Restenosis is amenable to repeat PCI, but it is not entirely clear whether lesions in which restenosis has developed are more prone to the development of restenosis after a subsequent percutaneous intervention.[380] Among patients with stable or unstable angina and restenosis, a 93 percent anatomical success rate after repeat angioplasty has been reported, and most patients experienced significant long-term clinical improvement. However, the likelihood of recurrent angina requiring subsequent bypass surgery was greater than in patients undergoing PTCA for the first time.[381] In patients undergoing a third PTCA for restenosis at the same site, an interval of less than 3 months between the second and third procedures was strongly associated with further restenosis, thus suggesting that such patients should be considered for CABG.[382]

CHRONIC TOTAL OCCLUSION.

Chronic total occlusions are present in 20 to 40 percent of patients with angiographic documentation of CAD[383] and are particularly frequent in patients with multivessel disease and left ventricular dysfunction, in whom a total occlusion is a formidable obstacle to PCI success and the completeness of revascularization. This problem is particularly relevant in the presence of bridging collaterals, an estimated duration of occlusion of more than 3 months, and vessel diameter less than 3 mm.[384] After initially successful elective coronary angioplasty of total occlusions, the restenosis rate was 45 percent in vessels with total occlusion in comparison with 34 percent in those with subtotal obstruction (p0.001), primarily because of an increased number of total occlusions at follow-up angiography[385] (19.2 vs. 5.0 percent for stenoses, p0.001).

Several studies have documented the feasibility of stenting in patients with chronic total occlusions,[386] and the apparent superiority of stenting over PTCA was suggested by the results of small randomized trials in highly selected patients. [387] [388]

PCI IN WOMEN.

The in-hospital mortality among women is slightly higher than among men; however, after a successful procedure, the long-term survival for women is excellent and similar to that for men. Still, women are more likely to experience a recurrence of angina.[389] However, in the BARI Trial, after multivariable adjustments, female gender was shown to be an independent predictor of improved 5-year survival after either form of revascularization.[390]

PCI IN THE ELDERLY.

Catheter-based revascularization is particularly attractive in the elderly because of age-related changes in cognitive function and cerebrovascular events after CABG surgery and because of the adverse effect of coexisting disease (which is frequent in the elderly) on

perioperative outcome.[391] Nonetheless, the increased prevalence of multivessel and diffuse disease and left ventricular dysfunction in the elderly diminishes the proportion of patients likely to have significant long-term benefits in comparison to CABG.[392] The more unfavorable coronary artery anatomy in the elderly population together with left ventricular dysfunction is reflected by the high mortality and periprocedural complication rates in the elderly undergoing PTCA, in addition to greater recurrence of angina in hospital survivors. Still, periprocedural outcomes are improving. Between 1990 and 1992 at the Mayo Clinic, 768 patients 65 years or older had PTCA and were compared with 982 patients who had the procedure between 1980 and 1989.[393] Despite the increased complexity and comorbidity of the latter group, procedural success rates were higher and periprocedural complications lower in the more recent group. However, event-free survival after discharge did not improve and was essentially the same in the two groups, with an overall rate of death from myocardial infarction during the initial hospitalization and 6-month follow-up of approximately 10 percent.[393]

PCI IN CORONARY BYPASS GRAFTS.

CABG and PCI are often considered competitive procedures, but it is more appropriate to view them as complementary. An increasing number of patients who have had CABG and later have recurrent ischemia undergo revascularization with a percutaneous interventional technique. At the Mayo Clinic, approximately 20 percent of all PCIs are in patients who have had previous CABG.[394]

The initial and subsequent success rates of PCI in venous bypass grafts are lower than in native vessels. Success rates are approximately 90 percent, with restenosis rates ranging from 40 to 70 percent. The results are better with dilatation of distal graft lesions.

Innovative approaches to the management of vein graft atherosclerosis include catheter-based aspiration systems, in which the techniques of aspiration and filters are combined to prevent distal emboli,[395] glycoprotein IIb/IIIa platelet receptor inhibitors,[396] and the use of coronary ultrasonography to lyse thrombi.[397] The most encouraging development in patients with vein graft stenoses has been the use of elective stent replacement, which in several initial studies appears to have decreased the long-term incidence of restenosis from 40 to 70 percent after PTCA to 17 to 30 percent with stenting.[398] Long-term results from stenting of saphenous vein grafts are not available

but appear to be superior to those after PTCA. An ACC Expert Consensus Document stated that in selected patients with saphenous vein graft disease, stents have resulted in improved initial success rates and larger acute angiographic gain, but restenosis rates and longer-term morbidity are still increased in comparison with stenting in large native coronary arteries.[398] Elective stent placement will probably become the treatment of choice in the management of vein graft stenosis. Whether these results will improve with the adjunctive use of other devices such as transluminal extraction cardiac atherectomy remains to be determined.

COMPARISON OF PCI AND CORONARY ARTERY BYPASS SURGERY. **See p. 1319 .**

OTHER CATHETER-BASED TECHNIQUES.

Lasers, rotablators, and atherectomy are discussed in Chapter 38 .

CONCLUSIONS.

PCI represents a major advance in the management of CAD, and new developments in interventional cardiology over the last 5 years have had a substantial effect on outcomes and on expanding the pool of patients eligible for these procedures. The practice of interventional cardiology has been revolutionized by coronary stenting, and further advances in coated stents and antithrombotic agents are likely. However, it must be appreciated that restenosis remains a problem, and management of a patient with chronic total occlusion by PCI is suboptimal. The latter is probably the major reason why patients are deemed unsuitable for PCI and referred for CABG. Also, it must be appreciated that a dilatable lesion represents an isolated target whereas atherosclerosis is a diffuse process. Thus, PCI is but one aspect of a comprehensive therapeutic strategy that should vigorously address the risk factors for CAD.

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Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Copyright © 2001 W. B. Saunders Company

Coronary Artery Bypass Surgery

In 1964, Garrett, Dennis, and DeBakey first used CABG as a "bailout" procedure.[399] Widespread use of the technique by Favoloro and Johnson and their respective collaborators followed in the late 1960s.[400] [401] Use of the IMA graft was pioneered by Kolessov in 1967 and by Green and colleagues in 1970.[402] [403]

The number of coronary bypass operators in the United States increased by 227 percent from 1979 to 1997, and in 1997, approximately 366,000 patients underwent coronary bypass surgery.[5] The advent of PCI may have blunted the growth of CABG. Nevertheless, CABG remains one of the most frequently performed operations in the United States; approximately 1 in every 1000 persons undergoes CABG on an annual basis, and this procedure results in the expenditure of almost $50 billion annually.

The appropriate use of invasive cardiovascular procedures is undergoing increasing scrutiny. It is therefore reassuring to note that in studies of coronary angiography and bypass surgery in New York State and Canada, only 6 and 4 percent of bypass procedures, respectively, were considered inappropriate.[404] In a study from The Netherlands, 84 percent of decisions to perform CABG were rated appropriate, 12 percent uncertain, and 4 percent inappropriate.[405] A recent review of surgical indications from a consortium of academic medical centers demonstrated that only 1.6 percent of operations were considered inappropriate and 7 percent were uncertain.[406]

Technical Considerations

When a decision has been reached to proceed with CABG, administration of beta blockers, nitrates, and calcium antagonists is continued until surgery. It is crucial to minimize perioperative damage and protect the myocardium. The most commonly used

method involves a single period of aortic cross-clamping with intermittent infusion of cold cardioplegia solution. A 1994 trial of cold crystalloid versus warm blood cardioplegia in elective bypass surgery in patients with well-preserved preoperative ventricular function demonstrated low mortality and morbidity with both techniques.[407] Cardioplegic solutions may be sanguineous and have high concentrations of potassium with or without added substances, such as O_2 , buffers, and free radical scavengers.[408] Retrograde cardioplegia through the coronary sinus facilitates more uniform distribution of cardioplegic solution. Many surgeons now use a combination of antegrade and retrograde perfusion,[409] as well as topical hypothermia with cold saline or ice slush as an adjunct.

Among patients with satisfactory preoperative cardiac function, a wide range of techniques have produced excellent results. This success is probably a reflection of the extent of myocardial functional reserve in those with well-preserved systolic function. In contrast, among patients with depressed left ventricular function (both acutely and chronically), it is easier to demonstrate a benefit with more

Figure 37-7 Aorticovenous anastomosis in a coronary artery-saphenous vein bypass graft. *A,* Direction of the anastomotic site for left-sided grafts. *B,* Details of aortic orifices. *C,* Direction of right coronary artery (RCA) grafts. *(From Cohn LH: Surgical techniques of emergency coronary revascularization. In Cohn LH [ed]: The Treatment of Acute Myocardial Ischemia: An Integrated Medical-Surgical Approach. Mt Kisco, NY, Futura, 1979, p 87. By permission.)*

specialized protocols, including the use of sanguineous cardioplegic techniques, with or without substrate enhancement,[408] and blood cardioplegia.[410] The theoretical advantages of blood cardioplegic solutions, which may be helpful in patients with severe chronic left ventricular dysfunction, include superior buffering capacity, enhanced flow rates at a capillary level, and a reduction in free radicals.[410]

Renewed interest in coronary bypass surgery without cardiopulmonary bypass has been stimulated by the desire to avoid blood transfusions, by economic issues, and by the wish to avoid the damaging neurological effects of bypass, particularly in the elderly and in patients with heavily calcified aortas.[411] An alternative approach to revascularization using the beating heart is off-pump coronary bypass, which frequently entails a conventional median sternotomy and mechanical suction stabilizing systems. This combination enhances surgical exposure and is particularly useful if multivessel bypass grafting is contemplated. This technique is particularly attractive in patients with diffuse aortic atherosclerosis, and preliminary results are encouraging.[412] [413] [414] [415]

MINIMALLY INVASIVE CABG.

Other approaches are termed "less invasive" or "minimally invasive" and include the use

of alternative incisions such as a left thoracotomy with or without cardiopulmonary bypass or fluoroscopic techniques. The ultimate success of these "nontraditional" approaches to CABG will depend on long-term graft patency and the development of new techniques that will increase exposure to allow for more complete revascularization. Initial reports are encouraging in regard to decreasing the number of days spent in the intensive care unit and hospital and reducing neurological complications, but additional large studies are needed.

An innovative approach to coronary revascularization is the "port access" method, which uses small thoracotomy ports for cardiac manipulation; cardiopulmonary bypass is established by groin cannulation. Experience with this technique is limited, although the two largest single-center series and the first report of the Port-Access International Registry, which documented the results of 555 bypass procedures, were encouraging. Nonetheless, follow-up has been short, and the results do not reflect the "learning curve." Limitations to the use of this technique include atherosclerotic involvement of the aortic arch, high cost, long operating times, and the risk of aortic dissection.[415] [416] [417]

A novel approach to coronary revascularization integrates coronary artery bypass with PTCA by combining a minimally invasive coronary bypass surgical procedure on the left anterior descending coronary artery with PTCA on the remaining vessels. Further experience is needed to clarify the selection criteria and long-term strategy and whether it offers any advantages over multivessel bypass surgery alone.[101] [418]

"The learning curve" of minimally invasive coronary bypass surgery has led to numerous reports of early graft failure.[419] In many centers, intraoperative or early postoperative angiography is performed to assess the quality of the anastomosis. It should be emphasized that with conventional surgical techniques, the *early* patency rates of an IMA graft are excellent (98.7 percent in one large series), and less than 50 percent stenosis was noted in 91 percent of grafts. The future of minimally invasive and other techniques will depend on their ability to equal these excellent patency rates.[420]

VENOUS CONDUITS.

The saphenous vein is used mainly for distal branches of the right and circumflex coronary arteries and for sequential grafts to these vessels and diagonal branches (Figs. 37-7 and 37-8) . In emergency situations, many surgeons prefer the saphenous vein, which can be harvested and grafted more rapidly, to the IMA. Arm vein grafts are not as effective as either IMA or saphenous vein grafts.

Eight to 12 percent of saphenous vein grafts become occluded during the early perioperative period. Trauma to the vein during surgical preparation can denude the endothelium, impair the intrinsic fibrinolytic activity of the saphenous vein, and damage the vessel wall, thereby predisposing to early thrombosis.[421] Careful harvesting of the

Figure 37-8 Venocoronary anastomosis to the proximal portion of the arteriotomy. *(From Cohn LH: Surgical techniques of emergency coronary revascularization. In Cohn LH [ed]: The Treatment of Acute*

Myocardial Ischemia: An Integrated Medical-Surgical Approach. Mt Kisco, NY, Futura, 1979, p 87. By permission.)

graft, with particular attention to avoidance of overdistention and the use of modified storage solutions, has been shown to improve patency and preserve the integrity of the graft in both animal models and the clinical setting.

INTERNAL MAMMARY ARTERY BYPASS GRAFTS.

The IMA, also known as the internal thoracic artery, is usually remarkably free of atheroma, especially in patients younger than 65 years. When it is grafted to a coronary artery (Figs. 37-9 and 37-10) , it appears to be virtually immune to the development of intimal hyperplasia, which is almost universally seen in aortocoronary vein grafts.[422] Atherosclerotic changes in the IMA develop in only a small percentage of patients after coronary bypass surgery. The IMA is delicate, so great care has to be taken to mobilize the vessel without traumatizing it.[423] The procedure is time consuming, and thus, the IMA is not often used for emergency surgery.

Comparative morphological and angiographic studies of IMA and saphenous vein bypass grafts that have been implanted long-term show that accelerated atherosclerosis occurs commonly in saphenous vein grafts but is extremely rare in IMA grafts. Several potential explanations may be offered for the superiority of the IMA graft.[423] The media of the artery may derive nourishment from the lumen as well as from the vasa vasorum, and the internal elastic lamina of the IMA is uniform. Moreover, the finding that the endothelium of the IMA produces significantly more prostacyclin than that of the saphenous vein may explain why endothelium-dependent relaxation is more pronounced, which may allow flow-dependent autoregulation to occur.[424] The diameter of the IMA graft is usually a closer match to that of the recipient coronary artery than is the diameter of a saphenous vein. The increasing popularity of the IMA as a conduit is reflected in the Society of Thoracic Surgeons data base. Among the patients in the United States who had first operations in 1990, the IMA was used in 48.5 percent, but this figure steadily increased to 79.77 percent by 1997.[425]

In one series, IMA grafts and saphenous vein grafts had patency rates of 95 and 93 percent, respectively, at 1 year,

Figure 37-9 Internal mammary grafting consisting of an in situ left internal mammary artery (IMA) graft to the left anterior descending artery (end to side) and diagonal branch (side to side), with the diamond anastomotic technique used for the latter. The details show the IMA pedicle rolled up over the diagonal coronary artery to facilitate exposure and the use of continuous suture. *(From Jones EL: Extended use of the internal mammary-coronary artery bypass. J Card Surg 1:13, 1986. By permission of Futura Publishing Co.)*

Figure 37-10 Different types of internal mammary artery grafts. A single attached internal mammary artery graft (either the right or left) remains attached proximally to the subclavian artery and is connected to the coronary arteries. Bilateral internal mammary artery grafts (right and left) are joined end to side to coronary arteries. Sequential internal mammary artery grafts consist of an attached or free internal mammary artery with one or more side-to-side anastomoses and one end-to-side anastomosis. The internal mammary artery Y graft has two terminal branches of either the attached or free internal mammary artery sutured to two coronary arteries. A free internal mammary graft is placed by transecting the right or left internal mammary artery near its origin in the subclavian artery and anastomosing the proximal portion of the artery to the aorta and the distal end to the coronary artery. *(From Tector AJ, Schmahl TM, Canino VR: Expanding the use of the internal mammary artery to improve patency in coronary artery bypass grafting. J Thorac Cardiovasc Surg 91:9, 1986. By permission of Mosby.)*

but at 5 and 10 years, the patency rates of the IMA grafts were 88 and 83 percent, superior to the 74 and 41 percent rates for saphenous vein grafts.[426] Excellent long-term results have also been achieved with use of the right IMA as a free or sequential graft.[427] However, fibrointimal proliferation occasionally develops in IMA grafts, and the resultant narrowing may be a factor in late graft closure.[423]

Patients receiving an IMA graft have a decreased risk of late death, myocardial infarction, cardiac events, and reoperations, and this clinical advantage persists for up to 20 years.[428] The contemporary standard for bypass grafting advocates routine use of the left IMA for grafting the left anterior descending coronary artery, with supplemental saphenous vein grafts to other vessels.

Although the benefits of a single IMA graft over a saphenous vein graft alone are not in dispute, the superiority of bilateral IMA grafts over a single IMA graft and one saphenous vein graft is less well accepted.[429] Initial enthusiasm for the use of bilateral IMA grafts was tempered by the higher rate of postoperative complications, including bleeding, wound infection, and prolonged ventilatory support. Subsequent series have shown that bilateral versus single IMA grafting is associated with lower rates of recurrent angina pectoris, reoperation, and myocardial infarction and a trend toward improved survival,[430] but at the cost of a higher rate of sternal wound infections, particularly among patients who are obese or diabetic or require prolonged ventilatory support.

COMPLICATIONS OF ARTERIAL CONDUITS.

Inadequate flow rates with evidence of myocardial ischemia in the perioperative period are rare after IMA grafts to the left anterior descending coronary artery or its

diagonal branches. [423] Perioperative spasm is the presumed cause and can be managed by the administration of sodium nitroprusside or a combination of glyceryl

trinitrate and verapamil.[431] Other complications include an increased incidence of sternal wound infections, which is more frequent in obese patients and diabetics and after bilateral IMA implants.

OTHER ARTERIAL CONDUITS.

The success of IMA grafts has stimulated interest in the use of other arterial conduits, particularly in patients who are younger, diabetic, or hyperlipidemic or in whom the saphenous veins are unsuitable or unavailable.[423] Initial enthusiasm for use of the radial artery was blunted by reports of high reocclusion rates. More recent experience, in which attention has been paid to avoiding spasm by minimizing manipulation and the use of calcium channel blockers, has been favorable. Brodman and colleagues reported a 95 percent 12-week patency rate in a large series of patients receiving radial artery grafts.[432] Another recent series reported an 84 percent 5-year patency rate in 100 consecutive recipients of radial grafts versus a 90 percent patency rate for the IMA.[433]

The right gastroepiploic artery can be harvested by extending the median sternotomy incision toward the umbilicus. It is frequently placed as a graft to the right coronary artery, but both the circumflex and the left anterior descending coronary arteries can be grafted with this conduit.[434] Early results demonstrated excellent patency rates, but there is a paucity of data on long-term results. Similarly, the inferior epigastric artery has been used as a free graft for coronary revascularization, with good short-term patency rates but without long-term data.[435] Cryopreserved homologous saphenous vein grafts and glutaraldehyde-treated umbilical veins have been used, but the patency rates are not optimal. These grafts should be used only as a last resort, and this restriction also applies to the use of bovine IMA, Dacron, and polytetrafluoroethylene (PTFE) grafts.[436]

THE DISTAL VASCULATURE.

The state of the distal coronary vasculature is important for the fate of bypass grafts. Late patency of grafts is related to coronary arterial runoff as determined by the diameter of the coronary artery into which the graft is inserted, the size of the distal vascular bed, and the severity of coronary atherosclerosis distal to the site of insertion of the graft. The highest graft patency rates are found when the lumina of the vessels distal to the graft insertion are greater than 1.5 mm in diameter, perfuse a large vascular bed, and are free of atheroma obstructing more than 25 percent of the vessel lumen. For saphenous veins, optimal patency rates are achieved with a lumen of 2.0 mm or greater.

FLOW RATES.

When measured at the time of surgery, flow rates through saphenous vein grafts average nearly 70 ml/min. Flow rates less than 45 ml/min--and especially less than 25 ml/min--are more frequently associated with graft closure than are flow rates exceeding 45 ml/min.[437] The utility of measuring flow rates is enhanced by taking into account the type of conduit used and the size of the distal vasculature. If flow rates are lower than expected, reassessment of the anastomosis with a probe may be helpful. Possible

causes of reduced flow include (1) subcritical obstruction of the coronary artery, (2) a technically poor anastomosis with narrowing of the lumen from kinking of the vessel or pinching at the site of anastomosis, (3) a small myocardial mass perfused by the graft, and (4) a diseased distal vascular bed.[438]

Other Surgical Procedures for Ischemic Heart Disease

Coronary bypass surgery may be combined with surgical procedures aimed at correction of atherosclerotic disease elsewhere in the cardiovascular system, such as correction of mechanical complications of myocardial infarction (mitral regurgitation or ventricular septal defect), left ventricular aneurysms, and concomitant valvular heart disease. Not unexpectedly, morbidity and mortality are correspondingly increased because of the added complexity of the procedure and, in many patients who require these other procedures, the presence of underlying left ventricular dysfunction (see below).

TRANSLASER MYOCARDIAL REVASCULARIZATION.

Translaser myocardial revascularization, an innovative approach to the treatment of ischemic heart disease, is currently under evaluation.[439] [440] The initial assumption was that laser-mediated channels would provide a network of functional connections between the left ventricular cavity and the ischemic myocardium. Subsequent observations demonstrating closure of the channels within hours or days despite apparent relief of symptoms have led to alternative explanations for the apparent clinical success of the procedure. These explanations include improved perfusion by stimulation of angiogenesis, a potential placebo effect, and an anesthetic effect mediated by the destruction of sympathetic nerves carrying pain-sensitive afferent fibers[441] [442] or periprocedural infarction. A recent study evaluated sympathetic innervation with [[11] C]hydroxyephedrine and demonstrated decreased myocardial uptake of this substance in most patients, without significant change in resting or stress myocardial perfusion, which suggests that the improvement in angina after the procedure may be partly due to sympathetic denervation.[442]

Initial clinical studies in patients with severe CAD often amenable to a bypass procedure have been promising in that the majority have demonstrated a clear reduction in anginal severity and improved exercise tolerance. Several small randomized trials of translaser myocardial revascularization have resulted in improvement in comparison with maximal medical therapy.[443] [444] [445] The results of one trial suggested improvement in perfusion as assessed by PET, but such improvement was not shown with thallium scintigraphy in another trial.[444] [445] In contrast to the positive studies, Schofield and associates reported no significant improvement in exercise time and 12-minute walking distance up to 1 year after translaser myocardial revascularization with a carbon dioxide laser,[446] although the laser-treated patients had a modest reduction in the frequency of angina. The subjective improvement in the severity of angina found in this study, in the absence of any measurable effect on myocardial perfusion or exercise tolerance, argues for a placebo effect or denervation. Two other randomized trials from the United States confirmed the improvement in angina in patients receiving surgical translaser myocardial revascularization, but no study has demonstrated a reduction in myocardial ischemia as

measured objectively, and laser revascularization was not associated in any of the three randomized trials with long-term improvement in left ventricular systolic function.[447] [448] On the basis of data from the randomized trials, it would appear that the widespread use of translaser myocardial revascularization as a "stand-alone" method cannot be justified, but it may still have a role as an adjunctive procedure during CABG in patients who have some vessels suitable for bypass but others that are unsuitable.

After the FDA approved carbon dioxide laser translaser myocardial revascularization for the sole treatment of Class III or IV angina in August 1998, interest has developed in other sources of laser energy, such as percutaneous myocardial revascularization (PCMR) in association with various techniques of left ventricular mapping (Fig. 37-11) . Initial results have been promising,[449] [450] and the randomized Potential Angina Class Improvement from Intramyocardial Channels (PACIFIC) Trial of 231 patients with Class III or IV angina suggested that the procedure was safe. Moreover, at 6 months the PCMR group had symptomatic improvement in comparison with the maximal medical therapy group (Osterle S, personal communication). Nonetheless, the placebo effect has not been eliminated, and randomized trials in which both patients and investigators are blinded are currently in progress. Because the mechanisms underlying the observed clinical benefits are not well defined, the future of this technique depends on well-designed randomized trials, but it is possible that translaser myocardial revascularization or PCMR may eventually be combined with other interventions such as incomplete bypass surgery or used as an adjunct to PCI. Whether this technique will fulfill its potential as a vehicle for the delivery of angiogenic factors and other forms of gene therapy remains to be determined.[451]

Surgical Outcomes

OPERATIVE MORTALITY.

Risk factors for death following coronary artery surgery may be separated into five categories: (1) preoperative factors related to CAD, including recent acute myocardial infarction, hemodynamic instability, left ventricular dysfunction, extensive CAD, the presence of left main CAD, and severe or unstable angina; (2) preoperative factors related to the aggressiveness of the arteriosclerotic process, as reflected in associated carotid or peripheral vascular disease; (3) preoperative biological factors (older age at surgery, diabetes mellitus, and perhaps female gender); (4) intraoperative factors (intraoperative ischemic damage and failure to use IMA grafts)[452] ; and (5) environmental

Figure 37-11 Schematic demonstrating the mechanism of percutaneous myocardial laser revascularization (PCMR). Left, A ventriculogram and coronary angiogram performed at the beginning of the procedure demonstrate that the left ventricular anatomy is suitable for treatment. A steerable catheter is delivered retrogradely across the aortic valve, and the catheter for energy delivery is advanced through

a guiding catheter and placed in the left ventricular chamber. The steerable catheter allows access to the endocardial surface. Right, When the energy delivery catheter is in contact with the endocardium, intramyocardial channels are made by tissue ablation. The channels cause intramyocardial hemorrhage by transecting the microvasculature (bold arrow). A=epicardial artery; v=epicardial vein. *(From Kantor B, McKenna CJ, Caccitolo JA, et al: Transmyocardial and percutaneous myocardial revascularization: Current and future role in the treatment of coronary artery disease. Mayo Clin Proc 74:585, 1999. By permission of Mayo Foundation for Medical Education and Research.)*

or institutional factors, including the specific surgeon and treatment protocols used.[453]

The patient population undergoing CABG has been changing over time, particularly with the wider use of PCI. In comparison with the 1970s, patients undergoing CABG today are older, include a higher percentage of women, and are "sicker" in that a greater proportion have unstable angina, three-vessel disease, previous coronary revascularization with either CABG or PCI, left ventricular dysfunction, and comorbid conditions, including hypertension, diabetes, and peripheral vascular disease.

In-hospital mortality after isolated coronary bypass surgery was characterized by a steady decline from 1967 to the 1980s. Recently, a plateau and perhaps even a slight increase has been noted in morbidity and mortality, findings reflective of the changing demographics toward an older and sicker population of patients undergoing initial surgery and a higher proportion undergoing reoperation.[454] In 1997, perioperative mortality among 174,806 patients undergoing coronary bypass surgery entered into the Society of Thoracic Surgeons data base was 2.8 percent. In patients undergoing an elective first isolated coronary bypass operation, the mortality in 1997 was 1.7 percent.[425]

With increasingly wide scrutiny of procedural results, it has become recognized that absolute rates of morbidity and mortality might not provide a fair basis for comparing institutions and individuals, unless the characteristics of the patients are considered. Several models have been developed and refined with the objective of predicting perioperative mortality.[455] Major determinants are advancing age, poor left ventricular function, and the urgency of surgery, but additional factors such as comorbid conditions and coronary anatomy have added independent predictive value.

A useful perspective of long-term survival after coronary bypass surgery is provided by the most recent follow-up data (mean, 15 years) from the CASS Registry. Ninety percent of patients were alive at 5 years, 74 percent at 10 years, and 56 percent at 15 years. The hazard function for death decreases rapidly after surgery to its nadir at 9 to 12 months, followed by a steady increase with a doubling of the hazard ratio at 15 years in comparison to that at 5 years.

PERIOPERATIVE COMPLICATIONS

Perioperative morbidity (also see Chap. 60) has also increased because of a larger fraction of higher-risk patients.

PERIOPERATIVE MYOCARDIAL INFARCTION.

Perioperative myocardial infarction, particularly if it is associated with hemodynamic or arrhythmic complications or preexisting left ventricular dysfunction, has a major adverse effect on early and late prognosis.[456] The cardiac troponins and myocardial creatine phosphokinase-MB (CK-MB) may be useful as markers of perioperative infarction.[457] Predictors of perioperative myocardial infarction in the CASS Trial were female gender, severe perioperative angina pectoris, severe stenosis of the left main coronary artery, and three-vessel disease.[456] Preconditioning the myocardium with short periods of ischemic stress interspersed with reperfusion increases the resistance to infarction and appears to reduce myocardial damage during cardiac surgery, but the appropriateness of this technique as a routine clinical tool has not been determined.

RESPIRATORY COMPLICATIONS.

Postoperative changes in pulmonary function after CABG are frequent and troublesome, but rarely serious, except in patients with preexisting chronic lung disease or the elderly. A potentially serious complication is phrenic nerve injury, which may be related to cold-induced damage during myocardial protection strategies or possibly to mechanical injury while harvesting the IMA. The pulmonary consequences vary and range from an asymptomatic

radiographic abnormality to severe pulmonary dysfunction requiring prolonged ventilation.[458]

BLEEDING.

Impaired hemostasis and bleeding complications are an inherent risk of CABG. Reoperation for bleeding is required in 2 to 5 percent of patients. Cardiopulmonary bypass causes derangement of the intrinsic coagulation and fibrinolytic systems in addition to platelet function. The risk of bleeding is increased with age, a smaller body surface area, reoperation, bilateral internal thoracic artery grafts, and the preoperative use of heparin, aspirin, and thrombolytic agents. Bleeding is less common in obese patients,[459] but this complication may be reduced with aprotinin and lysine analogs such as aminocaproic acid and tranexamic acid.[460]

WOUND INFECTIONS.

Major perioperative wound complications, especially mediastinitis and/or wound dehiscence, occur in approximately 1 percent of patients.[458] This risk is substantially increased by the use of double IMA grafts, particularly in diabetic patients,[461] and it is markedly increased in obese patients.[459] Preventive measures include careful skin

preparation, increased attention to sterility in the perioperative environment, and preoperative use of antimicrobial agents.[458] Other factors that may decrease perioperative infection include the avoidance of unnecessary blood transfusion in view of the immunosuppressive effect of the latter.

PULMONARY INSUFFICIENCY.

In the Society of Thoracic Surgeons data base,[425] postoperative pulmonary insufficiency requiring ventilation for more than 1 day was noted in 5.5 and 10.7 percent of patients undergoing a first operation and reoperation, respectively. The etiology is multifactorial and includes the presence of preexisting pulmonary disease and numerous perioperative factors related directly to anesthesia, cardiopulmonary bypass, incisional pain, chest tube placement, and occasionally, phrenic nerve damage.[458]

Severe chronic obstructive pulmonary disease, as defined by a forced expiratory volume in 1 second (FEV_1) of greater than 50 percent or an FEV_1/forced vital capacity (FVC) ratio less than 0.70, is associated with a high incidence of postoperative pulmonary complications (29 percent).[462] The left ventricular ejection fraction is also an important determinant of prolonged ventilation.[463]

POSTOPERATIVE HYPERTENSION.

Hypertension can occur in up to one-third of patients postoperatively. The mechanisms are unclear but may be related to increased levels of circulating catecholamines and other humoral factors in addition to vasoconstriction secondary to activation of the renin-angiotensin system. Control of postoperative hypertension is important to prevent myocardial ischemia, cardiac failure, perioperative bleeding, and diminished tissue perfusion.[464] Regardless of the cause, sodium nitroprusside is an effective approach to afterload reduction, and other drugs such as calcium antagonists, nitrates, and beta blockers, including short-acting esmolol, are helpful.[458]

CEREBROVASCULAR COMPLICATIONS.

Neurological abnormalities following cardiac surgery are dreaded complications. Postulated mechanisms include emboli from an atherosclerotic aorta or other vessels, emboli possibly from the cardiopulmonary bypass machine circuit and its tubing, and intraoperative hypotension, particularly in patients with preexisting hypertension.[458] [465] [466] Type I injury is associated with major neurological deficits, stupor, and coma, and type II is characterized by a deterioration in intellectual function and memory.[467] In a recent large multicenter series, the incidence of neurological abnormalities was 6.1 percent, and these abnormalities were almost evenly distributed between type I and type II deficits, with mortality rates of 21 and 10 percent, respectively.[467] Intellectual dysfunction in the early postoperative period, as expressed by a battery of neurocognitive defects, was noted in 75 percent of patients. However, major sequelae were unusual.[468] In regard to the neurological sequelae of cardiopulmonary bypass (including stroke, delirium, and neurocognitive dysfunction), older age in addition to other comorbid conditions associated with atherosclerosis is one of the more powerful

predictors.[466] In most studies, atherosclerosis of the proximal aorta has also been a strong predictor of stroke.[465]

Intraoperative manipulation of the aorta is a major cause of atheroemboli and neurological complications. Preoperative or intraoperative screening with transesophageal echocardiography or epiaortic echocardiography to detect mobile aortic atheromas is increasingly being used, although the sensitivity and specificity need to be better defined.[469] An aggressive approach to the management of severe aortic atherosclerosis includes changing the cannulation sites based on echocardiographic findings, no-clamp fibrillatory arrest, and replacement of the ascending aorta.

Bypass surgery performed on the beating heart without the use of cardiopulmonary bypass has less potential for generating cerebral emboli,[411] and it appears to produce a lower incidence of cognitive dysfunction in both short- and intermediate-term postoperative follow-up than does conventional coronary bypass surgery with cardiopulmonary bypass.

ATRIAL FIBRILLATION.

Atrial fibrillation is one of the most frequent complications of coronary bypass surgery. It occurs in up to 40 percent of patients, primarily within 2 to 3 days.[470] In the early postoperative period, rapid ventricular rates and loss of atrial transport may compromise systemic hemodynamics, increase the risk of embolization, and lead to a significant increase in duration of the hospital stay and charge and a twofold to threefold increase in postoperative stroke[471] (see also Chap. 60) .

CONDUCTION DISTURBANCES AND BRADYARRHYTHMIAS.

The incidence of postoperative bradyarrhythmias requiring permanent pacemaker implantation was 0.8 percent in a series of 1614 consecutive patients discharged from the hospital after coronary bypass surgery. Predictive factors were preoperative left bundle branch block, concomitant left ventricular aneurysmectomy, and older age. The majority of patients continued to require permanent pacemaker support during follow-up.

SYMPTOMATIC RESULTS.

Coronary bypass surgery is highly effective in the relief of angina and results in improved quality of life. Approximately 80 percent of patients are free of angina at 5 years and 63 percent at 10 years, but by 15 years only about 15 percent are alive and free of an ischemic event.[472] [473] The acceleration in adverse events after 5 to 15 years is due to gradual occlusion of vein grafts in addition to progressive disease in the native coronary vessels. Independent predictors of recurrence of angina are female gender, obesity, preoperative hypertension, and lack of use of the IMA as a conduit.[474] In patients with triple-vessel disease undergoing coronary bypass surgery, the completeness of revascularization was a significant determinant of the relief of symptoms over a 5-year period.[475]

In the bypass surgery arms of recent randomized trials of PTCA and CABG, recurrent angina pectoris was reported in 21.5 to 34 percent of patients at a follow-up ranging from 2 to 3 years, but (Canadian classification) grade III or IV angina was present in only 6 percent at 2.5 years in the RITA Trial[364] [476] (Fig. 37-12) .

RETURN TO EMPLOYMENT.

Return to full employment has been variable. Among participants in the surgical arm of the Emory Angioplasty Versus Surgery Trial (EAST), whose mean age was 61 years at entry, only 38.5 percent were gainfully employed at 3 years.[364] In contrast, in a study of patients younger than 65 years who were employed at the time of revascularization, 79 percent who had CABG were working at 1 year, and after adjustment for baseline characteristics, 1-year employment rates were the same among patients treated with surgery, PTCA, or medical

Figure 37-12 Prevalence and severity of angina by treatment group for each annual visit up to 7 years in the RITA-1 Trial. The prevalence of severe angina declines markedly from baseline (0-year follow-up) to the first year of follow-up. During the first few years, angina prevalence and severity are greater after percutaneous transluminal coronary angioplasty (PTCA), but no difference is seen at 7 years. CABG=coronary artery bypass graft. *(From Henderson RA, Pocock SJ, Sharp SJ, et al: Long-term results of RITA-1 trial: Clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet 352:1419, 1998. © by The Lancet Ltd., 1998.)*

therapy.[477] Factors that adversely affect the prospects of patients for returning to work include advanced age, postoperative angina, and a period of either unemployment or disability before surgery. Forty-seven percent of patients undergoing bypass surgery in the EAST Trial were able to engage in moderate or strenuous activity 3 years after the procedure.[364]

GRAFT PATENCY.

Experimental studies and observations in patients suggest that the development of disease in venous aortocoronary artery bypass grafts occurs in several phases. The occlusion rate, which is high in the first year, decreases substantially between the first and sixth years. Between 6 and 10 years after surgery, the attrition rate for grafts increases again. Early occlusion (before hospital discharge) occurs in 8 to 12 percent of venous grafts, and by 1 year, 15 to 30 percent of vein grafts have become occluded.[478] After the first year, the annual occlusion rate is 2 percent and rises to approximately 4 percent annually between years 6 and 10. At 10 years, approximately 50 percent of vein grafts have become occluded, and significant atherosclerosis is present in the substantial proportion of grafts remaining patent, with significant stenoses in 20 to 40

percent.[423] [473] [478] Patency rates with IMA grafts are superior.

EARLY PHASE (FIRST MONTH).

Technical factors that may cause thrombotic closure at the proximal or distal anastomoses include kinking because of excessive length, tension from insufficient length, poor graft flow, and inadequate distal runoff. Surgical manipulation of the saphenous vein during harvesting and preparation prior to grafting play key roles in initiating the sequence of endothelial damage with subsequent platelet and fibrin deposition leading to thrombosis.[421]

INTERMEDIATE PHASE (1 MONTH TO 1 YEAR).

Vein grafts that have been implanted in the arterial circulation for 1 month to 1 year are subject to substantial endothelial denudation and proliferation and to migration of medial cells to the intima. Migration of vascular smooth muscle cells through the internal elastic lamina into the intima may also occur.[421] This initial phase of rapid proliferation is followed after several months by a marked increase in the connective tissue matrix, which further increases intimal and medial thickness. This accelerated process of intimal hyperplasia and thickening is an early stage of atherosclerotic plaque formation and is believed to occur because of interaction between platelets and macrophages and endothelial damage. If the proliferation is severe and localized, as may occur at the site of anastomosis between the grafts and the recipient artery, total occlusion can occur within 1 year.

LATE PHASE (BEYOND 1 YEAR).

Some investigators believe that the development of atherosclerosis in vein grafts, as in native arteries, is a continuum starting from platelet deposition and advancing to smooth muscle cell proliferation and finally to lipid incorporation into the plaque. By 10 years, nearly half of venous grafts patent at 5 years have become occluded.[479] Beyond the first year, particularly after 3 to 5 years, the histological appearance of occluded or obstructed coronary bypass grafts is consistent with atherosclerosis. There is clear evidence of mature lipid-laden plaque, foam cells, cholesterol clefts, ulceration, and areas of calcification with disruption of the medial layer.[480] Late coronary atherosclerosis is often characterized by an extensive thrombotic burden and marked friability of the lesions; the resultant intermittent distal embolization in turn complicates repeat revascularization procedures either by percutaneous coronary reintervention or reoperation.[397] [481] [482]

DETERMINATION OF GRAFT PATENCY.

Although angiography is the most frequently used method for the determination of vein graft patency, the diffuseness of the atherosclerotic process, which in many patients decreases the luminal diameter of the entire vessel, may lead to an underestimation of the severity of a more focal lesion. Alternative approaches to the evaluation of vein graft patency that are being investigated include contrast-enhanced CT, phase-contrast

magnetic resonance angiography,[483] and transcutaneous [484] and magnetic resonance measurements of angiographic flow (see Chap. 10) .[485]

PROGRESSION OF DISEASE IN NONGRAFTED ARTERIES.

Disease progression, defined as worsening of a preexisting lesion or the appearance of a new diameter narrowing of 50 percent or greater, can occur at a rate of 20 to 40 percent over 5 to 10 years in nongrafted native vessels.[486] The rate of disease progression appears highest in arterial segments already showing evidence of disease,[487] and it is between three and six times higher in grafted native coronary arteries than in ungrafted native vessels. Disease progression is also greater in arteries with patent grafts than in arteries with occluded grafts[488] and usually occurs proximal to the site of graft insertion.[486] [487] These data suggest that bypassing an artery with minimal disease, even if initially successful, may ultimately be harmful to patients, who incur both the risk of graft closure and the increased risk of accelerated obstruction of native vessels.

EFFECTS OF THERAPY ON VEIN GRAFT OCCLUSION AND NATIVE VESSEL PROGRESSION

Measures aimed at enhancing long-term patency are generally directed at delaying the overall process of atherosclerosis, and as such, they may have several additional benefits.[482]

ANTIPLATELET THERAPY.

A meta-analysis of clinical trials conducted before 1990 suggests that antiplatelet or anticoagulant therapy after coronary artery bypass surgery may prevent graft occlusion.[489] Several trials have demonstrated the efficacy of aspirin therapy when started 1, 7, or 24 hours preoperatively, but the benefit is lost when aspirin is started more than 48 hours postoperatively.[490] Aspirin, 100 to 325 mg/d should be continued indefinitely.[491] The addition of dipyridamole or warfarin in conventional doses has not been shown to provide added benefit.[492] Ticlopidine is effective but not superior to aspirin, and its use should be confined to patients who are intolerant of aspirin. Although the effects of clopidogrel on graft patency have not been studied specifically,[493] it is likely to be at least as effective as aspirin.

LIPID-LOWERING THERAPY.

The rationale for lowering lipid levels in patients with CAD was extended to postoperative patients with at least one patent vein graft and LDL cholesterol concentrations between 130 and 175 mg/dl in the Post-Coronary Artery Bypass Graft Trial.[191] Patients who received aggressive treatment with lovastatin and, if needed, cholestyramine to decrease LDL cholesterol to less than 100 mg/dl, in comparison with "moderate" therapy resulting in an LDL cholesterol level of 134 mg/dl, had a lower rate of progressive atherosclerosis in grafts (27 vs. 39 percent, *p*0.001) and a lower rate of repeat revascularization procedures over a 4-year period. A similar benefit in both native vessels and grafts was noted in the Cholesterol-Lowering Atherosclerosis Study

(CLAS), which used combined colestipol and niacin therapy.[494] The Lipid Coronary Angiography Trial (LOCAT) compared gemfibrozil and placebo in patients with LDL cholesterol concentrations of 175 mg/dl or lower and an HDL cholesterol of less than 42 mg/dl. The treated group had a lower rate of progression of native coronary atherosclerosis and a lower incidence of new lesions in the vein graft (2 vs. 14 percent) after an average 32-month follow-up.[194]

SMOKING CESSATION.

Strong evidence from the CASS randomized trial and other series indicates that continued smoking after bypass surgery increases mortality, the recurrence rate of angina, the need for repeat hospitalization, and repeat revascularization procedures.[160] [161] Not unexpectedly, continued smoking has been associated with angiographic progression of graft disease.

Patient Selection

Indications for coronary bypass surgery consist of the need for improvement in the quality and/or the duration of life. Patients whose angina is not controlled by medical management or who have unacceptable side effects with such management should be considered for coronary revascularization. The decision to perform PCI or CABG is based partly on coronary anatomy, left ventricular function, and patient preference. Recent technological developments have enlarged the pool of patients with single-vessel or multivessel disease amenable to PCI. For patients who are suitable for PCI and who do not fulfill the criteria of anatomy requiring surgery (e.g., left main CAD or severe three-vessel disease and left ventricular dysfunction), PCI is generally the procedure of choice. However, if medical therapy has failed, i.e., the symptoms are severe or sufficient to impair quality of life, and the patient is not a good candidate for PCI, CABG should be strongly considered. This procedure is also indicated for patients with CAD, regardless of symptoms, in whom survival is likely to be prolonged, [495] and for patients in whom noninvasive testing suggests "high risk," independent of symptoms.[496]

In making the decision about revascularization, it is important to assess the patient's prognosis (Table 37-10) and

TABLE 37-10 -- DETERMINANTS OF ADVERSE PROGNOSIS IN PATIENTS WITH CORONARY ARTERY DISEASE

CARDIAC DETERMINANTS
Left ventricular dysfunction

Extent of myocardial jeopardy--extent of ischemia at rest and with exercise and the number of large vessels diseased
Extent of myocardium in jeopardy
Abnormal arrhythmic substrate
CLINICAL AND ELECTROCARDIOGRAPHIC MODIFYING FACTORS
Advanced age
History of congestive heart failure
Diabetes
Rapidly accelerating angina
Resting electrocardiographic abnormalities
Left ventricular hypertrophy and hypertension
Peripheral vascular disease
Hyperlipidemia

how it may be affected by surgery. The key initial step is to stratify patients into categories of risk with continued medical therapy based on an analysis of clinical, noninvasive, and, in some patients, angiographic variables. This process defines the *indications* for revascularization over medical therapy and, by implication, the indications for coronary angiography in patients with chronic stable angina. More recent randomized trial data are helpful in finding which *modality* of revascularization (PCI or surgery) is preferable.[496]

The four major determinants of risk in CAD are the extent of ischemia, the number of vessels diseased, left ventricular function, and the electrical substrate (Fig. 37-13) . The major effect of coronary revascularization is on ischemia,

Figure 37-13 Risk stratification in coronary artery disease (CAD). A Venn diagram illustrates factors affecting the prognosis of chronic CAD. Major determinants are the severity of symptoms and/or ischemia, presence of multivessel disease and in particular three-vessel disease, extent of myocardial jeopardy as defined by clinical stenoses in the left main coronary artery and proximal left anterior descending coronary artery, and left ventricular dysfunction. Interactions between an abnormal arrhythmic substrate, evidence of recent plaque rupture (acute coronary syndromes), and general health and coexisting conditions are important.

and the magnitude of the benefit compared with that of medical therapy is enhanced with left ventricular dysfunction, particularly in the presence of reversibly ischemic jeopardized myocardium. In this context, patients can be risk-stratified according to the expected benefit of revascularization versus medical therapy. Patients with more extensive and severe CAD have an increasing magnitude of benefit from CABG over medical therapy (Fig. 37-14 *A* and Table 37-11) . Selection of patients for surgery is based on clinical, angiographic, and noninvasive testing characteristics that may be considered markers or, in some cases, surrogates of the three major

predictors--ischemia, left ventricular function, and, to a lesser extent, arrhythmia. Other factors that must always be considered in the decision are general health and noncoronary comorbid conditions.

Natural History of Angina Pectoris

CLINICAL AND ELECTROCARDIOGRAPHIC CRITERIA.

Data from the Framingham Study, obtained before the widespread use of aspirin, beta blockers, and aggressive modification of risk factors, showed that the average annual mortality rate of patients with chronic stable angina was 4 percent.[497] The combination of these treatments has improved prognosis. Nonetheless, a recent study from the United Kingdom of patients evaluated for the first time with typical angina has suggested that the prognosis should be guarded because over a 15-month period, 4 percent mortality and a 7 percent rate of nonfatal myocardial infarction were noted, and only 11 percent had spontaneous remission of angina.[498] Several studies have shown that a composite risk score based on multiple clinical variables (e.g., age, sex, diabetes, previous myocardial infarction, and the nature of the chest pain) may be quite strongly predictive of the presence of severe CAD (triple-vessel or left main CAD) and thus provide a strong indication for angiography[35] [499] (see Fig. 37-14 and Table 37-11) . Numerous studies attest to the adverse prognostic effect of congestive heart failure (based on a clinical history of cardiomegaly on chest radiography), previous myocardial infarction, hypertension, and advanced age in patients with stable angina pectoris.[79] [497] [498] A third heart sound is a useful clinical predictor of an abnormal left ventricular ejection fraction and an adverse prognosis in patients with CAD. The severity of angina, especially the tempo of intensification, is also an important predictor of outcome.

On the other hand, a normal resting ECG in patients with stable angina pectoris speaks in favor of wellpreserved left ventricular function and a favorable long-term prognosis[364] (see p. 1277). Among 14,507 patients with chest pain enrolled in the CASS Registry, 91.8 percent of those with a normal ECG had an ejection fraction greater than 50 percent and only 0.6 percent had an ejection fraction

TABLE 37-11 -- IMPACT OF CORONARY BYPASS SURGERY ON SURVIVAL IN SUBSETS OF PATIENTS STUDIED IN THE CORONARY ARTERY SURGERY STUDY (CASS) RANDOMIZED TRIAL AND REGISTRY STUDIES

CATEGORY OF RISK	NUMBER OF VESSELS DISEASED	SEVERITY OF ISCHEMIA	EJECTION FRACTION	RESULTS OF SURGERY ON SURVIVAL
Mild	2	Mild	>0.50	Unchanged*
	3			Unchanged*

Moderate	2 3	Moderate to severe	>0.50	Unchanged* Improved
	2 3	Mild	<0.50	Unchanged* Improved
Severe	2 3	Moderate to severe	<0.50	Improved Improved

*Randomized trial.

Survival improved with surgery versus medicine. In the European Coronary Surgery Trial, patients with double-vessel disease and involvement of the paroxysmal left anterior descending coronary artery had improved survival with surgery irrespective of left ventricular function.

less than 35 percent.[500] Left ventricular hypertrophy, as determined on the ECG or echocardiogram, is associated with increased mortality. [501] Although the presence of calcium in the coronary arteries on chest radiography, fluoroscopy, or electron beam CT is associated with an adverse

Figure 37-14 *A,* Adjusted hazard (mortality) ratios comparing coronary artery bypass grafting (CABG) and medical therapy for nine coronary anatomy severity groups (GR) according to the number of vessels diseased (VD), the presence or absence of a 95 percent proximal stenosis (95 percent), and involvement of the left anterior descending coronary artery (LAD). *B,* Adjusted hazard (mortality) ratios comparing CABG and percutaneous transluminal angioplasty (PTCA) for nine coronary anatomy groups according to the number of vessels diseased, the presence or absence of a 95 percent proximal stenosis, and LAD involvement. Among patients with the least severe categories of disease, 5-year survival appears to be better with PTCA (single-vessel disease without proximal stenosis and without LAD involvement), whereas for patients with three-vessel disease and higher-grade, more complex two-vessel disease, a survival benefit is noted with surgery. For other subsets of patients with two-vessel disease, no difference in survival was seen in those treated with CABG or PTCA, and many of these patients are probably similar to those included in the randomized trials. *(Data from the Duke University data base. From Jones RH, Kesler K, Phillips HR III, et al: Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg 111:1013, 1996. By permission of Mosby.)*

prognosis and correlates to some extent with the severity of CAD, the presence and extent of calcification cannot be used at this stage as an indication for angiography or coronary revascularization.[35]

In summary, a comprehensive clinical evaluation provides useful prognostic information in addition to being an indispensable basis for assessing the risk of a procedure and the

likelihood of sustained benefits.

NONINVASIVE STRESS TESTING (see p. 1278).

One of the most valuable aspects of noninvasive imaging is the echocardiographic assessment of left ventricular function. Such testing is not necessary for all patients, and among patients with a normal ECG and no previous history of myocardial infarction, the likelihood of preserved left ventricular systolic function is high. In contrast, among patients with a history of myocardial infarction, ST-T wave changes, or conduction defects or Q waves on the ECG, left ventricular function should be measured with echocardiography or an equivalent technique.[35] In patients in whom left ventricular function and coronary anatomy have already been defined, stress testing may provide additional prognostic information about the functional significance of specific angiographic lesions.

The prognostic importance of the treadmill exercise test was determined by several observational studies in the 1980s and early 1990s, and these studies have had a major influence on current indications for coronary revascularization.[35] One of the most important and consistent predictors is the maximal exercise capacity, regardless of whether it is measured by exercise duration or workload achieved or whether the test was terminated because of dyspnea, fatigue, or angina.[35] [502] [503] Other factors with a poor prognosis identified in individual series of patients with chronic stable angina are described in Table 37-2 (see p. 1280).

Prognostic Scores.

The impact of the magnitude of exercise-induced ischemia on prognosis as defined by symptoms or ST segment deviation has led to the development of various prognostic scores that appear to work well in both the inpatient and outpatient settings. Mark and colleagues developed a prognostic score that incorporates exercise duration, the magnitude of ST segment deviation, and exercise-induced angina.[502] Patients were stratified into three groups with an average annual mortality of 0.25, 1.25, and 5.0 percent. Moreover, the score contained incremental information beyond that provided by clinical and catheterization data.[502]

Stress Thallium-201 Myocardial Perfusion Imaging (see also Chaps. 9 and 13 and p. 1278).

A normal stress thallium study is highly predictive of a favorable prognosis in patients with and without documented CAD.[35] [75] [504] In an analysis of 16 studies involving more than 3500 patients, the rate of cardiac death and myocardial infarction over a mean follow-up period of 29 months was only 0.9 percent. In patients with documented CAD, the single most powerful prognostic factor was the magnitude of the perfusion abnormality on SPECT thallium-201 scintigraphy.[505] Pharmacological stress perfusion imaging techniques with dipyridamole, adenosine, or dobutamine have an established place as an alternative to exercise perfusion imaging in establishing the prognosis in patients with stable CAD.[74] [506]

Stress Echocardiography

(see also Chap. 7 and p. 1279). Evidence is increasingly demonstrating that echocardiography with exercise or pharmacological stress (dobutamine, arbutamine, or dipyridamole) is both sensitive and specific for the identification of myocardial ischemia and for risk stratification in patients with chronic stable angina.[98] [507] [508] The presence or absence of inducible regional wall motion abnormalities and the response of the ejection fraction to exercise appear to provide incremental prognostic information in addition to the assessment of cardiac structure and function provided by the resting echocardiogram. Moreover, a negative stress test portends a very low risk for future events.[509] Although most studies demonstrated enhanced diagnostic accuracy for dobutamine stress echocardiography, the prognostic value of dipyridamole and dobutamine may be similar.[510]

The choice of a particular stress testing modality in a patient with chronic stable angina undergoing assessment for coronary revascularization depends on several clinical issues that may limit the technical quality of the echocardiographic images, such as the presence of obesity or chronic obstructive pulmonary disease. Nonetheless, the most vital factor to be considered is probably the level of expertise that an institution has with each technique.

ANGIOGRAPHIC CRITERIA.

The independent impact of multivessel disease and left ventricular dysfunction and their interaction on the prognosis of patients with CAD has been well documented[511] [512] and provides a logical framework for coronary angiography in the assessment of prognosis (Fig. 37-15) . These two risk factors are synergistic in that the adverse effects of impaired ventricular function on prognosis are more pronounced as the number of stenotic vessels increases.[511]

Although several indices have been used to quantify the extent of severity of CAD, the simple classification of disease into one-vessel, two-vessel, three-vessel, or left main CAD is the most widely used and is effective.[511] [513] Additional

Figure 37-15 Graphs showing survival for medically treated CASS patients. *A,* Patients with one-, two-, or three-vessel disease and an ejection fraction of 50 to 100 percent stratified by the number of diseased vessels (DISVES). *B,* Patients with one-, two-, or three-vessel disease and an ejection fraction of 35 to 49 percent stratified by the number of diseased vessels. *C,* Patients with one-, two-, or three-vessel disease and an ejection fraction of 0 to 34 percent stratified by the number of diseased vessels. *(From Emond M, Mock MB, Davis KB, et al: Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 90:2645, 1994. By permission of the American Heart Association, Inc.)*

prognostic information is provided by the severity of obstruction and the location, whether proximal or distal.[35] [514] The concept of the gradient of risk is illustrated in Figure 37-14 , which was derived from the Duke University data base of patients treated medically. Among medically treated patients in CASS, the 12-year survival rate was 91 percent among those with chronic angina and angiographically normal vessels. In the presence of single-vessel disease, it was 86 percent for patients with at least one obstruction of 30 to 50 percent, 79 percent for patients with at least one stenosis of 50 to 70 percent, and 74 percent for patients with single-vessel disease and stenosis of 70 percent or more.[511]

Studies of treated symptomatic patients have revealed that if only one of the three major coronary arteries has more than 50 percent stenosis, the annual mortality rate is approximately 2 percent.[515] The importance to survival of the quantity of myocardium that is jeopardized is reflected in the observation that an obstructive lesion proximal to the first septal perforating branch of the left anterior descending coronary artery was associated with a 5-year survival rate of 90 percent in comparison with 98 percent for patients with more distal lesions.[515] The survival rate of patients with isolated right CAD at 5 years appeared to be higher (96 percent) than for patients with disease of the left anterior descending coronary artery (92 percent). The overall survival of medically treated patients with left anterior descending and left circumflex CAD was not significantly different, but both were less than the survival of patients with isolated right CAD.[515]

The impact of left ventricular dysfunction is illustrated by the 12-year survival rates of unoperated patients in the CASS Registry, which were 73, 54, and 21 percent among patients with ejection fractions of 50 percent or higher, 35 to 49 percent, and less than 35 percent, respectively[511] (Fig. 37-15) .

In the example used in the ACC/AHA guidelines,[35] a 65-year-old man with three-vessel disease and stable angina has a 5-year survival rate ranging from 93 to 58 percent, according to the presence or absence of congestive heart failure and a decreased ejection fraction.

High-grade lesions of the left main coronary artery or its "equivalents," as defined by severe proximal left anterior descending and proximal left circumflex CAD, are particularly life threatening.[516] Mortality among medically treated patients has been reported to be 29 percent at 18 months, 39 percent at 2 years, and 43 percent at 5 years.[516] Survival is better for patients with 50 to 70 percent stenosis (1- and 3-year survival rates of 91 and 66 percent, respectively) than for patients with a left main coronary artery stenosis greater than 70 percent (1- and 3-year survival rates of 72 and 41 percent).[517] Furthermore, a number of characteristics found at catheterization or on noninvasive examination are predictors of an adverse prognosis in patients with 70 percent or greater left main coronary artery stenosis, including chest pain at rest, ST-T wave changes on resting ECG, cardiomegaly on chest radiography, a history of congestive heart failure, findings of left ventricular dysfunction at catheterization, and an

increase in the arterial-mixed venous oxygen difference.[517]

Limitations of Angiography.

The pathophysiological significance of coronary stenoses lies in their impact on resting and exercise-induced blood flow, in addition to their potential for plaque rupture with superimposed thrombotic occlusion. It is generally accepted that a stenosis of greater than 60 percent of the luminal diameter is hemodynamically significant in that it may be responsible for a reduction in exercise-induced myocardial blood flow and cause angina and ischemia[518] (see Chap. 34) . The functional significance of obstruction of "intermediate" severity (approximately 50 percent diameter stenosis) is less well established. Coronary angiography is not a reliable indicator of the functional significance of stenosis, nor is it sensitive to the presence of thrombus.[519] Moreover, the coronary angiographic determinants of the severity of stenosis are based on a decrease in the caliber of the lumen at the site of the lesion *relative* to adjacent reference segments, which are considered, often erroneously, to be relatively free of disease. This approach may lead to significant underestimation of the severity and extent of atherosclerosis.[520] Furthermore, assessment of left main stem disease, particularly in vessels with lesser degrees of obstruction, is not optimal.[521]

Another limitation to the routine use of coronary angiography for prognosis in patients with chronic stable angina is its inability to identify which coronary lesions can be considered to be at high risk for future events, such as myocardial infarction or sudden death. Although it is widely accepted that myocardial infarction is the result of thrombotic occlusion at the site of plaque rupture (see Chap. 35) , a growing body of evidence indicates that it is not necessarily the plaque causing the most severe stenosis that subsequently ruptures.[522] Several studies of patients undergoing serial coronary angiography indicate that myocardial infarction often arises from rupture of the plaque that did *not* cause critical obstruction. Lesions causing mild obstructions can rupture, thrombose, and occlude, thereby leading to myocardial infarction and sudden death.[523] [524] [525] In contrast, arteries with severe preexisting stenoses may proceed to clinically silent complete occlusion, often without infarction, presumably because of the formation of collaterals as ischemia gradually becomes more severe.

In summary, angiographic documentation of the extent of CAD is an indispensable step in the selection of patients for coronary revascularization, particularly if the interaction between the anatomical extent of disease, left ventricular function, and the severity of ischemia is taken into account. However, angiography is not helpful in predicting the site of subsequent occlusions that could cause myocardial infarction or sudden cardiac death, particularly in an individual patient.

In the characterization of lesion morphology and severity, intravascular ultrasonography (see Chap. 12) may be helpful, particularly in patients undergoing PCI.[526] Assessment of coronary flow reserve with Doppler techniques and assessment of transstenotic gradients at baseline and during maximal hyperemia (see Chap. 34) are tools that, in an experienced laboratory, may also be helpful in deciding on the flow-limiting significance of a specific lesion and the need for coronary revascularization.[527]

Results

In 1972, a committee of the AHA indicated that the most widely accepted indication for surgical revascularization was "significant disability from moderate to severe angina pectoris, unresponsive to optimal medical care." Three decades later, the realization that CABG prolongs survival in subgroups of patients with either minimal or mild to moderate symptoms has shifted the emphasis toward *ischemia* instead of *symptoms alone* as the target for coronary revascularization. Consequently and appropriately, CABG is currently performed in an increasing number of patients with multivessel disease and/or left ventricular dysfunction (particularly in the face of viable jeopardized dysfunctioning myocardium) and in patients with poor exercise tolerance in the presence of stress-induced ischemia. Severe ischemia and/or reversible left ventricular dysfunction provides a window of opportunity for improving survival (in comparison to medical therapy) that has resulted in an increase in the frequency of CABG in patients with unstable angina and in survivors of acute myocardial infarction. Left ventricular dysfunction, initially a relative contraindication for surgery, has become a major indication. Nonetheless, severe

symptoms or even moderate symptoms that interfere with the quality of life despite adequate medical therapy are still as firm an indication for coronary revascularization (PCI or CABG) as they were for CABG almost three decades ago.

Relief of Angina

CABG is highly effective in providing complete relief from angina in some patients and improvement in the severity of symptoms in most of the rest (Fig. 37-12) . In a series of patients who received saphenous vein grafts alone, approximately 90 percent were free of angina at 1 year. In the following 4 years, the recurrence rate was approximately 3 percent per year and 5 percent per year thereafter. Approximate rates of freedom from angina were 78 percent at 5 years, which decreased to 52 and 23 percent at 10 and 15 years, respectively.[528] The major randomized trials have all demonstrated greater relief of angina, better exercise performance, and a lower requirement for antianginal medications for surgically versus medically treated patients 5 years postoperatively.[495] [529] [530] [531] Beyond 5 years, differences in symptoms between patients initially treated medically and surgically are diminished, in part because of the high "crossover" rate from medical to surgical therapy in patients with continued symptoms and progression of disease in vein grafts and nonbypassed vessels in the surgical group.[529] [530] The 22-year follow-up of the Veterans Administration (VA) Trial demonstrated no difference in the severity of angina between medically and surgically treated groups after 10 years.[532] These results must be tempered by the low rate of initial complete revascularization, absence of the use of an IMA graft, and lack of platelet inhibitor therapy and risk factor reduction in this trial, which reflected the very early part of the "learning curve" of coronary bypass surgery.[533] The reoperation rate for recurrence of

symptoms has been reported to be in the range of 6 to 8 percent per year.[534]

For patients with persistent angina despite adequate medical therapy or for patients who do not tolerate medications or who are not suitable candidates for PCI, coronary bypass grafting provides excellent symptomatic relief.[35] With increasing use of IMA grafts, long-term relief from angina and freedom from subsequent cardiac events are improved in comparison to previous patient populations who received vein grafts alone.

In summary, after 5 years, approximately three-fourths of surgically treated patients can be predicted to be free of an ischemic event, sudden death, occurrence of myocardial infarction, or the recurrence of angina; about half remain free for approximately 10 years and about 15 percent for 15 or more years. Symptomatic improvement is best maintained in patients with the most complete revascularization.[453] [528]

Effects on Survival

Current clinical practice has been shaped by three major randomized trials that enrolled patients between 1972 and 1979: the VA Trial, the European Cardiac Society Study (ECSS), and the National Institutes of Health-supported CASS (Fig. 37-16 and Table 37-12) .[531] [535] [536] [537] [538] [539] These trials antedated widespread use of the IMA for revascularization, as well as the use of aspirin and coronary angioplasty. The extent of the completeness of coronary revascularization, graft patency rates, and perioperative mortality in the VA Trial fall far short of current expectations and reflect, in part, the initial learning experience of coronary bypass surgery.

In the VA Study, no significant difference was found in overall survival between the groups initially assigned to medical or surgical treatment after 11 years of follow-up. However, higher-risk subsets, including patients with left main coronary disease and patients who had three-vessel disease with impaired left ventricular function, initially had a significant survival advantage with surgery, although the magnitude of the difference decreased between 7 and 11 years. On retrospective analysis, a higher-risk subset, those with two or more of the following risk factors--New York Heart Association Class III or IV angina, a history of hypertension, a history of prior myocardial infarction, and ST segment depression on the resting ECG--experienced a survival benefit from surgery.[537]

Patients randomly assigned to an initial surgical approach also experienced an overall survival advantage in the ECSS.[531] Again, the benefits of surgery were greater in patients at higher risk, including those with multivessel disease that included the proximal left anterior descending coronary artery, older patients, those with evidence of ischemia or infarction on the resting ECG, patients with peripheral vascular disease, and those with a markedly positive stress test. No significant difference in survival was seen between medical and surgical treatment in patients with one-vessel disease and those with two-vessel disease without critical stenosis of the proximal left anterior descending coronary artery. In the CASS randomized trial, no difference in overall survival was found between the medically and surgically treated groups.[535] [539] However, survival of patients at higher risk, e.g., those with a left ventricular ejection fraction between 35 and

50 percent, was improved by surgery.[535]

Figure 37-16 Survival curves of the three large randomized trials and four smaller studies combined. *(Reproduced from Eagle KA, Guyton RA, Davidoff, R et al: ACC/AHA Guidelines for coronary artery bypass surgery. J Am Coll Cardiol 34:1262-1347, 1999.)*

LEFT MAIN CORONARY ARTERY STENOSIS.

It is widely agreed that surgical treatment improves survival in patients with left main coronary artery obstruction[540] or its "equivalent." The CASS Registry demonstrated that the superiority of revascularization was equivalent in both symptomatic and asymptomatic patients with disease affecting the left main coronary artery.[516] [541]

Whether a "left main equivalent" anatomy exists that has a natural history similar to that of left main CAD is uncertain. The condition in question may consist of disease in the proximal portions of both the left anterior descending and left circumflex coronary arteries. It is likely that significant left main coronary disease has an ominous nature, because a single event (rupture of a single plaque) can cause infarction of a very large quantity of myocardium. Consequently, although combined disease of the proximal left anterior descending and circumflex coronary arteries does identify a subgroup of high-risk patients, the prognosis is not as poor as it is for patients with left main CAD.[542] Nevertheless, patients with combined stenoses of 70 percent or greater in the left anterior descending coronary artery, before the first septal perforating branch, and in the proximal circumflex coronary artery, before the first obtuse marginal branch, who have impaired ventricular function also have improved survival and less angina following surgical revascularization than if they are treated medically, particularly in the face of left ventricular dysfunction. The median survival of surgically treated patients with left main-equivalent disease is 13.1 years versus 6.2 years for those medically treated.[541]

OVERVIEW OF THE RANDOMIZED TRIALS.

A systematic overview of the seven randomized trials (the three aforementioned large trials and four smaller trials) that compared coronary bypass surgery with medical therapy between 1972 and 1984 yielded 2649 patients (see Fig. 37-16 and Table 37-12) . In interpreting this overview, it must be appreciated that surgical treatment has improved significantly in the past 25 years and that outcomes have been improved, in particular with the widespread use of one or two IMAs. Patients undergoing CABG had a significantly lower mortality at 5, 7, and 10 years, but by 10 years, 41 percent of the patients initially randomly assigned to medical treatment had undergone CABG (so-called crossovers). The advantage for surgery was greatest in patients with left main CAD. An improvement in survival was also noted with surgical treatment in patients with one- or two-vessel disease and stenosis of the proximal left anterior descending

coronary artery. Among patients without obstruction of the proximal left anterior descending coronary artery, the reduction in mortality was confined to those with left main coronary artery or three-vessel disease.

To place the relevant and absolute benefits of coronary bypass surgery into perspective, patients were further stratified into high-, moderate- and low-risk subgroups by using criteria developed by the VA Cooperative Study.[537] These criteria were based on clinical findings and included the severity of angina, history of hypertension, prior myocardial infarction, and ST segment depression at rest. Low-risk patients had none of the four risk factors aside from ST segment depression, whereas those with two or three risk factors were considered to be at high risk. In patients at high risk, the mortality reduction was 29 percent at 10 years versus 10 percent for patients at moderate risk. In low-risk patients, a nonsignificant trend was seen toward greater mortality with bypass surgery.

The results of all the trials and registries[538] taken together

TABLE 37-12 -- EFFECTS OF CORONARY ARTERY BYPASS GRAFT SURGERY ON SURVIVAL*

SUBGROUP	MEDICAL TREATMENT MORTALITY RATE (%)	*p*VALUE FOR CABG SURGERY VS. MEDICAL TREATMENT
VESSEL DISEASE		
One vessel	9.9	0.18
Two vessels	11.7	0.45
Three vessels	17.6	<0.001
Left main artery	36.5	0.004
NO LAD DISEASE		
One or two vessels	8.3	0.88
Three vessels	14.5	0.02
Left main artery	45.8	0.03
Overall	12.3	0.05
LAD DISEASE PRESENT		
One or two vessels	14.6	0.05
Three vessels	19.1	0.009
Left main artery	32.7	0.02
Overall	18.3	0.001

LV FUNCTION		
Normal	13.3	<0.001
Abnormal	25.2	0.02
EXERCISE TEST STATUS		
Missing	17.4	0.10
Normal	11.6	0.38
Abnormal	16.8	<0.001
SEVERITY OF ANGINA		
Class 0, I, II	12.5	0.005
Class III, IV	22.4	0.001

LAD=left anterior descending artery; LV=left ventricular.

From Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass surgery on survival: Overview of 10-year results from randomized trials by the Coronary Artery Bypass Surgery Trialists Collaboration. Lancet 344:563, © by The Lancet Ltd., 1994.

*Systematic overview of the effect of coronary artery bypass graft (CABG) surgery versus medical therapy on survival based on data from the seven randomized trials comparing a strategy of initial CABG surgery with one of initial medical therapy. Subgroup results at 5 years are shown.

indicate that the "sicker" the patient (based on the severity of symptoms or ischemia, age, the number of vessels diseased, and the presence of left ventricular dysfunction), the greater the benefit of surgical over medical therapy on survival (see Table 37-12) .[348] [514] Among low-risk patients and patients with single-vessel disease, no trial has demonstrated any benefit on survival.

Thus, CABG prolongs survival in patients with significant left main CAD irrespective of symptoms, in patients with multivessel disease and impaired left ventricular function, and in patients with three-vessel disease that includes the proximal left anterior descending coronary artery (irrespective of left ventricular function).[495] [543] Surgical therapy has also been demonstrated to prolong life in patients with *two-vessel disease* and left ventricular dysfunction, particularly those with proximal narrowing of one or more coronary arteries and in the presence of severe angina.[544] Although no study has documented a survival benefit with surgical treatment in patients with *single-vessel disease*, some evidence indicates that such patients who have impaired left ventricular function have a poor long-term survival.[511] Such patients with angina or evidence of ischemia at a low or moderate level of exercise, especially those with obstruction of the proximal left anterior descending coronary artery, may benefit from coronary

revascularization by either PCI or bypass surgery.

The only randomized data comparing CABG with medical therapy in the current era are from the Asymptomatic Cardiac Ischemia Pilot (ACIP) Study of 558 patients[545] (Fig. 37-17) . This trial of angina-guided versus angina plus ischemia-guided medical therapy (using ambulatory monitoring) in comparison to revascularization by either PTCA (92 patients) or CABG (79 patients) enrolled relatively low-risk patients. After 2 years of follow-up, mortality was significantly lower among the patients assigned to routine revascularization (1.1 vs. 6.6 and 4.4 percent for the two medical groups [*p*0.02]), and rates of death or myocardial infarction were 12.1 (angina-guided medical therapy), 8.9 (ischemia-guided medical therapy), and 4.7 percent following coronary revascularization (*p*0.04). Although this trial was designed as a pilot study and the number of patients was relatively small, the observed risk reductions were statistically significant and suggest that the benefits of revascularization in the context of current revascularization technique may be greater than previously appreciated. The trial was not designed to assess differences between PTCA and bypass surgery but does point to the need for larger, more definitive randomized trials testing contemporary strategies of revascularization with optimal medical therapy and risk factor reduction.

EFFECT OF SURGERY ON SUBSEQUENT MYOCARDIAL INFARCTION.

The major randomized trials of patients with mild to moderate angina suggested that the likelihood of occurrence of myocardial infarction after 5 to 10 years of follow-up was similar in medically and surgically treated patients.[531] [537] [538] [546] [547] In both the VA Study and the CASS, the major benefit of surgery on myocardial infarction does not appear to be mediated by a decrease in the frequency of myocardial infarction but by a decrease in the case fatality rate of patients who subsequently have infarction.[548] Potential explanations are that previous bypass surgery results in smaller infarcts caused by distal occlusions and that the bypass may enhance myocardial perfusion distal to the obstructing lesion.[549]

Patients with Depressed Left Ventricular Function

Depressed *left ventricular function* is one of the most powerful predictors of perioperative and late mortality.[550] [551] [552] [553] In the Society of Thoracic Surgeons data base[425] *(www.ctsnenet.org),* the mean ejection fraction among approximately 161,000 patients undergoing initial coronary bypass in 1997 was approximately 51 percent, and approximately 25 percent had an ejection fraction less than 45 percent. Moreover, as the population ages and the proportion undergoing reoperation increases, the number of patients with preoperative left ventricular dysfunction and clinical heart failure will increase. In the CABG Patch Trial confined to patients with an ejection fraction of 35 percent of less, perioperative mortality was 3.5 percent for patients without clinical signs of heart failure versus 7.7 percent for those with New York Heart Association Class I to IV heart failure.[554] The latter was a powerful independent predictor of increased operative mortality in patients with ventricular dysfunction and a positive signal-averaged ECG[554] (odds ratio, 2.4; $p=0.01$).

Although the effect of a reduced ejection fraction on operative mortality cannot be

eliminated, careful attention to intraoperative metabolic, inotropic, and mechanical support, including preoperative intraaortic balloon counterpulsation in some patients, may decrease perioperative mortality in comparison with the mortality rates expected from prediction models.[555]

The powerful effect of the preoperative ejection fraction on late survival emphasizes that in the current era, the presence of left ventricular dysfunction has changed from a relative contraindication to coronary bypass to a very strong indication.[552] This shift in focus has been due to the realization that viable dysfunctioning myocardium may improve after coronary revascularization.[550] [556] Indeed, the

Figure 37-17 Two-year cumulative mortality rates for the three treatment strategies in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. Significant differences were seen between revascularization and angina-guided strategies *(p* 0.005) and between revascularization and ischemia-guided strategies *(p* 0.05). Angina-guided and ischemia-guided strategies were not significantly different from each other *(p*=0.34). Similar results were noted for the endpoints of cumulative rates of death, myocardial infarction, or cardiac hospitalization. *(From Davies RF, Goldberg AD, Forman S, et al: Asymptomatic Cardiac Ischemia Pilot [ACIP] study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 95:2037, 1997. By permission of the American Heart Association, Inc.)*

most striking survival benefits of CABG, as well as symptomatic and functional improvement, are shown by patients with seriously impaired left ventricular function in whom the prognosis of medical therapy is poor.[88] [555] [556] [557] [558] In patients with a history of congestive heart failure and multivessel (particularly three-vessel) disease, coronary bypass surgery may also reduce the incidence of sudden cardiac death.[559] Although preoperative left ventricular dysfunction creates the potential for significant benefit, the perioperative risk should not be underestimated, particularly in the setting of clinical congestive heart failure.[550] In the CASS Registry, operative mortality was 1.97 percent and the 5-year survival rate was 92 percent for patients with normal or nearly normal left ventricular function; operative mortality was 4.2 percent and the 5-year survival rate was 80 percent for those with an ejection fraction of 0.35 to 0.49, and for those with an ejection fraction less than 0.35, operative mortality was 6.2 percent and the 5-year survival rate was 65 percent.[560] A more recent series demonstrated an in-hospital operative mortality of 8.4 percent for patients with an ejection fraction of 0.30 or less.[550]

MYOCARDIAL HIBERNATION.

Improvement in survival and left ventricular function following CABG depends on successful reperfusion of viable, but noncontractile or poorly contracting myocardium (see Chaps. 13 , 14 , and 34) . Two related pathophysiological conditions have been described to explain reversible ischemic contractile dysfunction[561] : myocardial stunning

(prolonged but temporary postischemic ventricular dysfunction without myocardial necrosis) and myocardial hibernation (persistent left ventricular dysfunction when myocardial perfusion is chronically reduced but sufficient to maintain the viability of tissue). The reduction in myocardial contractility in hibernating myocardium conserves metabolic demands and may be protective, but more prolonged and severe hibernation may lead to severe ultrastructural abnormalities, irreversible loss of contractile units, and apoptosis.[562]

Hibernating myocardium can cause abnormal systolic or diastolic ventricular function or both. The predominant clinical feature of myocardial ischemia in these patients may not be angina, but dyspnea secondary to increased left ventricular diastolic pressure. Symptoms of heart failure resulting from chronic left ventricular dysfunction may be inappropriately ascribed to myocardial necrosis and scarring when the symptoms may, in fact, be reversed after the chronic ischemia is relieved by coronary revascularization.[103] [563]

Detection Of Hibernating Myocardium.

Several clinical markers may be used to determine the likelihood that a dysfunctional myocardial segment is viable or nonviable (Table 37-13) . A severe reduction in the diastolic wall thickness of dysfunctional left ventricular segments is indicative of scarring. On the other hand, akinetic or dyskinetic segments with preserved diastolic wall thickness may

TABLE 37-13 -- MARKERS OF VIABLE MYOCARDIUM

CLINICAL INDICATOR	DIAGNOSTIC TEST	ALTERNATIVE TEST
Diastolic wall thickness	Echo	CT, MRI
Systolic wall thickening	Echo	CT, MRI, gated SPECT
Regional wall motion	Echo	CT, MRI, gated SPECT
Regional blood flow	SPECT	PET
Myocardial metabolism	PET	SPECT
Cell membrane integrity	SPECT	PET
Contractile reserve	Dobutamine, Echo	Angiography, CT, MRI

CT=computed tomography; Echo=echocardiography; MRI=magnetic resonance imaging; PET=positron-emission tomography; SPECT=single-photon emission computed tomography.

Figure 37-18 Flow diagram for the practical assessment of noncontractile segments of myocardial wall potentially recoverable by revascularization procedures. An obviously reduced wall thickness is indicative of a postinfarction scar. Absence of contractile function in segments of the ventricular wall with preserved wall thickness may be caused by different mechanisms. An acute ischemic cause can be excluded by the

administration of sublingual nitrates. Stunning can be excluded by repeating the ventricular wall motion study several days after the last ischemic episode. Hibernating myocardium should be distinguished from a mixture of scar tissue and viable myocardial cells. *(From Maseri A: Ischemic Heart Disease: A Rational Basis for Clinical Practice and Clinical Research. New York, Churchill Livingstone, 1995. By permission.)*

represent a mixture of scarred and viable myocardium. A useful strategy for the assessment of dysfunctional segments has been developed by Maseri (Fig. 37-18) . Although a number of imaging tools may be used for this assessment (see Chaps. 7 , 9 , 10 , and 13) , the most readily available in most settings is low-dose dobutamine echocardiography.

The term *contractile reserve* describes the ability of hibernating myocardium to exhibit augmented contractility to a suitable temporary stimulus, often causing transient improvement in the global ejection fraction. Contractile reserve underscores the fact that many hypokinetic (and even akinetic) areas of the ventricular wall are composed entirely or in part of viable, hibernating myocardium or a mixture of the latter and fibrous scar. Viable muscle is capable of responding to a sympathomimetic agent. In contrast, necrotic tissue obviously cannot be stimulated to contract by any pharmacological or hemodynamic intervention or by improved perfusion. The most common method of identifying contractile reserve is echocardiographic imaging during infusion of a low dose of dobutamine.[561] Numerous studies have demonstrated that the finding of contractile reserve by low-dose dobutamine echocardiography identifies dysfunctional, but viable myocardium with the potential to improve in function after myocardial revascularization.[89] [102] [103] [561] [564]

PET (see Chap. 9) has emerged as an excellent method for demonstrating viable myocardium in patients with impaired left ventricular function.[89] [561] [563] [564] [565] [566] In comparative studies, PET has yielded the highest predictive accuracy of all imaging modalities in detecting dysfunctional myocardium that will improve after revascularization.[89] [564] However, the high cost, technical difficulty, and need for a cyclotron continue to limit this technique's widespread applicability.

Important advances in the assessment of myocardial viability with thallium-201 include rest-redistribution imaging to determine whether regions with hypoperfusion at rest manifest filling in of the resting defect with time and stress-redistribution-reinjection imaging, in which a second injection of thallium is administered to determine whether defects that do not redistribute after exercise represent fibrotic

myocardium or myocardium that is severely ischemic[88] [89] [102] [561] [567] (see Chap. 9) .

Prognostic Implications of Identifying Viable Myocardium.

A growing body of evidence indicates that the detection of viable myocardium in patients with CAD and left ventricular dysfunction not only identifies those in whom improvement

in cardiac function is likely after revascularization but also identifies a group of high-risk patients in whom revascularization improves survival (Fig. 37-19) . Studies with PET, thallium-201, and dobutamine echocardiography have uniformly demonstrated that patients with left ventricular dysfunction and evidence of hibernating myocardium have a high mortality rate during medical therapy and appear to have a better outcome with revascularization.[103] [568] [569] [570] [571] All these studies have limitations, including a small number of patients, the retrospective nature of the analysis, and lack of a randomized control group. However, the consistency of the findings has been striking. Recent data point out that viability assessment is also helpful in the selection of patients for revascularization because patients selected for revascularization on the basis of an imaging study demonstrating myocardial viability have lower operative mortality and a higher long-term survival rate than do those who have no evidence of important myocardial viability or those in whom a viability assessment is not performed.[88] [103] [572] Perioperative mortality in the latter patients approaches 10 percent.[88] [103] [572]

The mechanisms for improved survival after revascularization in patients with hibernating myocardium may be related to improvement in left ventricular function, but it is likely that other important factors are also operative. Revascularization of viable myocardium may also reduce left ventricular remodeling, the propensity for serious arrhythmias, and the likelihood of a future fatal acute ischemic event.[89] In this manner, patients with left ventricular dysfunction and hibernating myocardium may be viewed as other high-risk patients with left ventricular dysfunction, multivessel CAD, and jeopardized myocardium, in whom outcome is improved by revascularization. In this regard, survival may be enhanced by revascularization in such patients, even if left ventricular function does not improve after the procedure.

Surgical Treatment in Special Groups

WOMEN (see also Chap. 58) .

It is clear that CABG use is much lower in women than in men.[573] [574] However, what has not been established is whether these differences represent underutilization in women, overutilization in men, or both.[458] [575] In comparison with men, women who undergo coronary bypass surgery are "sicker," as defined by age, comorbid conditions, the severity of angina, and history of congestive heart failure.[574] [576] Many series have demonstrated higher morbidity and mortality in coronary surgery in women. The 1997 Society of Thoracic Surgeons data base showed that approximately 30 percent of isolated CABG procedures in the United States were performed in women, with a perioperative mortality of 3.9 percent versus 2.3 percent for men.[425]

Among patients 70 years or older in the Toronto Hospital experience, operative mortality in men in comparison with women was 5.4% vs 11.8% from 1982-1986, 3.8% vs 5.8% from 1987-1991 and 3.8% vs 6.3% from 1992-1996.[577] Perioperative morbidity, including myocardial infarction, respiratory failure, and stroke, was also significantly higher in women. A higher incidence of sternal wound infections may be related to obesity.[458] Most of the differences between men and women are the consequence of age, the "sicker" preoperative status of women, a higher rate of nonelective procedures, and the presence of more diffuse disease and left ventricular dysfunction in women

reaching surgery,[578] but the presence of smaller distal vessels (as a function of a smaller body surface area) and lower use of IMA grafts may also be contributing factors.[390] [579] However, a small independent detrimental effect of female gender persists in most multivariate analyses. Despite the increased perioperative mortality and morbidity in women, late survival is similar in men and women,[580] but the relief of anginal symptoms appears to be less in women.[577] [580] [581]

Independent risk factors for long-term prognosis in women are similar to those in men, including older age, previous coronary bypass surgery, previous myocardial infarction, and diabetes.[580] In the BARI Trial, in-hospital mortality was similar for men and women, as were the unadjusted 5.4-year mortality rates of 12.8 percent in women and 12 percent in men (p=NS). After adjustment for the higher risk profiles in women, including age, symptom severity, and comorbid conditions, the relative risk of death in women versus men was actually lower, 0.60 (95 percent confidence intervals, 0.43 to 0.84; p=0.003). However, these data may not be generalizable outside the confines of a randomized trial.

YOUNGER PATIENTS.

Patients 35 years or younger who undergo CABG usually have hyperlipidemia and other major risk factors for CAD.[582] Despite the severity of the underlying disease and the rapidity of the atherosclerotic process, CABG is associated with excellent actuarial survival rates of 94 percent at 5 years and 85 percent at 10 years.[582] Nonetheless, in the CASS Registry, patients younger than 35 years had markedly impaired survival over a 15-year period in comparison with an age- and sex-matched U.S. population.[581] This impaired survival is probably the result of progression of premature atherosclerotic disease, the presence of multiple risk factors, and the development of progressive vein graft disease. The latter underlies the current trend for the use of bilateral IMA grafts and other arterial conduits in younger patients.

THE ELDERLY (see also Chap. 57) .

A demographic tide in combination with marked improvement in perioperative care and in the outcomes of CABG has resulted in

Figure 37-19 Survival among 58 patients with coronary artery disease, left ventricular dysfunction, and contractile reserve detected by low-dose dobutamine echocardiography. Patients treated with revascularization have a significantly higher survival rate than those treated medically. EF=ejection fraction. *(From Chaudhry FA, Tauke JT, Alessandrini RS, et al: Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 34:730, 1999. Reprinted with permission from the American College of Cardiology.)*

a burgeoning population of elderly patients with extensive disease undergoing such surgery. In 1997, the median age of patients undergoing an initial coronary bypass procedure was approximately 65 years in the United States and 64 years in Canada.[425] In 1997 in the United States, among 17,806 patients undergoing isolated CABG, 34 percent of patients were older than 70 years, 8872 operations were performed on octogenarians, and 106 new patients were in their 90s.[425] Between 1987 and 1990 in the Medicare population, the number of patients older than 80 years undergoing coronary bypass surgery increased by 67 percent.[583]

Older patients are "sicker" than their younger counterparts in that they have a greater frequency of comorbid conditions, including peripheral vascular and cerebrovascular disease, more extensive triple-vessel and left main CAD, and a higher frequency of left ventricular dysfunction and history of congestive heart failure.[392] Not unexpectedly, these differences are translated into higher perioperative mortality and complication rates, with a sharp increase in the slope of the curve relating mortality to age seen in patients older than 70 years.[425] [458] [577] [581] [584] More encouraging data were recently presented from the Toronto Hospital: Over a 15-year period, despite an increase in the prevalence and severity of risk factors, operative mortality in patients 70 years or older declined from 7.2 percent to less than 5 percent overall, with a mortality of 3 percent for patients defined as "low" or "medium risk." [577]

Perioperative morbidity is also increased in the elderly, with high rates of low-output syndrome, stroke, gastrointestinal complications, wound infection, and postoperative atrial fibrillation.[458] [471] The major predictors of perioperative mortality in the elderly are similar to those in younger patients, but with an increasing emphasis on the number of associated comorbid conditions, including the presence of peripheral and cerebrovascular disease. Although chronological age is not the most powerful independent predictor for perioperative mortality, it is an *independent* predictor, which suggests that other less tangible factors associated with older age increase operative risk.[392] In addition, from an examination of Medicare data from 1987 to 1990, patients older than 70 years, in comparison with those 65 to 70 years old, had longer postoperative hospital stays (mean of 14.3 vs. 10.4 days), higher charges, and greater costs.[583]

Despite the difficulties and expense of performing coronary bypass surgery in the elderly, excellent *long-term* survival rates can be achieved in addition to having the elderly return to an active functional status.[581] [585] [586] [587] In the CASS Registry, among patients 65 and 75 years old at the time of surgery, 74 and 59 percent, respectively, were alive 10 years after surgery and 54 and 33 percent 15 years after surgery (now 90 years old).[581] The survival of these patients exceeded that of the average age- and sex-matched U.S. population, which probably reflects in part the benefit of coronary revascularization in addition to selection bias. Similarly, octogenarians who survived the perioperative period had a long-term survival rate similar to that of the general octogenarian population of the United States.[583]

Predictors of late outcome in the elderly are similar to those in younger patients, including left ventricular dysfunction, but the number of associated comorbid conditions in addition to chronological age has a major effect.[588] Although no randomized trials

have compared surgical and medical therapy in patients older than 65 years, a nonrandomized analysis of the CASS Registry demonstrated a significant benefit from surgery over medical therapy in the majority of patients who were considered to be at "high risk," whereas among the approximately 15 percent of low-risk patients who had mild angina, relatively good ventricular function, and no left main CAD, no survival differences were seen between those treated medically and those treated surgically. Therefore, the results in this registry are consistent with the randomized trials conducted during the same time in a younger population.[538]

Fundamental to successful performance of coronary bypass surgery is meticulous assessment of the patient, with mandatory attention to comorbid conditions, which can have a major detrimental effect on both perioperative morbidity and mortality and long-term survival. Evaluation of the elderly for coronary bypass surgery should take into account other less tangible factors related to quality of life and the potential ability to benefit from the operation. These factors include not only the chronological age of the patient but also the estimated physiological age, the patient's attitude, including understanding of the risks and expectations of the procedure, and an assessment of the patient's level of activity and current life style.

END-STAGE RENAL DISEASE.

Cardiovascular disease is the major predictor of mortality in patients with end-stage renal disease (ESRD) and accounts for 54 percent of deaths[589] (see Chap. 72) . Patients with ESRD have numerous risk factors that not only accelerate the development of CAD but also complicate its medical management. These risk factors include diabetes, hypertension with left ventricular hypertrophy, both systolic and diastolic dysfunction, abnormal lipid metabolism, anemia, and increased homocysteine levels.[458] Coronary revascularization with PCI or CABG is feasible and well documented in patients with ESRD, but the mortality and complication rates are increased.[458] [590] It has been suggested that for chronic dialysis patients, CABG is preferred for revascularization over PCI.[590] In one series, the 30-day mortality was 9 percent, but CABG produced a substantial improvement in the quality of life.[591] Another series reported a 68 percent cumulative survival rate over a 5-year period in patients with New York Heart Association Class II to III symptoms, which supports a policy of operating on symptomatic patients receiving dialysis but before the onset of severe congestive heart failure.[592] In the only randomized trial of surgical and medical therapy for insulin-dependent diabetic candidates for renal transplantation, 10 of 13 medically managed patients and 2 of 13 surgically treated ones had a major cardiovascular event during approximately 8 months of follow-up (p0.01).[593]

In summary, coronary bypass surgery can be performed with an acceptable risk and a reasonable expectation of long-term benefit in carefully selected patients with ESRD. As for all high-risk situations, careful attention to patient selection is essential.

PATIENTS REQUIRING REOPERATION.

Currently, approximately 10 percent of coronary artery procedures are reoperations, and in some centers, particularly tertiary care centers, the proportion is increasing rapidly

and accounts for 15 to 18 percent of all CABG operations.[458] The major indication for reoperation is late disease of saphenous vein grafts. Moreover, the patient population is elderly, and an added factor underlying recurrent symptoms is progression of disease in native vessels between the first and second operations. Several series have emphasized the "sicker" preoperative status of patients undergoing reoperation, including older age, more extensive comorbidity, associated valvular heart disease, and a greater prevalence of left ventricular dysfunction and greater extent of ischemic jeopardized myocardium.[594] Not unexpectedly, the mortality associated with reoperation is significantly higher than that of initial bypass procedures. In the 1997 data base of the Society of Thoracic Surgeons, the mortality among 99,810 patients undergoing an elective first CABG procedure was 1.7 percent versus 5.2 percent for elective reoperations. For patients undergoing first operations, mortality was 2.6 percent for urgent and 6 percent for emergency procedures in comparison with 7.4 and 13.5 percent, respectively, among patients undergoing repeat bypass surgery. Virtually every large series has demonstrated higher morbidity and twofold to threefold greater mortality for reoperation.[594] [595] The determinants of perioperative mortality are similar to those for a first operation, although a short time interval between the first operation and the repeat procedure is an added major predictor of increased mortality. Third- and even fourth-time coronary reoperations are increasing in frequency and are associated with substantial increases in perioperative complications, including bleeding and myocardial infarction.[595]

More encouraging are the late survival rates of approximately 77 to 90 percent at 5 years and 48 to 83 percent at 10 years.[594] [596] Although in one series 73 percent of patients were free of angina at 5 years, relief of angina is generally less complete than after an initial operation.

Indications for reoperation have not been defined by randomized trials, but in general, the same principles that apply to patients with initial disease should be followed. Information about the effect of graft stenosis on late survival

was recently provided by a large retrospective study of patients who had postoperative coronary angiography and in whom a stenosis of 20 percent or more was present in at least one graft (Fig. 37-20) . Stenoses in a vein graft to the left anterior descending coronary artery were associated with a reduction in survival, and the major improvement in survival after reoperation was particularly evident for patients in this category. Among these patients, survival rates were 84 and 74 percent for the reoperation group 2 and 4 years after catheterization versus 76 and 53 percent for the medically treated group (p=0.004). [597] Nonetheless, the greater risk and the less favorable outcome after reoperation than after the initial procedure need to be considered, and the indications should probably be more stringent than for patients with native vessel disease alone.

OTHER HIGH-RISK SUBGROUPS.

Patients with *familial hyperlipidemia* have long been considered to be at particular risk for an adverse late outcome after CABG. More encouraging results have been reported with the use of an IMA or other arterial conduit in conjunction with aggressive lipid-lowering therapy.[598] In comparison with age-matched nondiabetic patients, elderly *diabetic* patients with angiographically proven CAD are more likely to be female with evidence of peripheral vascular disease and a higher number of coronary occlusions.[599] In a cohort of CASS Registry patients, diabetes was an independent predictor of mortality. However, the relative survival benefit of CABG versus medical therapy was comparable in diabetic and nondiabetic patients, with a significant (44 percent) reduction in mortality provided by surgery over medical therapy in diabetics.[599] Other large studies have emphasized the independent adverse effect of diabetes on mortality after CABG. In the Duke data base, the 5-year unadjusted survival rate was 74 percent among diabetic patients and 86 percent among nondiabetic patients treated surgically.[363] In a diabetic population undergoing coronary revascularization, insulin dependence is an added adverse predictor of 5- and 10-year survival rates.[600]

Summary of Indications for Coronary Revascularization

1. Certain anatomical subsets of patients are candidates for CABG, regardless of the severity of symptoms or left ventricular dysfunction. Such patients include those with significant left main CAD and most patients with three-vessel disease that includes the proximal left anterior descending coronary artery, especially those with left ventricular dysfunction.
2. The benefits of coronary bypass surgery are well documented in patients with left ventricular dysfunction and multivessel disease, regardless of symptoms. In patients whose dominant symptom is heart failure without severe angina, the benefits of coronary revascularization are less well defined, but this approach should be considered in patients who also have evidence of severe ischemia (regardless of angina symptoms), particularly in the presence of a significant extent of potentially viable dysfunctioning (hibernating) myocardium.
3. The primary objective of coronary revascularization in patients with single-vessel disease is relief of significant symptoms or objective evidence of severe ischemia. For the majority of these patients, PCI is the revascularization modality of choice.
4. In patients with angina who are *not* considered to be at high risk, survival is similar for surgically and medically treated groups.
5. All the indications discussed above relate to the potential benefits of surgery over medical therapy on *survival*. Coronary revascularization with PCI or CABG is highly efficacious in relieving symptoms and may be considered for patients with moderate to severe ischemic symptoms who are dissatisfied with medical therapy, even if they are not in a high-risk subset. For such patients, the optimal method of revascularization is selected on the basis of left ventricular function and arteriographic findings and the likelihood of technical success.

Comparisons Between PTCA and CABG

OBSERVATIONAL STUDIES.

Since the catheter-based revascularizations in these comparative studies were limited largely to PTCA, this term instead of PCI is used in this section. Among the many comparative studies of PTCA and CABG in patients with multivessel disease, several included patients with single-vessel disease,[514] [601] [602] but in only five studies were the groups matched for differences in baseline characteristics.[514] [601] [603] [604] [605] Regardless of the limitations of these series and the differences in baseline characteristics, the results are quite consistent. Over a period of 1 to 5 years, the rates of mortality and nonfatal infarction were not significantly different between the two groups but recurrent events, including angina pectoris and the need for repeat revascularization procedures, were significantly more frequent in the PTCA than the CABG group. Among patients with left ventricular dysfunction, survival after CABG appears to be better than after PTCA, probably because of the ability to achieve more complete revascularization with the former.[606] Indeed, complete revascularization is achieved by PTCA in only 25 to 50 percent of patients with two-vessel disease and in 10 to 25 percent of those with three-vessel disease.[607] In the future, improvements in transcatheter techniques, particularly in the ability to treat chronic total occlusions, may improve the results of this approach in patients with left ventricular dysfunction.

Outcome data 1 year after PTCA in patients (most of

Figure 37-20 Survival of patients with late stenoses in saphenous grafts to the left anterior descending coronary artery. In this subgroup, patients undergoing reoperation had improved survival when compared with those receiving medical therapy. *(Data obtained from the Cleveland Clinic Series. From Lytle BW, Loop FD, Taylor PC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein bypass grafts to coronary arteries. J Thorac Cardiovasc Surg 105:605, 1993. By permission of Mosby.)*

Figure 37-21 Hazard ratios for coronary artery bypass graft surgery (CABG) versus percutaneous transluminal coronary angioplasty (PTCA). Points below 1.0 favor CABG. Prox LAD=proximal left anterior descending coronary artery; VD=vessel disease. *(From Mark DB, Nelson CL, Califf RM, et al: Continuing evolution of therapy for coronary artery disease: Initial results from the era of coronary angioplasty. Circulation 89:2015, 1994. By permission of the American Heart Association, Inc.)*

whom had single-vessel disease) indicate that recurrence of symptoms and/or the need for repeat revascularization procedures is high (approximately 40 percent) and that approximately 20 percent actually undergo CABG. In one report, after approximately 2 years, 49 percent of patients had had one repeat cardiac catheterization and approximately 25 percent had undergone multiple cardiac catheterizations.[603] These results need to be modified by a reduction in the rate of repeat revascularization procedures and recurrent angina in patients currently treated with stents instead of PTCA alone.[366] [608] CABG provided a clear survival benefit over PTCA in the Duke

University data base in patients with two-vessel disease that included 95 percent or greater obstruction of the proximal left anterior descending coronary artery and in all forms of three-vessel disease (Fig. 37-14 *B*, p. 1310; and Fig. 37-21) . However, the effect of the method of revascularization on survival was equal in patients with two-vessel disease who did not have obstruction of the proximal left anterior descending coronary artery. The New York State procedure registries of PTCA and CABG from 1993 to 1995 demonstrate an approximately 37 percent rate of repeat revascularization after PTCA over a 3-year period in comparison with 3.3 percent after surgery.[608] Hazard ratios for mortality are shown in Figure 37-22 (Figure Not Available) , which illustrates that the anatomical extent and specific site of the disease influence the results of the treatment chosen, whether PTCA or CABG.

RANDOMIZED TRIALS

PTCA Versus CABG in Patients with Single-Vessel Disease.

In the RITA Trial, 45 percent of patients had single-vessel disease, and both the Lausanne Trial and the MASS Trial from Brazil, which included a medical arm, were limited to patients with isolated disease of the proximal left anterior descending coronary artery.[369] [476] [609] The results of these small trials were consistent in that over 2 to 3 years the rates of mortality and myocardial infarction were similar in the two strategies, as was improvement in symptoms, but at the cost of more frequent reintervention in patients treated with PTCA. At 5 years in the Lausanne Trial, mortality rates and functional status were similar for the two groups; however, an excess incidence of nonQ-wave myocardial infarction was noted in patients treated with PTCA, but this complication did not affect vital status or symptomatic outcome.[610]

In summary, the results suggest that PTCA and CABG are highly effective in preventing symptoms in patients with single-vessel disease. Moreover, no difference in mortality is seen between these two methods of revascularization.

Figure 37-22 (Figure Not Available) Differences in adjusted percent survival at 3 years with percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG) in the New York State data base (1993 to 1995). Data are stratified according to the number of vessels diseased and whether the left anterior descending (LAD) coronary arteries are involved and according to whether the stenoses are proximal. Note the better survival with CABG among patients with three- or two-vessel disease in combination with proximal LAD involvement. *(From Hannan EL, Racz MJ, McCallister BD, et al: A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 33:63, 1999. Reprinted with permission from the American College of Cardiology.)*

Figure 37-23 Cumulative risk of death or myocardial infarction after percutaneous transluminal coronary angioplasty (PTCA) and bypass surgery in the RITA-1 trials (-----, PTCA; CABG). No significant difference was found in either death or the combined endpoint of death or myocardial infarction. *(From Henderson*

RA, Pocock SJ, Sharp SJ, et al: Long-term results of RITA-1 trial: Clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina. Lancet 352:1419, 1998. © by The Lancet Ltd., 1998.)

Multivessel Disease.

Seven published studies have compared PTCA with CABG in patients with multivessel disease. Another study, the Arterial Revascularization Therapy Study (ARTS), has recently been presented.[611] One of these trials (RITA) included patients with single-vessel disease.[352] [364] [476] [612] [613] [614] [614A] Despite the heterogeneity of the trials in regard to design, methods, and the patient population enrolled, the results are generally comparable and provide a consistent perspective of CABG and PTCA in selected patients with multivessel disease. A major limitation is that these trials, except for ARTS and ERACI-II,[620] were conducted before the widespread use of stents and other advances in PCI technology and adjunctive therapy, such as ticlopidine and glycoprotein IIb/IIIa platelet inhibition. Also, these trials lacked an aggressive approach to lipid lowering in both groups of patients. In the RITA, the ERACI-I, ARTS, and the French Monocentric trials, the ability to achieve "equivalent" degrees of revascularization in the two groups was an inclusion criterion.[364] [476] Moreover, the majority of patients entered into the trials had well-preserved left ventricular function and a mean ejection fraction exceeding 50 percent. In the main, patients enrolled in these trials were at relatively low risk, with predominantly two-vessel disease and well-preserved left ventricular function, i.e., a high proportion of patients in whom CABG surgery had *not* been previously shown to be superior to medical therapy in regard to survival. Thus, one would not expect a significant mortality difference between PTCA and CABG, particularly with the relatively small sample size of the trials (Fig. 37-23) .[365] [615]

The BARI Trial, initiated by the NHLBI, enrolled 1829 patients with multivessel disease in the United States and Canada. This trial is the largest of the randomized trials of PTCA and bypass surgery and the only trial with sufficient statistical power to detect a substantial mortality difference. At 5 years, overall survival rates were not different between the two groups (89.3 percent with CABG and 86.3 percent with PTCA [p=0.19]), nor was any difference noted in the incidence of Q wave myocardial infarction.[352] [616] An initially unexpected finding--but one that is also evident as a trend in the Coronary Angioplasty Versus Bypass Revascularisation Investigation (CABRI) and EAST trials (Rickards A, personal communication; King SB III, personal communication)--was that patients with previously treated diabetes who underwent PTCA had a mortality of 34.5 percent versus 19.4 percent for those who underwent CABG (p=0.003) (see also Chap. 63) .

Because of the heterogeneity among the trials, it is reassuring that the results are highly consistent within the trials and with observational studies. In these highly selected patients, neither procedure has demonstrated, after 1 to 5 years of follow-up, a clear superiority over the other for primary outcomes of mortality and Q wave myocardial infarction (Fig. 37-23) .[617] Although a meta-analysis by Pocock and colleagues demonstrated a trend in favor of bypass surgery, this trend did not reach statistical significance.[618]

CABG is initially associated with greater improvement in angina, which appears to be proportional to the more complete revascularization in patients with multivessel disease (Fig. 37-12) .[619] Moreover, as anticipated from the observational data, repeat revascularization procedures are more frequent after PTCA, although it is likely that more widespread use of stents will reduce the magnitude of the difference in repeat revascularization rates. In the RITA Trial, for example, after 5 years, repeat PTCA was performed in 27 percent of patients in the angioplasty group and CABG was performed in 26 percent; in comparison, among the patients treated initially with surgery only, 3 percent underwent reoperation and 9 percent subsequently required PTCA. What is encouraging among patients assigned to PTCA is the striking decrease in the need for reinterventions after the first 2 years, with a repeat revascularization rate of only 3 percent per year during years 3 to 5 of follow-up. In patients assigned to CABG, the reintervention rate remains steady at 2 percent per year, but it might be expected to increase after approximately 7 to 8 years of follow-up.[617] In the ARTS Trial, which compared multivessel stenting with CABG, repeat revascularization was performed in only 16.9 percent of patients in the stented group. This figure is lower than the repeat procedural rates noted in trials of angioplasty alone. Preliminary results from this study also suggested that 1-year costs were lower in the stented than in the bypass surgery group.[611] In the ERACI-II Study, preliminary results were similar to those in the ARTS Trial, with only 16 percent of patients who had PCI with stenting requiring repeat revascularization in follow-up versus 4.4 percent of bypass surgical patients (mean follow-up, 14.7 ± 6.4 months).[620]

Another consistent, but not unexpected finding was the lower in-hospital cost for patients undergoing PTCA.[364] However, the need for recurrent hospitalization and repeat revascularization procedures over the long term contributed to an increase in postdischarge cost in the PTCA

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arms, which resulted in similar overall cost over 3 to 5 years.[364] [373] [374] [621] A major determinant of lower cost is the presence of two-vessel disease; in comparison, patients with congestive heart failure, comorbid conditions, or diabetes are likely to accrue higher cost regardless of the procedure.[621] Other measures of procedural success, including indices of the quality of life, cognitive function, and return to employment, were similar between PTCA and CABG.[621] [622]

Indications for Revascularization: The Choice Between PCI and CABG (Fig. 37-24 and Table 37-14)

Medical management of chronic CAD as outlined on pp. 1282 , 1283 , 1284 , 1285 , 1286 , 1287 , 1288 , 1289 , 1290 , 1291 , 1292 , 1293 , 1294 , 1295 , 1296 , 1297 , and 1298 involves a reduction in reversible risk factors, life style alteration counseling, treatment of conditions that intensify angina, and pharmacological management of ischemia. When an unacceptable level of angina persists or the patient has troubling side effects from the antiischemic drugs, the coronary anatomy should be defined to

allow selection of the appropriate technique for revascularization. In patients in whom the angina is controlled, noninvasive testing is carried out and coronary arteriography performed in those with a "high-risk" result[365] (see p. 1280). After elucidation of the coronary anatomy, selection of the technique of revascularization is made as follows:

SINGLE-VESSEL DISEASE.

Among patients with single-vessel disease in whom revascularization is deemed necessary and the lesion is anatomically suitable, PCI is generally preferred over bypass surgery.

MULTIVESSEL DISEASE.

The first step is to decide whether a patient falls into the category of those who were included in randomized trials comparing PTCA and CABG. The majority of patients included in these trials were at lower risk, as defined by two-vessel disease and well-preserved ventricular function. Moreover, three trials required that equivalent degrees of revascularization be achievable

Figure 37-24 Indications for coronary revascularization with bypass surgery (CABG) or percutaneous coronary intervention (PCI) in patients with multivessel disease. The combination of triple-vessel disease and left ventricular (LV) dysfunction and/or left main coronary artery (LMCA) disease is primarily surgical, whereas the majority of the patients entered into the randomized trials were suitable for angioplasty on the basis of double-vessel disease, preserved left ventricular dysfunction, and suitable anatomy. Diabetics should be treated individually.

TABLE 37-14 -- COMPARISON OF REVASCULARIZATION STRATEGIES IN MULTIVESSEL DISEASE

ADVANTAGES	DISADVANTAGES
PERCUTANEOUS CORONARY INTERVENTION	
Less invasive	Restenosis
Shorter hospital stay	High incidence of incomplete revascularization
Lower initial cost	Relative inefficacy in patients with severe left ventricular dysfunction
Easily repeated	Uncertain long-term outcome (>10 yr)
Effective in relieving symptoms	Limited to specific anatomical subsets
CORONARY ARTERY BYPASS GRAFT SURGERY	
Effective in relieving symptoms	Cost
Improved survival in certain subsets	Increased risk of a repeat procedure because of late graft closure

Ability to achieve complete revascularization	Morbidity
Wider applicability	

Modified from Faxon DP: Coronary angioplasty for stable angina pectoris. In Beller G (ed): Chronic Ischemic Heart Disease. In Braunwald E (ed): Atlas of Heart Disease. Vol 5. Philadelphia, Current Medicine, 1995.

by both techniques. Most patients with chronically occluded coronary arteries were excluded, and of those who were clinically eligible, approximately two-thirds were excluded for angiographic reasons. The lack of any difference in late mortality and myocardial infarction between the two groups in such patients indicates that PCI is a reasonable *initial* strategy, provided that the patient accepts the distinct possibility of symptom recurrence and need for repeat revascularization. Patients with a single localized lesion in each affected vessel and preserved left ventricular function fare best with PCI.

NEED FOR COMPLETE REVASCULARIZATION.

Complete revascularization is an important goal in patients with left ventricular dysfunction and/or multivessel disease. The major advantage of CABG surgery over PCI is its greater ability to achieve complete revascularization, particularly in patients with three-vessel disease. In the majority of such patients, particularly those with chronic total coronary occlusion, left ventricular dysfunction, or left main CAD, CABG is the procedure of choice.[348] [475] Among patients with borderline left ventricular function (ejection fraction between 40 and 50 percent) and milder degrees of ischemia, PCI may provide adequate revascularization, even if it is not complete anatomically.

In many patients, either method of revascularization is suitable. Other factors that come into consideration include (1) access to a high-quality team and operator with an excellent record of success; (2) patient preference--some patients are made anxious by the idea that after PCI they remain at risk for symptom recurrence and may require reintervention (such patients are better candidates for surgical treatment); (3) advanced patient age and comorbidity--frail, very elderly patients and those with comorbid conditions, such as cancer or serious liver disease with a limited life expectancy, but who have disabling angina--are often better candidates for PCI; and (4) younger patient age--PCI is also often preferable in younger patients (<50 years) with the expectation that they may require CABG at some time in the future and that PCI will postpone the need for surgery; this sequence may be preferable to two operations. Patient preference is a pivotal aspect of the decision to perform PCI or CABG in these patient groups.

PTCA AND CORONARY BYPASS SURGERY IN DIABETIC PATIENTS (see alsoChap. 63) .

The poorer outcomes after PTCA than after CABG in treated diabetic patients in the

BARI Trial, together with similar trends in the EAST and CABRI trials, have raised concern about whether all diabetic patients with multivessel disease should be treated surgically. This important issue has significant economic implications, but further analysis suggests that treatment of diabetic patients can be individualized, as in nondiabetic patients. Despite the use of stents for multivessel PCI in the ARTS Trial, preliminary data suggest that the 1-year mortality in diabetic patients who received PCI and stenting was double that of those undergoing bypass surgery (6.3 vs. 3.1 percent).[623]

One explanation for the difference in outcomes may be an altered vascular biological response in diabetic patients to balloon injury and progression of disease in nondilated segments. The diabetic atherosclerotic milieu is characterized by a procoagulant state, decreased fibrinolytic activity, increased proliferation, and inflammation.[624]

Restenosis is more frequent in diabetic patients, as is disease progression. In a study of patients referred for diagnostic angiography 1 month or more after successful PTCA, the number of new narrowings in the arteries of diabetic patients increased by 22 percent, particularly at other sites in the artery that initially underwent PTCA.[625] Thus, CABG, which bypasses the majority of the vessel instead of a specific lesion, may offer a better long-term outcome.[626]

Another explanation for the results of PTCA and CABG is related to the patient selection criteria for enrollment into the trials. In the BARI Registry, in which patients were treated according to the preference of the individual physician, and in two large data base studies, poorer outcomes were noted for both CABG and PTCA in diabetics versus nondiabetics, but *among diabetics*, no survival difference was noted between PTCA and CABG.[627] Similar trends were noted in two large community studies.[363] [600] Diabetic patients as a group in BARI had a greater prevalence of three-vessel disease, left ventricular dysfunction, and a history of congestive heart failure. It is noteworthy that in the Emory University Study of diabetic patients, approximately 85 percent of those with three-vessel disease underwent bypass surgery, whereas the use of PTCA and CABG was similar among those with two-vessel disease.[600] A plausible explanation for the differences in results in the registry and data base studies and the randomized trials is that in the latter, sicker diabetic patients with three-vessel disease and left ventricular dysfunction, by design, were treated equally with bypass surgery and PTCA, whereas in clinical practice, such patients are referred appropriately for surgery, and earlier data base studies suggest that 3- to 5-year survival after CABG in the higher-risk subgroups is superior to that obtained with PCI.

The therapeutic implications of these observations are evident. The revascularization strategy in diabetic patients should be based on the number of vessels diseased, lesion-related technical factors, the caliber of the distal vessels, and the presence or absence of left ventricular dysfunction.

Coronary Bypass Surgery in Patients with Associated Vascular Disease

Management of patients with combined CAD and peripheral vascular disease involving the carotid arteries, the abdominal aorta, or the vessels of the lower extremities

presents many challenges.[32] Combined disease is becoming increasingly frequent as the population of patients under consideration for CABG ages and as technical improvements allow the application of coronary revascularization to ever more complex cases.

IMPACT OF CAD IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE.

Clinically apparent CAD occurs frequently in patients with peripheral vascular disease.[32] The prevalence of clinically unrecognized CAD, as documented by angiographic studies, is even higher.[628] Among patients undergoing peripheral vascular surgery, late outcomes are dominated by cardiac causes of morbidity and mortality.[628] [629] Conversely, in patients with CAD, the presence of peripheral vascular disease, even if asymptomatic, is associated with an adverse prognosis, presumably because of the greater total atherosclerotic burden borne by these patients.[33] [630]

If coronary revascularization is performed before vascular surgery in patients with combined peripheral vascular disease and CAD, the perioperative mortality of the vascular procedure is reduced.[32] In seven series totaling 1237 patients undergoing vascular surgical procedures, the mean operative mortality was 1.5 percent among patients with prior CABG surgery, similar to the 1.3 percent mortality rate in patients without clinically apparent CAD and substantially lower than the 6.8 percent mortality rate in patients with clinically suspected but uncorrected CAD.[32] Late mortality in patients with peripheral vascular disease is also reduced among those who have undergone prior CABG.[631] However, because patients with CAD and peripheral atherosclerosis tend to be older and have more widespread vascular disease and end-organ damage than do patients without peripheral atherosclerosis, the perioperative mortality and morbidity consequent to CABG are high and the late outcome not as favorable.[32] [628] [632] In the Northern New England Cardiovascular data base, in-hospital mortality after bypass surgery was 2.4-fold greater in patients with peripheral vascular disease than in those without it, particularly for patients with lower extremity disease.[633] In the BARI Trial, approximately one-third of patients had peripheral vascular disease, among whom the risk of major complications after both bypass surgery and PTCA was markedly increased in comparison to those without peripheral vascular disease, even after controlling for baseline differences.[634] *Diffuse atheroembolism* is a particularly serious complication of coronary bypass surgery in patients with peripheral vascular disease and aortic atherosclerosis. It is a major cause of perioperative death, stroke, neurocognitive dysfunction, and multiple organ dysfunction after CABG.

Not only is perioperative morbidity and mortality increased in patients with peripheral vascular disease, but the latter is also a strong marker of an adverse long-term outcome. At any point during a 10-year period, patients in either the medical or surgical group in the CASS Registry who had peripheral vascular disease had a 25 percent greater likelihood of mortality than did those without this condition.[33] Similarly, in the Northern New England Cardiovascular data base, the 5-year mortality remained approximately twofold greater in patients with peripheral vascular disease than in those without it, even after adjusting for comorbid conditions, which are more frequent in patients with peripheral vascular disease.[633] [635] In the BARI Trial, patients with asymptomatic lower extremity disease, as defined by the ankle-arm index, had an

almost fivefold greater mortality than did those without lower extremity arterial disease. Indeed, mortality was similar for patients with symptomatic and patients with asymptomatic lower extremity disease.

It is important to identify CAD and to estimate its severity in patients who are candidates for peripheral vascular surgery. The diagnostic problem is intensified because these patients often have limited walking capacity and may not develop effort angina. Pharmacological stress myocardial perfusion scintigraphy or echocardiography can be used. Identification of "high-risk" patients by these techniques (Table 37-2, p. 1280) should lead to coronary angiography in these patients even if they have no or only mild angina and, depending on the anatomical findings, should lead to coronary revascularization, often before peripheral vascular surgery.

Thus, the presence of peripheral vascular disease suggests that the patient may also have high-risk CAD, with potential benefit from CABG in the long term. In the ECSS, patients with CAD and peripheral vascular disease receiving CABG had a much better survival rate than did those who were treated medically.[531] In the CASS Registry, patients with peripheral vascular disease and three-vessel CAD who received surgical treatment also exhibited a major reduction in late mortality and morbidity in comparison

with those who were managed medically.[32] Observations such as these argue for *consideration* of CABG in patients with peripheral vascular disease who have significant CAD. The major indication for coronary revascularization before vascular surgery in patients with known chronic CAD is the intention of improving the *long-term* prognosis. A randomized trial of prophylactic coronary artery revascularization in patients undergoing elective vascular surgery is in progress.[636]

CAROTID ARTERY DISEASE.

In patients with stable CAD and *carotid artery disease* in whom coronary endarterectomy is planned, exercise stress testing and consideration of coronary revascularization can ordinarily be performed after the carotid surgery.[32] CAD is significantly associated with an increased risk of stroke after bypass surgery, and this association is also strongly correlated with age.[467] [637] However, many strokes are not ipsilateral to the site of stenosis, and the association most likely reflects the presence of diffuse aortic atherosclerosis. [638] The prevalence of significant carotid disease in an increasingly elderly population coming to CABG is high--approximately 17 to 22 percent have a stenosis of 50 percent or greater, 6 to 12 percent have a stenosis of 80 percent or greater, and the percentage is higher in patients with left main CAD.[458] [639] In patients for whom surgical treatment is considered for both carotid artery disease and CAD, the merits of a combined versus a staged approach are debated.[640] [641] Neither strategy has been demonstrated to be unequivocally superior to the other, and an individualized approach, depending on the patient's initial condition, the severity of symptoms, the anatomy of the coronary and carotid vessels, and individual institutional experience, is

most appropriate.[458] [642]

MANAGEMENT.

Patients with severe or unstable coronary disease requiring revascularization can be categorized into two groups according to the severity and instability of the accompanying vascular disease.[32] When the noncoronary vascular procedures are elective, they can generally be postponed until the cardiac symptoms have stabilized, either by intensive medical therapy or by revascularization. A combined procedure is necessary in patients with both unstable CAD and an unstable vascular condition, e.g., frequent recurrent transient ischemic attacks or a rapidly expanding abdominal aortic aneurysm.[640] [643] In some patients in this category, PCI offers the potential for stabilizing the patient's cardiac condition before proceeding with a definitive vascular repair.[644]

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Other Manifestations of Coronary Artery Disease

PRINZMETAL (VARIANT) ANGINA

In 1959, Prinzmetal and associates described an unusual syndrome of cardiac pain secondary to myocardial ischemia that occurs almost exclusively at rest, is not usually precipitated by physical exertion or emotional stress, and is associated with ECG ST segment elevations[645] (Fig. 37-25) . This syndrome, now known as *Prinzmetal,* or *variant, angina*, may be associated with acute myocardial infarction and severe cardiac arrhythmias, including ventricular tachycardia and fibrillation, as well as sudden death. A prevailing clinical impression, at least in North America, is that Prinzmetal angina has become less frequent for reasons that are unclear, perhaps because of the more widespread use of calcium antagonists, better nitrate regimens, or alterations in pathophysiology of the coronary disease process.[646] It appears to remain more common in Japan.

Mechanisms

The original hypothesis of Prinzmetal and colleagues, that variant angina was the result of transient increases in coronary vasomotor tone or vasospasm, was convincingly demonstrated by coronary angiography.[647] Vasospasm causes a transient, abrupt, marked decrease in the diameter of an epicardial (or large septal) coronary artery that results in myocardial ischemia. This event occurs in the absence of any preceding increases in myocardial O_2 demand, as reflected in an increased heart rate or blood pressure. The decrease in diameter can usually be reversed by nitroglycerin, sometimes requiring large doses, and can occur in either normal or diseased coronary arteries. Although the sites of vasospasm may correspond to areas of severe focal stenosis, in some patients with apparently normal vessels at angiography, the vasospastic

segments appear to occur at sites of at least minimal atherosclerotic change, as detected by intravascular ultrasonography.[648] Measurements of great cardiac vein flow and left anterior descending coronary artery diameter in patients with vasospastic angina suggest that not only epicardial but also the coronary resistance arteries are affected by the coronary vasomotion disorder.[649] This focal severe vasospasm should not be confused with vasoconstriction of both the large and small coronary vessels, a *normal* response to stimuli such as cold exposure. The latter response is much less intense and occurs diffusely throughout the coronary vascular bed.

In patients with Prinzmetal angina, basal coronary artery tone may be increased. Although responses to various vasoconstrictor substances, including catecholamines, thromboxane A_2 , serotonin, endothelin, and arginine vasopressin, are greater in spastic segments of the coronary arteries, hypersensitivity to vasoconstrictor stimuli also occurs throughout the entire coronary tree,[650] perhaps as a manifestation of a more generalized response to vasoactive stimuli.[651] The precise mechanisms have not been established, but a systemic alteration in NO production or an imbalance between endothelium-derived relaxing and contracting factors has been suggested.[650] [652]

In other patients, the sites of spasm in Prinzmetal angina may be adjacent to atheromatous plaque. It has been suggested that in this subgroup of patients, the basic abnormality may be hypercontractility of the arterial wall associated with the atherosclerotic process itself. Other suggested mechanisms include endothelial injury (which reverses the dilator response to a variety of stimuli, e.g., acetylcholine [see Chap. 34]) and hypercontractility of vascular smooth muscle as a result of vasoconstrictor mitogens, leukotrienes, serotonin, endothelin, angiotensin II, histamine,[653] [654] and higher local concentrations of blood-borne vasoconstrictors in areas adjacent to neovascularized atherosclerotic plaque.

The sequelae of coronary spasm may, but do not consistently, accelerate atherosclerosis and predispose to further spasm. One mechanism may involve the release of potent

Figure 37-25 Electrocardiogram (ECG) before an episode of Prinzmetal angina *(A)* and during an episode of Prinzmetal angina *(B)*. ST segments are now markedly elevated in the inferior leads, with reciprocal depression in the anterior leads. After nitroglycerin was given, the ECG returned to baseline. *(From Berman ND, McLaughlin PR, Huckell VF, et al: Prinzmetal's angina with coronary artery spasm. Angiographic, pharmacologic, metabolic and radionuclide perfusion studies. Am J Med 60:727, 1976. By permission of Excerpta Medica.)*

vasoconstrictor substances such as platelet-derived growth factors, in addition to activation of the coagulation system.[655] [656] The combination of a reduction in blood flow and an increase in platelet activation and local thrombosis may accelerate the process of atherosclerosis.[655] Histological findings in patients undergoing coronary atherectomy

suggest that repetitive coronary vasospasm may provoke vascular injury and lead to the formation of neointimal hyperplasia at the initial site of spasm. In this respect, coronary spasm may have a key role in the rapid progression of coronary stenosis in some patients.[657] Ergonovine stimulation has been demonstrated to provoke platelet aggregation and an increase in beta-thromboglobulin levels before ECG changes and chest pain in patients with coronary vasospasm.[658]

Imaging with iodine-123-labeled metaiodobenzylguanidine ([123] I-MIBG) has demonstrated regional myocardial sympathetic dysinnervation, which was not observed in patients with significant obstructive CAD and in subjects with normal coronary arteries.[659] The region of myocardial sympathetic dysinnervation is usually in the area of distribution of the vessel in which vasospasm developed.[659] [660]

Coronary spasm in patients with variant angina may induce stasis and result in the conversion of fibrinogen to fibrin in the coronary vessels, with elevated levels of plasma fibrinopeptide A, an index of fibrin formation.[661] The latter displays significant circadian variation in plasma concentration, with peak levels occurring from midnight to early morning, in parallel with the frequency of ischemic attacks in these patients.[662] In patients with variant angina, a significant variation in fibrinolytic activity (lowest in the early morning) corresponds with the occurrence of anginal episodes, which are most frequent in the early morning. The possibility that vasospasm may induce leukocyte adhesion in the coronary circulation at an early stage in the initiation of an inflammatory process has been suggested.[663]

Cigarette smoking is an important risk factor for Prinzmetal angina.[664] It has been reported that hypomagnesemia predisposes to variant angina,[665] and magnesium sulfate has been shown to terminate cold pressor-induced anginal attacks and the induction of future attacks[666] and to suppress attacks induced by hyperventilation[667] and exercise in these patients. [668]

Clinical Manifestations

Patients with variant angina tend to be younger than patients with chronic stable angina or unstable angina secondary to coronary atherosclerosis, and many do not exhibit classic coronary risk factors except that they are often heavy cigarette smokers. The anginal discomfort is often extremely severe, is generally referred to as "pain," and may be accompanied by syncope. Associated features in patients with syncope include inferior ST segment elevation and serious arrhythmias, either AV block and asystole or ventricular tachyarrhythmias[669] [670] [671] [672] (Fig. 37-26) .

Attacks of Prinzmetal angina tend to be clustered between midnight and 8 A.M.[662] Attacks sometimes occur in clusters of two or three within 30 to 60 minutes.[45] Patients studied by means of ambulatory ECG, even those without clinically apparent angina pectoris, show more frequent abnormalities in the morning. In contrast to patients with unstable angina, the pain at rest in patients with Prinzmetal angina has not usually progressed from a period of chronic stable angina. Although exercise capacity is generally well preserved in patients with Prinzmetal angina, some patients experience typical pain and ST segment elevations not only at rest but during or after exertion as

well. Acute myocardial infarction in patients with spasm and angiographically normal coronary arteries has been well documented.[673] [674]

Clinical features do not reliably differentiate patients with Prinzmetal angina and normal or mildly abnormal coronary arteriograms from those with this syndrome and severe coronary obstruction.[669] However, the latter may have a combination of fixed-threshold, exertion-induced angina with ST segment depression, as well as episodes of angina at rest with ST segment elevation. In rare cases, Prinzmetal angina develops after coronary artery bypass surgery,[675] and occasionally it appears to be a manifestation of a generalized vasospastic disorder associated with attacks of migraine and Raynaud's phenomenon; it has also been reported in association with aspirin-induced asthma.[676] Coronary spasm with ventricular fibrillation has been observed in thyrotoxicosis.[677] Some patients appear to demonstrate a distinct relationship between emotional distress and episodes of coronary vasospasm, which is consistent with studies suggesting that a sympathovagal imbalance may precipitate spasm in patients with variant angina.[672] Alcohol withdrawal may precipitate variant angina,[678] and conversely, alcohol ingestion may prevent coronary spasm.[679] Variant angina has been reported to be provoked by 5-fluorouracil[680] and by cyclophosphamide [681] (see Chap. 69) .

The results of cardiac examination are usually normal in the absence of ischemia (unless the patient has suffered a previous myocardial infarction), but signs of dyskinesia and impaired left ventricular function during episodes of myocardial ischemia are often revealed.

Figure 37-26 Arrhythmia during silent ischemia and reperfusion. Selected strips from a 2.5-minute continuous recording (lead II) in patient during an angiographically documented spasm of the right coronary artery are shown. Tracing A began 24 seconds after the onset of ST segment elevations (arrows) and demonstrates premature ventricular contractions and salvos. The top strip of tracing B was recorded 70 seconds after onset, immediately after the sublingual administration of nitroglycerin (1/150 grain); the bottom strip of tracing B was recorded 36 seconds later. Tracing C was recorded 130 seconds after onset and shows spontaneous reversion (asterisk) and atrial fibrillation. *(From Myerburg RJ, Kessler KM, Mallon SM, et al: Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary-artery spasm. N Engl J Med 326:1451, 1992. By permission of The Massachusetts Medical Society.)*

Electrocardiographic Studies

The key to the diagnosis of variant angina lies in the detection of ST segment elevation with pain (see Fig. 37-25) . In a series of patients with variant angina and normal coronary arteries monitored with a computerized 24-hour, 12-lead ECG recording and analysis system, approximately 90 percent of episodes were associated with ST segment elevation, with accompanying arrhythmias in 19 percent, but no arrhythmias were noted in the small proportion of patients with ST segment depression.[669] In some patients, episodes of ST segment depression follow episodes of ST segment elevation

and are associated with T wave changes, including peaking of T waves or pseudonormalization of previously depressed segments. ST segment and T wave alternans[682] and increased QT dispersion[683] are the result of ischemic conduction delay and may be associated with potentially lethal ventricular arrhythmias.[684] R wave "growth" may also be associated with the occurrence of ventricular arrhythmias.[685] Many patients exhibit multiple episodes of asymptomatic ST segment elevation (silent ischemia). ST segment deviations may be present in any leads; the concurrent presence of ST segment elevations in both the inferior and anterior leads (reflecting extensive ischemia) is associated with an increased risk of sudden death.[686] A pattern of *alternating* ST segment elevation between the precordial and inferior leads is associated with angiographically documented multivessel spasm involving both the left anterior descending and right coronary systems.[687]

Transient conduction disturbances may occur during episodes of ischemia.[670] [672] [685] Ventricular ectopic activity is more frequent during longer episodes of ischemia, is often associated with ST segment and T wave alternans,[685] and is of ominous prognostic import. In survivors of out-of-hospital cardiac arrest without flow-limiting coronary stenoses, spontaneous or induced focal coronary spasm has been found to be associated with life-threatening ventricular arrhythmias. In some patients, reperfusion rather than ischemia itself correlates with the onset of ventricular arrhythmias[688] (Fig. 37-26) . Myocardial cell damage, as reflected by the release of small quantities of CK-MB, may occur in the absence of persistent ECG changes in patients with prolonged attacks of variant angina; transient Q waves have been observed, which may be explained by a transient loss of normal cell membrane electrical activity during spasm.[689] Transmural myocardial infarction caused by coronary artery spasm in the absence of angiographically demonstrable obstructive CAD has been described.[673] [674]

Exercise testing in patients with variant angina is of limited value because the response is so variable. Approximately equal numbers of patients show ST segment depression, no change in ST segments during exercise, or ST segment elevation, which reflects the presence of underlying fixed CAD in some patients, the absence of significant lesions in others, and the provocation of spasm by exercise in the rest. Ambulatory ECG monitoring or the use of a telephone transmitter may be helpful in capturing ST segment elevation during symptomatic episodes.[690]

Hemodynamic and Arteriographic Studies

Spasm of a proximal coronary artery with resultant transmural ischemia and abnormalities in left ventricular function has been convincingly documented arteriographically and is the diagnostic hallmark of Prinzmetal angina.[691]

Significant fixed proximal coronary obstruction of at least one major vessel occurs in the majority of patients, and in these patients spasm usually occurs within 1 cm of the obstruction. The remainder have normal coronary arteries in the absence of ischemia. The process almost always involves large segments of the epicardial vessels at a single site, but at different times other sites may be involved (Fig. 37-27) . The right coronary artery is the most frequent site, followed by the left anterior descending coronary artery.[690] Among the 45 percent of patients in one series with multivessel spasm, three

different patterns were noted: (1) spasm at a different site on different occasions (migratory spasm), (2) spasm that sequentially affected two different sites, and (3) simultaneous spasm at more than one site. The duration of ST segment elevation was greater in patients with sequential and simultaneous spasm than in those with single-vessel spasm, as was the frequency of arrhythmias.[669] Patients with Prinzmetal angina and normal coronary arteriograms in the absence of pain are more likely to have purely nonexertional angina and ST segment elevations involving the inferior leads during pain. In contrast, patients with Prinzmetal angina who have fixed obstructive lesions with superimposed coronary artery spasm often have associated effort-induced angina and ischemia in the anterolateral leads. Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with associated severe obstructive lesions.[692]

PROVOCATIVE TESTS

THE ERGONOVINE TEST.

Several provocative tests for coronary spasm have been developed. Of these, the ergonovine test is the

Figure 37-27 Angiograms of the left coronary artery in patients with variant angina (left anterior oblique projection). Infusion of 10^{-4} M acetylcholine into the left coronary artery *(top panel)* induced spasm at three focal sites in the left anterior descending artery (arrows). Spasm was reversed after intracoronary nitroglycerin administration *(bottom)*. *(From Pepine CJ, el-Tamimi H, Lambert CR: Prinzmetal's angina [variant angina]. Heart Dis Stroke 1:281, 1992. By permission of The American Heart Association.)*

most sensitive. Ergonovine maleate, an ergot alkaloid that stimulates both alpha-adrenergic and serotonergic receptors and therefore exerts a direct constrictive effect on vascular smooth muscle,[693] has been used to induce coronary artery spasm, which results in chest pain and ST segment elevation in patients with Prinzmetal angina. Occasionally, ergonovine may produce a similar response in patients with more typical effort-related anginal symptoms.[690] Coronary arteries that constrict spontaneously appear to be abnormally sensitive to this agent. When administered intravenously in doses ranging from 0.05 to 0.40 mg, ergonovine provides a sensitive and specific test for provoking coronary artery spasm. The majority of patients who have a response to ergonovine do so at a dose of less than 0.2 mg.[690] An inverse correlation is found between the dose of ergonovine required to induce a positive test and the frequency of spontaneous attacks.[694] In low doses and in carefully controlled clinical situations, ergonovine is a relatively safe drug, but prolonged coronary artery spasm precipitated by ergonovine may cause myocardial infarction. Occasionally, conduction disturbances develop (heart block, asystole, or severe tachyarrhythmias).

Because of these hazards, it is recommended that ergonovine be administered only to

patients in whom coronary arteriography has demonstrated normal or nearly normal coronary arteries and in gradually increasing doses, beginning with a very low dose. Nitrates and calcium antagonists are usually effective in providing prompt relief from drug-induced spasm, and the intracoronary route is usually the most expeditious in patients already undergoing angiography. To ensure a valid test, nitrates and calcium antagonists must be withdrawn for 48 hours or more before testing. Women are more sensitive than men to ergonovine.[496] [695]

The ergonovine test should be conducted only in a setting where appropriate resuscitative equipment, drugs, and personnel are readily available, usually in the cardiac catheterization laboratory and with a catheter poised to enter the coronary arteries, so that the angiographic diagnosis of spasm can be made and intracoronary nitroglycerin administered to abolish the spasm. Absolute contraindications to ergonovine testing include pregnancy, severe hypertension, severe left ventricular dysfunction, moderate to severe aortic stenosis, and high-grade left main coronary artery stenosis. Relative contraindications include uncontrolled or unstable angina, uncontrolled ventricular arrhythmias, recent myocardial infarction, and advanced CAD.[496]

The response of the *normal* coronary arterial bed to larger doses (0.40 mg) of ergonovine is a diffuse reduction in arterial caliber.

HYPERVENTILATION.

This stimulus has also been demonstrated to provoke some episodes of intense angina,[696] ECG ST segment elevations, angiographic evidence of coronary artery spasm, and ventricular arrhythmias. A recent large series documented the relative specificity of the hyperventilation test in patients with vasospastic angina.[697] Patients with positive tests had a statistically significantly greater frequency of high disease activity (five or more attacks per week), severe arrhythmias during attacks, and multivessel spasm.

ACETYLCHOLINE.

Stimulation of acetylcholine receptors produces a uniform endothelium-dependent dilatation of coronary vessels of all sizes that leads to vasoconstriction when endothelial function is impaired.[698] In patients with variant angina, intracoronary injections of acetylcholine have been shown to induce severe coronary spasm and reproduce the clinical syndrome[699] (see Fig. 37-27) . This focal spasm should not be confused with the mild diffuse constriction that acetylcholine induces in patients with abnormal coronary endothelium. Because this method allows induction of spasm separately in the left and right coronary arteries, it is useful in patients with known multivessel disease or spasm. Acetylcholine is infused over a 1-minute period into a coronary artery in incremental doses of 10, 25, 50, and 100 mug, and doses should be separated by 5-minute intervals.[496] [695]

Histamine, dopamine, and serotonin can also induce coronary artery spasm.[700] [701] Like

ergonovine and acetylcholine, these agents are capable of causing marked coronary artery spasm in patients with variant angina who have severe underlying arteriosclerotic coronary artery narrowing and in those without such fixed stenoses.

Exercise, the cold pressor test, and induced alkalosis can all cause coronary spasm in patients with variant angina, but none of these tests is as sensitive as ergonovine or acetylcholine.

Management

The mainstay of therapy for vasospastic angina is a calcium channel blocker alone or in combination with long-acting nitrates. Nonetheless, several important differences can be seen between the optimal management of Prinzmetal variant angina and classic (stable and unstable) angina.

1. Patients with both variant and classic angina usually respond well to nitrates; sublingual or intravenous nitroglycerin often abolishes attacks of variant angina promptly, and long-acting nitrates are useful in preventing attacks.[702] However, the mechanism of action of the drugs may differ in the two types of angina. As already discussed (see p. 1287), in chronic (effort-induced) stable angina as well as in unstable angina, one important action of nitrates is to reduce myocardial O_2 need and another is to cause coronary vasodilation. In Prinzmetal angina, nitrates abolish or prevent myocardial ischemia *exclusively* by exerting a direct vasodilating effect on the spastic coronary arteries.
2. In patients with classic angina (stable and unstable), beta blockade is usually beneficial, but the response in patients with Prinzmetal angina to these agents is variable.[703] Some, particularly those with associated fixed lesions, exhibit a reduction in the frequency of exertion-induced angina caused primarily by augmentation of myocardial O_2 requirements. In others, however, nonselective beta-adrenoreceptor blockers may actually be detrimental because blockade of $beta_2$ receptors, which subserve coronary

dilation, allows unopposed alpha receptor-mediated coronary vasoconstriction to occur; in these patients, the duration of episodes of vasotonic angina may be prolonged by propranolol.[704]
3. In contrast to the variable effectiveness of beta blockers, calcium antagonists are extremely effective in preventing the coronary artery spasm of variant angina,[705] [706] and they should ordinarily be prescribed in maximally tolerated doses. These drugs, along with long- and short-acting nitrates, are the mainstay of therapy. Because calcium antagonists act through a different mechanism than nitrates, the vasodilatory actions of these two classes of drugs may be additive. All first-generation calcium channel antagonists have similar efficacy in producing relief of symptoms: 94 percent for nifedipine, 40 mg/d; 91 percent for diltiazem, 180 mg/d; and 86 percent for verapamil, 240 mg/d.[650] [705] [706] [707] [708] In rare instances, a patient responds to only one of these three agents, and even less

commonly**,** the simultaneous administration of two or even three calcium antagonists is required. Some patients need extremely high doses, although side effects are increased. Slow-release nifedipine has been shown to be highly effective in suppressing not only symptomatic but also asymptomatic myocardial ischemia in patients with variant angina.[707] Second-generation calcium blockers such as the vascular-selective agents felodipine and amlodipine have also been shown to be effective. In addition, once-daily felodipine has been demonstrated to be highly effective in preventing ergonovine-induced myocardial ischemia in patients with variant angina[709] and in patients with spontaneous Prinzmetal angina.[710] In a randomized trial, amlodipine, 5 to 10 mg/d, has also been shown to be effective.[711] Reports have suggested a rebound of symptoms when calcium antagonist therapy is discontinued.[708]

4. *Prazosin*, a selective alpha-adrenoreceptor blocker (see Chap. 29) , has also been found to be of value in patients with Prinzmetal angina.[712] *Nicorandil*, a vasodilator that influences coronary arterial tone by acting through potassium channel activation, appears to be effective for the treatment of vasospastic angina, as suggested by studies in Japan and Europe.[713] *Aspirin*, helpful in unstable angina (see Chap. 36) , may actually *increase* the severity of ischemic episodes in patients with Prinzmetal angina because it inhibits biosynthesis of the naturally occurring coronary vasodilator prostacyclin.[714] *ACE inhibition* with enalapril was shown to be ineffective in comparison with verapamil in patients with vasospastic angina.[715] Other novel but promising approaches to the management of vasospastic angina include troglitazone, an insulin sensitizer,[716] and denopamine, an adrenergic beta$_1$ agonist,[717] and in a small study of patients in whom vasospastic angina was induced by hyperventilation, the infusion of B-type (brain) natriuretic peptide was highly effective.[718]
5. PCI and occasionally CABG may be helpful in patients with variant angina and discrete, proximal fixed obstructive lesions.[719] Calcium antagonists should be continued for at least 6 months following successful revascularization. PCI and coronary artery bypass surgery are *contraindicated* in patients with isolated coronary artery spasm without accompanying fixed obstructive disease.

Prognosis

Many patients with Prinzmetal angina pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after diagnosis. Long-term survival at 5 years is excellent (89 to 97 percent).[686] In a large series of 277 patients with a median follow-up of 7.5 years, recurrent angina was common (39 percent), but cardiac death and myocardial infarction were relatively infrequent and occurred in 3.5 and 6.5 percent of patients, respectively.[720] However, recurrent myocardial infarction in the setting of normal coronary arteries and angiography has been described.[674] The extent and severity of the underlying CAD and the activity or the tempo of the syndrome have a major effect on the incidence of late mortality and myocardial infarction. Because occlusive coronary spasm may cause stasis with platelet aggregation and thrombosis, the duration of the episodes of spasm is probably a factor in the development of acute infarction.

Patients with variant angina in whom serious arrhythmias (ventricular tachycardia,

ventricular fibrillation, high-degree AV block, or asystole) develop during spontaneous episodes of pain have a higher risk of sudden death.[721] [722]

In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, the condition stabilizes and symptoms and cardiac events tend to diminish with time. In patients who experience such remissions, cautious tapering of calcium antagonists may be attempted. In one series, 16 percent of patients had spontaneous remission for 3 months after withdrawal of therapy, 44 percent continued to have symptoms despite treatment with calcium antagonists and nitrates, and the other 40 percent were free of angina but receiving treatment. Remission occurred more frequently in patients without significant coronary artery stenoses and in those who stopped smoking.[723]

For reasons that are not clear, some patients, after a relatively quiescent period of months or even years, experience a recrudescence of vasospastic activity with frequent and severe episodes of ischemia.[724] Fortunately, these patients respond to re-treatment with calcium antagonists and nitrates. Most patients in whom symptoms recur after a pain-free period demonstrate, on provocative testing, spasm at the same location as previously demonstrated and respond once more to treatment with nitrates and calcium antagonists.

CHEST PAIN WITH NORMAL CORONARY ARTERIOGRAM

The syndrome of angina or angina-like chest pain with a normal coronary arteriogram, often referred to as *syndrome X* (to be distinguished from the metabolic syndrome X characterized by abdominal obesity, hypertriglyceridemia, low HDL cholesterol, insulin resistance, hyperinsulinemia, and hypertension), is an important clinical entity that should be differentiated from classic ischemic heart disease caused by CAD. In this condition, the prognosis is usually excellent,[725] [726] in contrast to the variable outcome in patients with angina caused by coronary atherosclerosis. Patients with chest pain and normal coronary arteriograms may represent as many as 10 to 20 percent of those undergoing coronary arteriography because of clinical suspicion of angina. The cause(s) of the syndrome is unclear. True myocardial ischemia, reflected in the production of lactate by the myocardium during exercise or pacing, is present in some of these patients.[727] The incidence of coronary calcification on double-helical CT scanning is significantly higher than that of normal controls (63 vs. 22 percent), but lower than that in patients with organic heart disease (96 percent).[728]

It is postulated that the syndrome of angina pectoris with normal coronary arteries reflects a number of conditions. Included in syndrome X are patients with microvascular dysfunction or spasm in whom angina may be the result of ischemia.[729] [730] This condition is frequently referred to as *microvascular angina* (Fig. 37-28) . In others, chest discomfort without ischemia may be due to abnormal pain perception or sensitivity. This hypersensitivity may result in an awareness of chest pain in response to stimuli such as arterial stretch or changes in heart rate, rhythm, or contractility. A sympathovagal imbalance with sympathetic

Figure 37-28 Proposed pathogenetic mechanisms of microvascular angina. The syndrome results from a variable combination of two components: an increased sensitivity to painful stimuli associated with coronary microvascular dysfunction (indicated by recurring ST segment depression), both of which have a bell-shaped prevalence in the population. Furthermore, within any individual, either component may vary in time (indicated by the horizontal lines). In patients with markedly enhanced sensitivity to pain, even minimal microvascular dysfunction can cause angina. Conversely, some patients with severe microvascular dysfunction (indicated by recurring ST segment depression) may not come to medical attention if they have normal or low sensitivity to pain. *(From Maseri A: Ischemic Heart Disease: A Rational Basis for Clinical Practice and Clinical Research. New York, Churchill Livingstone, 1995. By permission.)*

predominance in some of these patients has also been postulated. At the time of cardiac catheterization, some patients with syndrome X are unusually sensitive to intracardiac instrumentation, with typical chest pain being consistently produced by direct right atrial stimulation and saline infusion.[731] Other patients appear to have a combination of microvascular dysfunction and abnormal pain sensitivity. Intravascular ultrasound studies have demonstrated the anatomical and physiological heterogeneity of syndrome X, with a spectrum ranging from normal coronary arteries to vessels with intimal thickening and atheromatous plaque.[732] On the other hand, many patients do not have metabolic evidence of ischemia despite abnormal coronary flow reserve after pacing.[733]

MICROVASCULAR DYSFUNCTION (INADEQUATE VASODILATOR RESERVE)(Fig. 37-28) .

Patients with chest pain, angiographically normal coronary arteries, and no evidence of large vessel spasm even after an acetylcholine challenge may demonstrate an abnormally reduced capacity to reduce coronary resistance and increase coronary flow in response to stimuli such as exercise, dipyridamole, and atrial pacing. These patients also have an exaggerated response of small coronary vessels to vasoconstrictor stimuli and an impaired response to intracoronary papavarine.[734] Some evidence indicates that increased endothelin concentrations may be associated with reduced coronary flow responses during atrial pacing.[735] This abnormality appears to affect the smaller resistance vessels that are not visible angiographically, whereas the large proximal conductance vessels are normal.[736] The reduced vasodilator reserve in the microcirculation may be associated with exercise-induced regional wall motion abnormalities, as well as abnormalities in diastolic function.[737] The reduced coronary flow reserve may cause abnormalities in myocardial perfusion that are detectable with PET.[738] It has been reported that these patients also have impaired vasodilator reserve in forearm vessels[739] and airway hyperresponsiveness,[740] which suggests that the smooth muscle of systemic arteries and other organs may be affected in addition to that of the coronary circulation.

A link between coronary microvascular dysfunction and ischemia in response to exercise is an attractive concept that could explain abnormal left ventricular function

resulting from exercise in some patients with chest pain and normal coronary arteries.[738] [741] Abnormal endothelial function and increased sympathetic drive or responsiveness have been reported.[742] [743]

EVIDENCE FOR ISCHEMIA.

Despite general acceptance that microvascular and/or endothelial dysfunction (see Fig. 37-28) is present in many patients with syndrome X, whether ischemia is in fact the putative cause of the symptoms in these patients is not clear.[731] [741] The development of left ventricular dysfunction and ECG or scintigraphic abnormalities during exercise in some of these patients supports an ischemic cause. However, transesophageal stress echocardiography with dobutamine has failed to demonstrate regional contraction abnormalities consistent with ischemia.[744] The lack of definitive evidence of ischemia in some patients with syndrome X has focused attention on alternative nonischemic causes of cardiac-related pain, including a decreased threshold for pain perception--the so-called sensitive heart syndrome.[731] [745] It is difficult to distinguish patients with syndrome X in whom chest pain is caused by ischemia from patients with noncardiac pain (see p. 1274). Behavioral or psychiatric disorders may be evident.[746] [747] Esophageal dysmotility and reproduction of pain after the infusion of hydrochloric acid into the esophagus (Bernstein test) or intraesophageal balloon distention have been reported in some of these patients.

Clinical Features

The syndrome of angina or angina-like chest pain with normal epicardial arteries occurs more frequently in women,[748] many of whom are premenopausal, whereas obstructive CAD is found more commonly in men and postmenopausal women. Fewer than half of patients with syndrome X have typical angina pectoris; the majority have a variety of forms of atypical chest pain. Although the features are frequently atypical, the chest pain may nonetheless be severe and disabling. [748] The condition may be benign in regard to survival, but it may have markedly adverse effects on the quality of life, employment, and use of health care resources.[749]

In some patients with minimal or no CAD, an exaggerated preoccupation with personal health is associated with the chest pain, and panic disorder may be responsible in a proportion of such patients. Potts and Bass found that two-thirds of patients with chest pain and normal coronary arteries have predominantly psychiatric disorders.[747] Others have reported that the incidence of obstructive CAD is extremely low in patients with atypical chest pain who are anxious and/or depressed.[750] The association between syndrome X and insulin resistance warrants further study.

PHYSICAL AND LABORATORY EXAMINATION.

Abnormal physical findings reflecting ischemia, such as a precordial bulge, gallop sound, and the murmur of mitral regurgitation, are uncommon in syndrome X. The resting ECG may be normal, but nonspecific ST-T wave abnormalities are often observed, sometimes occurring in association with the chest pain. Approximately 20

percent of patients with chest pain and normal coronary arteriograms have positive exercise tests. However, many patients with this syndrome do not complete the exercise test because of fatigue or mild chest discomfort. Left ventricular function is usually normal

at rest and during stress,[737] unlike the situation in obstructive CAD, in which function often becomes impaired during stress. A small percentage of patients with syndrome X exhibit lactate production and ST segment depression during exercise, a sign of significant ischemia. Some patients have abnormal myocardial perfusion reserve, but no consistent pattern of abnormal myocardial blood flow is seen.

PROGNOSIS.

Important prognostic information on patients with angina and either normal or nearly normal coronary arteriograms has been obtained from the CASS Registry.[725] In patients with an ejection fraction of 50 percent or more, the 7-year survival rate was 96 percent for patients with a normal arteriogram and 92 percent for those whose arteriographic study revealed mild disease (50 percent luminal stenosis). In such patients, an ischemic response to exercise was not associated with increased mortality, although a history of smoking or hypertension was. Thus, long-term survival of patients with anginal chest pain and normal coronary angiograms is excellent, markedly better than in patients with obstructive CAD and no different from that in an age-matched general population.[731] [741] [751] Nonetheless, the symptoms are persistent, and most patients continue to experience chest pain that leads to repeated cardiac catheterization and hospital admission.[741] [752]

Management

In patients with angina-like chest pain syndrome and normal epicardial coronary arteries, esophageal abnormalities should be considered (see p. 1273). Such patients may show either motility disorders of the esophagus or abnormal reflux. Exercise ECG and/or myocardial perfusion scintigraphy is often helpful in excluding obstructive CAD. When a noninvasive stress test is positive, or even in patients with serious disability and multiple hospital admissions in whom the test is negative, documentation of normal coronary arteries by coronary angiography provides an objective basis for firm reassurance.

In patients with syndrome X in whom ischemia can be demonstrated by noninvasive stress testing, a trial of antiischemic therapy with nitrates and beta blockers is logical, but the response to this therapy is often poor.[731] In contrast to patients with organic CAD, sublingual nitrates are ineffective in improving exercise tolerance in patients with syndrome X, and in some, exercise tolerance may deteriorate further.[753] Calcium antagonists are effective in reducing the frequency and severity of angina and improving exercise tolerance in some patients. When these conditions are present, treatment of

esophageal reflux and dysmotility may be effective.

Estrogen has been shown to attenuate normal coronary vasomotor responses to acetylcholine, increase coronary blood flow, and potentiate endothelium-dependent vasodilation in postmenopausal women.[754] Although estrogen would therefore seem to be a logical treatment for postmenopausal women with syndrome X, only short-term estrogen administration has been studied,[755] and long-term clinical effectiveness of estrogen therapy in these patients has not been documented. Imipramine (50 mg) has been reported to be helpful in some.[746]

Oral aminophylline (an adenosine receptor blocker) may have a favorable effect on the exercise-induced chest pain threshold without any effect on exercise-induced ST segment changes.[756]

SILENT MYOCARDIAL ISCHEMIA

The prognostic importance and the mechanisms of silent ischemia have been the subject of considerable interest for almost 30 years.[757] [758] Patients with silent ischemia have been stratified into three categories by Cohn.[759] The first and least common form, type I silent ischemia, occurs in totally asymptomatic patients with obstructive CAD (which may be severe), and these patients *do not experience angina at any time*; some type I patients do not even experience pain in the course of myocardial infarction. Epidemiological studies of sudden death (see Chap. 26) , as well as clinical and postmortem studies of patients with silent myocardial infarction and studies of patients with chronic angina pectoris, suggest that many patients with extensive coronary artery obstruction never experience angina pectoris in any of its recognized forms (stable, unstable, or variant). These patients with type I silent ischemia may be considered to have a *defective anginal warning system*. Type II silent ischemia is the form that occurs in patients with documented previous myocardial infarction.

The third and much more frequent form, designated type III silent ischemia, occurs in patients with the usual forms of chronic stable angina, unstable angina, and Prinzmetal angina. When monitored, patients with this form of silent ischemia exhibit some episodes of ischemia that are associated with chest discomfort and other episodes that are not--i.e., episodes of silent (asymptomatic) ischemia. The "total ischemic burden" in these patients refers to the total period of ischemia, both symptomatic and asymptomatic.

AMBULATORY ELECTROCARDIOGRAPHY.

The extensive use of ambulatory ECG monitoring has led to a greater appreciation of the high frequency of type III "silent" ischemia[760] (Fig. 37-29) . It has become apparent that anginal pain is a poor indicator and underestimates the frequency of significant cardiac ischemia.[761] Exercise-induced hemodynamic changes indicative of myocardial ischemia (increasing left ventricular end-diastolic pressure and decreasing left ventricular ejection fraction) occur in patients with CAD, regardless of the development

of ischemic discomfort.[762]

The role of myocardial O_2 demand in the genesis of myocardial ischemia has been evaluated by measuring the heart rate and blood pressure changes preceding silent ischemic events during ambulatory studies. In one series, 92

Figure 37-29 Ambulatory electrocardiograms and coronary angiogram of a severe left anterior descending stenosis in a patient with fatigue (but not angina) during a tennis match. In stage II of a treadmill exercise test (Bruce protocol), 4 mm of ST segment depression was seen in lead V_5 . Ambulatory Holter monitoring of lead V_5 demonstrates ischemic ST segment depression during a number of ordinary activities, e.g., walking, telephoning. During a game of tennis, marked ST segment depression was recorded when the patient was asymptomatic. *(From Nabel EG, Rocco MB, Selwyn AB: Characteristics and significance of ischemia detected by ambulatory electrocardiographic monitoring. Circulation 75[Suppl 5]:74, 1987. By permission of the American Heart Association, Inc.)*

percent of all episodes were silent, and 60 to 70 percent were preceded by significant increases in heart rate or blood pressure. The circadian variations in heart rate and blood pressure also paralleled the increase in silent ischemic events. This and other studies have suggested that increases in myocardial O_2 demand have a significant role in the genesis of silent ischemia but, in other patients, reductions in myocardial O_2 supply may make an important contribution to the initiation of both symptomatic and asymptomatic episodes.[763] The mechanisms underlying the development of ischemia, as detected by ambulatory ECG and exercise testing, may be different, and in patients in the ACIP Study, concordance between the ambulatory ECG and SPECT was only 50 percent. For identification of silent ischemia, the two techniques probably complement each other.[764]

Transient ST segment depression of 0.1 mV or more that lasts longer than 30 seconds is a very rare finding in normal subjects.[765] Patients with known CAD show a strong correlation between such transient ST segment depression and independent measurements of impaired regional myocardial perfusion and ischemia determined by rubidium-82 uptake as measured by PET.[766] In patients with type III silent ischemia, perfusion defects occur in the same myocardial regions during symptomatic and asymptomatic episodes of ST segment depression. Other methods of detecting "silent" ischemia include measurement of the left ventricular ejection fraction with a "nuclear vest" or the presence of regional wall motion abnormalities and perfusion defects on echocardiography or radionuclide scintigraphy.[764]

Type III silent ischemia is extremely common. Analysis of ambulatory ECG recordings among patients with CAD who had both symptomatic and silent myocardial ischemia found that 85 percent of ambulant ischemic episodes occur without chest pain and 66 percent of angina reports were unaccompanied by ST segment depression.[767] Their

frequency is such that it has been suggested that overt angina pectoris is merely the "tip of the ischemic iceberg." Among patients with stable CAD enrolled 1 to 6 months after hospitalization for an acute ischemic event, only 15 percent had angina with exercise, yet 28 percent had ST segment depression and 41 percent had reversible myocardial perfusion defects on thallium scintigraphy.[768] Episodes of silent ischemia have been estimated to be present in approximately half of all patients with angina, although a higher prevalence has been reported in diabetics.[760] [769] [770] Episodes of ST segment depression, both symptomatic and asymptomatic, exhibit a circadian rhythm and are more common in the morning. Asymptomatic nocturnal ST segment changes are almost invariably an indicator of two- or three-vessel CAD or left main coronary artery stenosis.

Pharmacological agents that reduce or abolish episodes of symptomatic ischemia, i.e., nitrates, beta blockers, and calcium antagonists, also reduce or abolish episodes of silent ischemia.[771]

MECHANISMS OF SILENT ISCHEMIA.

It is not clear why some patients with unequivocal evidence of ischemia do not experience chest pain whereas others are symptomatic. Maseri has proposed that silent ischemia results from a variable combination of decreased sensitivity to painful stimuli and coronary microvascular dysfunction[1] (Fig. 37-28) . Investigation into the causes of silent ischemia has focused primarily on five areas: (1) The association between diabetes and both silent ischemia and "painless infarctions" has been attributed to an autonomic neuropathy.[757] [770] [772] [773] (2) Patients with silent ischemia have been shown to have a high threshold for other forms of pain, such as that resulting from electrical shock, limb ischemia,[774] or cutaneous application of heat [775] or from balloon inflation in the coronary artery.[776] (3) Hypertensive patients who demonstrated a higher incidence of "silent" ischemia have been shown to have higher pain thresholds and lower reactions to tooth pulp stimulation than normotensive subjects.[776] It has been postulated that these patients produce an excessive quantity of endogenous opioids (and endorphins) that raise the pain threshold, but the existence of such a mechanism is debated.[777] (4) In patients with type III silent ischemia, the asymptomatic episodes may result from a less severe ischemia than the symptomatic episodes. In some of these patients, shorter periods of ischemia on Holter ECG tend to be asymptomatic, whereas longer periods are accompanied by angina.[778] [779] It has been postulated that the pain receptors are not stimulated by the milder episodes of ischemia. (5) A more recent area of investigation suggests that silent ischemia in some patients may not be due to peripheral nerve dysfunction but instead be the result of a defect in the cerebral cortex.[780] Frontal cortical activation appears necessary to experience cardiac pain, and some evidence indicates that in patients with silent ischemia, afferent pain messages from the heart are subject to abnormal neural processing.[764] [780] [781] The role of psychosocial factors in the perception of pain is controversial.[782]

PROGNOSIS.

Irrespective of the mechanism(s) responsible, ample evidence supports the view that episodes of myocardial ischemia, regardless of whether they are symptomatic or asymptomatic, are of prognostic importance in patients with CAD. As such, myocardial

ischemia, as opposed to symptoms alone, has been identified as a valid therapeutic target. In asymptomatic patients, the presence of exercise-induced ST segment depression has been shown to predict a fourfold to fivefold increase in cardiac mortality in comparison with patients without this finding.[783] In a series of patients in the CASS Registry with ST segment depression on treadmill exercise testing, the risk of subsequent myocardial infarction and sudden cardiac death and the relative benefits of surgery versus medical therapy were determined primarily by angiographic variables of CAD severity and not by the presence or absence of ischemia.[512] [784] A greater benefit was noted with CABG than with medical therapy in those with silent ischemia and three-vessel disease.[784] On the other hand, in some subsets of patients, e.g., stable patients with a previous myocardial infarction, the presence of painless exercise-induced ischemia has not been shown to provide additional prognostic information.[785]

It has been well established that the presence of myocardial ischemia on ambulatory ECG, whether silent or symptomatic, is associated with an adverse cardiac outcome, particularly if the episodes are frequent or accelerating.[334] [771] [786] What previously has been less clear is whether the detection of asymptomatic episodes of ischemia on ambulatory ECG adds *independent* prognostic information over and above that provided by the results of the stress test and the frequency and severity of symptoms.[787] [788] In the ACIP Study, among patients treated medically, myocardial ischemia detected by ambulatory ECG and by an abnormal exercise treadmill test were each *independently* associated with adverse cardiac outcomes.[789] Moreover, ischemia detected by ambulatory ECG monitoring did not correlate with the presence and extent of ischemia as quantified by stress SPECT scintigraphy, which suggests that these techniques detect different pathophysiological manifestations of ischemia.[790] Further support for this concept is provided by angiographic evidence from the ACIP Study data base, in which patients with ischemia and ambulatory ECG were more likely to have multivessel CAD, severe proximal stenoses, and a greater frequency of complex lesion morphology, including intracoronary thrombus, ulceration, and eccentric lesions, than were patients without evidence of ischemia on ambulatory monitoring. The presence of severe and complex CAD may partly explain the apparent independent effect of silent ischemia during ambulatory monitoring on prognosis.[791]

Whether the incremental prognostic information provided

by adding an ambulatory ECG to a standard stress test will justify the cost of using this modality as a tool for widespread screening remains to be determined, but it is unlikely. Exercise ECG can identify the majority of patients likely to have significant ischemia during their daily activities and remains the most important screening test for significant CAD. Many patients with type I silent ischemia have been identified because of an asymptomatic positive exercise ECG obtained following myocardial infarction. In such patients with a defective anginal warning system, it is reasonable to assume that asymptomatic ischemia has a significance similar to that of symptomatic ischemia and that their management with respect to coronary angiography and revascularization

should be similar.

MANAGEMENT.

Drugs that are effective in preventing episodes of symptomatic ischemia (nitrates, calcium antagonists, and beta blockers) are also effective in reducing or eliminating episodes of silent ischemia[757] [792] (Fig. 37-30) . In the Atenolol Silent Ischemia Study Trial (ASIST), 4 weeks of atenolol therapy decreased the number of ischemic episodes detected on ambulatory ECG (from 3.6 to 1.7; $p<0.001$) and also the average duration (from 30 to 16.4 minutes per 48 hours; $p<0.001$).[334] In another randomized study, long-acting metoprolol taken once daily was as effective as formulations requiring more frequent dosing.[793] In yet another randomized study, metoprolol was shown to be superior to diltiazem in decreasing the mean number of ischemic episodes and the mean duration of ischemia.[794] A combination of a beta blocker and a calcium antagonist is superior to either class of drug alone in suppressing ischemia detected by ambulatory ECG.

Although suppression of ischemia in patients with

Figure 37-30 Atenolol in Silent Ischemia Trial (ASIST). The recently reported ASIST is the first controlled trial to demonstrate modification of cardiac risk through treatment of silent myocardial ischemia (SMI). A total of 306 asymptomatic or minimally symptomatic patients with coronary artery disease, positive exercise tests, and ambulatory electrocardiographic (ECG) episodes of SMI were randomized to receive atenolol or placebo. Ambulatory ECG monitoring was repeated at 4 weeks, and outcome was assessed after 1 year. At 4 weeks, atenolol was associated with a significant reduction in SMI. After 1 year, a significant (56 percent) relative reduction in adverse events (death, resuscitated ventricular tachycardia and fibrillation, nonfatal myocardial infarction, and unstable or worsening angina) was found when patients given atenolol were compared with those given placebo. The presence of ischemia at 4 weeks was the most important independent factor associated with adverse outcomes after 1 year. *(From Bertolet BD, Pepine CJ: Silent myocardial ischemia. In Beller GA, Braunwald E [eds]: Chronic Ischemic Heart Disease. Atlas of Heart Diseases. Vol 5. Philadelphia, Current Medicine, 1995, p 8.9. By permission of W.B. Saunders Co.)*

asymptomatic ischemia is a worthwhile objective, whether treatment should be guided by symptoms or by ischemia as reflected by the ambulatory ECG has not been established. The ACIP Pilot Study showed that the proportion of patients free of ischemia on a 48-hour ambulatory ECG among medically treated patients assigned to an "ischemia-guided" strategy and those assigned to an "angina-guided" strategy was 31 and 36 percent, respectively, at 1 year (p=NS). Among patients treated with coronary revascularization, 57 percent were free of ischemia at 1 year ($p<0.001$). [795] Similar trends were noted in the results of exercise testing.[796]

Coronary revascularization is superior to medical therapy for the relief of both angina and ambulatory ischemia at 12 weeks.[797] Moreover, the early benefits of revascularization on ischemia are associated with improved clinical outcomes. In this pilot study with over 2 years of follow-up, total mortality was 6.6 percent with the angina-guided strategy, 4.4 percent with the ischemia-guided strategy, and 1.1 percent with the revascularization strategy ($p<0.02$). The rate of death or myocardial infarction

was 12.1 percent in the angina-guided strategy, 8.8 percent in the ischemia-guided strategy (see Fig. 37-17) , and 4.7 percent in the revascularization strategy, and a strong reduction was also seen in recurrent hospitalizations and the revascularization strategies. These differences were significant, but no differences were noted between the two strategies of medical therapy.[545]

HEART FAILURE IN ISCHEMIC HEART DISEASE

In the current era, the leading cause of heart failure in developed countries is CAD.[798] In the United States, CAD and its complications account for two-thirds to three-fourths of all cases of heart failure. In many patients, the progressive nature of heart failure reflects the progressive nature of the underlying CAD. The term *ischemic cardiomyopathy* is used for the clinical syndrome in which one or more of the above pathophysiological features result in left ventricular dysfunction and heart failure symptoms. This condition is the predominant form of heart failure related to CAD. Additional complications of CAD that may become superimposed on ischemic cardiomyopathy and precipitate heart failure are the development of left ventricular aneurysm and mitral regurgitation caused by papillary muscle dysfunction.

Ischemic Cardiomyopathy

In 1970, Burch and colleagues first used the term *ischemic cardiomyopathy* to describe the condition in which CAD results in severe myocardial dysfunction, with clinical manifestations often indistinguishable from those of primary dilated cardiomyopathy[799] (see Chap. 48) . Symptoms of heart failure caused by ischemic myocardial dysfunction and hibernation, diffuse fibrosis, or multiple infarctions, alone or in combination, may dominate the clinical picture of CAD. In some patients with chronic CAD, angina may be the principal clinical manifestation at one time, but later this symptom diminishes or even disappears as heart failure becomes more prominent. Other patients with ischemic cardiomyopathy have no history of angina or myocardial infarction (type I silent ischemia, see p. 1330), and it is in this subgroup that ischemic cardiomyopathy is most often confused with dilated cardiomyopathy.

It is important to recognize hibernating myocardium in patients with ischemic cardiomyopathy because symptoms resulting from chronic left ventricular dysfunction may be incorrectly thought to result from necrotic and scarred

myocardium rather than from a reversible ischemic process. Hibernating myocardium may be present in patients with known or suspected CAD with a degree of cardiac dysfunction or heart failure not readily accounted for by previous myocardial infarctions (see also p. 1316).

The outlook for patients with ischemic cardiomyopathy treated medically is quite poor, and revascularization or cardiac transplantation may be considered.[800] The prognosis is

particularly poor for patients in whom ischemic cardiomyopathy is due to multiple myocardial infarctions, in those with associated ventricular arrhythmias, and in those with extensive amounts of hibernating myocardium. However, this latter group of patients, whose heart failure, even if severe, is due to large segments of reversibly dysfunctional, but viable myocardium, has a significantly better prognosis after revascularization.[564] [568] [569] [570] [571] Revascularization in this group also significantly improves heart failure symptoms.[103] [563] [564] Thus, the key to management of patients with ischemic cardiomyopathy is to assess the extent of residual viable myocardium with a view to coronary revascularization of viable myocardium (see Chap. 13 and p. 50 and 51). Patients with little or no viable myocardium in whom heart failure is secondary to extensive myocardial infarction and/or fibrosis should be managed in a manner similar to those with dilated cardiomyopathy (see Chaps. 21 and 48) . Their prognosis is poor.

Left Ventricular Aneurysm

Left ventricular aneurysm is usually defined as a segment of the ventricular wall that exhibits paradoxical (dyskinetic) systolic expansion. Chronic fibrous aneurysms interfere with ventricular performance principally through loss of contractile tissue. Aneurysms made up largely of a mixture of scar tissue and viable myocardium or of thin scar tissue also impair left ventricular function by a combination of paradoxical expansion and loss of effective contraction. *False aneurysms* (pseudoaneurysms) represent localized myocardial rupture in which the hemorrhage is limited by pericardial adhesions, and they have a mouth that is considerably smaller than the maximal diameter (Fig. 37-31) . True and false aneurysms may coexist, although the combination is extremely rare.[801]

The frequency of ventricular aneurysms depends on the incidence of transmural myocardial infarction and congestive heart failure in the population studied. Left ventricular aneurysms and the need for aneurysmectomy have declined dramatically during the last 5 to 10 years in concert with the expanded use of acute reperfusion therapy in evolving myocardial infarction. More than 80 percent of left ventricular aneurysms are located anterolaterally near the apex. They are often associated with total occlusion of the left anterior descending coronary artery and a poor collateral blood supply.[802] Approximately 5 to 10 percent of aneurysms are located posteriorly. Three-quarters of patients with aneurysms have multivessel CAD.[803]

Left ventricular aneurysms can develop in patients who sustain a blunt chest injury (see Chap. 51) . The condition is attributed to myocardial contusion or to direct vascular damage causing myocardial necrosis; pseudoaneurysms of adjacent vascular structures, including the thoracic aorta, may be present in addition to valvular damage.[804] Death from rupture of a false aneurysm caused by nonpenetrating chest trauma has been described[805] and successfully repaired surgically.[806]

Figure 37-31 Hearts in systole and diastole with true and false anatomical and functional left ventricular aneurysms and healed myocardial infarction. A normal heart in systole and diastole is shown for comparison. A true anatomical left ventricular aneurysm protrudes during both systole and diastole, has a mouth that is as wide or wider than the maximal diameter, has a wall that was formerly the wall of the left ventricle, and is composed of fibrous tissue with or without residual myocardial fibers. A true aneurysm

may or may not contain thrombus and almost never ruptures once the wall is healed. A false anatomical left ventricular aneurysm protrudes during both systole and diastole, has a mouth that is considerably smaller than the maximal diameter of the aneurysm and represents a myocardial rupture site, has a wall made up of parietal pericardium, virtually always contains thrombus, and often ruptures. A functional left ventricular aneurysm protrudes during ventricular systole but not during diastole and consists of fibrous tissue with or without myocardial fibers. *(From Cabin HS, Roberts WC: Left ventricular aneurysm, intraaneurysmal thrombus and systemic embolus in coronary heart disease. Chest 77:586, 1980. By permission of The American College of Chest Physicians.)*

Almost 50 percent of patients with moderate or large aneurysms have symptoms of heart failure (with or without associated angina), approximately 33 percent have severe angina alone, and approximately 15 percent have symptomatic ventricular arrhythmias that may be intractable and life threatening.[807] Mural thrombi are found in almost half of patients with chronic left ventricular aneurysms and can be detected by angiography and two-dimensional echocardiography (see Chap. 7) . Systemic embolic events in patients with thrombi and left ventricular aneurysm tend to occur early after myocardial infarction. In the Mayo Clinic series of patients with chronic left ventricular aneurysm (documented at least 1 month after infarction), subsequent systemic emboli were extremely uncommon[808] (0.35 per 100 patient-years in patients not receiving anticoagulants).

DETECTION.

Clues to the presence of aneurysm include persistent ST segment elevations on the resting ECG (in the absence of chest pain)[809] and a characteristic bulge of the silhouette of the left ventricle on a chest roentgenogram. Marked calcification of the left ventricular silhouette may be present[810] (Fig. 37-32) . These findings, when clear-cut, are relatively specific, but they have limited sensitivity. Radionuclide ventriculography and two-dimensional echocardiography can demonstrate ventricular aneurysm more readily; the latter is also helpful in distinguishing between true and false aneurysms based on the demonstration of a narrow neck in relation to cavity size in the latter.[811] Color flow echocardiographic imaging is useful in establishing the diagnosis because flow "in and out" of the aneurysm as well as abnormal flow within the aneurysm can be detected, and subsequent pulsed Doppler imaging can reveal a "to-and-fro" pattern with characteristic respiratory variation in the peak systolic velocity. The use of transesophageal echocardiography and left-heart contrast agents in the assessment of pseudoaneurysms is being evaluated.[812] CT and magnetic resonance imaging are reliable noninvasive techniques for the identification of left ventricular aneurysms (Fig. 37-32 ; see Fig. 10-8) and screening for resectability.[813]

Tomographic three-dimensional echocardiographic calculation of left ventricular volume and systolic function compares favorably with the accuracy of magnetic resonance imaging and cineangiography and has the advantage of being less time consuming and less invasive; also, patient discomfort may be less.[814] However, biplane left ventriculography is still the most widely used method for outlining a true left ventricular aneurysm and assessing septal motion and the extent of residual functioning

myocardium. An assessment of the extent of stunned, hibernating but potentially viable, myocardium within the infarct zone is helpful in many patients, particularly those in whom the left ventricular aneurysm is less discrete.

LEFT VENTRICULAR ANEURYSMECTOMY.

True ventricular aneurysms do not rupture, and operative excision is carried out to improve the clinical manifestations, most often heart failure but sometimes also angina, embolization, and life-threatening tachyarrhythmias.[807] [815] Coronary revascularization is frequently performed along with aneurysmectomy, especially in patients in whom angina accompanies heart failure.

A large left ventricular aneurysm in a patient with symptoms of heart failure, particularly if angina pectoris is also present, is an indication for surgery. The operative mortality rate for left ventricular aneurysmectomy is approximately 10 percent (ranging from 0 to 19 percent),[815] [816] with rates of 6 and 7.2 percent reported in more recent series.[816] [817] Among 26 patients undergoing surgery between 1992 and 1994 with the new technique of endoventricular patchplasty, no operative mortality was reported.[817] Risk factors for early death include poor left ventricular function, recent myocardial infarction, the presence of mitral regurgitation, and intractable ventricular arrhythmias.[818] The presence of angina pectoris instead of dyspnea as the dominant preoperative symptom is a determinant of lower operative mortality.[817] Surgery carries a particularly high risk in patients with severe heart failure, a low-output state, and akinesis of the interventricular septum, as assessed echocardiographically.[803] Akinesis or dyskinesia of the posterior

Figure 37-32 Evaluation of an 83-year-old woman for chest discomfort. When she was about 50 years old, this woman had been hospitalized because of acute myocardial infarction of the anteroseptal wall. An electrocardiogram showed an abnormal image characteristic of anteroseptal cardiac aneurysm. A plain chest film *(A* and *B)* showed marked calcification on the left ventricular silhouette. A magnetic resonance image *(C)* of the heart showed thinning of the left ventricular wall. The patient's overall condition improved after treatment with isosorbide mononitrate and diuretics. *(From Nakajima O, Sano I, Akioka H: Marked calcified left ventricular aneurysm. Circulation 95:1974, 1997. By permission of the American Heart Association, Inc.)*

basal segment of the left ventricle and significant right coronary artery stenoses are additional risk factors.[803] Pseudoaneurysms rupture frequently and should therefore be resected on an urgent basis as soon as the diagnosis is established.[819]

Risk factors for late mortality following survival from surgery include incomplete revascularization, impaired systolic function of the basal segments of the ventricle and septum not involved by the aneurysm, the presence of a large aneurysm with a small quantity of residual viable myocardium, and the presence of severe cardiac failure as

the initial feature.[816] [817] [820]

Improvement in left ventricular function has been reported in survivors of resection of left ventricular aneurysms complicated by cardiac failure.[818] [821] By removing the abnormal mechanical burden, left ventricular aneurysmectomy has been associated with late improvement in overall systolic function and improvement in the performance of regional nonischemic myocardium in zones remote from the left ventricular aneurysm,[822] in addition to improvement in measures of ventricular relaxation and cardiovascular neuroregulatory mechanisms.[821] [823] A concomitant improvement in exercise performance and clinical symptoms may also occur, particularly in patients who have undergone complete revascularization. An early series of carefully selected patients documented a 10-year survival rate of 69 percent among patients undergoing left ventricular aneurysmectomy plus coronary revascularization in comparison with 57 percent after aneurysmectomy alone.

New surgical approaches to the repair of left ventricular aneurysms are designed to restore normal left ventricular geometry by using an alternative method of epicardial closure and/or an endocardial patch to divide the area of the aneurysm from the remainder of the ventricular cavity[824] [825] (Fig. 37-33) . Favorable clinical and hemodynamic results following the use of these newer techniques have been reported, with 5-year survival rates ranging from 73 to 87.5 percent[816] [820] and a corresponding improvement in hemodynamics and clinical symptoms. In one series, 88 percent of patients treated with the endoaneurysmorrhaphy technique were in New York Heart Association Class I or II after a mean follow-up of approximately 3.5 years.[826]

Mitral Regurgitation Secondary to Coronary Artery Disease (see also Chap. 46)

Mitral regurgitation is an important cause of heart failure in some patients with CAD. Rupture of a papillary muscle or the head of a papillary muscle usually causes severe acute mitral regurgitation in the course of acute myocardial infarction. The cause of chronic mitral regurgitation in patients with CAD is multifactorial, and the geometrical determinants are complex and include papillary muscle dysfunction from ischemia and fibrosis in conjunction with a wall motion abnormality and changes in ventricular shape in the region of the papillary muscle and/or dilatation of the mitral annulus.[827] [828] Enlargement of the mitral annulus at end systole is asymmetrical, with lengthening primarily involving the posterior annular segments and leading to prolapse of leaflet tissue tethered by the posterior papillary muscle and restriction of leaflet tissue attached to the anterior leaflet.[829] Most patients with chronic CAD and mitral regurgitation have suffered a previous myocardial infarction.

Clinical features that help identify mitral regurgitation secondary to papillary muscle dysfunction as the cause of acute pulmonary edema or the cause of milder symptoms of left-sided failure include a loud systolic murmur and demonstration of a flail mitral valve leaflet on echocardiography. In some patients with severe mitral regurgitation into a small "unprepared" left atrium, the murmur may be unimpressive or inaudible. Doppler echocardiography is helpful in assessing the severity of the regurgitation (see Chap. 7) .

As in mitral regurgitation of other causes, the left atrium is not usually greatly enlarged

unless mitral regurgitation has been present for more than 6 months. The ECG is nonspecific, and most patients have angiographic evidence of multivessel CAD.

In patients with posterior papillary muscle dysfunction resulting from acute myocardial infarction, reperfusion therapy with thrombolysis or PCI may be attempted initially because urgent surgery is often accompanied by high mortality. In patients with rupture of a papillary muscle or, more frequently, rupture of one or more heads of a papillary muscle, immediate surgery is required because the natural history after apparent stabilization with medical therapy is labile and unpredictable and sudden unexpected deterioration is frequent.[830]

In patients with severe mitral regurgitation, the indications for surgical correction, usually in association with coronary artery bypass, are fairly clear-cut. Mitral valve repair, as opposed to mitral replacement, is the procedure of choice, but the decision is based on the anatomical characteristics of the structures forming the mitral valve apparatus, the urgency of the need for surgery, and the severity of left ventricular dysfunction.[831] A more complex and frequently

Figure 37-33 Operative techniques used in left ventricular aneurysm repair. The figure depicts resection of the ventricular aneurysm enclosure by one of three methods. The conventional closure is illustrated on the left. The "T" closure and the endocardial patch techniques were developed in an attempt to restore normal left ventricular geometry. *(From Komeda M, David TE, Malik A, et al: Operative risks and long-term results of operation for left ventricular aneurysm. Ann Thorac Surg 53:22, 1992. By permission of The Society of Thoracic Surgeons.)*

encountered problem involves the indications for mitral valve surgery in patients undergoing coronary bypass surgery in whom the severity of mitral regurgitation is moderate. The decision is based partly on the presence or absence of structural abnormalities of the mitral apparatus and the amenability of the valve to repair. Intraoperative transesophageal echocardiography is invaluable in assessing the severity of regurgitation, the reparability of the valve, and the success of the integrity of the repair after discontinuation of cardiopulmonary bypass.[458]

The mortality associated with combined coronary bypass surgery and mitral valve placement in the 1997 Society of Thoracic Surgeons data base was 12.7 percent overall and 8.3 percent for patients undergoing an elective first procedure. For bypass surgery and mitral valve repair, mortality rates were 7.6 percent overall and 4.8 percent for patients undergoing an elective first procedure.[425] Predictors of early mortality include the need for replacement versus repair (in some but not all series) but, in addition, may include other variables such as age, comorbid conditions, the urgency of surgery, and left ventricular function.[831] [832] Late results are strongly influenced by the pathophysiological mechanisms underlying mitral regurgitation and are poorer in patients with regurgitation resulting from annular dilatation or restrictive leaflet motion

than in patients with chordal or papillary muscle rupture.[832] [833] It is encouraging that despite the relatively high operative mortality, late survival of hospital survivors is excellent. In patients with very poor left ventricular function and dilatation of the mitral annulus, mitral regurgitation can intensify the severity of left ventricular failure. In such patients, the risk of surgery is high and the benefits less obvious, and a trial of intensive medical therapy, including offload reduction to reduce left ventricular volume and the diameter of the annulus, may be worthwhile.

CARDIAC ARRHYTHMIAS (see also Chap. 25)

In some patients with CAD, cardiac arrhythmias are the dominant clinical manifestation of the disease. Various degrees and forms of ventricular ectopic activity are the most common arrhythmias in patients with CAD, but serious ventricular arrhythmias may be a major component of the clinical findings in other subgroups. Malignant ventricular arrhythmias in CAD may be dynamic, e.g., plaque rupture that causes acute ischemia, which results in polymorphic ventricular tachycardia or ventricular fibrillation.[834] A more frequent manifestation of ventricular arrhythmias in CAD occurs as a consequence of reentrant arrhythmias arising from fixed substrate composed of scar and residual viable myocardium.[835] In this situation, it is presumed that initially stable, sustained monomorphic ventricular tachycardia degenerates into ventricular fibrillation. The former situation is theoretically preventable by coronary revascularization alone, although for patients who have survived an out-of-hospital cardiac arrest, coronary revascularization alone is usually ineffective in preventing occurrences.[559] [836]

Surgical strategies for patients with CAD and ventricular tachycardia, in association with left ventricular aneurysms and/or myocardial scar, were directed primarily at removal of the extensive area of subendocardial scar tissue, with or without electrophysiological mapping.[837] [838] Surgical treatment of ventricular arrhythmias has declined markedly with the advent of the implantable cardioverter-defibrillator and, to a lesser extent, advances in electrophysiological mapping and catheter ablation. Recognition and management of patients with malignant ventricular arrhythmias and/or sudden cardiac death caused by chronic CAD are discussed in detail in Chapter 26 .

NONATHEROMATOUS CORONARY ARTERY DISEASE (see Table 35-1)

Although atherosclerosis is by far the most important cause of CAD, other conditions may also be responsible.[839] [840] The most common causes of nonatheromatous CAD resulting in myocardial ischemia are the syndrome of angina-like pain with normal coronary arteriograms, i.e., so-called syndrome X and Prinzmetal angina, both of which are discussed earlier in this chapter (see pp. 1324 and 1328).

Nonatheromatous CAD may result from other diverse abnormalities, including congenital abnormalities in the origin or distribution of the coronary arteries (see Chaps. 43 and 44) . The most important of these abnormalities are anomalous origin of a coronary artery (usually the left) from the pulmonary artery, origin of both coronary arteries from either the right or the left sinus of Valsalva, and coronary arteriovenous fistula. An anomalous origin of either the left main coronary artery or right coronary artery from the aorta with subsequent coursing between the aorta and pulmonary trunk

is a rare and sometimes fatal coronary arterial anomaly.[841]

In an autopsy study of 150 cases of sudden death in persons 35 years or younger, death was attributed to CAD in 48. In 16 of these cases, the disease was not atherosclerosis but attributable to abnormalities in the origin and course of the coronary arteries, including a deep intramyocardial course, ostial obstruction, an abnormal origin of the right or left coronary artery, or spontaneous dissection of a coronary artery. In one patient, effort-induced acute myocardial infarction was noted in the presence of an intramural coronary arterial trunk.[842]

Myocardial bridging causing systolic compression of the left anterior descending coronary artery is a well-recognized angiographic phenomenon of questionable clinical significance.

Several inherited connective tissue disorders are associated with myocardial ischemia (see Chap. 56) , including the Marfan syndrome (causing aortic and coronary artery dissection), Hurler syndrome (causing coronary obstruction), homocysteinuria (causing coronary artery thrombosis), Ehlers-Danlos syndrome (causing coronary artery dissection), and pseudoxanthoma elasticum (causing accelerated CAD). Kawasaki disease (the mucocutaneous lymph node syndrome) may cause coronary artery aneurysms and ischemic heart disease in children (see Chap. 45) .

Spontaneous coronary dissection is a rare cause of myocardial infarction and sudden cardiac death.[843] Chronic dissection manifested as congestive heart failure has been described. In one series, approximately 75 percent of cases were diagnosed at autopsy, and 75 percent occurred in women, half of which were associated with a postpartum state.[844] Some cases are associated with atherosclerosis. Hypertension has been postulated as a cause of multivessel spontaneous coronary dissection in some patients, and in others, no obvious cause has been identified. In the acute phase, thrombolytic therapy may be dangerous, but early angiography may identify patients who could benefit from stenting or bypass surgery.[845] In survivors of spontaneous coronary artery dissection, the subsequent 3-year mortality was 20 percent, but complete healing as defined angiographically may lead to a favorable outcome without intervention.[846]

Coronary vasculitis resulting from connective tissue diseases or autoimmune forms of vasculitis, including polyarteritis nodosa,[847] giant cell (temporal) arteritis,[848] and scleroderma, [849] is well described (see Chap. 67) . Coronary arteritis is seen at autopsy in about 20 percent of patients with rheumatoid arthritis but is rarely associated with clinical manifestations.[850] The incidence of CAD is increased in women with systemic lupus erythematosus.[851] In patients with systemic lupus erythematosus, CAD has been attributed to a vasculitis, immune complex-mediated endothelial damage, and coronary thrombosis from antiphospholipid antibodies,[851] [852] as well as accelerated atherosclerosis. Giant coronary artery aneurysm associated with systemic lupus erythematosus is an unusual manifestation that has been associated with the development of acute myocardial infarction despite therapy.[852] The antiphospholipid syndrome, which is characterized by arterial and venous thrombosis and is associated with the presence of antiphospholipid antibodies, may be associated with myocardial

infarction, angina, and diffuse left ventricular dysfunction.[853]

In rare cases, *Takayasu arteritis* (see Chap. 67) is associated with angina, myocardial infarction, and cardiac failure in patients younger than 40 years.[854] Coronary blood flow may be decreased by involvement of the ostia or proximal segments of the coronary arteries, but disease in distal coronary segments is rare.[855] The average age at the onset of symptoms is 24 years, and the event-free survival rate 10 years after diagnosis is approximately 60 percent.[854] Luetic aortitis may also produce myocardial ischemia by causing coronary ostial obstruction.

The occurrence of CAD and morbid cardiac events in young persons after mediastinal irradiation is highly suggestive of a cause-and-effect relationship.[856] [857] Pathological changes include adventitial scarring and medial hypertrophy with severe intimal atherosclerotic disease.[858] Radiation injury may be latent and may not be manifested clinically for many years after therapy. Contributory factors include higher doses than currently administered and the presence of cardiac risk factors.[859] Among patients without risk factors who receive an intermediate total dose of 30 and 40 Gy, the risk of cardiac death and myocardial infarction is low.[857]

Myocardial ischemia not caused by coronary atherosclerosis can also result from embolism, infective endocarditis (see Chap. 47) , implanted prosthetic cardiac valves (Chap. 46) , calcified aortic valves, mural thrombi, and primary cardiac tumors (Chap. 49) .

An interesting nonatherosclerotic myocardial ischemic syndrome has been described in workers in the nitrate industry, who apparently experience nitrate withdrawal symptoms on weekends. It is presumed to be secondary to coronary spasm in the absence of counterstimulation to the vasoconstriction that they undergo as an adaptation to the vasodilating actions of the high concentrations of nitrates to which they have been exposed.[860]

Cocaine, because of its widespread use, has become a well-documented cause of chest pain, myocardial infarction, and sudden cardiac death.[861] [862] In a population-based study of sudden death among persons 20 to 40 years old in Olmsted County over a 30-year period, a high prevalence of cocaine abuse was observed in the more recent cohort

of young adults who died suddenly.[863] The principal effects of cocaine are mediated by alpha-adrenergic stimulation, which causes an increase in myocardial O_2 demand and a reduction in O_2 supply because of coronary vasoconstriction.[862]

CARDIAC TRANSPLANT-ASSOCIATED CORONARY ARTERIOPATHY (see also Chap. 20) .

Worldwide, approximately 4500 patients undergo cardiac transplantation annually (2340 in the United States in 1998), and their survival has been extended by improved immunosuppression. Accelerated coronary atherosclerosis has become the principal cause of late death.[864] The link between chronic immune injury to the coronary endothelium of the donor heart and transplant CAD is unclear, but it is believed to be initiated by immunologically mediated damage, followed by intimal smooth muscle proliferation, accumulation of lipids in the vascular wall, and eventually, diffuse luminal narrowing.[865] Other suggested etiological factors include opportunistic infections (cytomegalovirus infection), immunosuppressive therapy, cyclosporine-induced endothelial injury, and dyslipidemia.[866]

By the time that the disease is diagnosed, it is well advanced, but its progression to myocardial infarction, sudden cardiac death, and diffuse left ventricular dysfunction may not be accompanied by chest pain or typical ECG changes. The diagnosis is usually made at coronary angiography, but this visualization technique may underestimate the severity or the extent of the disease.[867] Noninvasive approaches, including dobutamine stress echocardiography and stress thallium imaging, are promising tools that are being investigated.[868]

MANAGEMENT.

Management of cardiac transplant-associated arteriopathy includes retransplantation, PCI in selected patients with focal stenoses (although the incidence of subsequent restenosis is increased), and coronary bypass surgery; however, the latter is confined to a relatively few highly selected patients without distal involvement.[869] A preliminary study suggested that diltiazem may retard the reduction in coronary vessel diameter defined by quantitative angiography, but its clinical impact needs to be determined.[309] In comparison with dietary measures alone, a recent randomized trial demonstrated that the combination of a low-cholesterol diet and simvastatin after heart transplantation led to a significant reduction in cholesterol levels, a significantly higher long-term survival rate, and a lower incidence of accelerated graft vessel disease.[870] Among patients who were not treated with calcium channel blockers, ganciclovir, which is effective in preventing cytomegalovirus illness, appeared to decrease the incidence of CAD in the donor heart in comparison to placebo.

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GUIDELINES
MANAGEMENT OF CHRONIC ISCHEMIC HEART DISEASE

Thomas H. Lee

Multiple guidelines are relevant to the care of patients with chronic ischemic heart disease, including the 1999 guidelines developed by an American College of Cardiology/American Heart Association (ACC/AHA) task force.[1] These guidelines will be summarized, as well as the 1993 guidelines for percutaneous transluminal angioplasty[2] (PTCA) and 1999 guidelines for coronary artery bypass graft (CABG) surgery.[3]

According to the usual format of ACC/AHA guidelines, the appropriateness of various tests and procedures in different clinical settings was categorized into the following:

I.
Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

II.
Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure.

IIa.
Weight of evidence/opinion is in favor of usefulness/efficacy.

IIb.
Usefulness/efficacy is less well established by evidence/opinion.

III.
Conditions for which there is evidence and/or general agreement that the

procedure/treatment is no useful/effective and in some cases may be harmful.

Diagnosis

The ACC/AHA guidelines emphasize the importance of using clinical data to make a qualitative estimate of the patient's probability of coronary artery disease. Routine laboratory data that are considered appropriate (Class I) include hemoglobin, fasting glucose, a lipid profile, and resting electrocardiogram (ECG). Chest x-rays are considered appropriate for patients with signs or symptoms of cardiovascular disease but were considered to have uncertain appropriateness for other patients (Table 37-G-1) .

The exercise ECG is an appropriate first-line test for patients with an intermediate probability of coronary artery disease, including patients with complete right bundle branch block or less than 1 mm of ST depression at rest. Other technologies may be appropriate for patients whose ECG has mild ST depression in the setting of digoxin therapy or criteria for left ventricular hypertrophy or patients who had other ECG abnormalities described in Table 37-G-1 . The ACC/AHA guidelines indicate that exercise ECG should be the first-line test for women as well as men.

The ACC/AHA task force was not supportive of echocardiography as a routine test for diagnosis of the cause of acute chest pain unless the patient has a systolic murmur suggesting structural heart disease (Table 37-G-1) . The guidelines did, however, support the use of echocardiography to assess the extent or severity of ischemia when the study could be obtained during or shortly after chest pain.

Imaging during physical or pharmacological stress was considered to be appropriate (Class I) in patients at intermediate risk for coronary disease for whom exercise ECG was unlikely to be useful because of baseline ECG abnormalities. Exercise myocardial perfusion imaging was also considered an appropriate test for risk stratification of patients who had undergone prior revascularization with either PTCA or CABG. Pharmacological stress with adenosine or dipyridamole is appropriate for patients who are unable to exercise. Because of abnormal patterns of myocardial activation, stress echocardiography is *discouraged* as an imaging modality for patients with left bundle branch block.

Coronary angiography was not considered clearly appropriate for the diagnosis of chronic stable angina in most patients, except for those who had survived sudden cardiac death. Several patient subsets were considered possibly appropriate (Class II) for coronary angiography, such as patients whose diagnosis was still uncertain after noninvasive testing or those with an occupational requirement for a definitive diagnosis. Coronary angiography is, however, an important test in risk stratification (see below).

Risk Stratification

The ACC/AHA guidelines emphasize that most patients with stable angina do not need

routine echocardiography either for initial baseline studies or for reassessment (Table 37-G-1) . However, the ACC/AHA guidelines support the use of echocardiography or radionuclide angiography in patients with a history or ECG evidence of a prior myocardial infarction or symptoms or signs of congestive heart failure. Assessment of left ventricular function is also endorsed for patients with complex ventricular arrhythmias.

The ACC/AHA guidelines are supportive of exercise ECG as a first-line test for risk stratification or after a significant change in cardiac symptoms. Exceptions are made for patients in whom imaging technologies would provide more accurate information because of a history of CABG or PTCA or ECG abnormalities (see Table 37-G-1) . However, the guidelines do not provide strong support (Class IIb) for routine screening of patients 6 months after revascularization procedures.

Coronary angiography is supported as appropriate for patients with disabling angina despite medical therapy, as well as for those with high-risk exercise test results or signs of congestive heart failure and for survivors of sudden cardiac death. The ACC/AHA guidelines considered coronary angiography inappropriate in patients with Canadian Cardiovascular Society Class I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing (Table 37-G-1) .

Treatment

The ACC/AHA guidelines support the use of aspirin and beta blocker therapy in the absence of contraindications. Calcium antagonists or long-acting nitrates can be administered when beta blockers are contraindicated or ineffective. Short-acting dihydropyridine calcium antagonists are to be avoided.

Multiple efforts are endorsed to reduce the risk of progression of atherosclerosis. Lipid-lowering therapy is considered clearly appropriate (Class I) when low-density lipoprotein (LDL) cholesterol is greater than 130 mg/dl and possibly appropriate (Class IIa) when LDL is between 100 and 129 mg/dl. Also supported by the guidelines are interventions to treat hypertension according to Joint National Conference VI guidelines, cigarette smoking, diabetes, and obesity.

Guidelines for revascularization with CABG or PTCA are similar to those described for unstable angina (Table 37-G-2) . CABG is appropriate for patients with left main coronary artery disease, three-vessel disease, and subsets of patients with two-vessel disease. PTCA is considered appropriate for multivessel disease in patients who have normal left ventricular function and do not have diabetes. (See below for further information on appropriate indications for these procedures.)

FOLLOW-UP.

The same principles that define the appropriateness of the initial use of tests for patients with chronic stable angina characterize their use during follow-up in patients who have

new or worsening cardiovascular symptoms (see Table 37-G-1) . The guidelines are not supportive of annual treadmill exercise tests or other procedures in patients who have had no change in clinical status. For low-risk stable patients, the guidelines suggest that an interval of 3 years or longer between exercise tests may be appropriate.

Percutaneous Transluminal Coronary Angioplasty

The development of guidelines for PTCA is complicated by several trends, including technological innovations (e.g., stents), broadening of the patient population to which this procedure is applied, and lack of data identifying populations in which PTCA confers a survival advantage. As physicians have become more expert in performing this procedure, they have also become more ambitious, and PTCA is now frequently used for patients with acute myocardial infarction and patients with multivessel coronary artery disease. An additional reason for uncertainty over the optimal role for PTCA is that it is an alternative to more than one major strategy--medical therapy or CABG surgery. Hence, trials in which PTCA is directly compared with another strategy (e.g., CABG) do not address the full range of choices for clinicians.

Recent ACC/AHA guidelines for unstable angina[4] and chronic stable angina [1] are beginning to address the question of which patients should preferentially undergo PTCA or CABG. However, for many patients with chronic stable angina, clinical judgment remains the critical mechanism for deciding which procedure should be performed.

TABLE 37--G-1 -- ACC/AHA GUIDELINES FOR MANAGEMENT OF STABLE ANGINA

Issue	Class	Recommendation	Level of Evidence
History and physical examination	I	In patients with chest pain, a detailed symptom history, focused physical examination, and directed risk factor assessment should be performed. With this information, the clinician should estimate the probability of significant CAD (i.e., low, intermediate, high)	B
Initial laboratory tests for diagnosis	I	Hemoglobin	C
		Fasting glucose	C
		Fasting lipid panel, including total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol	C

ECG, chest x-ray, or electron beam computed tomography in the diagnosis of chronic stable angina	I	Rest ECG in patients without an obvious noncardiac cause of chest pain	B
		Rest ECG during an episode of chest pain	B
		Chest x-ray in patients with signs or symptoms of CHF, valvular heart disease, pericardial disease, or aortic dissection/aneurysm	B
	IIa	Chest x-ray in patients with signs or symptoms of pulmonary disease	B
	IIb	Chest x-ray in other patients	C
		Electron beam computed tomography	B
Diagnosis of obstructive CAD with exercise ECG testing without an imaging modality	I	Patients with an intermediate pretest probability of CAD based on age, gender, and symptoms, including those with complete right bundle branch block or <1 mm of ST depression at rest (exceptions are listed below in Classes II and III)	B
	IIa	Patients with suspected vasospastic angina	C
	IIb	Patients with a high pretest probability of CAD by age, gender, and symptoms	B
		Patients with a low pretest probability of CAD by age, gender, and symptoms	B
		Patients taking digoxin whose ECG has <1 mm of baseline ST segment depression	B
		Patients with ECG criteria for LV hypertrophy and <1 mm of baseline ST segment depression	B
	III	Patients with the following baseline ECG abnormalities:	
		Preexcitation (Wolff-Parkinson-White) syndrome	B
		Electronically paced ventricular rhythm	B
		More than 1 mm of ST depression at rest	B
		Complete left bundle branch block	B
		Patients with an established diagnosis of CAD from prior MI or coronary angiography; however, testing can	B

		Patients with an established diagnosis of CAD from prior MI or coronary angiography; however, testing can assess functional capacity and prognosis	B
Echocardiography for diagnosis of cause of chest pain in patients with suspected chronic stable angina pectoris	I	Patients with systolic murmur suggestive of aortic stenosis or hypertrophic cardiomyopathy	C
		Evaluation of extent (severity) of ischemia (e.g., LV segmental wall motion abnormality) when the echocardiogram can be obtained during pain or within 30 min after its abatement	C
	IIb	Patients with a click or murmur to diagnose mitral valve prolapse	C
	III	Patients with a normal ECG, no history of MI, and no signs or symptoms suggestive of heart failure, valvular heart disease, or hypertrophic cardiomyopathy	C
Cardiac stress imaging as the initial test for diagnosis in patients with chronic stable angina who are able to exercise	I	Exercise myocardial perfusion imaging or exercise echocardiography in patients with an intermediate pretest probability of CAD who have one of the following baseline ECG abnormalities:	
		Preexcitation (Wolff-Parkinson-White) syndrome	B
		More than 1 mm of ST depression at rest	B
		Exercise myocardial perfusion imaging or exercise echocardiography in patients with prior revascularization (either PTCA or CABG)	B
		Adenosine or dipyridamole myocardial perfusion imaging in patients with an intermediate pretest probability of CAD and one of the following baseline ECG abnormalities:	
		Electronically paced ventricular rhythm	C
		Left bundle branch block	B
	IIb	Exercise myocardial perfusion imaging and exercise echocardiography in patients with a low or high probability of CAD who have one of the following baseline ECG abnormalities:	
		Preexcitation (Wolff-Parkinson-White) syndrome	B

		Preexcitation (Wolff-Parkinson-White) syndrome	B
		More than 1 mm of ST depression	B
		Adenosine or dipyridamole myocardial perfusion imaging in patients with a low or high probability of CAD and one of the following baseline ECG abnormalities:	
		Electronically paced ventricular rhythm	
		Left bundle branch block	C
		Exercise myocardial perfusion imaging or exercise echocardiography in patients with an intermediate probability of CAD who have one of the following:	B
		Digoxin use with <1-mm ST depression on the baseline ECG	B
		LV hypertrophy with <1-mm ST depression on the baseline ECG	B
		Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography as the initial stress test in a patient with a normal rest ECG who is not taking digoxin	B
		Exercise or dobutamine echocardiography in patients with left bundle branch block	C

Cardiac stress imaging as the initial test for diagnosis in patients with chronic stable angina who are unable to exercise	I	Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with an intermediate pretest probability of CAD	B
		Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography in patients with prior revascularization (either PTCA or CABG)	B
	IIb	Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography in patients with a low or high probability of CAD in the absence of electronically paced ventricular rhythm or left bundle branch block	B
		Adenosine or dipyridamole myocardial perfusion imaging in patients with a low or a high probability of CAD and one of the following baseline ECG abnormalities:	
		Electronically paced ventricular rhythm	C
		Left bundle branch block	B
		Dobutamine echocardiography in patients with left bundle branch block	C

Coronary angiography to establish a diagnosis in patients with suspected angina, including those with known CAD who have a significant change in anginal symptoms	I	Patients with known or possible angina pectoris who have survived sudden cardiac death	B
	IIa	Patients with an uncertain diagnosis after noninvasive testing in whom the benefit of a more certain diagnosis outweighs the risk and cost of coronary angiography	C
		Patients who cannot undergo noninvasive testing because of disability, illness, or morbid obesity	C
		Patients with an occupational requirement for a definitive diagnosis	C
		Patients who by virtue of young age at onset of symptoms, noninvasive imaging, or other clinical parameters are suspected of having a nonatherosclerotic cause of myocardial ischemia (coronary artery anomaly, Kawasaki disease, primary coronary artery dissection, radiation-induced vasculoplasty)	C
		Patients in whom coronary artery spasm is suspected and provocative testing may be necessary	C
		Patients with a high pretest probability of left main or three-vessel CAD	C
	IIb	Patients with recurrent hospitalization for chest pain in whom a definite diagnosis is judged necessary	C
		Patients with an overriding desire for a definitive diagnosis and a greater than low probability of CAD	C
	III	Patients with significant comorbidity in whom the risk of coronary arteriography outweighs the benefit of the procedure	C
		Patients with an overriding personal desire for a definitive diagnosis and a low probability of CAD	C

Measurement of rest LV function by echocardiography or radionuclide angiography in patients with chronic stable angina	I	Echocardiography or radionuclide angiography to assess LV function in patients with a history of prior MI, pathological Q waves, or symptoms or signs suggestive of heart failure	B
		Echocardiography in patients with a systolic murmur suggesting mitral regurgitation to assess its severity and etiology	C
		Echocardiography or radionuclide angiography in patients with complex ventricular arrhythmias to assess LV function	B
	III	Routine periodic reassessment of stable patients for whom no new change in therapy is contemplated	C
		Patients with a normal ECG, no history of MI, and no symptoms or signs suggestive of CHF	B
Exercise testing for risk assessment and prognosis in patients with an intermediate or high probability of CAD	I	Patients undergoing initial evaluation (Exceptions are listed below in Classes IIb and III)	B
		Patients after a significant change in cardiac symptoms	
	IIb	Patients with the following ECG abnormalities:	
		Preexcitation (Wolff-Parkinson-White) syndrome	B
		Electronically paced ventricular rhythm	B
		More than 1 mm of ST depression at rest	B
		Complete left bundle branch block	B
		Patients who have undergone cardiac catheterization to identify ischemia in the distribution of a coronary lesion of borderline severity	C
		Postrevascularization patients who have a significant change in anginal pattern suggestive of ischemia	C
	III	Patients with severe comorbidity likely to limit life expectancy or prevent revascularization	C

Cardiac stress imaging as the initial test for risk stratification of patients with chronic stable angina who are able to exercise	I	Exercise myocardial perfusion imaging or exercise echocardiography to identify the extent, severity, and location of ischemia in patients who do not have left bundle branch block or an electronically paced ventricular rhythm and either have an abnormal rest ECG or are using digoxin	B
		Dipyridamole or adenosine myocardial perfusion imaging in patients with left bundle branch block or electronically paced ventricular rhythm	B
		Exercise myocardial perfusion imaging or exercise echocardiography to assess the functional significance of coronary lesions (if not already known) in planning PTCA	B
	IIb	Exercise or dobutamine echocardiography in patients with left bundle branch block	C
		Exercise, dipyridamole, or adenosine myocardial perfusion imaging or exercise or dobutamine echocardiography as the initial test in patients who have a normal rest ECG and who are not taking digoxin	B
	III	Exercise myocardial perfusion imaging in patients with left bundle branch block	C
		Exercise, dipyridamole, or adenosine myocardial perfusion imaging or exercise or dobutamine echocardiography in patients with severe comorbidity likely to limit life expectation or prevent revascularization	C

Cardiac stress imaging as the initial test for risk stratification of patients with chronic stable angina who are unable to exercise	I	Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography to identify the extent, severity, and location of ischemia in patients who do not have left bundle branch block or electronically paced ventricular rhythm	B
		Dipyridamole or adenosine myocardial perfusion imaging in patients with left bundle branch block or electronically paced ventricular rhythm	B
		Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography to assess the functional significance of coronary lesions (if not already known) in planning PTCA	B
	IIb	Dobutamine echocardiography in patients with left bundle branch block	C
	III	Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography in patients with severe comorbidity likely to limit life expectation or prevent revascularization	C

Coronary angiography for risk stratification in patients with chronic stable angina	I	Patients with disabling (CCS classes III and IV) chronic stable angina despite medical therapy	B
		Patients with high-risk criteria on noninvasive testing regardless of anginal severity	B
		Patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia	B
		Patients with angina and symptoms and signs of CHF	C
		Patients with clinical characteristics that indicate a high likelihood of severe CAD	C
	IIa	Patients with significant LV dysfunction (ejection fraction <45%), CCS class I or II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing	C
		Patients with inadequate prognostic information after noninvasive testing	C
	IIb	Patients with CCS class I or II angina, preserved LV function (ejection fraction >45%), and less than high-risk criteria on noninvasive testing	C
		Patients with CCS class III or IV angina, which with medical therapy improves to class I or II	C
		Patients with CCS class I or II angina but intolerance (unacceptable side effects) to adequate medical therapy	C
	III	Patients with CCS class I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing	C
		Patients who prefer to avoid revascularization	C

Pharmacotherapy to prevent MI and death and reduce symptoms	I	Aspirin in the absence of contraindications	A
		Beta blockers as initial therapy in the absence of contraindications in patients with prior MI	A
		Beta blockers as initial therapy in the absence of contraindications in patients without prior MI	B
		Calcium antagonists* or long-acting nitrates as initial therapy when beta blockers are contraindicated	B
		Calcium antagonists* or long-acting nitrates in combination with beta blockers when initial treatment with beta blockers is not successful	B
		Calcium antagonists* and long-acting nitrates as a substitute for beta blockers if initial treatment with beta blockers leads to unacceptable side effects	C
		Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina	C
		Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol >130 mg/dl, with a target LDL of <100 mg/dl	A
	IIa	Clopidogrel when aspirin is absolutely contraindicated	B
		Long-acting nondihydropyridine calcium antagonists* instead of beta blockers as initial therapy	B
		Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol of 100-129 mg/dl, with a target LDL of 100 mg/dl	B
	IIb	Low-intensity anticoagulation with warfarin in addition to aspirin	B
	III	Dipyridamole	B
		Chelation therapy	B

Treatment of risk factors	I	Treatment of hypertension according to Joint National Conference VI guidelines	A
		Smoking cessation therapy	B
		Management of diabetes	C
		Exercise training program	B
		Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol >130 mg/dl, with a target LDL of <100 mg/dl	A
		Weight reduction in obese patients with hypertension, hyperlipidemia, or diabetes mellitus	C
	IIa	Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol of 100-129 mg/dl, with a target LDL <100 mg/dl	B
	IIb	Hormone replacement therapy in postmenopausal women in the absence of contraindications	B
		Weight reduction in obese patients in the absence of hypertension, hyperlipidemia, or diabetes mellitus	C
		Folate therapy in patients with elevated homocysteine levels	C
		Vitamin C and E supplementation	B
		Identification and appropriate treatment of clinical depression	C
		Intervention directed at psychosocial stress reduction	C
	III	Chelation therapy	C
		Garlic	C
		Acupuncture	C

Revascularization with PTCA (or other catheter-based techniques) and CABG in patients with stable angina	I	CABG for patients with significant left main coronary disease	A
		CABG for patients with 3-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%)	A
		CABG for patients with 2-vessel CAD, with significant proximal LAD disease and either abnormal LV function (ejection fraction <50%) or demonstrable ischemia on noninvasive testing	A
		PTCA for patients with 2- or 3-vessel CAD and significant proximal LAD disease who have anatomy suitable for catheter-based therapy, have normal LV function, and do not have treated diabetes	B
		PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal LAD disease but with a large area of viable myocardium and high-risk criteria on noninvasive testing	B
		CABG for patients with 1- or 2-vessel CAD without significant proximal LAD disease who have survived sudden cardiac death or sustained ventricular tachycardia	C
		In patients with prior PTCA or CABG for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing	C
		PTCA or CABG for patients who have not been successfully treated by medical therapy and can undergo revascularization with acceptable risk	B
	IIa	Repeat CABG for patients with multiple saphenous vein graft stenoses, especially with significant stenosis of a graft supplying the LAD. It may be appropriate to use PTCA for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery	C
		Use of PTCA or CABG for patients with 1- or 2-vessel CAD without significant	B

		Use of PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal LAD disease but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing	B
		Use of PTCA or CABG for patients with 1-vessel CAD and significant proximal LAD disease	B
	IIb	Compared with CABG, PTCA for patients with 2- or 3-vessel CAD and significant proximal LAD disease who have anatomy suitable for catheter-based therapy and who have treated diabetes or abnormal LV function	B
		Use of PTCA for patients with significant left main coronary disease who are not candidates for CABG	C
		PTCA for patients with 1- or 2-vessel CAD without significant proximal LAD disease who have survived sudden cardiac death or sustained ventricular tachycardia	C
	III	Use of PTCA or CABG for patients with 1- or 2-vessel CAD without significant proximal LAD disease who have mild symptoms that are unlikely to be due to myocardial ischemia or who have not received an adequate trial of medical therapy and	C
		Have only a small area of viable myocardium or	
		Have no demonstrable ischemia on noninvasive testing	C
		Use of PTCA or CABG for patients with borderline coronary stenoses (50-60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing	C
		Use of PTCA or CABG for patients with insignificant coronary stenosis (<50% diameter)	C
		Use of PTCA in patients with significant left main coronary artery disease who are candidates for CABG	B

		Use of PTCA in patients with significant left main coronary artery disease who are candidates for CABG	B
Echocardiography, treadmill exercise testing, stress imaging studies, and coronary angiography during patient follow-up	I	Chest x-ray for patients with evidence of new or worsening CHF	C
		Assessment of LV ejection fraction and segmental wall motion in patients with new or worsening CHF or evidence of intervening MI by history or ECG	C
		Echocardiography for evidence of new or worsening valvular heart disease	C
		Treadmill exercise test for patients without prior revascularization who have a significant change in clinical status, are able to exercise, and do not have any of the ECG abnormalities listed below	C
		Stress imaging procedures for patients without prior revascularization who have a significant change in clinical status and are unable to exercise or have one of the following ECG abnormalities: Preexcitation (Wolff-Parkinson-White) syndrome Electronically paced ventricular rhythm More than 1 mm of rest ST depression Complete left bundle branch block	C C C C
		Stress imaging procedures for patients who have a significant change in clinical status and required a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results	C
		Stress imaging procedures for patients with prior revascularization who have a significant change in clinical status	C
		Coronary angiography in patients with marked limitation of ordinary activity (CCS class III) despite maximal medical therapy	C
	IIb	Annual treadmill exercise testing in patients who have no change in clinical	C

	IIb	Annual treadmill exercise testing in patients who have no change in clinical status, can exercise, have none of the ECG abnormalities listed above, and have an estimated annual mortality rate >1%	C
	III	Echocardiography or radionuclide imaging for assessment of LV ejection fraction and segmental wall motion in patients with a normal ECG, no history of MI, and no evidence of CHF	C
		Repeat treadmill exercise testing in <3 yr in patients who have no change in clinical status and an estimated annual mortality rate <1% on their initial evaluation, as demonstrated by one of the following:	C
		Low-risk Duke treadmill score (without imaging)	C
		Low-risk Duke treadmill score with negative imaging	C
		Normal LV function and a normal coronary angiogram	C
		Normal LV function and insignificant CAD	C
		Stress imaging procedures for patients who have no change in clinical status and a normal rest ECG, are not taking digoxin, are able to exercise, and did not require a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results	C
		Repeat coronary angiography in patients with no change in clinical status, no change on repeat exercise testing or stress imaging, and insignificant CAD on initial evaluation	C

Level of evidence: A=highest; B=intermediate; C=lowest

ACC/AHA=American College of Cardiology/American Heart Association; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CHF=congestive heart failure; CCS=Canadian Cardiovascular Society; ECG=electrocardiography; HDL=high-density lipoprotein; LAD=left anterior descending artery; LDL=low-density lipoprotein; LV=left ventricular; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty.

From Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). J Am Coll Cardiol 33:2092-2197, 1999. Reprinted with permission from the American College of Cardiology.

*Short-acting dihydropyridine calcium antagonists should be avoided.

An ACC/AHA task force published guidelines for PTCA in 1993[2] (new guidelines are being developed) that defined contraindications to *elective* angioplasty, including relative contraindications to coronary angiography. These guidelines stress that PTCA may be appropriate even in patients with these contraindications who are severely symptomatic and not candidates for CABG. *Absolute contraindications* included

1. Absence of a lesion that causes a 50 percent or greater reduction in coronary diameter
2. Presence of significant left main coronary disease unless this coronary distribution is protected by at least one nonobstructed bypass graft
3. Absence of a formal cardiac surgical program in the institution

Relative contraindications included

1. Conditions associated with an unacceptable risk of serious bleeding or thrombotic occlusion or a recently dilated vessel
2. Diffusely diseased saphenous vein grafts without a focal dilatable lesion
3. Diffusely diseased native coronary arteries with distal vessels suitable for bypass grafting
4. The vessel in question is the sole remaining vessel in the coronary circulation
5. Chronic total occlusions with clinical features suggesting a very low anticipated success rate
6. Borderline stenotic lesion (usually less than 50 percent stenosis)
7. Procedure proposed for a non-infarct-related artery in patients

with multivessel disease who are undergoing direct angioplasty for acute myocardial infarction

The ACC/AHA guidelines also considered anatomical features that increase the risk for abrupt closure (see Chap. 38) to be relative contraindications to PTCA. Because of the risk of such complications, the guidelines recommended that for all elective PTCA procedures, an experienced cardiovascular surgical team be present within the hospital to perform emergency CABG should the need arise. The AHA/ACC task force did not

consider formal surgical consultation mandatory before PTCA.

Under some circumstances, the AHA/ACC task force considered PTCA reasonable even if surgical back-up were not available. For patients with a high risk of acute myocardial infarction in whom thrombolytic therapy was contraindicated, emergency PTCA was "acceptable treatment" if the patient could not be transferred expeditiously to a center with surgical back-up. However, the guidelines noted that patients with unstable angina could and should usually be transferred to an institution with a cardiac surgical program before consideration of PTCA.

The experience of the operator is also a critical factor in determining the outcome of PTCA. Therefore, several task forces have provided recommendations for the minimum number of cases during PTCA training and for the minimum annual volume required to maintain competency.[5] [6] [7] The most recent statement from the ACC, published in 1998, concluded that the relationship between individual operator procedural volume and patient outcomes was statistically valid but complex.[7] These guidelines recommended that an institution performing PTCA have an activity level of at least 400 coronary procedures per year and that an institution performing fewer than 200 procedures per year consider discontinuing this service unless it is in a region that is underserved. Institutions offering coronary interventional services should have a physician-director with experience consisting of at least 500 procedures. The ACC statement indicated that individual operators should perform at least 75 procedures per year and that operators who perform 50 to 75 procedures per year should be very cautious in case selection. Ideally, the guidelines said, operators with annual procedural volumes below 75 should work only at institutions with an activity level greater than 600 procedures per year. Recommendations also included a "mentoring" relationship for low-volume operators with a highly experienced operator who has an annual procedural volume greater than 150 procedures per year.

Indications for PTCA

The 1993 AHA/ACC task force developed assessments of the appropriateness of PTCA in various clinical settings according to the same three classes used in other ACC/AHA guidelines.[2] These indications included consideration of the patient's coronary anatomy, symptomatic status, and the clinical syndrome.

SINGLE-VESSEL CORONARY DISEASE.

The ACC/AHA task force included different recommendations for patients with and without symptoms of coronary disease. For patients who were *asymptomatic* or only mildly symptomatic, regardless of whether they had received medical therapy, PTCA was considered appropriate (Class I) in those with a lesion resulting in a 50 percent or greater reduction in the diameter of a coronary artery that supplies a large area of viable myocardium if they also had evidence of myocardial ischemia induced by low levels of exercise (Bruce stage 1, or <4.0 METs, or a heart rate less than 100 beats/min) during noninvasive testing (see Table 37-10) . Other Class I indications for PTCA included prior cardiac arrest or sustained ventricular tachycardia in the absence of acute myocardial

infarction and the need to undergo major vascular surgery (such as aortic aneurysm repair, iliofemoral bypass, or carotid artery surgery) if patients had clinical evidence of ischemic heart disease.

In patients with less myocardium in jeopardy, the appropriateness of single-vessel angioplasty was less clear-cut. Indications for PTCA were considered equivocal (Class II) in patients whose stenotic coronary artery supplied a moderate- or large-sized area of viable myocardium if they had objective evidence of ischemia and had coronary anatomy suggesting that PTCA could be performed with a moderate likelihood of success and low risk of complications. PTCA was considered inappropriate (Class III) for patients with only a small area of viable myocardium at risk, no evidence of ischemia, or a moderate to high risk of complications.

For patients who are *symptomatic* from single-vessel coronary disease despite medical therapy, the ACC/AHA guidelines considered PTCA appropriate (Class I) even if only a moderate amount of myocardium was supplied by the stenosed vessel--if they showed evidence of ischemia despite medical therapy, had angina pectoris that was inadequately responsive to medical treatment, or were intolerant of medical therapy. "Inadequately responsive" indicates that the patient and physician agree that angina significantly interferes with the patient's occupation or ability to perform usual activities. All these patients should have at least a moderate likelihood of successful dilation and be at low or moderate risk for morbidity and mortality for PTCA to be considered clearly appropriate.

PTCA was considered to be of equivocal appropriateness (Class II) in patients with an increased risk of complications or failure of the procedure. The ACC/AHA guidelines did not support PTCA's appropriateness in patients with no or only a small area of myocardium at risk in the absence of disabling symptoms or in patients with a high risk of procedural failure or complications.

MULTIVESSEL CORONARY DISEASE.

For *asymptomatic* patients with multivessel disease, the AHA/ACC guidelines indicate that PTCA is reasonable (Class I) if dilation of one major coronary artery could lead to nearly complete revascularization and the chance of success was moderate or high. For PTCA to be considered appropriate in this population, patients should have the same clinical indications as for Class I in asymptomatic patients with single-vessel disease, including evidence of severe ischemia. The indications were less clear (Class II) if the amount of myocardium at risk was only moderate or if there were other coronary stenoses that affected a moderate amount of myocardium. PTCA was considered inappropriate if patients had only a small amount of viable myocardium at risk, had chronic total occlusions, or had a high risk of complications.

For symptomatic patients with multivessel coronary disease, appropriate (Class I) indications for PTCA were similar to those for symptomatic patients with single-vessel disease, except that these indications included patients who had lesions in two or more major arteries affecting at least moderately sized areas of viable myocardium. If these

patients had a moderate risk for complications or did not have objective evidence of myocardial ischemia, the appropriateness of PTCA was regarded as uncertain (Class II).

The ACC/AHA task force was also uncertain about the appropriateness of PTCA for patients with multivessel coronary disease and angina that was disabling despite medical therapy if these patients were poor candidates for surgery and were at moderate risk for complications from PTCA. The concern reflected in these guidelines is that PTCA might lead to abrupt closure of a coronary artery, thereby creating a dilemma in which the physicians must decide whether to send a poor surgical candidate for CABG.

Coronary Artery Bypass Graft Surgery

Guidelines for the use of CABG surgery were updated in 1999 by an ACC/AHA task force.[3] When compared with the 1991 guidelines for CABG from the ACC/AHA,[8] this revision reflects greater consideration of the impact of this procedure on relief of symptoms, as well as overall survival. For example, the authors of these guidelines considered CABG beneficial for younger patients without left ventricular dysfunction, even if no improvement in survival could be predicted, because CABG can be performed with low mortality in such patients and because their potential for resuming an active life style is high.

Indications (Table 37-G-2)

The 1999 update of the ACC/AHA guidelines designates an appropriateness class for patient subsets defined by major variables:

1. Symptomatic status
2. Severity of ischemia on noninvasive testing
3. Number of diseased coronary arteries
4. Involvement of the left main coronary artery
5. Involvement of the proximal left anterior descending coronary artery
6. Left ventricular function

In these guidelines, coronary stenosis is defined as a 50 percent or greater reduction in lumen diameter. Certain subsets of coronary anatomy have been found to have better prognoses with surgical than medical therapy and are therefore considered indications for CABG regardless of the patient's symptomatic status and severity of ischemia on noninvasive testing. In the ACC/AHA guidelines, CABG surgery is considered appropriate (Class I) for all patients with any of the following criteria:

1. Significant stenosis (>50 percent) of the left main coronary artery
2. Left main equivalent: significant (>70 percent) stenosis of the proximal left anterior descending coronary artery and proximal left circumflex artery

3. Three-vessel disease, especially if left ventricular function is reduced

TABLE 37--G-2 -- APPROPRIATENESS OF CABG FOR SPECIFIC PATIENT SUBSETS

Clinical Subset	Class I	Class IIa	Class IIb	Class III
Asymptomatic or mild angina	Significant left main coronary artery stenosis Left main equivalent: significant (70%) stenosis of the proximal LAD and proximal left circumflex artery Three-vessel disease	Proximal LAD stenosis with 1- or 2-vessel disease*	One- or 2-vessel disease not involving the proximal LAD	Other

Stable angina	Same as for patients with asymptomatic or mild angina, plus Two-vessel disease with significant proximal LAD stenosis and either an EF <0.50 or demonstrable ischemia on noninvasive testing One- or 2-vessel coronary artery disease without significant proximal LAD stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing Disabling angina despite maximal medical therapy	Proximal LAD stenosis with 1-vessel disease* One- or 2-vessel coronary artery disease without significant proximal LAD stenosis but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing	None	One- or 2-vessel disease not involving significant proximal LAD stenosis in patients who have mild symptoms that are unlikely to be due to myocardial ischemia or who have not received an adequate trial of medical therapy and Have only a small area of viable myocardium or Have no demonstrable ischemia on noninvasive testing Borderline coronary stenoses (50-60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing Insignificant coronary

				noninvasive testing Insignificant coronary stenosis (<50% diameter reduction)
Unstable angina/non-Q-wave MI	Significant left main coronary artery stenosis Left main equivalent: significant (70%) stenosis of the proximal LAD and proximal left circumflex artery Ongoing ischemia not responsive to maximal nonsurgical therapy	Proximal LAD stenosis with 1- or 2-vessel disease**	One- or 2-vessel disease not involving the proximal LAD	
ST segment elevation (Q wave) MI	None	Ongoing ischemia/infarction not responsive to maximal nonsurgical therapy	Progressive LV pump failure with coronary stenosis compromising viable myocardium outside the initial infarct area Primary reperfusion in the early hours (6 to 12 hr) of an evolving MI with ST segment elevation	Primary reperfusion late (12 hr) in evolving MI with ST segment elevation without ongoing ischemia

Poor LV function	Significant left main coronary artery stenosis Left main equivalent: significant (70%) stenosis of the proximal LAD and proximal left circumflex artery Proximal LAD stenosis with 2- or 3-vessel disease	Poor LV function with significant viable, noncontracting, revascularizable myocardium without any of the aforementioned anatomical patterns		Poor LV function without evidence of intermittent ischemia and without evidence of significant revascularizable, viable myocardium
Life-threatening ventricular arrhythmias	Left main coronary artery stenosis Three-vessel coronary disease	Bypassable 1- or 2-vessel disease causing life-threatening ventricular arrhythmias Proximal LAD disease with 1- or 2-vessel disease		Ventricular tachycardia with scar and no evidence of ischemia
After failed PTCA	Ongoing ischemia or threatened occlusion with significant myocardium at risk Hemodynamic compromise	Foreign body in crucial anatomical position Hemodynamic compromise in patients with impairment of coagulation system and without previous sternotomy	Hemodynamic compromise in patients with impairment of coagulation system and previous sternotomy	Absence of ischemia Inability to revascularize because of target anatomy or no-reflow state

With previous CABG	Disabling angina despite maximal noninvasive therapy	Bypassable distal vessel(s) with a larger area of threatened myocardium by noninvasive studies	Ischemia in the non-LAD distribution with a patent IMA graft to the LAD supplying functioning myocardium, without an aggressive attempt at medical management and/or percutaneous revascularization

CABG=coronary artery bypass grafting; EF=ejection fraction; IMA=internal mammary artery; LAD=left anterior descending artery; LV=left ventricular; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty.

From Eagle KA, Guyton RA, Davidoff R, et al: ACC/AHA guidelines for coronary artery bypass graft surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 34:1262-1347, 1999.

*Becomes Class I if extensive ischemia is documented by noninvasive study and/or the left ventricular ejection fraction is less than 50%.

Becomes Class I if there is a large area of viable myocardium and high-risk criteria on noninvasive testing.

Becomes Class I if the arrhythmia is resuscitated sudden cardiac death or sustained ventricular tachycardia.

CABG is considered appropriate in patients with one or more diseased vessels if they have a large area of viable myocardium and high-risk findings on noninvasive testing. The guidelines recommend a lower threshold for surgery in patients with proximal stenoses of the left anterior descending coronary artery than in other patients with one- or two-vessel disease, particularly if they have extensive evidence of ischemia on noninvasive studies or if they have a left ventricular ejection fraction less than 50 percent. The guidelines assume that surgery can be performed with acceptable risk. They also assume that patients' anginal symptoms are typical; if not, objective evidence of ischemia should be obtained.

ASYMPTOMATIC OR MILD ANGINA.

The ACC/AHA task force considered CABG appropriate for patients with no or only mild symptoms even if they had only one- or two-vessel disease as long as they also had evidence of large amounts of myocardium in jeopardy on noninvasive testing. Even in the absence of markedly positive noninvasive tests for ischemia, patients with one- or two-vessel disease were considered to have uncertain (Class II) appropriateness for CABG. These guidelines therefore do not explicitly label as inappropriate any indications for CABG in patients with coronary artery disease. Since these patients are, by definition, free of disabling symptoms, the goal of surgery in this population is to prolong life. Class I subsets represent the groups in which survival benefits are most likely to be realized.

STABLE ANGINA.

For patients with stable mild angina, indications for surgery are based on the likelihood of improving survival and on the probability of relieving life-threatening symptoms. Therefore, the ACC/AHA task force concluded that clearly appropriate indications for CABG in this population should include the same factors as for asymptomatic patients, as well as disabling angina. For patients with chronic stable angina and only moderate amounts of myocardium in jeopardy from ischemia on noninvasive stress testing, CABG was considered to be of uncertain appropriateness (Class IIa).

UNSTABLE ANGINA/NON-Q WAVE MYOCARDIAL INFARCTION.

The indications for CABG in these patients include those for patients with no or stable angina symptoms but reflect uncertainty about the optimal timing of surgery. The guidelines recommend stabilization with aggressive medical therapy if possible before proceeding to CABG.

ST SEGMENT ELEVATION (Q WAVE) MYOCARDIAL INFARCTION.

For patients with ST segment (Q wave) acute myocardial infarction, the ACC/AHA guidelines discourage the use of CABG in favor of thrombolytic therapy or coronary angioplasty. The guidelines recognize that CABG is warranted in certain conditions, such as the presence of left main stenosis, severe three-vessel disease, associated valve disease, and anatomy unsuitable for other forms of therapy. Otherwise, surgery is most likely to be appropriate when patients have not responded to maximal nonsurgical therapy (Class IIa). Recommendations on the optimal timing for repair of the mechanical complications of acute myocardial infarction (e.g., ventricular septal defect) were not included in these guidelines.

IMPAIRED LEFT VENTRICULAR FUNCTION.

CABG is considered an appropriate or potentially appropriate strategy for the management of patients with impaired left ventricular ejection fractions because of evidence that ventricular dysfunction may be due to viable but hibernating myocardium in patients with severe multivessel disease. The guidelines consider surgery to be especially appropriate if the patient has clinical evidence of intermittent ischemia and minimal or no congestive heart failure. In patients with clinical heart failure, the decision to operate should be based on objective evidence of hibernating myocardium.[9] [10]

LIFE-THREATENING VENTRICULAR ARRHYTHMIAS.

CABG can suppress arrhythmia induction in patients with ventricular arrhythmias, particularly when an ischemic etiology for the arrhythmia can be documented. However, because multiple other factors can contribute to the development of life-threatening ventricular arrhythmias, such as reentry pathways in scarred myocardium, concomitant insertion of an implantable cardioverter-defibrillator may be necessary for many patients who are candidates for CABG.

FAILED PTCA.

The decision to perform CABG after failed PTCA must consider a variety of factors, including the mechanism of the failed procedure, the potential to improve the situation surgically, the extent of myocardium in jeopardy, and the patient's ability to tolerate CABG. Surgery is clearly *appropriate* when patients have or are in danger of hemodynamic compromise or when a foreign body such as an undeployed stent must be retrieved. However, CABG is *inappropriate* when patients do not have active ischemia or when CABG is unlikely to lead to revascularization of the myocardium in jeopardy.

AFTER PRIOR CABG.

Reoperation after prior CABG is associated with increased risk and lower rates of relief of symptoms. Therefore, repeat CABG should be reserved for relief of disabling symptoms or clear evidence of life-threatening amounts of myocardium at risk. In patients with functioning internal mammary artery grafts to the left anterior descending artery, the potential loss of this graft with any repeat CABG is a significant disincentive to pursue this strategy.

Recommended Management Strategies

The ACC/AHA guidelines also offer recommendations on the evaluation and management of several specific issues before, during, and after CABG (Table 37-G-3) .

Among interventions aimed at reducing neurological damage after CABG is screening for carotid artery stenoses, which are often asymptomatic. Although the guidelines do not

TABLE 37--G-3 -- PROVEN MANAGEMENT STRATEGIES TO REDUCE PERIOPERATIVE AND LATE MORBIDITY AND MORTALITY

Timing	Class Indication	Intervention	Comments
Preoperative			
Carotid screening	I	Carotid duplex ultrasound in a defined population	Carotid endarterectomy if stenosis 80%
Perioperative			
Antimicrobials	I	Prophylactic antimicrobials	
Antifibrinolytics	IIa	Aprotinin in selected groups	Significant reduction in blood transfusion requirements
Antiarrhythmics	I	Beta blockers to prevent postoperative atrial fibrillation	Propafenone or amiodarone are alternatives if beta blockers are contraindicated
Antiinflammatory drugs	IIa	Minimize diffuse inflammatory response to cardiopulmonary bypass	
Postoperative			
Antiplatelets	I	Aspirin to prevent early vein graft attrition	Ticlopidine or clopidogrel are alternatives if aspirin is contraindicated
Lipid-lowering therapy	I	Cholesterol-lowering agent plus low-fat diet if low-density lipoprotein cholesterol >100 mg/dl	3-Hydroxy-3-methylglutaryl/coenzyme A reductase inhibitors preferred if elevated low-density lipoprotein is major aberration

Smoking cessation	I	Smoking cessation education and possibly counseling and pharmacotherapy

From Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). J Am Coll Cardiol 33:2092-2197, 1999. Reprinted with permission from the American College of Cardiology.

explicitly call for all patients to undergo such screening, they note that many centers screen all those 65 years or older. Other patients who should undergo carotid artery ultrasound screening include those with a prior history of cerebrovascular disease.

Aspirin for the first year after CABG is considered the drug of choice for prophylaxis against early saphenous graft closure from thrombus; most patients continue this therapy indefinitely to reduce the risk for myocardial infarction. Patients with LDL cholesterol levels above 100 mg/dl warrant dietary and nondietary interventions to improve their lipid profile. Smoking cessation counseling should also be a routine part of care. The guidelines also indicate that cardiac rehabilitation should be offered to all eligible patients.

ORGANIZATIONAL CONSIDERATIONS.

The ACC/AHA guidelines noted studies suggesting that survival after CABG is worse when performed at institutions or by operators performing a low volume of procedures annually. The guidelines commented that data support close monitoring of institutions or individuals performing fewer than 100 cases annually.

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Chapter 38 - Percutaneous Coronary and Valvular Intervention

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The use of percutaneous coronary intervention (PCI) in patients with ischemic coronary artery disease (CAD) has expanded dramatically over the past two decades. More than 650,000 patients underwent PCI in 1999 in the United States, far exceeding the number of patients undergoing coronary artery bypass graft surgery (CABG). Continual technological improvements (e.g., stents, atherectomy and thrombectomy devices), refinements in periprocedural adjunctive pharmacology (e.g., glycoprotein IIb-IIIa [GP IIb-IIIa] inhibitors), and a better understanding of early and late outcomes in patients with comorbidities have fostered the expanded use of PCI as definitive therapy for ischemic CAD.

This chapter will review (1) the current methods used for PCI, including conventional balloon angioplasty and new coronary devices; (2) the procedural outcomes and complication rates obtained with contemporary PCI methods; (3) the periprocedural pharmacological strategies to reduce acute complications and restenosis after PCI; and (4) recommendations for coronary revascularization in patients with ischemic CAD, with consideration of the alternatives of medical therapy, PCI, and CABG. A discussion of

the current issues in patient selection, technical performance, and outcomes associated with percutaneous mitral and aortic valvuloplasty is also included.

HISTORICAL PERSPECTIVE

Balloon angioplasty, or percutaneous transluminal coronary angioplasty (PTCA), was first performed by Andreas Gruentzig in 1977 with the use of a prototype, fixed-wire balloon catheter.[1] The procedure was initially limited to patients with symptomatic CAD who had focal lesions in proximal coronary vessels and was used as an alternative to CABG.[1] Because of an objective reduction in stenosis severity and consistent improvement in clinical ischemia with this novel method,[2] the number of patients treated with balloon PTCA expanded dramatically over the next decade.[3] Operator experience and equipment design also evolved rapidly, with a transition from poorly steerable, fixed-wire balloon dilatation catheters to highly steerable, over-the-wire, and rapid-exchange balloon dilatation systems. These catheter designs resulted in more flexible, trackable, and lower-profile balloon dilatation systems and allowed the expansion of PCI to a broader spectrum of patients, such as those with multivessel disease, "high-risk" anatomy, reduced left ventricular function, and other serious comorbid medical conditions.[3]

It soon became apparent that two major issues limited the widespread use of balloon PTCA in patients with symptomatic CAD. Abrupt vessel closure resulting from angioplasty-induced dissection and thrombus formation occurred in 6.8 to 8.3 percent of cases,[4] [5] [6] [50A] largely unpredictable in individual patients despite the description of several predisposing factors in a number of series.[7] [8] [9] [10] Although in-laboratory abrupt vessel closure was reversible in most patients, emergency CABG was occasionally (3 to 5 percent of cases) required to relieve ongoing transmural ischemia resulting from catheter-based complications. In some cases, the urgency of surgical revascularization mandated that saphenous vein grafts (SVGs) be used instead of the preferred arterial conduits. The second major limitation of balloon PTCA was the development of restenosis, either clinically manifested by symptom recurrence or identified as recurrent arterial narrowing by routine repeat angiography. The pathology of restenosis has remained poorly understood, and pharmacological agents have not consistently reduced its occurrence.

A number of new coronary devices were developed in the early 1990s to improve upon the early and late procedural outcomes achieved with balloon PTCA. These novel methods were designed to remove (e.g., directional, rotational, or extraction atherectomy), ablate (e.g., excimer laser angioplasty), or scaffold (e.g., stents) atherosclerotic plaque. Randomized clinical trials have shown that some devices (e.g., stents) resulted in better early and late clinical outcome while others (e.g., excimer laser angioplasty) imparted no incremental clinical benefit and were potentially detrimental in comparison to balloon PTCA.

Given these devices' diverse mechanisms of benefit and their niche application in selected patients, it became apparent that a "lesion-specific" approach to coronary angioplasty was required, with the specific type of revascularization tailored to the precise characteristics of the vessel wall pathology. Coronary angioplasty then

encompassed the use of both balloons and new devices, and the generic term *percutaneous coronary intervention* was introduced.

BALLOON PTCA

Balloon PTCA expands the coronary lumen by stretching and tearing the atherosclerotic plaque and vessel wall and, to a lesser extent, by redistributing atherosclerotic plaque along its longitudinal axis.[11] [12] There is no evidence that balloon PTCA compresses atherosclerotic plaque.

TECHNICAL ASPECTS.

Balloon PTCA is performed by over-the-wire, rapid-exchange, or fixed-wire balloon dilatation systems. A 1.0 to 1.1:1.0 balloon-to-artery ratio is optimal for balloon size selection; higher ratios are associated with complications, and lower ones predispose to restenosis.[13] Although "stand-alone" balloon PTCA is usually (>80 percent) effective in improving ischemic symptoms, it is limited by substantial early elastic recoil, which results in an average 30 to 35 percent residual stenosis. On occasion, propagation of a coronary dissection and superimposed platelet thrombus formation after balloon PTCA result in early complications, including abrupt vessel closure. An "optimal" angiographic result (<20 percent residual stenosis) is obtained in less than 25 percent of patients after balloon PTCA but is associated with a favorable late clinical outcome. Documentation of an "optimal" anatomical *and* physiological result with balloon PTCA requires the addition of Doppler flow measurements[14]

or determination of transstenosis pressure gradients (e.g., fractional flow reserve[15]) (see Chap. 12) . In a prospective study of 225 patients with an angiographically successful result after balloon PTCA, postprocedural distal coronary flow reserve and percent diameter stenosis were correlated with symptoms and the need for target lesion revascularization (TLR) 1 and 6 months later.[14] Distal coronary flow reserve of 2.5 or higher and residual percent diameter stenosis of 35 or less after balloon PTCA identified lesions with lower rates of 6-month symptom recurrence (23 vs. 47 percent; p=0.005), need for reintervention (16 vs. 34 percent; p=0.024), and restenosis (16 vs. 41 percent; p=0.002) when compared with patients who did not meet these criteria.[14]

Assessment of Outcome.

A number of indices have been used to assess both early and late procedural outcomes. *Anatomical* (or *angiographic*) *success* has been defined as achieving smaller than 50 percent residual diameter stenosis with Thrombolysis in Myocardial Infarction (TIMI) 3 flow (see Chap. 12) after balloon PTCA,[16] with or without a 20 percent or greater improvement in diameter stenosis.[3] Visually determined angiographic success rates may overestimate the results provided by more quantitative angiographic measurements by 10 to 20 percent, although visual assessment by investigators has

been correlated with clinical outcomes in at least one study.[17] *Procedural success* is generally defined as angiographic success without the occurrence of major complications (death, myocardial infarction, or CABG)[16] [18] either during the index hospitalization or within the 30 days of the procedure.[19] Periprocedural vessel closure is defined as *abrupt* (TIMI 0 or 1 flow), *subacute* (abrupt closure occurring after the patient leaves the catheterization laboratory but within 30 days of the procedure), and *threatened* (presence of two or more of the following: angina; ischemic electrocardiographic changes; residual diameter stenosis greater than 50 percent; National Heart, Lung, and Blood Institute [NHLBI] type B or C dissection, with length greater than 8 mm; or NHLBI type D, E, or F dissection or deteriorating angiographic appearance with TIMI flow of 0 to 2). (See Chapter 12 for definitions of TIMI flow grades and NHLBI dissection types.)

Procedure-induced non-Q-wave myocardial infarction, as defined by an elevation in creatine phosphokinase isoenzyme (CPK-MB) of three times normal or higher,[18] [20] [21] occurs in 5 to 10 percent of procedures, [20] [22] but its causal relationship to late mortality is unclear.[22] [23] *Clinical success* is defined as procedural success without the need for urgent repeat PCI or surgical revascularization within the first 30 days of the procedure.[18]

INITIAL CLINICAL RESULTS.

Procedural success rates after balloon PTCA have progressively improved over the past 20 years (Table 38-1) . An 88 percent angiographic success rate was obtained in patients with multivessel CAD enrolled in the 1988-1991 Bypass Angioplasty Revascularization Investigators (BARI) Trial, but major complications were frequent and included death (1.1 percent), Q wave myocardial infarction (2.1 percent), and CABG (6.3 percent).[26] Major complications after balloon PTCA in other registry series include in-hospital death (0.9 to 3.5 percent), Q wave myocardial infarction (1.0 to 1.7 percent), emergency CABG (2.1 to 6.0 percent) and stroke (<0.5 percent).[33] Minor complications after balloon PTCA include acute or subacute vessel closure requiring urgent repeat balloon PTCA, coronary dissection, sidebranch occlusion, ventricular arrhythmias, vascular access complications, renal insufficiency, coronary perforation, and rarely, cardiac tamponade.

The recent availability of "bailout" coronary stents has reduced the emergency CABG rate after balloon PTCA to less than 1 percent.[34] In one series reporting recent procedural outcomes in 34,752 procedures performed in Northern New England Cardiovascular Group hospitals, adjusted clinical success rates increased from 88.2 percent in 1990 to 1993 to 91.9 percent in 1995 to 1997 (p<0.001). [35] With the combination of balloon PTCA and new devices, higher (95 to 99 percent) procedural success rates are now reported, particularly in women.[36]

Early procedural outcome after balloon PTCA has been correlated with a number of clinical, angiographic, and procedural factors identified in the periprocedural period.[7] [8] [24] [33] *Clinical factors* include age, unstable and Canadian Cardiovascular Society (CCS) Class IV angina, congestive heart failure, cardiogenic shock, renal insufficiency, and preprocedural instability requiring intraaortic balloon pump support, among other

factors.[33] *Anatomical variables* include multivessel CAD, presence of thrombus, SVG intervention, and American College of Cardiology/American Heart Association (ACC/AHA) type C lesion morphology,[16] [33] including chronic total coronary occlusion. *Procedural factors* also affect procedure outcomes, including a higher final percent diameter stenosis, smaller minimal lumen diameter, and the presence of a residual dissection or transstenotic pressure gradient (see Chap. 12 for definitions of ACC/AHA lesion types). Procedural mortality is associated with balloon PTCA of arteries subtending 50 percent or more of the myocardium, a left ventricular ejection fraction less than 25 percent, a more severe preprocedural percent diameter stenosis, multivessel CAD, and female gender, among other factors.[37] [38] These latter factors indicate a greater risk for cardiovascular collapse should abrupt vessel closure occur.[39]

LATE CLINICAL OUTCOME.

Clinical events after balloon PTCA are attributable to arterial renarrowing at the PTCA site, progression or instability of atherosclerotic disease at remote sites, or both.[40] These processes can be partially distinguished by the time of occurrence of the event--with angiographic and clinical restenosis generally developing within 6 to 9 months after balloon PTCA[41] [42] and death, myocardial infarction, and progression of atherosclerosis occurring with a low, but constant hazard (1 to 2 percent risk per year) indefinitely after the procedure.

Predictors of higher risk of all-cause late mortality include advanced age,[43] reduced left ventricular function or congestive heart failure,[43] presence of diabetes mellitus,[27] [43] female gender,[44] number of diseased vessels, [43] [45] inoperable disease,[43] or severe concomitant disease.[43] In patients undergoing balloon PTCA, a 95 percent 10-year survival rate was reported in those with single-vessel CAD and an 81 percent 10-year survival rate in those with multivessel CAD.[45] Five-year cardiac mortality rates for patients enrolled in the PTCA Registry were 2.8 percent in patients with single-vessel disease, 6.1 percent in patients with two-vessel disease, and 9.9 percent in patients with three-vessel disease.[43] Higher 9-year mortality rates have also been reported in diabetic patients (35.9 vs. 17.9 percent in nondiabetic patients; $p<0.01$).[46]

The risk of restenosis after balloon PTCA is influenced by *clinical factors*, such as diabetes mellitus, unstable angina, acute myocardial infarction, and prior restenosis, by *anatomical factors*, such as total occlusions, proximal left anterior descending artery lesions, smaller vessel size, long lesions, and lesions involving an SVG, and by *procedural factors*, such as the final minimal lumen diameter or percent diameter stenosis. Exposure to infectious agents may also predispose to the development of restenosis.[47]

INDICATIONS FOR BALLOON PTCA.

A provisional strategy consisting of balloon PTCA with "bailout" (or "provisional") stenting for lesions with abrupt or threatened closure or suboptimal (>40 percent) residual stenosis may be chosen as an alternative to primary stenting in patients with vessel size 2.75 mm or greater and lesion length less than 25 mm, although the advantages of this approach have not been documented in randomized trials.

Provisional balloon PTCA may be preferred over primary stenting in small (<2.75 mm) vessels, long (
25 mm) lesions, anastomotic stenoses in SVGs, and others lesions deemed "high risk" for coronary stenting.

CORONARY ATHERECTOMY

Atherectomy devices provide symptomatic relief in patients with CAD by two primary mechanisms: (1) removal or ablation of the atherosclerotic plaque[48] and (2) improvement in vessel wall compliance by plaque fracture and excision.[49] The primary advantage of atherectomy over balloon PTCA is that a larger final minimal lumen diameter can be

TABLE 38-1 -- IN-HOSPITAL OUTCOMES ASSOCIATED WITH BALLOON PTCA OVER TI

VARIABLE	NHLBI-I	NHLBI-II	MAPS	MAPS	BARI	BOAT PTCA ARM	STRESS PTCA ARM	BENESTENT II PTCA ARM
Years of entry	1977-81	1985-86	1986-87	1991	1989-92	1994-95	1991-93	1995-96
Number of patients	1155	1802	400	200	915	492	203	413
New device use	No	No	No	Yes	No	"Bailout"	"Bailout"	"Bailout"
Baseline factors								
Mean age (yr)	54	58	58	62	62	58	60	50
Women (%)	25	26	29	30	27	24	27	23
Diabetes mellitus	9	14	19	25	19	14	16	13
Unstable angina (%)	37	49	48	51	63	NA	48	45
Multivessel disease (%)	26	53	100	100	100	NA	32	NA
Angiographic success (%)	68	91	NA	92	88	NA	92.6	99
Procedure success (%)	61	78	83.5	90	80	87	89.6	96
In-hospital complications	NA	NA	NA	NA	NA	3.3	7.9	7.0
Death (%)	1.2	1.0	1.0	1.0	1.1	0	1.5	0

Q wave infarction (%)	4.9	4.3	2.0	1.5	2.1	1.2	3.0	1.2
Emergency CABG (%)	5.8	3.4	5.5	1.0	6.3	2.0	4.0	0.7
Late clinical outcome	5 yr	5 yr	1 yr	1 yr	5.4 yr	1 yr	240 d	12 mo
Any event	NA	NA				31.1	23.8	23.2
Death (%)	4.9	8.3	NA	NA	13.7	1.6	0.4	1.0
Q wave MI (%)	9.7	9.1	NA	NA	21.3	1.6	0.5	1.9
Revascularization (%)	32.1	38.8	NA	NA	54.5	19.7	15.4	18.9
Repeat PTCA	22.5	30.9	16.2	13.2	23.2	NA	11.4	9.4
CABG	15.5	13.4	13.4	8.1	20.5	NA	4.5	1.9

CABG=coronary artery bypass graft; MI=myocardial infarction; NA=not available; PTCA=percutaneou transluminal coronary angioplasty.

Data from National Heart, Lung, and Blood Institute (NHLBI) Study I and II[3] ; Multivessel Angioplasty Study (MAPS) Group[24] [25] ; Bypass Angioplasty Revascularization Investigators (BARI)[26] [27] [28] [263A] ; Versus Optimal Atherectomy Trial (BOAT)[29] ; Stent Restenosis Study (STRESS) Investigators[30] ; Be Netherlands Stent (BENESTENT) II Trial[31] ; Cutting Balloon Angioplasty. [32]

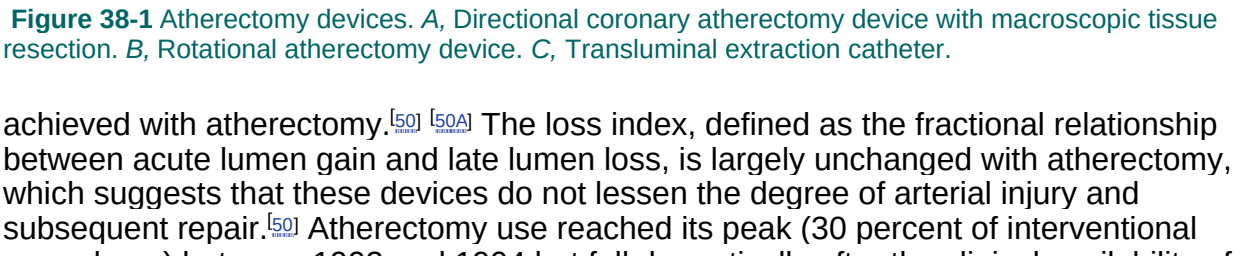

Figure 38-1 Atherectomy devices. *A,* Directional coronary atherectomy device with macroscopic tissue resection. *B,* Rotational atherectomy device. *C,* Transluminal extraction catheter.

achieved with atherectomy.[50] [50A] The loss index, defined as the fractional relationship between acute lumen gain and late lumen loss, is largely unchanged with atherectomy, which suggests that these devices do not lessen the degree of arterial injury and subsequent repair.[50] Atherectomy use reached its peak (30 percent of interventional procedures) between 1992 and 1994 but fell dramatically after the clinical availability of coronary stents. It is estimated that 5 to 20 percent of cases currently involve the use of atherectomy devices, alone or in combination with coronary stenting (Fig. 38-1) .

Directional Coronary Atherectomy

Directional coronary atherectomy (DCA) was first performed in coronary arteries in 1986 with large (7 French), stiff, prototype atherectomy devices. A clinical study of 873 patients treated with DCA was initiated in 1988 and reported a primary success rate (tissue removal,
20 percent reduction in diameter stenosis, and <50 percent residual stenosis after DCA

alone) of 85 percent, which increased to 92 percent after adjunct PTCA.[51] Procedural complications included death (0.5 percent), nonfatal Q wave myocardial infarction (0.9 percent), and emergency CABG (4.0 percent). Six-month angiography demonstrated a 42 percent restenosis rate (
50 percent diameter stenosis). The restenosis rate was lower in de novo than restenotic lesions in both native vessels (30 and 46 percent, respectively) and SVGs (31 and 68 percent, respectively).[51]

Approximately 18 to 20 mg of macroscopic tissue is removed with DCA, although plaque excision accounts for only 70 percent of the lumen gain achieved with DCA.[52] [53] The remaining lumen improvement is achieved through mechanical dilatation by the DCA catheter, balloon PTCA, and to a lesser extent, changes in radial compliance of the vessel by excision of deep wall elastic components.[53] Intravascular ultrasound (IVUS) studies show that a substantial amount (43 to 55 percent cross-sectional narrowing) of atherosclerotic plaque remains even after "optimal DCA." [53] [54] [55]

TECHNICAL ASPECTS.

The DCA catheter contains a 9-mm, 120-degree cutting window and a contralateral, low-inflation pressure (15 to 45 psi) balloon that forces atherosclerotic plaque into the cutting window. A cup-shaped rotating (2500 rpm) cutter excises macroscopic amounts of atherosclerotic plaque and stores it in a distal collection chamber until its removal. A 6F DCA catheter is recommended for smaller vessels (<3.0 mm) and a 7F DCA device for larger ones (
3.0 mm). Use of the 5F device is unusual and reserved for subtotal occlusions, calcified vessels, or moderately tortuous vessels; the amount of plaque retrieval with this device is limited.

Large (9.5F to10F) guiding catheters are generally needed for the 5F to 7F DCA catheters. Forceful advancement of the DCA catheter and deep seating of the guiding catheter should be avoided because the stiff guiding catheter may dissect the coronary ostium or proximal portion of the vessel. Tissue removal is achieved by positioning the DCA catheter across the target lesion, inflating the balloon to 10 to 20 psi, and advancing the motor-driven cutter forward slowly. The balloon is deflated after each cut and the device rotated 45 to 90 degrees to reorient it toward the residual plaque. Higher balloon inflation pressures may be used on subsequent cuts to increase the effective working diameter of the device. Adjunct balloon PTCA is often (80 percent) performed to further improve the residual lumen diameter or, less commonly, to treat DCA-induced dissection, although it may have limited incremental benefit on the prevention of restenosis if an "optimal" IVUS-guided DCA result is achieved.[55] An "optimal" DCA result is defined as a final diameter stenosis less than 10 percent, tissue removal, and the avoidance of major clinical complications (death, Q wave myocardial infarction, or emergency CABG).

INITIAL CLINICAL RESULTS.

"Optimal" DCA generally results in low (<20 percent) quantitatively determined residual stenosis and a smooth-appearing lumen without dissection; procedural success rates

greater than 95 percent have been reported by experienced centers[29] [53] [56] [57] (Table 38-2) . "Conservative" atherectomy using smaller DCA devices and no adjunct balloon PTCA results in higher (>25 percent) residual stenosis and more complications and has no benefit over balloon PTCA.[58] [59] [60]

Major complications after "optimal" DCA include procedural mortality (<1.0 percent), emergency CABG (
2.0 percent), Q wave myocardial

TABLE 38-2 -- EARLY AND LATE OUTCOMES AFTER DIRECTIONAL CORONARY ATHERECTOM
CORONARY ARTERIES

METHOD	CAVEAT		C-CAT		OARS	ABACUS		BOAT	
	PTCA	DCA	PTCA	DCA	IVUS+DCA	DCA	DCA+PTCA	PTCA	DCA
Years of entry	1991-92		1991-92		1993-95	1994-1995		1994-95	
Number of patients	500	512	136	138	199	106	108	492	497
Baseline factors									
Mean age (yr)	59	59	55	58	58	62	60	58	58
Diabetes mellitus (%)	19	19	15	17	17	19	21	14	14
Unstable angina (%)	70	66	52	39	78	30	22	NA	NA
Angiographic success (%)	80	89*	91	98	NR	95.1		NR	NR
Procedure success (%)	76	82+	88	94	98	99.5		87	93
Reference Diameter (mm)	2.9	2.9	3.13	3.23	3.28	3.24	3.21	3.20	3.25
MLD (mm)									
Baseline	NR	NR	0.89	0.94	1.19	1.04	1.03	1.04	1.07
Final	1.80	2.02*	2.10	2.34*	3.16	2.60	2.88§	2.33	2.82*
Follow-up	NR	NR	1.55	1.61	1.55	1.80	1.85	1.68	1.86

Percent diameter stenosis										
Baseline	73	71	71.5	70.6	63.5	68.7	68.0	NR	NR	
Final	36	29	33	26*	7.1	15.0	10.8§	28.1	14.7*	
Follow-up	NR	NR	48.4	48.7	37.0	32.3	33.4	45.6	40.1	
Restenosis rate (%)	57	50	43	46	28.9	19.6	23.6	39.8	31.4¶	
Early complications (T)	5	11*	6	5						
Death	0.4	0	0	0	0	0	0	0.4	0	
Q wave MI	2	2	0	0.7	1.5	0.9	0	1.6	2.0	
Emergency CABG	2	3	4.4	1.4	1.0	0	0	2.0	1.0	
Follow-up time	1 yr		6 mo		1 yr	1 yr		1 yr		
Late clinical events (%)	42.4	38.7	29	29		18.1	21.9	24.8	21.1*	
Death	0.6	2.2+	0	0.7	1.0	0	0	0.6	0.6	
Q wave MI	1.2	2.9	1.6	0	1.5	0.9	0	1.6	2.0	
TRL			27.9	28.7	17.8	15.2	21.9			
Repeat PCI	25.9	24.4	23.3	23.5	NR	NR	NR	NR	NR	
CABG	9.1	9.3	4.6	5.2	NR	NR	NR	NR	NR	

CABG=coronary artery bypass graft; DCA=directional coronary atherectomy; IVUS=intravascular ultra
MI=myocardial infarction; MLD=minimal lumen diameter; NR=not reported: PCI=percutaneous corona
intervention; PTCA=percutaneous transluminal coronary angioplasty; TLR=target lesion revasculariza

Data from Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT),[58] [59] *C-CAT=Canad*
Atherectomy Trial,[60] *Optimal Atherectomy Restenosis Study (OARS),*[53] *Adjunctive Balloon Angioplas*
Intravascular Ultrasound=Guided Optimal Directional Coronary Atherectomy (ABACUS),[55] *Balloon vs*
Atherectomy Trial (BOAT),[29] *Stent Versus Directional Coronary Atherectomy Randomized Trial (STA*
Stenting after Optimal Lesion Debulking (SOLD) Registry.[62]

*p<0.001.

Optimal angiographic (<30 percent diameter stenosis) result.

p<0.005.
§p<0.01.
¶p<0.05.
**Target vessel failure (death, Q percent diameter stenosis) result.

infarction, (<1.0 percent), and transient or sustained abrupt vessel closure (2.0 to 4.2 percent).[29] [53] [63] The occurrence of dissection resulting from guide catheter trauma,[64] distal nose cone injury, or guidewire trauma has been reduced with improvements in catheter design and greater operator experience. Other complications include perforation (1.0 percent), sidebranch occlusion (3 percent), vasospasm, "no reflow," and distal plaque embolization (2 percent).[65] The frequency of these complications, particularly atheroembolism, may be higher (13.4 percent) in SVGs.[63] No reflow can be treated with intracoronary agents such as verapamil (100 to 200 mug),[65] diltiazem (500 mug),[66] or nitroprusside (100 to 200 mug). Depending on the definition used, coronary aneurysms after successful DCA have been reported in a few cases.

Frequent (11.5 to 19.0 percent) elevations in creatine kinase isoenzymes (CK-MB) have been reported after DCA.[58] [60] Initial series reported an association between CPK-MB elevations and late mortality,[20] [59] although more recent, prospective studies suggest that clinically silent, low-level CPK-MB elevations may not be independently associated with worse outcomes[67] [68] [68A] [68B] ; the causal relationship between periprocedural myocardial necrosis and late mortality may be confounded by the degree of underlying atherosclerosis.[68] The GP IIb/IIIa blocker abciximab reduces the incidence of non-Q-wave myocardial infarction by more than 50 percent in patients undergoing DCA.[69]

LATE CLINICAL OUTCOME.

Arterial remodeling, or vessel constriction, between 1 and 6 months after DCA is the major cause of restenosis after this procedure,[54] although varying amounts of intimal hyperplasia may also occur. Significantly (p<0.05) lower angiographic restenosis rates are obtained in patients with discrete, native vessel lesions who undergo "optimal" DCA (31.4 percent) as compared with balloon PTCA (39.8 percent),[29] a finding attributable to the larger final lumen diameter achieved after DCA.[29] [50] "Conservative" atherectomy using smaller DCA devices (without adjunct balloon PTCA) confers no restenosis benefit over balloon PTCA.[58] [60] DCA does not reduce restenosis in de novo lesions located in the body of SVGs[63] and may lead to higher complication rates. Initial concerns that deep adventitial resection results in higher recurrence rates[70] have not been substantiated in larger series.[71]

One small (N=122) randomized trial has suggested that IVUS-guided "optimal" DCA results in lower angiographic restenosis rates than does stenting (15.8 vs. 33.9 percent; p=0.032), [61] although it is not known whether DCA is better than stenting when IVUS guidance is not performed. DCA has also been used prior to stent implantation for removal of atherosclerotic plaque, which potentially lessens the degree of late lumen loss and restenosis[62] [72] ; this effect was independent of the final minimal lumen

diameter in one case-matched series.[73] The AMIGO Trial, a large randomized trial comparing DCA followed by stent implantation and stent implantation alone, is under way to evaluate the effect of debulking prior to stenting on the prevention of late restenosis.

INDICATIONS.

DCA may be used as an alternative to balloon PTCA to prevent restenosis in patients with de novo lesions in vessels larger than 3.0 mm. DCA may also be used in bifurcation lesions involving a large branch, ostial lesions of the right coronary artery or SVG, and the ostium of the left anterior descending artery, particularly in the case of an acute angle with the origin of the left circumflex. DCA may also be useful for the treatment of in-stent restenosis in larger vessels. Although DCA can be used successfully to rescue failed or suboptimal balloon PTCA, the availability of coronary stents has markedly reduced DCA use in this circumstance. DCA is limited in its ability to remove plaque in the presence of significant (>180 degrees) superficial calcium.[74]

Rotational Atherectomy

The rotational atherectomy (RA) device, or Rotablator (Boston Scientific, Natick, MA), is considered an atherectomy device, although ablation occurs by plaque pulverization rather than by tissue removal. RA relies on differential plaque abrasion in which inelastic tissue (i.e., calcified plaque) is selectively abraded while elastic tissue (i.e., soft plaque) is deflected away from the atherectomy burr.[75] The microparticles generated, 2 to 5 mum in diameter, pass through the coronary microcirculation and are removed by the reticuloendothelial system without interfering with the coronary microcirculation.[75] [76] Lower (140,000 rpm) rotational speeds are associated with less platelet activation and aggregation than are higher (180,000 rpm) speeds.[77] The use of GP IIb-IIIa inhibitors also reduces the degree of platelet aggregation and hypoperfusion associated with RA.[78] Although coronary flow reserve may be impaired after RA,[79] there is generally no long-term impact on the global left ventricular ejection fraction.

TECHNICAL ASPECTS.

The Rotablator device consists of an olive-shaped, stainless steel burr with diamond chips measuring 20 to 50 mum in diameter embedded in its distal portion.[75] [80] The burr is advanced over a 0.009-inch stainless steel guidewire with a 0.017-inch radiopaque platinum coil at its distal tip. A lubricating 4.3F Teflon sheath encases the drive shaft, and a compressed-air turbine rotates it between 140,000 and 200,000 rpm. Burrs for coronary use are available in diameters ranging from 1.25 to 2.50 mm. Current guiding catheter technology allows the passage of 1.25- to 2.15-mm burrs through an 8F guiding catheter, a 2.25- and 2.38-mm burr through a 9F guiding catheter, and a 2.50-mm burr through a 10F guiding catheter.[75]

A prophylactic temporary pacemaker should be positioned prior to RA of right coronary lesions. Because vasodilator administration is routine during this procedure, all patients should be volume-expanded to avoid hypotension after nitrate or calcium channel

antagonist use. Two guidewires are available for RA--a floppy guidewire and an extra-support guidewire. The floppy wire minimizes guidewire bias, thereby preventing deep plaque ablation and tissue injury in regions of angulation or vessel tortuosity, and the extra-support guidewire is useful in lesions that require added wire support for burr advancement. After the burr has been advanced just proximal to the lesion in the reference segment, the "platform" speed is adjusted to 150,000 to 180,000 rpm. Short-duration (15 to 30 seconds) burr advancements are recommended, with rapid decelerations of greater then 5000 rpm avoided.[75] Deceleration below 140,000 rpm can lead to inadvertent stalling, burr entrapment, dissection, or vessel occlusion.[75] Two to four passes are made with each burr, with 30 to 60 seconds between passes to allow coronary perfusion.

A stepped-approach (0.50-mm increments up to 2.0 mm, then 0.25-mm increments thereafter) to RA is generally used in larger (>3.0 mm) vessels or for the treatment of diffuse or heavily calcified lesions. Aggressive RA (burr-to-artery ratios of >0.7) techniques do not provide a restenosis advantage over more conservative (burr-to-artery ratio of >0.7) methods.[81] Adjunctive balloon PTCA is used in most (82 to 88 percent) cases to reduce residual percent diameter stenosis or to treat coronary dissections.[82] [83] [84]

INITIAL CLINICAL RESULTS.

RA registries have reported high (88 to 98.6 percent) procedural success rates in complex lesions[82] [83] [85] [86] (Table 38-3) . In two large multicenter series, major complications were uncommon after RA but included death (0.31 percent), Q wave myocardial infarction (1 to 2.2 percent), and emergency CABG (0.4 to 0.9 percent).[83] [84] A higher (19 percent) incidence of non-Q-wave myocardial infarction after RA was reported in one study of long (>2 cm) lesions.[89] Other complications include transient or sustained dissection (12 percent), sidebranch occlusion (3 percent), distal embolization (3 percent), and abrupt closure (5 percent).[83] "No reflow" occurs significantly more often after RA (7.7 percent) than after balloon PTCA (0.3 percent) and may be improved with the periprocedural use of intracoronary calcium antagonists[66] or pretreatment with GP IIb-IIIa antagonists.[78] Perforations are rare after RA and may be successfully treated with prolonged balloon inflation.[90] Transient bradycardia and atrioventricular block are occasionally seen during RA, particularly during RA of the right coronary artery.

The procedural outcome in complex lesions may be better after RA than after other methods of PCI. In the Excimer, Rotablator, or Balloon Angioplasty for Complex Lesions (ERBAC) Study, patients with complex native coronary lesions were randomly assigned to treatment with RA, excimer laser angioplasty, or balloon PTCA. Procedure success rates were significantly (p=0.016) higher in patients treated with RA (89 percent) than in those treated with balloon PTCA (80 percent) or excimer laser angioplasty (77 percent); major complication rates did not differ among the three groups.[87]

Predictors of major ischemic complications after RA include female gender; lesions with irregularity, lesions 4 mm or longer, or lesions with outflow obstruction; right coronary artery lesions; angulated (
60 degrees) lesions; and lesions involving a bifurcation or 4 mm or longer.[84] Predictors

of "no reflow" include a recent history of myocardial infarction and a right coronary lesion.[84] [91] Larger decelerations (>5000 rpm) are also associated with higher complication rates after RA.[75]

LATE CLINICAL OUTCOME.

RA does not appear to reduce restenosis compared with balloon PTCA. Observational studies report high rates of clinical restenosis (38 percent), TLR (36 percent), and angiographic restenosis (31 to 59 percent) (see Table 38-3) . In the ERBAC Study, angiographic restenosis at 6 months was similar in patients treated with RA (57 percent), excimer laser angioplasty (59 percent), or balloon PTCA (47 percent).[87] Although smaller burrs were generally used in this study, no restenosis benefit was found in a randomized study of "aggressive" and "conservative" approaches to RA.[81] Predictors of 1-year clinical events after RA include male gender, high risk for surgery, bifurcation lesions, or lesions that are eccentric, long, or highly stenosed.[83] Two series have shown that adjunct stent placement after RA is associated with larger lumen diameter than attained with balloon

TABLE 38-3 -- EARLY AND LATE OUTCOME AFTER ROTATIONAL CORONARY ATHERE

VARIABLE	NACI REGISTRY	BEAUMONT RA	ELLIS RA	SETON RA	ERBAC			WASHINGT HOSPITAL CENTER	
					PTCA	RA	ELCA	RA	
Years of entry	1990-94	1988-91	1989-92	1990-92	1991-1993			1990-199	
Number of patients	525	104	316	242	222	231	232	147	
Baseline factors									
Mean age (yr)	65	58	64	63	63	62	62	67	
Women (%)	46	22	26	24	19	20	22	29	
Diabetes mellitus (%)	23	NA	24	22	16	15	17	17	
Unstable angina (%)	53	NA	39	35	12	18	16	37	
Multivessel disease (%)	59	62	59	45	52	59	52	NR	
Angiographic success (%)	89	96	NR	95	80	89	77	NR	

Procedure success (%)	88	NR	89.8	94	83.3	90.5	90.5	98.6	
Early complications (%)	NR		8.9	4.3	3.1	3.2	4.3		
Death	0.8	0.9	0.3	0	0.9	0.9	0.9	0	
Q wave infarction	1.1	4.4	2.2	3.3	1.8	1.3	1.3	0.68	
Emergency CABG	0.4	1.9	0.9	1.2	0.5	0.9	2.2	0.68	
CK-M B >3×normal	NA	2.7	5.7	NA	NA	NA	NA	14.7	
Reference diameter (mm)	2.77	3.20	NR	NR	2.80	2.88	2.99	3.20	
MLD (mm)									
Before RA	0.91	1.0	NR	NR	0.74	0.71	0.74	1.01	
After RA	1.53	1.4	NR	NR	NA	NA	NA	NR	
--After procedure	2.04	2.3	NR	NR	1.88	1.94	1.95	2.29	
Follow-up	NR	1.4	NR	NR	1.41	1.34	1.24		
Percent stenosis									
Before RA	70	70	NR	NR	75	76	75	68	
After RA	44	54	NR	NR	NA	NA	NA	NA	
After procedure	26	30	NR	NR	35	33	33	27	
Follow-up	NR	57	NR	NR	52	56	57	NR	
Restenosis rate (%)	NR	51	NR	NR	47	57	59	NR	
Late clinical outcome	1 yr	5 mo	NR	3 mo		1 yr			
Any MACE (%)	30	NR	NR	NR	36.6	45.9	47.9	NR	
Death (%)	5	2	NR	4.3	3.7	2.4	1.9	1	
Q wave MI (%)	2	0	NR	NR	2.6	2.4	2.4	NA	
Revascularization (%)	34	28	NR	21	15			28	
Repeat PTCA	26	28	NR	28	31.9	42.4	46.0	22	
CABG	12	8	NR	10	6.3	7.3	7.1	6	

CABG=coronary artery bypass graft surgery; ELCA=excimer laser coronary angioplasty; MACE=majo
events; MI=myocardial infarction; MLD=minimal lumen diameter; NR=not reported: RA=rotational athe

Data from New Approaches to Coronary Intervention (NACI) Registry[83] ; Beaumont Hospital[82] ; Ellis Medical Center[85] ; Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison (ER Washington Hospital Center[86] ; and Dilation versus Ablation Restenosis Trial (DART).[88]

*$p<0.001$.

angioplasty alone.[86] [92] The potential benefit of plaque debulking with RA followed by coronary stenting versus stent placement alone is being evaluated in the randomized SPORT trial.

INDICATIONS.

RA is indicated in lesions not suitable for balloon PTCA because of excess procedural risk, such as ostial and heavily calcified lesions, selected bifurcation lesions, and lesions that are undilatable with balloon PTCA.[93] RA may also be useful for the treatment of in-stent restenosis,[94] with one registry series suggesting a benefit for RA over balloon PTCA in diffuse lesions.[95] Although procedural success rates are high (97 percent) with the use of RA for in-stent restenosis, clinical recurrence is common (35 percent), and high (49 percent) angiographic restenosis rates have been reported.[96] RA should be avoided in the presence of focal or extensive dissection after balloon PTCA, visible thrombus, or extremely eccentric lesions located on the outer surface of a severe bend. The benefit of RA over balloon PTCA in long lesions is not known.

Transluminal Extraction Atherectomy

The transluminal extraction catheter (TEC) (InterVentional Technologies, San Diego, CA) is an over-the-wire, flexible aspiration device that uses a tip-mounted cutting blade and external vacuum to excise and remove thrombus and soft plaque from native vessels and SVGs.[97] The TEC device is less useful for removing laminated thrombus in large SVGs or for the excision of fibrous or fibrocalcific plaque.

TECHNICAL ASPECTS.

The TEC device contains two rotating (750 rpm) stainless steel blades attached to the distal end of the catheter. A hand-held motor drive unit attaches to the proximal end of the cutting catheter, and a vacuum bottle connected to the TEC instrument is used for collection of aspirated atheroma, thrombus, and other debris. A 10F guiding catheter is needed for larger (7.0F and 7.5F) TEC devices, and a 9F guide is used for smaller (5.5F, 6.0F, and 6.5F) ones. A specially designed 300-cm-long, 0.014-inch guidewire with a 2-cm floppy tip terminating in a 0.021-inch ball tip is used to advance the TEC device between two and five times across the lesion. Additional atherectomy or thrombectomy may be performed with larger devices guided by intermittent angiography

to assess the residual percent diameter stenosis.

INITIAL CLINICAL RESULTS.

The TEC device has been used for large thrombus-containing lesions and as primary or "rescue" treatment of patients with acute myocardial infarction.[98] Procedural success rates up to 94 percent can be achieved with optimal technique.[98] Complications after TEC use include death (0 to 5.9 percent), emergency CABG (0.7 to 3.9 percent), myocardial infarction (2.0 to 7.8 percent), and a need for transfusion (19 percent).[48] [98] [99] Other angiographic complications include sidebranch occlusion (2.7 percent), abrupt closure (2.7 percent), guide catheter dissection (2.2 percent), perforation (2.2 percent), and distal embolization (0.5 to 12.8 percent).[99] [100] [101] [102] [103]

The TEC or PTCA in Thrombus-Containing Lesions (TOPIT) Trial, a randomized study of 245 patients with unstable or postinfarction angina and thrombus-containing lesions, was performed to assess the value of TEC and balloon PTCA in these "high-risk" patients.[104] The composite rate of in-hospital major adverse cardiac events (death, myocardial infarction, bailout intervention, or emergent CABG) was 4.5 percent in patients treated with TEC and 11.2 percent in patients treated with balloon PTCA (p=0.06). A CPK-MB level greater than three times normal occurred significantly (p=0.03) less often in the TEC group (4.5 percent) than in the balloon PTCA group (15.4 percent). The TEC instrument has also been used in patients with friable SVG lesions with modest (80 to 90 percent) procedural success.[49] [99] [101] [103] Residual stenoses greater than 50 percent and frequent (33 percent) dissections require that adjunctive balloon angioplasty be used in most (90 percent) cases.[49] [99] Use of the TEC device to treat complex native coronary lesions without thrombus has met with more limited (85 to 95 percent) success.[100] [104]

LATE CLINICAL OUTCOME.

Extraction atherectomy does not reduce restenosis more than balloon PTCA does. Six-month clinical follow-up after TEC use demonstrated that late cardiac death (1.9 to 11 percent), Q wave myocardial infarction (1.3 to 4 percent), and repeat TLR (25.3 to 34.8 percent) were common,[49] [98] [100] probably related to the frequent treatment of friable SVG lesions in these series. Angiographic restenosis (>50 percent follow-up diameter stenosis) occurred in 52 to 69 percent of lesions treated with the TEC device[49] [99] and late vessel total occlusion was found in 11.9 to 29 percent.[49] [100]

INDICATIONS.

TEC atherectomy currently has limited clinical use but may be indicated for the removal of fresh thrombus in SVG and selected native vessel lesions. TEC should not be used for the treatment of dissection caused by other devices, in cases of extreme angulation or calcification, or in vessels less than 2.5 mm in diameter. TEC atherectomy is not useful for routine atherectomy in native vessels or SVG lesions.

ABLATIVE LASER-ASSISTED ANGIOPLASTY

Despite encouraging preclinical studies,[105] laser angioplasty has neither lowered procedural complications nor reduced restenosis in comparison to balloon PTCA.[87] [106] [107] [108] [109] Laser angioplasty is now reserved for a small subset of patients with complex lesion morphology unsuitable for therapy with other devices.

TECHNICAL ASPECTS.

Light amplification by stimulated emission of radiation (LASER) is the process of creating a high-energy, coherent beam of monochromatic light. Different wavelengths (ranging from 300 nm for ultraviolet light to 1,000 to 2,000 nm for infrared light) are produced, depending on the laser medium used. The xenon chloride (XeCl) excimer laser emits light at 308 nm (in the ultraviolet range), whereas the neodymium yttrium-aluminum-garnet (Nd:YAG) laser emits light above 2000 nm (in the infrared light range). Depending on the laser source, tissue ablation results from either vaporization of tissue (photothermal effects), ejection of debris (photoacoustic effect), or direct breakdown of molecules (photochemical dissociation).[110] Ultraviolet lasers result in atherosclerotic plaque absorption, whereas near-infrared lasers result in thermal energy and photocoagulation (e.g., holmium:YAG). Photoacoustic injury is worsened in the presence of blood and contrast agents.[111]

Two systems are currently available for use in coronary arteries: the XeCl excimer laser coronary angioplasty (ELCA) system and the Ho:YAG laser system. The ELCA system uses a catheter containing a concentric or eccentric array of 61- to 200-mm optical fibers emitting laser light at 308 nm,[110] [112] and the Ho:YAG system has a catheter containing 37 fibers and operates at a wavelength of 2100 nm.[113] A single, slow (0.5 to 1.0 mm/sec) pass of the laser catheter should be performed under fluoroscopic guidance for both systems. The saline flush technique makes certain that all blood and contrast medium are removed from the coronary artery by flushing the guide catheter with 30 ml or more of saline to minimize the degree of photoacoustic injury to the surrounding vessel.[114] [115] After successful laser passage, adjunctive balloon PTCA is needed in most (90 percent) cases to reduce the residual stenosis to below 30 percent.[116] [117] [118]

INITIAL CLINICAL RESULTS.

Clinical success rates with the ELCA system in complex lesion morphologies have ranged from 84 to 94 percent.[87] [106] [107] [119] [120] Three randomized trials have compared procedural outcomes with laser angioplasty and balloon PTCA. The Laser Angioplasty Versus Angioplasty (LAVA) Trial evaluated 215 patients randomly assigned to treatment with "laser-facilitated balloon angioplasty" using the holmium (TAG) laser system or balloon PTCA.[106] No differences were noted in early or late major clinical events between the two groups, although complications occurred significantly (p=0.0004) more often in laser-treated patients (18.0 percent) than in balloon PTCA-treated patients (3.1 percent).[106] The ERBAC Trial randomly assigned 620 patients with type B and C

lesions to treatment with ELCA, RA, or balloon PTCA.[87] Procedural outcome and complication rates were similar in patients undergoing ELCA or balloon PTCA.[87] The Amsterdam-Rotterdam (AMRO) Trial randomly assigned 308 patients with lesions 10 mm or longer to treatment with ELCA or balloon PTCA.[108] Procedural success rates were similar in patients treated with ELCA (80 percent) and balloon PTCA (79 percent).[108] The late restenosis rate was 51.6 percent in the laser group and 41.3 percent in the balloon-PTCA group.[108]

ELCA has also been used to treat aorto-ostial and shaft SVG lesions, longer (>15 mm) SVG lesions, lesions located in larger (>3.0 mm) friable SVGs, and lesions undilatable with balloon PTCA.[117] [119] Although laser angioplasty has been frequently used in total occlusions,[121] no restenosis benefit was shown with laser angioplasty over balloon PTCA in one study[107] two large registry series have reported the results of ELCA for the treatment of in-stent restenosis[122] [123] ; a trend toward reduced clinical events was observed in a nonrandomized series.[123] The ongoing Laser Angioplasty Restenosis Study (LARS) compares late angiographic and clinical outcomes in patients treated with ELCA or balloon PTCA for in-stent restenosis.

LATE CLINICAL OUTCOME.

Laser angioplasty does not reduce the occurrence of restenosis, with 47 to 54 percent of patients experiencing symptom recurrence after laser angioplasty.[87] [106] [108] [118] [121] The postprocedural lumen diameter is the most important predictor of restenosis in these series.[118] [120]

INDICATIONS.

Laser angioplasty has a limited role in PCI and is reserved for patients with in-stent restenosis, particularly those in SVGs, aorto-ostial SVG lesions, and potentially,

Figure 38-2 *A,* Thrombosed saphenous vein graft (SVG) to the obtuse marginal branch in a patient with unstable angina. *B,* An Angiojet thrombectomy catheter was used to remove thrombus within the vessel (arrow). *C,* A 4.0-mm Crown stent was deployed in the proximal segment of the SVG. *D,* Final angiographic result without evidence of distal embolization.

lesions located in friable SVGs. Laser angioplasty should not be used in patients with thrombus or in the presence of severe calcification.

CATHETER-BASED THROMBOLYSIS AND MECHANICAL THROMBECTOMY

Coronary thrombus mediates acute coronary syndromes in native coronary arteries and SVGs.[124] The presence of thrombus within the native vessel or SVG imparts a

substantial risk for distal embolization, "no reflow," or other embolic complications during PCI.[125] [126] Embolic complications in patients undergoing PCI of a degenerated SVG may also occur as a result of distal fragmentation of atheromatous debris and fibrointima caused by mechanical contact with the SVG.

CATHETER-BASED THROMBOLYTIC USE.

Infusion catheters for intraluminal urokinase administration have been used for the treatment of thrombotic total occlusions in native arteries[127] [128] and SVGs.[129] Recanalization of occluded SVGs was achieved in 69 percent of patients with an average of 3.7 million units of urokinase given by direct catheter-based infusion over a period of 25.4 hours in one study.[129] These favorable results were tempered by a stroke rate of 3 percent and overall mortality rate of 6.5 percent. A randomized study of 469 patients undergoing PCI for unstable angina found that prophylactic use of intracoronary urokinase was associated with a higher (10.2 percent) incidence of abrupt closure (vs. 4.3 percent in placebo-treated patients; $p<0.05$).[130] This unexpected outcome was possibly caused by plaque hemorrhage and dissection, reduced intimal sealing, or the procoagulant effects of urokinase as a result of platelet activation.

Urokinase may also be delivered directly to the thrombus surface by local drug delivery systems. The Dispatch catheter, an over-the-wire, nondilatation catheter with a 20-mm spiral inflation coil at its tip, has been used to deliver urokinase and has resulted in thrombus dissolution in native coronary and SVG lesions.[131] A hydrogel-coated balloon has been used as a drug delivery system to transfer urokinase locally to the site of thrombotic obstruction.[132] In aggregate, local

Figure 38-3 *A,* Degenerated saphenous vein graft (SVG) to the posterior descending artery with a diffuse stenosis in the proximal segment of the SVG (arrow). *B,* Normal distal perfusion of the SVG with demonstration of secondary and tertiary branches. Positioning of the PercuSurge balloon in the distal portion of the SVG *(C,* arrow) and a 4.0-mm stent in the proximal SVG (*D*) resulted in minimal residual stenosis (*E*) and no evidence of distal embolization (*F*).

thrombolytic therapy has had a limited role in the treatment of patients with unstable angina because of the efficacy of other therapies, such GP IIb-IIIa inhibitors, and the bleeding complications associated with urokinase.

THROMBECTOMY DEVICES.

The Cordis Hydrolyzer removes thrombus by Venturi vacuum suction with the use of an external MedRad power injector. Limited European use of this device has been reported in humans in peripheral vessels,[133] hemodialysis shunts,[134] and coronary artery and SVG lesions.[135] Low-frequency (41.9 kHz) intracoronary ultrasound as in the Acolysis

system is used therapeutically for thrombolysis.[136] The ATLAS Trial, a randomized clinical trial evaluating use of the Acolysis catheter and abciximab for the treatment of thrombus-containing SVG lesions, is under way.

RHEOLYTIC THROMBECTOMY.

The Angiojet (Possis Medical, Inc., Minneapolis, MN) is a 5F catheter with a stainless steel tip connected to a high-pressure flexible cylinder, or hypotube. Saline is injected into the hypotube at the distal tip, where three high-speed saline jets are directed toward the proximal end of the catheter lumen. Venturi suction is created at the catheter tip, and surrounding blood, thrombus, and saline are entrained into the tip opening. The jets fracture the thrombus into small particles and propel the fragments proximally through the catheter lumen, where they are removed from the body. Repeated passes of the Angiojet may be performed until angiography shows no further evidence of improvement in lumen diameter or thrombus burden (Fig. 38-2) .

Angiographic thrombus was reduced by 86 percent with the Angiojet in a multicenter registry of 90 patients with acute ischemic syndromes and evidence of intraluminal thrombus.[137] The Angiojet was successfully delivered in all cases, and the overall procedural success rate was 87 percent. Two (2.2 percent) procedure-related deaths occurred within 30 days of the procedure. Other complications included a reduced final TIMI flow grade of less than 3 (4.4 percent), persistent abrupt closure (3.3 percent), and coronary perforation (1.1 percent). The TLR rate was 15.6 percent and the overall target vessel failure rate was 27.5 percent at 1 year. The VEGAS-2 trial randomly assigned 349 patients with angiographic thrombus to treatment with the Angiojet or prolonged intraluminal urokinase consisting of a 250,000-unit bolus over a 30-minute period, followed by urokinase at 20,000 to 240,000 units/hr for 6 to 30 hours.[138] No significant differences were observed in the primary endpoint, target vessel failure, which is defined by at least one of the following: (1) occurrence of a major clinical event, i.e., death, myocardial infarction, or revascularization; (2) failure to achieve less than 50 percent diameter stenosis; (3) presence of final TIMI flow of less than 3; or (4) failure to achieve greater than 20 percent improvement in stenosis severity.[138] The procedure success rate was higher and the complication rate was lower in Angiojet-treated patients.[138]

The Angiojet is currently indicated in patients with moderate to large thrombus-containing native vessels or SVGs prior to definitive therapy with balloon PTCA and stents. The Angiojet is useful for the treatment of recent thrombus, particularly in the setting of acute myocardial infarction or failed thrombolytic therapy. The Angiojet should not be used in small (
2.0 mm) vessels because of the risk of perforation.

DISTAL EMBOLIC PROTECTION DEVICES.

Several devices have been developed to prevent (or trap) macroparticulate embolic material from passing into the distal microcirculation during PCI. The PercuSurge Guardwire is a compliant balloon mounted on a hypotube that can function as a 0.014-inch steerable guidewire for catheter transport.[139] Once positioned across the

lesion, the balloon is inflated to block the flow of blood in the vessel and PCI is performed over the Guardwire. Liberated debris is trapped by the inflated Guardwire balloon, and an aspiration catheter is used to remove blood and suspended debris. The Guardwire balloon is then deflated and distal flow to the vessel is restored. The aspirated material contains thrombus and macroparticulate atheromatous debris.[139] This device and others are now undergoing clinical evaluation in patients at risk for distal embolization during PCI (Fig. 38-3) .

Figure 38-4 Representative stents: coil stent proposed by Dotter *(A)*, Gianturco-Roubin stent *(B)*, Guidant Duet stent *(C)*, Medtronic-AVE GFX stent *(D)*, Guidant Multilink stent *(E)*, Cordis Crown *(F)*, Paragon stent *(G)*, and Bard XT stent *(H)*.

CORONARY STENTS

Coronary stents have fundamentally changed the practice of interventional cardiology by reducing early complications and improving late clinical outcomes in a broad array of patients. Charles Dotter introduced the concept of a temporary endoluminal splint to scaffold an occluded peripheral vessel nearly 40 years ago,[140] but the first human coronary implantation was not performed until 1986, when Puel and colleagues[141] and, subsequently, Sigwart and associates[142] deployed self-expanding stents to prevent abrupt closure and reduce restenosis after balloon PTCA. Over the next decade an explosive growth in the use of coronary stents took place as a result of both an expanding number of randomized trials demonstrating benefit in specific lesion subsets and clinicians' empirical satisfaction with the early and late benefits of stents (Fig. 38-4) .

Although it is estimated that 50 to 80 percent of PCI procedures now involve the use of at least one stent,[143] the majority of patients receiving a stent do not meet the criteria for currently approved indications. In a series of 700 patients, less than 20 percent would have been candidates for the initial randomized trials demonstrating the benefit of stents.[144] Expanded "off-label" coronary stent use has identified patients at "high-risk" for recurrent symptoms after stenting,[144] such as those with smaller (<2.75 mm) vessels and diffuse (lesions >25 mm) disease. One study has suggested that patients undergoing "off-label" stent use have a risk of angiographic restenosis that is nearly three times higher than observed in patients undergoing stent placement for approved indications.[144] Randomized trials with balloon PTCA in these subsets are ongoing. The results of randomized trials comparing coronary stenting and balloon PTCA are reviewed (Table 38-4) .

Indications

DE NOVO OR RESTENOTIC NATIVE VESSEL LESIONS.

At least five randomized trials have shown that coronary stent use in larger (>3.0 mm), de novo native coronary vessels is associated with an improved outcome when compared with balloon PTCA (Fig. 38-5) . In the first two of these studies, the Stent Restenosis Study (STRESS) and the Belgium Netherlands Stent (BENESTENT) Trial, Palmaz-Schatz stent placement resulted in a 26 to 31 percent reduction in angiographic restenosis and a 27 to 31 percent lowering of 1-year clinical events when compared with balloon PTCA.[30] [145] A third study, the Stent Versus Angioplasty Restenosis Trial (START), demonstrated similar findings that were maintained up to 4 years after the procedure.[149]

The benefit of stent use over balloon PTCA in restenotic lesions was shown in the Restenosis Stent (REST) Study, a randomized trial of 383 patients with restenosis after balloon PTCA who were randomly assigned to Palmaz-Schatz stent placement or repeat balloon PTCA.[146] Angiographic restenosis (>50 percent follow-up diameter stenosis) was lower (18 percent) in stent-treated patients (vs. 32 percent in balloon PTCA-treated patients; *p*=0.03); TLR also occurred less often (10 percent) in stent-treated patients (vs. 27 percent in balloon PTCA-treated patients; *p*=0.001).

ABRUPT OR THREATENED CLOSURE AFTER BALLOON PTCA.

Patients in whom periprocedural coronary occlusion develops during balloon PTCA have substantially higher morbidity and mortality than do those in whom this complication does not develop,[4] including death (4 percent),

TABLE 38-4 -- EARLY AND LATE OUTCOME IN RANDOMIZED TRIALS OF CORONARY STEN PLACEMENT VERSUS BALLOON PTCA

VARIABLE	STRESS		BENESTENT		BENESTENT II		REST		SAVED	
	PTCA	Stent	PTCA	Stent	PTCA	Stent	PTCA	Stent	PTCA	Stent
Lesion type	De novo, native		De novo, native		De novo, native		Restenotic, native		SVGs	
Years of entry	1991-93		1991-93		1995-96		1991-96		1993-95	
Number of patients	202	205	257	259	410	413	176	178	107	108
Baseline factors										
Mean age (yr)	60	60	58	57	59	50	60	59	66	66
Women (%)	27	17	18	20	20	23	18	20	21	18
Diabetes mellitus (%)	16	15	6	7	11	13	15	20	36	23

Unstable angina (%)	48	47	NA	NA	40	45	22	17	77	82
Multivessel disease (%)	32	36	NA	NA	NA	NA	32	33	NA	NA
Angiographic success (%)	92.6	99.5	98.1	96.9	99	99	93.2	98.9	86	97
Clinical success (%)	89.6	96.1	91.1	92.7	95	96	100	100	69	92
Reference diameter (mm)	2.99	3.03	3.01	2.99	2.93	2.96	3.04	3.01	3.19	3.18
Final % stenosis	35	19	33	22	29	16	30	6	32	12
Stent use (%)	6.9	96.1	5.1	94.6	13.4	96.6	6.8	98.9	7.0	97
Early complications	0-14 d		In-hospital		1 Mo		In-hospital		In-hospital	
Death (%)	1.5	0	0	0	0.2	0	0.6	1.1	2	2
Q wave infarction (%)	3.0	2.9	0.8	1.9	1.0	1.2	0.6	2.8	1	2
Emergency CABG (%)	4.0	2.4	1.6	1.9	0.5	0.7	0.6	1.1	4	2
Late clinical outcome	15-240 d		7 mos		12 mos		6 mos		240 d	
Death (%)	0	1.5	0.4	0.8	1.0	1.0	1.1	1.1	9	7
Q wave MI (%)	0.5	1.0	1.6	2.7	1.5	1.9	0.6	2.8	4	5
Revascularization (%)	15.4	10.2	NA	NA	NA	NA	NA	NA	NA	NA
Repeat PTCA	11.4	9.8	20.6	10.0	15.6	9.4	26.6	10.3	16	13
CABG	4.5	2.4	2.3	3.1	1.5	1.9	0.6	2.2	12	7
Follow-up angiography										
Restenosis (%)	42.1	31.6	32	22	31	16	32	18	47	36
Follow-up MLD (mm)	1.56	1.74	1.73	1.82	1.66	1.89	1.85	2.04	1.49	1.73
Follow-up % stenosis	49	42	43	38	43	35	47	30	51	46
Any bleeding complication (%)	4.0	7.3	3.1	13.5	1.0	1.2	1.1	11.2	5	17

Data from Stent Restenosis Study (STRESS),[30] Belgium Netherlands Stent (BENESTENT) Trial I[145] II,[31] Restenosis Stent Study (REST),[146] Saphenous Vein Graft De Novo Trial (SAVED),[147] and Stent Chronic Coronary Occlusion (SICCO) Trial.[148]

Figure 38-5 A focal, de novo stenosis is identified in a patient treated with tissue-type plasminogen activator for acute myocardial infarction *(A*, magnified in *B)*. Direct advancement of a 3.0-mm Guidant Duet across the lesion and inflation to 16 atm *(C)* resulted in an excellent angiographic result *(D*, magnified in *E)*.

Figure 38-6 *A,* Emergency coronary arteriography in a patient with an acute myocardial infarction demonstrates a total occlusion in the midportion of the left anterior descending coronary artery (LAD). *B,* A "nipple" found on a magnified view (arrow) allowed an entry point for the coronary guidewire to pass into the distal segment of the LAD. Reperfusion is reestablished *(C),* and a 3.5-mm stent deployed at the site of occlusion *(D)* resulted in 0% residual stenosis and TIMI 3 flow into the distal part of the vessel *(E)*.

myocardial infarction (20 percent), or the need for urgent CABG (7 percent).[4] Self-expanding[141] [142] and balloon-expandable coiled[150] and slotted tube[151] stents were first used to scaffold coronary dissections in patients with balloon PTCA-induced complications. The Trial of Angioplasty and Stents in Canada (TASC II), a randomized evaluation of 43 patients with abrupt closure assigned to primary Palmaz-Schatz stent placement or prolonged autoperfusion balloon PTCA with "bailout" stent placement, showed a higher clinical success rate in stent-treated patients (90 vs. 42 percent).[152] Subsequent attempts to compared prolonged balloon inflation with primary stent placement for abrupt closure were unable to recruit patients[153] given the dramatic effect that stents had on the correction of major coronary dissections and avoidance of emergency CABG. Stents are currently indicated for the treatment of abrupt and threatened closure after balloon or new device PCI.

SAPHENOUS VEIN GRAFTS.

Although balloon PTCA of SVG lesions is associated with high (88 percent) procedural success rates,[154] clinical recurrence because of restenosis or progression of disease at other SVG sites is common.[154] Restenosis rates are highest in ostial lesions (58 percent) and in the body of the SVG (52 percent).[154] The Saphenous Vein Graft De Novo (SAVED) Trial randomly assigned 220 patients with de novo SVG lesions to treatment with Palmaz-Schatz stent placement or balloon PTCA alone.[147] Stenting was associated with higher procedural success rates (92 vs. 69 percent in balloon-treated patients; $p<0.001$) at the expense of more bleeding events (17 vs. 5 percent in balloon PTCA-treated patients; $p<0.01$) attributable to the aggressive anticoagulation regimen used in this study. Although restenosis was not significantly lower in stent-treated patients (37 percent) than in balloon PTCA-treated patients (46 percent), freedom from

significant cardiac events was better in the stent group (73 vs. 58 percent in balloon PTCA-treated patients; p=0.03). [147] Stents are the preferred therapy in patients with ostial or body SVG lesions. The risk of "no reflow" or distal embolization is higher in patients with severe SVG friability and in those with SVG thrombus.

TOTAL CORONARY OCCLUSIONS.

Balloon PTCA of chronic coronary occlusions is associated with reduced (47 to 69 percent) procedural success[155] [156] [157] and frequent (45 to 55 percent) recurrence,[158] [159] [160] [161] often (19 percent) as total coronary occlusion. Procedural success rates with total occlusion have steadily increased over the past several years, partly as a result of the introduction of hydrophilic guidewires[162] for crossing the occluded segments, but late (6 to 9 months) recurrence rates remain high (Fig. 38-6) .

After beneficial results were shown in pilot studies,[163] [164] three randomized trials confirmed the benefit of stent placement over balloon PTCA alone in patients with chronic occlusions.[148] [165] [166] In the Stenting in Chronic Coronary Occlusion (SICCO) Study, 119 patients with successful balloon PTCA of a chronic coronary occlusion were assigned to no further intervention or to Palmaz-Schatz stent placement.[148] Angiographic restenosis occurred less often in stent-treated patients (32 percent) than in patients receiving no further therapy (74 percent) (p<0.001). TLR was also needed less often in stent-treated patients (22 percent) than in balloon PTCA-treated patients (42 percent) (p=0.025). [148] This benefit was sustained at late follow-up.[167] In the Gruppo Italiano per lo Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) trial, 110 patients with total occlusions successfully treated by balloon PTCA were assigned to Palmaz-Schatz stent implantation or to no further

Figure 38-7 Acute posterior wall myocardial infarction caused by an acute left circumflex coronary artery in the right anterior oblique *(A,* arrow) and left anterior oblique *(B,* arrow) projection. A 3.0-mm balloon was used to recanalized the vessel *(C),* and placement of two 3.5-mm S670 stents resulted in an excellent final angiographic result *(D)*.

therapy. Angiographic restenosis occurred less often in stent-treated patients (32 vs. 68 percent in patients without stent placement; p<0.001). Stent-treated patients also had lower rates of reocclusion (8 vs. 34 percent; p=0.003) and TLR (5.3 vs. 22 percent; p=0.038).[165] A third study showed similar benefit with the Wiktor stent.[161]

ACUTE MYOCARDIAL INFARCTION.

When compared with thrombolytic therapy, primary balloon PTCA improves TIMI 3 flow rates and reduces the frequency of mortality, reinfarction, and stroke[168] [169] [170] [171] [172] [173] [174] (Fig. 38-7) . Primary balloon PTCA is limited in some cases by recurrent

in-hospital ischemia or reinfarction (10 to 15 percent), restenosis (37 to 49 percent), or late reocclusion (9 to 14 percent).[175] Failed primary balloon PTCA is associated with high (31 percent) in-hospital mortality rates and occurs more often in patients in cardiogenic shock and those with multivessel CAD.[176]

Stent placement may be useful in patients with acute myocardial infarction, either as primary therapy or as a "bailout" for the treatment of coronary dissection or residual stenosis after balloon PTCA. In a pilot multicenter study of 312 patients treated with primary PCI for acute myocardial infarction, stent placement was attempted in all eligible patients, provided that the infarct-related artery was between 3.0 and 4.0 mm, the lesion required only one or two stents, and no large thrombus, major sidebranch jeopardy, or excessive proximal tortuosity or calcification in the infarct-related artery occurred after PTCA.[177] Stenting was performed in 77 percent of patients and was successful in 98 percent, with TIMI 3 flow in 96 percent. Patients treated with stents had low rates of in-hospital death (0.8 percent), reinfarction (1.7 percent), recurrent ischemia (3.8 percent), and predischarge TLR for recurrent ischemia (1.3 percent).[177]

Smaller randomized trials comparing primary stenting and balloon PTCA in patients with acute myocardial infarction have shown a benefit for primary stent placement.[178] [179] [180] [181] [182] The Primary Angioplasty in Myocardial Infarction (PAMI) stent trial randomly assigned 900 patients with acute myocardial infarction to treatment with primary balloon PTCA or placement of the Palmaz-Schatz heparin-coated stent.[183] After 6 months, fewer patients in the stent group had angina (11.3 vs. 16.9 percent in the balloon group; p=0.02) or needed TLR (7.7 vs. 17.0 percent in the balloon group; p<0.001). Angiographic restenosis also occurred less often in stent-treated patients (20.3 vs. 33.5 percent in balloon-treated patients; p<0.001). [183]

Based on these results, primary PTCA (and primary or "provisional" stent placement) is indicated as an alternative to thrombolytic therapy in patients with acute myocardial infarction who are seen within 12 hours of symptom onset (or
12 hours with persistent symptoms), provided that the door-to-balloon time is less than 90 minutes, the hospital performs more than 200 PCI procedures per year, and the operator meets the ACC/AHA proficiency standards of more than 75 cases per year.[184] Primary PTCA is also indicated in patients in cardiogenic shock, provided that revascularization can be performed within 18 hours of the onset of cardiogenic shock, and in patients who have a contraindication to thrombolytic therapy.[184]

OTHER LESION SUBSETS.

It is less clear whether primary stent placement is preferred over balloon PTCA with "bailout" stenting in other lesion subsets.[184A] Although a subset analysis of STRESS suggested an advantage of stenting over balloon PTCA in smaller (<3.0 mm) vessels,[185] other studies have shown a worse outcome when stents are used in this setting.[143] It is not known whether primary stenting (vs. balloon PCA with "bailout"

stenting) is preferred in bifurcation lesions, diffuse disease, ostial lesions, or unprotected or protected (Fig. 38-8) left main lesions in patients with patent grafts to one or more left coronary territories.[143] Larger trials in the subsets are ongoing.

Complications

THROMBOSIS.

The early use of coronary stents was limited by high (3.5 to 8.6 percent) subacute thrombosis rates[30] [145] [151] [186] [187] [188] despite aggressive antithrombotic therapy with aspirin (
325 mg daily), dipyridamole (225 mg daily), periprocedural dextran 40, and intravenous heparin followed by oral warfarin. Clinical events associated with subacute thrombosis were profound, virtually always resulting in an untoward outcome (e.g., death, myocardial infarction, or emergency revascularization). Patients at "high-risk" for subacute thrombosis included those with unstable angina, residual proximal or distal dissection, angiographic thrombus or a filling defect, in-laboratory transient or sustained abrupt closure, multiple (more than three) stent implants, smaller (<3.0 mm) vessels, total occlusions, complex (type "C") morphology, left anterior descending or left circumflex lesion location, failed balloon PTCA, or recent (<1 week) myocardial infarction. Anatomical factors after stent deployment (e.g., underdilation of the stent, proximal and distal dissections, poor inflow or outflow obstruction, <3-mm vessel diameter) appeared to play more of a role than did suboptimal anticoagulation regimens in the development of subacute thrombosis in the early stent experience.[189] [190] [191] Lower frequencies of subacute stent thrombosis have been achieved with optimal stent deployment.[190]

Prompt vessel recanalization is paramount for the management of subacute thrombosis after stent placement. Although repeat balloon dilatation and, less commonly, CABG are the most prompt and effective methods of establishing reperfusion, intravenous thrombolysis should be used when a catheterization facility is not readily available.[192] Although recanalization can often be achieved after subacute thrombosis within 2 hours of symptom onset, myocardial infarction may still occur.[192]

BLEEDING.

Hemorrhagic complications were a major limitation associated with the use of coronary stents,[30] [145] [193] [194] particularly when aggressive anticoagulation regimens that included warfarin (Coumadin) were used. The introduction of reduced anticoagulation regimens has had a profound impact on the reduction of bleeding complications after stent placement. Brachial[195] and radial[196] [197] access sites, percutaneous vascular closure devices, and collagen implants have also reduced bleeding complications with modest success.[198] The safety and efficacy of collagen implants for sealing the femoral puncture site after stent implantation have also been evaluated.[198]

OTHER COMPLICATIONS.

Other problems include sidebranch occlusion (6 to 14 percent),[199] particularly in bifurcation lesions involving the origin of the sidebranch.[200] The clinical importance of the sidebranch occlusion relates to the size of the sidebranch and extent of myocardium that the sidebranch supplies. Open-cell and coiled stent designs may provide better access to sidebranches than afforded by

Figure 38-8 Complex stenosis involving the distal segment of the left main and proximal segment of the left anterior descending coronary arteries *(A,* arrow). After predilation, placement of a 3.0×18 mm NIR stent across the stenosis *(B)* resulted in the final angiographic result *(C)*.

the closed-cell, tubular slotted stent designs. Stent dislodgment from the delivery catheter is an uncommon occurrence with second- and third-generation stents with enhanced retention designs, but it may occur more often when stents are "hand-crimped" onto a balloon catheter. Stent embolization within the coronary artery is generally benign.[201] Stent margin dissections can occur during stent deployment or during postdeployment stent dilatation, particularly when stent dilatation strategies are directed at maximizing the internal stent diameter. The availability of shorter (15 mm), noncompliant balloons allows more precise stent dilatation when using high (16 atm) pressure, thereby reducing the frequency of edge dissections. Coronary perforation is also an uncommon occurrence after stent deployment, but it may occur during poststent deployment dilatation with an oversized balloon inflated to high pressure. No evidence indicates that higher balloon inflation pressures predispose to higher rates of stent restenosis.

RESTENOSIS.

"Very late" (>1 year) restenosis is a rare occurrence after coronary stenting in native coronary arteries. Three-year angiographic and clinical follow-up was obtained in 143 patients (147 lesions) who underwent Palmaz-Schatz stent placement in native coronaries.[202] After 14 months, TLR was necessary in only 2.1 percent of patients, whereas balloon PTCA of a new lesion was required in 7.7 percent of patients. Follow-up coronary angiography showed no further decrease in minimal lumen diameter between 6 months and 1 year (1.95 mm in both groups), as well as a significant (p<0.001) improvement in minimal lumen diameter between 6 months (1.94 mm) and 3 years (2.09 mm).[202] Similar very late improvements in lumen diameter have been reported in two other series,[203] [204] and sustained improvement in the very late (3 to 9 year) clinical outcomes of patients treated with stents has also been reported.[205] [206]

Designs

A number of balloon-expandable and self-expanding stents have become available for

clinical use over the past several years (Tables 38-5 and 38-6) . Each of these stents varies with respect to its metallic composition, strut design, stent length, delivery and deployment system, and arterial surface coverage, among other factors. One classification system suggested for stent design includes mesh stents, tubular stents, coil stents, ring stents, multidesign stents, and custom-designed stents.[207] Given the proliferation of new stent designs, it is likely that the classification system for stent design will also remain in continuous evolution. A number of stent-versus-stent trials have been used to evaluate the clinical equivalency of these stent designs. Although no stent has proved superior to the Palmaz-Schatz design for the prevention of restenosis in these series, substantial differences in clinical outcome may be found with the various stent designs as their use is expanded beyond the scope of randomized clinical study.[208]

PALMAZ-SCHATZ STENT.

The Palmaz-Schatz PS-153 stent (Cordis Corp., Warren, NJ) is a 15-mm, articulated slotted tube composed of 316L stainless steel that is available on a 5F delivery sheath in the United States or as a freestanding stent that is "crimped" onto a conventional balloon outside the United States. The Palmaz-Schatz stent was the first to show superiority over balloon PTCA for the prevention of restenosis[30] [145] [147] and has also been used for the treatment of major dissections and acute and threatened closure.[151] [209] Its slotted tube design imparted high radial compressive strength and yielded symmetrical expansion after deployment. The Palmaz-Schatz stent is no longer used clinically because it is relatively inflexible, is available in only a single 15-mm length, has a 1-mm articulation defect, which is a potential site for restenosis because of protrusion through the articulation site, and lends tenuous access to large sidebranches, among other factors. Because of deformation of the PS-153 at larger expansion diameters, other slotted tube stents, e.g., the P-104, P-154, and PS-204 biliary stents, were used "off-label" for the treatment of large (>4.0 to 5.0 mm) native coronaries and SVGs.[210] Newer stent designs with larger expansion diameters have obviated the need for these stents in current practice.

THE GIANTURCO-ROUBIN STENT.

The Gianturco-Roubin (GR) stent was the first stent approved for the treatment of abrupt vessel closure after balloon PTCA.[211] The GR stent is composed of a single 0.006-inch 316L stainless steel wire coiled into a series of interdigitating loops in a "clamshell" design; its 25-mm length provided adequate coverage for lesions up to 20 mm long. The major limitations of the first-generation GR stent were its relative inflexibility, requirement for larger (8F to 9F guides) guiding catheters for 3.5- and 4.0-mm stents, and an inability to precisely localize the position of the stent after deployment. The second-generation GR-II stent, available in 20- and 40-mm lengths, has gold radiopaque markers at both ends of the stent to allow easy visualization of the proximal and distal stent margins. A flat wire design and a central articulation spine prevent stent axial shortening on expansion. The GR-II stent is approved for the treatment of abrupt and threatened closure after balloon PTCA. It has limited use because of high restenosis rates associated with the clinical use of this stent.[212]

THE WIKTOR CORONARY STENT.

The Medtronic Wiktor stent is composed of a 0.005-inch tantalum wire arranged in a sinusoidal helical wave. Its radiopacity, preserved access to sidebranches, and flexibility led to its clinical evaluation and subsequent Food and Drug Administration approval for the treatment of abrupt and threatened closure after balloon PTCA.[213] The major disadvantages of the Wiktor stent are its potential for longitudinal elongation and lack of radial scaffolding in ostial lesions. Unraveling of the stent wire may also occur during withdrawal of the balloon catheter, from guide catheter trauma,[214] or after high-pressure balloon dilatation.

THE MULTILINK AND DUET STENTS.

The Multilink stent (Guidant Corp., Santa Clara, CA) is a 15-mm balloon-expandable, stainless steel stent designed with multiple rings connected by multiple links. The Multilink stent provides unique longitudinal flexibility, high radial compressive strength, minimal (<5 percent) longitudinal shortening after deployment, and lack of an articulation defect. A low (16.0 percent) restenosis rate was reported in the ASCENT Trial.[215] The DUET stent, a more flexible, radiopaque, next-generation balloon-expandable stent, is approved for the prevention of restenosis in larger (>2.75 mm) native vessels and for the management of abrupt or threatened closure. Strut thickness has been increased from 0.0022 to 0.0055 inches, and to improve stent flexibility, the shape of the ring has been rounded at its apex and the number of articulations between repeating units has been decreased from three articulations per unit to alternating three and two articulations per unit.[207] Edge dissections have been noted after clinical use of the DUET stent and are due to proximal and distal balloon margins up to 1.8 mm beyond the axial stent length and asymmetrical stent expansion as a result of stent compression from "dogboning" of the balloon if the balloon is inflated too rapidly. The TriStar stent with its very short (0.4 mm) balloon margin and a novel centering technology has reduced the frequency of these findings in early clinical experience; this stent was approved for clinical use in the United States in December 1999.

AVE MODULAR STENTS.

The Microstent II (Medtronic-Arterial Vascular Engineering, Santa Rosa, CA) is a balloon-expandable stent with 3-mm ring segments arranged in a zigzag design with eight axial struts connected by four crowns. Its major advantages are its marked flexibility in tortuous vessel and through previously deployed stents and its radiopacity for precise positioning in ostial locations or in bifurcation lesions. The Microstent II[216] has been progressively replaced with subsequent generations of the stent, the GFX and GFX-2 and, more recently, the S670 on the discrete balloon. These stents have shortened the repeating subunit from 3 to 2 mm for the GFX and GFX-2 stents and 1.5 mm for the S670 stent; these changes were accompanied by an increase in the number of crowns and laser junction points per unit. The S670 and S660 (for vessels <2.75 mm) are broadly functional stents that are distinguished by their ability to position the stent in

distal lesions with proximal tortuosity and through previously stented regions.

THE NIR STENT.

The NIR stent (Boston Scientific, Natick, MA) is a balloon-expandable stent composed of 316L stainless steel that is etched from a metal sheet, folded, and welded into its slotted tube design.[207] The NIR stent has seven or nine closed cells around its circumference[207] that impart a unique "transformable geometry" resulting in longitudinal flexibility during stent advancement and radial strength after stent deployment. The NIR stent provides symmetrical arterial scaffolding, and the smooth initial angiographic lumen contour is associated with infrequent late clinical events.[217] An equivalency study comparing the NIR stent with the PS-153 stent demonstrated comparable early and late clinical outcomes, with subsequent clinical approval in the United States.[218] Potential drawbacks of the NIR stent are its radiolucency, closed-cell design that limits access to large sidebranches, and lack of a high-pressure deployment balloon. Each of these issues has been addressed with subsequent NIR stent generations, including the NIR-ON-SOX high-pressure deployment system and the NIR Royal gold-plated stent, which enhances visualization.

THE CROSSFLEX-LC STENT.

The first-generation Cordis CrossFlex stent was a 15-mm balloon-expandable stent composed of a 0.005-inch tantalum wire arranged in a single, sinusoidal helical coil. Its major advantage was that it was flexible and radiopaque.[219] The current generation of the CrossFlex-LC is laser-cut from a 316L stainless steel hypotube configured into a dual-spine "S" wave design, now available in a broad range of diameters and stent lengths. Improved

TABLE 38-5 -- STENT AND STENT FILAMENT CHARAC

STENT	MANUFACTURER	STENT DESIGN	STENT MATERIAL	FILAMENT CONFIGURATION	STRUT THICKNESS (Inch)
PS 153	Cordis	ST	316L SS	Diamond shaped	0.0025
Crown	Cordis	ST	316L SS	Diamond shaped	0.0027
CrossFlex	Cordis	ST	316L SS	Dual-spine S wave design	0.0055
Minicrown	Cordis	ST	316L SS	Diamond shaped	0.0025
Bx Velocity	Cordis	ST	316L SS	Flex segment	0.0055

GR-II	Cook, Inc	Coil	316L SS	Flat wire coil with interdigitating spine	0.0055
Magic Wallstent	BSC	Mesh	Platinum-cobalt alloy	Braided wire mesh	0.003-0.004
Radius	BSC	ST	Nitinol	Zigzag struts constrained by outer sheath	0.0046
NIR	BSC	ST	316L SS	Multicellular slotted tube design	0.004
Multilink	Guidant	MC	316L SS	Multiple tubular rings interconnected with "S," "W," and "U" shapes	0.0022
DUET	Guidant	MC	316L SS	Corrugated ring design	0.0055
TriStar	Guidant	MC	316L SS	Corrugated ring design	0.0025
Wiktor	Medtronic-AVE	Coil	Tantalum	Single wire	0.005
GFX	Medtronic-AVE	Ring	316L SS	2-mm elliptorectangular sinusoidal rings with welded subunits	0.005
S670	Medtronic-AVE	Ring	316L SS	Elliptorectangular	0.0055
Bard XT	Medtronic-AVE	Ring	316L VM SS	2.1-mm zigzag modules connected by an interdigitating spine	0.0060
beStent	Medtronic-AVE	Ring	316L SS	Rectangular serpentine mesh shape with 2 gold markers at each end	0.004 × 0.0035
DivYsio	Biocompatibles	MC	316L SS	Interlocking arrowhead	0.0033
Paragon	Tyco, Inc	ST	Martinsitic Nitinol	Flat stent with short ST and interconnected sinusoidal links	0.0033 0.0072

BE=balloon expandable; BSC=Boston-Scientific-SciMed; MC=multicellular; Ring=ringed elements; SE
tube.

TABLE 38-6 -- CHARACTERISTICS OF NEW CORONARY STENTS

STENT	AVAILABLE DIAMETERS (mm)	IMPLANTABLE LENGTHS (mm)	MINIMUM GUIDE ID (Inch)	SHEATH	CROSSING PROFILE (Inch)	DEPLOYMENT PRESSURE (atm)
PS-153	3.0, 3.5, 4.0	15	0.084	Yes	0.065	4
Crown	3.0, 3.5, 4.0	15, 22, 30	3.0/3.5 mm--0.064 inch 4.0 mm--0.072 inch	No	0.051-0.057	7
CrossFlex	3.0, 3.5, 4.0	13, 18, 23, 28	0.064	No	0.047-0.054	10
Minicrown	2.25-3.25	11, 15	0.064	No	0.044-0.046	10
Bx Velocity	2.25-5.0	8-33	0.064	No	0.042-0.059	10
GR-II	2.5-5.0	12, 20 40	0.058-0.075 inch	No	0.056-0.073	4-6
Magic Wallstent	4.0-6.0 for RD of 3.0-5.5	15-47	0.064	Yes	0.056-0.058	NA
Radius	3.0, 3.5, 4.0	14, 20, 31	0.066	Yes	0.056	NA
NIR	2.5, 3.0, 3.5, 4.0	9, 16, 25, 32	0.064	No	0.043-0.049	7
Multilink	3.0, 3.5	15, 25	0.072	No	0.058	6
DUET	2.5-4.0	8-38	0.064	No	0.043-0.049	9
TriStar	2.5-4.0	8-38	0.064	No	0.043-0.049	8

Wiktor	3.0-4.5	16	2.5/3.0 mm--0.062 inch 3.5 mm--0.073 inch 4.0 mm--0.086 inch	No	NR	8
GFX	2.5-4.0	8, 12, 18, 24	0.064	No		9
S670			0.064	No	0.035	8
Bard XT	3.0, 3.5, 4.0	NR	NR	NR	NR	NR
BeStent	3.0, 3.5, 4.0	NR	NR	NR	NR	NR
DivYsio	2.0-4.0	10-28	0.064	No	0.029-0.0473	6
Paragon	3.0, 3.5, 4.0	9-36	0.062	No	0.052	8

ID=inner diameter; NR=not reported.

TABLE 38-7 -- EARLY AND LATE OUTCOME IN RANDOMIZED TRIALS OF STENT-VERSU
EQUIVALANCY TRIALS IN NATIVE VESSELS

VARIABLE	ASCENT		SMART		NIRVANA		SCORES		WIN	
	PS-153	Multilink	PS-153	MS-II	PS-153	NIR	PS-153	Radius	PTCA*	
Number of patients	522	518	331	330	430	418	551	545	287	
Lesion type	Focal <25 mm De novo lesion 3.00-3.75 mm		Focal <25 mm De novo or RS 3.00-4.00 mm		Focal <25 mm De novo or RS 3.00-3.75 mm		Focal <30 mm De novo or RS 2.75-4.25 mm		Focal <35 mm De novo or RS 3.00-5.50 mm	
Baseline factors										
Mean age (yr)	61	61	64	63	62	62	62	62	62	
Women (%)	31	33	30	31	32	30	32	30	27	

Diabetes mellitus (%)	20	19	17	19	22	23	19	22	23
Unstable angina (%)	70	69	69	65	73	75	65	65	68
LAD location (%)	44	42	42	47	40	42	38	40	23
Lesion Length (mm)	11.0	10.9	12.1	11.5	13.3	13.3	13.1	12.8	13.0
ACC/AHA B2 or C (%)	59	63	63	62	65	69	NR	NR	63
Maximum inflation (%) pressure (atm)	17.1	16.7	17.1	16.6	16.6	15.5	16.7	13.3	11.6
Reference diameter (mm)	2.94	2.95	2.93	2.93	3.03	2.97	3.05	3.06	3.09
MLD (mm)									
Baseline	1.05	1.05	1.06	1.02	1.08	1.04	0.99	1.01	1.04
Final	2.72	2.77	2.77	2.85	2.79	2.78	2.80	2.86	2.34
Follow-up	1.92	1.96	2.00	1.86	1.90	2.00	1.88	1.88	1.70
Percent diameter stenosis									
Baseline	64	64	64	65	64	65	66.5	67.3	66
Final	10	8	8	5	8	8	11.8	12.2	26
Follow-up	32	35	34	37	37	34	36.1	36.3	46
Restenosis rate (%)	22.1	16.0	22.9	24.8	22.4	19.3	18.7	24.2	38
Device success (%)	96.9	98.8	95.2	97.8	97.9	99.5	95.3	98.3	60
Procedural success (%)	93.9	95.7	94.7	94.1	94.3	95.4	93.5	97.0	96.2
30-Day event rates (%)	6.5	5.0	5.1	6.4	4.4[§]	4.3	3.1	2.9	5.9
Death	1.1	0[+]	0.3	0.6	0.2	0	0.4	0.4	0.4

Q wave infarction	1.0	0.6	0.6	0.6	0.9	0.5	0.4	0.2	0.4	
Emergency CABG	0.8	0.6	1.2	0.6	0	0.2	0.7	0.9	0.9	
Subacute thrombosis	1.8	0.6	0.3	0	0.5	0.5	0.4	0.2	0.7	
Follow-up period	9 mo		6 mo		9 mo		9 mo		6 mo	
Target vessel failure (%)	16.7	15.1	12.3	14.2	17.2	16.0	20.1	19.3	16.7	
TLR (%)	9.8	7.7	8.1	8.4	13.4	12.2	10.7	9.5	15.1	
Late clinical events (%)			14.8	16.1						
Death	2.5	1.4	0.3	1.5	0.9	1.0	1.1	1.5	3.5	
Q wave MI	1.0	0.6	0.0	0.3	0.9	0.7	0.5	0.7	1.7	
CABG	2.9	2.3	1.2	3.0	3.0	2.4	5.3	5.1	1.7	
Repeat PCI	6.9	5.4	8.2	6.7	8.6	7.2	11.1	10.3	18.8	

ACC/AHA=American College of Cardiology/American Heart Association; CABG=coronary artery bypa
LAD=left anterior descending artery; MI=myocardial infarction; MLD=minimal lumen diameter; NR=no
PCI=percutaneous coronary intervention; PS=Palmaz-Schatz; RS=restenotic lesion; TLR=target lesio
revascularization.

*Data from ASCENT,[215] SMART,[216] NIRVANA,[218] Stent Comparative Restenosis (SCORES) Trial,[222
Native Coronary Arteries (WIN) Trial,[223] and Paragon Stent Study.[224]*

*Balloon PTCA with "bailout" stenting.

$p < 0.05$.

$p < 0.005$.
§ In=hospital events.
¶ $p < 0.01$.

vessel scaffolding and access to large sidebranches are the major clinical advantages of the CrossFlex-LC over previous iterations of this stent.[220] It can be applied in a broad range of lesion morphologies. The SLAM Trial will compare the results of the CrossFlex-LC and balloon PTCA for the treatment of long lesions.

RADIUS STENT.

The Radius stent is a self-expanding, multiple-zigzag, nitinol stent that has a flexible restraining sheath allowing access to distal lesions, regions of calcification, and vessels distal to previously deployed stents.[207] Proper sizing is essential because the stent will not expand beyond its parent diameter.[207] Once deployed, Radius stents that are slightly larger than the vessel diameter will continue to expand after adjunct balloon PTCA.[221] A limitation of the Radius stent is that it requires precise positioning to avoid distal stent deployment. The Radius stent was approved for use in the United States in native coronary and SVG lesions based on results of the Stent Comparative Restenosis (SCORES) Trial, which demonstrated equivalency to the PS-153 stent in late clinical outcome.[222]

THE MAGIC WALLSTENT.

The Magic Wallstent is a self-expanding, wire mesh stent composed of a cobalt-based alloy with a platinum core. The Magic Wallstent is notable for its longitudinal flexibility, but precise localization can be somewhat difficult because of its somewhat unpredictable shortening (up to 20 percent) after deployment. Its major clinical uses are large (>4.0 mm) native vessels, particularly the right coronary artery, and SVGs. Sidebranch access is limited with the use of this stent, and it cannot be expanded beyond its nominal unconstrained diameter.

Stent-Versus-Stent Equivalency Studies

The Palmaz-Schatz PS-153 stent has been the traditional "gold standard" for regulatory-based stent comparisons (Table 38-7) . A series of randomized stent-versus-stent equivalency studies were performed to ensure the safety and efficacy of late outcomes associated with newer stent designs.[216] [224] Although these studies were designed to compare freedom from late target vessel failure, i.e., procedure success and freedom from TLR, death, or large myocardial infarction, it is now apparent that selection of stents by interventionists for clinical use is based on a number of secondary factors, including the profile, flexibility, and ease of use of the stent.

Stent equivalency trials have included patients with focal or restenotic native vessel lesions approachable with one or two coronary stents (lesion length <25 mm). In general, lesions were selected for treatment if they were suitable for Palmaz-Schatz stenting, and lesions with angulation greater than 45 degrees, proximal tortuosity, calcification, and thrombus were generally not included. It is likely

Figure 38-9 Two cases of in-stent restenosis. *A,* Diffuse in-stent restenosis in the proximal segment of the left anterior descending artery. A magnified view demonstrates diffuse tissue growth within the axial length of the stent (arrows). *B,* Another case of in-stent restenosis involving the left anterior descending artery (arrow). A focal region of renarrowing (large arrows) is seen in the proximal portion *(C)* and margin

(D) of the stent (small arrows).

Figure 38-10 *A,* Restenosis after coronary stent placement in the midportion of the left circumflex coronary artery. *B,* After rotational atherectomy and balloon angioplasty with a 3.5-mm balloon, an excellent angiographic result is obtained. This patient was enrolled in the randomized Stent and Radiation Therapy (START) Trial, which used catheter-based brachytherapy with strontium-90. *C,* The catheter is positioned (large arrows) and the radiation source train is advanced to the midportion of the circumflex artery (small arrows) to cover the margins of the injured segment by 5 to 10 mm.

that a performance difference may have been shown with the second- and third-generation stents had more complex lesion subsets been included in the studies.

These stent trials have identified a number of multivariable predictors of angiographic restenosis, including patient age, history of diabetes, left anterior descending artery lesion location, small postprocedural minimal lumen diameters, and longer lesion and total stent length. Multivariable predictors of target vessel revascularization (or failure) after stent placement include male gender, presence of thrombus, smaller postprocedural minimal lumen or reference vessel diameters, proximal left anterior descending artery location, longer lesion and total stent length, total number of stents, type C lesions, mandated follow-up angiography, restenotic lesions, or lesion calcification.

In-Stent Restenosis

The mechanism of restenosis after stent placement in virtually all cases is neointimal proliferation within the axial stent length.[225] Recurrence of symptoms may occur in 10 to 20 percent of patients within 12 months after stent implantation; after 6 to 12 months, it appears that contraction of intimal tissue results in slightly larger lumen dimensions over time.[226] Although some patients with multivessel CAD or multiple stent restenoses are best served by referral CABG, the majority of patients with in-stent restenosis can be safety and effectively treated with repeat PCI.[227] The mechanism of benefit of balloon angioplasty relates to both expansion of the stent and extrusion of the tissue through the stent struts and axially along its length.[228] Early tissue recoil may account for loss of 2.0 mm^2 in nearly 30 percent of patients within 40 minutes of the procedure.[229] Recurrence rates after balloon PTCA for stent restenosis ranged from 11 to 17 percent in two large series,[230] [231] although higher (up to 80 percent) recurrence rates have been reported depending on vessel size, pattern of restenosis (e.g., intrastent, stent margin, or remote disease), and the time to presentation[231A] (Fig. 38-9) .

Atheroablation by DCA, RA, or ELCA has been used in patients at "high risk" of recurrence after PCI for in-stent restenosis,[227] but an advantage over conventional balloon PTCA alone has not been demonstrated in a prospective, randomized study. A consecutive registry series of 60 patients with "diffuse" native vessel in-stent restenosis

compared early and late outcomes in patients treated with either conventional balloon PTCA or debulking by RA or DCA followed by balloon PTCA.[232] The procedural success rate was 100 percent in both groups, and despite longer lesion lengths in the debulking group (18.4 vs. 13.5 mm in the PTCA-only group; *p*=0.09), treatment with atherectomy resulted in a lower frequency of postprocedure stenoses (18 vs. 26 percent in the PTCA-only group; *p*=0.01). One-year repeat TLR was required in 28 percent of patients in the debulking group and 46 percent in the balloon PTCA group (*p*=0.18). Pending the results of additional randomized studies, it appears that debulking is most useful in patients with diffuse (>15 mm) in-stent restenosis.

Three studies have shown the value of gamma irradiation with iridium-192 in preventing angiographic and clinical recurrence in patients undergoing treatment for in-stent restenosis. In the Scripps Radiation to Inhibit Proliferation after Stent Implantation (SCRIPPS) Trial, 55 patients were randomly assigned to the iridium-192 group or placebo group after treatment of stent restenosis. Angiographic restenosis occurred in 17 percent of the iridium-treated patients and 54 percent of the placebo-treated patients (*p*=0.01) as a result of a reduction in late lumen loss in the iridium-192 group (0.38 vs. 1.03 mm in placebo-treated patients; *p*=0.03). [233] These effects have been sustained for up to 3 years after the procedure.[233A] Two other larger studies have shown similar benefits.[234] [235] Studies evaluating results of the use of beta radiation for the treatment of in-stent restenosis are ongoing (Fig. 38-10) .

ANTICOAGULATION DURING PERCUTANEOUS CORONARY INTERVENTIONS (See also Chap. 62)

The safety of PCI has been substantially improved over recent years with the routine use of conventional (e.g., aspirin, ticlopidine, clopidogrel) and novel (e.g., GP IIb-IIIa inhibitors) platelet inhibitors and conventional (e.g., unfractionated

heparin, low-molecular-weight heparin [LMWH]) thrombin inhibitors.[236] [237] [238] The safety and efficacy of second-generation direct thrombin inhibitors (e.g., hirudin, bivalirudin [Hirulog], argatroban) have also been evaluated in the setting of PCI, but their clinical use is currently limited to the setting of heparin-induced thrombocytopenia syndromes.

Antiplatelet Therapy

ASPIRIN.

This agent reduces the frequency of ischemic complications after PCI by 64 to 77 percent.[236] [239] Although the minimum effective aspirin dosage is not known, doses ranging between 80 and 325 mg are generally given 2 or more hours before PCI. The use of dipyridamole provides no incremental value over aspirin alone, so dipyridamole is not currently recommended.[240] Aspirin-intolerant patients may be treated with

thienopyridine blockers of platelet adenosine diphosphate (ADP) receptors, such as ticlopidine (250 mg twice daily)[239] or clopidogrel (300-mg loading dose followed by 75 mg daily), but these agents should be given earlier than 24 hours prior to elective PCI to achieve maximum platelet inhibition.[241]

TICLOPIDINE.

In patients undergoing stent implantation, ticlopidine, as an adjunct to aspirin, reduces the frequency of 30-day clinical events, including the occurrence of subacute thrombosis.[242] [243] In a clinical trial of 517 patients at "high risk" for stent thrombosis after Palmaz-Schatz stenting, those treated with aspirin plus ticlopidine experienced a 75 percent reduction in early complications in comparison to those who received aspirin plus intravenous heparin plus phenprocoumon.[242] Patients receiving antiplatelet therapy also had an 82 percent lower risk of myocardial infarction and a 78 percent lower need for repeat balloon PTCA than did patients receiving anticoagulation therapy.[242] Bleeding complications were also lower in patients treated with antiplatelet therapy.[242] The Stent Anti-thrombotic Regimen Study (STARS) evaluated the effect of aspirin alone, aspirin plus ticlopidine, and aspirin plus warfarin on the occurrence of 30-day ischemic endpoints in 1653 "low-risk" patients undergoing successful Palmaz-Schatz stent placement.[243] Clinical events, including subacute thrombosis, were reduced by 85 percent in patients treated with aspirin plus ticlopidine.[243]

Ticlopidine has a number of significant side effects in comparison to aspirin, including gastrointestinal distress (20 percent), cutaneous rashes (4.8 to 15 percent), and liver function test abnormalities. Severe, but generally reversible neutropenia and aplastic anemia occur in 1 percent or less of patients. Rare episodes of fatal thrombotic thrombocytopenic purpura have also been reported with ticlopidine.[244] A shorter (10 to 14 days) duration of ticlopidine therapy may reduce the risk of these side effects.[245] [246]

CLOPIDOGREL.

This newer thienopyridine inhibitor of ADP-mediated platelet aggregation has also been used in patients undergoing stent placement.[247] [248] The CLASSICS trial showed no difference in clinical efficacy between clopidogrel and ticlopidine, with fewer side effects in patients treated with clopidogrel.[249] Based on randomized studies and single center registries that did not show a difference in outcome with these two agents,[250] [250A] clopidogrel may be used as an alternative to ticlopidine in patients undergoing stent implantation.

GLYCOPROTEIN IIb-IIIa INHIBITORS.

Aspirin is only a partial inhibitor of platelet function, and early ischemic events develop in 3.0 to 12.8 percent of aspirin-treated patients undergoing PCI.[5] [6] [9] Thrombin and collagen are potent platelet agonists that can cause ADP and serotonin release and activate GP IIb-IIIa fibrinogen receptors on the platelet surface.[251] Functionally active GP IIb-IIIa activation serves as the "final common pathway" of platelet aggregation by binding fibrinogen and other adhesive proteins that bridge adjacent platelets.[252] A

number of intravenous and oral inhibitors of the GP IIb-IIIa receptor have been developed for clinical use.

ABCIXIMAB

The safety and efficacy of abciximab was first evaluated in the Evaluation of 7E3 for the Prevention of Ischemic *C*omplications (EPIC) Trial, a clinical study of 2099 patients at "high risk" for complications after PCI[19] (Table 38-8) . "High-risk" criteria included patients with acute myocardial infarction, refractory unstable angina, and "high-risk" clinical and angiographic features. All patients received aspirin 325 mg and a non-weight-adjusted, 10,000- to 12,000-IU heparin bolus prior to PCI and were then randomly assigned to treatment with placebo, a bolus of abciximab 0.25 mg/kg, or the same bolus of abciximab followed by a 12-hour abciximab infusion at 10 mug/min. Bolus and infusion abciximab was associated with a 35 percent reduction in frequency of the composite clinical endpoint, defined as death, nonfatal myocardial infarction, repeat revascularization, or procedural failure (8.3 vs. 12.8 percent in placebo-treated patients; p=0.008). [19] This benefit was greatest in patients with unstable clinical syndromes (acute myocardial infarction and refractory unstable angina).[259] [259A] Pretreatment with abciximab in a randomized trial of 429 patients with acute myocardial infarction was associated with a significant (p=0.03) reduction in the incidence of death, reinfarction, or urgent target vessel revascularization at 30 days in patients treated with abciximab (4.9 percent) versus placebo (10.3 percent). No difference in 6-month restenosis was noted between the two groups.[260]

The Evaluation of PTCA to Improve Long-Term Outcome by Abciximab GP IIb-IIIa Blockade (EPILOG) Trial randomly assigned 2792 "low-risk" patients who were treated with aspirin to standard-dose, weight-adjusted (100 units/kg) heparin and placebo; standard-dose, weight-adjusted heparin and abciximab; or low-dose, weight-adjusted (70 units/kg) heparin. The 30-day composite event rate was significantly (p<0.001) lower in patients treated with abciximab and low-dose (5.2 percent) or standard-dose (5.4 percent) heparin than in patients treated with standard-dose heparin and placebo (11.7 percent).[253] While one study suggested a beneficial effect with abciximab in patients undergoing SVG angioplasty,[261] a larger study failed to demonstrate a convincing reduction in these patients at high risk for macroembolization.[262] "Bailout" abciximab is often given during or just after PCI for the presence of residual dissection, thrombus, or suboptimal results,[263] although its value has not been demonstrated in prospective studies.

The EPISTENT trial randomly assigned 2399 patients with ischemic CAD to stenting plus placebo, stenting plus abciximab, or balloon PTCA plus abciximab.[254] The primary 30-day endpoint, a combination of death, myocardial infarction, or need for urgent revascularization, occurred in 10.8 percent of patients in the stent-plus-placebo group, 5.3 percent of patients in the stent-plus-abciximab group (hazard ratio 0.48; p<0.001), and 6.9 percent of patients in the balloon-plus-abciximab group (hazard ratio 0.63; p=0.007). [254] The occurrence of death and large (CPK-MB more than five times normal) myocardial infarction occurred in 7.8 percent of the placebo group versus 3.0 percent of the stent-plus-abciximab group (p<0.001) and 4.7 percent of the balloon PTCA-plus-abciximab group (p=0.01). [254] No significant differences in bleeding

complications were noted among the groups.[254] The need for late revascularization was not significantly (p=0.22) lower in patients receiving stenting plus abciximab (8.7 percent) than in patients receiving stenting plus placebo (10.6 percent).[255] However, a significant (p=0.02) reduction was seen in revascularization in diabetic patients assigned to stenting plus abciximab (8.1 percent) when compared with patients receiving stenting plus placebo (16.6 percent).[255] A pooled analysis also suggests that abciximab may reduce mortality in diabetic patients.[263A]

EPTIFIBATIDE

The effect of eptifibatide (Integrelin) on 30-day clinical events was evaluated in 4010 patients undergoing PCI. The patients were assigned to placebo, an eptifibatide bolus of 135 mug/kg followed by a low-dose eptifibatide infusion at 0.5 mug/kg/min for 20 to 24 hours, or the same eptifibatide bolus and a higher-dose infusion at 0.75 mug/kg/min for 20 to 24 hours.[256] The primary endpoint was a 30-day composite occurrence of death, myocardial infarction, unplanned CABG or repeat PCI, or coronary stenting for abrupt closure. Such events occurred in 11.4 percent of patients in the placebo group versus 9.2 percent in the 135/0.5 eptifibatide group (p=0.063) and 9.9 percent in the eptifibatide 135/0.75 group (p=0.22). [256] In a treatment-received analysis, the eptifibatide 135/0.5 regimen produced a significant reduction in the composite endpoint (9.1 vs. 11.6 percent in placebo-treated patients; p=0.035), but the eptifibatide 135/0.75 regimen produced a less substantial reduction (10.0 vs. 11.6 percent in placebo-treated patients; p=0.18). Eptifibatide treatment did not increase rates of major bleeding or transfusion. It is now recognized that the eptifibatide infusion dosage in the Integrelin to Minimise Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) Trial was insufficient to provide adequate platelet inhibition. The ongoing randomized ESPRIT Trial will compare a 180-mug/kg double bolus of eptifibatide

TABLE 38-8 -- EARLY AND LATE OUTCOME IN RANDOMIZED TRIALS OF GLYCOPROTEIN INTERVENTION

VARIABLE	EPID			EPILOG		
	Placebo	Abciximab		Placebo+SD Heparin	Abciximab	
		Bolus	*Bolus+Infusion*		*+ SD Heparin*	*+ LD Heparin*
Lesion type		High risk			Low risk	
Years of entry		11/91-11/92			2/95-12.95	
Number of patients	697	695	708	939	918	935
Baseline factors						
Mean age (yr)	61	60	62	60	60	60

Women (%)	27	28	29	28	27	29
Diabetes mellitus (%)	26	23	23	24	22	23
Unstable angina (%)	NA	NA	NA	50	46	46
Stent use (%)	0.6	1.7	0.6	NR	NR	NR
Composite primary endpoint (%)	12.8	11.4	8.3	11.7	5.4	5.2
Early complications (%)						
Death	1.7	1.3	1.7	0.8	0.4	0.3
Q wave infarction	2.3	1.0	3.0	0.8	0.5	0.4
Emergency CABG	3.6	2.3	2.4	1.7	0.9	0.4
Emergency PTCA	4.5	3.6	0.8	3.8	1.5	1.2
Major bleeding (%)	7	11	14	3.1	3.5	2.0
Follow-up time		3 yr			6 mo	
Late clinical outcome (%)	47.2	47.4	41.1	25.8	22.3	22.8
Death	8.6	8.1	6.8	1.7	1.4	1.1
Q wave MI	13.6	12.2	10.7	1.6	1.4	1.3
Revascularization	40.1	38.6	34.8	19.4	18.4	19.0
Repeat PTCA	NR	NR	NR	NR	NR	NR
CABG	NR	NR	NR	NR	NR	NR

*$p < 0.001$.

$p < 0.005$.

CABG=coronary artery bypass grafting; LD=low dose; MI=myocardial infarction; PTCA=percutaneous

Data from Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) Trial,[19] Evaluation o Glycoprotein IIb-IIIa Blockade (EPILOG) Trial,[253] EPISTENT,[254] [255] Integrelin to Minimise Platelet Ag Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE).[257] [258]

followed by a 2.0-mug/kg/min infusion with placebo in lower-risk patients undergoing

stent implantation.

TIROFIBAN

The effect of tirofiban, a nonpeptidyl tyrosine derivative, on outcomes after PCI was evaluated in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) Trial, a randomized, double-blind, placebo-controlled study involving 2139 patients undergoing PCI who were seen within 72 hours of an acute coronary syndrome.[257] All patients received aspirin and heparin and were randomly assigned to a tirofiban bolus (10 mug/kg over a 3-minute period) plus infusion (0.15 mug/kg/min) or to a placebo bolus plus infusion for 36 hours after PCI. The primary 30-day composite endpoint was 16 percent lower with tirofiban treatment (p=0.160), although a 38 percent relative reduction in the composite end point was noted at 48 hours (p=0.005) and a 27 percent relative reduction at 7 days (p=0.022). [257] When only urgent or emergency balloon PTCA or CABG were included in the composite endpoint, the 30-day event rates were 10.5 percent for the placebo group and 8.0 percent for the tirofiban group, a relative reduction of 24 percent (p=0.052). Major bleeding tended to be higher in tirofiban-treated patients (5.3 vs. 3.7 percent in the placebo-treated patients; p=0.096), although no difference in bleeding events could be found when using the TIMI criteria[264] for major bleeding.[257] A prospective trial, the TARGET study, will compare clinical outcome in over 4000 patients undergoing PCI treated with either abciximab or tirofiban.

As a class of agents, the GP IIb-IIIa inhibitors (i.e., abciximab, eptifibatide, and tirofiban) have demonstrated benefit in improving clinical outcomes within the first 30 days after PCI. The primary effect of these agents has been on the reduction of ischemic complications, including non-Q-wave myocardial infarction and recurrent ischemia. No consistent evidence indicates that GP IIb-IIIa inhibitors reduce the frequency of restenosis. These agents should be considered for use in all patients undergoing PCI, particularly in those with unstable angina, primary balloon PTCA, or stent placement for acute myocardial infarction, and in other patients at higher risk for ischemic complications after PCI.

Antithrombin Therapy

UNFRACTIONATED HEPARIN (see also Chap. 62) .

Unfractionated heparin is the most common thrombin inhibitor used during PCI, although other antithrombin III-dependent agents (e.g., LMWH) and antithrombin III-independent agents (e.g., hirudin, bivalirudin, and argatroban) have also been tried. Intravenous heparin is used during PCI to prevent arterial thrombus formation at the site of vessel wall injury and on coronary guidewires and other catheter equipment used for coronary dilatation.[265] Patients with acute coronary syndromes may also benefit from prolonged (>24 hours) heparin therapy alone before PCI[266] or in combination with GP IIb-IIIa inhibitors.[267] [268] [269]

Activated partial thromboplastin times have been used to monitor the intensity of anticoagulation *before* and *after* PCI, but these methods have been less useful for

monitoring anticoagulation *during* PCI inasmuch as large amounts of heparin are required to prevent thrombus formation during arterial manipulations.[270] "Near-patient" activated clotting time (ACT) monitoring has facilitated heparin dose titration during PCI,[271] although ACT responses have shown marked variability in patients who received a non-weight-adjusted heparin bolus. These differences have been attributed to patient-to-patient differences in heparin sensitivity and clearance, body weight, nitroglycerin use, and coexisting conditions that predispose to heparin resistance (e.g., heparin antibodies, oral contraceptive use, endocarditis, disseminated intravascular coagulation, and placement of an intraaortic balloon pump). Patients with unstable angina and those with complex coronary lesions (irregular borders, overhanging edges, or filling defects) also have higher heparin dosing requirements.[272]

At least two studies have retrospectively related the ACT value to clinical outcome after PCI.[237] [238] Patients who had complications after PCI in one study had lower mean baseline ACT (HemoTec) values after the initial heparin bolus and at the end of the procedure than did those without complications,[238] although this finding may be confounded because heparin resistance may be a marker of high-risk anatomy.[273] In another study, patients with abrupt closure had a lower mean ACT (Hemochron) at the time of first balloon inflation than did those without this complication (352 vs. 388 seconds; $p<0.002$). [237] An inverse relationship was shown between in-laboratory ACT values and the probability of abrupt closure ($p=0.018$). [237] Higher ACT levels [274] and other markers of excess anticoagulation[193] are also independent predictors of bleeding complications after PCI.

More recent studies have also evaluated the safety of lower-dose heparin during PCI. Low-dose bolus heparin at 5000 IU, followed by early (<12 hours) postprocedural sheath removal, in 1375 consecutive patients was associated with infrequent fatal complications (0.3 percent), emergency CABG (1.7 percent), myocardial infarction (3.3 percent), or repeat angioplasty within 48 hours (0.7 percent).[275] In a randomized study of 400 patients assigned to fixed-dose heparin at 15,000 IU or weight-adjusted heparin at 100 IU/kg, clinical outcomes were similar in the two groups (95 percent success rates).[276] Use of the weight-adjusted heparin did result in earlier sheath removal and more rapid transfer to a step-down unit.[276] Lower anticoagulation levels are also needed to avoid bleeding complications during the concomitant administration of agents such as GP IIb-IIIa inhibitors.[253]

The effect of subcutaneous heparin on the reduction in bleeding complications was evaluated in 151 patients treated either with an intravenous heparin infusion at 1000 units/hr for 12 to 18 hours after angioplasty or with subcutaneous heparin at 12,5000 units every 12 hours for three doses and early sheath removal.[277] The rate of ischemic complications was similar in both groups, but the risk of bleeding was significantly lower in the group managed with early (<12 hours) sheath removal and treated with subcutaneous heparin.[277]

Weight-adjusted heparin dosing regimens of 70 to 100 IU/kg or sex-adjusted bolus heparin consisting of 7000 units for women and 8000 units for men is now used in an attempt to avoid "overshooting" the ACT.[278] It is generally recommended that sufficient unfractionated heparin be administered during PCI to achieve an ACT between 250 and

300 seconds with the HemoTec monitor and between 300 and 350 seconds when using the Hemochron monitor.[271] When heparin is not adjusted by weight, the ACT should be monitored frequently and additional, smaller heparin boluses of 2000 to 5000 IU given until the target ACT is achieved. Routine use of intravenous heparin after PCI is no longer indicated because of several randomized studies showing no benefit in reducing ischemic complications and higher access site bleeding complication rates.[279] [280] Early sheath removal is strongly encouraged when the ACT falls to less than 150 to 180 seconds.

LOW-MOLECULAR-WEIGHT HEPARIN (see also Chap. 62) .

An increasing number of patients with unstable angina are treated with LMWH prior to PCI.[281] Because of the difficulty monitoring anticoagulation levels with LMWH during PCI, conventional dosages of unfractionated heparin are also recommended. In this setting, conventional monitoring methods, such as the ACT, may underestimate the true degree of periprocedural anticoagulation. A pilot randomized trial of 60 patients undergoing PCI and treated with unfractionated heparin or enoxaparin (1 mg/kg intravenously) showed no difference in safety between the two anticoagulants.[282] Routine use of LMWH as the sole anticoagulant during PCI cannot be recommended at this time pending the results of large, multicenter trials evaluating the use of LMWH during PCI.

DIRECT THROMBIN INHIBITORS

A number of direct thrombin inhibitors have been evaluated during PCI. In the Hirudin in a European Trial Versus Heparin in the Prevention of Restenosis after PTCA (HELVETICA) Study,[283] 1141 patients with unstable angina scheduled for PCI were treated with aspirin and randomized to receive a heparin bolus of 10,000 units plus infusion at 15 units/kg/hr for 24 hours; a hirudin bolus of 40 mg plus intravenous infusion at 0.2 mg/kg/hr for 24 hours; or a hirudin bolus of 40 mg, intravenous infusion at 0.2 mg/kg/hr for 24 hours, and subcutaneous infusion of 40 mg twice daily for an additional 3 days. Hirudin use was associated with a 39 percent reduction in early cardiac events (p=0.023), although clinical outcomes were similar 7 months later in the three groups. A recombinant hirudin (lepirudin) bolus of 0.4 mg/kg and infusion at 0.15 mg/kg/hr is approved for use in the United States in patients with heparin-induced thrombocytopenia.

Bivalirudin (Hirulog or AngioMax) was compared with unfractionated heparin in the Hirulog Angioplasty Study, a randomized trial of 4098 patients with postinfarction or unstable angina undergoing coronary angioplasty and then assigned to receive a heparin bolus at 175 units/kg and a 15-unit/kg/hr infusion for 18 to 24 hours or to receive a bivalirudin bolus of 1.0 mg/kg and a 2.5-mg/kg/hr infusion for 4 hours, followed by 0.2 mg/kg/hr for 14 to 20 hours.[284] Although bivalirudin did not reduce the likelihood of in-hospital death, Q wave or non-Q-wave myocardial infarction, or emergency CABG,

bivalirudin therapy reduced the likelihood of bleeding complications (odds ratio of 0.4; $p<0.001$). [284] In the prospectively stratified cohort of 704 patients with post-myocardial infarction angina, bivalirudin resulted in lower rates of major ischemic complications (9.1 vs. 14.2 percent in heparin-treated patients; $p=0.04$) and lower rates of bleeding (3.0 vs. 11.1 percent in heparin-treated patients; $p<0.001$).

PHARMACOLOGICAL APPROACHES TO RESTENOSIS

IVUS studies have provided unique insight into the dynamic changes that occur within the vessel wall after PCI and suggest that arterial remodeling[285] and, to a lesser extent, intimal thickening account for most of the lumen renarrowing that occurs after balloon PTCA or coronary atherectomy.[12] [285] [286] In contrast, restenosis after stent implantation is due to intimal thickening within the axial length of the stent and its border in virtually all cases.[225] Conventional pharmacological strategies have not consistently reduced the frequency of angiographic or clinical restenosis indices after PCI (Table 38-9) despite a large number of agents having been tried.[287]

PLATELET INHIBITORS.

Randomized studies evaluating the effect of aspirin on restenosis have produced conflicting results, potentially attributable to the varied dosage and duration of aspirin therapy.[236] [288] [289] [290] The majority of these studies have shown little, if any sustained effect of aspirin on restenosis prevention, although long-term aspirin at dosages greater than 100 mg daily is recommended after PCI for secondary prevention of cardiac events.[278] Platelet thromboxane A_2 and serotonin receptor antagonists, such as

TABLE 38-9 -- ANGIOGRPAHIC AND CLINICAL ENDPOINTS FOR RESTENOSIS PERCUTANEOUS CORONARY INTERVENTION

ANGIOGRAPHIC	CLINICAL
Binary	**Binary**
>50% follow-up diameter stenosis	Death
	Nonfatal myocardial infarction
>0.72-mm loss in lumen diameter	
	Revascularization
>20% loss in gain achieved	Target vessel failure
	Target lesion revascularization
Continuous	
Follow-up minimal lumen diameter	Target vessel revascularization
	Recurrence of angina
Follow-up % diameter stenosis	**Continuous**
	Exercise test duration

Late lumen loss Loss index	

sulotroban, ketanserin, and prostacyclin, have also been tried without success.[291] [292] [293] [294] [295]

Platelet aggregation during PCI may occur as a result of GP IIb-IIIa activation by a number of agonists, which renders the inhibition of a single agonist problematic for the prevention of restenosis. "Final common pathway" GP IIb-IIIa platelet receptor inhibitors provide potent (>80 percent) blockade of platelet aggregation during PCI, irrespective of the platelet agonist. The EPIC study reported a 23 percent reduction in cumulative 6-month clinical events (p=0.001),[296] but these events were primarily related to the prevention of early (<30 day) periprocedural events.[19] Other studies did not show a consistent reduction in clinical or angiographic restenosis with GP IIb-IIIa inhibitors.[258] A subgroup analysis of diabetic patients undergoing stent implantation in EPISTENT demonstrated a reduction in clinical restenosis at 12 months from 22.4 percent in those receiving placebo to 13.7 percent in those receiving abciximab.[297] These findings in diabetic patients require confirmation in future prospective trials.

ANTITHROMBINS.

Neither intravenous[279] or subcutaneous[298] unfractionated heparin nor LMWH, including enoxaparin, reviparin, nadroparin, and fraxiparin,[299] [300] [301] prevents restenosis after PCI. Antithrombin III-independent thrombin inhibitors such as bivalirudin,[302] hirudin, [283] and long-term warfarin[303] also have had little effect on the prevention of restenosis. It is not known whether local delivery of LMWH will result in a reduction in restenosis after stent placement, although studies evaluating this method of delivery are ongoing.

VASODILATORS.

Although calcium channel antagonists may reduce the occurrence of coronary vasospasm early after PCI, diltiazem and verapamil do not prevent restenosis after PCI.[304] Treatment with the nitric oxide donors linsidomine and molsidomine was associated with a modest improvement in the long-term angiographic result after PCI but had no effect on clinical outcome.[305] The improved angiographic result related mostly to a better immediate procedural result because late lumen loss did not differ significantly between groups.[305]

ANTIPROLIFERATIVE AGENTS.

Agents thought to interfere with smooth muscle cell migration and proliferation, such as cilazapril[306] [307] and fosinopril,[308] do not reduce the frequency of restenosis after balloon PTCA, although their effect after stent placement is less well studied.[309] Angiopeptin, a nonspecific growth factor inhibitor, has had inconsistent effects on restenosis, related in part to the short half-life and varied administration among studies.[310] [311] Preliminary studies using trapidil, an agent that may antagonize

platelet-derived growth factor, have been favorable,[312] but larger studies are needed.

ANTIINFLAMMATORY AGENTS AND ANTIOXIDANTS.

Probucol, an anti-antioxidant agent, has been shown to reduce restenosis after balloon angioplasty,[313] [314] primarily as a result of its effect on the prevention of arterial remodeling.[314] In one study, 317 patients undergoing PCI were randomly assigned to either twice-daily placebo; probucol 500 mg; multivitamins consisting of 30,000 IU of beta-carotene, 500 mg of vitamin C, and 700 IU of vitamin E; or both probucol and multivitamins for 4 weeks before and 6 months after PCI. Restenosis rates were 20.7 percent in the probucol group, 28.9 percent in the combined-treatment group, 40.3 percent in the multivitamin group, and 38.9 percent in the placebo group (p=0.003 for probucol vs. no probucol).[314] Probucol, not marketed in the United States, lowers high-density lipoprotein levels. Tranilast, an antiallergic drug used widely in Japan, has been shown to reduce restenosis after successful DCA from 26 percent in patients not treated with tranilast to 11 percent in patients treated with tranilast (p=0.03). [315] A large-scale trial evaluating the effect of tranilast on the prevention of restenosis is ongoing. Other antiinflammatory agents such as dexamethasone[316]

and colchicines[317] have had limited effect on the prevention of restenosis.

LIPID-LOWERING AGENTS.

Several lipid-lowering agents, such as lovastatin, [318] [319] pravastatin,[320] and fluvastatin,[321] have been evaluated as treatment to prevent restenosis after PTCA. While these agents have had limited clinical success in preventing restenosis, lipid reduction therapy is indicated after PCI for the progression of atherosclerosis at remote sites.[322] [323] At least one pilot study has shown that low-density lipoprotein (LDL) apheresis may also reduce restenosis after PCI.[324]

While meta-analysis of several smaller studies suggests a benefit of fish oil on the prevention of restenosis,[325] little evidence supports the routine use of omega-3 fatty acid supplements for preventing restenosis after PTCA[326] [327] [328] [329] despite initially encouraging pilot studies. [330] [331] [332]

WHY DRUGS HAVE NOT BEEN EFFECTIVE.

The limited success in identifying a single pharmacological agent to prevent restenosis after PCI may be related to several factors. Most importantly, our understanding of the pathogenesis of restenosis after PCI has changed dramatically over the past 5 years. Arterial remodeling and contraction of the arterial wall have emerged as important contributors to restenosis after balloon PTCA,[12] [285] although the factors leading to these dynamic changes are not known. Animal models have been poorly predictive of

agents that prevent restenosis in clinical studies, possibly because of differences in the pathogenesis of restenosis in different models (i.e., lipid-rich narrowings in hypercholesterolemic rabbits vs. intimal hyperplasia in arteries injured by overexpanded balloons [rats] or stents [pig]). Also, drug dosages higher than the dosage clinically tolerable in humans have been used in the experimental models,[333] [306] and the ineffectiveness of some agents may relate to inadequate drug levels. Given the differences in the pathogenesis of balloon PTCA and stent restenosis, it is possible that agents found ineffective for the prevention of restenosis after balloon PTCA may have value in preventing stent restenosis.

RADIATION THERAPY TO RETARD RESTENOSIS.

Emerging data suggest that intracoronary radiotherapy can reduce the intimal hyperplasia in animal models of restenosis.[334] [335] [336] [337] Early pilot trials have suggested that both gamma[338] and beta[339] sources prevent restenosis after PCI in native coronary lesions.[340] [341] [342] A number of studies are currently ongoing to assess the effect of radiation on the prevention of de novo and restenotic coronary lesions.

INDICATIONS FOR PERCUTANEOUS CORONARY INTERVENTIONS

The major value of coronary revascularization, whether performed by surgical or percutaneous methods, is the relief of symptoms and signs of ischemic CAD caused by obstructive epicardial disease. While two studies have suggested that PCI may reduce mortality and subsequent myocardial infarction risk when compared with medical therapy,[343] these events are better treated with systemic therapies aimed at reducing the extent of atherosclerosis, such as lipid-lowering therapy.[344] In contrast, CABG prolongs life in certain anatomical subsets, such as patients with left main disease, three-vessel CAD, or left anterior descending artery disease with involvement of one or two additional vessels, irrespective of left ventricular function.[345] The risks and benefits of coronary revascularization must be carefully reviewed with the patient and family members, if appropriate, before these procedures are performed. Guidelines for the performance of PCI and CABG have been published by the ACC/AHA.[18] [345]

ASYMPTOMATIC PATIENTS OR THOSE WITH MILD ANGINA.

Patients who are asymptomatic or have only mild symptoms are generally best treated with medical therapy, unless one or more significant lesions subtend a large area of viable myocardium confirmed by objective noninvasive testing, the patient prefers to maintain an aggressive life style or has a high-risk occupation, and the procedure can be performed with a high chance of success and low likelihood of complications.[18] Coronary revascularization should not be performed in patients with no or mild symptoms if only a small area of myocardium is at risk, if no objective evidence of ischemia can be found, or if the likelihood of success is low or the chance of complications is high.[18]

PATIENTS WITH MODERATE TO SEVERE ANGINA (see Chap. 37) .

Patients with CCS Class II to IV angina, particularly those who are refractory to medical therapy, are suitable candidates for coronary revascularization, provided that the lesion subtends a moderate to large area of viable myocardium as determined by noninvasive testing.[18] Patients with recurrent symptoms while receiving medical therapy are candidates for revascularization even if they have a higher risk for an adverse outcome with revascularization.[18] Patients with Class II to IV symptoms should not undergo revascularization without noninvasive evidence of myocardial ischemia or a trial of medical therapy, particularly if only a small region of myocardium is at risk, the likelihood of success is low, or the chance of complications is high.

PATIENTS WITH UNSTABLE ANGINA OR NON-Q-WAVE MYOCARDIAL INFARCTION (see Chap. 36) .

Cardiac catheterization and coronary revascularization in selected patients with unstable angina or non-Q-wave myocardial infarction may improve the prognosis, although it is less clear whether *routine* angiography and revascularization are indicated in all patients with acute coronary syndromes. The TIMI IIIB trial found no difference in 1-year death or myocardial infarction in patients undergoing routine angiography and those undergoing angiography and revascularization only for recurrent ischemia, although patients treated with an aggressive approach experienced less angina and were rehospitalized less often than those treated with a conservative approach.[346] Patients assigned to early catheterization and revascularization in the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial experienced no reduction in the rate of death or the composite of death and myocardial infarction 1 year later when compared with patients assigned to cardiac catheterization and revascularization only for recurrent ischemia, although the mortality rate was high (>10 percent) in patients undergoing CABG in the aggressive limb.[347] In contrast to these studies, the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) Study demonstrated a 22 percent reduction (p=0.031) in death or myocardial infarction at 6 months in patients assigned to routine catheterization and revascularization (9.4 percent) versus those assigned to a conservative approach (12.1 percent).[343]

Pending the results of additional trials such as the TACTICS (TIMI-18) Study, early catheterization and coronary revascularization are indicated in patients with acute coronary syndromes at "intermediate" or "high" risk of subsequent death or myocardial infarction.[348] High-risk features include prolonged ongoing (>20 minutes) chest pain, pulmonary edema or worsening mitral regurgitation, dynamic ST segment depression of 1 mm or greater, or hypotension. [348] Intermediate-risk features include angina at rest (>20 minutes) that is relieved with rest or sublingual nitroglycerin, angina associated with dynamic electrocardiographic changes, recent-onset angina with a high likelihood of CAD, pathological Q waves or ST segment depression less than 1 mm in multiple leads, or age older than 65 years. [348] Coronary revascularization is not indicated in patients with unstable angina who do not demonstrate high-risk criteria upon exercise testing after stabilization with

medical therapy, patients who do not have objective signs of coronary ischemia, or those in whom revascularization will not improve the quality of life.[348]

PATIENTS WITH ACUTE MYOCARDIAL INFARCTION TREATED WITH THROMBOLYTIC THERAPY (see Chap. 35) .

Cardiac catheterization and selective coronary revascularization in patients who have received thrombolytic therapy are indicated in those with recurrent ischemia, in patients with cardiogenic shock or those in whom it later develops, or in those in whom signs of reperfusion fail to develop after thrombolytic administration.[16] Routine coronary revascularization is not indicated within hours to days in patients who are asymptomatic and have no evidence of substantial residual myocardium at risk. Patients in whom recurrent ischemia develops spontaneously or after exercise provocation are candidates for revascularization. In the Danish Trial in Acute Myocardial Infarction (DANAMI) Study, 503 patients with inducible myocardial ischemia after thrombolytic treatment of acute myocardial infarction were assigned to an invasive strategy of coronary revascularization between 2 and 10 weeks after the acute myocardial infarction or to a conservative strategy of revascularization 2 months later.[349] At a 2.4-year follow-up (median), mortality was similar in both groups, although patients treated with the invasive strategy had a lower incidence of acute myocardial infarction (5.6 vs. 10.5 percent; p=0.0038) and a lower incidence of admission for unstable angina (17.9 vs. 29.5 percent; p<0.00001) than did conservatively treated patients.[349]

OPTIONS FOR MEDICAL THERAPY OR CORONARY REVASCULARIZATION (see also Chap. 37)

In patients with symptomatic CAD, the clinician must decide whether medical therapy or referral for coronary revascularization by PCI or CABG will provide the best prognosis for the individual patient. A number of factors will ultimately affect the decision to undertake one strategy over another, including (1) the patient's general vigor, comorbid conditions, initial symptoms, and personal preferences; (2) the coronary anatomy, number of lesions, and their location and morphology, including the presence of total occlusions; (3) left ventricular function; and (4) whether CABG has already been performed.

PCI VERSUS MEDICAL THERAPY (See Chap. 37)

At least four randomized studies have compared the outcomes of patients assigned to medical therapy or PCI for the treatment of ischemic CAD. In the Veterans Administration Angioplasty Compared to Medicine (ACME) trial, 212 patients with single-vessel coronary disease and stable angina were randomly assigned to medical therapy or balloon PTCA.[350] Although rates of death and myocardial infarction were similar in the two groups, superior symptom control and a better exercise duration were found in patients treated with balloon PTCA.[350] These effects were less pronounced in patients with two-vessel CAD.[351] More recently, the Atorvastatin Versus

Revascularization Therapy (AVERT) Trial compared the effect of aggressive lipid lowering with atorvastatin 80 mg daily and coronary angioplasty in 341 patients with asymptomatic or mildly symptomatic (Class I or II) CAD.[352] At an 18-month follow-up, 13 percent of medically treated patients experienced an ischemic event as compared with 21 percent of patients treated with PCI (p=0.048). Although patients in both groups experienced improvement in their angina, more improvement was found at follow-up in patients treated with PCI.[352]

In the second Randomized Intervention Treatment of Angina (RITA-2) Trial, 1018 patients with single-vessel and/or multivessel disease and grade 2 or higher angina were randomly assigned to medical therapy or PCI.[353] Death or definite myocardial infarction occurred significantly (p=0.02) more often in PCI-treated patients (6.3 percent) than in medically treated patients (3.3 percent), primarily attributable to the occurrence of periprocedural myocardial infarction. More angina improvement and better exercise durations were achieved in the PCI group.[353] These benefits of PTCA were greatest in patients with more severe baseline angina.[353] The authors concluded that in patients with CAD considered suitable for either PCI or medical care, early PCI was associated with greater symptomatic improvement, especially in patients with more severe angina, although these benefits should be weighed against the small excess hazard for periprocedural myocardial infarction.[353]

In the Asymptomatic Cardiac Ischemia Pilot (ACIP) Study, 558 patients with asymptomatic ischemia by stress testing and ambulatory ischemia monitoring were randomly assigned to angina-guided therapy (n=183), angina plus ischemia-guided therapy (n=183), or revascularization using PCI or CABG.[348] The incidence of death or myocardial infarction at 2 years was significantly lower (p<0.01) in patients treated with revascularization (4.7 percent) than in patients assigned to angina-guided (12.1 percent) or ischemia-guided (8.8 percent) therapy.

These studies suggest that patients with mild Class I or II angina have a favorable prognosis, whether treated with medical therapy or PCI, although angina relief is greater in patients treated with PCI. A pilot randomized trial suggested that the prognosis is improved with revascularization (PCI or CABG) in patients with Holter monitor-documented ischemia,[354] but these findings will require confirmation in larger studies. Patients with moderate to severe angina, particularly those who have failed medical therapy, should be considered candidates for PCI.

PCI VERSUS CABG (See Chap. 37)

At least nine randomized trials have evaluated the relative value of PCI and CABG in patients with multivessel CAD.[345] [355] [356] [357] [358] [359] [360] [361] [362] While these trials were designed to address a critical issue for clinicians managing patients with multivessel CAD, they have had certain unavoidable design limitations, including relatively small sample sizes (127 to 1792 patients), inclusion of both patients with single-vessel and multivessel CAD, low screened-to-recruitment ratios (limiting the generalizability of the study), and limited (1 to 5 years) follow-up. The relatively low, late-term mortality rates (0 to 13.7 percent) and small sample sizes in these studies make it difficult to exclude the *possibility* of a difference between these two strategies (type II error). Not

withstanding these limitations, a number of important conclusions can be drawn from these trials.

In the largest randomized trial, BARI, 1792 patients with multivessel CAD were assigned to initial treatment with PCI or CABG. In-hospital Q wave myocardial infarction was significantly (p<0.05) higher in patients assigned to CABG (4.6 percent) than PCI (2.1 percent), although 6.3 percent of PCI-treated patients required emergency CABG for procedure-induced complications. No significant differences were found in long-term survival or freedom from myocardial infarction at 5.4 years' follow-up, although PCI patients had more repeat hospitalization and required more repeat procedures than did CABG patients. One subset was identified in BARI that benefited from CABG over PCI. Diabetic patients assigned to PCI had a significantly (p=0.003) worse survival rate (65.5 percent) than did diabetic patients assigned to CABG (80.6 percent), primarily because of a reduced cardiac mortality rate (20.6 percent in PCI patients vs. 5.8 percent in CABG patients; p=0.003).[26] [27] [28] [263A] Placement of at least one internal mammary graft was the primary factor contributing to the improved prognosis with CABG in diabetic patients.

A weighted analysis of patients enrolled in the nine randomized trials comparing CABG and PCI for the treatment of single-vessel and multivessel CAD demonstrated similar in-hospital major clinical events, including death (1.3 percent in CABG patients and 1.0 percent in PCI patients) and Q wave myocardial infarction (4.1 percent in CABG patients and 2.3 percent in PCI patients).[345] Late major clinical events were also similar in the two groups and included death (6.5 percent in CABG patients and 7.7 percent in PCI patients) and Q wave myocardial infarction (11.3 percent in CABG patients and 11.0 percent in PCI patients). CABG patients had less frequent recurrence of angina (10.4 percent in CABG patients and 15.5 percent in PCI patients) and fewer repeat revascularization procedures (7.3 percent in CABG patients and 42.3 percent in PCI patients).[345] It should be noted that these trials were completed before the widespread use of stents, GP IIb-IIIa inhibitors, and postprocedural lipid-lowering therapies.

The ultimate choice of the method of revascularization should be made after a frank discussion with the patient about the options of revascularization. In a patient with diffuse involvement of three coronary vessels, particularly in the setting of complex anatomy, including total occlusions, CABG may provide a more definitive long-term benefit, especially if one or more arterial conduits are used. In contrast, in a patient with focal lesions involving two or three large epicardial vessels, multivessel coronary stent placement may be the preferred approach since it is associated with a lower risk of Q wave myocardial infarction and a shorter hospital stay than CABG is. Diabetic patients with diffuse two- or three-vessel CAD are best served with CABG. These recommendations in diabetic patients are supported by preliminary results from the ARTS Trial, a randomized trial of multivessel stenting or CABG in patients with multivessel disease.[363] In all patients with multivessel CAD who are undergoing CABG or PCI, aggressive

risk factor modification is warranted, with a target LDL cholesterol of less than 100 mg/dl.[344]

TRAINING STANDARDS AND PROFICIENCY IN INTERVENTIONAL CARDIOLOGY

Standards for core curriculum development and procedural proficiency for interventional cardiology training programs have been established by the ACC[364] ; these criteria, coupled with standards for the maintenance of technical competency,[364] [365] [366] are now prerequisites for the Certification Examination for Added Qualification in Interventional Cardiology, established by the American Board of Internal Medicine.[367] Proficiency requirements for interventional training have become more rigorous over time, with the minimum case volume for interventional training increasing from 125 to 250 cases as the primary operator[366] [368] ; maintenance of proficiency now requires more than 75 cases per year as the primary operator, unless special circumstances are identified.[366] Operator- and hospital-specific procedural outcomes after PCI are also collected by governmental and managed care organizations.

The focus on minimum volume criteria is based on studies that relate procedural outcome after PCI to both hospital and individual operator volumes[369] [370] [371] [372] [373] (Tables 38-10 and 38-11) . PCI complication rates are higher when the hospital procedural volume is less than 200 to 400 cases per year or individual operator volume is less than 75 to 100 coronary interventions per year.[369] [370] [371] [372] The ACC has recommended that hospitals perform more than 200 to 400 cases per year and individual operators perform more than 75 cases per year.[18] [366] It has been suggested that many interventional cardiologists do not meet these minimal procedural requirements.[373]

Individual institutions need to establish valid methods for peer review, including documentation of procedural success and failure rates of individual operators, minimum volume performance for the hospital and individual operators, quality of the laboratory facility, and training of the support staff. Establishment of an outcomes data base is strongly encouraged for all institutions.[384]

PERCUTANEOUS VALVULOPLASTY (see also Chap. 46)

Percutaneous valve dilatation has been used as an alternative to definitive surgical repair or replacement in selected patients with symptomatic valvular heart disease. After a decade of experience with these techniques, it is clear that mitral valvuloplasty is a safe and effective alternative to surgical repair in selected patients with mitral stenosis[385] whereas aortic valvuloplasty provides only short-term palliation and should be reserved for inoperable patients

TABLE 38-10 -- RELATIONSHIP BETWEEN HOSPITAL PROCEDURAL VOLUME AND OUTCOME AFTER CORONARY INTERVENTION

STUDY	TIME PERIOD	DATA SOURCE	NUMBER OF PATIENTS	NUMBER OF OPERATORS	CONCLUSIONS	COMMENTS

Hartz et al.[374]	1989-91	Wisconsin Medicare	2091	16	No relationship between volume and outcome	Very low number of cases and hospitals examined
Ritchie et al.[375]	1989	California State	24,883	110	Increased CABG (not death) with <200 cases/yr; finding is valid for both acute MI and non-MI patients	
Jollis et al.[373]	1987-90	MEDPAR	217,836	1194	Death and CABG inversely related to low volume (risk increases with Medicare patient volume [<100-200 total/yr for death, <200-300/yr for CABG])	
Kimmel et al.[372]	1992-93	SCAI Registry	19,594	48	Fewer major complications for labs with >400 cases/yr	Able to risk-adjust more completely than in other studies
GUSTO IIb[168]	NA	GUSTO	565	59	No difference between 200 and 625 cases/yr vs. >625 cases/yr for acute MI patients	All operators >50 cases per year
O'Neill et al.[376]	NA	PAMI-II	1100	34	No difference between <500, 501-1000, and >1,000 cases/yr for acute MI	

Jollis et al.[373]	1992	Medicare	97,498	984	Incremental decrease in death + CABG as hospital Medicare volume increased from <100, 100-200, and >200 cases/yr	
Tiefenbrunn et al.[377]	NA	Second NRMI	4939	NA	Increased acute MI mortality for hospitals with <25 acute MI cases/yr	
Hannan et al.[370]	1991-94	New York State	62,670	31	Death alone and same-stay CABG increased with caseloads <600/yr	Risk adjusted
Zahn et al.[378]	1992-95	German Hospital Constortium	4625	NA	For patients with acute MI, increased mortality in hospital with <40 acute MI PTCA/yr	No risk adjustment

* Medicare patients usually account for 35 to 50 percent of the total interventional caseload.

CABG=coronary artery bypass graft surgery; MI=myocardial infarction; NRMI=National Registry of Myocardial Infarction; PAMI=Primary Angioplasty Myocardial Infarction Study; PTCA=percutaneous transluminal coronary angioplasty; SCAI=Society for Cardiac Angiography and Intervention.

Modified from Hirshfeld J, Ellis S, Faxon D: American College of Cardiology Clinical Competency Statement: Recommendations for the assessment and maintenance of proficiency in coronary interventional procedures. J Am Coll Cardiol 31:722-743, 1998.

TABLE 38-11 -- RELATIONSHIP BETWEEN INDIVIDUAL PROCEDURAL VOLUME AND OUTCOME AFTER PERCUTANEOUS CORONARY INTERVENTION

STUDY	TIME PERIOD	DATA SOURCE	NUMBER OF PATIENTS	NUMBER OF OPERATORS	CONCLUSIONS	COMMENTS
Hamad et al.[379]	1986-87	Single center	787	17	Lower success with complex lesions (B-C) for operators with <100 cases/yr and no differences noted for simple lesions	
Shook et al.[371]	1991-94	Single center	2350	38	Higher risk of emergency CABG with operators performing <50 cases/yr, but no difference in mortality	
Ellis et al.[369]	1993-95	High-volume centers	12,941	38	Risk of death and risk of death, MI, or emergency CABG inversely related to caseload but not to years of experience; no volume cutoff, but risk accelerates with less than 100/yr	Able to risk-adjust more completely than other studies
Krone et al.[380]	1992	SCAI data base	7747	122	No differences in <50, 50-99, or >100 cases/yr	Able to risk-adjust more completely than other studies
Bon Tempo et al.[381]	1992-94	Single center	3127	45	Weak trend toward increased risk of abrupt closure and late PTCA with higher-volume operators	No risk adjustment

O'Neill et al.[376]	NA	PAMI-II	1100	NA	No difference for <75 or >75 cases/yr	Selected interventionalists
Jollis et al.[373]	1992	Medicare	97,478	6115	More death + CABG for annual medical volume <501	
McGrath et al.[382]	1990-93	Northern NE Registry	12,033	31	Success and emergency CABG, but not death was related to volume tercile (23-85, 89-143, 153-450)	
Hannan et al.[370]	1991-94	New York State	62,670	NA	Success and emergency CABG increase with annual caseload <75; an operator-hospital caseload interaction affecting outcome also observed	Risk adjusted
Klein et al.[383]	1992-95	Single center	1389	9	Despite performing only an average of 51 PTCA/yr, results (death=1.0%, CABG=0.9%) were acceptable when compared with contemporary registry data	

* Medicare patients usually account for 35 to 50 percent of the total interventional caseload.

CABG=coronary artery bypass graft surgery; MI=myocardial infarction; NE=New England; PAMI=Primary Angioplasty Myocardial Infarction Study; PTCA=percutaneous transluminal coronary angioplasty; SCAI=Society for Cardiac Angiography and Intervention.

Modified from Hirshfeld J, Ellis S, Faxon D: American College of Cardiology Clinical Competency Statement: Recommendations for the assessment and maintenance of proficiency in coronary interventional procedures. J Am Coll Cardiol 31:722-743, 1998.

with degenerative calcific aortic stenosis.[385] [386] The indications and contraindications for mitral and aortic valvuloplasty are reviewed in detail elsewhere (see Chap. 46) . This chapter focuses on the technical issues, patient selection, and outcomes associated with mitral and aortic valvuloplasty.

Mitral Valvuloplasty (See also Chap. 46)

Percutaneous mitral valvuloplasty (PMV) was first performed in 1984 as an alternative to surgical mitral valve commissurotomy,[387] and later reports confirmed the immediate and long-term benefits of this procedure.[388] [389] [390] Although the majority of PMV procedures are performed in developing countries,[389] [391] where rheumatic fever and valvular heart disease continue to be endemic, a few specialized centers in Western countries have developed technical expertise in PMV, and their single[392] and multicenter[393] reports have provided valuable insight into the outcomes associated with PMV.

TECHNICAL ISSUES

A variety of technical approaches may be used for PMV.[385] A transvenous, or anterograde, method is most commonly performed, with a transseptal puncture used to gain access to the left atrium. A wire (or balloon) is then passed across the mitral valve into the left ventricle. Less often, a retrograde, transarterial approach is used to avoid the creation of a large atrial septal defect. Two retrograde methods have been described. In the first, a 0.038-inch exchange wire passed from the right atrium to the left atrium via a transseptal puncture is advanced through the left ventricle into the descending aorta, where it is retrieved with a snare.[394] The mitral valve dilatation balloon is then advanced retrogradely through the descending and ascending aorta into the left ventricle and across the mitral valve.[394] This method has had limited application because it is time consuming, requires advanced technical expertise, and mandates the use of large arterial sheaths. The second retrograde technique involves the use of a specially designed catheter to gain access to the left atrium from the left ventricle while avoiding transseptal puncture.[395] [396] [397] Experience with this method is limited except for a few specialized centers.

Two types of balloon approaches are used for PMV.[398] With the double-balloon method, a transseptal puncture is performed and a balloon catheter is advanced across the mitral valve into the left ventricle.[385] Two long exchange wires are then positioned in the left ventricle, and the interatrial septum is dilated with a 6- to 8-mm peripheral dilatation balloon. A combination of two mitral valvuloplasty balloons (trefoil balloon or conventional balloon) are advanced across the mitral valve and inflated.[385] The second technique uses the Inoue balloon,[399] [400] which is a self-positioning, pressure-distensible balloon that allows progressive diameter dilatation by increasing the inflation pressure[385] (Fig. 38-11) . A stepwise dilatation technique is performed to minimize the risk of mitral valve rupture and mitral regurgitation. Selection of balloon size is generally based on patient height, body surface area, and diameter of the mitral annulus.

Figure 38-11 Mitral valvoloplasty. After transseptal puncture, a Mullins sheath is advanced into the left atrium, as demonstrated by contrast injection *(A)*. An Inoue guidewire is coiled in the left atrium and a Inoue dilator is advanced across the intraatrial septum *(B)*. Advancement of the Inoue balloon dilatation catheter into the left ventricle *(C)* and inflation *(D)* resulted in a successful procedure. (Courtesy of Andrew Eisenhauer, M.D.).

Comparative studies of these two techniques have shown similar clinical success rates,[391] [401] but shorter procedure times and higher disposable costs with the Inoue technique.[391] [401] The Inoue balloon has also been used in patients with severe mitral valve calcification[402] and subvalvular fibrosis[403] with reported success.

HEMODYNAMIC ASSESSMENT

Serial hemodynamic measurements, alone or in combination with echocardiography, may be used to evaluate the result achieved with PMV.[385] An immediate improvement in left atrial mean pressure (and reduction of the transmittal gradient) should be seen, with a gradual decrease in pulmonary artery pressure and an increase in cardiac output.[385] Criteria for termination of the procedure include (1) a mitral valve area larger than 1 cm^2 per square meter of body surface area, (2) complete opening of at least one commissure, or (3) the appearance or an increment in mitral regurgitation.[385] Transesophageal echocardiography may also be performed during the procedure[404] [405] [406] [407] and, in particular, may guide the transseptal puncture in patients with obscure cardiac landmarks or skeletal deformity.[408]

PROCEDURE OUTCOME.

Procedure success has been related to institutional volume (>25 cases per year), baseline mitral valve area (>0.5 cm^2), and the age of the patient (<70 years).[393] Procedural mortality associated with mitral valvuloplasty ranges from 0 to 3 percent in most series and is primarily related to the development of left ventricular perforation[409] resulting from the transseptal technique or advancement of the guidewire or balloon catheter into the left ventricle[410] or to general patient comorbidity. [411] Cerebral or coronary emboli occur in 0.5 to 5.0 percent of patients and are related to dislodgment of thromboembolic material from the left atrium or air within the dilatation apparatus.[412] Severe mitral regurgitation resulting from rupture of the chordae tendineae or papillary muscle rupture may also occur. Atrial septal defects are commonly (80 percent) seen after PMV, but the magnitude of the left-to-right shunt is generally insignificant.[405] The atrial septal defect also closes in the majority (90 to 100 percent) of cases within 3 months after PMV.[405] [413] Emergency surgery may be required in a minority of cases after PMV. When PMV is required for mitral regurgitation, left ventricular

TABLE 38-12 -- ECHOCARDIOGRAPHIC ANATOMICAL CLASSIFICATION OF THE MITRAL VALVE IN RELATION TO SUITABILITY FOR PERCUTANEOUS VALVULOPLASTY

POINTS	ECHOCARDIOGRAPHIC VARIABLE
	LEAFLET MOBILITY
1	Highly mobile valve with restriction of only the leaflet tips
2	Midportion and base of leaflets have reduced mobility
3	Valve leaflets move forward in diastole mainly at the base
4	No or minimal forward movement of the leaflets in diastole
	VALVULAR THICKENING
1	Leaflets near normal (4-5 mm)
2	Midleaflet thickening, marked thickening at the margins
3	Thickening extends through the entire leaflets (5-8 mm)
4	Marked thickening of all leaflet tissue (>8-10 mm)
	SUBVALVULAR THICKENING
1	Minimal thickening of chordal structures just below the valve
2	Thickening of the chordae extending up to one-third of chordal length
3	Thickening extending to the distal third of the chordae
4	Extensive thickening and shortening of all chordae extending down to the papillary muscles
	VALVULAR CALCIFICATION
1	A single area of increased echo brightness
2	Scattered areas of brightness confined to leaflet margins
3	Brightness extending into the midportion of the leaflets
4	Extensive brightness through most of the leaflet tissue

Adapted from Wilkins G, Gillam L, Weyman A, et al: Percutaneous balloon dilatation of the mitral valve: An analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 60:299-308, 1988.

rupture, or the development of a left-to-right shunt or as a result of a failed procedure, the mortality rate rises substantially.[414]

LATE OUTCOME.

Transthoracic echocardiography may be useful to assess the prognosis after PMV by semiquantitatively scoring leaflet mobility, valvular and subvalvular thickening, and valvular calcification[415] [416] (Table 38-12) . In one series of 136 patients undergoing successful PMV, the estimated 5-year mortality rate was 24 percent; the 5-year event rate (i.e., mitral valve replacement, repeat valvuloplasty, or death from cardiac causes) was 49 percent.[392] Multivariable predictors of late events after PMV were a high mitral valve echocardiographic score, an elevated left ventricular end-diastolic pressure, and a worse New York Heart Association (NYHA) functional class (p=0.04).[392] Patients with fewer than two risk factors for early restenosis (echocardiographic score >8, left ventricular end-diastolic pressure >10 mm Hg, or NYHA functional Class IV) had a predicted 5-year event-free survival rate of 60 to 84 percent, whereas patients with two or three risk factors had a predicted 5-year event-free survival rate of only 13 to 41 percent.[392]

Aortic Valvuloplasty (See also Chap. 46)

The most frequent cause of acquired valvular heart disease in Western countries is degenerative calcific aortic stenosis.[385] Percutaneous aortic valvuloplasty (PAV) fractures the calcified aortic leaflets, thereby increasing their flexibility, but its overall effect is modest and hemodynamic improvements are transient (days to weeks).[385] The long-term clinical benefit associated with PAV for calcific aortic stenosis is limited.[417] [418] [419] [420] [421]

PAV is generally reserved for adult patients with severe calcific aortic stenosis who have severe comorbidities that preclude aortic valve replacement,[422] [423] [424] such as in patients with cardiogenic shock or other significant comorbid conditions, in patients as a "bridge" to definitive surgical correction,[425] [426] [427] [428] or in patients with severe left ventricular dysfunction (i.e., "low flow, low gradient") in whom the hemodynamic response to aortic valve replacement cannot be determined.[429] [430] In the absence of these indications, definitive aortic valve replacement rather than PAV should be performed, even in elderly patients.[431] PAV in patients with congenital aortic stenosis is discussed in Chapters 43 and 44 .

TECHNICAL ISSUES

The femoral approach is most frequently used for PAV.[385] After crossing the aortic valve with a guidewire, an extra-stiff 0.038-inch wire is inserted into the apex of the left ventricle to stabilize the balloon during inflation. In patients with severe peripheral vascular disease, a brachial approach or anterograde approach using a transseptal puncture can be used to pass a long wire through the left ventricle, across the aortic valve, and into the descending aorta.[385] The interatrium septum is then dilated with a peripheral balloon, and the PAV balloon is then advanced across the aortic valve.

PAV balloons ranging in diameter between 15 and 25 mm and in length between 3 and

5 cm have variable shapes, including a conventional, bifoil, trifoil, and double-sized configuration, with the proximal portion measuring 20 to 23 mm and the distal portion 15 to 18 mm.[385] The size of the balloon should not exceed 1.2 to 1.3 times the diameter of the aortic ring.[385]

HEMODYNAMIC ASSESSMENT

The transaortic valve gradient should be reduced immediately after the procedure, although little change may be noted in cardiac output.[385] After successful dilatation, 25 to 47 percent of patients will obtain a final valve area larger than 1 cm^2 , while 22 to 39 percent of patients achieve a valve area less than 0.7 cm^2 . [385]

PROCEDURAL SUCCESS AND COMPLICATION RATES.

The clinical success rate for patients undergoing PAV ranges from 68 to 75 percent.[420] [432] [433] [434] Hospital mortality after PAV varies from 3.5 to 13.5 percent, and 20 to 25 percent of patients experience at least one complication during their hospitalization.[385] [433] [435] [436] Complications include a need for vascular access repair, embolic cerebrovascular events, aortic regurgitation, and with the use of oversized balloons, rupture of the aortic ring[434] [437] (Fig. 38-12) . Predictors of procedural mortality include the patient's age,[438] NYHA Class,[438] concomitant coronary artery disease, [438] congestive heart failure,[438] lower initial left ventricular systolic pressure,[435] [438] smaller final aortic valve area,[435] lower baseline cardiac output,[434] [435] [438] and the development of procedural complications. [385] [435] Predictors of patient morbidity are depressed left ventricular function, low cardiac output, diffuse coronary disease, and final valve area smaller than 0.7 cm^2 .[385] [432] [439] [440]

The major limitation of PAV is the early recurrence of symptoms in most patients. The estimated incidence of late restenosis is 36 to 80 percent in the first year.[441] [442] [443] [444] Determinants of late outcomes after PAV were studied in 205 patients undergoing this procedure.[445] The event-free survival rate, defined as survival without recurrent symptoms, repeated valvuloplasty, or aortic valve replacement, was 18 percent over the 24-month follow-up (range, 1 to 47 months). [445] Significant predictors of event-free survival included the left ventricular ejection fraction, left ventricular and aortic systolic pressure before PAV, and percent reduction in the aortic valve pressure gradient; the pulmonary capillary wedge pressure was inversely associated with event-free survival.[445] Although the predicted event-free survival rate for the entire patient group was 50 percent at 1 year and 25 percent at 2 years, the probability of event-free survival at 1 year varied between 23 and 65 percent when patients were stratified according to three independent predictors: aortic systolic pressure, pulmonary capillary wedge pressure, and percent reduction in the peak aortic valve gradient.[445] The best long-term results after valvuloplasty were observed among patients who would also have been expected to have excellent long-term results after aortic valve replacement.[445] Repeat PAV for symptom recurrence has also been reported.[446]

Figure 38-12 Aortic valvuloplasty. A 16-mm aortic valvuloplasty balloon is inflated across the aortic valve *(A)* and exchanged for a 24-mm balloon *(B)* because of a persistent gradient. To further improve the aortic gradient, two 16-mm valvuloplasty balloons are advanced across the aortic valve *(C)*. Because of the relative oversizing of the balloons to the aortic ring, aortic regurgitation results *(D)*.

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Chapter 39 - Comprehensive Rehabilitation of Patients with Coronary Artery Disease

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Coronary artery disease (CAD) is the most important public health problem in developed societies. Although the cardiovascular mortality rate for the United States has declined in recent decades, CAD remains the single leading cause of death. Each year, more than 1 million persons in the United States have a myocardial infarction.[1] The economic costs of CAD in the United States are increasing, with estimates of at least $50 billion annually[2] (see Chaps. 1 and 2) .

Long-term analysis of case fatality rates for acute myocardial infarction in the community suggests that at least some of the reduction in cardiovascular disease mortality in recent decades can be attributed to the benefits of primary and secondary prevention strategies[3] (see Chap. 32) . The American Heart Association has stated that "compelling scientific evidence, including data from recent studies in patients with CAD, demonstrates that comprehensive risk factor interventions extend overall survival, improve the quality of life, decrease the need for interventional procedures such as

angioplasty and bypass grafting, and reduce the incidence of subsequent myocardial infarction."[4] [4A] Both genders benefit.[4B]

Comprehensive cardiac rehabilitation and secondary prevention of atherosclerotic cardiovascular disease are complex tasks because of the marked heterogeneity of patients and the numerous factors influencing prognosis and symptoms. Although management by a cardiovascular specialist does confer a survival advantage in patients after myocardial infarction when compared with patients treated by generalists,[5] even cardiologists underuse recommended therapies. Risk factor interventions shown to be effective in clinical trials often do not prove equally effective in community practice, perhaps in part as a result of a paucity of resources, especially nonphysician personnel to facilitate appropriate follow-up of patients. Case management systems with nurses trained to initiate interventions in smoking cessation, exercise training, and pharmacological therapy for hyperlipidemia have proved to be considerably more effective than usual medical care for modification of coronary risk factors after myocardial infarction.[6]

In this chapter, we present the background, science, and implementation of comprehensive rehabilitation in patients with CAD. Principles of secondary prevention are discussed in Chapter 32 and are summarized in Table 39-1 . The approach to cardiac rehabilitation and secondary prevention is shown in Table 39-2 .

REHABILITATION PROGRAMS

Inpatient Programs

Hospitalization for cardiovascular illnesses or operations now tends to be brief. Consequently, comprehensive, multifaceted inpatient cardiac rehabilitation programs are presently impractical. After initial treatment of an acute coronary syndrome (or following coronary artery bypass surgery) is completed and the patient stabilized, having the patient sit in an armchair should be encouraged, even in the intensive care unit, to minimize the loss of postural reflexes and the onset of orthostatic hypotension resulting from bed rest.[7] Limited range-of-motion exercises are usually safe at this point, except in very unstable patients, and are advisable to minimize deconditioning.[8] Once the patient is moved from the intensive care unit, walking, at first with assistance, should be encouraged as long as the patient is not severely symptomatic. The period of hospitalization is the optimal time to begin long-term pharmacological therapies to improve the patient's risk factor profile, minimize symptoms, and improve long-term event-free survival. Since acute myocardial infarction may result in a transient decline in total and high-density lipoprotein cholesterol,[9] [10] it is important to base initiation of pharmacological therapy for hyperlipidemia on lipid data from prehospital records or from blood drawn at the time of admission.[9]

EDUCATION.

It is vital to begin intensive efforts to educate the patient and family regarding the nature of the patient's illness, prognosis, symptoms, medications, and important life style

changes. Only one-third of patients maintain risk factor modification long-term.[4] Physicians and paramedical personnel must attempt to influence the patient at a time when concern about heart disease is at its highest. Multimedia approaches are useful adjuncts to verbal and written presentations. Educational efforts must address the need for reinforcement, variations in patient learning styles, and impediments to learning, including anxiety, pain, and sleep deprivation. Dietary guidelines, smoking cessation intervention, and instructions about walking, driving, and resumption of sexual activity[10A] are needed to minimize confusion and anxiety and to foster resumption of a normal life style.

Patients should be taught the proper response to certain symptoms should they arise after discharge, including how

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TABLE 39-1 -- GUIDE TO COMPREHENSIVE RISK REDUCTION FOR PATIENTS WITH CORONARY AND OTHER VASCULAR DISEASE

RISK INTERVENTION	RECOMMENDATIONS
Smoking Goal: Complete cessation	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal cessation programs as appropriate
Blood pressure control Goal: 140/90 mm Hg	Initiate life style modification--weight control, physical activity, alcohol moderation, and moderate sodium restriction--in all patients with blood pressure >140 mm Hg systolic or 90 mm Hg diastolic Add blood pressure medication, individualized to other patient requirements and characteristics (i.e., age, race, need for drugs with specific benefits) if blood pressure is not <140 mm Hg systolic or 90 mm Hg diastolic in 3 mo or if *initial* blood pressure is >160 mm Hg systolic or >100 mm Hg diastolic
Lipid management	Start AHA step II diet in all patients: 30% fat, <7% saturated fat, and <200 mg/d cholesterol and promote physical activity
Primary goal LDL <100 mg/dl	Assess fasting lipid profile. In post-MI patients, lipid profile may take 4-6 wk to stabilize. Add drug therapy according to the following guide

	LDL <100 md/dl	**LDL 100-130 mg/dl**	**LDL >130 mg/dl**	**HDL <35 mg/dl**

Secondary goals HDL >35 mg/dl TG <200 mg/dl	No drug therapy	Consider adding drug therapy to diet, as follows:	Add drug therapy to diet, as follows:	Emphasize weight management and physical activity. Advise smoking cessation If needed to achieve LDL goals, consider niacin, statin, fibrates

Suggested Drug Therapy

TG <200 mg/dl	***TG 200-400 mg/dl***	***TG >400 mg/dl***
Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrates, statin)

If LDL goal not achieved, consider combination drug therapy

Weight management	Start intensive diet and appropriate physical intervention, as outlined above, in patients with BMI >25 kg/m^2 for weight Emphasize need for weight loss especially in patients with hypertension or elevated TG or glucose levels
Antiplatelet agents/anticoagulants	Start aspirin 80-325 mg/d if not contraindicated Manage warfarin to international normalized ratio of 2-3.5 in post-MI patients not able to take aspirin
ACE inhibitors post-MI	Start early post-MI in stable high-risk patients (anterior MI, previous MI, Killip class II [S_3 gallop, rales, radiographic heart failure]) Continued indefinitely for all with LV dysfunction (ejection fraction 40%) or symptoms of failure Use as needed to manage blood pressure or symptoms in all other patients
Beta blockers	Start in high-risk post-MI patients (arrhythmia, LV dysfunction, inducible ischemia) at 5-28 d. Continue 6 mo minimum. Observe usual contraindications Use as needed to manage angina, rhythm, or blood pressure in all other patients
Estrogens	Consider estrogen replacement in all postmenopausal women Individualize recommendation consistent with other health risks

ACE=angiotensin-converting enzyme; AHA=American Heart Association; BMI=body mass index; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LV=left ventricular; MI=myocardial infarction; TG=triglycerides.

Modified from Consensus Panel Statement: Preventing heart attack and death in patients with coronary disease. Circulation 92:2-4, 1995.

to access local first-responder systems. Unfortunately, patients with CAD frequently do not seek help at the onset of acute myocardial infarction for multiple reasons. Some patients do not recognize the symptoms of acute myocardial infarction, particularly when they are not severe or consist of chest pressure, dyspnea, or nausea.[11] Other patients simply deny the symptoms in the hope that they will resolve.[12] [13]

TABLE 39-2 -- TRENDS IN CARDIAC REHABILITATION AND SECONDARY PREVENTION

Aggressive risk factor modification
Primary prevention in families of those with atherosclerotic vascular disease
Home telephone--electrocardiographically monitored cardiac rehabilitation exercise
Home individualized nonmonitored cardiac rehabilitation exercise
Behavior modification and compliance intervention
A greater role in managed and capitated care

Still others are too embarrassed to seek medical care if the symptoms do not seem typically cardiac for fear of wasting a physician's time because of a "false alarm." Patients who are alone, particularly when they are away from home, may respond more rapidly than if surrounded by the comforts of home and family members.[14] Consequently, education of the family is helpful in minimizing delays. Understanding the emotions of patients as they cope with acute myocardial infarction is important.[15] One should not expect that large amounts of information will be assimilated by most patients during their brief hospitalization. Continued reinforcement of these points at follow-up visits is essential and can be done quite effectively in an outpatient cardiac rehabilitation and secondary prevention setting. Broad areas, including end-of-life care, can be discussed.[15A]

Outpatient Programs

Outpatient exercise activity can be accomplished by using different formats, including supervised, nonsupervised, home (group and individual), monitored, and nonmonitored settings.

Figure 39-1 Format of a typical aerobic exercise training session illustrating the warm-up, stimulus, and cool-down phases along with a representative heart rate response. The target heart rate zone for training corresponds to 70 to 85 percent of the peak heart rate achieved during symptom-limited exercise testing. *(From Franklin BA, McCullough PA, Timmis GC: Exercise. In Hennekens CH [ed]: Clinical Trials in*

Cardiovascular Disease. Philadelphia, WB Saunders, 1999, pp 278-295.)

SUPERVISED PROGRAMS.

An exercise test and supervision are essential for this type of program.[16] The cardiovascular manifestations that require precautions can vary but usually include ventricular tachycardia, other symptomatic or hemodynamically significant arrhythmias (see Chap. 25) , chest discomfort consistent with angina pectoris, exercise-induced ST depression of 2 mm or greater, or a decrease in systolic blood pressure of 20 mm Hg or greater from baseline.

Exercise testing is performed in the usual fashion (see Chap. 6) , with the heart rate at which ischemia or arrhythmia is manifested used to determine the training intensity (Fig. 39-1) . If the patient continues the exercise test to a high level of effort, a heart rate of 50 to 60 percent of maximum can be used if it falls at least 10 beats/min below the level at which symptoms, ST depression, or arrhythmia occurs. Otherwise, the recommended peak training heart rate is 10 beats/min less than that associated with symptoms, ST depression, or arrhythmia. It is desirable that these patients have medically supervised cardiac rehabilitation and reevaluation to "restratify" them 6 to 12 weeks later. Exercise testing should be repeated at least yearly. These supervised programs are usually conducted in a group hospital or center-based setting and include electrocardiographic (ECG) monitoring until a subject is restratified to low risk.

NONSUPERVISED PROGRAMS.

Exercise intensity in these programs should approximate 50 to 80 percent of maximum oxygen consumption (O_{2max}), as determined by an exercise test or the estimated metabolic equivalent (MET).[16] If a test is not done initially, a target of 20 beats/min above the resting heart rate is adequate until testing is performed.

The exercise training heart rate should be designated as 50 to 75 percent of the heart rate reserve ([maximal heart rate-resting heart rate]×50 to 75 percent) plus the resting heart rate. Activities can be prescribed according to the work intensity at which the training heart rate is achieved after 5 to 10 minutes at the same workload (steady state). This intensity may be expressed as watts on an ergometer, speed on a treadmill, or METs. If a patient cannot assess intensity, heart rate counting (manually or with a cardiotachometer) is especially useful. Heart rate counters are widely available and generally accurate for low- to moderate-intensity exercise. However, erroneous readings may occur in patients with irregular rhythms. Group programs may be followed by home programs of various types. Patients can be given an exercise prescription form (Fig. 39-2 , Table 39-3) .

Figure 39-2 Exercise prescription form. *(From Franklin BA, McCullough PA, Timmis GC: Exercise. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease. Philadelphia, WB Saunders, 1999, pp*

278-295.)

TABLE 39-3 -- FUNDAMENTALS IN DEVELOPING AN EXERCISE PRESCRIPTION

Obtain the maximum exercise heart rate--preferably with exercise testing
Designate a target heart rate at a level 60-80% of the maximum heart rate
Begin at a low level (60-70%) and progress over 4-6 wk to the 80% level
Exercise activity should be done for 30-60 min, 4-6 times weekly, preferably on most days
Exercise sessions should incorporate aerobic activity, such as walking, jogging, cycling, or water aerobics, with appropriate warm-up and cool-down
Resistance activities such as light weights should be used on a less frequent basis--2-3 times weekly

Home Programs

Strategies for cardiac rehabilitation have changed over recent years. Currently, less emphasis is being placed on office or hospital visits for ECG monitoring and supervised group programs. Many patients are unable to participate in such programs because of travel considerations, expense, or inconvenience. Consequently, more are being managed individually through home programs. These programs involve aggressive coronary risk modification with specific emphasis on smoking cessation, lipid control, blood pressure control, and physical activity.

MONITORED PROGRAMS.

Home telephone ECG-monitored programs have been evaluated in several studies. Such monitoring is done by means of a telephone ECG transmitter, in concert with voice transmission, through a standard telephone system. These voice and ECG signals are transmitted, locally or long distance, to a central monitoring station with nurse supervision for interpretation. During these sessions, voice communication may be useful for sharing information, obtaining exercise advice, or discussing safety concerns. The ECG signal is used to document the heart rate and rhythm. A recent study comparing home-monitored exercise with standard hospital-based programs found home programs to be safe and effective in providing rehabilitative exercise.[17] [17A]

UNMONITORED PROGRAMS.

Home exercise programs without telephone monitoring are also used by cardiologists

and primary care physicians for patients who have been evaluated with an exercise test. Such individual programs should, however, include periodic face-to-face physician counseling. Patients assigned to these programs are predominantly those at low risk as defined by the American Heart Association[16] and show no evidence of left ventricular dysfunction, high-grade arrhythmias, unstable angina pectoris, or other compromising medical problems. An initial exercise test is important for these patients, and some physicians periodically repeat the test to ensure the safety and efficacy of the program, as well as to confirm that the level of exercise training is appropriate.

Exercise Physiology

The circulatory response to exercise involves a complex series of adjustments resulting in a large increase in cardiac output proportional to the increased metabolic demands. These changes ensure that the metabolic needs of exercising muscles are met, that hyperthermia does not occur, and that blood flow to essential organs is protected.

HEART RATE RESPONSE TO EXERCISE.

At the transition from rest to strenuous exercise, the heart rate increases rapidly to values of 160 to 180 beats/min. During short periods of maximal exercise, rates as high as 240 beats/min have been recorded. The initial rapid increase is thought to be the result of central command influences or a brisk reflex from muscle mechanoreceptors. The almost instantaneous acceleration in heart rate is due more to vagal withdrawal than an increase in sympathetic tone. Later increases stem from reflex activation of pulmonary stretch receptors, which trigger increased sympathetic tone and additional parasympathetic withdrawal. Increased circulating catecholamines from the adrenal glands play a role as well. It has been shown that during exercise the increase in heart rate accounts for a greater percentage of the increase in cardiac output than does the increase in stroke volume. For instance, stroke volume normally reaches its maximum when cardiac output has increased by only half its maximum. Any further increase in cardiac output occurs by increasing the heart rate alone (Fig. 39-3) .

STROKE VOLUME CHANGES WITH EXERCISE.

Two physiological mechanisms influence stroke volume. The first involves enhanced cardiac filling secondary to increased venous return, followed by a more forceful contraction (increased preload, Frank-Starling mechanism). The second mechanism involves normal ventricular filling, but with a more forceful contraction secondary to neurohormonal influences that leads to more complete emptying (increased inotropy).

Greater ventricular filling during diastole, or preload, is enhanced by a slower heart rate, increased venous return, and application of the Frank-Starling principle (see Chap. 14) . Cardiac output and stroke volume are highest in the supine position. In this position, stroke volume is nearly maximal at rest and increases only slightly during exercise. In the upright position at rest, the diminished venous return to the heart results in smaller stroke volume and cardiac output. During upright exercise, however, stroke volume can approach the maximum stroke volume observed in the recumbent position, usually

without an increase in ventricular diastolic dimensions.[18] This effect is achieved in part by increased venous tone and skeletal muscle compression.

DISTRIBUTION OF CARDIAC OUTPUT DURING EXERCISE.

During exertion, parasympathetic activity is withdrawn and sympathetic activity is maximal. This shift in activity results in increased release of norepinephrine from sympathetic postganglionic nerve endings. Plasma epinephrine levels are also increased. As a result, the majority of the vascular beds of the body are constricted, except those in the exercising muscles and the coronary and cerebral circulations. Blood flow to the skin increases during light and moderate exercise to facilitate body cooling. Further increases in workload cause a progressive decrease in skin flow as the rising cutaneous sympathetic vascular tone overcomes the thermoregulatory vasodilatory response.[19] The kidneys

Figure 39-3 Graphic display of the relationship of heart rate and stroke volume increase. Of note, stroke volume reaches its maximum when oxygen uptake has increased by only half maximum.

and splanchnic tissue extract 10 to 25 percent of the oxygen delivered. Consequently, considerable reductions in blood flow to these tissues can be tolerated through increased extraction of oxygen from the available blood supply.[20] At rest, the heart extracts about 75 percent of the oxygen in the coronary blood flow. Because of this limited reserve, the increased myocardial oxygen demands during exercise are met mainly by a fourfold increase in coronary blood flow. Cerebral blood flow also increases during exercise by approximately 25 to 30 percent.[21] During maximal exercise, however, cerebral flow may also decrease in association with hyperventilation and respiratory alkalosis.

On cessation of exercise, an abrupt decrease in heart rate and cardiac output occurs secondary to removal of sympathetic drive and reactivation of vagal activity. In contrast, systemic vascular resistance remains lower for some time because of persistent vasodilation in muscles. As a result, arterial pressure falls, often below preexercise levels, for periods of up to 12 hours into recovery.[22] Blood pressure is then stabilized at normal levels by baroreceptor reflexes.

CARDIOVASCULAR RESPONSE TO DIFFERENT TYPES OF EXERCISE.

Different types of exercise impose various loads on the cardiovascular system. Isotonic (dynamic) exercise is defined as muscular contraction of large muscle groups that results in movement and primarily places a volume load on the heart. *Isometric* (static) exercise is defined as a constant muscular contraction of smaller muscle groups without movement and results in more pressure than volume load on the heart. Significant

increases in both cardiac output and oxygen consumption and a fall in systemic vascular resistance characterize the acute load posed by isotonic exercise. In contrast, isometric exercise acutely increases systemic vascular resistance and blood pressure while producing only minimal changes in cardiac output and oxygen consumption.[23] *Resistance* exercise is a combination of isometric and isotonic exercise that produces muscular contraction with movement, as in free weight lifting. Most activities (such as sports or employment-related activities) usually combine all three types of exercise.

CHRONIC ADAPTATIONS TO EXERCISE.

Physical conditioning or exercise training affects the cardiovascular and skeletal muscle systems in a variety of ways to improve work performance. The response of the cardiovascular system to regular exercise is an increase in its capacity to deliver oxygen to the active muscle. Physical training also improves the ability of the muscles to use oxygen. Conditioning induced by repetitive periods of dynamic exercise may increase maximum oxygen consumption twofold to threefold. About half of this increase is due to increased cardiac output, and about half is induced by peripheral adaptations that improve oxygen extraction.[24]

RISKS OF EXERCISE TRAINING.

Exercise has both risks and benefits, and the challenge to the physician is to provide guidelines that minimize risks and maximize benefits. Many factors affect the risk associated with exercise. Three of the most important are age, presence of heart disease, and intensity of exercise. Sudden cardiac death is rare in apparently healthy individuals (see Chap. 26) . In individuals younger than 35 years, sudden cardiac death is usually attributed to hypertrophic cardiomyopathy or congenital heart disease, whereas CAD is a more likely cause for those older than 35 (see Chap. 59) . Selected studies reporting risk of sudden cardiac arrest during exercise training indicate that in the general population, the risk of sudden cardiac death during vigorous exercise is very low.[16] Since these studies were not randomized controlled trials, the contribution of all potential variables to sudden cardiac arrest or death cannot be determined. However, it is generally believed that the benefits of exercise exceed the risks, and individuals should be encouraged to exercise prudently.

Efficacy of Cardiac Rehabilitation

Several studies have evaluated the cardioprotective effect of exercise training in the setting of cardiac rehabilitation programs for survivors of myocardial infarction (see Chap. 35) . A review of these trials revealed that cardiovascular rehabilitation programs lead to improved functional capacity and cardiovascular efficiency, as well as an enhanced sense of well-being.[25] The evidence, however, fell short of indicating that exercise conditioning programs can independently reduce fatal or nonfatal coronary events. Anginal thresholds remain unchanged (Fig. 39-4) .

Although more than 4700 patients have been studied in randomized trials of cardiac rehabilitation, most of the individual trials enrolled small numbers of patients and did not

have sufficient power to distinguish significant differences between groups.[26] The largest study performed in the United States was the National Exercise and Heart Disease Project, which randomized 651 men who survived myocardial infarction to exercise training or to a control group.[27] The favorable trends seen in both overall mortality and cardiovascular mortality after 3 years in the exercise group failed to reach statistical significance. Recent analysis of the data, however, has revealed that increases in maximum physical work capacity on exercise testing in the study (1-MET increase at each stage) were associated with a reduction in all-cause mortality of 8 to 14 percent for up to 19 years.[28]

Two meta-analyses have examined the effect of cardiovascular rehabilitation. The first combined the results of 10 randomized clinical trials involving over 4300 patients.[29] The rehabilitation programs began 8 weeks to 3 years after myocardial infarction. The duration of the programs ranged from 6 weeks to 4 years. Cardiac rehabilitation resulted in a beneficial effect on mortality but not on nonfatal recurrent myocardial infarction. All-cause mortality was decreased by 24 percent and cardiovascular mortality by 25 percent for patients in the rehabilitation program. The reason for the lack of benefit on recurrent nonfatal myocardial infarction is unclear. The second meta-analysis reported a 20 percent decrease in both overall mortality and cardiovascular mortality.[26] The results were apparent as early as 1 year after randomization and persisted for at least 3 years after infarction. Trials that used a multifactorial approach to risk factor modification showed a greater reduction in mortality than did those that used only exercise training, which suggests that not all of the benefit could be attributed to exercise alone (Fig. 39-5) .

Exercise training is the mainstay of cardiac rehabilitation

Figure 39-4 Effect of physical conditioning on the product of heart rate (HR)×systolic blood pressure (SBP) and on myocardial O_2 consumption (M_{O_2}) at submaximal and peak exercise. Peak body O_2 uptake and workload are augmented by exercise. Myocardial O_2 requirements are reduced at a given workload of O_2 uptake, but angina occurs at the same HR×SBP product. *(From Franklin BA, McCullough PA, Timmis GC: Exercise. In Hennekens CH [ed]: Clinical Trials in Cardiovascular Disease. Philadelphia, WB Saunders, 1999, pp 278-295.)*

Figure 39-5 Chart of effects of pooling from randomized trials of cardiac rehabilitation on the estimate of mortality 3 years after randomization. Short vertical lines indicate point estimates; horizontal lines depict 95 percent confidence intervals. "Exercise Plus" usually refers to the life style and dietary modifications in both the exercise and control groups. *(From O'Connor GT, Buring JE, Yusuf S, et al: An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 80:234, 1989. By permission of the American Heart Association, Inc.)*

and can be used with impressive benefits for many cardiac patients.[29A] [29E] Recent studies using coronary arteriography have shown regression or lack of progression of coronary lesions in patients who performed high-intensity exercise and were also ingesting a low-fat diet.[30] [31] These changes were maintained during a follow-up period of 6 years. High-intensity exercise training has been shown to result in a higher left ventricular ejection fraction in men with CAD than has low-intensity exercise.[32] Other studies report that exercise training programs either have no harmful effects or have significant beneficial effects on ventricular function and/or "remodeling" in subjects with CAD.[33] [34] [35]

Cardiac rehabilitation must be carried out simultaneously with an aggressive program to reduce risk factors (secondary prevention), including antiplatelet and antithrombotic therapy, beta blockade, angiotensin-converting enzyme (ACE) inhibition, and statin therapy. Secondary prevention is described in Chapter 32 .

Secondary Prevention

ASPIRIN (See Chap. 62) .

Ensuring that patients seen in the cardiac rehabilitation and secondary prevention center are receiving optimal antiplatelet/anticoagulant therapy is very important. Aspirin in a dose of 81 to 325 mg daily should be used chronically in all patients with CAD who are not intolerant of or allergic to it and who do not have other definite indications for warfarin anticoagulation.[36] An initial dose of 325 mg should be used in acute settings. For those who are unable to take aspirin and do not require warfarin, clopidogrel 75 mg daily is recommended and may be substituted for or added to aspirin in patients with peripheral arterial disease.[37]

BETA BLOCKADE.

Beta-adrenergic blocking agents are a "cornerstone" of pharmacological therapy for CAD (see Chap. 37) and should be used within rehabilitation programs whenever possible. Although multiple clinical trials have documented the benefits of beta blockers initiated as a secondary prevention measure during hospitalization for acute myocardial infarction, continued long-term beta blockade remains underused.[38]

Following myocardial infarction, survival of patients who receive beta blockers is greatly improved in comparison to those who do not receive them, predominantly because of fewer sudden deaths. Greater benefit is seen in those with poor left ventricular function.[38] In one study of beta-blocker therapy following acute myocardial infarction, 6 lives were saved per 100 nondiabetic patients treated with beta blockers as opposed to 13 lives saved per 100 diabetics.[39] Because a reduction in heart rate is important, beta blockers with intrinsic sympathomimetic effects should not be used in patients with CAD.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS.

ACE inhibitors are a mainstay in the treatment of patients following myocardial

infarction. Heart failure develops in half of all patients seen with acute myocardial infarction.[40] More than 120,000 patients in major clinical trials have been randomized to receive either an ACE inhibitor or placebo in addition to optimal conventional therapy for acute myocardial infarction (see Chap. 35) . As a consequence of these studies, ACE inhibitors have been shown to reduce mortality and morbidity during and following myocardial infarction.[41] [42] [43]

Most of the benefits associated with early ACE inhibitor use occur during the first week after myocardial infarction, when mortality is the highest.[43] The absolute benefit in mortality reduction is greatest in high-risk groups, such as patients with tachycardia or anterior wall myocardial infarction.[43] In the Trandolapril Cardiac Evaluation (TRACE) Study, trandolapril saved 87 lives per 1000 people treated over a 3-year period. Patients with hypertension and diabetes mellitus benefited the most.[44] Five lives per 1000 are saved in the first week alone if ACE inhibitor therapy is started within the first 36 hours after acute myocardial infarction.[43] Acute, short-term ACE inhibitor therapy was not found to be harmful in any subgroup in a meta-analysis of 100,000 patients with acute myocardial infarction, but hypotension and renal dysfunction were more common side effects in patients older than 75 years.[43] Current recommendations are that ACE inhibitors be continued indefinitely in patients with clinical heart failure or impaired left ventricular systolic dysfunction, but their use may be discontinued after 6 weeks if neither is present.[45] These recommendations should be implemented routinely in the secondary prevention phase of patient care.

ACE inhibitors attenuate the progressive left ventricular dilatation after large, especially anterior myocardial infarction[46] (Fig. 39-6) (see Chap. 35) . ACE inhibitors have also been shown to reduce the likelihood of clinical heart failure in patients with asymptomatic left ventricular dysfunction.[47] Large prospective clinical trials are evaluating the potential efficacy of ACE inhibitors in reducing ischemic events

Figure 39-6 Attenuation of left ventricular enlargement by captopril therapy after anterior wall myocardial infarction (MI). *(Modified from Quigg R, Salyer J, Mohanty PK, Simpson P: Impaired exercise capacity late after cardiac transplantation: Influence of chronotropic incompetence, hypertension, and calcium channel blockers. Am Heart J 136:465-473, 1998.)*

and mortality in patients with CAD and preserved left ventricular systolic function (Prevention of Events with Angiotensin-Converting Enzyme Inhibition[48] [PEACE]) and in patients at high risk for CAD[49] (Heart Outcomes Prevention Evaluation [HOPE]). In the HOPE Study, nearly 10,000 patients, most older than 65 years, were randomized to the ACE inhibitor ramipril or to placebo (see Chap. 37) . The trial was terminated by the Data and Safety Monitoring Board after 4.5 years because of the clinically important benefit of ramipril therapy.[50] The results of the HOPE Trial suggest that ACE inhibitors can be continued indefinitely in post-myocardial infarction patients with normal left ventricular function.

By blocking the production of angiotensin II and the degradation of bradykinin, ACE inhibitors cause vasodilatation, increased production of nitric oxide, decreased aldosterone secretion (lessening salt and water retention), decreased sympathetic tone, improved endothelial function, reduced left ventricular mass, antiplatelet effects, and reduced blood pressure.[51] [52] [53] [54] ACE inhibitors also have an antiischemic effect, with a 25 percent reduction in the risk of subsequent myocardial infarction. Patients in the Survival and Ventricular Enlargement[55] (SAVE) and Studies of Left Ventricular Dysfunction[47] (SOLVD) trials had a reduced need for coronary revascularization and fewer admissions for unstable angina while receiving ACE inhibitor therapy.[47] [51] [55]

ACE inhibitors have important clinical benefits, are easy to use, and are safe, but they are underused.[56] [57] Angiotensin II receptor blockers, which are now more widely used, may be administered to patients in whom ACE inhibitors cause coughing. Both these classes of drugs have similar effects and must be appropriately used in cardiac rehabilitation and secondary prevention programs.

STATIN THERAPY (see Chaps. 31 to 33).

A wealth of clinical data strongly support the use of cholesterol reduction therapy for secondary prevention in patients with established CAD. This conclusion results from a large number of well-controlled clinical trials, the most convincing of which used the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statin drugs. The relationship between on-treatment low-density lipoprotein (LDL) cholesterol and the relative risk of coronary heart disease is probably curvilinear, with diminishing returns as LDL cholesterol is reduced.[58] [59] In general, it is recommended that LDL cholesterol be reduced to less than 100 mg/dl.[60] Some have proposed that even a lower goal would be better, a hypothesis that has not yet been tested in clinical trials but will be addressed by the Treat to New Targets (TNT) Study.

Statin therapy is remarkably safe and may exert beneficial effects by several mechanisms other than reduction of LDL cholesterol, including stimulation of endothelial nitric oxide production,[61] as well as antiinflammatory[62] and antithrombotic properties.[63] [64] The survival curves of patients with cardiovascular disease who are taking statins in general diverge quickly (at 6 to 12 months) from those of patients randomized to placebo in major trials. It is believed that plaque stabilization by reducing LDL core size, inflammation, and thrombosis leads to decreased rates of plaque rupture and fissuring, thereby accounting for a decrease in cardiovascular events and improved survival.[65]

Lipid treatment strategies are progressively being refined. Published studies indicate that nurse-managed facilities can give as good, if not better results than physician-managed facilities.[6] Lipid-lowering therapy is one of the most effective areas of cardiac therapeutics (see Chaps. 33 and 37) . When combined with a proper diet and exercise, meaningful improvement in lipids is feasible in most patients, who should not be denied these benefits because they are the cornerstone of modern secondary prevention of CAD.

DIETARY SUPPLEMENTS AND ALTERNATIVE THERAPIES.

Nonprescription medications are used widely throughout the United States. In one series of patients undergoing periodic general health examinations, 61 percent were taking dietary supplements. Only half of them reported using these substances on questionnaires completed just before the examination.[66] Because of extensive attention to this subject in the lay press, it is possible that an even higher percentage of patients entering cardiac rehabilitation and secondary prevention might be using dietary supplements. Although plausible biological mechanisms for the beneficial effects of many of these supplements have been proposed, data supporting their use in clinical practice are limited to cohort and retrospective observational studies. Few significant data have been derived from controlled clinical trials.

SMOKING CESSATION.

Cigarette smoking increases platelet aggregation, serum fibrinogen, and oxidation of LDL cholesterol. Cessation also reduces high-density lipoprotein cholesterol and induces coronary artery spasm, with consequently decreased coronary and collateral flow reserve as a result of endothelial dysfunction.[67]

The dose-dependent effect of smoking is clearly defined. A 20-year follow-up study of British male physicians found that those who smoked 25 or more cigarettes per day had 2.3 times the relative risk of mortality from coronary heart disease as nonsmokers do.[68]

Patients who continue to smoke after a myocardial infarction have twice the risk of death from recurrent myocardial infarction than those who stop.[69] Many studies, including the Atherosclerosis Risk in Community Study, have shown a substantial increase in the risk of progression of atherosclerosis that is greatest in those who actively smoke, intermediate in those who formerly smoked, and lowest in those who never smoked.[70] Cigarette smoking was believed to be the single most substantial risk factor for progression of disease and a particularly potent factor in patients who had other risk factors such as hypertension or diabetes mellitus. The influence of smoking on disease progression holds for both native vessels[71] and coronary artery bypass grafts.[72]

The cardiovascular benefits of smoking cessation are striking.[73] [74] The risk of myocardial infarction declines quickly after smoking cessation. By 1 year, the risk has declined by approximately one-third from peak values, and by 3 to 4 years after cessation, the risk is equivalent to that of patients who have never smoked. The total cardiovascular mortality rate, however, takes about 10 years to decline to the level of nonsmokers.

Addiction to nicotine is difficult to break. Most patients who are able to terminate the habit have made five or more attempts before they are ultimately successful.[75] Measures such as nicotine replacement, bupropion, and continuous reinforcement by medical professionals are helpful and safe.[75] [76] Patients who smoke more than 20

cigarettes per day, who smoke within 30 minutes of awakening in the morning, or who have significant withdrawal symptoms and relapse within a week of cessation on initial attempts or those who have a current or a past history of a significant psychiatric disorder are generally considered the most difficult to treat.[75]

Unfortunately, success rates at 1 year range from only approximately 6 percent with physician counseling as the sole intervention to 20 to 40 percent with pharmacological interventions. Nonetheless, organized smoking cessation programs appear to be cost-effective and can be implemented

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in concert with secondary prevention programs. One program that reported a 22 percent smoking cessation rate at 1 year costs approximately $400 per patient (clinic visits plus drug costs). It was estimated that the cost of a net year of life gained (YLG) by the program was $6128, which compares favorably with the cost of pneumococcal vaccine in the elderly ($1500/YLG), treatment of mild to moderate hypertension ($11,300 to $24,400/YLG), heart transplantation ($16,200/YLG), and breast cancer screening ($26,800/YLG).[77]

Fear of weight gain, particularly in women, can be an impediment to smoking cessation. However, exercise improves aerobic capacity and delays weight gain after smoking cessation and can thus be a helpful part of smoking cessation programs.[78] Since a high percentage of patients coming to a cardiac rehabilitation and secondary prevention clinic for advice and follow-up are smokers, it is natural that such clinics would incorporate smoking cessation as a major focus. Evidence-based clinical guidelines from the Agency for Health Care Policy and Research and other professional organizations now define treatment strategies for physicians and health care delivery systems.[79] Because of the importance of the problem, further refinement and proliferation of such guidelines are likely to occur.[80] Smoking cessation is therefore one of the most important components of secondary prevention of CAD and should be aggressively implemented in every patient. Nicotine chewing gum, skin patches, nasal sprays and inhalers, drugs such as mecamylamine and clonidine, serotonergic treatments such as buspirone, antidepressants such as bupropion, and cigarette substitutes are techniques that can be tried. [81]

Heart Failure

Although convincing data indicating that cardiac rehabilitation prolongs life in heart failure patients do not exist, it is clear that rehabilitation is safe and helpful in improving quality of life and exercise tolerance in both medically treated patients and those who have undergone cardiac transplantation.[82] [83] Leg fatigue and exercise intolerance are common symptoms in patients with heart failure (Fig. 39-7) . Decreased cardiac reserve as a result of left ventricular systolic dysfunction is important as a cause of exercise intolerance, but the left ventricular ejection fraction and pulmonary capillary wedge pressure actually correlate quite poorly with exercise limitation.[84] [85] Abnormalities of

skeletal muscle, including reductions in the number of type I muscle fibers, concentration of aerobic enzymes, and capillary density, as well as changes in contractile muscle proteins, are present in heart failure patients.[86] However, oxygen extraction (utilization) is not impaired.

Rehabilitation exercise programs for heart failure patients typically use aerobic exercises that increase cardiac output, such as treadmill walking and cycling,[87] but these exercises may also increase filling pressure.[88] One study suggested that cardiac rehabilitation was helpful only in patients who had a normal cardiac output response to exercise.[89] In another study, 68 clinically stable patients already receiving maximum medical therapy and awaiting heart transplantation were prescribed a walking program for 6 months. Walking 20 to 30 minutes at moderate intensity for a distance of up to 2 miles, four times a week, led to improved peak exercise tolerance in 38 of the 68 patients. Thirty-one of the 38 responders were subsequently removed from the heart transplant waiting list.[90] A recent randomized Italian study of predominantly men with ischemic cardiomyopathy showed a decreased rate of hospital readmission for heart failure in patients randomized to moderate exercise training (5/50) versus no exercise (14/49) during 14 months of follow-up.[91] Fewer deaths were observed in the exercise group (9/50) than in the nonexercise group (20/49).[92]

An aerobic exercise program in patients who are able to

Figure 39-7 Peripheral abnormalities leading to physical deconditioning are responsible for some of the exercise intolerance symptoms in chronic heart failure; by reducing physical deconditioning, exercise training is able to partially reverse peripheral and autonomic abnormalities and thus slow or block the vicious cycle. *(Modified from Piepoli MF, Flather M, Coats AJ: Overview of studies of exercise training in chronic heart failure: The need for a prospective randomized multicentre European trial. Eur Heart J 19:830-841, 1998.)*

tolerate it is an important adjunct to pharmacological therapy for congestive heart failure. Large randomized trials are needed to further define mechanisms of benefit, selection of patients most likely to benefit, optimal modes of training, risks, and costs.[92]

Cardiac Transplantation (see Chap. 20)

Cardiac transplantation is well established as an effective treatment in selected patients with end-stage heart disease. Cardiac rehabilitation following cardiac transplantation is recommended for its salutary effects on functional capacity.[93] [94] [95]

In the only currently available randomized trial, 27 cardiac transplant recipients were assigned to participate in a 6-month structured cardiac rehabilitation program or to undergo unstructured therapy at home.[95] Despite spending more time on the transplant waiting list and being more likely to undergo urgent transplantation, the group

randomized to structured cardiac rehabilitation manifested greater increases in peak oxygen consumption and workload, as well as a greater reduction in the ventilatory equivalent for carbon dioxide.[95] The structured rehabilitation cohort demonstrated greater exercise capacity at 1 year despite inferior performance 1 month after transplantation. Although exercise training yields significant improvement at 1 year,[95] [96] [97] peak oxygen consumption fails to improve further over the ensuing 4 to 5 years,[98] [99] primarily because of limited improvement in chronotropic response beyond the first year.[98] [100]

The impaired chronotropic response of the denervated cardiac allograft is manifested by a high resting heart rate, reduced heart rate reserve, and diminished maximum heart rate during exercise. The allograft is dependent on elevated levels of circulating catecholamines for increases in stroke work and heart rate during exercise.[101] Although biochemical [102] and physiological[103] evidence of reinnervation following human cardiac transplantation is mounting, such reinnervation is usually clinically insignificant.[100] [104]

PERIPHERAL ABNORMALITIES IN OXYGEN TRANSPORT.

In addition to chronotropic incompetence and diastolic dysfunction, peripheral abnormalities in oxygen transport/utilization have been reported.[99] [105] These abnormalities may be the result of pretransplantation deconditioning (see Fig. 39-7) or posttransplantation corticosteroid use. Studies in patients with severe heart failure awaiting heart transplantation have demonstrated abnormalities in skeletal muscle morphology and bioenergetics, including reductions in type I fibers, capillary density, and oxidative enzyme activity.[86] Similar findings are seen in patients following transplantation and may contribute to the impaired exercise performance.[106] A longitudinal study of 12 transplant recipients during the first postoperative year suggested improvement in (but not complete normalization of) myocyte fiber cross-sectional area and skeletal muscle enzyme activity commensurate with gains in peak oxygen consumption.[106] Capillary density and fiber-type distribution did not change during follow-up despite 3 months of structured physical rehabilitation.[106] These observations have prompted recommendations for resistance weight training as part of posttransplantation rehabilitation.[93] [94] [107]

In the immediate postoperative phase, rehabilitation is limited to passive and active range of motion.[108] Following extubation, rehabilitation continues with mobilization, progressive ambulation, and incentive spirometry to aid pulmonary toilet. Predischarge exercise testing of patients free of acute allograft rejection or surgical complications has been suggested as a guide for outpatient exercise prescription.[94]

EXERCISE PRESCRIPTIONS IN TRANSPLANT RECIPIENTS.

The abnormal exercise physiology of cardiac transplant recipients mandates modification of standard exercise prescriptions. Target heart rates are problematic because of the chronotropic incompetence and diminished heart rate reserve of the denervated allograft. Many authorities recommend the use of Borg[109] ratings of perceived exertion.[93] [94] [108] However, individuals vary considerably in the percentage of maximum heart rate or peak oxygen consumption that they achieve at commonly

prescribed levels of perceived exertion.[110] Such variability limits the safety and efficacy of this approach in some patients.[110] Some suggest that exercise training be predicated on fixed-distance/fixed-speed prescriptions fine-tuned by perceived exertion ratings.[110]

The general principles of cardiac rehabilitation, including frequency, intensity, duration, and progression of training, apply to the heart transplantation population. Longer duration of exercise may be appropriate to allow for the delayed response to circulating catecholamines by the denervated allograft. Warm-up and cool-down periods with appropriate stretching before and after exercise are important. At least 20 minutes of sustained exercise at the prescribed intensity is desirable.

Initiation of supervised rehabilitation will vary according to the preoperative status of the recipient and the postoperative course. Generally, training can start 2 to 6 weeks after surgery[111] and should continue for at least 6 to 8 weeks.[94] Although significant improvement in exercise capacity and strength has been demonstrated with prolonged, home-based training in motivated patients, many programs start with supervised sessions 3 days per week. One study recently demonstrated the benefits of adding supervised aerobic and resistive exercise training to progressive, home-based therapy.[95] Resistive arm training should be deferred for 6 weeks to allow adequate healing of the sternotomy.[111] It should be incorporated thereafter to increase strength and functionality and to improve the skeletal muscle abnormalities of chronic heart failure and mitigate the deleterious muscular effects of immunosuppressive agents. It may also combat the osteoporosis common to this population.

Ideally, initial exercise sessions should be guided by graded exercise test results with a rating of perceived exertion that matches the ventilatory threshold,[97] or 60 to 70 percent of peak oxygen consumption. If rating of perceived exertion alone is used, an initial target of 11 to 13 is appropriate for those debilitated by chronic heart failure or postoperative recovery.[94] The exercise prescription should be advanced as the ventilatory and lactate thresholds, peak oxygen consumption, and maximum heart rate predictably improve with training and postoperative convalescence.[96] [97] [112]

Cardiovascular Rehabilitation in Obese Patients

Weight loss is a key component of cardiovascular rehabilitation in an obese patient.[112A] Exercise training is an important contributor to weight loss, although the effect of exercise is quite variable. It is not clear how much exercise is required to prevent weight gain or weight regain, although it has been suggested that the levels may be much higher than the currently recommended doses of physical activity.[113] Most controlled exercise training studies show only modest weight loss (approximately 2 to 3 kg) in the exercise group. However, when caloric restriction is added to the exercise program, the average weight loss is 8.5 kg, most of which is body fat, while diet alone results in less weight loss (5.1 kg). Over the same study period, those undergoing neither diet nor exercise programming increase weight by an average of 1.7 kg.[114] [115]

These data strongly support a role for both exercise and diet in weight loss programs. Body composition and fat distribution are linked to cardiovascular mortality[114] and are improved by exercise. Physically active men and women have a more favorable

waist-to-hip ratio (i.e., less central obesity) than do sedentary individuals.[116] In general, exercise for the obese should be low-impact exercise, such as brisk walking or cycle ergometry, and be performed with greater duration and frequency and less intensity.

One study (unpublished) in obese patients with CAD in a cardiac rehabilitation program compared one group receiving extreme calorie restriction and moderate-intensity exercise with another receiving moderate caloric restriction and high-intensity exercise. The intervention results revealed that the extreme caloric restriction-moderate-intensity exercise group lost significantly more weight over the 6-month study period.

Cardiovascular Rehabilitation in Elderly Patients (see Chap. 57)

A critical factor in an elderly (
70 years) person's ability to function independently is mobility, the ability to move without assistance.[117] [118] [119] [120] [121] [122] [123] [123A] The overall focus for cardiac rehabilitation and exercise training in the elderly should be to enhance health-related conditioning while simultaneously assisting in the reduction of risk factors for various chronic diseases and improving the overall quality of life. Considerable evidence exists that physical activity, both endurance and resistance-type exercise, can provide for functional independence and overall well-being in older adults.[123B]

Exercise prescription guidelines as described previously are generally appropriate for older participants. As with younger persons, the combination of endurance and resistance

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exercise is best for achieving health and conditioning goals.[124] [125] [126] [127] [128] The exercise capacity of the elderly, both before and after exercise training, is usually lower than that observed in younger persons[117] [129] (Table 39-4) . Thus, it is important to recommend activities that require low-level energy expenditure (40 to 50 percent of O_{2max}), particularly during the first few weeks of the program. High-intensity exercise training must be recommended with caution in this age group because of the potential for musculoskeletal injury. Those whose exercise duration is limited (
15 minutes per session) because of physical or psychosocial limitations should also attempt to exercise more frequently. Conversely, lengthening the duration of activity to as much as 45 to 60 minutes per session is valuable for increasing caloric expenditure despite lower-intensity exercise.

Cardiovascular Rehabilitation in Patients with Peripheral Vascular Disease (see Chap. 41)

Patients with symptomatic peripheral vascular disease commonly have many traditional risk factors for atherosclerosis and often have severe coexistent CAD that may be symptomatic or clinically silent.[130] Frequently, occult CAD is found in these patients by screening pharmacological stress tests or angiography because exercise is often limited by claudication before the onset of cardiac symptoms. This limited exercise capacity

may decrease the diagnostic accuracy of exercise stress testing. CAD is usually the life-limiting illness in these patients.[131] Consequently, aggressive risk factor modification is needed not only to slow the pace of peripheral vascular disease but also to reduce cardiovascular events and the rate of progression of coexisting CAD. Measures to protect the feet and prompt treatment of foot ulcers appear to reduce the risk of amputation.[132]

The initial therapeutic intervention for most patients with intermittent claudication is a walking program. Thirty to 45 minutes of walking performed 4 or more days weekly was reported to increase walking distance by 200 percent or more.[133] However, therapeutic trials in patients with claudication have commonly treated only a small number of patients, are often not randomized, and are difficult to interpret because of a large placebo effect and publication bias.[134] [135] [136] [137] A recent meta-analysis of such studies, including only 112 patients, concluded that the increase in pain-free walking distance at the end of an exercise program was 140 meters with a concomitant increase in total walking distance of 180 meters.[134] Thus, although exercise programs are safe and improve physical conditioning, weight control, and hypertension, the magnitude of the treatment effect is not well defined.

Small studies comparing supervised versus home-based training of claudication patients suggest an advantage in favor of the supervised setting.[134] [137] [138] Since the data are so limited at this point, prescription of expensive supervised programs is controversial and cannot yet be recommended on a routine basis.[134] However, in patients who are already enrolled in cardiac rehabilitation programs, where benefit is more readily demonstrable and better documented, treatment of peripheral vascular disease with an exercise program can be an additional benefit.

Peripheral vascular disease usually coexists with CAD. Cardiac rehabilitation programs are beneficial to patients

TABLE 39-4 -- AGE-ASSOCIATED CHANGES IN THE PHYSIOLOGICAL RESPONSE TO AEROBIC EXERCISE

Reduced aerobic capacity--a decline in maximum oxygen consumption of 8-10% per yr in nontrained populations
Reduced maximum heart rate of 1 beat/min/yr
More rapid increase in systolic blood pressure with exercise
Attenuated elevation in left ventricular ejection fraction

with peripheral vascular disease, and walking improves claudication, but the mode of exercise may need to be altered (treadmill, cycle, or swimming) to limit the likelihood that claudication will prevent a training effect. Secondary preventive measures (smoking cessation, lipid-lowering therapy) are just as important as they are in patients undergoing rehabilitation for CAD alone.

Cardiovascular Rehabilitation in Patients with End-Stage Renal Disease (see Chap. 72)

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD).[139] Although many patients with ESRD are candidates, cardiac rehabilitation is underused in this high-risk cohort.

In one multicenter study of chronic hemodialysis patients, 76 percent manifested ventricular arrhythmias and 69 percent demonstrated supraventricular arrhythmias on 48-hour ambulatory monitoring.[140] Thirty-nine percent manifested multiple episodes of complex ventricular ectopy. The frequency of ventricular arrhythmias increased significantly in the second hour of dialysis and lasted up to 5 hours after dialysis. These findings suggest that close ECG monitoring and avoidance of the early postdialysis period would be prudent in scheduling exercise training sessions.

Several alterations in physiology have an impact on the rehabilitation process. Autonomic insufficiency is common in ESRD and mandates monitoring of supine and standing vital signs and caution with positional changes. Problematic contributing factors include underlying systemic disease (e.g., diabetes mellitus, amyloidosis), antihypertensive medications, aluminum toxicity, and uremia.[141] [142]

Many factors contribute to an imbalance in myocardial oxygen supply and demand in patients with ESRD.[143] Hypertension, increased intravascular volume, diastolic left ventricular dysfunction, valvular heart disease, and left ventricular systolic dysfunction can all contribute to elevated left ventricular end-diastolic pressure and reduced coronary perfusion pressure. Tachycardia-induced shortening of diastolic perfusion time, reduced coronary perfusion pressure, anemia, and dialysis-induced shifts in the hemoglobin oxygen dissociation curve conspire to reduce myocardial oxygen supply. These factors contribute to a propensity for ischemia, including ischemia during exercise training. Coupled with the higher prevalence of silent ischemia in patients with ESRD, these features make supervised, monitored exercise programs prudent for this population.

Many patients with ESRD have reduced exercise capacity[144] as a result of age, malnutrition, comorbidity, deconditioning, immobility, and advanced cardiovascular disease. Fortunately, exercising to target heart rates 50 to 70 percent of those achieved on screening maximum exercise tests achieve improvements in exercise capacity and symptomatology that are similar to those attained with traditional targets of 70 to 85 percent.[93]

Several small studies of dialysis patients free of obvious CAD suggest that intradialysis exercise programs improve quality of life, blood pressure, and some measures of metabolic health.[145] [146] [147] The safety of such programs in patients with recent acute coronary events has not been established and cannot be assumed. Limited data suggest potential hemodynamic compromise with exercise in later stages of hemodialysis sessions.[148]

The benefits of exercise training in ESRD patients after major cardiac events should be similar to those derived by others with ESRD and the cardiac rehabilitation population at large. However, profound limitations in exercise capacity may limit the effectiveness of

cardiac rehabilitation for some, thus mandating careful selection of rehabilitation candidates and appropriate medical supervision.

PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CORONARY ARTERY DISEASE

General principles of cardiac rehabilitation are applicable to patients with chronic obstructive pulmonary disease who have suffered a major cardiac event. Those who manifest resting or exercise-induced hypoxia (oxygen saturation less than 88 percent) should receive continuous supplemental oxygen during training sessions. High-risk individuals should be monitored closely in supervised programs and are not candidates for home-based programs.[149] These patients demonstrate less improvement in peak O_2 than those participating in cardiac rehabilitation.

Cardiovascular Rehabilitation in Patients with Diabetes Mellitus (see Chap. 63)

Ninety percent of all diabetics manifest insulin resistance as a primary metabolic derangement.[150] These type II diabetics manifest a high prevalence of hypertension, dyslipidemia, abdominal obesity, and endothelial dysfunction, all remedial by weight loss and exercise. Thus cardiac rehabilitation is particularly beneficial in this high-risk population.

In addition to standard pharmacological intervention,

comprehensive cardiac rehabilitation is an important intervention for diabetics after major coronary events. Because of the far-ranging benefits of weight loss and exercise on the atherogenic physiology of insulin resistance, this population is particularly well suited for exercise training, behavioral counseling, and risk factor modification. Their increased risk of cardiovascular events suggests that supervised programs may be more appropriate following acute coronary events. Several unique features of this population warrant consideration during exercise training.

The adrenergic response to exercise can exacerbate hyperglycemia in suboptimally treated diabetics. Conversely, patients treated with insulin or sulfonylurea medications can experience hypoglycemia during or after exercise.[151] Monitoring blood sugar before and after exercise is an important tool during exercise training. Results should be used to tailor therapy, educate and reassure patients, and ensure safety during training sessions.[152] If preexercise glucose levels are less than 100 mg/dl, oral glucose should be administered before exercising. Fruit, a starch, or 4 to 5 gm of oral glucose tablets is recommended.[151] Emergency equipment, including glucose tablets or gels and glucagon injection kits, should be readily available to treat hypoglycemic episodes. Recurrent episodes of hypoglycemia should lead to downward adjustment of preexercise sulfonylurea or insulin doses or prompt ingestion of carbohydrate before exercise. Evening exercise sessions can occasionally induce early morning hypoglycemia and necessitate bedtime snacks or a change in the timing of exercise

sessions.

To avoid excessive hyperglycemia, exercise should be avoided in the setting of poor glycemic control. If preexercise finger-stick glucose levels exceed 300 mg/dl (or if lesser degrees of hyperglycemia are present in the setting of ketonuria), exercise should be postponed until glycemic control has improved.[151]

DIABETIC NEUROPATHY.

Somatic neuropathy puts patients at risk for cutaneous and orthopedic injury during exercise. As many as 22 percent of diabetics with somatic neuropathy and cutaneous foot ulcers have radiographic evidence of foot fractures, often asymptomatic.[153] Screening for sensory deficits, cutaneous lesions, ingrown toenails, or foot deformities is an important part of intake evaluation for exercise rehabilitation programs. Patients with sensory deficits should be coached in regular foot examination before and after exercise. Proper athletic footwear, with orthotics when appropriate, is essential to minimize the risk of injury. Patients with severe neuropathy, including those with Charcot joints, should pursue non-weight-bearing exercises such as swimming, bicycling, rowing, and arm or chair calisthenics.[154]

Exercise training in patients with autonomic neuropathy should be conducted to minimize the adverse consequences of orthostatic hypotension, silent ischemia, and arrhythmia. Patients should be adequately hydrated before exercise. They should avoid exercising after meals or during the morning when orthostatic hypotension is more likely. They should adjust doses or the timing of antihypertensive medications to minimize orthostatic hypotension during or after exercise and avoid vasodilation caused by environmental heat or ethanol ingestion during training sessions. They should use compressive stockings when appropriate and exercise in a supervised setting with ECG monitoring and resuscitative equipment in the early stages after an acute coronary event.[151]

Targets for exercise should be predicated on perceived exertion rather than the heart rate in patients with autonomic neuropathy because of decreased maximum heart rates and resting tachycardia. Moderate levels of perceived exertion should be sought over 2 to 4 weeks of gradual training.[154]

Patients with nonproliferative retinopathy can engage in most forms of exercise with minimal risk of progressive disease. However, most authorities suggest limiting diabetics with severe nonproliferative retinopathy in a similar fashion to those with proliferative disease.[155] [156]

Psychological Factors in Cardiovascular Rehabilitation (see Chap. 70)

RISK FACTORS.

The concept that mental stress contributes to CAD pathogenesis or events seems logical. Blood pressure and serum lipids increase with mental stress. Factors promoting

thrombosis, decreased endothelial-dependent vasodilation, and paradoxical coronary artery constriction during mental stress have also been identified.[157] [158] However, the type A personality concept and its relationship to CAD remain controversial.[159]

Several studies have indicated that depression often precedes acute myocardial infarction. More commonly, depression begins during hospitalization for the infarction and is first noticed by the patient, family members, and/or caregivers upon the patient's return home.[160] Patients with major depression have a fivefold increase in mortality in the first 6 months following myocardial infarction, and even those with mild depression exhibit increased risk.[161] [162]

PREVENTIVE MEASURES.

Cardiac rehabilitation programs improve anxiety and depression in the short term, but proof of long-term benefit is lacking.[163] One 4-month, randomized trial of aerobic exercise, stress management, or standard medical therapy showed a statistically significant 74 percent reduction in cardiac events in the stress management group. Although the patients randomized to the exercise limb improved their aerobic conditioning and lost weight, their risk of cardiac events was not statistically different from that of the standard medical therapy group.[164] However, a meta-analysis of 23 randomized controlled trials concluded that the addition of psychological treatment to standard cardiac rehabilitation programs reduces mortality and morbidity the first 2 years after treatment.[165]

Practical approaches include vigorous measures to encourage and enable patients to return to work[166] because return to work often provides reassurance, helps focus attention away from health problems, and may address the concern that low-income patients have higher mortality after myocardial infarction.[167] Experienced clinicians frequently recount having seen widows or widowers who themselves die shortly after returning home from hospitalization for acute myocardial infarction within months of the death of their spouse. Attempts should also be made to have patients avoid social isolation inasmuch as those living alone after myocardial infarction seem to have higher mortality than those who do not live alone.[168]

Clearly, the cardiac rehabilitation and secondary prevention clinic is most appropriate to address the psychological needs of cardiac patients. These issues need to be dealt with openly and with great sensitivity on the part of all concerned. As the psychological contributions to CAD are better refined, more explicit guidelines will be feasible.

Compliance with Rehabilitation Programs

A recent review of studies regarding physical activity interventions and compliance in health care settings included 12 studies in apparently healthy subjects and 24 randomized studies in patients with cardiovascular disease.[169] Only about half of the programs were successful in increasing physical activity or cardiorespiratory training in their subjects. Characteristics of successful interventions included long-term sustained intervention and multiple contacts, supervised exercise (such as in a cardiac rehabilitation program), provision of exercise equipment, and behavioral approaches.

Importantly, the behavioral component fostered subject selection of an enjoyable activity, as well as setting realistic goals, identifying barriers, problem solving, self-monitoring, providing feedback and positive reinforcement, and enhancing social support.[170] Continuing intervention and behavioral approaches have been shown to increase activity levels in CAD patients for as long as 4 to 5 years.[171] [172]

One approach to promote an increase in physical activity

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is for exercise to begin slowly and then gradually progress to the recommended exercise prescription, with assessment of success and reinforcement provided regularly. Patients can begin at a more moderate intensity, shorter duration, and lower frequency than the ultimate goal. Not only are gradual increases in activity safer for sedentary people and for patients with CAD, but short-term successes may also increase the patient's self efficacy in being physically active.[173] The health care provider can use this positive outcome for feedback and reinforcement. Such an approach requires repeated follow-up visits. The most effective interventions--those with multiple components and a continued maintenance intervention--can be delivered via a model in which physicians provide advice and other members of the health care team provide more in-depth behavioral counseling and follow-up.[174]

For successful implementation of physical activity counseling in a health care setting, a coordinated, multilevel intervention should encompass strategies directed toward the practice environment, patients, and providers.[175] Systematic delivery of a counseling program might be enhanced through the use of encounter forms[176] and case management systems.[177] In addition, achieving greater implementation of physical activity interventions in health care settings will require improved education and training of health professionals and attention to health care policy and reimbursement issues. The cardiac rehabilitation setting is an excellent milieu in which to use the aforementioned modalities to implement physical activity and improve compliance in a motivated population.

Cost-Effectiveness of Cardiac Rehabilitation (see Chap. 2)

A comprehensive economic analysis of cardiac rehabilitation and secondary prevention includes not only the direct costs of the cardiac rehabilitation intervention but also indirect costs and cost savings attributed to treatment benefits. In addition to the expense of the cardiac rehabilitation program and exercise tests, diminished work time while attending the program, transportation, rehospitalization, costs of medical disability, and the medical and pension costs of enhanced longevity must be considered.[178] A number of studies have addressed these issues, but unfortunately, no single study is comprehensive, randomized, and controlled. Furthermore, studies performed in one area or region or in one country are not necessarily relevant in another area or country because of variations in health plans, differences in incentives to return to work, and wide diversity in management "styles" and the availability of revascularization

procedures.

One method shown to be effective 3 weeks after myocardial infarction is the performance of an "occupational work evaluation." This intervention consists of an exercise test and advice about exercise with specific recommendations for early return to work in patients stratified by the exercise test to a low-risk category.[179] When compared with a usual care control group, patients randomized to the intervention had an earlier return to work with an average increase in individual earnings of $2100 over a 6-month period. They also realized a decrease of $500 per patient in total medical costs during follow-up.

Several investigations from Sweden and the United States have evaluated the effect of cardiac rehabilitation participation on subsequent rehospitalization and cost. In an American study, the authors investigated the effect of cardiac rehabilitation on subsequent rehospitalization cost in 580 patients over a mean follow-up period of 21 months.[180] In the rehabilitation group, per capita charges for cardiac rehospitalizations were $739 lower than in control patients. The cost difference was explained by both fewer hospitalizations and lower cost per hospitalization in the cardiac rehabilitation intervention group. Of note, admissions for evaluation of chest pain decreased by 42 percent.

The results of three controlled trials from Sweden further support decreased health care cost after cardiac rehabilitation.[181] [182] [183] In an initial study of 147 coronary bypass patients, hospital readmissions over a 1-year period were reduced by 62 percent in the comprehensive cardiac rehabilitation group.[183] Another controlled trial of 190 patients 65 years of age or older after myocardial infarction defined the effects of a nurse-managed education program lasting 4 months and low-intensity exercise training of 8 weeks' duration.[182] This program resulted in lower rates of rehospitalization (32 vs. 47 percent) over a 1-year period and significantly fewer visits to the emergency department.

The most detailed economic evaluation to date compared comprehensive cardiac rehabilitation (exercise and risk factor modification) with usual care in 305 nonselected myocardial infarction patients over a 5-year period.[181] In addition to a lower rate of total cardiac events (39 vs. 53 percent), the average total duration of in-hospital care was reduced from 16.1 to 10.7 days in the intervention group. The authors concluded that the actual cost of rehabilitation was balanced over the 5-year period by the decrease in hospital readmissions for cardiovascular disease. They also noted that cardiac rehabilitation patients had a higher 5-year return-to-work rate (43 vs. 38 percent). Increased work productivity (i.e., less disability and sick leave) resulted in $12,250 savings per patient to the Swedish disability system.

Finally, a randomized trial of an 8-week cardiac rehabilitation intervention that focused on anxious or depressed patients after myocardial infarction noted a cost-effectiveness of $9200 per quality-adjusted life year,[184] similar to the cost-effectiveness of well-established medical interventions such as coronary bypass surgery for left main coronary disease and beta-adrenergic blockers after myocardial infarction. It is more cost-effective than other accepted practices such as ACE inhibitors for the treatment of

hypertension and lovastatin for hypercholesterolemia.[185] Therefore, limited data support the cost-effectiveness of cardiac rehabilitation in the care of patients after a coronary event.

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Chapter 40 - Diseases of the Aorta

ERIC M. ISSELBACHER

THE NORMAL AORTA

FUNCTION

Appropriately called "the greatest artery" by the ancients, the aorta is admirably suited for its task. In an average lifetime, this thin but large and remarkably tough vessel must absorb the impact of 2.3 to 3 billion heartbeats while carrying roughly 200 million liters of blood through the body. Arteries can be categorized as either *conductance* or *resistance* vessels. Conductance vessels are conduits for blood, and the aorta is the ultimate conductance vessel.

The aorta is composed of three layers: the thin inner layer, or *intima;* a thick middle layer, or *media;* and a rather thin outer layer, the *adventitia.* The strength of the aorta lies in the media, which is composed of laminated but intertwining sheets of elastic tissue arranged in a spiral manner that affords maximum tensile strength. Indeed, as thin as it is, experimentally the aortic wall can withstand the pressure of thousands of millimeters of mercury without bursting. In contrast to the peripheral arteries, the aortic media contains multiple layers of elastic laminae (see Chap. 30) . It is this tremendous

accretion of elastic tissue that gives the aorta not only tensile strength but also distensibility and elasticity, which serve a vital circulatory role. The aortic intima is a thin, delicate layer that is lined by endothelium and easily traumatized. The adventitia contains mainly collagen and carries the important vasa vasorum, which nourish the outer half of the aortic wall, including much of the media.

During ventricular systole, the aorta is distended by the force of the blood ejected into it by the left ventricle, and in this manner, part of the kinetic energy generated by the contracting left ventricle is converted into potential energy stored in the aortic wall. Then, during diastole, this potential energy is transformed back into kinetic energy as the aortic walls recoil and propel the blood in the aortic lumen distally into the arterial bed. Thus, the aorta plays an essential role in maintaining forward circulation of the blood in diastole after it is delivered into the aorta by the left ventricle during systole. The pulse wave itself, with its milking effect, is transmitted along the aorta to the periphery at a speed of about 5 meter/sec. This speed is much faster than the velocity of the intraluminal blood itself, which travels at only 40 to 50 cm/sec.

The systolic pressure developing within the aorta is a function of the volume of blood ejected into the aorta, the compliance or distensibility of the aorta, and resistance to blood flow. This resistance is determined primarily by the tone of the peripheral muscular arteries and arterioles and, to a slight extent, by the inertia of the column of blood in the aorta when systole commences.

In addition to its conductance and pumping functions, the aorta also plays a role in indirectly controlling systemic vascular resistance and heart rate. Pressure-responsive receptors, analogous to those in the carotid sinus, lie in the ascending aorta and aortic arch and send afferent signals to the vasomotor center in the brain stem by way of the vagus nerves. An increase in intraaortic pressure causes reflex bradycardia and a reduction in systemic vascular resistance, whereas a decrease in intraaortic pressure increases the heart rate and vascular resistance.

ANATOMICAL CONSIDERATIONS

The aorta is divided anatomically into thoracic and abdominal components. The thoracic aorta is further divided into the *ascending, arch,* and *descending* segments*,* while the abdominal aorta consists of *suprarenal* and *infrarenal* segments.

The *ascending aorta* is some 5 cm long and has two distinct segments. The lower segment is the *aortic root*, which begins at the level of the aortic valve and extends to the sinotubular junction. This portion of the ascending aorta is the widest and measures about 3.3 cm. The bases of the aortic leaflets are supported by the aortic root, from which the three sinuses of Valsalva bulge outward to allow for full excursion of the aortic valve leaflets during systole. In addition, the two coronary arteries arise from these sinuses of Valsalva. The upper tubular segment of the ascending aorta rises to join the aortic arch. Normally, the ascending aorta sits just to the right of midline, with its proximal portion lying within the pericardial cavity.

The *arch of the aorta* gives rise to all the brachiocephalic arteries. From the ascending

aorta it courses slightly leftward in front of the trachea and then proceeds posteriorly to the left of the trachea and esophagus. The pulmonary artery bifurcation and right pulmonary artery lie inferior to the arch, as does the left lung.

The *descending thoracic aorta* begins in the posterior mediastinum to the left of the vertebral column and gradually courses in front of the vertebral column as it descends, where it occupies a position immediately behind the esophagus. Distally, it passes through the diaphragm, usually at the level of the 12th thoracic vertebra.

The point at which the aortic arch joins the descending aorta is called the *aortic isthmus.* The aorta is especially vulnerable to trauma at this site because it is here that the relatively mobile portion of the aorta--the ascending aorta and arch--becomes relatively fixed to the thoracic cage by the pleural reflections, the paired intercostal arteries, and the left subclavian artery. This point is also where coarctations of the aorta are located.

The abdominal aorta continues from the thoracic aorta, gives rise to the mesenteric and renal arteries, and ends at its bifurcation at the level of the fourth lumbar vertebra.

AGING OF THE AORTA

As discussed above, the elastic properties of the aorta are crucial to its normal function. However, the elasticity and distensibility of the aorta decline with age. Such changes occur even in normal healthy adults, and for unknown reasons, these changes occur earlier and are more progressive in men than women.[1] The loss of elasticity and aortic compliance probably accounts for the increase in pulse pressure commonly seen in the elderly. This progressive loss of aortic elasticity with aging is accelerated among those with hypertension when compared with age-matched normotensive controls.[2] Similarly, those with hypercholesterolemia[3] or coronary artery disease show a greater loss of elasticity than do controls.[4] Conversely, among healthy athletes, aortic elasticity is higher than in their age-matched controls.[4]

Histologically, the aging aortic wall exhibits fragmentation of elastin with a concomitant increase in collagen that results in an increased collagen-to-elastin ratio, which contributes to the loss of aortic distensibility observed physiologically.[5] Recent experimental animal data suggest that impairment of vasa vasorum flow to the aortic wall results in stiffening of the aorta with similar histological changes and may therefore be one cause of the degenerative changes seen with age.[6]

In animal models, loss of aortic distensibility directly affects the mechanical performance of the left ventricle, with increases noted in left ventricular systolic pressure and wall tension and in end-diastolic pressure and volume.[7] Furthermore, reduced aortic compliance causes a 20 to 40 percent increase in myocardial oxygen consumption to maintain a given stroke volume.[8] It is therefore likely that over time, the changes in aortic compliance seen with age may cause clinically important alternations in cardiac function.[7]

EXAMINATION OF THE AORTA

Unless the aorta is abnormally enlarged, the only location in which it can be palpated is the abdomen. The ease with which it can be felt depends largely on body habitus and

pulse pressure: It is readily felt in thin individuals. It may be quite sensitive to palpation. Auscultation is usually unrevealing in aortic diseases, except for occasional bruits at sites of narrowing of the aorta or its arterial branches. Diseases of the aortic root and proximal ascending aorta sometimes involve the aortic valve, with resultant aortic regurgitation that may be detectable on auscultation. Regurgitant murmurs secondary to root dilatation rather than primary valvular disease are often loudest along the right sternal border.

Chest radiography and fluoroscopy are valuable and simple procedures for assessing the aorta. Normally, the ascending aorta is not visible on the direct anteroposterior chest roentgenogram. The aorta is seen as a "knob" in the superior mediastinum just to the left of the vertebral column. The lateral border of the descending thoracic aorta can often be found to the left of the spine. On the lateral chest roentgenogram, the aortic root and proximal ascending aorta are visible as an indistinct shadow in the middle of the mediastinum arising from the base of the heart. The ascending aorta and arch are best demonstrated in a left anterior oblique projection--a view that should always be included when disease of the thoracic aorta is suspected.

A number of imaging modalities are available for diagnostic examination of the aorta, including aortography, computed tomography (CT), magnetic resonance imaging (MRI), and both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). The respective utility of these imaging modalities is discussed below in the context of specific aortic diseases.

AORTIC ANEURYSMS

The term *aortic aneurysm* refers to a pathological dilatation of the normal aortic lumen involving one or several segments. Although perhaps no definition is universally accepted, an aortic aneurysm is best described as a permanent localized dilatation of the aorta having a diameter at least 1.5 times that of the expected normal diameter of that given aortic segment.[9] Aneurysms are usually described in terms of their location, size, morphology, and etiology. The morphology of an aortic aneurysm is typically either *fusiform,* which is the more common shape, or *saccular.* A fusiform aneurysm is fairly uniform in shape, with symmetrical dilatation that involves the full circumference of the aortic wall. The dilatation seen in saccular aneurysms, on the other hand, is more localized and appears as an outpouching of only a portion of the aortic wall. In addition, the aorta may have a *pseudoaneurysm* or *false aneurysm,* which is not actually an aneurysm at all, but rather a well-defined collection of blood and connective tissue

outside the vessel wall. This defect may be a consequence of a contained rupture of the aortic wall.

The presence of an aortic aneurysm may be a marker of more diffuse aortic disease. Overall, up to 13 percent of all patients in whom an aortic aneurysm is diagnosed are found to have multiple aneurysms,[10] with up to 25 to 28 percent of those with thoracic aortic aneurysms having concomitant abdominal aortic aneurysms.[11] [12] For this reason, Crawford and Cohen have recommended that a patient in whom an aortic aneurysm is discovered should undergo examination of the entire aorta for the possible presence of other aneurysms.[10]

Abdominal Aortic Aneurysms

Abdominal aortic aneurysms are much more common than thoracic aortic aneurysms. Age is an important risk factor inasmuch as the incidence rises rapidly after 55 years of age in men and 70 years of age in women,[13] and abdominal aortic aneurysms occur four to five times more frequently in men than women. The incidence of abdominal aneurysms has increased threefold in recent decades, from 8.7 per 100,000 person-years in 1951 to 36.5 to 60 per 100,000 person-years in 1971 to 1980.[14] Because the incidence of abdominal aneurysms of all sizes has increased, it is believed that these data at least in part reflect a true increase in disease incidence. Other factors that may have contributed to the marked rise in the incidence of such aneurysms include the increasing mean age of the population, a greater awareness of the association of aneurysmal disease with other prevalent cardiovascular conditions, and improvements in diagnostic evaluation. The prevalence of abdominal aortic aneurysms in the population 50 years of age and older is at least 3 percent.[15]

ETIOLOGY AND PATHOGENESIS

Although it is now evident that abdominal aortic aneurysms arise as a consequence of multiple interacting factors, classically, atherosclerosis has been considered the common underlying etiology. (See also Chap. 30.) The infrarenal abdominal aorta is most affected by the atherosclerotic process and is similarly the most common site of abdominal aneurysm formation; only a fraction of abdominal aortic aneurysms are suprarenal, with these tending to arise only as an extension of a thoracic (thoracoabdominal) aneurysm. The atherosclerotic process less often involves the thoracic aorta.

Atherosclerotic disease of the aorta may produce either stenotic obstruction, a process that tends to be confined to the infrarenal abdominal aorta, or aneurysmal dilatation; why one process should predominate over the other in any given individual, however, is unknown.[15] Although the mechanism by which atherosclerosis results in aortic aneurysms is obscure, a recent hypothesis may account for the disease's predilection for the infrarenal abdominal aorta over other segments.[16] The media of the infrarenal aorta in humans has no vasa vasorum, and as a consequence, at least the inner media must receive oxygen and nutrients by diffusion from the aortic lumen. Atherosclerotic disease causes thickening of the intima and may thereby compromise the diffusion of such oxygen and nutrients to the medial layer. Exacerbated by increases in aortic wall

stress from hypertension, this tissue hypoxia may injure the media and thus initiate a process of degeneration of the media and its elastic elements.[16] The damage produces a weakening of the aortic wall that over time allows the formation of fusiform or, less commonly, saccular dilatation of the aorta. As the aorta then widens, tension in the vessel wall rises in accordance with Laplace's law, which states that tension is proportional to the product of pressure and radius. Further widening results in even greater wall tension, which in turn leads to acceleration of aneurysm enlargement. A vicious circle is thus established in which the dilatation is often rapidly progressive.

Although atherosclerosis certainly contributes to the pathogenesis of abdominal aortic aneurysms, genetic and cellular factors play important roles as well. A genetic predisposition to the development of abdominal aortic aneurysms has been repeatedly suggested by studies of familial incidence, with up to 28 percent of patients who have an abdominal aortic aneurysm having a first-degree relative similarly affected.[17] A report analyzing 313 pedigrees has confirmed the importance of familial factors in the pathogenesis of abdominal aortic aneurysms and supports the hypothesis that abdominal aortic aneurysm might be a predominantly genetic disease.[18] At present, however, few single gene mutations are known to cause aneurysm formation (e.g., Marfan syndrome and Ehlers-Danlos syndrome type IV).[18A] (See also Chap. 56.) It appears likely that the genetic factors involved may be polygenic.

An area of expanding investigation is the role of cellular mechanisms in the pathogenesis of aortic aneurysms. Destruction of the media and its elastic tissue is the striking histological feature of aortic aneurysms when compared with the normal aorta. Experimental evidence indicates excessive activity of proteolytic enzymes in the aortas of affected patients, which may lead to deterioration of structural matrix proteins such as elastin and collagen in the aortic media and thereby promote or perpetuate the formation of aneurysms.[19] Studies have shown that aneurysmal aortas contain elastolytic activity with an active elastase not present in the normal aorta[20] and that other active proteolytic enzymes are present as well. An active inflammatory process may also contribute, given that an abnormal presence of macrophages[21] and elevated levels of cytokines[22] have been demonstrated in aneurysmal aortic tissue.

As a result of flow disturbance through the aneurysmal aortic segment, blood may stagnate along the walls and thus allow the formation of mural thrombus. Such thrombus, as well as atherosclerotic debris, may embolize distally and compromise the circulation of tributary arteries. However, the major risk posed by abdominal aortic aneurysms is that of aneurysm rupture. When rupture does occur, 80 percent rupture into the left retroperitoneum, which may

contain the rupture, whereas most of the remainder rupture into the peritoneal cavity and cause uncontrolled hemorrhage and rapid circulatory collapse.[23] Rarely, an aneurysm may rupture into the inferior vena cava, iliac vein, or renal vein.

Clinical Manifestations

The majority of abdominal aortic aneurysms are asymptomatic and discovered incidentally on routine physical examination or on an abdominal roentgenogram[14] or ultrasound scan ordered for other indications. Younger patients (50 years old or less), however, are several times more likely to be symptomatic at the time of diagnosis.[24] Among these patients, pain is the most frequent complaint[14] and is usually located in the hypogastrium or lower part of the back. The pain is usually steady, has a gnawing quality, and may last for hours to days at a time. In contrast to musculoskeletal back pain, aneurysm pain is not affected by movement, although patients may be more comfortable in certain positions, such as with the legs drawn up.

RUPTURED ANEURYSM.

Expansion and impending rupture are heralded by the development of new or worsening pain, often of sudden onset. This pain is characteristically constant, severe, and located in the back or lower part of the abdomen, sometimes with radiation into the groin, buttocks, or legs. Actual rupture is associated with abrupt onset of back pain along with abdominal pain and tenderness. Most patients have a palpable, pulsatile abdominal mass, and many are hypotensive when initially seen. However, this familiar triad of abdominal/back pain, a pulsatile abdominal mass, and hypotension--recognized as pathognomonic of a ruptured abdominal aortic aneurysm--is seen in as few as one-third of cases.[25] Moreover, a ruptured aneurysm may mimic other acute abdominal conditions, such as renal colic, diverticulitis, or a gastrointestinal hemorrhage, and may therefore be initially misdiagnosed in as many as 30 percent of cases.[2]

Patients who suffer rupture of an abdominal aortic aneurysm are critically ill. Hemorrhagic shock may ensue rapidly and is manifested by hypotension, vasoconstriction, mottled skin, diaphoresis, mental obtundation, and oliguria and, terminally, by arrhythmias and cardiac arrest. Retroperitoneal hemorrhage may be signaled by hematomas in the flanks and groin. Rupture into the abdominal cavity may result in abdominal distention, whereas rupture into the duodenum is manifested as massive gastrointestinal hemorrhage.

PHYSICAL EXAMINATION.

Many aneurysms can be detected on physical examination,[26A] although even large aneurysms may be difficult or impossible to detect in obese individuals.[27] When palpable, a pulsatile mass extending variably from the xiphoid process to the umbilicus may be appreciated. Because of difficulty distinguishing the abdominal aorta from surrounding structures by palpation, the size of an aneurysm tends to be overestimated on physical examination. Moreover, it may be difficult to differentiate a tortuous, ectatic aorta from true aneurysmal dilatation. Aneurysms are often sensitive to palpation and may be quite tender if rapidly expanding or about to rupture. While tender aneurysms should be examined cautiously, no risk is known to be associated with palpation of the

abdominal aorta.[27]

Associated occlusive arterial disease is sometimes present in the femoral pulses and distal pulses in the legs and feet. Bruits arising from associated narrowed arteries may be heard over the aneurysm. Occasionally, an arteriovenous fistula may be formed by spontaneous rupture into the inferior vena cava, iliac vein, or renal vein and cause a syndrome of hemodynamic collapse and acute high-output cardiac failure.

DIAGNOSIS AND SIZING.

Several diagnostic imaging modalities are currently used for detecting, sizing, and serially monitoring abdominal aortic aneurysms, as well as for precisely defining the aortic anatomy preoperatively. Abdominal ultrasonography is perhaps the most practical way to screen for abdominal aortic aneurysms. It can visualize an aneurysm in the transverse and longitudinal planes, has a sensitivity of nearly 100 percent,[28] and can accurately define aneurysm size to within ±0.3 cm.[29] [30] Its major advantages are that it is inexpensive and noninvasive and does not require the use of a contrast agent. However, ultrasound is limited by its inability to visualize the cephalic or pelvic extent of disease or define the associated mesenteric and renal arterial anatomy. Therefore, it is insufficient for planning operative repair.

Computed tomography is an extremely accurate method for both diagnosing aortic aneurysms (Fig. 40-1) and sizing them to within ±0.2 cm.[31] CT has an advantage over ultrasonography in that it can better define the shape and extent of the aneurysm as well as the local anatomical relationships of the visceral and renal vessels. Its disadvantages are that the procedure is more expensive and less widely available than ultrasonography, and it also requires the use of ionizing radiation and intravenous contrast. Although CT may therefore be less practical than ultrasonography as a screening tool, its high accuracy in sizing aneurysms makes it an excellent modality for serially monitoring changes in aneurysm size.[30] It is important to note that CT measurements of aneurysm size tend to be larger than ultrasound measurements by an average of 0.27 cm.[32] Conventional CT scanning is limited in the preoperative evaluation of abdominal aortic aneurysms because it does not provide information regarding renal or mesenteric arterial occlusive disease. However, newer techniques such as spiral (helical) CT with three-dimensional display of the aorta and its branches[33] provide more comprehensive preoperative evaluation of the anatomy of an abdominal aortic aneurysm.

Aortography has long been the standard imaging modality for the preoperative definition of abdominal aortic aneurysm anatomy. Although it is well recognized that aortography may underestimate aneurysm size in the presence of nonopacified mural thrombus lining the aneurysm walls, it nevertheless remains an excellent technique for defining the suprarenal extent of the aneurysm and any associated iliofemoral disease. It is also excellent for defining renal and mesenteric arterial anatomy. The need for routine preoperative aortography is open to debate,[34] and in fact, many surgeons now use it only selectively.[35] Its disadvantages are that it is expensive, it is an invasive procedure with inherent risks, and it requires the use of intraarterial contrast and ionizing radiation.

Most recently, *magnetic resonance (MR) angiography* has been promoted as an alternative to aortography for the preoperative evaluation of aortic aneurysms.[34] Whereas flowing blood appears as a signal void on conventional spin-echo MRI, with the use of MR angiography blood has a bright appearance and vessels can be displayed in a projective fashion similar to what is seen with traditional angiography. Moreover, because tomographic images are reconstructed to create a three-dimensional image, the aorta may be visualized from a series of projections to facilitate appreciation of anatomical relationships. MR angiography is extremely accurate in determining aneurysm size, and it correctly defines the proximal extent of disease and iliofemoral involvement in greater than 80 percent of cases.[34] The exact role of MR angiography in the evaluation of abdominal aortic aneurysms continues to be investigated.[34] [36]

An important, but unresolved, issue regarding the detection of abdominal aortic aneurysms is the potential place, if any, of screening asymptomatic patients for the presence of aneurysms. At present, no controlled trials of aneurysm screening have provided outcomes data that might be used in guiding any such recommendations. A recent study based on the existing literature suggests that screening men 60 to 80 years of age by physical examination is cost-effective,

Figure 40-1 *A,* Axial contrast-enhanced CT scan showing a 6.6-cm abdominal aortic aneurysm (A) lined with mural thrombus (T). Blistering of the aneurysm (B) is indicative of a weakened aortic wall and suggests impending rupture. *B,* Three-dimensional shaded-surface display of the same CT scan. This anteroposterior projection demonstrates that the aneurysm (A) is infrarenal and displays its anatomical relationship to surrounding structures, including the renal arteries (R) proximally and the aortic bifurcation distally. *(Courtesy of John A. Kaufman, M.D., Division of Vascular Radiology, Massachusetts General Hospital, Boston.)*

although of small benefit, whereas screening the same population with ultrasonography is at the upper limit of cost-effectiveness and of modest benefit.[37] Repeated screening was found to be not cost-effective. Many authors currently recommend the use of screening ultrasonography only for those at high risk, in particular those with a family history of abdominal aortic aneurysm[17] or those older than 60 years with a history of smoking or hypertension.

NATURAL HISTORY.

The paramount concern in managing abdominal aortic aneurysms is their tendency to rupture. Mortality from rupture is quite high: Sixty percent of patients die before receiving medical attention[38] and the operative mortality for those reaching the hospital is approximately 50 percent,[29] for an overall mortality from rupture of 80 percent. In 1950, before the introduction of modern surgical repair, Estes first assessed survival

rates for those with abdominal aortic aneurysms[39] and found survival at 3 and 5 years to be 49 percent and 19 percent, respectively, far lower than for age-matched controls, with two-thirds of deaths caused by aneurysm rupture. However, after the introduction of modern surgical repair, it was found that survival among abdominal aortic aneurysm patients undergoing operative repair was significantly higher than among those managed nonoperatively. Surgical repair thus remains the therapy of choice for aneurysms considered to be at risk of rupture.

Darling and colleagues convincingly demonstrated that the risk of rupture increases with aneurysm size.[40] Present estimates suggest that aneurysms smaller than 4.0 cm have a 0 to 2 percent risk of rupture,[41] [42] whereas those larger than 5.0 cm have a 22 percent risk of rupture within 2 years.[42] Because 80 percent of abdominal aortic aneurysms expand over time--with as many as 15 to 20 percent expanding rapidly (>0.5 cm/yr)--the risk of rupture may concomitantly increase with time.

Accordingly, the ability to predict rates of aortic aneurysm expansion would be useful in estimating the risk of future rupture. Although the mean rate of abdominal aortic aneurysm expansion appears to be approximately 0.4 cm/yr,[29] the rates of expansion within a population are extremely variable, and expansion rates even vary within one individual over time. Baseline aneurysm size is perhaps the best predictor of aneurysm expansion rate,[29] with larger aneurysms expanding more rapidly than small ones--probably as a consequence of Laplace's law. A rapid rate of expansion apparently also predicts aneurysm rupture, especially abdominal aneurysms 5.0 cm or greater in diameter.[43] Many surgeons therefore consider both large size and rapid expansion to be indications for repair.

Management

SURGICAL TREATMENT.

Debate on the optimal timing of surgical repair in asymptomatic abdominal aortic aneurysms is ongoing. The decision to operate must weigh the natural history of the aneurysm and life expectancy of the patient against the anticipated morbidity and mortality of the proposed surgical procedure. Operative mortality is 4 to 6 percent overall for elective aneurysm repair and as low as 2 percent in low-risk patients. However, operative mortality rises to 19 percent for urgent aortic repair and reaches 50 percent for repair of a ruptured aneurysm.[29] [44] As of this writing, aneurysm size remains the primary indicator for repair of asymptomatic aneurysms, although no clear consensus yet exists regarding the minimum aneurysm diameter that necessitates surgery. Whereas all vascular surgeons would operate for an abdominal aortic aneurysm larger than 6.0 cm in diameter and most for aneurysms larger than 5.0 cm in patients who are reasonable surgical risks, few would operate for an asymptomatic aneurysm smaller than 4.0 cm. The benefit of surgery for asymptomatic aneurysms 4.0 to 5.0 cm in size, however, has not yet been defined. The recommendation of the

Society for Vascular Surgery and the International Society for Cardiovascular Surgery is for elective repair of abdominal aortic aneurysms 4.0 cm or larger in diameter,[29] although many other surgeons still consider 5.0 cm or larger to be the indication for surgery.[44A] Prospective controlled multicenter trials currently under way in the United States, Canada, and the United Kingdom should help address the optimal timing of surgery based on aneurysm size.[45] [46]

Surgical repair of abdominal aortic aneurysms consists of opening of the aneurysm and insertion of a synthetic prosthesis, usually fabricated of Dacron or expanded polytetrafluoroethylene (Gore-Tex). Sometimes, a simple tube graft is all that is necessary, although frequently the operation must be carried distally into one or both of the iliac arteries to excise the aneurysm completely. In the case of large aneurysms, much of the aneurysm wall may be left in situ ("intrasaccular approach of Creech"), thereby reducing the need for extensive dissection and thus decreasing aortic cross-clamping time.

A promising new interventional option for the treatment of abdominal aortic aneurysms is the use of percutaneously implanted, expanding endovascular stent-grafts (see Figs. 42-5 and 42-6) . The device consists of a collapsible prosthetic tube graft that is inserted remotely (e.g., via the femoral artery), advanced transluminally across the aneurysm under fluoroscopic guidance, and then secured at both its proximal and distal ends with an expandable stent attachment system. For aortic aneurysm repair, the stent-graft serves to bridge the region of the aneurysm, thereby excluding it from the circulation while allowing aortic blood flow to continue distally through the prosthetic stent-graft lumen. In some cases, stent-grafts are bifurcated, with two arms on the distal end designed to extend into the common iliac arteries when these vessels are aneurysmal as well. The rate of successful stent-graft implantation in several recent series ranged from 78 to 94 percent,[47] [48] [49] [50] with some outcome variability resulting from differing definitions of procedural success. Despite these promising results, only 30 to 60 percent of patients with abdominal aortic aneurysms have aneurysm anatomy suitable for possible endovascular repair. Moreover, the long-term outcomes of endovascular repair versus conventional surgical repair are not yet known. One of the major technical difficulties associated with the stent-graft technique that has yet to be overcome is the frequent occurrence of *endoleaks,* which are seen angiographically as persistent contrast flow into the aneurysm sac because of failure to completely exclude the aneurysm from the aortic circulation. Such endoleaks, if left untreated, may leave the patient at continued risk for aneurysm expansion or rupture.[51] Therefore, the use of stent-grafts for endovascular repair of abdominal aortic aneurysms is at present limited to a subset of patients, typically older patients or those at high operative risk.[51A]

Assessing Operative Risk (See also Chap. 61) .

Because patients with abdominal aortic aneurysms, by definition, have vascular disease, their high likelihood of concomitant coronary, renal, and cerebrovascular arterial disease significantly increases the risk of major vascular surgery. Indeed, Hertzer found that half of all perioperative deaths from aneurysm repair are due to myocardial infarction.[52] In addition, routine coronary arteriography in those undergoing aneurysm repair revealed severe correctable coronary artery disease in 31 percent of all

patients, including an 18 percent incidence in patients without prior clinical manifestations of coronary disease.[53] Moreover, among those with angiographically significant coronary artery disease, multivessel disease was seen in the majority.[53]

Studies by Boucher and colleagues[54] and Eagle and associates [55] have suggested that dipyridamole-thallium cardiac scanning is an effective means of identifying patients at highest risk for perioperative ischemic events (see also Chaps. 9 and 13) . Patients with reversible thallium defects in multiple segments of myocardium are at highest risk,[56] and it is in this subgroup that coronary angiography is likely to be most helpful. The safety of dipyridamole-thallium studies in such patients has been well established. Although exercise thallium scintigraphy is also a useful screening method, many patients with vascular disease fail to achieve an adequate heart rate because of limited exercise capacity. Other techniques shown to be effective for preoperative evaluation of myocardial ischemia include dobutamine stress echocardiography and electrocardiographic exercise testing in patients with a normal baseline electrocardiogram and adequate exercise tolerance.

Selective preoperative evaluation to identify the presence and severity of coronary artery disease in patients with clinical markers of coronary artery disease has been widely advocated,[57] and some further suggest screening those with strong cardiac risk factors despite the absence of clinical evidence of coronary artery disease.[58] Although patients found to have significant correctable coronary artery disease are presumed to benefit from preoperative coronary revascularization with selective coronary artery bypass surgery or angioplasty, at present this conclusion remains unproved.[58] Data available from nonrandomized studies of patients with significant coronary artery disease undergoing vascular surgery do demonstrate lower mortality for those who have undergone coronary bypass surgery.[59] Furthermore,

a recent randomized study has demonstrated that the long-term outcome of patients with combined peripheral vascular disease and high-risk coronary artery disease is improved by coronary artery revascularization in those with three-vessel coronary disease.[60] As is the case for coronary artery bypass surgery, no data are yet available to confirm that preoperative coronary angioplasty for significant coronary stenoses decreases the risk from major vascular surgery.

In addition to such preoperative screening and potential coronary revascularization, operative risk secondary to cardiac ischemic events may be further reduced through the use of perioperative invasive hemodynamic monitoring and careful perioperative surveillance for evidence of ischemia. Furthermore, myocardial ischemia and perhaps myocardial infarction may be prevented by using beta-adrenergic blockers perioperatively.[61]

Late Survival.

A review by Kiell and Ernst of late survival following abdominal aortic aneurysm repair among almost 2500 patients revealed 1-, 5-, and 10-year survival rates of 93, 63, and 40 percent, respectively.[25] The long-term survival of patients with concomitant coronary artery disease has been found to be approximately 10 percent lower than that for those without overt coronary disease.[62]

MEDICAL MANAGEMENT.

Risk factor modification is fundamental in the medical management of abdominal aortic aneurysms. Hypercholesterolemia and hypertension should be carefully controlled. Most patients with abdominal aortic aneurysms are cigarette smokers, and smoking must be discontinued. Beta blockers have long been considered an important therapy for reducing the risk of aneurysm expansion and rupture, and both animal and human studies support such a role. Brophy and coworkers demonstrated that propranolol delays the development of aneurysms in a mouse model prone to spontaneous aortic aneurysms. [63] Interestingly, it appears that the drug's efficacy in this model may have been independent of reductions in blood pressure or diminution of the force of left ventricular ejection (dP/dt) and, instead, may have been the result of changes in connective tissue metabolism and the structure of the aortic wall. In humans, a recent study has shown that the mean rate of abdominal aortic aneurysm expansion was slower in patients treated with beta blockers than in those not treated with beta blockers, with the effect most marked in large aneurysms.[43]

Should one elect to observe an abdominal aortic aneurysm 4.0 cm in size or larger, careful routine follow-up is indicated to detect either rapid expansion (0.5 cm/yr) or an increase in size to 5.0 cm or larger, either of which is an indication for surgery.[64] CT scanning every 6 months, perhaps as frequently as every 3 months for those at higher risk, has been advocated as an effective method of follow-up in such patients.[29] CT scanning is preferable to ultrasound for monitoring aneurysm growth because CT measurements of aneurysm size are more accurate.

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms are much less common than aneurysms of the abdominal aorta, and their incidence did not increase over the same 30-year period that saw a marked increase in the incidence of abdominal aortic aneurysms[12] (as noted above). Thoracic aneurysms are classified by the portion of aorta involved, i.e., the ascending, arch, or descending thoracic aorta. This anatomical distinction is important because the etiology, natural history, and treatment of thoracic aneurysms differ for each of these segments. Aneurysms of the descending aorta occur most commonly, followed by aneurysms of the ascending aorta, whereas arch aneurysms occur much less often.[11] In addition, descending thoracic aneurysms may extend distally to involve the abdominal aorta and create what is known as a *thoracoabdominal aortic aneurysm*. Sometimes, the entire aorta may be ectatic, with localized aneurysms seen at sites in both the thoracic and abdominal aorta.

ETIOLOGY AND PATHOGENESIS.

Aneurysms of the ascending thoracic aorta most often result from the process of *cystic medial degeneration* (or *cystic medial necrosis*). Histologically, cystic medial degeneration has the appearance of smooth muscle cell necrosis and elastic fiber degeneration, with the presence in the media of cystic spaces filled with mucoid material. Although these changes occur most frequently in the ascending aorta, in some cases the entire aorta may be similarly affected. The histological changes lead to weakening of the aortic wall, which in turn results in the formation of a fusiform aneurysm. Such aneurysms often involve the aortic root and may consequently result in aortic regurgitation. The term *annuloaortic ectasia* is often used to describe this condition (see below).

Cystic medial degeneration is found in virtually all cases of the Marfan syndrome[65] and may be associated with other connective tissue disorders as well, such as the Ehlers-Danlos syndrome. The Marfan syndrome (see Chap. 56) is an autosomal dominant heritable disorder of connective tissue that has been discovered to be due to mutations in one of the genes for fibrillin, a structural protein that helps direct and orient elastin in the developing aorta.[66] These mutations result in a decrease in the amount of elastin in the aortic wall,[67] together with a loss of elastin's normally highly organized structure. As a consequence, from an early age a marfanoid aorta exhibits markedly abnormal elastic properties and increased systemic pulse wave velocities, and over time the aorta exhibits progressively increasing degrees of stiffness and dilatation.[68]

In patients without the Marfan syndrome, however, it is not possible to recognize the histological diagnosis of cystic medial degeneration prospectively (i.e., without surgery or necropsy).[69] This fact has significantly limited our understanding of medial degeneration and its natural history, and it remains unclear to what extent this syndrome may represent an independent disease process versus a manifestation of another disease state. It has long been suspected that some patients who have annuloaortic ectasia and proven cystic medial degeneration without the classic phenotypic manifestations of the Marfan syndrome may, in fact, have a variation, or *forme fruste,* of the Marfan syndrome,[70] although this theory remains unproved. On the contrary, many patients with ascending thoracic aortic aneurysms appear to have nothing more than idiopathic cystic medial degeneration.

ATHEROSCLEROSIS.

Atherosclerotic aneurysms infrequently occur in the ascending aorta and, when they do, tend to be associated with diffuse aortic atherosclerosis. Aneurysms in the aortic arch are often contiguous with aneurysms of the ascending or descending aorta. They may be due to atherosclerotic disease, cystic medial degeneration, syphilis, or other infections. The predominant etiology of aneurysms of the descending thoracic aorta is atherosclerosis.[71] These aneurysms tend to originate just distal to the origin of the left subclavian artery and may be either fusiform or saccular.[72] The pathogenesis of such atherosclerotic aneurysms in the thoracic aorta may be similar to that of abdominal

aneurysms but has not been extensively examined.

SYPHILIS.

Syphilis was once a common cause of ascending thoracic aortic aneurysm, but today it has become a rarity in most major medical centers[12] [73] as a result of aggressive antibiotic treatment of the disease in its early stages. The latent period from initial spirochetal infection to aortic complications may range from 5 to 40 years but is most commonly 10 to 25 years. During the secondary phase of the disease, spirochetes directly infect the aortic media, most commonly involving the ascending aorta. The muscular and elastic medial elements are destroyed by the infection and inflammatory response and are replaced by fibrous tissue that frequently calcifies. Weakening of the aortic wall from medial destruction results in progressive aneurysmal dilatation. In addition, the infection may spread into the aortic root, and the subsequent root dilatation may result in aortic regurgitation.

INFECTIOUS AORTITIS.

This rare cause of aortic aneurysm may result from a primary infection of the aortic wall causing aortic dilatation with the formation of fusiform or saccular aneurysms. More commonly, infected or *mycotic* aneurysms may arise secondarily from an infection occurring in a preexisting aneurysm of another etiology. When an infected aneurysm involves the ascending aorta, it is often the consequence of direct spread from aortic valve bacterial endocarditis.

Several other causes of thoracic aortic aneurysms are discussed in detail elsewhere in this or other chapters, including giant cell arteritis (see Chap. 67) , aortic trauma (see Chap. 5) , and aortic dissection (p. 1431). Note that the clinical features, natural history, and treatment of thoracic aneurysms discussed below apply specifically to *nondissecting thoracic aortic aneurysms*.

Figure 40-2 MRI in the coronal projection of a large thoracic aortic aneurysm in an elderly woman with a complaint of dyspnea and cough. In this view the markedly dilated aortic arch (A) is compressing the trachea (T) and causing rightward tracheal deviation. The aneurysm is also compressing the left main stem bronchus (B). In addition, all four cardiac chambers are dilated, consistent with the patient's known idiopathic dilated cardiomyopathy.

Clinical Manifestations

Forty percent of patients with thoracic aortic aneurysms are asymptomatic at the time of diagnosis,[11] with such aneurysms typically discovered as incidental findings on a routine physical examination or chest roentgenogram. When patients do experience

symptoms, the symptoms tend to reflect either a vascular consequence of the aneurysm or a local mass effect. Vascular consequences include aortic regurgitation from dilatation of the aortic root, often associated with secondary congestive heart failure; sinus of Valsalva aneurysms that may rupture into the right side of the heart and cause a continuous murmur and congestive heart failure; and thromboembolism causing stroke, lower extremity ischemia, renal infarction, or mesenteric ischemia.

A local mass effect from an ascending or arch aneurysm may cause superior vena cava syndrome as a result of obstruction of venous return via compression of the superior vena cava or innominate veins. Aneurysms of the arch or descending aorta may compress the trachea (Fig. 40-2) or main stem bronchus and produce tracheal deviation, wheezing, cough, dyspnea (with symptoms that may be positional), hemoptysis, or recurrent pneumonitis. Compression of the esophagus may produce dysphagia, and compression of the recurrent laryngeal nerve may cause hoarseness. Chest pain and back pain occur in 37 and 21 percent, respectively, of nondissecting aneurysms[11] and result from direct compression of other intrathoracic structures or the chest wall or from erosion into adjacent bone. Typically, such pain is steady, deep, boring, and at times extremely severe.

As with abdominal aortic aneurysms, the most worrisome consequence of thoracic aneurysms is leakage or rupture. Rupture is accompanied by the dramatic onset of excruciating pain, usually in the region where less severe pain had previously existed. Rupture occurs most commonly into the left intrapleural space or the intrapericardial space and is manifested as hypotension. The third most common site of rupture is from the descending thoracic aorta into the adjacent esophagus (an aortoesophageal fistula), which causes life-threatening hematemesis.[74] Acute aneurysm expansion, which may herald rupture, can cause similar pain. Thoracic aneurysms may also be accompanied by aortic dissection, as discussed in detail later in this chapter.

DIAGNOSIS AND SIZING.

Many thoracic aneurysms are readily visible on chest roentgenograms (Fig. 40-3) and are characterized by widening of the mediastinal silhouette, enlargement of the aortic knob, or displacement of the trachea from the midline. Unfortunately, smaller aneurysms, especially saccular ones, may not be evident on the chest roentgenogram; therefore, this technique cannot exclude the diagnosis of aortic aneurysm.

Aortography is still the preferred modality for the preoperative evaluation of thoracic aortic aneurysms and for precise definition of the anatomy of the aneurysm and great vessels (Fig. 40-4) . As for abdominal aortic aneurysms, contrast-enhanced CT scanning is very accurate in detecting and sizing thoracic aortic aneurysms[75] and is useful as a method to monitor aneurysm size (see Fig. 10-49) . MRI is also useful in defining thoracic aortic anatomy and detecting aneurysms[76] (see Fig. 40-2) and is of particular utility in patients with preexisting aortic disease. MR angiography may prove especially useful in defining the anatomy of aortic branch vessels.

TTE (Figs. 7-113 and 7-114) is not very accurate for diagnosing thoracic aneurysms and is particularly limited in its ability to examine the descending thoracic aorta. TEE, a

far more accurate method for assessing the thoracic aorta, has become widely used for detection of aortic dissection. There has been less experience with TEE, however, in the evaluation of nondissecting thoracic aneurysms. (The advantages and disadvantage of each imaging modality are discussed in greater detail on p. 1437.)

NATURAL HISTORY.

Defining the natural history of thoracic aortic aneurysms is complex given the numerous contributing factors. The cause of an aneurysm may affect both its rate of growth and propensity for rupture. The presence or absence of aneurysm symptoms is another important predictor inasmuch as symptomatic patients have a much poorer prognosis than do those without symptoms,[71] in large part because the onset of new symptoms is frequently a harbinger of rupture or death. Moreover, the high prevalence

Figure 40-3 Chest roentgenogram of a patient with a very large aneurysm of the ascending thoracic aorta. Evident are both marked widening of the mediastinum and an abnormal aortic contour.

Figure 40-4 Lateral aortogram in a man with annuloaortic ectasia and aneurysmal dilation of the ascending thoracic aorta. The bulbous, pear-shaped aortic root can easily be seen. The left ventricle is partially opacified because of aortic regurgitation.

of additional cardiovascular disease in these patients may have a dramatic impact on mortality; in fact, next to aneurysm rupture, the most common causes of death in this population are other cardiovascular diseases.[72] [77]

Several small studies of the natural history of thoracic aortic aneurysms have been reported, but the data are far more limited than those available regarding abdominal aortic aneurysms. In the largest modern series, the 1-, 3-, and 5-year survival rates for patients with thoracic aortic aneurysms not undergoing surgical repair were approximately 65, 36, and 20 percent, respectively.[12] [77] [78] Aneurysm rupture occurs in 32 to 68 percent of patients not treated surgically, with rupture accounting for 32 to 47 percent of all patient deaths.[71] [77] [78] Fewer than half of patients with rupture may arrive at the hospital alive[73] ; mortality at 6 hours is 54 percent and at 24 hours reaches 76 percent.[73] No apparent association has been made between thoracic aneurysm location and the risk of death from rupture.[77]

Because size is an important predictor of the risk of aneurysm rupture, several studies have examined the rate of expansion of thoracic aortic aneurysms. As with abdominal aneurysms, initial size is the only independent predictor of the rate of thoracic aneurysm growth,[75] although some data also suggest that descending thoracic aneurysms may

expand more slowly than others.[79] Dapunt and colleagues monitored 67 patients with thoracic aortic aneurysms by serial CT scanning and found a mean rate of expansion of 0.43 cm/yr.[80] The only independent predictor of rapid expansion (>0.5 cm/yr) was an initial aortic diameter larger than 5.0 cm. Aneurysms that were 5.0 cm or smaller showed mean growth rates of 0.17 cm/yr, whereas those larger than 5.0 cm grew by 0.79 cm/yr. Unfortunately, even when controlling for initial aneurysm size, substantial variation was still seen in individual aneurysm growth rates, thus making such mean growth rates of little value in predicting aneurysm growth for a given patient. More helpful, however, was the finding that growth rates among small aneurysms were more consistent, with only 1 of 25 aneurysms 4.0 cm or smaller at baseline showing rapid growth. Two additional findings in this series were that no aneurysm smaller than 5.0 cm ruptured during the follow-up period and that the only predictor of survival was initial aneurysm size.

Management

SURGICAL TREATMENT.

The optimal timing of surgical repair of thoracic aortic aneurysms remains uncertain for several reasons. First, as noted above, the data available on the natural history of thoracic aneurysms are limited, especially with respect to the outcomes of surgical intervention. Second, with the high incidence of coexisting cardiovascular disease in this population, many patients die of other cardiovascular diseases before their aneurysms ever rupture. Finally, significant risks are associated with thoracic aortic surgery, particularly in the arch and descending aorta, which in many cases may outweigh the potential benefits of aortic repair.

We currently recommend surgery when aneurysms of the ascending thoracic aorta reach 5.5 to 6.0 cm and those of the descending thoracic aorta reach 6.0 cm or larger, or often 7.0 cm or larger in patients at high operative risk. Indications for surgery in patients with smaller aneurysms include a rapid rate of expansion, associated significant aortic regurgitation, or the presence of aneurysm-related symptoms. In patients with the Marfan syndrome, given their higher risk of dissection and rupture, we recommend repair of thoracic aneurysms when they reach only 5.5 cm in size.[81] Surgery should be considered even sooner in Marfan syndrome patients at especially high risk, such as those with rapid and progressive aortic dilatation, those with a family history of the Marfan syndrome plus aortic dissection, or women planning pregnancy.[82] Of course, the aggressiveness with which surgical repair is undertaken in any case should be appropriately influenced by the general condition of the individual patient.

Thoracic aortic aneurysms are generally resected and replaced with a prosthetic sleeve of appropriate size. Cardiopulmonary bypass is necessary for the removal of ascending aortic aneurysms, and partial bypass to support the circulation distal to the aneurysm while the aortic site being repaired is cross-clamped is often advisable when resecting descending thoracic aortic aneurysms.[83] The use of such adjuncts is less important, however, than the nature and extent of the aneurysm in determining the incidence of postoperative complications.[84]

The use of a composite graft consisting of a Dacron tube with a prosthetic aortic valve sewn into one end (the Bentall procedure) is generally the method of choice in treating ascending thoracic aneurysms involving the root and associated with significant aortic regurgitation.[85] The valve and graft are sewn directly into the aortic annulus and the coronary arteries, then reimplanted into the Dacron aortic graft (Fig. 40-5) . The operative risk for mortality is about 5 percent.[85] For patients with structurally normal aortic valve leaflets whose aortic regurgitation is secondary to dilatation of the root, David and colleagues have successfully repaired the native valve by either reimplanting it in a Dacron graft or reconstructing the aortic root. In a series of 45 patients, 41 had mild or no aortic regurgitation after this method of aortic valve repair and were stable postoperatively at a mean of 18 months.[86]

Aneurysms of the aortic arch may be successfully excised surgically, but the procedure may be particularly challenging. The brachiocephalic vessels must be removed from the aortic arch before its resection. Then, after interposition of the prosthetic tube graft, the island of native aortic tissue containing the brachiocephalic vessels is reimplanted into the graft and normal cerebral perfusion restored. However, the risk of stroke is significantly increased because of variable periods of cerebral ischemia. The incidence of stroke in recent series is 3 to 7 percent.[87] [88] The

Figure 40-5 Technique for the composite graft replacement of an aneurysm of the ascending aorta. *Top,* The aneurysm is shown involving the sinuses of Valsalva. The patient is maintained on total cardiopulmonary bypass. *Bottom,* The composite graft is shown, with a low-profile, tilting disc aortic prosthesis attached to its inferior end. (1) The aneurysm is resected with the native aortic valve. (2) The coronary ostia have been excised and mobilized with a button of aortic wall. (3) The composite graft has been secured in place with Teflon felt reinforcement for the suture line. The coronary artery ostia are then reimplanted directly into the graft.

standard method for carrying out this operation today is with the use of profound hypothermic circulatory arrest, as reported by Griepp and coworkers in 1975.[89] Some have attempted to add selective cerebral perfusion during aneurysmectomy, but cannulation techniques are difficult. In fact, the incidence of stroke may actually be as high or higher with this method, possibly because of cannulation-induced cerebral emboli.[88] [90] A more recent adjunct for cerebral protection during hypothermic arrest is the use of retrograde cerebral perfusion via a superior vena cava cannula.[87] Not only does this technique provide nutrients and oxygen to the brain,[91] but it may also serve to flush out both air and particulate matter from the cerebral and carotid arteries that would otherwise embolize. The results of retrograde cerebral perfusion have been quite encouraging, with trends toward lower stroke rates.[92] [93]

More than half of patients undergoing surgical repair of a thoracic aortic aneurysm in Crawford and colleagues' series had multiple aortic segments involved, and almost

three-quarters of those with descending thoracic aneurysms had multiple involvement.[94] Such widespread aneurysmal dilatation of the aorta presents a particular challenge to the surgeon and often precludes surgery. However, Crawford and associates have demonstrated that it is possible to successfully replace virtually the entire diseased thoracic and abdominal aorta.[94] A method known as the "elephant trunk" technique, carried out in sequential stages of aortic replacement, has been shown to facilitate such extensive surgical procedures and reduce the associated risks.[92] [95]

Elective surgical repair of ascending and descending thoracic aortic aneurysms is associated with a 90 to 95 percent early survival rate in most centers.[96] [97] Major complications are technical, especially hemorrhage from tearing of the diseased aorta. A catastrophic complication of resection of descending thoracic aortic aneurysms is postoperative paraplegia secondary to interruption of the blood supply to the spinal cord. The incidence of paraplegia ranges from 0 to 17 percent,[83] [84] although most series show an incidence of about 5 to 6 percent.[84] [98] [98A] A number of methods have been proposed to reduce the likelihood of paraplegia, although none has proved to be consistently safe and effective. One of the more promising techniques involves regional hypothermic protection of the spinal cord with epidural cooling during surgical repair of the aorta, which has reduced the frequency of spinal cord complications to 3 percent in one large series by Cambria and colleagues.[99] Other important techniques that may also reduce the risk of spinal cord injury include the reimplantation of patent critical intercostal arteries,[99] cerebrospinal fluid drainage,[100] the use of intraoperative somatosensory evoked potential monitoring,[101] and maintenance of distal aortic perfusion during surgery with the use of atriofemoral bypass.[99] Controlled trials might better clarify the efficacy of such techniques.

An alternative approach to the surgical management of descending thoracic aneurysms is the use of a transluminally placed endovascular stent-graft (see Fig. 42-7). This technique has the advantage of being far less invasive than surgery with potentially fewer postoperative complications and lower morbidity. Dake and coworkers recently reported the results of a large series in which "first-generation" endovascular stent-grafts were implanted in 103 patients with thoracic aortic aneurysms, only 62 (60 percent) of whom were judged to be reasonable candidates for traditional surgical aortic repair.[102] Complete thrombosis of the aortic aneurysm was achieved in 83 percent of patients, but rates of early stroke and paraplegia were 3 and 7 percent, respectively. The authors suggest that with newer and more refined devices together with more precise stent-graft deployment, the overall success rates should rise and complication rates fall. Although still experimental at present, such a device may in the future have an important role in the management of patients who are at risk for aortic rupture but are otherwise poor surgical candidates. Unfortunately, the curvilinear nature of the ascending aorta and arch makes application of similar techniques to aneurysms of these proximal aortic segments far more problematic.

Complications of associated atherosclerosis, such as myocardial infarction, cerebrovascular accidents, and renal failure, often become manifested under the massive physiological stress of aortic surgery. The most frequent causes of early postoperative death are myocardial infarction, congestive heart failure, stroke, renal

failure, hemorrhage, respiratory failure, and sepsis. Advanced age, emergency surgery,

prolonged aortic cross-clamp time, extent of the aneurysm, diabetes, prior aortic surgery, aneurysm symptoms, and intraoperative hypotension are the most important factors determining perioperative morbidity and mortality. Many patients with atherosclerotic aneurysms are heavy smokers, and pulmonary complications following surgery are common. The left lung may be severely traumatized by compression during resection of large aneurysms of the descending thoracic aorta, a complication that may seriously jeopardize the patient's survival, particularly in the setting of underlying pulmonary disease.

Late deaths are usually associated with cardiac complications, aneurysm rupture, respiratory failure, or stroke.[96] Aneurysm rupture may be due to aneurysm formation at the graft margins or the appearance of new aneurysms at other aortic sites.[11]

MEDICAL MANAGEMENT.

The long-term impact of medical therapy on aneurysm growth and survival in patients with typical atherosclerotic thoracic aneurysms has not been examined. However, in a recent report, Shores and colleagues examined the efficacy of beta blockers in adult patients with the Marfan syndrome.[103] They randomized 70 patients to treatment with propranolol versus no beta blocker therapy and monitored them over a 10-year period. The treated group showed a significantly slower rate of aortic dilatation, fewer adverse clinical endpoints (death, aortic dissection, aortic regurgitation, aortic root >6 cm), and significantly lower mortality from the 4-year point onward.[103] Although this study examined only the effect of beta blockade in the Marfan syndrome, it follows logically that medical therapy to reduce dP/dt and control blood pressure is essential to the treatment of thoracic aortic aneurysms, both for those with smaller aneurysms being monitored serially and for patients having undergone aortic aneurysm repair.

Annuloaortic Ectasia

The term *annuloaortic ectasia* was first used by Ellis and colleagues in 1961 to describe a clinicopathological condition seen in a subset of patients with thoracic aortic aneurysms in whom idiopathic dilatation of the proximal aorta and the aortic annulus leads to pure aortic regurgitation.[104] The entity has subsequently been recognized with increasing frequency and makes up about 5 to 10 percent of the population undergoing aortic valve replacement for pure aortic regurgitation. Annuloaortic ectasia is more common in men than women, typically occurring in the fourth, fifth, and sixth decades with progressively more severe aortic regurgitation. Sudden onset of symptoms followed by rapid progression is occasionally seen.

The common pathological feature shared by patients with annuloaortic ectasia is that of cystic medial degeneration of the afflicted aortic wall leading to progressive dilatation.

With widening of the aortic root, the valve annulus dilates and the aortic leaflets are pulled apart, thereby resulting in aortic regurgitation despite the fact that the aortic valve leaflets themselves are structurally normal. The weakened aortic walls are also prone to dissection.

Clinically, little distinguishes aortic regurgitation in patients with annuloaortic ectasia from that due to other causes. On physical examination, the diastolic murmur tends to be of greater intensity to the right of the sternum in cases of annuloaortic ectasia and to the left of the sternum in cases of primary aortic regurgitation. Lemon and White found that two features--acute or subacute development of symptoms and the presence of associated chest pain--were more common in patients with annuloaortic ectasia than primary aortic regurgitation.[105]

The chest roentgenogram usually shows a grossly dilated aortic root and ascending aorta with left ventricular enlargement proportional to the degree of aortic regurgitation. Aortographically, annuloaortic ectasia has one of three typical appearances. Most common is a pear-shaped enlargement of the ascending aorta (see Fig. 40-4) . Also seen are diffuse symmetrical dilatation and dilatation limited to the aortic root.[105]

Surgical correction is usually undertaken for relief of aortic regurgitation when it is severe and responsible for symptoms of left ventricular failure or when the left ventricle or ascending aorta is increasing in size. In such cases, the aortic valve together with the proximal ascending aorta is usually replaced with a composite prosthetic graft (see Chap. 46) .

AORTIC DISSECTION

Acute aortic dissection is an uncommon but potentially catastrophic illness that occurs with an incidence of at least 2000 cases per year in the United States. Early mortality is as high as 1 percent per hour if untreated,[106] but survival may be significantly improved by the timely institution of appropriate medical and/or surgical therapy. Prompt clinical recognition and definitive diagnostic testing are therefore essential in the management of patients with aortic dissection.

Aortic dissection is believed to begin with the formation of a tear in the aortic intima that directly exposes an underlying diseased medial layer to the driving force (or pulse pressure) of intraluminal blood (Fig. 40-6 *A*). This blood penetrates the diseased medial layer and cleaves the media longitudinally, thereby dissecting the aortic wall. Driven by persistent intraluminal pressure, the dissection process extends a variable length along the aortic wall, typically antegrade (driven by the forward force of aortic blood flow) but sometimes retrograde from the site of the intimal tear. The blood-filled space between the dissected layers of the aortic wall becomes the *false lumen.* Shear forces may lead to further tears in the *intimal flap* (the inner portion of the dissected aortic wall) and produce exit sites or additional entry sites for blood flow into the false lumen. Distention of the false lumen with blood may cause the intimal flap to bow into the *true lumen* and thereby narrow its caliber and distort its shape.

It has also been suggested that aortic dissection may begin instead with rupture of the

vasa vasorum within the aortic media, i.e., with the development of an intramural hematoma (Fig. 40-6 *B*). Local hemorrhage then secondarily ruptures through the intima layer and creates the intimal tear and aortic dissection. Since in autopsy series as many as 13 percent of aortic dissections do not have an identifiable intimal tear,[107] at least in a minority of cases independent medial hemorrhage does appear to be the primary cause of dissection. On the other hand, one might argue that the lack of an intimal tear in these patients indicates they do not, in fact, have classic aortic dissection, but rather have intramural hematoma of the aorta, a closely related condition (see below).

CLASSIFICATION.

Most classification schemes for aortic dissection are based on the fact that the vast majority of aortic dissections originate in one of two locations: (1) the ascending aorta, within several centimeters of the aortic valve, and (2) the descending aorta, just distal to the origin of the left subclavian artery at the site of the ligamentum arteriosum. Sixty-five percent of intimal tears occur in the ascending aorta, 20 percent in the descending aorta, 10 percent in the aortic arch, and 5 percent in the abdominal aorta.[90]

Three major classification systems are used to define the location and extent of aortic involvement, as defined in Table 40-1 and depicted in Figure 40-7 : (1) DeBakey types I, II, and III[108] ; (2) Stanford types A and B[109] ; and (3) the anatomical categories "proximal" and "distal." All three

Figure 40-6 Proposed mechanism of initiation of aortic dissection.

schemes share the same basic principle of distinguishing aortic dissections with and without ascending aortic involvement for prognostic and therapeutic reasons; in general, surgery is indicated for dissections involving the ascending aorta, whereas medical management is reserved for dissections without ascending aortic involvement. Accordingly, because both DeBakey types I and II involve the ascending aorta, they are grouped together for simplicity in the Stanford (type A) and anatomical (proximal) classification systems. Aortic dissections confined to the abdominal aorta, although quite uncommon, are best categorized as type B or distal dissections. Proximal or type A dissections occur in about two-thirds of cases, with distal dissections composing the remaining third.

In addition to its location, aortic dissection is also classified according to its duration, defined as the length of time from symptom onset to medical evaluation. The mortality from dissection and its risk of progression decrease progressively

TABLE 40-1 -- COMMONLY USED CLASSIFICATION SYSTEMS TO DESCRIBE AORTIC DISSECTION

TYPE	SITE OF ORIGIN AND EXTENT OF AORTIC INVOLVEMENT
DeBakey	
Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates in and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta
Stanford	
Type A	All dissections involving the ascending aorta, regardless of the site of origin
Type B	All dissections not involving the ascending aorta
Descriptive	
Proximal	Includes DeBakey types I and II or Stanford type A
Distal	Includes DeBakey type III or Stanford type B

over time, which makes therapeutic strategies for longstanding aortic dissections quite different from those seen acutely. A dissection present less than 2 weeks is defined as "acute," whereas those present 2 weeks or more are defined as "chronic" because the mortality curve for untreated aortic dissections begins to level off at 75 to 80 percent at this time.[106] At diagnosis, about two-thirds of aortic dissections are acute while the remaining third are chronic.[110]

ETIOLOGY AND PATHOGENESIS.

Medial degeneration, as evidenced by deterioration of medial collagen and elastin, is considered to be the chief predisposing factor in most nontraumatic cases of aortic dissection.[69] [87] Therefore, any disease process or other condition that undermines the integrity of the elastic or muscular components of the media

Figure 40-7 Commonly used classification systems for aortic dissection. (Refer to Table 40-1 for definitions.)

predisposes the aorta to dissection. Cystic medial degeneration is an intrinsic feature of several hereditary defects of connective tissue, most notably the Marfan and EhlersDanlos (see Chap. 56) syndromes. In addition to their propensity for thoracic aortic aneurysms, patients with the Marfan syndrome are indeed at high risk for aortic dissection--especially proximal dissection--at a relatively young age. In fact, the Marfan syndrome accounts for 5 to 9 percent of all aortic dissections.[110] [111] [112] (See also

Chap. 56.)

In the absence of the Marfan syndrome, histologically classic cystic medial degeneration is identified in only a minority of cases of aortic dissection.[110] [111] Nevertheless, the degree of medial degeneration found in most other cases of aortic dissection still tends to be qualitatively and quantitatively much greater than that expected as part of the aging process. Although the cause of such medial degeneration remains unclear, advanced age and hypertension appear to be two of the most important factors.

The peak incidence of aortic dissection is in the sixth and seventh decades of life, with men affected twice as often as women.[112] A coexisting history of hypertension is found in 72 to 80 percent of cases of aortic dissection.[112] A bicuspid aortic valve is a well-established risk factor for proximal aortic dissection and has historically been found in 7 to 14 percent of all aortic dissections.[110] [111] Interestingly, the risk of aortic dissection appears to be independent of the severity of the bicuspid valve stenosis.[111] Certain other congenital cardiovascular abnormalities predispose the aorta to dissection, including coarctation of the aorta.[111] Aortic dissection has also been reported to occur in association with the Noonan and Turner syndromes.[110] [113] Rarely, aortic dissection complicates arteritis involving the aorta (see Chap. 67) , particularly giant cell arteritis.[114] A number of reports describe aortic dissection in association with cocaine abuse among younger men,[115] [116] but no direct causal relationship has yet been established.

An unexplained relationship exists between pregnancy and aortic dissection (see Chap. 65) . About half of all aortic dissections in women younger than 40 years occur during pregnancy, typically in the third trimester[117] and also occasionally in the early postpartum period.[118] The increases in blood volume, cardiac output, and blood pressure seen in late pregnancy may contribute to the risk, although this explanation cannot account for postpartum occurrence. Women with the Marfan syndrome and a dilated aortic root are at particular risk for acute aortic dissection during pregnancy,[119] and in some cases, diagnosis of the Marfan syndrome is first made when such women are evaluated for peripartum aortic dissection.

Direct trauma to the aorta may also cause aortic dissection. Blunt trauma tends to cause localized tears, hematomas, or frank aortic transection (see Chap. 51) and only rarely causes classic aortic dissection.[120] Iatrogenic trauma, on the other hand, is associated with true aortic dissection. Both intraarterial catheterization[121] and the insertion of intraaortic balloon pumps[122] may induce aortic dissection, probably from direct trauma to the aortic intima. Cardiac surgery is associated with a very small risk of acute aortic dissection. The majority of these dissections are discovered intraoperatively and repaired at that time, although 20 percent are detected only after a delay.[123] In addition, aortic dissection sometimes occurs late (months to years) after cardiac surgery; in fact, as many as 18 percent of those with acute aortic dissection have a history of prior cardiac surgery.[112] Of cardiac surgical patients, those undergoing aortic valve replacement are at highest risk for aortic dissection as a late complication.[124] [125] von Kodolitsch and colleagues have found that patients with a dilated ascending aorta together with aortic regurgitation or a thinned aortic wall at the time of aortic valve

replacement are most likely to have such a late aortic dissection.[126]

Clinical Manifestations

SYMPTOMS.

Much of the data presented regarding the clinical manifestations of aortic dissection are from the earlier clinical series of Slater and DeSanctis[127] and Spittel and colleagues, [110] as well as from a recent series from the International Registry of Aortic Dissection (IRAD), which studied 464 consecutive patients with acute aortic dissection from 12 international referral centers.[112] By far the most common initial symptom of acute aortic dissection is severe pain, which is found in up to 96 percent of cases,[110] [127] [112] whereas the large majority of those without pain are found to have chronic dissections.[110] The pain is typically severe and of sudden onset[112] and is as severe at its inception as it ever becomes, in contrast to the pain of myocardial infarction, which usually has a crescendo-like onset. In fact, the pain may be all but unbearable in some instances and force the patient to writhe in agony, fall to the ground, or pace restlessly in an attempt to gain relief. Several features of the pain should arouse suspicion of aortic dissection. The quality of the pain as described by the patient is often morbidly appropriate to the actual event, with adjectives such as "tearing," "ripping," "sharp," and "stabbing" frequently used.[112] Another important characteristic of the pain of aortic dissection is its tendency to migrate from its point of origin to other sites, generally following the path of the dissection as it extends through the aorta. However, such migratory pain is described in as few as 17 percent of cases.[112]

The location of pain may be quite helpful in suggesting the location of the aortic dissection because localized symptoms tend to reflect involvement of the underlying aorta. In the series of Spittell and associates, when the location of chest pain was anterior only (or if the most severe pain was anterior), more than 90 percent of patients had involvement of the ascending aorta.[110] Conversely, when the chest pain was interscapular only (or when the most severe pain was interscapular), more than 90 percent of patients had involvement of the descending thoracic aorta (i.e., DeBakey type I or III). The presence of any pain in the neck, throat, jaw, or face strongly predicted involvement of the ascending aorta, whereas pain anywhere in the back, abdomen, or lower extremities strongly predicted involvement of the descending aorta. In rare cases the presenting pain is only pleuritic in nature, due to acute pericarditis that results from hemorrhage into the pericardial space froom the dissected ascending aorta. In such cases the underlying diagnosis may be overlooked if one does not search for other symptoms or signs that might suggest the presence of aortic dissection.

Less common symptoms at initial evaluation, occurring with or without associated chest pain, include congestive heart failure (7 percent), syncope (9 percent), cerebrovascular accident (5 percent),[112] ischemic peripheral neuropathy, paraplegia, and cardiac arrest or sudden death. The presence of acute congestive heart failure in this setting is almost invariably due to severe aortic regurgitation induced by a proximal aortic dissection (discussed below). The occurrence of syncope without focal neurological signs, found in 4 to 5 percent of aortic dissections,[110] [127] may be an ominous sign suggesting a surgical emergency. It is associated most often with rupture of a proximal aortic

dissection into the pericardial cavity with resultant cardiac tamponade and, less often, associated with rupture of the descending thoracic aorta into the intrapleural space.[110] On occasion, a patient presents with acute chest pain, and the initial imaging study reveals hemopericardium yet fails to demonstrate an aortic dissection. In such a scenario, unless another diagnosis--such as tumor metastatic to the pericardium--is evident, one must still suspect the presence of acute aortic dissection (or contained aortic rupture). Ideally, such a patient would be taken presumptively to the operating room or, at the very least, immediately undergo additional

imaging with other modalities to confirm the diagnosis.[127A]

PHYSICAL FINDINGS.

Although extremely variable, findings on physical examination generally reflect the location of aortic dissection and the extent of associated cardiovascular involvement. In some cases, physical findings alone may be sufficient to suggest the diagnosis, whereas in other cases, such pertinent physical findings may be subtle or absent, even in the presence of extensive aortic dissection. Hypertension is seen in 70 percent of those with distal aortic dissection but in only 36 percent with proximal dissection.[112] Hypotension, on the other hand, occurs much more commonly among those with proximal than with distal aortic dissection (25 and 4 percent, respectively).[112] [127] True hypotension is usually the result of cardiac tamponade, acute severe aortic regurgitation, intrapleural rupture, or intraperitoneal rupture. Dissection involving the brachiocephalic vessels may result in "pseudohypotension," an inaccurate measurement of blood pressure caused by compromise or occlusion of the brachial arteries.

The physical findings most typically associated with aortic dissection--pulse deficits, the murmur of aortic regurgitation, and neurological manifestations--are more characteristic of proximal than distal dissection. Reduced or absent pulses in patients with acute chest pain strongly suggest the presence of aortic dissection. Such pulse abnormalities are present in about 50 percent of proximal aortic dissections and occur throughout the arterial tree, but they are seen in only 15 percent of distal dissections, where they usually involve the femoral or left subclavian artery. Impaired pulses--and similarly, visceral ischemia--result from extension of the dissection flap into a branch artery with compression of the true lumen by the false channel, which diminishes blood flow in the aortic true lumen because of narrowing or obliteration by the distended false lumen (occurring most commonly in the descending or abdominal aorta); impaired pulses may also result from proximal obstruction of flow caused by a mobile portion of the intimal flap overlying the branch vessel's orifice. Whichever the cause, the pulse deficits in aortic dissection may be transient, secondary to decompression of the false lumen by distal reentry into the true lumen or secondary to movement of the intimal flap away from the occluded orifice.

Aortic regurgitation is an important feature of proximal aortic dissection, with the murmur of aortic regurgitation detected in 32 percent of cases.[112] When aortic regurgitation is present in patients with distal dissection, it generally antedates the dissection and may be the result of preexisting dilatation of the aortic root from the underlying aortic pathology, such as cystic medial degeneration. The murmur of aortic regurgitation may wax and wane, the intensity varying directly with the height of the arterial blood pressure. Depending on the severity of the regurgitation, other peripheral signs of aortic incompetence may be present, such as collapsing pulses and a wide pulse pressure. However, in some cases, congestive heart failure secondary to severe acute aortic regurgitation may occur with little or no murmur and no peripheral signs of aortic runoff.

The acute aortic regurgitation associated with proximal aortic dissection, which occurs in one-half to two-thirds of cases,[128] may result from any of several mechanisms as depicted in Figure 40-8 . First, the dissection may dilate the aortic root, thereby widening the sinotubular junction from which the aortic leaflets hang so that the leaflets are unable to coapt properly in diastole (incomplete closure). Second, the dissection may extend into the aortic root and detach one or more aortic leaflets from their commissural attachments at the sinotubular junction, thereby resulting in diastolic leaflet prolapse. Not infrequently, both incomplete closure and leaflet prolapse are present at the same time. Finally, in the setting of an extensive or circumferential intimal tear the unsupported intimal flap may prolapse into the left ventricular outflow tract,[129] occasionally appearing as frank intimal intussusception,[130] and produce severe aortic regurgitation.

Neurological manifestations occur in as many as 6 to 19 percent of all aortic dissections[110] [127] [131] but are more common with proximal dissection. Cerebrovascular accidents may occur in 3 to 6 percent when the innominate or left common carotid arteries are directly involved.[131] Less frequently, patients may have altered consciousness or even coma. When spinal artery perfusion is compromised (more common in distal dissection[110]), ischemic spinal cord damage may produce paraparesis or paraplegia.

In a small minority, about 1 to 2 percent of cases,[110] [132] a proximal dissection flap may involve the ostium of a coronary artery and cause acute myocardial infarction. The dissection more often affects the right coronary artery than the left, which explains why these myocardial infarctions tend to be inferior in location.[110] Unfortunately, when secondary myocardial infarction does occur, its symptoms may complicate the clinical picture by obscuring symptoms of the primary aortic dissection. Most worrisome is the possibility that in the setting of electrocardiographic evidence of myocardial infarction, the underlying aortic dissection may go unrecognized. Moreover, the consequences of such a misdiagnosis in the era of thrombolytic therapy can be catastrophic. In a review of the literature, Kamp and colleagues described an early mortality of 71 percent (many from cardiac tamponade) among 21 cases of aortic dissection treated

Figure 40-8 Mechanisms of aortic regurgitation in proximal aortic dissection. *A,* Normal aortic valve

anatomy, with the leaflets suspended (dotted lines) from the sinotubular junction. *B,* A type A dissection dilates the ascending aorta, which in turn widens the sinotubular junction from which the aortic leaflets hang so that the leaflets are unable to coapt properly in diastole (incomplete closure). Aortic regurgitation (arrow) results. *C,* A type A dissection extends into the aortic root and detaches an aortic leaflet from its commissural attachment to the sinotubular junction. Diastolic leaflet prolapse results. *D,* In the setting of an extensive or circumferential intimal tear, the unsupported intimal flap may prolapse across the aortic valve and into the left ventricular outflow tract and prevent normal leaflet coaptation.

with thrombolysis.[133] It thus remains essential that when evaluating patients with acute myocardial infarction--particularly inferior infarctions--one carefully consider the possibility of an underlying aortic dissection before thrombolytic or anticoagulant therapy is instituted. Although some physicians feel reassured that performing a chest roentgenogram before the institution of thrombolysis is adequate to exclude the diagnosis of dissection, a blinded study of roentgenogram interpretation in this setting suggests that chest radiography is not sufficient.[134]

Extension of aortic dissection into the abdominal aorta may cause other vascular complications. Compromise of one or both renal arteries occurs in about 5 to 8 percent[131] [135] and may lead to renal ischemia or frank infarction and, eventually, severe hypertension and acute renal failure. Mesenteric ischemia and infarction are also occasional complications of abdominal dissection seen in 3 to 5 percent of cases.[131] [135] In addition, aortic dissection may extend into the iliac arteries and cause diminished femoral pulses (12 percent[131]) and acute lower extremity ischemia. If in such cases the associated chest pain is minimal or absent, the pulse deficit and ischemic peripheral neuropathy may be mistaken for a peripheral embolic event.

Additional clinical manifestations of aortic dissection include the presence of pleural effusions, seen more commonly on the left side. The effusion typically arises secondary to an inflammatory reaction around the involved aorta, but in some cases it may result from hemothorax caused by a transient rupture or leak from a descending dissection. Several rarely encountered clinical manifestations of aortic dissection include hoarseness, upper airway obstruction, rupture into the tracheobronchial tree with hemoptysis, dysphagia, hematemesis from rupture into the esophagus, superior vena cava syndrome, pulsating neck masses, Horner syndrome, and unexplained fever. Other rare findings associated with the presence of a continuous murmur include rupture of the aortic dissection into the right atrium, into the right ventricle, or into the left atrium with secondary congestive heart failure.

A variety of conditions may mimic aortic dissection, including myocardial infarction or ischemia, acute aortic regurgitation without dissection, nondissecting thoracic or abdominal aortic aneurysms, pericarditis, musculoskeletal pain, or mediastinal tumors. Diagnostic confusion may be particularly likely when a patient with chest pain coincidentally has another clinical symptom, physical finding, or chest roentgenographic finding typically associated with aortic dissection.[136]

LABORATORY FINDINGS.

Chest roentgenography is included in the discussion of clinical manifestations of aortic dissection rather than the discussion of diagnostic techniques because an abnormal incidental finding on a routine chest roentgenogram may first raise clinical suspicion of aortic dissection. Moreover, although chest roentgenography may help support a diagnosis of suspected aortic dissection, the findings are nonspecific and rarely diagnostic. The results of chest roentgenography therefore add to the other available clinical data used in deciding whether suspicion of aortic dissection warrants proceeding to a more definitive diagnostic study.

The most common abnormality seen on chest radiography in aortic dissection is widening of the aortic silhouette, which appears in 81 to 90 percent of cases.[110] [127] Less often, nonspecific widening of the superior mediastinum is seen. If calcification of the aortic knob is present, separation of the intimal calcification from the outer aortic soft tissue border by more than 1.0 cm--the "calcium sign"--is suggestive, although not diagnostic, of aortic dissection. Comparison of the current chest roentgenogram with a previous study may reveal acute changes in the aortic or mediastinal silhouettes that would otherwise have gone unrecognized (Fig. 40-9) . Pleural effusions are common, typically

Figure 40-9 Chest roentgenogram of a patient with aortic dissection. *A,* The patient's baseline study 3 years before admission shows a normal-appearing aorta. *B,* The chest roentgenogram on admission is remarkable for the interval enlargement of the aortic knob (arrow). The patient was found to have proximal aortic dissection. *(From Isselbacher EM, Cigarroa JE, Eagle KA: Aortic dissection. In Creager M [ed]: Vascular Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 7. Philadelphia, Current Medicine, 1996.)*

occur on the left side, and are more often associated with dissection involving the descending aorta. Although the majority of patients with aortic dissection have one or more of these roentgenographic abnormalities, the remainder, up to 12 percent,[110] [137] have chest roentgenograms that appear unremarkable. Therefore, a normal chest roentgenogram can never exclude the presence of aortic dissection.

Electrocardiographic findings in aortic dissection are nonspecific. One-third of electrocardiograms show changes consistent with left ventricular hypertrophy, while another third are normal. Nevertheless, obtaining an electrocardiogram is diagnostically important for two reasons: (1) in aortic dissection, nonspecific chest pain and the absence of ischemic ST segment and T wave changes on electrocardiogram may argue against the diagnosis of myocardial ischemia and thereby prompt consideration of other chest pain syndromes, including aortic dissection, and (2) in patients with proximal dissection, the electrocardiogram may reveal acute myocardial infarction when the

dissection flap has involved a coronary artery.

A promising new biochemical method has recently been introduced that uses serial immunoassays of monoclonal antibodies to smooth muscle myosin heavy chains to detect the presence of acute aortic dissection. In a small prospective study of 27 patients with aortic dissection, the sensitivity and specificity of the assay within the first 12 hours of acute dissection were 90 and 97 percent, respectively.[138] Importantly, the method could also accurately differentiate myocardial infarction from aortic dissection.

Because of the variable extent of aortic, branch vessel, and cardiac involvement occurring with aortic dissection, the signs and symptoms associated with the condition occur sporadically. Consequently, the presence or absence of aortic dissection cannot be diagnosed accurately in most cases on the basis of symptoms and clinical findings alone. In the series of Spittell and associates, of all aortic dissections (without a known diagnosis), the initial clinical diagnosis was aortic dissection in only 62 percent,[110] and the other 38 percent were initially thought to have myocardial ischemia, congestive heart failure, nondissecting aneurysms of the thoracic or abdominal aorta, symptomatic aortic stenosis, pulmonary embolism, and so forth. Among this 38 percent in whom aortic dissection went undiagnosed at initial evaluation, nearly two-thirds had their aortic dissection detected incidentally while undergoing a diagnostic procedure for other clinical questions, and in nearly one-third the aortic dissection remained undiagnosed until necropsy.[110] Given the clinical challenge that detection of aortic dissection presents, physicians should remain vigilant for any risk factors, symptoms, and signs consistent with aortic dissection if a timely diagnosis is to be made.

Diagnostic Techniques

Once the diagnosis of aortic dissection is suspected on clinical grounds, it is essential to confirm the diagnosis both promptly and accurately.[139] The diagnostic modalities currently

Figure 40-10 Thoracic aortogram in the anteroposterior view demonstrating the presence of proximal aortic dissection. *A,* The well-opacified true lumen (T) and the poorly opacified false lumen (F) are separated by an intimal flap (I) that is visible within the ascending aorta as a thin radiolucent line. In addition, the proximal portions of both coronary arteries are well visualized. *B,* In a subsequent aortographic exposure, the false lumen has filled in late and the intimal flap is now clearly visible as it courses distally down the descending aorta. *(A reprinted, by permission, from Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA: Diagnostic imaging in the evaluation of suspected aortic dissection: Old standards and new directions. N Engl J Med 328:35, 1993. B from Isselbacher EM, Cigarroa JE, Eagle KA: Aortic dissection. In Creager M [ed]: Vascular Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 7. Philadelphia, Current Medicine, 1996.)*

available for this purpose include aortography, contrast-enhanced CT, MRI, and TTE or TEE. Each modality has certain advantages and disadvantages with respect to

diagnostic accuracy, speed, convenience, risk, and cost, but none is appropriate in all situations.

When comparing the four imaging modalities, one must begin by considering what diagnostic information is needed.[140] First and foremost, the study must confirm or refute the diagnosis of aortic dissection. Second, it must determine whether the dissection involves the ascending aorta (i.e., proximal or type A) or is confined to the descending aorta or arch (i.e., distal or type B). Third, if possible, it should identify a number of the anatomical features of the dissection, including its extent, the sites of entry and reentry, the presence of thrombus in the false lumen, branch vessel involvement by the dissection, the presence and severity of aortic regurgitation, the presence or absence of pericardial effusion, and any coronary artery involvement by the intimal flap. Unfortunately, no single imaging modality provides all of this anatomical detail. The choice of diagnostic modalities should therefore be guided by the clinical scenario and by targeting information that will best assist patient management.

AORTOGRAPHY.

Retrograde aortography was the first accurate diagnostic technique for evaluating suspected aortic dissection. The diagnosis of aortic dissection is based on direct angiographic signs, including visualization of two lumina or an intimal flap (considered diagnostic), as in Figure 40-10 , or on indirect signs (considered suggestive), such as deformity of the aortic lumen, thickening of the aortic walls, branch vessel abnormalities, and aortic regurgitation.[141] Earnest and colleagues showed that the false lumen was visualized in 87 percent, the intimal flap in 70 percent, and the site of intimal tear in 56 percent of dissections.[142]

Aortography had long been considered the diagnostic standard for the evaluation of aortic dissection because for several decades it was the only accurate method of diagnosing aortic dissection antemortem, although its true sensitivity could not be defined. However, the more recent introduction of alternative diagnostic modalities has shown that aortography is not as sensitive as previously thought. A prospective study by Erbel and colleagues found that for the diagnosis of aortic dissection, the sensitivity and specificity of aortography were 88 and 94 percent, respectively.[143] Furthermore, a series by Bansal and associates found that the sensitivity of aortography was only 77 percent when the definition of aortic dissection included intramural hematoma with noncommunicating dissection.[144] False-negative aortograms occur because of thrombosis of the false lumen, equal and simultaneous opacification of both the true and false lumina,[145] or the presence of an intramural hematoma.

Figure 40-11 Aortogram in the left oblique view demonstrating proximal aortic dissection and its associated cardiovascular complications. *A,* The aortic root is dilated. The true lumen (T) and false lumen (F) are separated by the intimal flap (I), which is faintly visible as a radiolucent line following the contour of the pigtail catheter. The abundance of contrast in the left ventricle (LV) is indicative of significant aortic regurgitation (see Fig. 40-8) . *B,* The true lumen is better opacified than the false lumen, and two planes of the intimal flap can now be distinguished (arrows). The branch vessels are opacified, along with marked narrowing of the right carotid artery (CA), which suggests that its lumen is compromised by the

dissection. *(A reprinted, by permission, from Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA: Diagnostic imaging in the evaluation of suspected aortic dissection: Old standards and new directions. N Engl J Med 328:35, 1993. B from Isselbacher EM, Cigarroa JE, Eagle KA: Aortic dissection. In Creager M [ed]: Vascular Disease. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 7. Philadelphia, Current Medicine, 1996.)*

Figure 40-12 Digital subtraction angiogram of the abdominal aorta to assess the status of renal perfusion in a patient with distal thoracic aortic dissection. This study confirmed the presence of an intimal flap extending down into the left common iliac artery. The celiac axis, superior mesenteric artery, and right renal artery are widely patent and fill from the true lumen. The left renal artery fills from the false lumen, with the intimal flap involving the ostium of the artery and impairing distal flow. As a consequence, minimal contrast is excreted by the left kidney in comparison to the right.

Important advantages of aortography include its ability to delineate the extent of the aortic dissection, including branch vessel involvement (Figs. 40-11 and 40-12). It is also useful in detecting some of the major complications of aortic dissection, such as the presence of aortic regurgitation (see Fig. 40-11), and often useful in revealing patency of the coronary arteries (see Fig. 40-10). In addition to the limited sensitivity of aortography, other disadvantages are the inherent risks of the invasive procedure, the risks associated with the use of contrast material, and the time needed to complete the study, both in assembling an angiography team and the long duration of the procedure. Finally, aortography requires that potentially unstable patients travel to the angiography suite.

COMPUTED TOMOGRAPHY.

In contrast-enhanced CT scanning, aortic dissection is diagnosed by the presence of two distinct aortic lumina, either visibly separated by an intimal flap (Fig. 40-13) or distinguished by a differential rate of contrast opacification. In two large prospective series of patients with suspected aortic dissection, Erbel and colleagues found conventional contrast-enhanced CT scanning to have a sensitivity of 83 percent with a specificity of 100 percent,[143] while Nienaber and coworkers found a sensitivity of 94 percent with a specificity of 87 percent.[146] Spiral (helical) CT scanning, which was introduced more recently and permits three-dimensional display of the aorta and its branches (Fig. 40-14) , has improved the accuracy of CT in diagnosing aortic dissection, as well as in defining anatomical features.[147] Indeed, two small series have found that spiral CT scanning has both a sensitivity and specificity for acute aortic dissection of 96 to 100 percent.[148] [149] (See also Figs. 10-48 and 10-49 .)

CT scanning has the advantage that unlike aortography, it is noninvasive. However, it does require the use of an intravenous contrast agent. Most hospitals are equipped with a readily accessible CT scanner available on an emergency basis. CT is also helpful in identifying the presence of thrombus in the false lumen and in detecting pericardial effusion. A disadvantage of CT scanning is that the site of intimal tear is rarely identified.

CT scanning also cannot reliably detect the presence of aortic regurgitation.

MAGNETIC RESONANCE IMAGING.

The use of MRI has particular appeal for diagnosing aortic dissection in that it is entirely noninvasive and does not require the use of intravenous contrast material or ionizing radiation. Furthermore, MRI produces high-quality images in the transverse, sagittal, and coronal planes, as well as in a left anterior oblique view that displays the entire thoracic aorta in one plane (see Figs. 10-28 , 10-29 , and 10-30). The availability of these multiple views facilitates the diagnosis of aortic dissection and determination of its extent and in many cases reveals the presence of branch vessel involvement. MRI is ideal for the evaluation of patients with preexisting aortic disease, such as those with thoracic aortic aneurysms or prior aortic graft repair, because it provides sufficient

Figure 40-13 Contrast-enhanced CT scan of the chest at the level of the left ventricle showing an intimal flap separating the contrast-filled true (T) and false (F) lumina of an aortic dissection of the descending thoracic aorta.

Figure 40-14 Reformatted left anterior oblique view of a contrast-enhanced CT angiogram of the thoracic aorta (same patient as in Fig. 40-13) showing aortic dissection of the descending thoracic aorta. The intimal flap originates beyond the left subclavian artery and extends distally well into the abdominal aorta. The true lumen (T) and false lumen (F) are easily distinguished and separated by the dark intimal flap (I).

anatomical detail to distinguish aortic dissection from other aortic pathology.[135]

In the series by Nienaber and colleagues, MRI was used to evaluate 105 patients with suspected aortic dissection and found to have both a sensitivity and specificity of 98 percent,[146] consistent with previous findings.[150] [151] MRI had a sensitivity of 88 percent for identifying the site of intimal tear, 98 percent for the presence of thrombus, and 100 percent for the presence of pericardial effusion. Furthermore, use of the cine-MRI technique in a subset of these patients showed 85 percent sensitivity for detecting aortic regurgitation.

The remarkably high accuracy of MRI has made it the current gold standard for diagnosing the presence or absence of aortic dissection. Still, MRI does have a number of disadvantages. It is contraindicated in patients with pacemakers, certain types of vascular clips, and certain older types of metallic prosthetic heart valves.[152] MRI provides only limited images of branch vessels and does not consistently identify the presence of aortic regurgitation. MR scanners are not available in many hospitals and, when present, may not be readily available on an emergency basis. Many patients with aortic dissection are hemodynamically unstable, often intubated or receiving intravenous

antihypertensive medications with arterial pressure monitoring, but MR scanners limit the presence of many monitoring and support devices in the imaging suite and also limit patient accessibility during the lengthy study. Understandably, concern for the safety of unstable patients has led many physicians to conclude that the use of MRI is relatively contraindicated for unstable patients. Notably, despite such concerns, in the studies of Nienaber and colleagues, no complications occurred among their patients with unstable aortic dissection during the performance of MRI.[146] [150]

ECHOCARDIOGRAPHY.

Echocardiography is well suited for the evaluation of patients with suspected aortic dissection because it is readily available in most hospitals, it is noninvasive and quick to perform, and the full examination can be completed at the bedside. The echocardiographic finding considered diagnostic of an aortic dissection is the presence of an undulating intimal flap within the aortic lumen that separates the true and false channels. Reverberations and other artifacts can cause linear echodensities within the aortic lumen that mimic aortic dissection; to definitively distinguish an intimal flap from such artifacts, the flap should be identified in more than one view, it should have motion independent of that of the aortic walls or other cardiac structures, and a differential in color Doppler flow patterns should be noted between the two lumina. In cases in which the false lumen is thrombosed, displacement of intimal calcification[143] or thickening of the aortic wall may suggest aortic dissection.

Transthoracic Echocardiography.

TTE has a sensitivity of 59 to 85 percent and specificity of 63 to 96 percent for the diagnosis of aortic dissection.[140] Such poor sensitivity significantly limits the general utility of this technique. Furthermore, image quality is often adversely affected by obesity, emphysema, mechanical ventilation, or small intercostal spaces.

Transesophageal Echocardiography.

The proximity of the esophagus to the aorta enables TEE to overcome many of the limitations of transthoracic imaging and permits the use of higher frequency ultrasonography, which provides better anatomical detail (Fig. 40-15) . The examination is generally performed at the bedside with the patient under sedation or light general anesthesia and typically requires 10 to 15 minutes to complete. The procedure is relatively noninvasive and requires no intravenous contrast or ionizing radiation. Relative contraindications include known esophageal disease (strictures, tumors, and varices), and the required esophageal intubation may not be tolerated in up to 3 percent of patients.[153] The incidence of important side effects (such as hypertension, bradycardia, bronchospasm, or rarely, esophageal perforation) is much less than 1 percent.[153] One important disadvantage of TEE is its limited ability to visualize the distal ascending aorta and proximal arch because of interposition of the air-filled trachea and main stem bronchus.[154]

The results of large prospective studies by Erbel and colleagues[143] and Nienaber and

associates[146] demonstrated that the sensitivity of TEE

Figure 40-15 Cross-sectional transesophageal echocardiogram of the descending thoracic aorta demonstrating aortic dissection. The aorta is dilated. Evident is an intimal flap (I) dividing the true lumen (T) anteriorly and the false lumen (F) posteriorly. The true lumen fills during systole and is therefore seen bowing slightly into the false lumen in this systolic image.

Figure 40-16 Cross-sectional transesophageal echocardiogram of a descending aortic dissection demonstrating a site of intimal tear. Blood flow (in orange) is evident in the true lumen (T) during systole, while a narrow jet of high-velocity blood (in blue) crosses into the false lumen (F) through a tear in the intimal flap (I).

Figure 40-17 Transesophageal echocardiogram of the proximal ascending aorta in long-axis view in a patient with proximal aortic dissection. \i\A,\r\ The left atrium (LA) is closest to the transducer. The aortic valve (AV) is seen on the left in this view, with the ascending aorta extending to the right. Within the proximal aorta is an intimal flap (I) that originates just at the level of the sinotubular junction above the right sinus of Valsalva. The true lumen (T) and the false lumen (F) are separated by the intimal flap. \i\B,\r\ The addition of color flow Doppler in the same view confirms the presence of two distinct lumina. The true lumen (T) fills completely with brisk blood flow (bright blue color), while at the same time minimal retrograde flow (dark orange) is seen in the false lumen (F)

for aortic dissection is 98 to 99 percent. The sensitivity for detecting an intimal tear was 73 percent (Fig. 40-16) , and for detecting the presence of thrombus in the false lumen, the sensitivity was 68 percent.[146] Furthermore, TEE detected both aortic regurgitation and pericardial effusion in 100 percent.[146] The specificity of TEE for the diagnosis of aortic dissection was less well defined in these series. Although Erbel and colleagues found the specificity to be as high as 97 percent,[143] Nienaber and coworkers found it to be 77 percent.[146] However, in the latter study the early inexperience of those performing the examinations and the use of monoplane transducers may have contributed to the incidence of false-positives. More recent studies using biplane or multiplane TEE have consistently demonstrated a specificity of 94 to 95 percent.[149] [155]

Several methods have been suggested to reduce the possibility of a false-positive diagnosis by TEE,[140] including the use of multiplane ultrasound transducers to confirm the presence of the intimal flap in multiple planes, the confirmation of two lumina by the demonstration of differential color flow patterns (Fig. 40-17) , and the use of M-mode echocardiography to distinguish artifacts.[156] We have proposed that if, in addition to an intimal flap, confirmatory evidence of at least one other echocardiographic feature of aortic dissection is identified, the aortic dissection may be called "definite."[140] If an intimal flap alone is seen (i.e., one that is not considered an artifact) with no other

supporting evidence, the diagnosis of dissection should not be considered definitive, and examination with another imaging modality should be performed to exclude the possibility of a false-positive. If this conservative approach were applied to echocardiographic interpretation in the study by Nienaber and colleagues,[146] the specificity of "definite" aortic dissection would have been 100 percent.[140]

In addition to its high sensitivity for detecting aortic dissection, TEE may provide other important information useful to the surgeon. Some surgeons wish to know preoperatively whether the intimal flap involves the ostia of the coronary arteries, but this determination has traditionally required the performance of coronary angiography.[157] Ballal and colleagues performed TEE on 34 patients with aortic dissection, 7 of whom had coronary artery involvement confirmed at surgery.[158] In 6 of these 7 patients, TEE identified the intimal flap extending into the coronary ostia. However, TEE delineates only the very proximal portions of the coronary arteries, so when assessment of coronary atherosclerosis is necessary, coronary angiography is still required (see below).

Among patients with suspected aortic dissection, the diagnosis is excluded in 42 to 68 percent,[150] [159] which yields a group of patients with a chest pain syndrome of unknown etiology. Chan found that among patients determined to not have dissection, TEE detected other aortic abnormalities in 73 percent and evidence of acute myocardial infarction or ischemia in 23 percent.[160] More recently, Armstrong and associates identified such alternative cardiovascular diagnoses by TEE in 66 percent of those found to not have aortic dissection.[137]

INTRAVASCULAR ULTRASONOGRAPHY.

One of the more recent developments in the echocardiographic evaluation of aortic dissection has been the use of intravascular ultrasound to define the detailed anatomy of the involved aorta and determine the extent of dissection. The intravascular ultrasound catheter is inserted through an introducer in the femoral artery and positioned within the aortic lumen under fluoroscopic guidance. The aorta is then imaged in a transverse plane through its short axis, which allows visualization of the two lumina and intimal flap.

The most extensive assessment of this technique to date was reported by Yamada and coauthors, who studied 15 patients with previously known chronic aortic dissection and compared the findings of intravascular ultrasound with those of other established imaging modalities.[161] Intravascular ultrasound accurately detected the intimal flap in all segments of the aorta, although it was poor at detecting the sites of intimal tear in the thoracic aorta, probably because of vessel curvature. However, intravascular ultrasound was quite useful in evaluation of the abdominal aorta: It demonstrated the origins of the renal arteries and the distal extent of dissection in all cases and identified the site of intimal tear of the abdominal aorta in 78 percent of cases. Accurate assessment of the abdominal aorta with this technique may have particular relevance given the inability of TEE to image this portion of the aorta. It may also have advantages over TEE in fully imaging the aortic arch.[162] Furthermore, intravascular ultrasound may play an important role in the positioning and deployment of endovascular stenting devices[163] (see below).

Nevertheless, the potential future role of intravascular ultrasound in both the evaluation and management of patients with aortic dissection requires further study.

Selecting an Imaging Modality

Each of the four imaging modalities has particular advantages and disadvantages. In selecting among them, one must consider the accuracy as well as the safety and availability of each test. Given its unsurpassed sensitivity and specificity, MRI is considered by most to be the present gold standard for evaluating aortic dissection. The four modalities differ in their ability to detect complications associated with dissection, so the specific diagnostic information sought by the treating physician and/or surgeon should have a bearing on the procedure chosen. A summary of the diagnostic performance of each of the four imaging modalities is presented in Table 40-2 .

Both the accessibility of imaging studies and the time required to complete them are key considerations given the high early mortality associated with unoperated proximal aortic dissection. Aortography can only rarely be performed on an emergency basis because it requires assembly of an angiography team at night and is subject to the risks associated with an invasive procedure and use of a contrast agent. MRI, although optimal in its accuracy, is also generally unavailable on an emergency basis and poses the risk of limited patient monitoring and accessibility during the lengthy procedure. CT scanning is more readily available in most emergency departments and is quickly completed. TEE is also readily available in most larger centers and can be completed quickly at the bedside, which makes it ideal for evaluating unstable patients. A practical assessment of the four imaging modalities is summarized in Table 40-3 (Table Not Available) .

In a setting in which all these imaging modalities are available, we believe that TEE should be considered first in the evaluation of suspected aortic dissection in light of its accuracy, safety, speed, and convenience. In many institutions, TEE has indeed become the procedure of

TABLE 40-2 -- DIAGNOSTIC PERFORMANCE OF IMAGING MODALITIES IN THE EVALUATION OF SUSPECTED AORTIC DISSECTION

DIAGNOSTIC PERFORMANCE	ANGIO	CT	MRI	TEE
Sensitivity	++	+++	+++	+++
Specificity	+++	+++	+++	+++
Site of intimal tear	++	+	+++	++
Presence of thrombus	+++	++	+++	+
Presence of aortic insufficiency	+++	-	+	+++
Pericardial effusion	-	++	+++	+++
Branch vessel involvement	+++	++	++	+
Coronary artery involvement	++	-	-	++

+++=excellent; ++=good; +=fair; -=not detected.

Angio=angiography; CT=computed tomography; MRI=magnetic resonance imaging; TEE=transesophageal echocardiography

.Modified from Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA: Diagnostic imaging in the evaluation of suspected aortic dissection: Old standards and new directions. N Engl J Med 328:35, 1993.

TABLE 40-3 -- PRACTICAL ASSESSMENT OF IMAGING MODALITIES IN THE EVALUATION OF SUSPECTED AORTIC DISSECTION

(Not Available)

Modified from Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA: Diagnostic imaging in the evaluation of suspected aortic dissection: Old standards and new directions. N Engl J Med 328:35, 1993.

choice, [137] [155] [164] with surgeons taking patients to the operating room on the basis of echocardiographic findings alone.[165] [166] In institutions where TEE is not readily available, CT scanning is instead the recommended imaging modality for the evaluation of suspected aortic dissection. However, if the diagnosis of aortic dissection is confirmed by CT, after patient transfer to a tertiary care center an additional diagnostic study may be required to more completely define the aortic anatomy before surgery. However, in such instances, the patient may be taken directly to the operating room, where TEE can then be performed to confirm the diagnosis and better define the dissection anatomy without unduly delaying surgery.[165]

Although MRI is less practical than other modalities for the assessment of suspected acute aortic dissection, it is nonetheless well suited for stable or chronic dissections. Given its extraordinary accuracy and high-quality detailed images, we recommend the use of MRI for monitoring patients with aortic dissection, whether treated medically or surgically, as a means of identifying subsequent aneurysm formation, extension of the dissection, or other complications.

Despite its relative disadvantages, aortography still plays an important role when clear definition of the anatomy of the branch vessels is essential for management. Performance of aortography should also be considered when a definitive diagnosis is not made by one or more of the other imaging modalities.

In the final analysis, each institution must determine its own best diagnostic approach to the evaluation of suspected aortic dissection and base it on available human and material resources and the speed with which such resources can be mobilized. It must be emphasized that regardless of which of the four imaging modalities are available at a given institution, the level of skill and experience of those who carry out each diagnostic procedure must, with good reason, also be be considerations in deciding the study of

choice.

The Role of Coronary Angiography

The importance of assessing the status of coronary artery patency before surgical repair of acute aortic dissection continues to be controversial. Some surgeons believe that obtaining this information before surgery is essential, whereas others are content to assess the coronaries intraoperatively. Two types of coronary artery involvement must be considered in the setting of aortic dissection. The first is acute proximal coronary narrowing or occlusion as a result of the dissection itself, often caused by occlusion of the coronary ostia by the intimal flap. The second is the possible presence of chronic atherosclerotic coronary artery disease, which although generally independent of the dissection process, may complicate its surgical management.

In some cases, coronary involvement by the intimal flap is self-evident if the electrocardiogram shows evidence of acute myocardial ischemia or infarction. However, should this acute process not be clinically evident, TEE can effectively define the patency of the proximal coronaries in a majority of cases.[158] Aortography may also reveal such coronary artery involvement. More comprehensive evaluation requires the performance of coronary angiography; however, this study may be risky in patients with aortic dissection and often prolongs the time to aortic repair by several hours. Moreover, catheterization of the coronary arteries is sometimes unsuccessful in patients with proximal dissection and a dilated root, in which case the added procedural delay gains no potential benefit. In addition, such proximal coronary obstructions can usually be readily identified at the time of surgery.

Chronic coronary artery disease is seen in about one-quarter of patients with aortic dissection. Identifying the presence of this underlying coronary disease is beyond the capability of any of the four imaging modalities discussed above. Furthermore, accurately defining such atherosclerotic disease intraoperatively is challenging, although Rizzo and coworkers have suggested probing of the proximal coronaries, epicardial palpation, and angioscopy as possible means to identify coronary stenoses.[165]

The impact of unrecognized coronary artery disease on outcome is not certain. In a 10-year review examining 54 patients undergoing urgent aortic repair, Kern and colleagues found that only 1 of 27 patients with a proximal dissection had a perioperative myocardial infarction; this patient had a prior history of coronary artery disease.[157] In addition, Rizzo and associates observed that of those in whom unrecognized coronary artery disease was discovered at autopsy, none died of coronary ischemia but several died of aortic rupture.[165] Lastly, Penn and colleagues studied 122 consecutive patients undergoing emergency aortic repair and found no difference in in-hospital mortality between those who had preoperative angiography and those who did not.[166A] Accordingly, we and others[157] recommend avoiding preoperative coronary angiography unless a specific indication exists, such as a known history of coronary artery disease, prior coronary artery bypass grafting,[167] or the presence of ischemic electrocardiographic changes. Conversely, Creswell and coauthors reported good outcomes when performing combined aortic repair and coronary artery bypass grafting in patients with underlying coronary artery disease and therefore argue that all stable

patients with acute proximal dissection should undergo preoperative coronary angiography.[168] While the debate continues unresolved, the trend in the literature has been a retreat from the routine performance of coronary angiography in acute aortic dissection.

Management

Therapy for aortic dissection is directed at halting progression of the dissecting hematoma because lethal complications

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arise not from the intimal tear itself but rather from the subsequent course taken by the dissecting aorta, e.g., vascular compromise or aortic rupture. [137] Without treatment, aortic dissection has a high mortality. In a collective review of long-term survival in untreated aortic dissection, more than 25 percent of all patients died within the first 24 hours after the onset of dissection, more than 50 percent died within the first week, more than 75 percent died within 1 month, and more than 90 percent died within 1 year.[169]

The first surgical approach to aortic dissection was a fenestration procedure in which the dissected aorta was incised and a distal communication created between the true and false channels, thereby decompressing the false lumen. This procedure is, in fact, still used by some surgeons in selected cases of dissection involving the descending aorta to relieve limb, renal, or mesenteric ischemia.[170] Definitive surgical therapy was pioneered by DeBakey and colleagues in the early 1950s.[171] Its purpose is to excise the intimal tear, obliterate the false channel by oversewing the aortic edges, reconstitute the aorta directly or with the interposition of a synthetic graft, and in the case of proximal dissection, restore aortic valve competence either by resuspension of the displaced aortic leaflets or by prosthetic aortic valve replacement.

Aggressive medical treatment of aortic dissection was first advocated by Wheat and colleagues.[172] They established reduction of systolic blood pressure and diminution of the force of left ventricular ejection (dP/dt) as the two primary goals of pharmacological therapy. This force is thought to be a major stress acting on the aortic wall that contributes to both the genesis and subsequent propagation of aortic dissection. Originally introduced for patients too ill to withstand surgery, medical therapy is now the initial treatment for virtually all patients with aortic dissection before definitive diagnosis and furthermore serves as the primary long-term therapy in a subset of patients, particularly those with distal dissections.

Immediate Medical Management

All patients in whom acute aortic dissection is strongly suspected should immediately be placed in an acute care setting for hemodynamic stabilization and monitoring of blood pressure, cardiac rhythm, and urine output. Two large-bore intravenous catheters

should be inserted for intravenous medications and fluid resuscitation if necessary. An arterial line should be placed, preferably in the right arm so that it remains functional during surgery when the aorta is cross-clamped. However, in cases in which the blood pressure is significantly greater on the left than on the right, the arterial line should be placed on the left. In those with a lower likelihood of dissection who are hemodynamically stable, a automatic blood pressure cuff should suffice.

A central venous or pulmonary arterial line to monitor central venous or pulmonary artery wedge pressure and cardiac output should be considered in patients with hypotension or congestive heart failure. Femoral lines and blood gas studies should be avoided if possible to conserve these sites for bypass cannulation during potential aortic repair. If a femoral line must be placed urgently, the opposite groin site should be protected from needle puncture.

BLOOD PRESSURE REDUCTION.

Initial therapeutic goals include the elimination of pain and reduction of systolic blood pressure to 100 to 120 mm Hg (mean of 60 to 75 mm Hg) or the lowest level commensurate with adequate vital organ (cardiac, cerebral, renal) perfusion. Simultaneously, arterial dP/dt, which reflects the force of left ventricular ejection, should be reduced through the use of beta-blocking agents, regardless of whether pain or systolic hypertension is present. The use of long-acting medications should be avoided in patients who are surgical candidates because they may complicate intraoperative arterial pressure management. Pain, which may itself exacerbate hypertension and tachycardia, should be promptly treated with intravenous morphine sulfate.

For the acute reduction of arterial pressure, the potent vasodilator sodium nitroprusside is very effective. It is initially infused at 20 mug/min with the dosage titrated upward, as high as 800 mug/min, according to the blood pressure response. When used alone, however, sodium nitroprusside can actually cause an increase in dP/dt, which in turn may potentially contribute to propagation of the dissection. Therefore, when this drug is used concomitantly achieving adequate beta blockade is essential.

To reduce dP/dt acutely, an intravenous beta blocker should be administered in incremental doses until evidence of satisfactory beta blockade is noted, usually indicated by a heart rate of 60 to 80 beats/min in the acute setting. Because propranolol was the first generally available beta blocker, it has been used most widely in treating aortic dissection. However, it is believed that other noncardioselective beta blockers are equally effective. Propranolol should be administered in intravenous doses of 1 mg every 3 to 5 minutes until the desired effect is achieved, although the maximum initial dose should not exceed 0.15 mg/kg (or approximately 10 mg). To maintain adequate beta blockade, as evidenced by the heart rate, additional propranolol should be given intravenously every 4 to 6 hours, usually in doses somewhat lower than the total initial dose, i.e., 2 to 6 mg.

Labetalol, which acts as both an alpha- and beta-adrenergic receptor blocker, may be especially useful in the setting of aortic dissection because it effectively lowers both dP/dt and arterial pressure. The initial dose of labetalol is 20 mg, administered

intravenously over a 2-minute period, followed by additional doses of 40 to 80 mg every 10 to 15 minutes (up to a maximum total dose of 300 mg) until the heart rate and blood pressure have been controlled. Maintenance dosing may then be achieved with a continuous intravenous infusion starting at 2 mg/min and titrating up to 5 to 10 mg/min.

The ultra-short-acting beta blocker esmolol may be particularly useful in patients with labile arterial pressure, especially if surgery is planned, because use of this drug can be abruptly discontinued if necessary. It is administered as a 500 mcg/kg intravenous bolus followed by continuous infusion at 50 mcg/kg/min and titrated up to 200 mcg/kg/min. Esmolol may also be useful as a means to test beta blocker safety and tolerance in patients with a history of obstructive pulmonary disease who may be at uncertain risk for bronchospasm from beta blockade. In such patients, a cardioselective beta blocker, such as atenolol or metoprolol, may be considered.

When contraindications exist to the use of beta blockers--including sinus bradycardia, second- or third-degree atrioventricular block, congestive heart failure, or bronchospasm--other agents to reduce arterial pressure and dP/dt should be considered. Calcium channel antagonists, which are effective in managing hypertensive crisis, are used on occasion in the treatment of aortic dissection. The combined vasodilator and negative inotropic effects of both diltiazem and verapamil make these agents well suited for the treatment of aortic dissection. Moreover, both these agents may be administered intravenously. Nifedipine has the advantage that it can be given immediately by the sublingual route while other medications are being prepared. A key limitation of nifedipine, however, is that it has little negative chronotropic or inotropic effect.

Refractory hypertension may result when a dissection flap compromises one or both of the renal arteries, thereby causing the release of large amounts of renin. In this situation,

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the most efficacious antihypertensive may be the intravenous angiotensin-converting enzyme (ACE) inhibitor enalaprilat, which is administered initially in doses of 0.625 mg every 4 to 6 hours and the dose then titrated upward.

In the event that a patient with suspected aortic dissection has significant hypotension, rapid volume expansion should be considered given the possible presence of cardiac tamponade or aortic rupture. Before initiating aggressive treatment of such hypotension, however, the possibility of pseudohypotension, which occurs when arterial pressure is being measured in an extremity whose circulation is selectively compromised by the dissection, should be carefully excluded. If vasopressors are absolutely required for refractory hypotension, norepinephrine (Levophed) or phenylephrine (Neo-Synephrine) is preferred. Dopamine should be reserved for improving renal perfusion and used only at very low doses, given that it may raise dP/dt.

Once appropriate medical therapy has been initiated and the patient sufficiently stabilized, a definitive diagnostic study should be promptly undertaken. If a patient remains unstable, TEE is preferred because it can be performed at the bedside in the emergency department or intensive care unit, thereby allowing both monitoring and therapeutic intervention to continue uninterrupted. When a patient with a strongly suspected dissection becomes extremely unstable, aortic rupture or cardiac tamponade is likely and the patient should go directly to the operating room rather than delaying surgery for diagnostic imaging. In such situations, intraoperative TEE can be used both to confirm the diagnosis and to guide surgical repair.

MANAGEMENT OF CARDIAC TAMPONADE.

Cardiac tamponade frequently complicates acute proximal aortic dissection and is one of the most common mechanisms of death in these patients. It is often the cause of hypotension when patients have aortic dissection, and pericardiocentesis is commonly performed in this setting in an effort to stabilize patients while they await definitive surgical repair. However, in a retrospective series we found that pericardiocentesis may be harmful rather than beneficial in this setting because it may precipitate hemodynamic collapse and death rather than stabilize the patient as intended.[173] Seven patients in this series were relatively stable initially (six hypotensive, one normotensive). Three of four who underwent successful pericardiocentesis died suddenly between 5 and 40 minutes after the procedure secondary to acute electromechanical dissociation. In contrast, none of the three patients without pericardiocentesis died before surgery. It may be that in such patients the increase in intraaortic pressure that follows pericardiocentesis causes a closed communication between the false lumen and pericardial space to reopen, thereby leading to recurrent hemorrhage and lethal cardiac tamponade.

Therefore, when a patient with acute aortic dissection complicated by cardiac tamponade is relatively stable, the risks of pericardiocentesis probably outweigh the benefits and *every effort should be made to proceed as urgently as possible to the operating room for direct surgical repair of the aorta with intraoperative drainage of the hemopericardium*. However, when patients have electromechanical dissociation or marked hypotension, an attempt to resuscitate the patient with pericardiocentesis is warranted. A prudent strategy in such cases might be to aspirate only enough pericardial fluid to raise blood pressure to the lowest acceptable level.[173]

Definitive Therapy

Despite minor variations from center to center, a reasonable consensus regarding definitive therapy for aortic dissection has evolved over the past several decades. It is universally agreed that surgical therapy is superior to medical therapy for acute proximal dissection.[174] [175] With even limited progression of a proximal dissection, patients may suffer the potentially devastating consequences of aortic rupture or cardiac tamponade, acute aortic regurgitation, or neurological compromise. Thus, by controlling this risk, immediate surgical repair promises a better outcome. Occasional patients with proximal dissection who refuse surgery or for whom surgery is contraindicated (e.g., by age or

prior debilitating illness) may potentially be treated successfully with medical therapy with a 30-day survival rate of up to 42 percent.[112]

Patients suffering acute distal aortic dissection, on the other hand, are generally at lower risk of early death from complications of the dissection than are those with proximal dissection.[128] Furthermore, because patients with distal dissection tend to be older and have a relatively increased prevalence of advanced atherosclerosis or cardiopulmonary disease, their surgical risk is often considerably higher. A large retrospective series involving patients from both Duke and Stanford universities has, by multivariate analysis, shown that medical therapy provides an outcome equivalent to that of surgical therapy in patients with uncomplicated distal dissection.[176] As a consequence, medical therapy for such patients is currently favored by most groups. An important exception is that when distal dissection is complicated by rupture, expansion, saccular aneurysm formation, vital organ or limb ischemia, or continued pain, the results of medical therapy are poor and surgery is therefore recommended.[170] [175]

Patients with chronic aortic dissection have, through self-selection, survived the early period of highest mortality, and whether treated medically or surgically, their subsequent hospital survival rate is approximately 90 percent. [177] Accordingly, medical therapy is recommended for the management of all stable patients with chronic proximal and distal dissection, again unless complicated by rupture, aneurysm formation, aortic regurgitation, arterial occlusion, or extension or recurrence of dissection.

SURGICAL MANAGEMENT.

Generally advocated indications for definitive surgical therapy are summarized in Table 40-4 . Surgical candidacy should be determined whenever possible at the start of the patient's evaluation because this option guides the selection of diagnostic studies. Surgical risk for all patients is increased by age, comorbid disease (especially pulmonary emphysema), aneurysm leakage, cardiac tamponade, shock, or vital organ compromise as a result of such conditions as myocardial infarction, cerebrovascular accident, and in particular, preexisting renal failure.

Preoperative mortality in patients with acute dissection ranges from 3 percent when surgery is expedited to as high as 20 percent when the preoperative evaluation is more prolonged.[165] These data reinforce the need for prompt diagnosis

TABLE 40-4 -- INDICATIONS FOR DEFINITIVE SURGICAL AND MEDICAL THERAPY IN AORTIC DISSECTION

SURGICAL
Treatment of choice for acute proximal dissection
Treatment for acute distal dissection complicated by the following:
Progression with vital organ compromise
Rupture or impending rupture (e.g., saccular aneurysm formation)
Retrograde extension into the ascending aorta

Dissection in the Marfan syndrome

MEDICAL

Treatment of choice for uncomplicated distal dissection

Treatment for stable, isolated arch dissection

Treatment of choice for stable chronic dissection (uncomplicated dissection presenting 2 weeks or later after onset)

and repair to prevent even minimal progression of the dissection, which might lead to further complications.[88]

The usual objectives of definitive surgical therapy include resection of the most severely damaged segment of aorta, excision of the intimal tear when possible, and obliteration of entry into the false lumen by suturing the edges of the dissected aorta both proximally and distally. After resecting the diseased segment containing the intimal tear, typically a segment of the ascending aorta in proximal dissections or the proximal descending aorta in distal dissections, aortic continuity is then reestablished by interposing a prosthetic sleeve graft between the two ends of the aorta (Fig. 40-18) .

Importantly, Miller and colleagues have found that the immediate and long-term survival of patients treated surgically was not significantly affected by failure to excise the intimal tear.[174] [178] Some patients with proximal dissection have an intimal tear located in the aortic arch. Because surgical repair of the arch may increase the morbidity and mortality associated with the procedure and because resection of the tear may not necessarily improve mortality,[178A] many authors have elected to not repair the arch if the sole purpose of surgery is resection of the intimal tear.[178] However, with improvements in surgical technique during the last decade, several groups now suggest that even these challenging lesions can be resected with favorable results.[179] [180]

When aortic regurgitation complicates aortic dissection, simple decompression of the false lumen is sometimes all that is required to allow resuspension of the aortic leaflets and restoration of valvular competence. More often, however, preservation of the aortic valve requires approximation of the two layers of dissected aortic wall and resuspension of the commissures with pledgeted sutures. In this setting, the use of intraoperative TEE may be particularly helpful to the surgeon in guiding aortic valve repair.[181] This resuspension technique has had favorable results with a fairly low incidence of recurrent aortic regurgitation in long-term follow-up.[118] [182] Preserving the aortic valve in this fashion may avoid the complications associated with prosthetic valve replacement, especially the requirement for oral anticoagulation, which may pose an added risk in patients prone to future aortic rupture.

Prosthetic aortic valve replacement is sometimes necessary, however, either because attempts at valve repair are unsuccessful or in the setting of preexisting valvular disease

or the Marfan syndrome.[182] Many surgeons are aggressive about replacing the aortic valve if it appears that even moderate aortic regurgitation will remain after the leaflets are resuspended and choose to avoid the risk of having to replace the aortic valve at some later date in a second operation through a diseased aorta. When the proximal aorta is fragile or badly torn, most use the Bentall procedure in which a composite prosthetic graft--a prosthetic aortic valve sewn onto the end of a Dacron tube graft--facilitates replacement of both the ascending aorta and aortic valve together (see Fig. 40-5). The coronary arteries are then reimplanted as buttons of aortic tissue into the graft wall. The operative procedure in aortic dissection is technically demanding. The wall of the diseased aorta is often friable, and the repair must be performed with meticulous care. The use of Teflon felt to buttress the wall and prevent sutures from tearing through the fragile aorta is essential (see Fig. 40-18) . Determining the sources of vital organ perfusion distal to the surgical site by diagnostic imaging studies may be of critical importance. For example, if one or both renal arteries are supplied by the false lumen and are not going to be directly corrected surgically, the surgeon may leave communication between the true and false channels distal to the site of aortic repair so that renal perfusion is not jeopardized.

COMPLICATIONS.

Bleeding, infection, pulmonary failure, and renal insufficiency constitute the most common early complications of surgical therapy. Spinal cord ischemia with paraplegia caused by inadvertent interruption of the blood supply from the anterior spinal or intercostal arteries is an uncommon but dreaded consequence of descending thoracic aortic repair. Late complications include progressive aortic regurgitation if the aortic valve has not been replaced, localized aneurysm formation, and recurrent dissection at the original site or at a secondary site.[178] With modern operative techniques, 30-day surgical survival rates for proximal and distal dissections are 74 and 69 percent, respectively. [112]

NEWER SURGICAL TECHNIQUES.

As a modification of more standard operative techniques, several investigators have unified the layers of the dissected aortic wall by using either a fibrin sealant[183] or gelatin-resorcine-formaldehyde glue.[184] After resection of the diseased aortic segment, this glue is used in place of pledgeted sutures to seal the false lumen of the aortic stumps, before implantation of the Dacron prosthesis. The glue not only hardens and reinforces the fragile dissected

Figure 40-18 Several steps in the surgical repair of proximal *(A, B,* and *C)* and distal *(D, E,* and *F)* aortic dissection. *A* and *D* show the dissections and intimal tears. *B,* The aorta has been transected, and the ends of the aorta have been oversewn to obliterate the false lumen and buttressed with Teflon felt to prevent the sutures from tearing through the fragile tissue. *C,* The aortic ends are brought together in such a way that the Teflon is again used to reinforce the suture line between the two ends of the aorta and between the aorta and a sleeve graft, if such a graft is necessary for reconstitution of the aorta. *E,* Resection of a distal dissection, with a Teflon graft interposed in *F*. *(D, E, and F reprinted, by permission, from Austen WG, DeSanctis RW: Surgical treatment of dissecting aneurysm of the thoracic aorta. N Engl*

J Med 272:1314, 1965.)

aortic tissue but may also simplify the operation, facilitate resuspension of the aortic valve, and potentially reduce the incidence of late aortic root aneurysm formation.[183] Another group has used such glue in carrying out direct surgical repair of the aorta without an interposing graft by first suturing the intimal tear, then applying the glue in the false lumen to unify the layers of the dissected aorta, and finally reattaching the free aortic ends. Although early reports show favorable morbidity and mortality with the use of these new techniques,[184] direct comparison with standard operative techniques is needed.

ENDOVASCULAR TECHNIQUES (see also Chap. 42) .

One of the more promising avenues of investigation is the use of endovascular techniques for treating high-risk patients with aortic dissection. For example, because patients with renal or visceral artery compromise from dissection have operative mortality rates exceeding 50 percent,[185] [186] alternative management strategies are desirable. Two endovascular techniques have been used in many centers to manage patients with acute vascular complications secondary to aortic dissection. The first is balloon fenestration of the intimal flap, which involves crossing an intact intimal flap with a wire, passing a balloon-tipped catheter over the wire, and then expanding the balloon to tear a hole in the intimal flap. The hole acts as a site of reentry to allow blood to flow from the false into the true lumen, thereby decompressing the distended false lumen. The second technique involves percutaneous stenting of an affected arterial branch whose flow has been compromised by the dissection process. Slonim and coauthors reported the use of percutaneous management of ischemic complications of aortic dissection in a series of 22 patients.[186] Sixteen patients were treated with endovascular stents, 3 with balloon fenestration of the intimal flap, and 3 with fenestration in combination with stenting of the aorta or its branches; revascularization with clinical success was achieved in all 22 patients, with excellent long-term outcomes. The utility of aortic intimal flap fenestration in restoring blood flow to hypoperfused organs has also been demonstrated in animal models.[187] In the large IRAD series of acute aortic dissection, 3.2 percent of patients were treated with percutaneous fenestration procedures.[112]

More definitive endovascular techniques have also been introduced. Sutureless intraluminal prostheses placed during cardiopulmonary bypass are intended to improve outcome by decreasing intraoperative and postoperative bleeding complications. These devices have been used successfully with good outcomes in two small series of patients with proximal aortic dissection.[188] [189]

More recently, intraluminal stent-grafts placed percutaneously by the transfemoral catheter technique have been introduced as a potential alternative to aortic repair.[190] [191] [192] The purpose of this procedure is to close the site of entry into the false lumen

(intimal tear), decompress and promote thrombosis of the false lumen, and relieve any obstruction of branch vessels that may accompany the dissection. It is hoped that this approach will reduce the morbidity and mortality of aortic dissection and reduce the risk of subsequent aneurysm formation. Nienaber and colleagues compared the use of stent-graft placement with standard surgical repair in a group of 24 patients with subacute or chronic type B aortic dissection and a patent false lumen.[191] No procedural complications occurred among the 12 patients undergoing stent-graft treatment, and when compared with the surgical group, the stent-graft group had a significantly shorter hospital stay, lower morbidity, and lower 1-year postprocedural mortality. Dake and colleagues inserted stent-grafts in the descending thoracic aortas of 19 patients with acute aortic dissection and a patent false lumen who suffered from obstruction of branch vessels, acute aortic rupture, or persistent back pain.[192] Endovascular stent-graft deployment was successful in all cases, with complete thrombosis of the false lumen in 79 percent and partial thrombosis in the remaining 21 percent. Restoration of flow to ischemic arterial branches with relief of corresponding symptoms occurred in 76 percent of obstructed branches. The results of these two series are extremely promising, but larger studies with more patients and longer follow-up will be required before stent-graft therapy becomes an accepted therapy for aortic dissection.[193]

DEFINITIVE MEDICAL MANAGEMENT.

The indications for definitive medical therapy are summarized in Table 40-4 . As discussed above, we prefer medical therapy for stable patients with uncomplicated acute distal dissection given that the 30-day survival rate for those with distal dissection treated medically is 92 percent.[112] However, surgery clearly must be performed in cases of medical management failure, such as in the presence of rupture or impending rupture, progression of the dissection with vital organ compromise, an inability to control pain with medicines, or retrograde progression of a type B dissection into the ascending aorta. Because of the extreme difficulty of surgery to repair the aortic arch when it is involved by the dissection, medical therapy is also usually advocated for distal dissections that either originate in the arch or extend retrograde into the arch. Operative therapy is again reserved for those with serious complications. Medical therapy is also generally recommended for patients with chronic aortic dissection, whether proximal or distal, unless late complications of the dissection, such as aortic regurgitation or localized aneurysm formation, necessitate surgery.

Severe hypertension is relatively common during the period of hospitalization after acute aortic dissection and may be seen even in patients without a history of significant hypertension. The etiology for this hypertensive response is unclear but it may reflect a marked increase in sympathetic tone triggered by the severe inflammation of the aortic wall that accompanies dissection. While such hypertension often prompts clinicians to order a CT or MR angiogram to rule out renal artery compromise by the dissection, in our experience, renal ischemia is rarely the cause.[194] In most cases, blood pressure begins to fall and becomes more easily controlled about 5 to 7 days after onset of the aortic dissection.

Long-Term Therapy and Late Follow-Up

Late follow-up of patients leaving the hospital with treated aortic dissection shows an actuarial survival rate not much worse than that of individuals of comparable age without dissection. No significant differences are seen among discharged patients when comparing proximal versus distal dissection, acute versus chronic dissection, or medical versus surgical treatment.[128] Five-year survival rates for all these groups are typically 75 to 82 percent.[128] [174] [178] Thus, the initial success of surgical or medical therapy is usually sustained on long-term follow-up. Late complications include aortic regurgitation, recurrent dissection, and aneurysm formation or rupture.

Long-term medical therapy to control hypertension and reduce dP/dt is indicated for all patients who have sustained an aortic dissection, regardless of whether their in-hospital definitive treatment was surgical or medical. Indeed, one study found that late aneurysm rupture after aortic dissection was 10 times more common in patients with poorly controlled hypertension than in those with controlled blood pressure,[195] which dramatically demonstrates the importance of aggressive lifelong antihypertensive therapy. Systolic blood pressure should be maintained at or below 130 mm Hg. The preferred agents are beta blockers or, if contraindicated, other agents with a negative inotropic as well as a hypotensive effect such as verapamil or diltiazem. Pure vasodilators, such as dihydropyridine calcium channel antagonists or hydralazine, may cause an increase in dP/dt and should therefore be used only in conjunction with adequate beta blockade. ACE inhibitors are attractive antihypertensive agents for treating aortic dissection and may be of particular benefit in those with some degree of renal ischemia as a consequence of the dissection.

Up to 29 percent of late deaths following surgery result from rupture of either the dissecting aneurysm or an another aneurysm at a remote site. Moreover, the incidence of subsequent aneurysm formation at a site remote from the surgical repair is 17 to 25 percent,[108] [196] with these remote aneurysms accounting for many of the rupture-related deaths. The mean time interval from primary aortic dissection to the appearance of subsequent aneurysms is 18 months, with the majority appearing within 2 years.[196] Many such aneurysms occur from dilatation of the residual false lumen in the more distal aortic segments not resected at the time of surgery. Because the dissected aneurysm wall is relatively thin and consists of only the outer half of the original aortic wall, these aneurysms rupture more frequently than do typical atherosclerotic thoracic aneurysms.[78] [196] Thus, an aggressive approach to treating such late-appearing aneurysms may be indicated.

The high incidence of late aneurysm formation and rupture

emphasizes both the diffuse nature of the aortic disease process in this population and the tremendous importance of careful follow-up. The primary goal of long-term surveillance is the early detection of aortic lesions that might require subsequent surgical intervention, such as the appearance of new aneurysms or rapid aneurysm

expansion, progression or recurrence of dissection, aortic regurgitation, or peripheral vascular compromise.

Follow-up evaluation of patients after aortic dissection should include careful and repeated physical examinations, periodic chest roentgenograms, and serial aortic imaging with TEE, CT,[175] or MRI.[170] [197] We generally prefer MRI for serially monitoring these patients because it is completely noninvasive and provides excellent anatomical detail that may be exceedingly helpful in evaluating interval changes.[198] Patients are at highest risk immediately after hospitalization and during the first 2 years, with the risk progressively declining thereafter. It is therefore important to have more frequent early follow-up; for example, patients may be seen at 3 and 6 months initially and then return every 6 months for 2 years, after which time they may be reevaluated at 6- to 12-month intervals, depending on the given patient's risk.

Atypical Aortic Dissection

In recent years it has become increasingly clear that in addition to aortic dissection as classically described, two other diseases of the aorta are closely related, *intramural hematoma* of the aorta and *penetrating atherosclerotic ulcer* of the aorta. These two conditions share with aortic dissection many of the predisposing risk factors and initial symptoms, and indeed, both may lead to either classic aortic dissection or aortic rupture. In light of their clinical similarities, it is appropriate to consider classic aortic dissection and its variants collectively among the "acute thoracic aortic syndromes," a category that also includes traumatic aortic transection and rupture, contained rupture (pseudoaneurysm), or acute expansion of thoracic aortic aneurysms.

INTRAMURAL HEMATOMA.

Intramural hematoma is essentially a hemorrhage contained within the medial layer of the aortic wall. Although the pathogenesis of intramural hematoma is still uncertain, rupture of the vasa vasorum is believed to be the initiating event and results in hemorrhage into the outer media and extending into the adventitia.[199] This complication may produce a localized or discrete hematoma, but more often the hemorrhage extends for a variable distance by dissecting along the outer media beneath the adventitia.[200] Intramural hematoma is distinguished from typical aortic dissection by the lack of an associated tear in the intima or direct communication between the media and aortic lumen; hence, some have termed it *aortic dissection without intimal rupture.* [199] Previous pathological studies of what were considered clinically to be aortic dissections have found that 3 to 13 percent did not have an identifiable intimal tear,[106] [107] [201] and it is possible that such cases were in fact actually intramural hematomas. Moreover, it remains uncertain whether intramural hematoma is a distinct pathological entity or instead represents a reversible precursor of classic aortic dissection.

Clinically, intramural hematoma may be indistinguishable from true aortic dissection. In the IRAD series of 464 patients with the clinical diagnosis of acute aortic dissection, 10 percent were found by imaging studies to have an intramural hematoma rather than classic dissection and two-thirds of these intramural hematomas were classified as type B.[112] The majority of patients are elderly with a history of hypertension and typically

have extensive aortic atherosclerosis.[202] [203] Almost all patients have the chest and back

Figure 40-19 Intramural hematoma of the descending thoracic aorta. *A,* An axial CT scan without contrast enhancement demonstrates crescentic thickening of the aortic wall that is of increased density (H), consistent with an intramural hematoma of the aorta. A left pleural effusion (E) is also present. *B,* Subsequent contrast-enhanced images of the same patient demonstrating a contrast-filled aortic lumen with dark crescentic thickening of the aortic wall (H) that does not enhance, confirming the presence of an intramural hematoma that does not communicate with the aortic lumen. Note that neither the size nor the shape of the aortic lumen is distorted the way it would typically be in the presence of a classic aortic dissection.

pain symptoms typical of classic aortic dissection. Aortic regurgitation and pulse deficits may be present. One-half of patients may have an associated left pleural effusion[199] [202] that may not appear until several days after the hematoma develops.[199] Pericardial effusion may appear when the ascending aorta is involved.[202]

Intramural hematoma is best diagnosed by CT scanning. On a non-contrast-enhanced CT scan (Fig. 40-19 *A*) it appears as a continuous, crescentic, high-attenuation area along the aortic wall without evidence of an intimal tear, false lumen, or associated intimal atherosclerotic ulcer.[200] This first examination is followed by a contrast-enhanced CT scan (Fig. 40-19 *B*), which demonstrates failure of the intramural hematoma to enhance (appearing as a darker crescentic thickening of the aortic wall), thereby excluding communication with the aortic lumen. In some cases it may be difficult to distinguish intramural hematoma from aortic dissection with thrombosis of the false lumen or from mural thrombus within an aortic aneurysm.[199] However, with an intramural hematoma, the aortic lumen retains its overall size and shape, unlike the case with aortic dissection.

On MRI, an intramural hematoma appears as a crescentic high-intensity area along the aortic wall.[199] On TEE, it is manifested as a continuous crescentic or nearly concentric circular thickening of the aortic wall that in some cases may be difficult to distinguish from severe atherosclerotic thickening of the aortic wall.[204] [205] Aortography, on the other hand, often fails to detect the presence of an intramural hematoma because no contrast escapes the aortic lumen and the intramural hematoma does not usually compress the aortic lumen to produce recognizable aortographic signs such as seen with aortic dissection.[199] In fact, the sensitivity of aortography for detecting intramural hematoma is as low as 19 percent[206] ; therefore, while a negative aortogram may exclude the presence of classic aortic dissection, it does not reliably exclude the important variant of intramural hematoma.

The natural history of intramural hematoma is not yet well defined. Involvement of the ascending aorta appears to carry a high risk of death or complications requiring surgical repair, whereas hematomas of the descending aorta have a more favorable prognosis.

In a retrospective series, Nienaber and coworkers determined that 13 percent of 195 patients with aortic dissection-like syndromes in fact had intramural hematoma.[204] The actuarial survival rates were similar for the groups with intramural hematoma and overt aortic dissection.[204] Of patients with proximal intramural hematoma, 30-day mortality was 80 percent for those treated medically versus 0 percent for those undergoing early repair. On the other hand, early mortality for distal intramural hematoma was 9 percent and did not differ significantly between medical and surgical treatment.

Intramural hematomas may regress with time or even completely resolve on follow-up imaging.[199] However, should the intramural hematoma completely resolve, the affected portion of the aorta is still at risk for progressive enlargement and fusiform aneurysm formation.[207] Alternatively, intramural hematoma may progress to overt aortic dissection within days[204] to months of initial examination.[200] Nienaber and colleagues found progression to overt dissection, aortic rupture, or cardiac tamponade in one-third of their patients.[204]

The limited data on the natural history of intramural hematoma suggest that it behaves very much like classic aortic dissection and should therefore be treated in a similar fashion. Thus, surgical therapy is best for proximal hematomas, whereas medical therapy is reasonable for distal hematomas. Physicians should have a low threshold, however, for proceeding to surgery in distal disease if symptoms persist or evidence of progression is seen. Medical management should therefore include serial imaging studies to monitor progression or regression of the intramural hematoma.

PENETRATING ATHEROSCLEROTIC ULCER.

Penetrating atherosclerotic ulcer, first defined in the literature in 1986 by Stanson and coauthors in 1986,[208] is an ulceration of an atherosclerotic lesion of the aorta that penetrates the internal elastic lamina and allows hematoma formation within the media of the aortic wall (Fig. 40-20) (Figure Not Available) . Although such ulcerations occur almost exclusively in the descending thoracic aorta,[209] they may also occur in the arch or rarely in the ascending aorta.[210] [211] The hematoma that results from a penetrating atherosclerotic ulcer usually remains localized or extends several centimeters in length, but a false lumen typically does not develop.[212] However, it has also been suggested that some cases of intramural hematoma of the aorta may in fact be secondary to small penetrating atherosclerotic ulcers that have escaped detection on imaging studies but are later identified at the time of surgery.[213]

Atherosclerotic aortic ulcers penetrate through the media in one-quarter of cases to cause aortic pseudoaneurysms or through the adventitia in 8 percent to cause transmural aortic rupture[210] (Fig. 40-20) (Figure Not Available) . Rarely, a penetrating atherosclerotic ulcer may progress to an extensive classic aortic dissection.[211] Over time, penetrating atherosclerotic ulcers frequently lead to the formation of saccular or fusiform aortic aneurysms.[214]

Patients in whom penetrating atherosclerotic ulcers develop tend to be elderly with a history of hypertension and

Figure 40-20 (Figure Not Available) Evolution of a penetrating atherosclerotic ulcer of the aorta. Once an intimal ulcer has formed, it may then progress to a variable depth. Penetration through the intima causes a medial hematoma, while penetration through the media leads to the formation of a pseudoaneurysm, and perforation through the adventitial layer results in aortic rupture. *(From Stanson AW, Kazmier FJ, Hollier LH, et al: Penetrating atherosclerotic ulcers of the thoracic aorta: Natural history and clinicopathological correlations. Ann Vasc Surg 1:15, 1986.)*

Figure 40-21 Thoracic aortogram demonstrating a penetrating atherosclerotic ulcer of the distal end of the descending aorta (arrow). The hematoma of the aortic wall is evident as a localized contrast-filled outpouching of the aorta. The remainder of the aorta is diffusely atherosclerotic.

evidence of other atherosclerotic cardiovascular disease.[209] Initial symptoms include chest and back pain similar to that of aortic dissection, and the majority are hypertensive at initial evaluation.[209] However, since penetrating atherosclerotic ulcers tend to be localized, the vascular compromise or aortic regurgitation that often complicates aortic dissection does not develop.[208]

Chest roentgenograms often demonstrate a dilated descending thoracic aorta as well as left-sided or bilateral pleural effusions.[209] Aortography is the diagnostic standard for detecting a penetrating atherosclerotic ulcer, with the lesion appearing as a contrast-filled outpouching in the descending aorta in the absence of an intimal flap or false lumen[210] (Fig. 40-21) . On CT scanning or MRI the lesion appears as a focal ulceration, with thickening of the aortic wall and inward displacement of intimal calcification consistent with intramural hematoma. TEE may identify the presence of a culprit atherosclerotic ulcer in the setting of a visible intramural hematoma,[215] but diagnosis is difficult. [154]

The natural history of a penetrating atherosclerotic ulcer remains largely unclear, and at present no definitive treatment strategy is available. Certainly, patients who are hemodynamically unstable or who have evidence of pseudoaneurysm formation or transmural rupture should undergo urgent surgical repair. Continued or recurrent pain, distal embolization, and progressive aneurysmal dilatation are also indications for surgery.[212] In the near future, transluminal placement of an endovascular stent-graft may become an alternative to surgery in such patients.[216] Those without such complications should be treated with antihypertensive medications and monitored closely with follow-up imaging studies, similar to the management of a patient with a distal aortic dissection.

Aortic Trauma

See Chapter 51 .

AORTIC ATHEROMATOUS DISEASE (see also Chap. 41)

AORTOGENIC ATHEROTHROMBOTIC EMBOLI.

The clinical importance of atherosclerotic disease of the aorta has long been recognized inasmuch as atheromatous or fibrinous material, thrombi, or cholesterol particles dislodged from atherosclerotic plaque may cause cerebral or peripheral embolic phenomena.[217] However, assessing the degree of such atherosclerotic disease antemortem has been limited by the inability of the several imaging modalities to directly visualize the aortic intima.[218] Aortography demonstrates the aortic lumen rather than the aortic walls themselves and can thus detect only gross atherosclerotic changes, whereas CT scanning or MRI rarely detects protruding atheromas because the normal pulsatile motion of the aorta may limit definition of the aortic wall on the tomographic images. On the other hand, TEE is uniquely suited to assess atherosclerotic disease of the aorta in real time and has been demonstrated to have greater sensitivity for aortic arch atherosclerosis than is the case with chest roentgenography, aortography, or CT scanning.[218] On echocardiography, mild atherosclerosis appears as intimal thickening, irregularity, and calcification, whereas more severe disease appears as thick plaque with protruding atheromas (Fig. 40-22) . In some cases, protruding lesions have highly mobile components that probably represent atheroma with superimposed thrombus.[219]

Risk factors for aortic atherosclerosis include age, hypertension, diabetes,[220] hyperlipidemia,[221] and other vascular disease. [222] Through the use of TEE, the prevalence and extent of macroscopic atherosclerotic disease have now been documented in a variety of patient populations. Atheromatous disease is least common in the ascending aorta, more common in the arch, and most common in the descending thoracic aorta.[223] [224] While aortic atheromas are detected in as few as 2 percent of patients without a history of stroke or known aortic disease, they are found in 38 percent of those with significant carotid artery disease,[225] 60 percent of those with ischemic stroke,[223] and up to 90 percent of those with obstructive coronary artery disease.[226]

In an autopsy series, Amarenco and colleagues found that the presence of ulcerated plaque in the aortic arch was a significant independent risk factor for stroke, particularly cryptogenic stroke,[222] and multiple clinical studies using

Figure 40-22 Cross-sectional transesophageal echocardiogram of the descending thoracic aorta demonstrating extensive atherosclerotic disease. This patient had recently suffered an embolic stoke of uncertain etiology. Multiple atheromatous plaques up to 7 mm in thickness protrude into the aortic lumen. When viewed in real time, two plaques (arrows) had small mobile intraluminal components.

TEE have found an association between aortic atherosclerosis and stroke, as well as

other peripheral embolic events.[217] [221] [227] In both retrospective and prospective studies, protruding aortic atheromas are detected in 7 to 8 percent of patients undergoing routine TEE,[217] [228] with about a 33 percent incidence of embolic vascular events over a 2-year follow-up period.[228] The embolic risk is even higher in patients with pedunculated or mobile lesions and those undergoing invasive aortic procedures.[217]

In a prospective case-control study, Amarenco and associates found atherosclerotic plaque measuring 4 mm or greater in the ascending aorta or proximal arch in 14 percent of patients with ischemic stroke as compared with only 2 percent of controls. After adjustment for atherosclerotic risk factors, the odds ratio for stroke was 9.1 for ischemic stroke and 4.7 for cryptogenic stroke, with an even higher risk ratio for complex atheromas than for simple ones.[223] However, the increased risk of stroke was associated only with large atheromas involving the ascending aorta and proximal arch, not with atheromas in the distal arch or descending aorta,[223] thus supporting the hypothesis that atheromas in the ascending aorta and proximal portion of the aortic arch embolize directly into the cerebral circulation and cause ischemic strokes in such patients.[229]

Little is known about the natural history of atheromatous lesions[230] of the aorta, although one prospective trial has demonstrated that individual lesion morphology is dynamic in that mobile components both form on some atheromas and resolve on others during the same time period.[231] At present, therapeutic strategies are limited. Potential approaches for chronic management include the use of antithrombotic[232] [233] or antiplatelet[230] therapy to prevent thrombus formation. In two recent prospective but nonrandomized studies, patients having aortic plaque 4 mm or more in thickness or mobile aortic atheromas on TEE examination were found to have a high rate of recurrent vascular events. Of these study subjects, those subsequently treated with warfarin therapy had a significantly lower rate of recurrent embolic events than did those treated with antiplatelet therapy, which suggests that warfarin may be efficacious in this high-risk population.[234] [235] A prospective randomized trial is clearly needed to confirm the benefits of oral anticoagulant therapy for aortic atheromas. Some investigators have reported the surgical removal, under hypothermic circulatory arrest, of protruding atheromas detected in patients after embolic events.[227] However, this surgery carries the risk of an early adverse outcome, and at present no controlled data suggest that it actually reduces the incidence of future embolization in this population.

CARDIAC SURGERY AND ATHEROEMBOLISM.

Perioperative dislodgement with embolization of atherosclerotic material from the aorta is a well-recognized hazard of cardiac surgery and has been increasingly implicated as an important cause of postoperative stroke and other embolic events in these patients. The incidence of cerebral ischemic events after cardiac surgery typically ranges from 1 to 3 percent, with an increased risk among the elderly.[220] [236] In an autopsy series of patients who underwent cardiac surgery, Blauth and colleagues identified atheroemboli in 22 percent of cases.[237] Atheroembolic events occurred in 37 percent of those with severe atherosclerosis of the ascending aorta versus only 2 percent of those without significant ascending aortic atherosclerosis. Moreover, 96 percent of patients with perioperative atheroemboli had severe atherosclerosis of their ascending aorta.[237]

Mobile pedunculated lesions appear more prone to embolize.[217]

Mechanisms by which aortic atherosclerotic debris may be dislodged during cardiac surgery include external manipulation of the aorta during palpation,[236] cross-clamping, cannula placement, anastomosis of the bypass grafts to the aorta,[220] and the "sandblasting" effect of the high-velocity jet of blood that exits the aortic cannula and strikes the atherosclerotic intima of the opposite aortic wall.[236] [237] Although surgeons have long relied on direct digital palpation to detect the presence of atherosclerosis in the ascending aorta, this method underestimates the incidence, severity, and extent of atherosclerotic disease.[238] In contrast, ultrasonography is superior for delineating the presence and severity of atherosclerotic disease of the ascending aorta,[217] with intraoperative epi-aortic ultrasound found to be even more sensitive than TEE.[239]

Several studies have examined the potential role of aortic ultrasonography in identifying patients at highest risk for perioperative atheroemboli. In 8 to 17 percent of cases, the ultrasonographic findings led to modifications in surgical technique such as changing the sites of aortic cannulation (with cannulation of the distal aorta or femoral artery instead), cross-clamping, or anastomosis of vein grafts.[220] [236] [238] [240] The results of such procedural modifications have been promising, with several reports showing a trend toward a reduction in stroke rates.

CHOLESTEROL EMBOLIZATION SYNDROME (see also Chap. 41) .

Cholesterol embolization syndrome is caused by distal showering of cholesterol crystals from ulcerated atheromatous plaque in the aorta or iliac and proximal femoral arteries in patients with diffuse atherosclerosis. These cholesterol crystals then obstruct small peripheral arteries (100 to 300 mum in size), where they cause local tissue ischemia or necrosis and frequently induce a local inflammatory reaction that may contribute to the arteriolar occlusive process.[241]

The precise mechanisms that precipitate cholesterol embolization are unclear. The syndrome is most commonly seen following instrumentation of the aorta, such as with cardiac catheterization, percutaneous transluminal coronary angiography, angiography, or intraaortic balloon pump insertion.[242] The overall incidence following cardiac catheterization was 0.1 percent in the Coronary Artery Surgery Study.[243] Cholesterol embolization may also complicate aortic surgery or cardiopulmonary bypass. At times, cholesterol embolization syndrome may occur spontaneously. Studies have suggested a possible causal relationship between warfarin therapy and such spontaneous cholesterol embolization.[244]

The clinical manifestations depend on the organs affected. Cutaneous manifestations, typically of the lower extremities, are most common and include livedo reticularis, gangrene, cyanosis, and ulceration. Acute onset of pain with digital ischemia and small areas of cutaneous gangrene is often referred to as the "blue toe" or "purple toe syndrome"[244] (see Fig. 41-23) . The presence of preserved pedal pulses in the setting of peripheral ischemia distinguishes this syndrome from embolic occlusion of larger arteries.

Acute nonoliguric renal failure with or without hypertension is a common consequence of renal emboli, often seen as a rise in creatinine over several weeks, followed by a slow but progressive worsening of renal function that may become severe and irreversible. Cholesterol embolization to the central nervous system is quite uncommon and may be manifested as focal neurological deficits, amaurosis fugax from retinal emboli, paralysis from spinal cord emboli, or a diffuse encephalopathy. Mesenteric embolization may cause abdominal pain, gastrointestinal bleeding, or pancreatitis. Finally, multiple organ systems may be simultaneously involved and mimic vasculitis or bacterial endocarditis.[241]

When the cholesterol embolization syndrome occurs as the consequence of an invasive procedure, the temporal relationship of events often suggests the diagnosis. In the case of spontaneous embolization, however, recognizing the syndrome remains extremely challenging, and diagnosis in the absence of cutaneous manifestations is especially difficult. An elevated erythrocyte sedimentation rate, eosinophilia, and a reduced complement level are helpful in suggesting the diagnosis, but making a definitive diagnosis requires tissue biopsy. Paraffin-fixed sections reveal needle-shaped

clefts in the arteriolar lumina that represent the spaces occupied by cholesterol particles before fixation.

No specific therapy effectively treats cholesterol embolization syndrome. Because cholesterol embolization resembles other atheroembolic phenomena, some have advocated the use of anticoagulant therapy. However, such therapy is typically unsuccessful and may even exacerbate the condition,[245] whereas discontinuing anticoagulation may improve the condition in some cases.[246] Glucocorticoid therapy has also been tried without success. Surgical therapy is generally limited to the amputation of an ischemic or gangrenous extremity. Overall, the prognosis for those suffering cholesterol embolization syndrome is quite poor, with a mortality rate of 38 to 80 percent.[247] [248]

ACUTE AORTIC OCCLUSION

Acute aortic occlusion is an infrequent, but potentially catastrophic, condition with an early mortality of 31 to 52 percent. [249] [250] [251] It is caused by either embolic occlusion of the infrarenal aorta at the bifurcation, known as a "saddle embolus," or acute thrombosis of the abdominal aorta. At least 95 percent of aortic emboli originate from the left side of the heart,[250] typically as a thrombus from the left atrium secondary to atrial fibrillation, particularly in the setting of rheumatic mitral stenosis, or from the left ventricle secondary to myocardial infarction, aneurysm, or dilated cardiomyopathy. Less common cardiac sources of emboli include atrial myxoma, prosthetic valve thrombus, and acute bacterial or fungal endocarditis.[252] Primary thrombosis accounts for the remaining 35 to 92 percent of acute aortic occlusions.[249] [250] Seventy-five to 80 percent of thrombotic

aortic occlusions occur in the setting of underlying severe aortoiliac occlusive disease and are frequently precipitated by a low-flow state secondary to heart failure or dehydration. In those without aortoiliac occlusive disease, a hypercoagulable state may precipitate thrombosis of an abdominal aortic aneurysm and lead to aortic occlusion.[249] [250]

Acute aortic occlusion is in most cases heralded by the sudden onset of excruciating bilateral lower extremity pain--usually radiating from the midportion of the thigh distally--associated with weakness, numbness, and paresthesias. Nonclassic manifestations include sudden onset of bilateral lower extremity weakness, severe hypertension from renal artery involvement, and abdominal pain from mesenteric ischemia. Persistent ischemia may lead to myonecrosis with secondary hypotension, hyperkalemia, myoglobinuria, and acute tubular necrosis. If perfusion is not reestablished within hours, death is almost inevitable.

DIAGNOSIS.

Physical examination reveals cold pale extremities that are cyanotic and often exhibit a mottled, reticulated, and reddish blue appearance that may progress to the blue-black color of gangrene. Pulses are notably absent below the abdominal aorta, and capillary refill is absent. Signs of ischemic neuropathy are present and include symmetrical weakness, loss of all modalities of sensation (usually with demarcation at the level of the midthigh), and diminished or absent deep tendon reflexes. When neurological symptoms predominate, patients are often mistakenly thought to have spinal cord infarction or compression and their ischemic symptoms may initially be overlooked. In fact, as many as 11 to 17 percent of such patients may first undergo neurological or neurosurgical evaluation before the vascular etiology is recognized.[249] [250]

The diagnosis of acute aortic occlusion is confirmed by aortography. While some suggest that all stable patients should undergo the procedure,[249] others advise prompt surgical intervention without angiography if the diagnosis is strongly suspected since added delays increase the likelihood of irreversible ischemic damage to the limbs.[250] [251] Aortography is desirable in the presence of concomitant abdominal pain, hypertension, or anuria to evaluate the possibility of renal and mesenteric arterial involvement.[250]

MANAGEMENT.

Once a clinical diagnosis of acute aortic occlusion is made, intravenous heparin therapy should be initiated while awaiting immediate surgery. A saddle embolus can be removed by using Fogarty balloon-tipped catheters inserted through a transfemoral arterial approach under local anesthesia. If the embolus cannot be retrieved with Fogarty catheters, removal by direct transabdominal aortotomy is undertaken. Patients with thrombotic occlusion generally undergo either direct aortic reconstruction or revascularization with aortofemoral or axillofemoral bypass. Operative mortality for acute aortic occlusion is 31 to 40 percent[250] [251] and as high as 85 percent among those with severe left ventricular dysfunction or a hypercoagulable state.[249] Limb salvage rates are as high as 98 percent.[250] [251] Lifelong anticoagulant therapy is necessary

following surgery in almost all cases to prevent recurrent emboli.[253]

AORTOARTERITIS SYNDROMES

See also Chapter 47 .

BACTERIAL INFECTIONS OF THE AORTA.

Infected aortic aneurysms are rare, with as few as one case per year recently reported from a large medical center.[254] In an effort to avoid confusion with infections truly of fungal origin, the term "infected aneurysm" has gradually replaced the original designation "mycotic aneurysm" used by Osler to define localized dilatation in the wall of the aorta caused by sepsis. While saccular aneurysms are seen most commonly, infections can also cause fusiform and false aneurysms. In a minority of cases, infection may arise in a pre-existent aortic aneurysm, typically atherosclerotic ones. Rarely, one may encounter nonaneurysmal bacterial aortitis.[254] [255]

Pathogenesis.

Aortic infection may arise by several mechanisms. A septic embolus from bacterial endocarditis was once the most common etiology but has become rare in the era of efficacious antibiotic treatment of septicemia. Contiguous spread of infection from adjacent sites is also infrequently seen. The most common cause of an infected aneurysm is direct deposition of circulating bacteria in a diseased, atherosclerotic, or traumatized aortic intima,[254] after which organisms penetrate the aortic wall through breeches in intimal integrity to cause microbial arteritis. Recent reports suggest that the majority of aortic infections occur in patients with impaired immunity as a consequence of chronic disease, immunosuppressive therapy, or immune deficiency.[254] [256]

Microbiology.

Although virtually any organism may infect the aorta, certain bacteria seem to have a proclivity for this site. *Staphylococcus aureus* and *Salmonella* species are consistently the most frequently identified organisms.[257] [258] *Salmonella* commonly infects atherosclerotic arteries[255] but may also adhere to a normal aortic wall and directly penetrate an intact intima.[259] In fact, secondary aortic infection may develop in as many as one-quarter of patients older than 50 years who experience *Salmonella* bacteremia.[259] Other gram-positive organisms, particularly *Pneumococcus*, and gram-negative organisms may also cause infected aortic aneurysms. *Pseudomonas*, *Bacteroides fragilis*, *Campylobacter fetus*, *Neisseria gonorrhoeae*, and fungal infections are seen less often.[254] Aortic infections with unusual organisms are now seen with increasing frequency in the overtly immunocompromised population.[254]

Clinical Manifestations.

Most patients with infected aortic aneurysm are febrile, with extremely high fevers and

rigors being common. Symptoms may arise from localized expansion of an infected aneurysm, which is palpable in as

many as 50 percent of patients and almost always tender.[260] A tender and pulsatile abdominal mass in a febrile patient should therefore be considered an infected aneurysm until proved otherwise.

Leukocytosis and an elevated erythrocyte sedimentation rate are present in most cases. When positive, blood cultures are helpful in suggesting the diagnosis and identifying the pathogen. In any patient with fever of unknown origin and documented *Salmonella* bacteremia, an arterial source of infection should be considered.[255] The absence of positive blood cultures, however, does not exclude the diagnosis of infected aortic aneurysm because cultures have been found to be negative in 25 percent of cases.

Although abdominal ultrasonography may identify the presence of an aortic aneurysm, CT scanning is superior in demonstrating associated pathological findings suggestive of an infectious etiology.[261] However, sometimes the aorta is normal in size when bacterial aortitis is first evaluated, so lack of aneurysmal dilatation does not exclude the diagnosis.[257] In such cases, if a patient's fever, leukocytosis, and pain persist, follow-up imaging should be performed because the aorta may rapidly dilate during the course of the infection. Aortography may also be used to make the diagnosis and is generally performed preoperatively to assist in surgical planning.

The natural history of infected aortic aneurysms is that of expansion and eventual rupture, with extremely rapid progression.[254] [257] *Salmonella* and gram-negative infections have a greater tendency to early rupture and death.[260] Overall mortality from infected aortic aneurysms is over 50 percent despite advances in therapy.[255] [262]

Management.

Infected aortic aneurysms are treated with intravenous antibiotics and surgical excision. The standard surgical approach involves resection of the infected aneurysm and infected retroperitoneal tissue, oversewing of the native aorta as stumps, and restoration of distal perfusion by placement of an extraanatomical bypass graft tunneled through unaffected tissue planes to avoid placing a graft in a contaminated region. Antibiotic therapy must be continued postoperatively for at least 6 weeks. Several reports suggest that in selected patients with localized infection and no gross pus, an effective and simpler surgical approach is in situ reconstruction of the aorta with a prosthetic graft.[256] [262]

PRIMARY TUMORS OF THE AORTA

Primary tumors of the aorta are quite rare, with only 47 cases reported in the literature from 1873 to the present. The frequency of such reports has increased significantly over

the past decade, probably as a result of improvements in noninvasive imaging techniques. Most are diagnosed in the seventh to eighth decades of life. The thoracic aorta and abdominal aorta are involved with equal frequency. In several cases, aortic tumors have appeared in association with previously inserted Dacron aortic grafts.[263] Histologically, the majority of primary aortic tumors are classified as sarcomas, with the malignant fibrous histiocytoma subtype especially common.

The majority of primary aortic tumors arise in the intima[264] and grow along the intimal surface and into the aortic lumen to form polypoid masses (often with superimposed thrombus), but they tend to not invade the aortic wall. Intimal tumors may be characterized by symptoms of vascular obstruction from narrowing of the aortic lumen or, more typically, by signs and symptoms of peripheral embolization identical to those of atherothrombotic emboli. Emboli are commonly a mixture of tumor and thrombus, and the correct diagnosis may remain obscure until histological analysis of an embolectomy specimen is completed.

Figure 40-23 Transesophageal echocardiogram in a long-axis view of the descending thoracic aorta demonstrating a primary tumor of the aorta (arrows) protruding into the lumen. The tumor, which is 3.5 cm in length, involves the intimal layer but does not appear to be invading any farther into the aortic wall.

Less commonly, aortic tumors arise in the medial or adventitial layers of the aortic wall. Such tumors tend to not invade the aortic lumen but, instead, behave as aggressive mass lesions and cause constitutional symptoms or back pain.

Since primary aortic tumors are so uncommon and their features nonspecific, the diagnosis is rarely considered before surgical exploration or necropsy. However, several imaging modalities may be helpful in suggesting the diagnosis. Aortography demonstrates narrowing of the lumen or an intraluminal filling defect in the presence of an intimal tumor, but it may be negative if the tumor is adventitial.[265] Intraaortic biopsy of an intraluminal aortic mass with intravascular biopsy forceps guided by aortography has been reported.[266] [267] CT scanning can detect intimal tumors but may not easily differentiate these masses from protruding atheromas.[265] MRI may better define both the tumor anatomy and the extent of invasion.[268] Finally, the ability of TEE to image the aortic intima may make it especially useful in the detection of intimal tumors of the thoracic aorta[269] (Fig. 40-23) .

Treatment of primary aortic tumors has met with little success. Because the majority of patients initially have metastatic disease, surgical approaches are often only palliative, i.e., to prevent further embolization. Many die secondary to the consequences of multiple emboli to vital organs. Of those undergoing surgical therapy, the large majority die within days to months postoperatively.

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Chapter 41 - Peripheral Arterial Diseases

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Peripheral Arterial Disease

The term *peripheral arterial disease* (PAD) generally refers to atherosclerosis when it obstructs the blood supply to the lower or upper extremities. Other nomenclature includes peripheral arterial occlusive disease and arteriosclerosis obliterans, although the latter term has fallen into disuse. The term *peripheral vascular disease* should be avoided when referring specifically to PAD since it fails to convey the nature of the problem and is more appropriately used to designate a group of diseases affecting blood vessels, including PAD, vasculitis, vasospasm, venous thrombosis, venous insufficiency, and lymphatic disorders.

Traditionally, cardiologists have devoted most of their efforts to diagnosis and treatment of arterial disease in the coronary tree. While diseases of the aorta have often been accorded a place in cardiology training and practice, focus on disease of the peripheral arteries has lagged. PAD is a strong marker of risk for major cardiovascular events since it is frequently associated with coronary and cerebral atherosclerosis. Moreover, symptoms of PAD, including intermittent claudication, jeopardize quality of life and

independence for many patients. In contrast to coronary artery afflictions, PAD is commonly underdiagnosed and undertreated. Thus, practitioners of cardiology have increasing interest in the diagnosis and management of PAD. This chapter aims to provide a framework for an approach to the diagnosis and management of patients with PAD.

EPIDEMIOLOGY

The prevalence of PAD depends on the population studied, the diagnostic method used, and whether symptoms are included to derive estimates. Most epidemiologic studies have used a noninvasive measurement, the ankle/brachial index (ABI), to diagnose PAD. The ABI is the ratio of ankle to brachial systolic blood pressure and is described in greater detail on p. 1464. In relatively large population-based studies conducted in the United States, Europe, and the Middle East, the prevalence of PAD based on an abnormal ABI ranged from 4.6 to 19.1 percent (Table 41-1) .[1] [2] [3] [4] [5] [6] [7] In a free-living population participating in a lipid research clinic protocol, PAD was detected in less than 3 percent of those younger than 60 but in more than 20 percent of those 75 years and older and was 27 percent more prevalent in men than women.[1] In other studies, however, the prevalence was similar or greater in women.[2] [5] Taking these aggregate data into consideration, approximately 8 to 10 million individuals in the United States have PAD.

The prevalence of symptomatic disease in these populations can be assessed by questionnaires specifically designed to elicit symptoms of intermittent claudication. Estimates have varied depending on the age and gender of the population but generally indicate that only one-third to one-half of patients with PAD have symptoms of claudication. In the Whitehall Study of 18,388 male civil servants living in London and aged 40 to 64 years, approximately 1 percent were thought to have claudication.[8] Other estimates of claudication range from 1.6 to 4.5 percent of a population typically older than 40 years.[1] [3] [5] [6] [9] [10] [11] In the Edinburgh Artery Study of 1592 subjects aged 55 to 74 years, 116 new cases of claudication developed over a 5-year period, for an incidence of claudication of 15.5 per 1000 patient-years.[12] The prevalence and incidence of claudication increase with age (Fig. 41-1) and are greater in men than in women in most, but not all studies.[1] [2] [3] [5] [11] [13] [14] [15] In the Framingham Study of 5209 subjects aged 35 to 84 years, the 2-year incidence of claudication was 7.1 per 1000 for men and 3.6 per 1000 for women.[16]

Less information is available regarding the incidence of critical limb ischemia. In a prospective 7-year study of hospitals in northern Italy, the incidence of critical limb ischemia was 450 per million population per year, and the incidence of amputation was 112 per million per year.[17] Similarly, the Vascular Surgery Society of Great Britain estimated the incidence of critical limb ischemia in Britain and Ireland at 400 cases per million population per year. In Denmark, approximately 250 per million population per year underwent amputation because of critical limb ischemia.[18]

Contribution of Risk Factors

The well-known modifiable risk factors associated with coronary atherosclerosis also

contribute to atherosclerosis of the peripheral circulation. Cigarette smoking, diabetes mellitus, dyslipidemia, hypertension, and hyperhomocysteinemia increase the risk of PAD (Table 41-2) .

SMOKING.

Data derived from several observational studies (including the Edinburgh Artery Study, the Framingham

TABLE 41-1 -- PREVALENCE OF PERIPHERAL ARTERIAL DISEASE

STUDY/LOCATION	POPULATION (No.)	AGE (yr)	PREVALENCE (%)
San Diego[1]	613	38-82	11.7
Jerusalem Lipid Research Clinic Prevalence Study[2]	1592	35	4.6
Edinburgh Artery Study[3]	1592	55-74	9.0
Cardiovascular Health Study[4]	5084	65	12.4
Rotterdam Study[5]	7715	55	19.1
Limburg PAOD Study[6]	3650	40-78	12.4
Strong Heart Study[7]	4549	45-74	5.3

Figure 41-1 Age-related incidence of intermittent claudication derived from large population-based studies. (From Dormandy JA, Rutherford RB: Management of peripheral arterial disease [PAD]. TASC Working Group. J Vasc Surg 31[Suppl]:1-296, 2000.)

Heart Study, and the Cardiovascular Health Study, among others) indicate a twofold to fivefold increased risk of PAD in smokers.[2] [4] [10] [11] [14] [19] [20] [31] In the Whitehall Study, approximately 84 percent of patients with claudication were current smokers or ex-smokers,[8] and in another large recent study, 90 percent of patients with PAD were current or former smokers.[32] Progression of disease to critical limb ischemia and limb loss is more likely to occur in patients who continue to smoke than in those who stop.[33] Smoking may even increase the risk of development of PAD more than it does coronary artery disease.[19] [34]

DIABETES MELLITUS.

In patients with diabetes mellitus, PAD is often extensive and severe, and these patients have a greater propensity for vascular calcification. Involvement of the femoral and popliteal arteries is similar to that of nondiabetic persons, but distal disease affecting the tibial and peroneal arteries occurs more frequently. The risk of development of PAD increases threefold to fourfold in patients with diabetes mellitus.[4] [14] [16] [19] [21] In the Framingham cohort, glucose intolerance contributed more as a risk factor for claudication than it did for coronary artery disease or stroke.[34]

LIPID DISORDERS.

Abnormalities in lipid metabolism are also associated with an increased prevalence of PAD. Elevations in total or low-density lipoprotein (LDL) cholesterol increased the risk of PAD and claudication in some studies but not in others.[2] [10] [13] [14] [35] In a large Israeli study involving 10,059 men aged 40 to 65 years, the odds ratio for development of claudication was 1.35 for each increase in serum cholesterol of 50 mg/dl.[10] Similar observations were made in the Framingham Heart Study, in which the odds ratio for claudication was 1.2 for each 40-mg/dl increase in total cholesterol.[14] In a cohort of patients participating in a lipid research clinic protocol, however, LDL cholesterol was not associated with PAD based on a multiple logistic regression analysis that included cigarette smoking, blood pressure, glucose, and obesity. Hypertriglyceridemia independently predicts risk for PAD.[36] [37] Increased levels of lipoprotein (a) impart a twofold increased risk of PAD, with

TABLE 41-2 -- RISK OF PERIPHERAL ARTERIAL DISEASE IN PERSONS WITH MODIFIABLE RISK FACTORS

RISK FACTOR	ESTIMATED RELATIVE RISK
Cigarette smoking[2] [4] [10] [19] [20]	2.0-5.0
Diabetes mellitus[4] [14] [16] [19] [21]	3.0-4.0
Hypertension[14] [16] [19]	1.1-2.2
Hypercholesterolemia (per 40- to 50-mg/dl increase in total cholesterol)[10] [14]	1.2-1.4
Fibrinogen (per 0.7-gm/liter increase in fibrinogen)[22] [23] [24] [25] [26]	1.35
C-reactive protein[27]	2.1
Hyperhomocysteinemia[28] [29] [30]	2.0-3.2

higher levels associated with a greater risk for critical limb ischemia.[38]

HYPERTENSION.

Hypertension increased the risk of claudication 2.5-fold in men and 4-fold in women in the Framingham Heart Study,[16] and the risk increased proportionally with the severity of

hypertension.[14] [16] Similarly, in the Edinburgh Artery Study, elevations in systolic blood pressure correlated with PAD. However, this finding has not been consistently shown in all epidemiological studies. In the British Whitehall Study and a large Finnish study, hypertension was not found to be associated with claudication.[8] [13]

HYPERHOMOCYSTEINEMIA.

Hyperhomocysteinemia increases the risk of atherosclerosis by approximately twofold to threefold.[28] [29] [30] In a meta-analysis of studies relating homocysteine to atherosclerotic disease, the odds ratio for PAD in patients with increased homocysteine levels was 6.8.[30] High levels of homocysteine have been detected in 30 to 40 percent of patients with PAD.[39] [40] Prospective studies have not consistently confirmed a relationship of hyperhomocysteinemia with cardiovascular events, however (see Chap. 31) . Plasma levels of B complex vitamins, including folate, cobalamin, and pyridoxal 5 -phosphate, all inversely relate to the plasma homocysteine concentration, and patients taking B vitamin supplements have a lower risk of vascular disease.[29]

FIBRINOGEN.

An increase in fibrinogen is also associated with an increased risk of PAD.[11] [22] [23] [24] [41] The Edinburgh Artery Study noted a 35 percent increased risk for PAD over 5 years for each 0.70-gm/liter increase in fibrinogen.[25] [26] Patients with PAD have elevated levels of C-reactive protein, a serological marker of systemic inflammation. In the Physicians' Health Study, the relative risk of development of PAD among men in the highest quartile for C-reactive protein concentration was 2.1[27] (see also Chap. 31) .

The risk of PAD and intermittent claudication developing increases progressively with the burden of contributing factors. In the Framingham Heart Study, the occurrence of claudication in men whose risk factor was smoking versus nonsmoking was 2.6 versus 0.8 per 8 years per 1000 population.[16] In male smokers who were also hypertensive, hypercholesterolemic, and diabetic, the risk was 44.3 per 8 years per 1000 (Fig. 41-2) .[16] Similar observations have been made in women.

PATHOBIOLOGY

Heterogeneity of Blood Vessels in Different Circulatory Beds

Atherosclerosis preferentially affects certain locations in the circulation. As discussed in Chapter 30 , atheromatous lesions tend to form at flow dividers and branch points in arteries and usually spare veins. In the last several years, progress has been made in understanding the link between hydrodynamics of the circulation, the cellular and molecular

Figure 41-2 The incidence of intermittent claudication in the Framingham Heart Study in smokers and nonsmokers is compounded by an increased burden of risk factors. (From Murabito JM, D'Agostino RB, Silbershatz H, et al: Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation 96:44-49, 1997. By permission of the American Heart Association, Inc.)

mechanisms of atherosclerosis, and the atheroprotective functions of vascular wall cells. Chapter 30 discusses the focality of atherosclerosis in terms of local hemodynamic differences. However, questions remain: Are blood vessels intrinsically different in different regions of the circulation? Do regional variations in the propensity for atherosclerosis merely depend on the external hemodynamic forces that impinge on them? Indeed, vessels in different beds have distinct morphology, physiology, and pharmacology and therefore intrinsic heterogeneity. Recent work has elucidated the biological basis of differences among blood vessels. This section will consider, in turn, new information regarding the development of blood vessels related to arterial heterogeneity, differences in functions of blood vessels depending on the circulatory bed, and finally, whether the mechanisms leading to clinical manifestations of arterial disease vary from one circulatory bed (e.g., the coronary circulation) to another and in different arteries (e.g., the carotid or the distal aorta).

DEVELOPMENTAL BIOLOGY OF HETEROGENEITY AMONG BLOOD VESSELS

Endothelial cells have a common origin but acquire bed-specific characteristics during development. The endothelial cells that form the inner lining of all blood vessels arise during embryogenesis from regions known as the blood islands located on the embryo's periphery. Angioblasts, which are predecessors of endothelial cells, share this site with the precursors of blood cells. Despite arising from the same site, cells display considerable heterogeneity even during embryological and early postnatal development. Although presumably derived from a common precursor, the signals that endothelial cells encounter during vessel development differ. As rudimentary blood vessels begin to form, endothelial precursors interact with the surrounding cells. This interchange permits spatial and temporal gradients of various stimuli and their receptors on endothelial cells, which leads to heterogeneity of this cell type in the adult.

Differential expression of endothelial genes in various types of blood vessels depend on transcriptional regulation by the local environment. For example, the promoter region of the gene that encodes von Willebrand factor directs expression of brain and heart microvessels in the endothelium but not in larger arteries.[42] Indeed, coculture of endothelial cells with cardiac myocytes, but not other cell types, could selectively activate a von Willebrand factor gene promoter construct. Likewise, endothelial nitric oxide synthase gene activity in the heart shows bed-specific regulation.[43] A recently recognized family of tyrosine kinase receptors known as EPH and their ligands known as epherins display heterogeneous expression in arterial versus venous endothelial cells during development.[44] These examples illustrate how the common precursor of endothelial cells shows molecular diversity early in life that depends on its location in the

circulation.

SMOOTH MUSCLE CELLS DERIVE FROM MULTIPLE, LOCAL SOURCES DURING DEVELOPMENT

In contrast to endothelial cells, which derive from a common precursor, smooth muscle cells can arise from many sources. After endothelial cells form tubular anlage, or rudimentary, precursor of blood vessels, they recruit the cells that will become smooth muscle, or pericytes (smooth muscle-like cells associated with microvessels). In the descending aorta and arteries of the lower half of the body, regional mesoderm serves as the source of smooth muscle precursors. Mesodermal cells in somites give rise to the smooth muscle cells that invest much of the distal aorta and its branches. In arteries of the upper part of the body, however, smooth muscle cells actually derive from a completely different germ layer, neuroectoderm rather than mesoderm. Before the neural tube closes, neuroectodermal cells migrate and become the precursors of smooth muscle cells in the ascending aorta and some of its branches, including the carotid arteries.[45] Smooth muscle cells in the coronary arteries are derived from mesoderm, but in a special way. The precursors of coronary artery smooth muscle cells arise from a structure known as the proepicardial organ.[46] [47]

As in the case of endothelial cells, smooth muscle cells show molecular heterogeneity early during development. For example, the promoter of a characteristic smooth muscle gene known as SM22 drives gene expression in venous but not arterial smooth muscle cells during embryogenesis.[48] Much of the localization of structures in embryos depends on a family of genes known as homeobox genes. Deletion of a pair of homeobox genes known as *Prx1/Prx2* that are involved in mesenchymal pattern development causes selective impairment in development of the great vessels and the ductus arteriosus while sparing morphogenesis of other vessels.[49] Transcription factors also play an important role in determining the phenotype of cells. A specific transcription factor known as dHAND signals the recruitment of mesenchyme by endothelial cells in an anatomically heterogeneous manner during development. In particular, dHAND regulation selectively participates in the recruitment of mesenchyme in upper body blood vessels versus those of the more caudal portions of the embryo.[50]

CLINICAL IMPLICATIONS OF VASCULAR DEVELOPMENTAL BIOLOGY.

Far from being of mere theoretical concern, the developmental biology of the arterial tree has important clinical implications regarding issues that arise in daily practice. The distinct embryonic origins of smooth muscle cells in various arteries may help explain why some regions of the arterial tree are particularly prone to atheroma formation. While local hydrodynamics doubtless controls the expression of genes that protect against or promote atherogenesis (see Chap. 30) , the cellular substrate acted on by biomechanical forces varies as described above.

Intimal cushions, which consist of expanded regions populated by smooth muscle cells and extracellular matrix (Fig. 41-3) , develop in very interesting regions of the arterial tree early in life. Two regions of intimal cushion formation of particular consequence for cardiologists are the proximal left anterior descending coronary artery and the carotid siphon.[51] [52] The intimal cushion in the proximal left anterior descending coronary artery

begins to form even during intrauterine life. It progresses rapidly in early postnatal life and leads to intimal cushions in the proximal left anterior coronary artery in all humans by 2 years of age.[51] It remains unclear to what extent lineage differences versus local hemodynamic forces contribute to the formation of these intimal cushions in arteries prone to the development of atherosclerosis. These cushions of smooth muscle and connective tissue form the "soil" in which atheromatous lesions can grow in later life.[53]

HETEROGENEITY IN VASCULAR FUNCTIONS.

The functions of blood vessels differ in various regions of the circulation as evidenced by the preferential effects of many vasoactive drugs commonly used in the practice of cardiology on selected vascular beds. Nitrates dilate both arteries and veins, whereas other vasodilators, such as hydralazine, act primarily as arterial vasodilators. The well-recognized differences in clinical outcomes of saphenous vein and internal mammary artery bypass grafts furnish another example

Figure 41-3 An intimal cushion shown in a cross section through the internal carotid artery of a 10-week-old male infant. Areas where intimal cushions form in early life are prone to the development of atheroma more commonly in later years. The bar shows 0.5 mm. (From Weninger WJ, Muller GB, Reiter C, et al: Intimal hyperplasia of the infant parasellar carotid artery: A potential developmental factor in atherosclerosis and SIDS. Circ Res 85:970-975, 1999. By permission of the American Heart Association, Inc.)

of clinically relevant heterogeneity among vessels. Internal mammary arteries release more nitric oxide than do saphenous veins. In addition, saphenous veins produce more vasoconstrictor endothelial-derived cyclooxygenase products than do internal mammary arteries. Such differences may help explain the superior clinical outcomes with internal mammary grafts versus autologous venous bypass grafts.[54]

Indeed, the reactions of blood vessels or vascular cells from various regions of the circulation sometimes differ directionally. The pulmonary vasoconstrictive versus systemic vasodilator response to hypoxia and the disparate response of the cerebral versus the systemic arterial circulation to carbon dioxide are commonly encountered examples. Neuroectoderm-derived smooth muscle cells in upper body blood vessels grow in response to transforming growth factor-beta; however, mesenchymal-derived smooth muscle cells from lower body arteries actually show growth inhibition when exposed to this mediator.[55] Perhaps, the different embryonic origins of smooth muscle cells in the ascending versus the descending aorta explain why certain gene defects express themselves primarily in the ascending aorta. In Marfan syndrome, for example, the fibrillin mutation characteristically involves the ascending aorta first (see also Chap. 56) . Likewise, in Williams syndrome, elastin is genetically defective throughout the body, yet the vascular phenotype of these patients is localized to the supervalvular

portion of the ascending aorta.[45]

Heterogeneity of the Clinical Manifestations of Arterial Disease

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study collected arterial specimens from Americans younger than 35 years who died of non-cardiac causes. This study found that fatty streaks and raised arterial lesions initially localize in the dorsal portion of the abdominal aorta. Involvement of the thoracic aorta with fatty streaks or early atheroma follows lesion formation in the abdominal aorta. The PDAY data suggest that the formation of coronary atheroma actually lags behind the development of fatty lesions in the aorta.[56] [57]

The most dreaded clinical consequence of atherosclerosis is thrombosis, the cause of most myocardial infarctions and many strokes. Physical disruption of the atherosclerotic plaque causes most fatal coronary events. The role of plaque disruption as a cause of thrombosis in other arterial beds has received less attention. The discussion above has highlighted the developmental and anatomical reasons why coronary arteries may differ from peripheral arteries. In addition, the hemodynamic stresses impinging on lesions in the coronary versus the peripheral arterial tree differ as well. Notably, most coronary artery flow occurs during diastole, whereas peak pressure and flow in peripheral arteries occur during systole. Thus, the underlying mechanism of the thrombotic complications of atheroma might well differ in coronary versus peripheral arteries.

In the aorta, mural thrombi seldom develop into occlusive clots because of the high flow. Nonetheless, aortic plaque frequently ruptures, and aortic thrombi are recognized as a clinically important source of embolic disease (Fig. 41-4). (Figure Not Available) Plaque in the aorta encounters high "hoop" (circumferential) stress as a result of the large radius, according to the Laplace relationship. This difference may account for the prevalence of disrupted plaque in an atherosclerotic aorta. Recent evidence suggests that plaque rupture also underlies symptoms of carotid arterial disease. In one study, histopathological evaluation of carotid artery specimens removed by endarterectomy revealed plaque rupture in 74 percent of symptomatic versus only 32 percent of asymptomatic patients.[58] The degree of stenosis was similar in both symptomatic and asymptomatic individuals in this study. Ulcerated plaque with superimposed thrombus was found in six of seven occluded internal carotid arteries in a neuropathological autopsy series.[59] Features

Figure 41-4 (Figure Not Available) Atherosclerotic aorta of a patient with atheroemboli. Multiple protruding, shaggy atheromas with superimposed mural thrombi are present. (Courtesy of R.M. Mitchell, M.D., Ph.D., Department of Pathology, Brigham and Women's Hospital, Boston.)

associated with vulnerability of coronary plaque, including foam cells and thinning of the fibrous cap, are more frequent in symptomatic than in asymptomatic carotid plaque.[58] As in unstable coronary plaque, inflammatory cells infiltrate and are activated (determined by expression of the histocompatibility antigen HLA-DR). The proportion of

active inflammatory cells is consistently higher in ruptured plaque than in asymptomatic carotid plaque with a similar degree of stenosis.[60]

An independent line of clinical evidence supports a commonality in the mechanisms of complication shared by carotid and coronary arteries. A recent large study dichotomized patients with symptomatic carotid artery lesions into those with and those without irregularity of the carotid lesion by angiography. Over 10 years of follow-up, those with irregular carotid lesions had a greater than twofold higher cumulative incidence of non-stroke-related vascular death (mostly caused by coronary events) than did those with smooth lesions.[61] Nonvascular deaths and the risk factors assessed in this study did not differ between groups. Similar mechanisms are likely to account for acute thromboses in peripheral arteries, although detailed investigations are not available. Despite the considerable biological and functional heterogeneity among arterial beds, the mechanisms causing the most important clinical manifestations appear to be similar.

PATHOPHYSIOLOGY OF LIMB ISCHEMIA

Pathophysiological considerations in patients with PAD must take into account the balance of the circulatory supply of nutrients to the skeletal muscle and the oxygen and nutrient demand of skeletal muscle (Table 41-3) .

FACTORS REGULATING BLOOD SUPPLY(see alsoChap. 34)

The primary determinant of inadequate blood supply to the extremity is a flow-limiting lesion of a conduit artery. Flow through an artery is directly proportional to perfusion pressure and inversely proportional to vascular resistance. If atherosclerosis causes a stenosis, flow through the artery is reduced as described in the Poiseuille equation, in which Q=Delta$P$pir^4 8eta$l$, where Delta$P$ is the pressure gradient across the stenosis, r is the radius of the residual lumen, eta is blood viscosity, and l is the length of the vessel affected by the stenosis. As the severity of a stenotic lesion increases, flow becomes progressively reduced. The pressure gradient across the stenosis increases in a nonlinear manner, thus emphasizing the importance of a stenosis at high blood flow rates. Usually, a blood pressure gradient exists at rest if the stenosis reduces luminal diameter by more than 50 percent because kinetic energy is lost as turbulence develops.[62] A stenosis that does not cause a pressure gradient at rest may cause a gradient during exercise, when blood flow rises consequent to higher cardiac output and decreased vascular resistance. Thus, as flow through a stenosis increases, distal perfusion pressure is not maintained. Also, as the metabolic demand of exercising muscle outstrips its blood supply, local metabolites, including adenosine, nitric oxide, potassium, and hydrogen ion, accumulate and peripheral resistance vessels dilate.

TABLE 41-3 -- PATHOPHYSIOLOGICAL CONSIDERATIONS IN PERIPHERAL ARTERIAL DISEASE

Factors regulating blood supply to limb
Flow-limiting lesion (stenosis severity, inadequate collaterals)

Impaired vasodilation (decreased nitric oxide and reduced responsiveness to vasodilators)

Accentuated vasoconstriction (thromboxane, serotonin, angiotensin II, endothelin, norepinephrine)

Abnormal rheology (reduced red blood cell deformability, increased leukocyte adhesiveness, platelet aggregation, microthombosis, increased fibrinogen)

Altered skeletal muscle structure and function

Axonal denervation of skeletal muscle

Loss of type II, glycolytic fast twitch fibers

Increased mitochondrial enzymatic activity

This response results in a further drop in perfusion pressure since the stenosis limits flow. In addition, intramuscular pressure rises during exercise and may exceed the arterial pressure distal to an occlusion and cause blood flow to cease.[62] Flow through collateral blood vessels is usually adequate to meet the resting metabolic needs of skeletal muscle tissue, but it is not enough during exercise.

Functional abnormalities in vasomotor reactivity may also interfere with blood flow. The vasodilator capability of both conduit and resistance vessels is impaired in patients with peripheral atherosclerosis. Normally, arteries dilate in response to pharmacological and biochemical stimuli, such as acetylcholine, serotonin, thrombin, or bradykinin, as well as in response to shear stress induced by increases in blood flow. This vasodilator response results from the release of biologically active substances from the endothelium, particularly nitric oxide (see also Chap. 34) . The vascular relaxation of a conduit vessel that occurs after a flow stimulus, such as that induced by exercise, may facilitate the delivery of blood to exercising muscles in healthy persons. Vasodilation subsequent to flow or pharmacological stimuli does not occur in the atherosclerotic femoral arteries and calf resistance vessels of patients with PAD.[63] This failure of vasodilation might prevent an increase in nutritive blood supply to exercising muscle since endothelium-derived nitric oxide has been shown to contribute to hyperemic blood volume following an ischemic stimulus.[63] [64] Preliminary studies have suggested that L-arginine, the precursor for endothelium-derived nitric oxide, increases muscle blood flow and improves claudication distance in patients with PAD, further supporting the contention that endothelium-dependent vasodilation is abnormal in these individuals.[65] [66] It is not known whether vasodilator function with respect to prostacyclin, adenosine, or ion channels is abnormal in peripheral atherosclerotic arteries. Endogenous vasoconstrictor substances such as prostanoids and other lipid mediators, thrombin, serotonin, angiotensin II, endothelin, and norepinephrine may interfere with vasodilation.

SKELETAL MUSCLE STRUCTURE AND METABOLIC FUNCTION

Electrophysiological and histopathological examination has found evidence of partial axonal denervation of skeletal muscle in legs affected by PAD.[67] Type I, oxidative slow-twitch fibers are preserved, but type II, or glycolytic, fast twitch fibers are lost in the skeletal muscle of patients with PAD.[68] Loss of type II fibers is associated with

decreased muscle strength and reduced exercise capacity.[68] Within skeletal muscle, metabolism shifts to anaerobic earlier during exercise and it persists longer after cessation of exercise. Patients with claudication have increased lactate release and accumulation of acylcarnitines during exercise, indicative of ineffective oxidative metabolism.[69] [70] Yet, mitochondrial enzymatic activity is increased in the skeletal muscle of patients with claudication, possibly reflecting a metabolic adaptation to the reduced blood supply.[71] [72]

Pathophysiology of Critical Limb Ischemia

Abnormalities in the microcirculation contribute to the pathophysiology of critical limb ischemia. The number of perfused skin capillaries is reduced in patients with severe limb ischemia.[73] Other potential causes of decreased capillary perfusion in this condition include reduced red cell deformability, increased leukocyte adhesivity, platelet aggregates, fibrinogen, microthrombosis, excessive vasoconstriction, and interstitial edema (Fig. 41-5) .[74] [75] [76] Intravascular pressure may also be decreased because precapillary arterioles are dilated as a result of locally released vasoactive metabolites.[77]

CLINICAL FEATURES

Symptoms

INTERMITTENT CLAUDICATION.

The two cardinal symptoms of PAD are intermittent claudication and pain at rest. The term *claudication* is derived from the Latin word *claudicare,* to limp. Intermittent claudication is characterized by pain, ache, a sense of fatigue, or other discomfort that occurs in the affected leg during exercise, particularly walking, and resolves with rest. Claudication occurs when skeletal muscle oxygen demand during effort exceeds the blood supply and results from activation of local sensory receptors

Figure 41-5 Schematic representation of potential pathophysiological mechanisms that lead to microvascular obstruction in patients with critical limb ischemia. (From Second European Consensus Document on chronic critical leg ischemia. Circulation 84[Suppl 4]:1-26, 1991. By permission of the American Heart Association, Inc.)

by the accumulation of lactate or other metabolites. The location of the symptom often relates to the site of the most proximal stenosis. Buttock, hip, or thigh claudication is typical of patients with obstruction of the aorta and iliac arteries. Calf claudication occurs in patients with femoral and popliteal artery stenoses. The gastrocnemius muscle consumes more oxygen during ambulation than do other muscle groups in the leg and

hence causes the most frequent symptom reported by patients. Ankle or pedal claudication occurs in patients with tibial and peroneal artery disease. Similarly, stenoses of the subclavian, axillary, and brachial arteries may cause shoulder, biceps, or forearm claudication, respectively. Symptoms should resolve several minutes following cessation of effort. Calf and thigh pain that occurs at rest, such as nocturnal cramps, should not be confused with claudication and is not a symptom of PAD. The history obtained from claudicants should note the distance walked, speed, and incline that precipitates claudication to evaluate disability and to provide a baseline qualitative measure with which to determine stability, improvement, or deterioration during subsequent encounters with the patient. Symptoms other than claudication can limit functional capacity.[78] Patients with PAD walk more slowly and have less walking endurance than do patients without PAD.[79] [80]

Several questionnaires have been developed to assess the presence and severity of claudication. The Rose Questionnaire was initially developed to diagnose both angina and intermittent claudication in epidemiological surveys.[81] It queries whether pain develops in either calf with walking and whether it occurs at rest, while walking at an ordinary or hurried pace, or when walking uphill. Several modifications of this questionnaire have been made, including the Edinburgh Claudication Questionnaire and the San Diego Claudication Questionnaire,[82] [83] which are both more sensitive and specific in comparison to a physician's diagnosis of intermittent claudication based on walking distance, walking speed, and nature of the symptoms. A more recently validated instrument, the Walking Impairment Questionnaire, asks a series of questions and assigns a point score based on walking distance, walking speed, and nature of the symptoms.[84]

Limb claudication may occasionally result from nonatherosclerotic causes of arterial occlusive disease (Table 41-4) . Several of these causes are discussed later in the chapter and include arterial embolism; vasculitides such as thromboangiitis obliterans (TAO), Takayasu arteritis, or giant cell arteritis; aortic coarctation; fibromuscular dysplasia; irradiation; and extravascular compression secondary to arterial entrapment or an adventitial cyst (see also Chap. 67) .

Several nonvascular causes of exertional leg pain should be considered in patients with symptoms suggestive of intermittent claudication (Table 41-4) . Lumbosacral radiculopathy resulting from degenerative joint disease, spinal stenosis, and herniated discs may cause pain in the buttock, hip, thigh, calf, and/or foot with walking, often after very short distances or even with standing.[85] [86] The term *neurogenic pseudoclaudication* has been used to describe this symptom. Lumbosacral spine disease and PAD each affect the elderly, and as such, both may be present in the same individual. Arthritis of the hips and knees also provokes leg pain with walking. Typically, the pain is localized to the affected joint and may be elicited on physical examination by palpation and range-of-motion maneuvers. Rarely, skeletal muscle disorders such as myositis can cause exertional leg pain. Muscle tenderness, abnormal neuromuscular examination findings, elevated skeletal muscle enzymes, and a normal pulse examination should distinguish myositis from PAD. McArdle syndrome, characterized by a deficiency of skeletal muscle phosphorylase, can cause symptoms mimicking the claudication of PAD. Patients with chronic venous regurgitation may complain of leg discomfort with exertion, a condition designated venous claudication.[87] [88] [89] Venous

hypertension during exercise increases resistance and limits blood flow. In the case of venous insufficiency, the elevated extravascular pressure caused by interstitial edema further diminishes capillary perfusion. A physical examination demonstrating peripheral edema, venous stasis pigmentation, and occasionally, venous varicosities will identify this unusual cause of exertional leg pain.

REST PAIN.

Pain at rest occurs in patients with critical limb ischemia in whom the resting metabolic needs of the tissue are not adequately met by the available blood supply. Typically, patients complain of pain or paresthesias in the foot or toes of the affected extremity. This discomfort is worsened by leg elevation and improved by leg dependency, as might be anticipated by the respective effects of gravity on perfusion pressure. The pain may be particularly severe at sites of skin fissuring, ulceration, or necrosis. Of

TABLE 41-4 -- DIFFERENTIAL DIAGNOSIS OF EXERTIONAL LEG PAIN

Vascular Causes
Atherosclerosis
Thrombosis
Embolism
Vasculitis
Thromboangiitis obliterans
Takayasu arteritis
Giant cell arteritis
Aortic coarctation
Fibromuscular dysplasia
Irradiation
Extravascular compression
Arterial entrapment (e.g., popliteal artery entrapment, thoracic outlet syndrome)
Adventitial cysts
Nonvascular Causes
Lumbosacral radiculopathy
Degenerative arthritis
Spinal stenosis
Herniated disc
Arthritis
Hip, knees
Venous insufficiency
Myositis
McArdle syndrome

Figure 41-6 *Left,* Typical arterial ulcer. It is a discrete, circumscribed, necrotic ulcer located on the great toe. *Right,* Trophic ulcer in a patient with diabetes mellitus located on the volar surface of the foot beneath the head of the first metatarsal bone, a typical area of pressure; its base has granulation tissue.

ten, the skin is very sensitive, and even the weight of bedclothes or sheets elicits pain. Patients may sit on the edge of the bed and dangle their legs to alleviate the discomfort. However, patients with ischemic or diabetic neuropathy may have little or no pain despite the presence of severe ischemia.

Critical limb and digital ischemia may result from arterial occlusions other than those caused by atherosclerosis. Such conditions include vasculitides such as TAO, connective tissue disorders such as systemic lupus erythematosus and scleroderma, vasospasm, atheromatous embolism, and acute arterial occlusion caused by thrombosis or embolism. Many of these disorders are discussed later in this chapter. Acute gouty arthritis, trauma, and sensory neuropathy such as that caused by diabetes mellitus, lumbosacral radiculopathy, and reflex sympathetic dystrophy can cause foot pain. Leg ulcers also occur in patients with venous insufficiency and sensory neuropathy, particularly that related to diabetes. These ulcers are easily distinguished from arterial ulcers, which are described below. A venous ulcer is usually located near the medial malleolus, its border is irregular, and its base is pink with granulation tissue. The pain accompanying venous ulcers is milder than that of arterial ulcers. Neurotrophic ulcers occur with pressure or trauma, usually on the sole of the foot. These ulcers are deep, frequently infected, and not usually painful because of the loss of sensation (Fig. 41-6 , right panel).

Physical Findings

A careful vascular examination includes palpation of pulses and auscultation of accessible arteries for bruits. Pulses that are readily palpable in healthy individuals include the brachial, radial, and ulnar arteries of the upper extremity and the femoral, popliteal, dorsalis pedis, and posterior tibial arteries of the lower extremities. The aorta also can be palpated in asthenic persons. A decreased or absent pulse provides insight into the location of arterial stenoses. For example, a normal right femoral pulse but absent left femoral pulse suggests the presence of left iliofemoral arterial stenosis. A normal femoral artery pulse but absent popliteal artery pulse would indicate a stenosis in the superficial femoral artery or proximal popliteal artery. Similarly, disease of the anterior and posterior tibial arteries may be inferred when the popliteal artery pulse is present but the dorsalis pedis and posterior tibial pulses, respectively, are not palpable. Bruits are often indicative of accelerated blood flow velocity and turbulence at sites of stenosis. A stethoscope should be used to auscultate the supraclavicular and infraclavicular fossae for evidence of subclavian artery stenosis; the abdomen, flank, and pelvis for evidence of stenoses in the aorta and its branch vessels; and each groin for evidence of femoral artery stenoses. Pallor may be elicited on the soles of the feet of some patients with PAD by performing a maneuver in which the feet are elevated above the level of the heart and the calf muscles are exercised by repeated dorsiflexion and plantar flexion of the ankle. The legs are then placed in the dependent position and the time to the onset of hyperemia and venous distention is measured. Each of these parameters is dependent on the rate of blood flow, which is influenced by the severity of

the stenosis and the adequacy of collateral vessels.

Muscle atrophy may be apparent in the legs of patients with chronic aortoiliac disease. Additional signs of chronic low-grade ischemia include hair loss, thickened and brittle toenails, smooth and shiny skin, and subcutaneous fat atrophy of the digital pads. The skin is cool in patients with severe limb ischemia, and they may have petechiae, persistent cyanosis or pallor, dependent rubor, pedal edema resulting from prolonged dependency, skin fissures, ulceration, or gangrene. Arterial ulcers typically have a pale base with irregular borders and usually involve the tips of the toes or the heel of the foot or develop at sites of pressure (Fig. 41-6, left panel). These ulcers vary in size and may be as small as 3 to 5 mm.

Categorization of PAD

Patients with PAD may be classified according to the severity of the symptoms and abnormalities detected on physical examination. Categorization of the clinical manifestations of PAD improves communication among professionals caring for these patients and provides a structure for defining guidelines for therapeutic intervention. The traditional scheme described by Fontaine classified patients in one of four stages progressing from asymptomatic to critical limb ischemia (Table 41-5) . A contemporary, more descriptive classification has been adopted by several professional vascular societies and includes asymptomatic patients, three

TABLE 41-5 -- FONTAINE CLASSIFICATION OF PERIPHERAL ARTERIAL DISEASE

STAGE	SYMPTOMS
I	Asymptomatic
II	Intermittent claudication
IIa	Pain free, claudication walking >200 meters
IIb	Pain free, claudication walking <200 meters
III	Rest and nocturnal pain
IV	Necrosis, gangrene

TABLE 41-6 -- CLINICAL CATEGORIES OF CHRONIC LIMB ISCHEMIA

GRADE	CATEGORY	CLINICAL DESCRIPTION
	0	Asymptomatic, not hemodynamically correct
I	1	Mild claudication
	2	Moderate claudication

	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ulcer
III	6	Major tissue loss extending above the transmetatarsal level, functional foot no longer salvageable

Adapted from Rutherford RB, Baker JD, Ernst C, et al: Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg 26:517-538, 1997.

grades of claudication, and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss (Table 41-6) . [90]

DIAGNOSTIC TESTS

Segmental Pressure Measurement

One of the most useful and simplest noninvasive tests to evaluate the presence and severity of stenoses in the peripheral arteries is the measurement of systolic blood pressure along selected segments of each extremity. In the lower extremities, pneumatic cuffs are placed on the upper and lower portions of the thigh, on the calf, above the ankle, and often over the metatarsal area of the foot. Likewise, in the upper extremity, pneumatic cuffs are placed on the upper part of the arm over the biceps, on the forearm below the elbow, and at the wrist. Systolic blood pressure at each respective limb segment can be measured by first inflating the pneumatic cuff to suprasystolic pressure and then determining the pressure at which blood flow occurs during cuff deflation. The onset of flow can be assessed by placing a Doppler ultrasound flow probe over an artery distal to the cuff. In the lower extremities, it is most convenient to place the Doppler probe on the foot over the posterior tibial artery as it courses inferior and posterior to the medial malleolus or over the dorsalis pedis artery on the dorsum of the metatarsal arch. In the upper extremities, the Doppler probe can be placed over the brachial artery in the antecubital fossa or over the radial and ulnar arteries at the wrist.

Left ventricular contraction creates the kinetic energy for blood pressure, which is maintained throughout the large and medium-sized vessels. Systolic blood pressure in the more distal vessels may be higher than that in the aorta and proximal vessels because of reflection of blood pressure waves.[91] Stenosis can cause loss of pressure energy as a result of increased frictional forces and turbulence at the site of the stenosis. Approximately 90 percent of the cross-sectional area of the aorta must be narrowed before a pressure gradient develops. In smaller vessels such as the iliac and femoral arteries, a 70 to 90 percent decrease in cross-sectional area will cause a resting pressure gradient sufficient to decrease systolic blood pressure distal to the stenosis. Taking into consideration the precision of this noninvasive method and the variability in blood pressure over even short periods, a blood pressure gradient in excess of 20 mm Hg between successive cuffs is generally used as evidence of arterial stenosis in the

lower extremity, whereas a 10-mm Hg gradient between sequential cuffs in the upper extremity is indicative of stenosis (Table 41-7) . Systolic blood pressure in the toes and fingers approximates 60 percent of the systolic blood pressure at the ankle and wrist, respectively, as additional pressure energy is lost in the smaller distal vessels.

Ankle/Brachial Index

Determination of the ABI furnishes a simplified application of leg segmental blood pressure measurements that can readily be used at the bedside. The ABI is the ratio of systolic blood pressure measured at the ankle to systolic blood pressure at the brachial artery. A pneumatic cuff placed around the ankle is inflated to suprasystolic pressure and subsequently deflated while the onset of flow is detected with a Doppler ultrasound probe placed over the dorsalis pedis and posterior tibial arteries, thus denoting ankle systolic blood pressure. Brachial artery systolic pressure can be assessed in routine manner by using either a stethoscope to listen for the first Korotkoff sound or a Doppler probe to listen for the onset of flow during cuff deflation. A normal ABI should be 1.0 or greater. However, in view of the variability intrinsic to sequential blood pressure measurements, an ABI less than 0.90 is considered abnormal and is 95 percent sensitive for angiographically verified peripheral arterial stenosis.[15] [92] The ABI is often used to gauge the severity of PAD. Patients with symptoms of leg claudication often have ABIs ranging from 0.5 t0 0.8, and patients with critical limb ischemia usually have an ABI less than 0.5. In patients with skin ulcerations, ankle pressure less than 55 mm Hg predicts poor ulcer healing.[93] [94]

One limitation of leg blood pressure recordings is that they cannot be used reliably in patients with calcified vessels, as might occur in persons with diabetes mellitus or renal insufficiency. The calcified vessel cannot be compressed during inflation of the pneumatic cuff, and therefore the Doppler probe indicates continuous blood flow, even when the mercury manometer records pressure in excess of 250 mm Hg.

PULSE VOLUME RECORDING

The pulse volume recording graphically illustrates the volumetric change in a segment of the limb that occurs with each pulse. Plethysmographic instruments, typically with strain gauges or pneumatic cuffs, are used to transduce volumetric changes in the limb that can be displayed on a graphic recorder. These transducers are strategically placed along the limb to record the pulse volume in its different segments, such as the thigh, calf, ankle, metatarsal region, and toes, or the upper part of the arm, forearm, and fingers. The normal pulse volume contour is influenced by both local arterial pressure and vascular wall distensibility and resembles a blood pressure waveform. It

TABLE 41-7 -- LEG SEGMENTAL PRESSURE MEASUREMENTS (mm Hg) IN A PATIENT WITH BILATERAL CALF CLAUDICATION

Brachial artery	152/84	
	RIGHT LEG	**LEFT LEG**
Upper thigh	160	162

Lower thigh	110	140
Calf	108	100
Ankle	64	78
A/B index	0.42	0.51

The right leg has pressure gradients between upper and lower parts of the thigh and between the calf and ankle. These gradients are indicative of stenoses in the superficial femoral artery and in the tibioperoneal arteries. The left leg has pressure gradients between the upper and lower parts of the thigh, between the lower part of the thigh and calf, and between the calf and ankle. These gradients are indicative of stenoses in the superficial femoral and popliteal arteries and in the tibioperoneal arteries.

A/B=ankle/brachial.

Figure 41-7 *Left panel,* Normal pulse volume recordings from the upper part of the thigh, lower part of the thigh, calf, and ankle showing a characteristic waveform consisting of a rapid systolic upstroke, a sharp peak, a dicrotic notch, and a concave downslope. *Right panel,* Abnormal pulse volume recordings showing a slower rate of rise, absence of a dicrotic notch, decreased amplitude, and slower descent.

comprises a sharp systolic upstroke that rises rapidly to a peak, a dicrotic notch, and a concave downslope that drops off gradually toward baseline (Fig. 41-7) .[94] [95] The contour of the pulse wave changes distal to a stenosis, with loss of the dicrotic notch, a slower rate of rise, a more rounded peak, and a slower descent. The amplitude becomes lower with increasing severity of disease, and the pulse wave may not be recordable at all in a critically ischemic limb.[94] Segmental analysis of the pulse wave may indicate the location of an arterial stenosis, which is likely to be found in the artery between a normal and abnormal pulse volume recording. The pulse volume wave also provides information regarding the integrity of blood flow when blood pressure measurements cannot be accurately obtained because of noncompressible vessels.

DOPPLER ULTRASOUND

Continuous-wave and pulsed-wave Doppler systems transmit and receive high-frequency ultrasound signals. The Doppler frequency shift caused by moving red blood cells is proportional to the velocity of blood flow. Typically, the perceived frequency shift is between 1 and 20 kHz and is within the audible range of the human ear. Therefore, placement of a Doppler probe along an artery enables the examiner to hear whether blood flow is present and the vessel is patent. Processing and graphically recording the Doppler signal permit more detailed analysis of the frequency components.

Doppler instruments can be used with or without gray-scale imaging to evaluate an artery for the presence of stenoses. The Doppler probe is positioned at approximately a 60-degree angle over the common femoral, superficial femoral, popliteal, dorsalis pedis, and posterior tibial arteries. A normal Doppler waveform has three components: a rapid forward flow component during systole, transient flow reversal during early diastole, and a slow antegrade component during late diastole. The Doppler waveform becomes altered if the probe is placed distal to an arterial stenosis and is characterized by deceleration of systolic flow, loss of the early diastolic reversal, and diminished peak frequencies. Arteries in a limb with critical ischemia may not show any Doppler frequency shift. As with pulse volume recordings, change from a normal to an abnormal Doppler waveform as the artery is interrogated more distally provides inferential evidence of the location of a stenosis.[95] [96]

DUPLEX ULTRASOUND IMAGING

Duplex ultrasound imaging provides a direct, noninvasive means of assessing both the anatomical characteristics of peripheral arteries and the functional significance of arterial stenoses. The methodology incorporates gray-scale B-mode ultrasound imaging, pulsed Doppler velocity measurements, and color coding of the Doppler shift information (Fig. 41-8). Real-time ultrasound scanners emit and receive high-frequency sound waves, typically ranging from 2 to 10 mHz, to construct an image. The acoustic properties of the vascular wall differ from those of the surrounding tissue, which enables them to be imaged easily. Atherosclerotic plaque may be present and visible on gray-scale images (Fig. 41-9) . Pulsed-wave Doppler systems emit ultrasound beams at precise times and can therefore sample the reflected ultrasound waves at specific depths, which enables the examiner to sample the blood cell velocity within the lumen of the artery. By positioning the pulsed Doppler beam at a known angle, blood flow velocity is calculated according to the equation $Df = 2VF\cos O/C$, where Df is the frequency shift, V is the velocity, F is the frequency of the transmitted sound, O is the angle between the transmitted sound and the velocity vector, and C is the velocity of sound in tissue. For optimal measurements, the angle of the pulsed Doppler beam should be less than 60 degrees. With color Doppler, the frequency shift information

Figure 41-8 Duplex ultrasound of the common femoral artery bifurcation into the superficial and deep femoral arteries. The *upper* image shows a normal gray-scale image of the artery in which the intima is not thickened and the lumen is widely patent. The *lower* image is a recording of the pulsed Doppler velocity sampled from the superficial femoral artery. The triphasic profile is apparent, the envelope is thin, and the peak systolic velocity is within normal limits.

within the entire field sampled by the ultrasound beam can be superimposed on the gray-scale image to provide a composite real-time display of flow velocity within the vessel.

Color-assisted duplex ultrasound imaging is an effective means of localizing peripheral arterial stenoses. Normal arteries have laminar flow with the highest velocity at the center of the artery. The representative color image is usually homogeneous, with relatively constant hue and intensity. In the presence of an arterial stenosis, blood flow velocity increases through the narrowed lumen. As the velocity increases, progressive desaturation of the color display can be noted, and flow disturbance distal to the stenosis causes changes in hue and color. Pulsed Doppler velocity measurements can be made along the length of the artery and particularly at areas of flow abnormalities suggested by the color images. A twofold or greater increase in peak systolic velocity at the site of an atherosclerotic plaque indicates a 50 percent or greater diameter stenosis (Fig. 41-9) .[97] [98] A threefold increase in velocity is suggestive of a 75 percent or greater stenosis. No Doppler signal is obtained if the artery is occluded. With contrast angiography used as a reference standard, the specificity and sensitivity of duplex ultrasound imaging for identifying sites of arterial stenoses are approximately 95 and 80 to 85 percent, respectively.[97] [98] [99] [100] [101]

TREADMILL EXERCISE TESTING

Treadmill exercise testing is used to evaluate the clinical significance of peripheral arterial stenoses and to provide objective evidence of the patient's walking capacity. The initial claudication distance is defined as the point at which symptoms of claudication first develop, and the absolute claudication distance is the point at which the patient is no longer able to continue walking because of severe leg discomfort. This standardized and more objective measurement of walking capacity supplements the patient's history and thus provides quantitative assessment of the patient's disability, as well as a metric that can be monitored after therapeutic interventions.

Treadmill exercise protocols use a motorized treadmill that incorporates fixed or progressive speeds and angles of incline.[102] [103] [104] A fixed workload test usually maintains a constant grade of 12 percent and speed of 1.5 to 2.0 mph. A progressive, or graded, treadmill protocol typically maintains a constant speed of 2 mph while gradually increasing the grade by 2 percent every 2 to 3 minutes.[102] [103] Reproducibility of repeated treadmill tests is reportedly better with progressive-grade than with constant-grade protocols.[103] [105]

Treadmill testing provides a means to determine whether arterial stenoses contribute to the patient's symptoms of exertional leg pain. During exercise, blood flow through a stenosis increases as vascular resistance falls in the exercising muscle. According to Poiseuille's law, described previously, the pressure gradient across the stenosis increases in a manner that is directly proportional to flow. Thus, ankle and brachial systolic blood pressures are measured under resting conditions before treadmill exercise, within 1 minute after exercise, and repeatedly until baseline values are reestablished. Normally, the blood pressure increase that occurs during exercise should be the same in both the upper and lower extremities, with maintenance of constant ABI of 1.0 or greater. In the presence of peripheral arterial stenosis, the ABI decreases because the increase in blood pressure that is observed in the arm is not matched by a comparable increase in ankle blood pressure. A 25 percent or greater decrease in ABI

after exercise in a patient whose walking capacity is limited by claudication is considered diagnostic and implicates PAD as a cause of the patient's symptoms.

Many patients with PAD also have coronary atherosclerosis. The addition of cardiac monitoring to the exercise protocol may provide adjunctive information regarding the presence of myocardial ischemia. A workload sufficient to increase myocardial oxygen demand and provoke myocardial ischemia may not be achieved in patients whose exercise capacity is limited by claudication. Nonetheless, electrocardiographic change, particularly during low levels of treadmill exercise, may provide evidence of severe coronary artery disease.

Figure 41-9 Duplex ultrasound of the common femoral artery. The *upper* image shows a gray-scale image of the artery in which plaque is present and encroaching on the lumen. The *lower* image is a recording of the pulsed Doppler velocity sampled from the common femoral artery. The peak velocity of 350 cm/sec is elevated. These features are consistent with significant stenosis.

Magnetic Resonance Angiography (see also Chaps. 10 and 42)

Magnetic resonance angiography (MRA) is a noninvasive means to visualize the aorta and the peripheral arteries. A detailed description of the instrumentation and technique is beyond the scope of this chapter. Resolution of the vascular anatomy with gadolinium-enhanced MRA approaches that of conventional contrast digital subtraction angiography (Fig. 41-10). Comparative studies have reported sensitivities of 93 to 100 percent and specificities of 96 to 100 percent for the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries.[106] [107] [108] [109] Its current utility may be greatest for the evaluation of symptomatic patients to assist decision-making prior to performance of an endovascular intervention or in patients at risk for renal, allergic, or other complications during conventional angiography. As the technology improves, MRA may play a greater role in the preoperative evaluation of patients with PAD.

Contrast Angiography

Conventional angiography with a radioiodinated or other contrast agent is indicated for evaluation of arterial anatomy prior to a revascularization procedure. It is used occasionally when the diagnosis is in doubt. Most contemporary angiography laboratories use digital subtraction techniques after the intraarterial administration of contrast to enhance resolution. A retrograde transfemoral catheterization technique is generally used to evaluate the aorta and the peripheral

Figure 41-10 Gadolinium-enhanced two-dimensional magnetic resonance angiogram of both legs from

the knee to above the ankle. Resolution of the popliteal and crural arteries is excellent.

arteries. Injection of the radiocontrast material into the aorta permits visualization of the aorta and iliac arteries, and injection of contrast into the iliofemoral segment of the involved leg permits optimal visualization of the femoral, popliteal, tibial, and peroneal arteries (Fig. 41-11) . In patients with aortic occlusion, catheterization of the fermoral arteries is not feasible. The aorta can be approached by brachial or axillary artery cannulation or, if necessary, directly by a translumbar approach.

PROGNOSIS

The prognosis of patients with PAD is affected by an increased risk for adverse cardiovascular events, as well as the risk of limb loss (Fig. 41-12) .[110] Patients with PAD frequently have concomitant coronary artery disease and cerebrovascular disease.[32] [111] The relative prevalence of each depends, in part, on the diagnostic criteria used to establish the diagnosis of each of these entities. In the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) Trial, 21 percent of the patients with PAD had a history of myocardial infarction and 26 percent had angina. In the Cardiovascular Health Study, patients with abnormal ABIs were twice as likely to have a history of myocardial infarction, angina, congestive heart failure, or cerebrovascular ischemia as those with normal ABIs.[4] Approximately 15 to 25 percent of patients with PAD have significant carotid artery stenoses by duplex ultrasound. [112] [113] Epidemiological studies have found that the risk of death from cardiovascular causes is increased 2.5- to 6-fold in patients with PAD and the annual mortality rate is 4.3 to 4.9 percent.[4] [8] [12] [13] [32] [114] [115] [116] [117] [118] [119] [120] The risk of death is greatest in those with the most severe PAD, and mortality correlates with decreasing ABI (Fig. 41-13) . [121] [122] Approximately 25 percent of patients with critical limb ischemia die within 1 year, and the 1 year mortality rate in patients who have undergone amputation may be as high as 45 percent.[114] [123]

Angiographic progression of PAD occurs in over 60 percent of patients studied 5 years after the initial diagnosis.[124] Worsening symptoms develop in approximately 25 percent of patients with claudication[110] [125] Clinical progression to critical limb ischemia occurs in 7.5 to 8.0 percent of patients with claudication in the first year after diagnosis and approximately 2.2 percent each year thereafter.[12] [125] Both smoking and diabetes mellitus independently predict progression of disease.[33] [120] [126] [127] Of patients with PAD, those with diabetes mellitus have a 21 percent risk of major amputation as compared with 3 percent in non-diabetic persons.[127]

TREATMENT

The goals of therapy for PAD include a reduction in cardiovascular morbidity and mortality and improvement in quality of life by decreasing symptoms of claudication, eliminating rest pain, and preserving limb viability. Therapeutic considerations therefore include risk factor modification and antiplatelet therapy to reduce the risk of adverse cardiovascular events, such as myocardial infarction, stroke, and death. Symptoms of claudication can improve with pharmacotherapy or exercise rehabilitation, whereas optimal management of critical limb ischemia often includes endovascular interventions

or surgical reconstruction to improve blood supply and maintain limb viability.

Risk Factor Modification (see also Chaps. 32 and 33)

Lipid-lowering therapy reduces the risk of adverse cardiovascular events in patients with coronary artery disease.

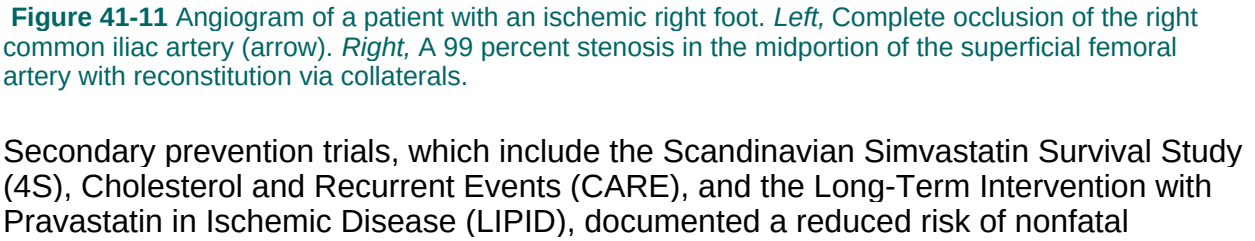

Figure 41-11 Angiogram of a patient with an ischemic right foot. *Left,* Complete occlusion of the right common iliac artery (arrow). *Right,* A 99 percent stenosis in the midportion of the superficial femoral artery with reconstitution via collaterals.

Secondary prevention trials, which include the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID), documented a reduced risk of nonfatal myocardial infarction or death from coronary artery disease by 24 to 34 percent (see also Chap. 33) .[128] [129] [130] No studies to date, however, have prospectively evaluated the effect of lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors on these cardiovascular outcomes in patients with PAD. Pending such studies, recommendations for lipid-lowering therapy for patients with PAD are the same as recommendations for those with coronary artery disease. The National Cholesterol Education Program has advised that patients with atherosclerosis and hypercholesterolemia be treated with diet and drug therapy to achieve a target LDL cholesterol of 100 mg/dl or less.[131] Several clinical trials have found that lipid-lowering therapy with diet, niacin,

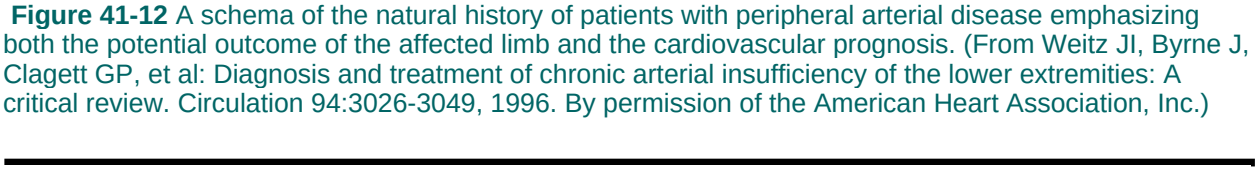

Figure 41-12 A schema of the natural history of patients with peripheral arterial disease emphasizing both the potential outcome of the affected limb and the cardiovascular prognosis. (From Weitz JI, Byrne J, Clagett GP, et al: Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: A critical review. Circulation 94:3026-3049, 1996. By permission of the American Heart Association, Inc.)

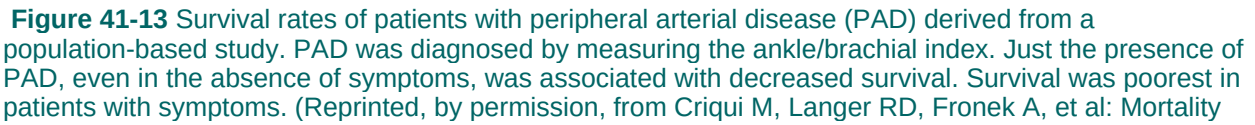

Figure 41-13 Survival rates of patients with peripheral arterial disease (PAD) derived from a population-based study. PAD was diagnosed by measuring the ankle/brachial index. Just the presence of PAD, even in the absence of symptoms, was associated with decreased survival. Survival was poorest in patients with symptoms. (Reprinted, by permission, from Criqui M, Langer RD, Fronek A, et al: Mortality

over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 326:381-386, 1992.)

binding resins, or clofibrate reduces the progression of femoral artery atherosclerosis.[132] [133] In one study, the addition of probucol to cholestyramine did not affect femoral atherosclerosis.[134] Lipid-lowering therapy may also reduce the incidence or severity of claudication. The Program on the Surgical Control of the Hyperlipidemias (POSCH) found that partial ileal bypass surgery, a surgical procedure that lowers cholesterol levels, reduced the incidence of intermittent claudication or critical limb ischemia by 34 percent and reduced the risk of development of an abnormal ABI by 44 percent.[135] A post hoc analysis of the 4S found that simvastatin reduced the risk of new or worsening claudication by 38 percent in comparison to placebo (Fig. 41-14) . [136]

Smoking Cessation

Prospective trials examining the benefits of smoking cessation are lacking. However observational evidence unequivocally supports the notion that cigarette smoking increases the risk of atherosclerosis and its clinical sequelae. In patients with PAD, survival rates are better in nonsmokers than in those who have smoked or continue to smoke, and those who discontinue smoking have approximately twice the 5-year survival rate of those who continue to smoke.[137] [138] In one study of patients with PAD, the 10-year rate of myocardial infarction was 53 percent in smokers and 11 percent in nonsmokers.[33] Smoking cessation also lowers the risk for critical limb ischemia.[33]

Treatment of Diabetes (see also Chap. 63)

Aggressive treatment of diabetes decreases the risk for microangiopathic events such as nephropathy and retinopathy; however, only limited data support the benefit of aggressive treatment of diabetes on the clinical manifestations of atherosclerosis. In the Diabetes Control and Complications Trial (DCCT), which involved patients with type I diabetes mellitus, post hoc analysis found that intensive insulin therapy versus usual care caused a nonsignificant 42 percent reduction in cardiovascular events, including a 22 percent reduction in events related to PAD.[139] The United Kingdom Prospective Diabetes Study (UKPDS) of patients with type II diabetes mellitus found that intensive treatment with sulfonylureas or insulin was associated with

Figure 41-14 In the Scandinavian Simvastatin Survival Study, lipid-lowering therapy with simvastatin reduced the incidence of new or worsening claudication. (Adapted from Pedersen TR, Kjekshus J, Pyorala K, et al: Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 81:333-335, 1998.)

a 16 percent reduction in myocardial infarction, a finding of borderline statistical significance, and a trend for a decrease in death or amputation from PAD.[140]

Blood Pressure Control

Antihypertensive therapy reduces the risk of stroke, coronary artery disease, and vascular death.[141] It is not known whether antihypertensive therapy prevents the development or progression of PAD. It is conceivable, however, that treatment of hypertension may decrease perfusion pressure to extremities that are already compromised by peripheral arterial stenoses. In addition, concern has been raised regarding the potential adverse affects of beta-adrenergic receptor blockers on peripheral blood flow and symptoms of claudication or critical limb ischemia. Beta blockers have been found to worsen claudication in some trials, but not in others.[142] [143] [144] [145] [146] A meta-analysis that included 11 studies of beta blocker therapy in patients with intermittent claudication found no significant impairment in walking capacity in comparison to placebo.[147] Beta blockers have been shown to reduce the risk of myocardial infarction and death in patients with coronary artery disease, a problem affecting many patients with PAD.[148] [149] Thus, if clinically indicated for other conditions, these drugs should not be withheld in patients with PAD. The balance of evidence would support treatment of hypertension in patients with PAD according to established clinical guidelines (see Chap. 29) .[150]

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce coronary events in patients with left ventricular dysfunction.[151] [152] In the Heart Outcomes Prevention Evaluation (HOPE) Study, the ACE inhibitor ramipril decreased the risk of vascular death, myocardial infarction, or stroke by 22 percent. Forty-four percent of the patients enrolled in the HOPE Trial had evidence of PAD as manifested by an ABI of less than 0.9. Ramipril reduced cardiovascular events in patients with PAD to a comparable degree as in those without PAD.[153]

Antiplatelet Therapy

Substantial evidence supports the use of antiplatelet agents to reduce adverse cardiovascular outcome in patients with atherosclerosis. A meta-analysis that included approximately 70,000 high-risk patients with atherosclerosis, including those with acute and prior myocardial infarction, stroke, and transient cerebrovascular ischemia, as well as other high-risk groups such as those with PAD, found that antiplatelet therapy was associated with a 27 percent odds reduction for subsequent vascular death, myocardial infarction, or stroke (see also Chap. 62) . [154] Of the 3295 patients with claudication included in this analysis, a statistically insignificant 18 percent reduction was noted in the risk of myocardial infarction, stroke, or death after 27 months of antiplatelet therapy.[155] The Swedish Ticlopidine Multicenter Study (STIMS) found that ticlopidine reduced mortality by 29 percent in patients with claudication. The CAPRIE Trial compared the efficacy of clopidogrel and aspirin in preventing ischemic events in patients with recent myocardial infarction, recent ischemic stroke, or PAD. Overall, an 8.7 percent relative risk reduction for myocardial infarction, ischemic stroke, or vascular death was seen in the group treated with clopidogrel.[32] Notably, of the 6452 patients in the PAD subgroup, clopidogrel treatment reduced adverse cardiovascular events by 23.8 percent.

Antiplatelet therapy also prevents occlusion in the peripheral circulation after revascularization procedures (Fig. 41-15). Of approximately 3000 patients with peripheral arterial procedures analyzed by the Antiplatelet Trialists Collaboration, the odds reduction for arterial or graft occlusion by antiplatelet therapy, primarily aspirin or aspirin plus dipyridamole, was 43 percent.[155] Ticlopidine also improves the long-term patency of peripheral saphenous vein bypass grafts.[156] Several studies have suggested that ticlopidine improves claudication or reduces the need for reconstructive vascular surgery, but these observations require confirmation in additional clinical trials.[157] [158]

Pharmacotherapy

The development of effective pharmacotherapy for treating symptoms of PAD has lagged substantially behind that for treating coronary artery disease. A report of 75 trials that included 33 drugs for the treatment of intermittent claudication found that approximately 75 percent of the trials were flawed by lack of a placebo control or blinded randomization, inappropriate endpoints, or small sample size.[159] Published consensus guidelines for conducting clinical trials of pharmacological agents for the treatment of patients with PAD should provide common ground for the objective evaluation of new drugs.[160] [161] Most studies of vasodilator therapy have failed to demonstrate any efficacy in patients with intermittent claudication.[162] Several pathophysiological explanations may account for the failure of vasodilator therapy in PAD. During exercise, resistance vessels distal to a stenosis dilate in response to ischemia. Vasodilators would have minimal, if any, effect on these endogenously dilated vessels but would decrease resistance in other vessels and thereby create a relative steal phenomenon

Figure 41-15 Effect of antiplatelet therapy on arterial occlusion in patients with peripheral arterial disease based on the Antiplatelet Trialists' Collaboration. The odds ratios are shown for patients with claudication, infrainguinal bypass grafts, and percutaneous transluminal angioplasty. (From Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 308:81-106, 1994.)

Figure 41-16 Effect of pentoxifylline on claudication distance based on a pooled analysis of two studies. ICD=initial claudication distance; ACD=absolute claudication distance. Number of patients = 278. (Data from Porter JM, Cutler BS, Lee BY, et al: Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. Am Heart J 104:66-72, 1982; Lindgarde F, Labs KH, Rossner M: The pentoxifylline experience: Exercise testing reconsidered. Vasc Med 1:145-154, 1996; Lindgarde F, Jelnes R, Bjorkman H, et al: Conservative drug treatment in patients with moderately severe chronic occlusive

peripheral arterial disease. Scandinavian Study Group. Circulation 80:1549-1556, 1989.)

that reduces blood flow and perfusion pressure to the affected leg. Moreover, in contrast to their effects on myocardial oxygen consumption in patients with coronary artery disease (because of afterload reduction), vasodilators do not reduce skeletal muscle oxygen demand.

In the United States, the Food and Drug Administration (FDA) has approved two drugs, pentoxifylline (Trental) and cilostazol (Pletal), for treating claudication in patients with PAD. Additional drugs have been approved by licensing bodies in Europe, Asia, and South America.

PENTOXIFYLLINE.

Pentoxifylline is a xanthine derivative that is used to treat patients with intermittent claudication. Its action is thought to be mediated via its hemorrheological properties, including its ability to decrease blood viscosity and improve erythrocyte flexibility.[163] It also has antiinflammatory and antiproliferative effects.[164] [165] Two prospective multicenter trials found that pentoxifylline increased absolute claudication distance after 24 weeks of treatment by approximately 20 percent (Fig. 41-16) .[166] [167] [168] Two meta-analyses of randomized placebo-controlled trials of pentoxifylline found that it increased initial claudication distance by approximately 20 to 30 meters and absolute claudication distance by approximately 45 to 50 meters.[169] [170] Another meta-analysis, however, concluded that the quality of reported data precluded a reliable estimate of pentoxifylline's efficacy.[171]

CILOSTAZOL.

This quinolinone derivative inhibits phosphodiesterase III, thereby decreasing cyclic adenosine monophosphate degradation and increasing its concentration in platelets and blood vessels. Although cilostazol inhibits platelet aggregation and causes vasodilation in experimental animals, its mechanism of action in patients with PAD is not known.[172] [173] Several trials have reported that cilostazol improves absolute claudication distance by 40 to 50 percent in comparison to placebo (Fig. 41-17) .[174] [175] Quality-of-life measures, as assessed by the Medical Outcomes Scale (SF-36) and the Walking Impairment Questionnaire, also improved. In addition, one study found that absolute walking distance improves more with cilostazol than with either pentoxyfilline or placebo, with the latter two having equivalent efficacy.[176] An advisory from the FDA has stated that cilostazol should not be used in patients with congestive heart failure since other phosphodiesterase III inhibitors have been shown to decrease survival in these patients.[177] [178] The effect of cilostazol on cardiac morbidity and mortality is not known.

OTHER DRUGS.

Many other drugs are under investigation for the treatment of either claudication or critical limb ischemia, including serotonin (5-hydroxytryptamine) antagonists, calcium channel blockers, L-arginine, carnitine derivatives, vasodilator prostaglandins, and

angiogenic growth factors. One serotonin antagonist, ketanserin, did not improve claudication distance in a multicenter trial,[179] whereas another, naftidrofuryl, has been reported to improve symptoms of claudication in some trials and is currently available for use in Europe.[180] [181] L-Arginine, the precursor for endothelium-derived nitric oxide, was found to improve claudication distance after 3 weeks of intravenous therapy.[65] Propionyl L-carnitine, a cofactor for fatty acid metabolism, has also been reported to improve claudication, particularly in patients whose baseline maximum walking distance is less than 250 meters.[182] [183]

Therapy with vasodilator prostaglandins has been investigated in patients with intermittent claudication and in those with critical limb ischemia. Intravenous administration of prostaglandin E_1 (PGE_1) or its precursor improved claudication distance in preliminary trials.[65] [184] Phase III studies with oral prostacyclin derivatives in patients with intermittent claudication are in progress or have been completed recently, and the results are pending. In a large trial of 1560 patients with critical limb ischemia, PGE_1 administered intravenously for up to 28 days reduced the composite endpoint of death, major amputation, persistence of critical limb ischemia, acute myocardial infarction, and stroke at the time of hospital discharge from 73 to 64 percent, but its effect on this outcome was not significantly different from that of placebo at the 6-month time point.[185] Most of the benefit of PGE_1 in this trial was related to recovery from leg ischemia.

The therapeutic use of angiogenic growth factors has engendered considerable enthusiasm. Administration of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) as protein or gene therapy increases collateral blood vessel development, capillary

Figure 41-17 Effect of cilostazol versus pentoxifylline and placebo on maximal walking distance. (From Dawson DL, Cutler BS, Hiatt WR, et al: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med, in press.)

Figure 41-18 Effect of supervised exercise training on peak treadmill exercise time in patients with intermittent claudication. (Adapted from Hiatt WR, Regensteiner JG, Hargarten ME, et al: Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 81:602-609, 1990.)

number, and blood flow in experimental models of hindlimb ischemia.[186] [187] [188] [189] [190] [191] Gene transfer of human plasmid phVEGF165 by an intraarterial catheter-based technique or by intramuscular injection into the ischemic extremity improved collateral blood vessel development in small case series.[192] [193] Placebo-controlled clinical trials of angiogenic growth factors in patients with either claudication or critical limb ischemia

are in progress.

Exercise

Supervised exercise rehabilitation programs improve symptoms of claudication in patients with PAD (Fig. 41-18) .[194] A meta-analysis of 21 controlled studies of exercise rehabilitation found that a supervised exercise program increased the average distance walked to the onset of claudication by 179 percent and the maximal distance walked by 122 percent.[195] The greatest benefit occurred when sessions were at least 30 minutes in duration at least three times per week for 6 months and when walking was used as the mode of exercise. In a randomized study, exercise training resulted in greater improvement in maximal walking distance than did percutaneous transluminal angioplasty (PTA).[196]

The mechanisms through which exercise training improves claudication are not known. Studies in experimental models of hindlimb ischemia have suggested that regular exercise increases the development of collateral blood vessels.[197] [198] [199] Expression of angiogenic factors is increased by exercise, particularly in hypoxic tissue.[200] [201] [202] Exercise training has been shown to improve endothelium-dependent vasodilation of coronary arteries in patients with coronary atherosclerosis and in the peripheral circulation of patients with congestive heart failure.[203] [204] [205] However, improvement in calf blood flow commensurate with improvement in walking distance has not been demonstrated in patients with claudication following exercise training.[194] [206] [207] To date, imaging studies demonstrating increased collateral blood vessels following exercise training in patients with PAD have not been reported.

The benefits of exercise training in patients with PAD may result from changes in skeletal muscle function, such as increased muscle mitochondrial enzyme activity and adenosine triphosphate production rate and decreased lactate production.[208] [209] In patients with PAD, improvement in exercise performance is associated with a decrease in plasma and skeletal muscle short-chain acylcarnitine concentrations, which indicate improvement in oxidative metabolism, as well as increased peak oxygen consumption.[194] [210] Training may also enhance biomechanical performance and enable patients to walk more efficiently with less energy expenditure.

Percutaneous Transluminal Angioplasty and Stents (see also pp. 1485-1488)

PTA and stent placement are being increasingly used in the management of patients with PAD, particularly those with disabling claudication and critical limb ischemia. Various endpoints have served to indicate the efficacy of these interventions, including the ABI, vessel patency by duplex ultrasound or conventional angiography, relief of symptoms, and limb salvage. In general, the efficacy of percutaneous interventions is better for treatment of stenoses than occlusions and when targeting vessels with good runoff (i.e., patent distal vessels) as opposed to poor runoff.[15] [211] [212] [213]

Iliac artery PTA alone is associated with 4- to 5-year patency rates of approximately 60 to 80 percent.[211] [214] [215] Iliac artery stent placement yields 4- to 5-year patency rates

that range from 70 to 95 percent.[216] [217] [218] A meta-analysis of six iliac PTA studies comprising 1300 patients and eight iliac stent placement studies involving 816 patients found that the long-term patency rate was greater with stent placement than with PTA alone (Fig. 41-19) .[219] Overall, stent placement reduced late failure by 39 percent. The Dutch Iliac Stent Trial Group found that primary PTA followed by selective stent placement was more cost-effective than primary stent placement.[220] [221] Clinical success at 2 years was 78 percent for primary stent placement and 77 percent for selective stent placement. Quality of life improved comparably in each group.[221] [222] In a study comparing stent placement with surgery in patients with aortoiliac disease, the long-term patency rate was less in those who received stents.[223]

The overall efficacy of PTA of the femoral-popliteal arteries is less than that of the iliac arteries.[213] [216] [224] [225] [226] [227] Several large institutional series have found that primary patency rates 1, 3, and 5 years after femoral-popliteal PTA average 60, 50, and 45 percent, respectively.[224] [226] [227] [228] A life table based on a meta-analysis of seven femoral-popliteal PTA studies yielded a 5-year patency rate of approximately 45 percent.[229] An analysis comparing femoral-popliteal PTA with bypass surgery suggested that PTA was more cost-effective than surgery in patients with claudication who had either stenoses or occlusions and in patients with critical limb ischemia who had stenoses. Surgery, however, was more cost-effective than PTA in patients with critical limb ischemia who had arterial occlusions.[229] [230]

PTA of the tibial and peroneal arteries is technically more difficult and associated with a poorer outcome than is endovascular treatment of more proximal lesions,[213] possibly because most series included patients with critical limb ischemia who were considered high risk for bypass surgery. Long-term success appears to be greater in those with focal stenoses in whom distal perfusion is restored.[231] [232] [233] [234]

Figure 41-19 Four-year patency rate after percutaneous transluminal angioplasty (PTA) alone or stent placement for iliac artery lesions based on a meta-analysis of six iliac PTA studies and eight iliac stent studies. (From Bosch JL, Hunink MG: Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. Radiology 204:87-96, 1997.)

Figure 41-20 Schematic of an aortobifemoral bypass. The infrarenal aorta has been transected and stapled closed. The proximal end of the graft is anastomosed end to end with the aorta. The distal limbs are anastomosed to the common femoral arteries via retroperitoneal tunnels. (From Whittemore AD, Mannick JA: Principles of vascular surgery. *In* Loscalzo J, Creager MA, Dzau VJ (eds): Vascular Medicine. 2nd ed. Boston, Little, Brown, 1996, pp 675-702.)

Limb salvage rates at 1 and 2 years ranged from 50 to 75 percent.[233] [235] [236] [237]

Innominate and subclavian artery PTA and stent placement are considered for localized lesions in patients with arm claudication or vertebrobasilar insufficiency secondary to subclavian steal. Initial success is achieved in approximately 80 to 90 percent of cases, and the 1-year patency rate averages 85 percent.[238] [239] [240]

Complications occur in approximately 4 to 6 percent of endovascular interventions and usually relate to the severity of arterial disease and the complexity of the procedure.[15] Local complications include thrombosis, dissection, hematoma, and pseudoaneurysm, and occasionally these complications require surgical repair.

Peripheral Arterial Surgery

Surgical revascularization is generally indicated to improve quality of life in patients with disabling claudication who are receiving maximal medical therapy and to relieve rest pain and preserve limb viability in patients with critical limb ischemia. The specific operation must take into account the anatomical location of the arterial lesions and the presence of comorbid conditions. The surgical procedure is planned after angiographic identification of the arterial obstruction to ensure sufficient arterial inflow to and outflow from the graft to maintain patency. Preoperative evaluation to assess the risk of vascular surgery should be performed since many of these patients have coexisting coronary artery disease. Guidelines for this evaluation have been established and are beyond the scope of this chapter (see Chap. 61) .[241]

Aortobifemoral bypass is the most frequent operation for patients with aortoiliac disease. Typically, a knitted or woven prosthesis made of Dacron or polytetrafluoroethylene (PTFE) is anastomosed proximally to the aorta and distally to each common femoral artery (Fig. 41-20) . [242] Occasionally, the iliac artery is used for the distal anastomosis to maintain antegrade flow into at least one hypogastric artery. A recent meta-analysis of aortic bifurcation grafts in 23 studies reported from 1970 to 1996 noted that 5- and 10-year limb patency rates were 91 and 87 percent for claudicants, respectively, and 88 and 82 percent for patients with critical limb ischemia, respectively.[243] Among the more recent series in this analysis, operative morbidity and mortality rates were 8.3 and 3.3 percent, respectively.[243]

Extraanatomical surgical reconstructive procedures for aortoiliac disease include axillobifemoral bypass, iliobifemoral bypass, and femorofemoral bypass. These bypass grafts, made of Dacron or PTFE, circumvent the aorta and iliac arteries and are generally used in high-risk patients with critical limb ischemia.[244] [245] Long-term patency rates are inferior to those of aortobifemoral bypass procedures. A recent Veteran's Administration Cooperative Study that included 340 femorofemoral bypass procedures and 79 axillofemoral or axillobifemoral bypass operations performed primarily in patients with critical limb ischemia reported a 5-year primary patency rate of approximately 50 percent. In other series, 5-year patency rates for axillobifemoral bypass operations have been reported to range from 50 to 70 percent, and those for femorofemoral bypass grafts have ranged from 70 to 80 percent.[246] [247] [248] [249] The operative mortality for extraanatomical bypass procedures is 3 to 5 percent, which reflects, in part, the serious comorbid conditions and advanced atherosclerosis of many of the patients who undergo

these procedures.

Reconstructive surgery for infrainguinal arterial disease includes femoropopliteal, femorotibial, or femoroperoneal artery bypass. *In situ* or reversed autologous saphenous veins or synthetic grafts made of PTFE are used for the infrainguinal bypass. Patency rates for autologous saphenous vein bypass grafts are superior to those seen with PTFE grafts.[250] [251] [252] Also, patency rates are better for grafts in which the distal anastomosis is placed in the popliteal artery above the knee versus below the knee.[250] [251] [253] [254] [255] Five-year primary patency rates for femoropopliteal reconstruction in claudicants are approximately 80 and 75 percent for autogenous vein or PTFE grafts, respectively, and in patients with critical limb ischemia they are approximately 65 and 45 percent, respectively.[229] [253] [254] [255] [256] For femoral below-knee bypass, including tibioperoneal artery reconstruction, five-year patency rates for saphenous vein grafts in patients with claudication or critical limb ischemia are comparable to those of femoropopliteal above-knee grafts and range from 60 to 80 percent,[229] [244] [251] [253] [254] [255] [257] whereas 5-year patency rates for PTFE grafts in the infrapopliteal position are considerably inferior, approximating 65 percent in claudicants and 33 percent in patients with critical limb ischemia.[229] [244] [250] Operative mortality for infrainguinal bypass operations based on recent series is 1 to 2 percent.[258] [259] [260] [261]

Graft stenoses may result from technical errors at the time of surgery, such as retained valve cuffs or intimal flap or valvutome injury; from fibrous intimal hyperplasia, usually within 6 months of surgery; or from atherosclerosis, usually occurring within the vein graft at least 1 to 2 years after surgery.[255] [262] Institution of graft surveillance protocols using color-assisted duplex ultrasonography has enabled the identification of graft stenoses, thereby prompting graft revision and avoiding complete graft failure.[263] [264] [265] [266] [267] Several studies have reported improved graft outcome as a result of routine ultrasound surveillance.[263] [266]

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Vasculitis (see also Chap. 67)

THROMBOANGIITIS OBLITERANS

TAO is a segmental vasculitis that affects the distal arteries, veins, and nerves of the upper and lower extremities. It typically occurs in young persons who smoke. A patient with characteristics of TAO was described initially by von Winiwater in 1879.[268] Leo Buerger coined the term "thromboangiitis obliterans" and described its pathology in 11 amputated limbs.[269]

PATHOLOGY AND PATHOGENESIS.

TAO primarily affects the medium and small vessels of the arms, including the radial, ulnar, palmar, and digital arteries, and their counterparts in the legs, including the tibial, peroneal, plantar, and digital arteries. The cerebral, coronary, renal,

mesenteric, aortoiliac, and pulmonary arteries may also be involved.[270] [271] [272] [273] The pathology is characterized by an occlusive, highly cellular thrombus composed of polymorphonuclear leukocytes forming microabscesses and, occasionally, multinucleated giant cells.[274] [275] The inflammatory infiltrate may also affect the vascular wall, but the internal elastic membrane remains intact. In the chronic phase of the disease, the thrombus becomes organized and the vascular wall becomes fibrotic.

The precise cause of TAO is not known. Tobacco use or exposure is present in virtually

every patient.[274] [276] [277] [278] Potential immunological mechanisms include increased cellular sensitivity to type I and type III collagen or the presence of anti-endothelial cell antibodies.[279] [280] Decreased endothelium-dependent vasodilation to acetylcholine has been observed in both the affected and unaffected limbs of patients with TAO, which raises the possibility that reduced bioavailability of nitric oxide contributes to the disorder.[281]

CLINICAL FINDINGS.

The prevalence of TAO is greater in Asia than North America or Western Europe. In the United States, TAO occurs in approximately 13 per 100,000 population.[282] [283] [284] Most patients with TAO have symptoms before 45 years of age, and 75 to 90 percent are men.[284] [285]

Patients may have claudication of the hands, forearms, feet, or calves. The majority of patients with TAO have pain at rest and digital ulcerations. Often, more than one extremity is affected. Raynaud phenomenon occurs in approximately 45 percent of patients, and superficial thrombophlebitis, which may be migratory, occurs in approximately 40 percent of patients.[285]

The radial, ulnar, dorsalis pedis, and posterior tibial pulses may be absent if the corresponding vessel is involved. The clinical characteristics of critical limb ischemia and ischemic digital ulceration were described earlier in this chapter. The Allen test is abnormal in two-thirds of patients.[285] To perform this test, both the radial and ulnar arteries are compressed while the hand is clenched and then opened.[286] This activity causes palmar blanching. Release of compression from either pulse should normally produce palmar erythema if the palmar arches are patent. If they are occluded, pallor persists on the side where compression is maintained. Discrete, tender, erythematous subcutaneous cords, indicating a superficial thrombophlebitis, may be present on the distal aspects of the extremities.

DIAGNOSIS.

No specific laboratory tests, other than biopsy, can be used to diagnose TAO. Most tests, therefore, are required to exclude other diseases that might have similar clinical features, including autoimmune diseases such as scleroderma or systemic lupus erythematosus, hypercoagulable states, diabetes, or acute arterial occlusion secondary to embolism. The erythrocyte sedimentation rate and acute phase reactants, such as C-reactive protein, are usually normal. Serum immunological markers, including antinuclear antibodies, rheumatoid factor, and antiphospholipid antibodies, should not be present, and serum complement levels should be normal. If clinically indicated, a proximal source of embolism should be excluded by cardiac and vascular ultrasound or by arteriography. Arteriography of an affected limb supports the diagnosis of TAO if the patient has segmental occlusion of small- and medium-sized arteries, absence of atherosclerosis, and corkscrew collaterals circumventing the occlusion (Fig. 41-21). These same findings, however, may occur in scleroderma, systemic lupus erythematosus, mixed connective tissue disease, and antiphospholipid antibody syndrome. The pathognomonic test is a biopsy showing the classic pathological

findings. Biopsy is otherwise rarely indicated, and biopsy sites may fail to heal because of severe ischemia. The diagnosis, therefore, is usually based on an age of onset younger than 45 years, a history of tobacco use, physical examination demonstrating distal limb ischemia, exclusion of other diseases, and if necessary, angiographic demonstration of typical lesions.[287] [288] [289]

TREATMENT.

The cornerstone of treatment is cessation of tobacco use. Amputation rarely ensues in patients without gangrene who stop smoking.[290] [291] In contrast, one or more amputations may ultimately be required in 40 to 45 percent of patients with TAO who continue to smoke.

Several drugs have been reported to benefit patients with TAO. The prostacyclin analogue iloprost administered 6 hours per day for 28 days was more effective than aspirin in relieving rest pain and healing ulcers.[292] In a multicenter trial, however, oral iloprost administered for 8 weeks was no more effective than placebo in healing ulcers, although it was somewhat more effective in relieving pain at low doses.[293] A naked plasmid DNA encoding vascular endothelial growth factor (phVEGF165) was intramuscularly injected into seven limbs of six patients with TAO, with subsequent healing of ulcers in three to five limbs and relief of rest pain in two others.[294]

Vascular reconstructive surgery is not usually a viable option because of the segmental nature of this disease and involvement of distal vessels. An autogenous saphenous vein bypass graft can be considered if a target vessel for the distal anastomosis is available. Long-term patency rates are better in ex-smokers than smokers.[295] [296]

Figure 41-21 Angiogram of a young woman with thromboangiitis obliterans. *Left,* Occlusion of the anterior tibial arteries (arrows). *Right,* Occlusion of the distal portion of the posterior tibial artery (arrow) with bridging collaterals.

TAKAYASU ARTERITIS AND GIANT CELL ARTERITIS

See Chapter 67 .

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Acute Limb Ischemia

Acute limb ischemia occurs when blood flow to the arm or leg is suddenly reduced by arterial occlusion. Perfusion is inadequate to meet the metabolic needs of the tissue, and limb viability is jeopardized. The clinical features of patients with acute limb ischemia are related to the location of the arterial occlusion and the resulting decrease in blood flow. Depending on the severity of ischemia, patients may note disabling claudication or pain at rest. Pain may develop over a short period and is manifested in the affected extremity distal to the site of obstruction. It is not necessarily confined to the foot or toes or to the hand or fingers as is usually the case in chronic limb ischemia. Concurrent ischemia of peripheral nerves causes sensory loss and motor dysfunction.

Physical examination findings may include absence of pulses distal to the occlusion, cool skin, pallor, delayed capillary return and venous filling, diminished or absent sensory perception, and muscular weakness or paralysis. This constellation of symptoms and signs is often recalled as the five P's: pain, pulselessness, pallor, paresthesias, and paralysis.

Prognosis

Comorbid cardiovascular disorders are usually present in patients with acute limb ischemia and may even be responsible for the event. As such, the long-term prognosis is limited in this population. Five-year survival rates after acute limb ischemia caused by thrombosis approximate 45 percent and after embolism are less than 20 percent.[297] The 1-month survival rate in persons older than 75 years with acute limb ischemia approximates 40 percent.[298] The risk of limb loss depends on the severity of the ischemia and the time elapsed before a revascularization procedure is undertaken. Amputation rates are approximately 6 percent if revascularization is performed within 12

hours of the onset of symptoms, 12 percent if performed between 12 and 24 hours, and 20 percent if delayed for more than 24 hours after symptom onset.[299]

A classification scheme that takes into consideration the severity of ischemia and viability of the limb, along with related neurological findings and Doppler signals, has been developed by the Society for Vascular Surgery and the International Society for Cardiovascular Surgery (Table 41-8) . A viable limb, category I, is not immediately threatened, has neither sensory nor motor abnormalities, and has blood flow detectable by Doppler. Threatened viability, category II, indicates that the severity of ischemia will cause limb loss unless the blood supply is restored promptly. The category is subdivided into marginally and immediately threatened limbs, the latter characterized by pain, sensory deficits, and muscular weakness. Arterial blood flow cannot be detected by Doppler. Irreversible limb ischemia leading to tissue loss and requiring amputation, category III, is characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins distal to the occlusion.

Pathogenesis

The causes of acute limb ischemia include arterial embolism, thrombosis in situ, dissection, and trauma.[300] Most arterial emboli arise from thrombotic sources in the heart. Atrial fibrillation complicating valvular heart disease, congestive heart failure, coronary artery disease, and hypertension accounts for approximately 50 percent of cardiac emboli to the limbs. Other sources include rheumatic or prosthetic cardiac valves, ventricular thrombus resulting from myocardial infarction or left ventricular aneurysm, paradoxical embolism of venous thrombi through the intraatrial or intraventricular communications, and cardiac tumors such as left atrial myxomas. Aneurysms of the aorta or peripheral arteries may harbor thrombi that subsequently embolize to more distal arterial sites, usually lodging at branch points where the artery decreases in size.

Thrombosis in situ occurs in atherosclerotic peripheral arteries, infrainguinal bypass grafts, and peripheral artery aneurysms, as well as in normal arteries of patients with hypercoagulable states. In patients with peripheral atherosclerosis, thrombosis in situ may complicate plaque rupture and cause acute arterial occlusion and limb ischemia in a manner analogous to what occurs in coronary arteries in patients with acute myocardial infarction. Thrombosis complicating popliteal artery aneurysms is a much more common complication than rupture and may account for 10 percent of cases of acute limb ischemia in elderly men.[15] [301] Acute thrombotic occlusion of a normal artery is unusual but may occur in patients with procoagulant disorders such as antiphospholipid antibody syndrome, activated protein C resistance (factor V Leiden), deficiency of protein C or S, heparin-induced thrombocytopenia, essential thrombocythemia, and hyperhomocysteinemia. One of the most common causes of acute limb ischemia is thrombotic occlusion of an infrainguinal bypass graft, as discussed previously.

Diagnostic Tests

The history and physical examination usually establish the diagnosis of acute limb

ischemia. Time available for diagnostic tests is often limited, and urgent revascularization

TABLE 41-8 -- CLINICAL CATEGORIES OF ACUTE LIMB ISCHEMIA (MODIFIED FROM THE SVS/ISCVS CLASSIFICATION)

		FINDINGS		DOPPLER SIGNALS	
CATEGORY	**DESCRIPTION/PROGNOSIS**	**Sensory Loss**	**Muscle Weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
b. Immediately	Salvageable with immediate revascularization			(Usually) inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

SVS/ISCVS=Society for Vascular Surgery/International Society for Cardiovascular Surgery.*Adapted from Rutherford RB, Baker JD, Ernst C, et al: Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg 26:517-538, 1997.*

TABLE 41-9 -- COMPARISON OF CATHETER-DIRECTED THROMBOLYSIS AND SURGICAL REVASCULARIZATION IN TREATMENT OF LIMB ISCHEMIA

		CATHETER-DIRECTED THROMBOLYSIS			SURGICAL REVASCULARIZATION		
STUDY	**RESULTS AT**	**Patients (No.)**	**Limb Salvage (%)**	**Mortality (%)**	**Patients (No.)**	**Limb Salvage (%)**	**Mortality (%)**
Rochester[312]	12 mo	57	82	16	57	82	42
STILE[313]	6 mo	246	88.2	6.5	141	89.4	8.5
TOPAS[314]	12 mo	144	82.7	13.3	54	81.1	15.7

From Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD). TASC Working Group. J Vasc Surg 31(Suppl):1-296, 2000.

procedures should not be delayed if limb viability is immediately threatened. The pressure in the affected limb and corresponding ABI can be measured if flow is detectable by Doppler ultrasound. A Doppler probe can be used to detect the presence of blood flow in peripheral arteries, particularly when pulses are not palpable. Color-assisted duplex ultrasonography can be used to determine the site of occlusion. It is particularly applicable for evaluation of the patency of infrainguinal bypass grafts. Contrast arteriography demonstrates the site of occlusion and provides an anatomical guide for revascularization.

Treatment

Analgesic medications should be administered to reduce pain. For patients with acute leg ischemia, the bed should be positioned such that the feet are lower than chest level, thereby increasing limb perfusion pressure via gravitational effects. Proper bed positioning can be accomplished by putting blocks under the posts at the head of the bed. Effort should be made to reduce pressure on the heels, on bony prominences, and between the toes by appropriate placement of soft material on the bed, such as sheepskin, and between the toes, such as lamb's wool. The room should be kept warm to prevent cold-induced cutaneous vasoconstriction.

Heparin is administered intravenously as soon as the diagnosis of acute limb ischemia is made.[15] The dose should be sufficient to increase the partial thromboplastin time by 1.5 to 2.5 times control values to prevent thrombus propagation or recurrent embolism. It is not known whether low-molecular-weight heparin would be as effective as unfractionated heparin in patients with acute limb ischemia.

Catheter-directed intraarterial thrombolysis is an initial treatment option for patients with category I and IIa acute limb ischemia if they have no contraindication to thrombolysis.[15] [302] Catheter-based thrombolysis can also be considered for patients with more severe limb ischemia who are considered high risk for surgical intervention. Long-term

Figure 41-22 Management algorithm for treatment of acute limb ischemia. (Adapted from Dormandy JA, Rutherford RB: Management of peripheral arterial disease [PAD]. TASC Working Group. J Vasc Surg 31[Suppl]:1-296, 2000.)

patency after thrombolysis is greater in patients with category I and II critical limb ischemia than in those with category III, in native arteries than in grafts, and in vein grafts than in prosthetic grafts.[303] [304] [305] Identification and repair of a graft stenosis after successful thrombolysis improve long-term graft patency.[306] [307] Thrombolytic regimens have used streptokinase, urokinase, recombinant tissue-type plasminogen

activator (rt-PA), and reteplase. Outcome has varied among the published reports, but small studies have suggested that initial success in achieving graft patency is greater with urokinase than with streptokinase and greater with rt-PA than with urokinase.[306] [308] The duration of catheter-based thrombolytic therapy should generally be less than 48 hours to achieve optimal benefit and limit the risk of bleeding.

Surgical revascularization is indicated for patients with category IIb and early category III acute limb ischemia.[15] The surgical procedure depends on the nature and location of the arterial occlusion. Thromboembolectomy is the procedure of choice, particularly in patients whose acute limb ischemia is due to systemic embolism.[242] [309] [310] [311] After completion of an embolectomy procedure, angiography should be performed to search for residual thrombus, which can be treated with repeated passage of the balloon embolectomy catheter or by intraoperative thrombolysis. If thromboembolectomy is neither feasible nor successful, surgical reconstruction to bypass the occluded area should be performed. These techniques were discussed previously in this chapter.

Three prospective randomized trials have compared the benefits and risks of thrombolysis and surgical reconstruction in patients with acute limb ischemia (Table 41-9) . In the first of these, often referred to as the Rochester Trial, 114 patients with acute arterial occlusion secondary to thrombosis or embolism and involving either native arteries or bypass grafts were randomized to intraarterial urokinase or surgical revascularization.[312] After 1 year of follow-up, limb salvage rates were 82 percent in each group; however, the survival rate was only 58 percent in the group randomized to surgery versus 84 percent in the group receiving thrombolysis. The higher mortality rate in the surgical treatment group was attributed to cardiopulmonary complications.

The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial compared thrombolysis with either rt-PA or urokinase to surgery after native artery or graft occlusion in patients with limb ischemia of less than 6 months' duration. The trial was stopped prematurely after enrollment of 393 patients. The composite outcome of death, ongoing or recurrent ischemia, major amputation, and major morbidity occurred in 62 percent of the group randomized to thrombolysis as compared with 36 percent of those randomized to surgery. Of patients who had symptoms for less than 14 days, however, amputation-free survival at 6 months was greater in patients treated with thrombolysis than in those treated with surgery.[313] In the Thrombolysis or Peripheral Arterial Study (TOPAS), intraarterial thrombolysis with urokinase was compared with surgery in 554 patients with acute limb ischemia of less than 14 days. Amputation-free survival rates at 6 and 12 months were 72 and 65 percent, respectively, in the thrombolysis group, and 75 and 70 percent, respectively, in the surgery group.[314] Taken together, the findings from these trials would suggest that catheter-based thrombolysis is an appropriate initial option in patients with category I and IIa acute limb ischemia of less than 7 days' duration, whereas surgical revascularization would be more appropriate for those with category IIb and early category III acute limb ischemia and in those whose symptoms have been present for more than 7 days (Fig. 41-22) .

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Atheroembolism (see also Chap. 40)

Atheroembolism refers to the occlusion of arteries resulting from detachment and embolization of atheromatous debris, including fibrin, platelets, cholesterol crystals, and calcium fragments. Other terms include atherogenic embolism and cholesterol embolism. Atheroemboli originate most frequently from shaggy protruding atheromas of the aorta and less frequently from atherosclerotic branch arteries. The atheroemboli typically occlude small downstream arteries and arterioles of the extremities, brain, eyes, kidneys, or mesentery.[315]

The prevalence of atheroembolism in the general population is not known. Most affected individuals are men older than 60 who have clinical evidence of atherosclerosis.[316] [317] [318] The Dutch National Pathology Information System reported an incidence of atheroemboli of 6.2 patients per million per year, and atheroemboli were present in 0.3 percent of autopsy cases.[316] In autopsy series of persons older than 60 years, the incidence of atheroembolism has ranged from 0.8 to 2.4 percent.[319] [320] Atheroembolism accounted for 5 to 10 percent of acute renal failure encountered in a nephrology consulting service and was found in 1 percent of renal biopsy specimens obtained from patients with an unexplained decline in renal function.[321] [322]

Pathogenesis

The risk of atheroembolism is greatest in patients with aortic atherosclerosis characterized by large protuding atheromas (see Fig. 41-4) (Figure Not Available) . A strong association is observed between large aortic plaque identified by ultrasound and previous embolic disease.[323] [324] Similarly, identification of large protruding atheromas by transesophageal echocardiography predicts future embolic events.[323] [325] [326]

Approximately 50 percent of atheroemboli involve vessels in the lower extremities.

Catheter manipulation is responsible for a large proportion of atheroemboli.[327] [328] [329] [330] [331] [332] Similarly, surgical manipulation of the aorta during cardiac or vascular operations may precipitate atheroembolism in 2 to 3 percent of patients.[333] [334] It remains controversial whether anticoagulants or thrombolytic drugs contribute to atheroembolism.[335] [336] [337] [338] In the Stroke Prevention and Atrial Fibrillation (SPAF) Study, atheroembolism occurred in 0.7 percent per patient-year in those assigned to adjusted-dose warfarin.[339] In the French Study of Aortic Plaques in Stroke Group, in no patient receiving warfarin did clinical evidence of atheroembolism develop.[326] Muscle biopsies at the time of coronary artery bypass surgery in patients with recent myocardial infarction detected atheroemboli in 14 percent of patients who received thrombolysis and in 10 percent of those who did not.[340] Atheroembolism may entail an inflammatory component inasmuch as cholesterol crystals can activate complement in vitro.[341] Hypocomplementemia can occur in patients with atheroembolism, an indication of complement activation in vivo.[315]

Clinical Findings

The most notable clinical features of atheroembolism to the extremities include painful cyanotic toes resulting in the appelation "blue toe syndrome" (Fig. 41-23). Livedo reticularis occurs in approximately 50 percent of patients.[342] Local areas of erythematous or violaceous discoloration may be present on the lateral aspects of the feet, on the soles, and also on the calves.[315] [343] Other findings include digital and foot ulcerations, nodules, purpura, and petechiae.[342] Pedal pulses are typically present since the emboli tend to lodge in the more distal digital arteries and arterioles. Symptoms and signs indicating additional organ involvement with atheroemboli should be sought. Hollenhorst plaque may be seen with funduscopic examination in patients with visual loss secondary to retinal ischemia or infarction. Renal involvement manifested by increased blood pressure and azotemia commonly occurs in patients with

Figure 41-23 Atheroemboli to the foot: "blue toe syndrome." Cyanotic discoloration of the first, fourth, and fifth toes is apparent as well as localized areas of violaceous discoloration along the lateral aspect of the foot. (From Halperin JL, Creager MA: Arterial occlusive diseases of the extremities. *In* Loscalzo J, Creager MA, Dzau VJ (eds): Vascular Medicine. 2nd ed. Boston, Little, Brown, 1996, pp 825-852.)

peripheral atheroemboli.[344] Patients may also have evidence of mesenteric or bladder ischemia and splenic infarction.

The clinical setting and findings are usually sufficient to diagnose atheroembolism. However, some of the manifestations of atheroemboli may be present with other diseases. As discussed previously, critical limb ischemia occurs in patients with severe peripheral atherosclerosis, and acute limb ischemia is a consequence of

thrombembolism, each of which would be characterized by an abnormal pulse examination. Vasculitides secondary to connective tissue diseases, infections, drugs, polyarteritis nodosa, or cryglobulinemia, for example, may be characterized by multisystem organ damage and cutaneous findings of purpura, ulcers, and digital ischemia, similar to findings that result from atheroemboli (see also Chap. 67) . Procoagulant disorders such as antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, and myeloproliferative disorders such as essential thrombocythemia can cause digital artery thrombosis with resultant digital ischemia, cyanosis, and ulceration.

Diagnostic Tests

Laboratory studies that are consistent with atheroembolism include an elevated erythrocyte sedimentation rate, eosinophilia, and eosinophiluria.[344] Other findings may include anemia, thrombocytopenia, hypocomplementemia, and azotemia. Imaging of the aorta with ultrasound, magnetic resonance angiography, or computed tomography may identify sites of severe atherosclerosis and shaggy atheroma indicative of a source for atheroemboli (see Fig. 40-22) . The only definitive test for atheroembolism is pathological confirmation by skin or muscle biopsy. Pathognomonic findings include elongated needle-shaped clefts in small arteries that are caused by cholesterol crystals, often accompanied by inflammatory infiltrates composed of lymphocytes and possibly giant cells and eosinophils, intimal thickening, and perivascular fibrosis.[315]

Treatment

No definitive treatment is known for atheroembolism. Analgesics should be administered for pain. Local foot care should be provided as described previously for patients with critical limb ischemia. It may be necessary to excise or amputate necrotic areas.

These patients are subject to recurrent atheroembolic events. Risk factor modification such as lipid-lowering therapy and smoking cessation may have favorable effects on the overall outcome from atherosclerosis, but it is not known whether such intervention will prevent recurrent atheroembolism. The use of antiplatelet drugs to prevent recurrent atheroembolism has been advocated by some and refuted by others.[345] [346] It is reasonable, however, to administer antiplatelet agents even in the absence of strong clinical evidence of efficacy since these agents will prevent other adverse cardiovascular events in patients with atherosclerosis. The use of warfarin is also controversial, and some have even suggested that anticoagulants precipitate atheroemboli.[323] [336] [347] Others have found that warfarin reduces atheroembolic events, particularly in patients with mobile aortic atheroma.[338]

Surgical removal of the source should be considered in patients with atheroembolism, particularly those in whom it recurs. Surgical procedures include excision and replacement of affected portions of the aorta, endarterectomy, and bypass operations.[348] Operative intervention is targeted to the site of the aorta or the iliac or femoral arteries where an aneurysm has formed or where obvious shaggy friable atherosclerotic plaque is present. Oftentimes, the aorta is diffusely affected by severe atherosclerosis and it is not possible to identify the precise segment that is responsible

for atheroembolism. In addition, many of these patients are elderly and have coexisting coronary artery disease, which increases the risk associated with major vascular operations.

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Chapter 42 - Extracardiac Vascular Interventions

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The exciting development and widespread use of endovascular procedures for managing extracardiac vascular disease are explained by several factors, including rising health care costs, advances in percutaneous catheter technology, and a high level of acceptance by patients of nonoperative interventions for the management of arterial occlusive disease, aneurysms, arterial hemorrhage, neoplastic disease, arterial-venous malformations, and venous disease. In this chapter we provide a review of the experience for each general topic along with the limitations and complications of these procedures. The application of various endovascular techniques, including percutaneous transluminal angioplasty (PTA), stents, and stent-grafts, to this wide spectrum of vascular disease is also addressed. It is beyond the scope of this presentation to discuss percutaneous procedures directed at dialysis access lesions, bypass graft stenoses, abnormalities affecting variant native anatomy, and uncommon causes of vascular disease.

Over the past decade a consensus has evolved regarding the indications and benefits of percutaneous treatment of extracardiac vascular disease. There is now a tremendous enthusiasm and potential for further growth of percutaneous endovascular therapies

based on the ease, safety, short recuperation, and long-term results associated with these procedures.

ARTERIAL INTERVENTIONS

From the time of the great Charles Dotter, the father of interventional therapy, on, the focus of this therapy has been trained in on the problem of arterial occlusive disease. Atherosclerotic disease is the leading cause of death in the United States, and its presence in the heart reflects its presence elsewhere. The heart serves as a microcosm of the treatment of atherosclerosis in the periphery. The tools of the trade are essentially the same, and hence no detailed description of stents, thrombolytic agents, mechanical thrombectomy devices, or angioplasty balloons is provided in this chapter (see Chap. 38) . Whether in the coronary or extracardiac circulations, the bane of successful intervention is restenosis. For the most part, the approaches to restenosis in the coronary arteries should apply to the periphery. The early results of brachytherapy in the coronaries are promising.[1] Coated stents, local drug therapy, and gene therapy also deserve careful evaluation.

Iliac Interventions

If there is an ideal substrate for percutaneous intervention, it is the iliac artery. The iliac is a large vessel, it is close to the puncture site, and the surgical alternative to iliac interventions is usually a major operation. For all the apparent simplicity of percutaneous treatment, however, closer inspection reveals layers of complexity that make definitive answers about the specifics of the role of iliac intervention elusive. Thus, a brief primer on unresolved issues in the iliacs includes, but is not limited to: (1) surgery versus percutaneous intervention in complex iliac occlusions; (2) primary stenting versus secondary stenting for PTA failure; (3) the role of lesion morphology (i.e., eccentricity, degree of calcification, and tortuosity) in decision-making between PTA and stenting; (4) efficacy of treatment in stenoses versus occlusions; (5) the importance or lack thereof in maintaining the patency of the hypogastrics during interventions; (6) the role of thrombolysis in chronic occlusions; (7) the choice of stent from among a now dizzying variety; (8) the acceptable residual pressure gradient after iliac intervention; (9) the appropriate length of stent for a given lesion length; (10) the maximum lesion length that is appropriate for percutaneous therapy; (11) the optimum strategy for treating lesions at the aortic bifurcation; and (12) the conditions that make it appropriate to treat an iliac lesion through contralateral access. All of these issues have very practical implications on the daily decision-making facing an interventionalist who, in essentially every case involving treatment of the iliac segment, must address each of them in determining the appropriate therapy.

Rarely can the solutions to these problems be found in the literature. More often, one is left to confront them armed only with one's experience and the conflicting dogmas of various experts. Although iliac angioplasty/stenting is technically among the more straightforward arterial interventions, the issues surrounding such a seemingly well-explored territory reveal large gaps in our knowledge. As in many areas, the rapidity of technology development, the multiple competitive stent technologies, the plethora of variables to be controlled, and the many specific questions needing to be

answered have conspired to make controlled, randomized studies of percutaneous iliac intervention daunting. At the same time, the absence of such trials will always provide ammunition to the skeptics who dismiss percutaneous iliac therapy as a quick fix.

Iliac angioplasty has been shown safe and effective (Fig. 42-1) , with impressive patencies, based on several studies.[2] [3] [4] The evidence for the efficacy of iliac stent placement also has been established through the many large series that have been published to date.[5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] Lack of standardized reporting and vast differences in technique, stents employed, and lesion type have made it difficult to draw conclusions from these studies (Table 42-1) . Bosch and Hunink [19] published a meta-analysis of iliac angioplasty and stent placement in an attempt to consolidate the findings of many series to yield meaningful information. It serves both as a

Figure 42-1 Iliac artery stent placement. *A,* Initial pelvic arteriogram demonstrates bilateral common iliac artery occlusions in a 52-year-old man with severe bilateral lower extremity claudication. *B,* After bilateral Palmaz stent (Johnson and Johnson, Miami Lakes, FL) placement, final arteriogram demonstrates restoration of normal-caliber common iliac arteries without residual stenosis. No pressure gradient was present after intervention.

useful review of studies done to that date and as a reasonable comparison of PTA with stent placement in the iliacs. The conclusion that there is a 39 percent reduction of late failure with stent placement as opposed to PTA gave comfort to those who intuitively believed that primary stent placement was a superior strategy. Those hopes were deflated by a later cost-effectiveness analysis by the same group[20] based on their meta-analysis[19] and an additional randomized trial of iliac PTA versus stent by the same group.[21] The cost-effectiveness evaluation[20] reveals that PTA with selective stent placement is a more cost-effective strategy than primary stent placement. This conclusion is based on stent and balloon costs in Holland, which the investigators acknowledge is higher than those in the United States. The findings are also based on patients being treated for claudication who are found to have stenotic disease rather than an occlusion. These caveats provide a glimmer of hope for proponents of the primary stent strategy in the United States.

Femoropopliteal Interventions

It is reasonable to question whether atherosclerotic disease of the superficial femoral artery (SFA) should be treated at all. This consideration has enormous implications: approximately 1 million people in the United States develop claudication each year.[22] The vessel may occlude and be asymptomatic in about 10 percent of those who progress to occlusion,[22] [23] or it may result in mild claudication, which improves with walking.[24] The profunda femoris artery shoulders the burden as a collateral in the case of SFA occlusion. The natural history of femoropopliteal (FP) disease is well

documented.[23] [24] In the tabulations of McDaniel and Cronenwett, [23] the 5-year outcome for claudicators is as follows: mortality, 29 percent; need for operation, 25 percent; improved or stable, 55 percent; claudication worse, 16 percent; and amputation, 4 percent. Similar numbers have been confirmed in other published reports.[25] The high mortality in this population reflects the role of peripheral vascular disease as a marker for generalized atherosclerosis. These data, culled from a large number of first-rate studies that for the most part preceded the era of percutaneous therapy, are hardly compelling when used to support arguments for intervention in this population. A walking program may be as effective as more aggressive approaches,[24] [26] although the study of Price and associates [26] found that at 6 years the results of PTA and an exercise program were equivalent in their lack of benefit to the patient. The message has emerged that conservative therapy is appropriate for patients with stable claudication. Intervention is usually warranted for patients with progressive claudication, severe life-style limitation, or critical ischemia (rest pain, tissue loss); it is this population that gives rise to the debate over appropriate treatment.

Approaching the field of PTA of the FP segment invites confusion. A wide array of reports have come from many quarters with disparate results. Reporting methods and definitions vary. The word "patency", for example, takes on all shades of meaning, prompting some authors to discuss at considerable length what is meant by the term. PTA in the FP segment has been accepted by most, albeit begrudgingly by some, as a useful tool in the treatment of chronic lower extremity ischemia. The appropriate use of this procedure remains an issue clouded by the glaring disparity in quoted patency rates in the literature.

TABLE 42-1 -- RESULTS OF ILIAC ARTERY STENT PLA

AUTHOR	REFERENCE	YEAR	NO.PATIENTS	LESIONS TREATED	PERCENT WITH OCCLUSIONS	TECHNICAL SUCCESS (%)	
Murphy, T*	14	1998	65	90	31	97	
Tetteroo	21	1998	143	187	9	NA	
Reyes	18	1997	59	61	100	92	
Dyet	17	1997	72	72	100	93	
Vorwerk	6	1996	109	118	0	100	
Spoval	8	1996	95	101	43	99	
Murphy, T	13	1996	66	94	41	91	

Henry	5	1995	184	184	9	100	
Vorwork	16	1995	127	103	100	79	
Martin	9	1995	140	171	9	97	
Murphy	10	1995	83	108	21.4	100	
Vorwerk	7	1992	125	125	50	98	
Palmaz	12	1992	486	567	13.5	NA	

A=all types; ABI=ankle-brachial index; NA=not available; P=Palmaz; W=Wallstent

*Data from this series partially included in reference 13.

At latest follow-up interval

Fortunately, the amassed body of experience is large enough to allow reasonable conclusions about indications for FP PTA. An exhaustive analysis of PTA and surgical revascularization is provided by Hunink and coworkers,[27] who set out to establish when PTA and when bypass surgery is the preferred method of FP level revascularization. This analysis in turn was based on data from a prior meta-analysis by the same investigators[28] that summarized the results of 7 series of PTA and 10 series of bypass surgery to determine patency rates. The metric used to evaluate outcome in this study is the quality-adjusted life-year (QALY). The data were deemed appropriate or not based on the reporting methods used, and only those studies adhering to the chosen reporting criteria were included. Several large series, therefore, were excluded.[29] Using a theoretical model, the authors determined that, for a 65-year-old man with life style-limiting claudication or chronic critical ischemia (tissue loss or rest pain) and a *stenotic* lesion in the FP segment, PTA was the more cost-effective strategy. For the same cohort with claudication and an *occlusion*, PTA was also the optimal strategy. For chronic critical ischemia and FP occlusion, bypass surgery is the optimal initial strategy. The population is narrowly defined and the results based on assumptions, but the methods employed in this analysis were stringent. This generalized conclusion notwithstanding, application of such rules in individual patients, with a host of medical and social factors influencing treatment choices, may be extremely difficult.

The degree to which anatomical and technical factors sway one in choosing a method of revascularization cannot be overestimated. The larger series include subgroup analyses of impressive specificity. For example, the series by Capek and colleagues[30] breaks down the data in terms of presenting symptoms, risk factors, lesion number and distribution, lesion length and severity, lesion characteristics (calcification, eccentricity, irregularity), and runoff status. Life table analyses are performed on several variables. Those factors having a statistically significant impact on outcome included presence of

other vascular disease, diabetes, severity of presenting symptoms, eccentricity of lesion, degree of stenosis, and lesion length. The effect of lesion length is further subdivided, with all the permutations, among lesions of 0 to 2 cm, 2 to 5 cm, 5 to 10 cm, and larger than 10 cm. Comparisons among all these groups reveal a significant difference in outcome between lesions 0 to 2 cm and those larger than 10 cm and between those 2 to 5 cm and those larger than 10 cm. Given the multiplicity of factors analyzed, it is striking that the greatest statistical significance ($p<0.001$) was found for presence of a palpable pulse at the conclusion of the procedure as a predictor of good outcome. This finding is highly reassuring to those of us for whom the first move after performing SFA PTA is to check for a pedal pulse by physical examination. Interestingly, if technical failures are omitted from the numbers for interventional treatment of FP occlusions, there is no statistical difference in patency between stenosis and occlusion. The 5-year patency of 42 percent for FP PTA is comparable with other recent large series,[31] [32] in which secondary patencies range from 38 to 45 percent. The complication rate for FP PTA is about 10 percent.[25] [33] Of these, only about 2 percent require surgical intervention and 0.2 percent result in death.[25] The specific techniques of PTA are rarely a focus of various studies, although differences in technique may account for the wide variation in patency. Proper balloon sizing and balloon length are important factors in angioplasty success, but they are seldom described in sufficient detail to be of use to the reader. In addition, some adjunctive techniques, such as prolonged balloon inflation to improve the result following suboptimal initial PTA, have been published.[34]

The role of stents in the FP segment is uncertain. One large study by Henry and associates[5] reported a 4-year secondary patency rate of 95 percent for SFA stents. These results have not been duplicated by others.[9] [35] The consensus appears to be that stents are only warranted for salvage in the FP segment for a PTA failure.[9]

Infrapopliteal Interventions

Anatomy, the limitations of technology, and a misplaced sense of futility have until recently kept the infrapopliteal vessels beyond the reach of the interventionist. Anatomy continues to be an obstacle, whereby occlusion of the main conduit, the FP segment, thwarts efforts to treat lesions below the knee. As for equipment limitations, the balloon technology has improved immensely and multiple low-profile, highly flexible balloon catheters are now available on long shafts to access the trifurcation vessels. Digital angiography provides excellent anatomical detail and superb real-time fluoroscopic guidance enhanced by angiographic image overlay ("roadmapping"); and steerable guidewires, with liberal use of intraarterial vasodilators, have allowed access to the ankle and beyond.

The nihilistic attitude adopted by some when treating infrapopliteal disease does not hold up to scrutiny. Usually called on in a last ditch effort at limb salvage, after surgery has been ruled out or failed, tibial angioplasty is performed on a skewed population of those with the most severe critical ischemia, facing imminent amputation, and frequently having the most significant comorbid conditions. Such heroic interventions are occasionally doomed to failure by the underlying anatomy but attempted nonetheless, the interventionalist responding to pressure from the referring surgeon or from the

patient to salvage the limb. In spite of these obstacles, many series report an impressive limb salvage rate given the circumstances. Saab and coworkers[36] reported on 14 tibial PTA procedures with technical success in 10, of which seven patients were spared amputation. Bakal and colleagues,[37] in a series of 53 patients, achieved a successful clinical response in 67 percent of patients overall, 85 percent of whom were diabetic, and in 97 percent of patients in whom straight line flow to the foot was restored through PTA. The series of Matsi and colleagues[38] had a technical success rate of 83 percent of 84 limbs treated for tibial disease, with a limb salvage rate of 63 percent at 2 years among those in whom one to three calf vessel runoff was restored. Schwarten reported a 2-year limb salvage rate of 83 percent in his series of 96 patients.[39] His series imposed restrictions on suitability for angioplasty: a maximum of five lesions and a maximum occlusion length of 5 cm. Other large series[40] [41] also report respectable limb salvage rates.

There are those who still challenge the appropriateness of infrapopliteal angioplasty.[42] [43] A vigorous defense is delivered by Bakal and coworkers,[44] who offer an excellent review of the literature and rebuttal of the juxtaposed submission by Fraser and associates.[42] There is agreement that uniform reporting standards and improved patient selection would aid in analysis of the published data and that a controlled randomized trial would be helpful in determining the cost-effectiveness of PTA versus surgery for infrapopliteal disease. Such trials are more easily designed than done, as partisans of one modality or the other often have little enthusiasm for enrolling patients.

Aortic Interventions

The large caliber of the aorta can mask significant atherosclerotic disease. Stenotic disease, resulting in a pressure gradient, is therefore uncommon, especially in a location not contiguous with the aortic bifurcation.

Reasonable concerns about angioplasty or stenting the infrarenal abdominal aorta, where vessel rupture could be rapidly fatal, have

not been validated by the few series thus far published. Hallisey and coworkers[45] reported a series of 14 patients in which 100 percent technical success was achieved, with clinical success in 93 percent and no significant complications.

Infrarenal aortic stent placement was reported in a small series by Long and colleagues,[46] also achieving a 0 percent morbidity rate. The clinical success in the series of seven patients was more difficult to deduce because of associated iliac segment disease. Comparison of aortic PTA and stenting was made through analysis of a subgroup of the SCVIR Transluminal Angioplasty and Revascularization (STAR) registry.[47] Stent placement, at least in the short term, bestowed no clinical benefit in the retrospective analysis of 25 patients.

Renal Artery Interventions (See also Chap. 48)

Several aspects of renovascular disease (RVD) make its treatment unique among those discussed here. The outcome measures are systemic physiological parameters (blood pressure, serum creatinine concentration) rather than improvement of a specific symptom. As paired organs, often with multiple arteries feeding each, the kidneys may play a sort of anatomical shell game, through which it may be difficult to determine which kidney or which artery is the culprit in a hypertensive patient. To complicate matters, renal artery stenosis (RAS) has a domino effect, whereby the stenotic lesion provokes a humoral response leading to hypertension and this hypertension proceeds to nephropathy in the seemingly uninvolved kidney. Furthermore, in addition to eliciting a hyperreninemic response, decreased blood flow to the kidney causes a separate ischemic nephropathy, leading to a loss of glomeruli and renal mass. Ischemia often causes shrinkage of the affected kidney. It is these secondary effects of RAS that probably lead to the occasionally tepid responses to interventional therapy. The damage to the kidney has already been done, and the intervention merely retards further deterioration. On the other hand, somewhat mysteriously, patients with severe RAS, involving one or both kidneys, may be normotensive and have normal function. Other factors, such as renal size, differential function, and the importance of nonatherosclerotic stenosis (fibromuscular dysplasia, Takayasu's arteritis), further distinguish RAS from stenotic disease elsewhere in the arterial system.

RVD is common, occurring in 27 percent of the population evaluated arteriographically for atherosclerotic disease in the lower extremities, in whom RVD was unexpected.[48] Given the prevalence of hypertension and the aging population, this subgroup constitutes a large cohort. Furthermore, the rapid progression of disease with deterioration of renal function is documented in the same study.[48] Aortorenal bypass surgery produces good clinical results, but at the cost of relatively high morbidity, length of hospital stay, and cost.

Renal angioplasty and stent placement have emerged as elegant solutions to the problems imposed by RVD (Fig. 42-2) . Numerous studies have been done to date supporting the effectiveness of percutaneous intervention for RAS.[49] [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] The results of several of the more recent series on renal artery stent placement may be found in Table 42-2 . Many of the findings of these studies have also been summarized in the excellent review article by Rees and associates,[64] which also includes data from the U.S. multicenter trial of stents in renal arteries. The data presented therein are striking: the technical success for renal stent placement approaches 100 percent benefit; achieved in 61 percent of patients treated for hypertension and improvement or stabilization of renal function in 70 percent of patients after stenting. The beneficial effects of stent placement on azotemia are particularly well displayed in a series by Harden and associates,[51] in which reciprocal serum creatinine plots dramatically flatten at the time of stent placement. One recent trial deemed the effectiveness of renal artery angioplasty vs. antihypertensive drug therapy similar.[64A] However, the follow-up of these patients was limited to 12 months, the use of stents does not reflect current practice, and there was a high degree of "cross-over" to PTCA

from the drug-treated group, tempering the ability to generalize these results.[64B] [64C]

With regard to the issue of angioplasty versus stenting, a recent randomized study by van de Ven and colleagues[65] suggests that primary renal artery stenting is a superior strategy for ostial atherosclerotic RAS when compared to angioplasty with selective stent placement for angioplasty failure. The relative roles of angioplasty and stent placement in *nonostial* atherosclerotic RAS are not as clear-cut and probably favor initial angioplasty with selective stenting. One recent retrospective analysis[66] comparing renal PTA, renal stenting, and aortorenal bypass surgery provides evidence that percutaneous therapy is more cost effective and that PTA is probably the procedure of choice in nonostial RAS. In renal stent procedures, the complication rate hovers around 20 percent, including both major and minor complications.[67] The complication rate depends, however, on operator experience.[64] Aspects of this procedure aided by operator experience include exercising judgment in case selection, choice of access, what procedure to perform, and when to desist.

In summary, it stands to reason that improvement of renal blood flow is desirable, not only to improve function and ameliorate hypertension but also to spare renal parenchyma. It can be argued that early intervention for RAS may be warranted even *before* azotemia has occurred and in normotensive patients. Although this is far from proven, and renal intervention in the absence of these known indications is often eschewed, delaying renal artery interventions until clear end-organ damage has been done seems analogous to allowing asymptomatic patients with carotid disease to progress to stroke before action is taken. Clearly, the timing of intervention in this context warrants careful study.

Visceral Artery Interventions

Occlusive disease of the visceral vessels does not often lead to mesenteric ischemia, owing primarily to the redundancy in the system. Multiple collateral pathways exist among the celiac artery, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). When mesenteric ischemia does occur, it is rarely thought of a priori because the symptoms mimic those of peptic ulcer disease and because the frequent accompanying weight loss usually precipitates a work-up for malignancy. A careful history, however, usually reveals that patients maintain their appetites but experience such excruciating pain after eating that they avoid food altogether.

Patients with the classic symptoms and endoscopic evidence of bowel ischemia have a high likelihood of having significant stenotic disease of at least two of three mesenteric vessels on angiography.[68] If a single vessel is involved, however, it is usually the SMA, which is almost invariably involved when patients have confirmed visceral ischemia. It should be noted that both computed tomographic angiography and magnetic resonance angiography are of sufficient quality to be used as screening tests for stenotic disease of the visceral vessels. Surgical treatment of this disease has a high incidence of morbidity, given the patients' generally advanced age and diffuse atherosclerotic disease. Mateo and coworkers[69] reported an 8 percent mortality rate and a 45 percent complication rate among 85 patients in their series. These were similar to numbers

reported by Kihara and colleagues.[70]

The common refrain is again sounded that less invasive

Figure 42-2 Renal artery stent placement. *A,* Initial renal arteriogram demonstrates a critical left renal artery ostial stenosis in a 48-year-old man with renal insufficiency and hypertension. *B,* Arteriogram obtained after stent placement demonstrates no significant residual stenosis. No pressure gradient was detectable after stent placement. *C,* The patient also received a stent in the right renal artery and was able to be taken off dialysis with a creatinine level stabilized in the 3 to 4 mg/dl range.

therapy should go a long way toward improving on these high rates of surgical morbidity (Fig. 42-3) . To that end, several series of both angioplasty[68] [71] [72] [73] [74] and stent placement (Table 42-3) [75] in the visceral vessels have demonstrated a high degree of technical success and clinical effectiveness. The complication rate and the mortality rate are not inconsequential, although both are lower than that presented in surgical series. A skewing of the populations can be seen as a result of patient selection, with patients undergoing percutaneous therapy if deemed poor operative candidates. This is the case in the series by Allen and associates, for example. The results of percutaneous therapy might well have been even more impressive were all patients with mesenteric ischemia, irrespective of comorbidities, given that option.

Supraaortic Interventions

The treatment of occlusive disease of the brachiocephalic vessels has followed the typical progression from surgical management, to PTA, to stent placement, all within the past decade. Percutaneous intervention has been advocated as the primary treatment for symptomatic subclavian artery stenosis or occlusion.[76] [77] Treatment of common carotid lesions is somewhat more problematic, especially when combined with carotid endarterectomy at the bifurcation.[78] The treatment of carotid bifurcation lesions by stent placement is addressed below. The innominate artery tends to be included in reports of subclavian artery intervention,[78] although separate reports of innominate stenting contain excellent results.[79] [80]

TABLE 42-2 -- RESULTS OF RENAL ARTERY STE

AUTHOR	REFERENCE	YEAR	PATIENTS	ARTERIES TREATED	STENT TYPE	OSTIAL LESIONS (%)	TECHNICAL SUCCESS (%)

Rodriguez-Lopez	59	1999	108	125	P	66	97.6
Rees	64	1999	123	296	P	80	98
Xue	66	1999	39	45	P/W	23	93
Dorros	61	1998	163	202	P	NA	99
Tuttle	62	1998	129	148	P	100	98
Rundback	50	1998	45	54	P	80	94
Harden	51	1997	32	33	P	NA	100
Boisclair	58	1997	33	35	P	54	100
Blum	60	1997	68	74	P	100	100
Henry	54	1996	59	64	P	53	100
van de Ven	49	1995	24	28	P	100	100
Hennequin	57	1994	21	21	W	33	100

The follow-up intervals for the various outcome parameters are highly variable and are omitted here fo

NA=not available; P=Palmaz; W=Wallstent

TABLE 42-3 -- RESULTS OF INTERVENTION FOR VISCERAL I

AUTHOR	REFERENCE	YEAR	PATIENTS	TECHNICAL SUCCESS (%)	CLINICAL SUCCESS (%)	PRIMARY PATENCY (%)	SECONDARY PATENCY (%)
Hallisey	71	1995	16	88	75	75	75
Matsumoto	68	1995	19	79	80	83	92
Maspes	73	1998	23	90	77	88	100
Allen	72	1996	19	95	79	NA	92
Sheeran*	75	1999	12	92	NA	74	83

NA=not available.

*Stent study.

Figure 42-3 Recanalization and stent placement for superior mesenteric artery (SMA) occlusion in a 78-year-old man with recent 30-lb. weight loss, severe postprandial pain, and food avoidance. *A,* Lateral

abdominal aortogram demonstrates occlusion of the SMA 4 mm beyond its origin. Faint reconstitution of the SMA can be seen (arrowhead). Severe stenosis at the origin of the celiac axis can also be seen (curved arrow). *B,* After recanalization and primary stent placement, antegrade flow in the SMA has been restored without significant residual stenosis. The patient's symptoms resolved immediately, and he gained back much of the weight he lost.

Crucial to patient selection in the treatment of subclavian occlusive disease is establishing the presence of symptoms referable to the lesion. When proximal subclavian occlusion occurs it is often asymptomatic. In such cases, intervention is not warranted. Upper extremity claudication and vertebrobasilar insufficiency are the most common presenting symptoms.[78] [81] [82] [82A] Technique for recanalization of occlusions may involve femoral and/or brachial access. Results of PTA alone in the subclavian show a clinical success rate of 68 to 92 percent.[76] [82] [83] For subclavian stent placement, clinical success ranged from 83 to 100 percent.[78] [84] [85] [86] [86A] The much-feared complication of embolization into the vertebral artery has only rarely occurred in these series. Some protection from this is naturally afforded by the delay in reversal of flow in the vertebral artery after antegrade subclavian flow is reestablished.

A separate and expanding indication for left subclavian intervention follows the advent of left internal mammary artery (LIMA) coronary artery bypass grafting (CABG). Several case reports and small series have been published describing the syndrome of coronary steal and its treatment by percutaneous therapy, with generally excellent results.[87] [88] [89] [90] [91] [92] [93] [94] [95]

Common carotid artery interventions are uncommon and are usually done in conjunction with planned carotid bifurcation surgery to guarantee adequate postoperative inflow. PTA or stenting of the proximal common carotid is most frequently performed intraoperatively with direct carotid puncture. In this fashion the technical difficulty introduced by navigating from the groin is obviated and distal control of the vessel may be obtained to prevent embolization at the time of intervention.

Vertebral artery PTA and stenting are rarely performed. The single small series in the literature does, however, demonstrate an adjunctive role for vertebral artery stenting.[96]

Carotid Interventions

One look at the inside of a carotid bifurcation gives one a good idea why surgeons are skeptical about carotid angioplasty and stenting. The plaque is usually an ulcerated, pockmarked, craggy mess, with friable wisps of thrombus and tenuously attached fronds of atheroma. The suggestion that someone should pass a large-caliber catheter through this figurative minefield, inflate a balloon, and then deploy a stent over the path of destruction seems unthinkable. Contrary to expectation, however, this procedure is feasible and unexpectedly safe (Fig. 42-4) . As with most procedures in interventional radiology, what remains to be seen is how well it works, and for how long.

Few areas have provoked more controversy. Editorials concerning carotid interventions flood the literature.[97] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107] [108] [109] Several things about carotid interventions specifically make it a hotbed of controversy. Compare it, for

example, to iliac interventions. Unlike iliac percutaneous interventions, those in the carotid eliminate the need for an operation of very *low* morbidity and mortality.[110] [111] [112] [113] As opposed to aortofemoral surgery, hospital stays for carotid surgery are generally

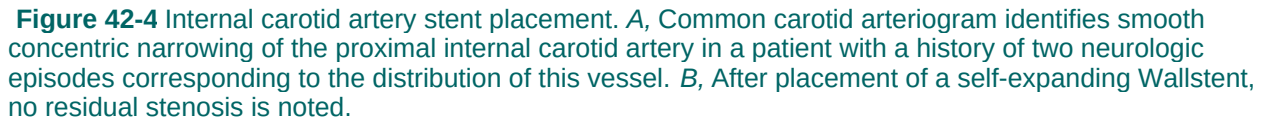

Figure 42-4 Internal carotid artery stent placement. *A,* Common carotid arteriogram identifies smooth concentric narrowing of the proximal internal carotid artery in a patient with a history of two neurologic episodes corresponding to the distribution of this vessel. *B,* After placement of a self-expanding Wallstent, no residual stenosis is noted.

short. In the iliacs, intervention does not burn any surgical bridges. In the carotid, stent placement makes surgery at the very least difficult and perhaps impossible. Emboli precipitated by iliac interventions can usually be managed percutaneously and rarely have long-term sequelae. In the carotid, emboli can be catastrophic, for obvious reasons. Fear of downstream embolization has led, in fact, to a burgeoning industry in various filtering or blocking devices deployed distal to the carotid bifurcation during interventions to trap emboli.

Careful scrutiny of the carotid endarterectomy trials[112] [113] reveals that a large number of patients were excluded from them for a variety of comorbid conditions. It is often precisely these patients who are offered carotid stent placement, and it is therefore not surprising that the complication rate may be higher in this population. Furthermore, stent technology is evolving, techniques are improving, and operator skills have been honed. As a result, it stands to reason that results of carotid stent placement will only improve. There have been few recent innovations in carotid surgery. At the same time, those series that have involved carotid stents in high-risk patients have demonstrated favorable results, certainly better than those of the medical alternative.[114] [115] [116] One aborted randomized trial,[117] in which 5 of 7 patients suffered strokes in the early stent experience, is difficult to reconcile with the superb results published in other series.[118] [119] Clinical and angiographic criteria may help in selecting patients at risk for complications of carotid interventions.[119A] In one large series, Yadav and colleagues treated 126 carotid arteries in 107 consecutive patients. The patients were often in a risk category that would have excluded them from the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[112] or Asymptomatic Carotid Atherosclerosis Study (ACAS)[113] by virtue of their carotid arterial anatomy and/or preexisting medical conditions. Despite this relatively high risk group, the overall 30-day stroke plus death rate was 9.3 percent, and the major stroke plus death rate was 2.8 percent. These numbers compare favorably with surgical complication rates sufficiently well to justify further investigation.

A randomized trial of carotid stenting versus carotid endarterectomy has recently been funded by the National Institutes of Health. The Carotid Revascularization Endarterectomy versus Stent (CREST) trial has enrolled sites and will soon be under way. Such a controlled, randomized trial should help clarify the role of percutaneous

carotid intervention, an issue that involves hundreds of thousands of patients each year and has huge repercussions as a major health care concern.

Disease of the Aorta

Aortic Dissection (See also Chap. 40)

There is currently much discussion among vascular interventionalists over the percutaneous therapy for aortic dissection, an unusual but potentially devastating complication of arterial disease. Even the most vehement naysayers concerning endovascular therapies must acknowledge the inroads interventionalists have made on the management of aortic dissection. Surgical results in this disease are mediocre;

and although medical control of hypertension is of great importance still in preventing extension of the dissection, current data support the role of interventional treatment of the ischemic complications. Aortic dissection frequently causes acute ischemia in the renal, mesenteric, and lower extremity vascular beds.

The largest series published to date is that of Slonim and associates,[120] in which 40 patients were treated for ischemic complications of aortic dissection by stent placement and/or percutaneous balloon fenestration of the dissection flap. Ninety-three percent were successfully revascularized, although 25 percent died within 30 days, most often due to irreversible ischemic damage acquired before revascularization. These results were closely matched by those of Williams and colleagues.[121]

The latest innovation in the treatment of acute aortic dissection is the use of stent-grafts to cover the primary entry tear.[122] In one series of 19 patients, 76 percent had restoration of flow to the ischemic bed by placement of the stent-graft alone and there was 100 percent technical success in stent-graft placement.

INTERVENTIONS FOR ANEURYSMAL DISEASE

The covered stent, or stent-graft, represents the next great area of promise in minimally invasive therapy. At present, it cannot be referred to as *percutaneous* therapy, because currently available devices require a cutdown for arterial access. However, with the technology advancing at a rapid pace, minification of the equipment to percutaneously manageable sizes is inevitable. The current reservations over this approach involve the training of individuals who should place stent-grafts and technical limitations of current devices. Increasingly, case reports of late endoleaks (see later) have called into question the long-term viability of the technology in its current form. As in other arenas of vascular intervention, more comparative data will be required to evaluate the role of surgical and interventional approaches to abdominal aortic aneurysm treatment.

ABDOMINAL AORTIC ANEURYSM.

Abdominal aortic aneurysm (AAA) is a significant health care issue in terms of the prevalence of the problem and the expense to treat it (see Chap. 40) . As the population ages, and for unknown other reasons, the incidence of AAA is increasing.[123] [124] Standard therapy, open surgical excision of the aneurysm, is well tolerated in most patients, but significant morbidity occurs in a large percentage of patients.[125] The pressure applied by increased health care costs has driven physicians to seek less invasive, less morbid, and less costly procedures to meet this demand. The standard set by surgical treatment, however, is a high one, and surgeons have had about 40 years to perfect their craft.

The patent literature on endoluminal aneurysm repair dates to 1979, but it was not until Parodi's first series in humans that interest broadened in this approach.[126] Recognizing the aforementioned pressures and the presence of an untapped market, industry and vascular specialists have moved rapidly to address the need. As a result, a daunting profusion of devices has become available. Stiff competition has emerged to enroll patients in trials of various devices. The lay press has entered the fray, and many patients

Figure 42-5 Modular, bifurcated endovascular grafts for the treatment of abdominal aortic aneurysm. *A,* Talent endograft (World Medical, Inc./AVE Inc., Sunrise, FL) is constructed with a series of serpentine nitinol self-expandable springs attached to a polyester surgical graft by a continuous series of polyester sutures. The Talent system allows for transrenal fixation of the device using a proximal bare stent design. This may help to secure the position of the endograft in patients with short (less than 15 mm) infrarenal aneurysm necks. *B,* Excluder endograft (W. L. Gore and Associates, Inc., Sunnyvale, CA) is composed of thin-wall polytetrafluoroethylene graft material that lines a self-expanding nitinol stent exoskeleton. The modular bifurcated design includes proximal hooks to provide enhanced fixation to the proximal neck and a polytetrafluoroethylene cuff to prevent leaks. *C,* Zenith prosthesis (Cook, Inc., Bloomington, IN) is constructed with a series of Z-stents and polyester graft material. This device utilizes a proximal uncovered stent framework with hooks to secure attachment of the endograft to the aortic wall and allow treatment of relatively short proximal aneurysm necks.

express interest in innovative and less invasive alternatives to surgery.

Whereas open surgical repair has stood the test of time, current follow-up of endoluminal repair is necessarily shorter, with measures of effectiveness given for 2-year, rather than 10-year, follow-up. However, prolonged follow-up of patients with endoluminal AAA repair will help establish the utility of such procedures with time.

The natural history of untreated AAA is fairly well documented,[127] and its unpredictability has led to a gradual, but stepwise, reduction in the size of an aneurysm at which elective repair should be recommended.[128] With the advent of a new

technology that promises greatly decreased morbidity, the bar may be lowered farther. The issue remains, however, to what extent the placement of an endoluminal graft alters the long-term natural history of AAA. A new array of problems has accompanied the emergence of endoluminal aneurysm repair, problems only recognizable because of the superb imaging capabilities of computed tomography, ultrasonography, and digital subtraction angiography.

Aneurysm elongation, widening of the infrarenal neck, increasing tortuosity, persistence of collaterals through the IMA and lumbars, and incomplete apposition of the proximal and/or distal fixation of a device, all can be determined with serial imaging, and the information has identified a new problem: the "endoleak." Endoleaks are continued flow within the aneurysm sac, external to the device, after endoluminal repair. The degree to which an endoleak may be tolerated is unknown currently, although it is the object of intense scrutiny.[129] [130] [131] [132] [133] [134] [135] [136] [137] [138] Endoleaks may resolve spontaneously, but they may also persist,[139] and the specter of continued rupture risk looms in such situations. Unfortunately, even when aneurysm size decreases after stent-graft repair, there is still a risk of rupture.[140]

DEVICES AVAILABLE FOR AORTIC ENDOLUMINAL REPAIR.

Appreciation of the rarity of having a distal aneurysm neck has dictated the terms of stent-graft design. The two major categories of devices are (1) aortounilateral iliac with contralateral blocker and (2) bifurcated. Most of the commercially developed devices are bifurcated (Fig. 42-5) . Most are composed of either polyester or polytetrafluoroethylene (PTFE), with a fully supported endoskeleton of either nitinol or stainless steel. The main exception is the EGS (Endovascular Technologies, Menlo Park, CA) device, that incorporates self-expanding metallic cuffs with radially arrayed hooks at the fixation points and is not fully supported. Some evidence has been published that suggests advantages to a system that is fully supported[141] (Fig. 42-6) . Each device, used under a U.S. Food and Drug Administration (FDA)-approved protocol or on a compassionate use basis, has its own set of imaging criteria to determine which patients have anatomy suitable for inclusion, primarily focusing on infrarenal neck length, diameter, and angulation, as well as diameter and tortuosity of the iliac arteries.

DEVICE INTRODUCTIONS.

Devices all require introduction through a sheath, usually 18 to 24 French. This is

Figure 42-6 Endovascular stent-graft management of an abdominal aortic aneurysm. *A,* Abdominal aortogram demonstrates a large eccentric infrarenal abdominal aortic aneurysm before stent-graft deployment. An Excluder (W. L. Gore and Associates, Inc., Sunnyvale, CA) constrained on its delivery catheter (arrow) is located in the abdominal aorta before deployment. *B,* Completion abdominal aortogram after placement of the modular, bifurcated stent-graft demonstrates good flow through the prosthesis without evidence of an endoleak into the aneurysm sac.

done by femoral cutdown, although modifications of technique involving iliac or direct aortic access are sometimes necessary. Procedures are performed under general or spinal anesthesia, either in the operating room or in the angiography suite equipped with operating room-quality air. Combined suites are being built in many centers. Correct positioning of the device is critical, requiring both knowledge of the underlying anatomy and the characteristics of the particular device's deployment. Malpositioning of the device may lead to occlusion of the renal arteries or caudal placement too near the aneurysm sac, the latter necessitating addition of extender cuffs. Open repair, for the most part, does not impose the same anatomical constraints on selection of aneurysm.

All currently available devices, because of the similarity of their construction, have similar shortcomings. None of the devices can be repositioned after deployment. Most of them have a self-expanding metal frame that springs into place, often very rapidly and without opportunity to alter the position during deployment. Many of the devices flare proximally during placement, creating a potential "windsock" effect, through which aortic flow pushes against the briefly occlusive, partially opened stent-graft. This tends to push the device caudally, and this displacement may result in a suboptimal final position. Although some of the devices can be partially pulled back during deployment, none can be significantly advanced once deployment has begun. Therefore, correction of this caudal shift during placement requires additional devices, as mentioned earlier. Reports of material failure and device migration have surfaced,[134] [138] [140] [142] and this may in part result from the somewhat awkward juxtaposition of the graft and metallic components, which do not lend themselves easily to bonding. In addition, sutures holding the two components together must endure significant cumulative stress for years, perhaps decades, after implantation. Anatomical constraints have eliminated many patients from being considered for endoluminal repair. Inadequate infrarenal aneurysm proximal neck is invoked most frequently, and devices most often require 1.5 to 2.0 cm of relatively normal caliber aorta to facilitate sealing.[143] [144] Until devices can be designed that duplicate the security of a surgically constructed suture line, these limitations will continue to cast doubt on the long-term effectiveness of the technology as it stands.

RESULTS.

Despite the above reservations, endoluminal AAA repair displays promising results.[139] [145] [146] [147] [148] [149] [150] [151] [152] [153] Irrespective of the particular product involved, technical success rate is high, aneurysm exclusion is achieved 80 to 95 percent of the time, and conversion to open repair is rare. Complications are not uncommon, however. Numerous case reports and small series of various complications have emerged,[131] [132] [134] [135] [154] [155] [156] and some of these report relatively late sequelae. The degree to which these late complications affect patients with stent-graft AAA repair will determine which device or devices, if any, will prove superior and guide the development of second generation stent-graft systems.

THORACIC ANEURYSMS (see also Chap. 40) .

Open repair of thoracic aortic aneurysms is a major surgical undertaking with an attendant high morbidity and mortality rate. This fact, coupled with the development of stent-graft technology,[126] [157] [158] has led inexorably to the application of stent-graft technology to thoracic aneurysm repair.

As in most stent-graft applications, the underlying lesional anatomy imposes great challenges. In the case of thoracic aortic aneurysms, it is the frequent juxtaposition of the aneurysm to the left subclavian artery that restricts the use of the device, or forces adjunctive surgical transposition of the left subclavian to left carotid (Fig. 42-7). Furthermore, the large caliber of the thoracic aorta in general challenges the limits of deliverability, because one can only percutaneously introduce devices through sheaths up to about 30 French. Moreover, the natural curvature of the aortic arch and proximal descending thoracic aorta must be accommodated by the device, which in its current incarnations contains a metal skeleton limited in its ability to handle such curves. Finally, there is concern about the occlusion of intercostal arteries, anastomoses from which may supply the spinal cord.

Despite these potential pitfalls, the procedure has been used with success in several series.[159] [160] [161] [161A] In the largest of these, Mitchell and colleagues report the results of 103 patients receiving stent-grafts for treatment of aneurysms of the descending thoracic aorta.[159] Sixty percent of these patients were not deemed operative candidates. Primary success was achieved in 73 percent of patients, and secondary success occurred in another 12 percent, but only 53 percent of patients were free of treatment failure at 3.7 years. Complications were common, and major perioperative morbidity occurred in 31 patients. Paraplegia occurred in 3 patients, and was associated with concomitant or preceding abdominal aortic aneurysm repair. There was one conversion to open repair in the series, and 5 patients required late operative intervention for persistent endoleaks. The patient population offered endoluminal repair was obviously a skewed one, with coexistent disease severe enough to exclude well over half from consideration for open surgery. Nonetheless, the results underscore the challenge of treating this disease for the reasons outlined earlier and that the technology must undergo further refinement if it is to become the mainstay of treatment. In a more selected patient population, the results were much better.[161]

Stent-grafts have also been used with success in the treatment of mycotic aneurysms of the thoracic aorta[162] and in patients with acute rupture of the thoracic aorta, even in those with traumatic rupture.[163]

ILIAC ANEURYSMS

Isolated iliac aneurysms are uncommon. When they occur, however, they may be very dangerous, with an unpredictable course. They are not easily detected on physical examination, and rupture may not be discovered until it is too late because the diagnosis was not considered. Even in elective cases the mortality of open surgical

repair is relatively high; and in emergency cases it is about 50 percent.[164] [165]

Several investigators have now demonstrated that stent-graft repair of isolated iliac artery aneurysms is feasible.[166] [167] [168] [169] All studies demonstrated 100 percent technical success with the exception of a single patient in the series by Quinn and coworkers,[168] the single failure attributed to marked tortuosity of the iliac artery. All but one patient has achieved complete aneurysm exclusion in these series, although the follow-up periods are generally short. Complications in all series were rare.

Stent-grafts have also been used to exclude isolated internal iliac aneurysms.[170] The outflow of the internal iliac artery is coil embolized, and the origin of the internal iliac is then occluded by placement of a stent-graft across it, from the common to external iliac artery. This approach effectively excludes the aneurysm by shutting off both inflow and outflow.

OTHER APPLICATIONS OF STENT-GRAFTS

Stent-grafts have been used in a variety of clinical applications beyond those discussed earlier. The repair of aneurysms and arteriovenous fistulas in the region of the subclavian artery[171] [172] has proven successful. In fact, the first report of placement of a covered stent in a patient documented use of a silicone-coated balloon expandable stent in the subclavian artery.[173] Marin and associates [172] have also reported on repair of femoral pseudoaneurysms with stent-grafts. Autologous vein-stent combinations have also been used for the treatment of internal carotid pseudoaneu

Figure 42-7 Stent-graft placement for treatment of a fusiform aneurysm involving the descending thoracic aorta. *A,* Thoracic aortogram in a left anterior oblique projection shows a large aneurysm of the proximal descending thoracic aorta associated with a relatively short proximal neck distal to the left subclavian artery. *B,* After placement of a thoracic Excluder (W. L. Gore and Associates, Inc., Sunnyvale, CA), a balloon is inflated within the proximal aspect of the device to fully expand the prosthesis within the proximal neck and smooth out any graft wrinkles. *C,* Similar left anterior oblique projection of a thoracic aortogram after stent-graft placement shows no further filling of the aneurysm sac and good positioning of the device.

rysm [174] and pseudoaneurysm of the SMA.[175] Covered stents have been used with reasonable success in transjugular intrahepatic portosystemic shunt (TIPS) treatment of patients with complications of portal hypertension, a procedure associated with considerable restenosis.[176]

VENOUS INTERVENTIONS

The conventional wisdom regarded venous interventions with considerable skepticism. The venous endothelium was considered too delicate, the flow too slow, and the walls of

the veins too flimsy for seemingly crude techniques applied to the more robust arterial circulation. Surgeons learned this lesson long ago. It is with surprise, then, that vascular specialists have found that the veins can prove quite responsive to interventions. Especially surprising are the results seen in aggressive treatment of lower extremity deep venous thrombosis (DVT). Important roles are also played by interventionalists in treating upper extremity venous thrombosis and in the management of superior vena cava (SVC) syndrome. As on the arterial side, it appears that the size of the conduit and restoration of in-line, anatomical flow channels are the crucial factors in maintaining patency.

LOWER EXTREMITY VENOUS INTERVENTIONS.

Lower extremity deep venous thrombosis (LEDVT) is a common disease. Pulmonary embolus (PE) is the most dangerous consequence of LEDVT. However, the post-thrombotic syndrome, resulting in chronic pain and leg swelling, causes considerable morbidity and a decrease in quality of life. Although warfarin anticoagulation can limit PE, it does little to alter the course of post-thrombotic syndrome. The presence of clot within the veins eventually leads to inflammation and scarring, causing permanent damage to the venous valves and rendering them incompetent. It is the aim of more aggressive therapy of LEDVT to intervene before the onset of irreversible valve damage, and thereby salvage venous valve function.

Thrombolysis.

The mainstay of this more aggressive therapy is thrombolysis. Lysis potentially clears the vein of

clot, restores flow, and hence aborts the cycle of events leading to valve damage. Furthermore, many patients who develop LEDVT have an underlying anatomical lesion leading to thrombosis. Lysis of clot uncovers these lesions, which may then be treated by stenting. Semba and Dake published the first large series using lytic agents for the treatment of iliofemoral DVT and produced excellent results,[177] and this prompted the creation of a national venous registry. The preliminary results of that registry, representing 287 patients subjected to lysis, have confirmed the efficacy of this more aggressive approach to LEDVT.[178] What has emerged is an understanding of the importance of early treatment of DVT. Patients in whom evidence of chronic DVT was found demonstrated less complete lysis and less impressive patency rates than those with acute DVT.[178] The overall 1-year primary patency was 60 percent. Following these patients for several years will be necessary to establish the impact of treatment on the development of post-thrombotic syndrome. Fatal complications occurred in 2 of 287 patients (<1 percent), and 6 patients had pulmonary emboli.

INTERVENTIONS FOR PAGET-SCHROETTER SYNDROME.

Effort vein thrombosis, or Paget-Schroetter syndrome, occurs as a result of mechanical trauma to the subclavian vein at the thoracic outlet. It can occur at any age but has a predilection for young, athletic individuals. A developmental anomaly resulting in impingement on the vein may be present.[179] The natural history of the disorder is typically one of chronic venous obstruction with development of a painful, swollen extremity.

A multidisciplinary approach to its management has emerged, in which thrombolysis is performed in the acute setting and surgical decompression is performed after a variable interval of oral anticoagulation.[180] [181] [182] [183] PTA of the subclavian vein may prove a useful adjunct as well.[180] [181] Other studies, however, found no benefit to PTA in this setting.[184] The role of stent placement in this region is controversial. An emerging consensus that stenting is to be avoided has arisen from experience with stent fracture in this region. Encouraging results of stent placement for Paget-Schroetter syndrome, however, have been reported.[185] [186]

INTERVENTIONS IN SUPERIOR VENA CAVA SYNDROME.

Obstruction of the superior vena cava (SVC) is most frequently a result of malignant disease invading the mediastinum (see also Chap. 69) . To an increasing extent, however, benign causes are responsible, especially obstruction secondary to multiple central venous catheter placements. Not all patients with SVC obstruction are symptomatic. When symptoms do occur, however, they are dramatic: intense facial and upper extremity swelling gives patients a gargoyle-like appearance, which is intensely uncomfortable and unsettling not only to the patient but to the family as well. Patients also suffer from intense headaches, exacerbated while supine, making sleep difficult. Cognitive dysfunction occasionally occurs because of progressive brain edema brought on by venous obstruction. Although patients with malignant SVC syndrome generally have a short life expectancy, the quality of that life is abysmal if the obstruction is untreated. It is in that spirit that aggressive palliative therapy is offered.

Radiation therapy has been the mainstay of treatment for malignant SVC syndrome. The occasionally slow response to radiation and the achievement of maximum radiation dosages without relief have prompted a gradual shift away from brachytherapy to initial percutaneous interventional therapy when it is available. Although some small series of surgical treatment of malignant SVC syndrome report excellent results,[187] such interventions are proposed with curative intent, only applicable in a small minority of patients with malignant mediastinal involvement with tumor.

SVC stent placement has been demonstrated in numerous reports to provide rapid relief of symptoms of SVC syndrome[188] [189] (Fig. 42-8) . The largest series in the literature was produced by Kee and coworkers,[188] in which a series of 59 patients, 16 of whom had a benign etiology, presented with SVC syndrome. Occlusion of the SVC was found in 31 of these patients, of whom 28 underwent catheter directed thrombolysis before stent placement. In patients with malignant disease, the clinical patency rate was 93 percent; and in those with benign disease, it was 85 percent. Relief of symptoms is often instantaneous and dramatic. Even in patients with a short life expectancy, SVC

stent placement greatly improves the quality of their remaining time. In patients with benign disease, patency is comparable to surgery, with less morbidity. In institutions where expertise is available, stent placement is a reasonable first choice in the treatment of SVC syndrome.

Venous Filtration (See also Chap. 52)

Inferior vena cava (IVC) filter placement is one of the more common venous interventions. The utility of such devices would be even broader pending development of temporary and/or retrievable filters, the applications of which could be far reaching in trauma and perioperative management.

IVC FILTERS.

Although there remains some uncertainty about the indications for IVC filter placement, there is general agreement on the core indications: (1) contraindication to anticoagulation; (2) failure of anticoagulation; (3) complication of anticoagulation; and (4) free-floating iliocaval thrombus. The use of filters for prophylaxis against PE in the absence of documented DVT is controversial. Four filter designs are in wide use in the United States, all with purported advantages relative to other designs. Each has been subjected to scrutiny through both single center experiences[190] [191] [192] [193] [194] and review articles.[195] [196]

The major advantage of the Simon Nitinol filter (Nitinol Medical Technologies, Woburn, MA) is its flexibility and low profile (9F), allowing introduction through an antecubital vein.[193] This is particularly useful in patients with coagulopathy or on anticoagulation, in whom the risk of bleeding is higher. Antecubital veins are easily compressed, and there is less risk of clinically significant hematoma than in a jugular or femoral puncture.

The Vena Tech LGM (B. Braun Vena Tech, Evanston, IL) filter is the easiest to place, according to the manufacturer's advertising and in the opinion of many interventionalists. Questions have been raised about the rate of caval occlusion with Vena Tech filters,[194] which have been addressed in later publications.[192] Filter retraction has also been reported.[192]

The Bird's Nest Filter (Cook, Bloomington, IN) can be deployed in IVCs up to 40 mm in diameter, significantly larger than the 28-mm maximum of the other filters. It is also typically less expensive than the other filters. Arguably, a Bird's Nest Filter designed for jugular access is appropriate for treating any patient requiring a filter.

The titanium Greenfield filter (Medi-Tech/Boston Scientific, Watertown, MA) is the more sleek offspring of the earlier stainless steel Greenfield filter (Medi-Tech/Boston Scientific, Watertown, MA). The latest incarnation of this filter allows for delivery over the wire, although this apparently offers no advantage over standard deployment.[191]

All filters are reasonably effective in their primary function of preventing PE, with recurrent PE rates ranging from 1 to 5 percent.[195] The rate of development of caval

thrombus is difficult to accurately ascertain but appears to be on the order of 5 to 25 percent.[195]

The introduction of an effective temporary filter would go a long way toward solving the problem of filter placement for prophylaxis. To date, no temporary filters are approved, although some are undergoing trials. Experimental results with one retrievable filter are encouraging.[197]

Figure 42-8 Endovascular stent placement for management of venous obstruction in a 68-year-old man with symptoms of superior vena cava syndrome. *A,* Right arm venogram demonstrates obstruction of the right subclavian and brachiocephalic veins with a highly developed collateral network that includes chest wall veins. *B,* Left internal jugular venogram identifies occlusion of the left jugular system and brachiocephalic vein. *C,* Chest radiograph demonstrates a series of balloon expandable stents (Corinthian, Cordis, Inc., Miami, FL) placed in the right subclavian, right brachiocephalic, left brachiocephalic, and superior vena cava. *D,* Bilateral upper extremity venogram performed after stent placement demonstrates reestablished flow within the previously occluded mediastinal veins. Full expansion of the stented segments is apparent, and a paucity of collateral flow is evident.

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Part V - DISEASES OF THE HEART, PERICARDIUM, AND PULMONARY VASCULAR BED

Chapter 43 - Congenital Heart Disease in Infancy and Childhood

WILLIAM F. FRIEDMAN
NORMAN SILVERMAN

General Considerations

DEFINITION

Congenital cardiovascular disease is defined as an *abnormality in cardiocirculatory structure or function that is present at birth, even if it is discovered much later.*[1A] [1B]

Congenital cardiovascular malformations usually result from altered embryonic development of a normal structure or failure of such a structure to progress beyond an early stage of embryonic or fetal development. The aberrant patterns of flow created by an anatomical defect may, in turn, significantly influence the structural and functional development of the remainder of the circulation. For instance, the presence in utero of mitral atresia may prohibit normal development of the left ventricle, aortic valve, and ascending aorta. Similarly, constriction of the fetal ductus arteriosus may result directly in right ventricular dilatation and tricuspid regurgitation in the fetus and newborn, it may contribute importantly to the development of pulmonary arterial aneurysms in the presence of ventricular septal defect (VSD) and absent pulmonic valve, or, further, it may result in an alteration in the number and caliber of fetal and newborn pulmonary vascular resistance vessels.

POSTNATAL EVENTS.

These may markedly influence the clinical presentation of a specific "isolated" malformation. Infants with Ebstein's malformation of the tricuspid valve may improve dramatically as the magnitude of tricuspid regurgitation diminishes with normal fall in pulmonary vascular resistance after birth; infants with hypoplastic left heart syndrome or interrupted aortic arch may not exhibit circulatory collapse; and infants with pulmonic atresia or severe stenosis may not become cyanotic until normal spontaneous closure of a patent ductus arteriosus occurs. Ductal constriction many days after birth also may be a central factor in some infants in the development of coarctation of the aorta. Still later in life, patients with a VSD may experience spontaneous closure of the abnormal communication or may develop right ventricular outflow tract obstruction and/or aortic regurgitation or pulmonary vascular obstructive disease. These selected examples serve to emphasize that anatomical and physiological changes in the heart and circulation may continue indefinitely from prenatal life in association with any specific congenital cardiocirculatory lesion.

Certain congenital defects are not apparent on gross inspection of the heart or circulation. Examples include the electrophysiological pathways for ventricular preexcitation or interruptions in the cardiac conduction system giving rise to paroxysmal supraventricular tachycardia or congenital complete heart block, respectively. Similarly, abnormalities in the development of myocardial autonomic innervation or in the ultrastructure of myocardial cells may ultimately prove to contribute to asymmetrical septal hypertrophy and left ventricular outflow tract obstruction. These examples make clear that occasional difficulties arise in distinguishing between congenital anomalies that are readily apparent at or shortly after birth and lesions that may have as their basis a subtle or undetectable abnormality that is present at birth.

INCIDENCE.

The true incidence of congenital cardiovascular malformations is difficult to determine

accurately, partly because of the difficulties in definition discussed earlier. About 0.8 percent of live births are complicated by a cardiovascular malformation.[1] This figure does not take into account what may be the two most common cardiac anomalies: the congenital, nonstenotic bicuspid aortic valve[2] and the leaflet abnormality associated with mitral valve prolapse.[3] Moreover, the widely quoted 0.8 percent incidence figure fails to include small preterm infants, almost all of whom have persistent patent ductus arteriosus. Further, if the calculations were to include stillbirths and abortuses, the incidence would be greatly increased. Cardiac malformations occur 10 times more often in stillborn than in liveborn babies, and many early spontaneous abortions are associated with chromosomal defects (see Chap. 56).[1] Thus, it is clear that past statistical analyses have seriously *underestimated* the incidence of congenital heart disease.

Precise data concerning the frequency of individual congenital lesions also are lacking, and the results of many analyses differ, depending on the source (living or dead) and the selection of the study population. Table 43-1 is a compilation from both clinical and pathological studies that approximates the frequency of occurrence of specific cardiovascular malformations.[4] [5] [6]

Considered in toto, children with congenital heart disease are predominantly male. Moreover, specific defects may show a definite gender preponderance; patent ductus

TABLE 43-1 -- RELATIVE FREQUENCY OF OCCURRENCE OF CARDIAC MALFORMATIONS AT BIRTH

DISEASE	PERCENTAGE
Ventricular septal defect	30.5
Atrial septal defect	9.8
Patent ductus arteriosus	9.7
Pulmonic stenosis	6.9
Coarctation of the aorta	6.8
Aortic stenosis	6.1
Tetralogy of Fallot	5.8
Complete transposition of the great arteries	4.2
Persistent truncus arteriosus	2.2
Tricuspid atresia	1.3
All others	16.5
Data based on 2310 cases.	

arteriosus, Ebstein's anomaly of the tricuspid valve, and atrial septal defect are more common in *females,* whereas valvular aortic stenosis, coarctation of the aorta, hypoplastic left heart, pulmonary and tricuspid atresia, and transposition of the great arteries are more common in *males.*[7]

Extracardiac anomalies occur in about 25 percent of infants with significant cardiac disease,[10] and their presence may significantly increase mortality. The extracardiac anomalies often are multiple, in part involving the musculoskeletal system; one-third of infants with both cardiac and extracardiac anomalies have some established syndrome.

ETIOLOGY

Malformations appear to result from an interaction between multifactorial genetic and environmental systems too complex to allow a single specification of cause[8] ; in most instances, a causal factor cannot be identified. However, the explosion of new genetic research suggests that genetic causes are far more common than thought previously.[8] [9] Maternal rubella, ingestion of thalidomide and isotretinoin early during gestation, and chronic maternal alcohol abuse are environmental insults known to interfere with normal cardiogenesis in humans.[10] [11] *Rubella syndrome* consists of cataracts, deafness, microcephaly, and, either singly or in combination, patent ductus arteriosus, pulmonic valvular and/or arterial stenosis, and atrial septal defect. *Thalidomide* exposure is associated with major limb deformities and, occasionally, with cardiac malformations without predilection for a specific lesion. Tricuspid valve anomalies are associated with ingestion of *lithium* during pregnancy. The *fetal alcohol syndrome* consists of microcephaly, micrognathia, microphthalmia, prenatal growth retardation, developmental delay, and cardiac defects. The latter--often defects of the ventricular septum--occur in about 45 percent of affected infants. *Maternal lupus erythematosus* during pregnancy has been linked to congenital complete heart block. Animal experiments have incriminated hypoxia, deficiency or excess of several vitamins, intake of several categories of drugs, and ionizing irradiation as teratogens capable of causing cardiac malformations. The precise relation of these animal teratogens to human malformations is not clear.

The genetic aspects of congenital heart disease are discussed extensively in Chapter 56 . A single gene mutation may be causative in the familial forms of atrial septal defect with prolonged atrioventricular (AV) conduction, mitral valve prolapse, VSD, congenital heart block, situs inversus, pulmonary hypertension, and the syndromes of Noonan, LEOPARD, Ellis-van Creveld, and Kartagener. The genes responsible for several defects have either been mapped (e.g., long QT syndrome, Holt-Oram syndrome) or identified (e.g., Marfan syndrome, hypertrophic cardiomyopathy, supravalvular aortic stenosis). Contiguous gene defects on the long arm of chromosome 22 likely underlie the conotruncal malformations of the DiGeorge and velocardiofacial syndromes.[12] Table 43-2 (Table Not Available) provides a partial list of syndromes in which cardiovascular anomalies may be manifestations of the pleiotropic effects of single genes or examples of gross chromosomal defects. At present, less than 15 percent of all cardiac malformations can be accounted for by chromosomal aberrations or genetic mutations or transmission.

The finding that, with some exceptions, only one of a pair of monozygotic twins is affected by congenital heart disease indicates that the vast majority of cardiovascular malformations are not inherited in a simple manner.[13] However, this observation may have led, in the past, to an underestimation of genetic contribution, because most recent

twin studies reveal more than double the incidence of

TABLE 43-2 -- SYNDROMES WITH ASSOCIATED CARDIOVASCULAR INVOLVEMENT

(Not Available)

Modified from Friedman WF, Child JS: Congenital heart disease. In Fauci A,, Braunwald E, Isselbacher KJ, et al (eds): Harrison's Principles of Internal Medicine. 14th ed. New York, McGraw-Hill, 1998, p 1300. © 1998 The McGraw-Hill Companies, Inc.

heart defects in monozygotic twins but usually in only one of the pair.[14] Family studies indicate a 2-fold to 10-fold increase in the incidence of congenital heart disease in siblings of affected patients or in the offspring of an affected parent. Malformations often are concordant or partially concordant within families.[15] [16] Because the incidence of congenital heart disease in the offspring or siblings of an index patient is only 2 to 10 percent, it is seldom wise to discourage

Figure 43-1 Diagrammatic representation of the atrial septa at 30 days *(A)*, at 33 days *(B)*, at 33 days (seen from the right side) *(C)*, at 37 days *(D)*, and in the newborn *(E)*; the newborn atrial septum viewed from the right *(F)*. *(From Clark EB, Van Mierop LHS: Development of the cardiovascular system. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al [eds]: Moss' Heart Disease in Infants, Children, and Adolescents. 4th ed. Baltimore, © Williams & Wilkins, 1989.)*

the parents of one affected child from having additional children if either parent is free of a cardiovascular anomaly.[1] Moreover, the low recurrence rate and the increasing possibilities for effective treatment for nearly all cardiac lesions usually justify a positive approach to family counseling. When two or more members of the family are affected, the recurrence risk may be quite high, and a pedigree should be obtained before further counseling. If a dominant or recessive mendelian pattern is established, the mendelian laws apply, and the risk of recurrence in each pregnancy is equal.

PREVENTION

The feasibility of preventive programs depends on what is learned in the future about

the 85 percent or more of cardiovascular anomalies for which no cause currently is known. Strict animal testing of new drugs that may be teratogenic when taken during pregnancy may be expected to reduce the chances of another thalidomide tragedy. In this regard, the dictum cannot be emphasized too strongly that no medication should be taken during pregnancy without prior consultation with a physician. Physicians who deal with pregnant women should be aware of known teratogens as well as drugs that may have a functional rather than a structural damaging influence on the fetal and newborn heart and circulation, and they should recognize that for many drugs, information about their teratogenic potential is inadequate. Similarly, appropriate radiological equipment and techniques for reducing gonadal and fetal radiation exposure should always be used to reduce the potential hazards of this likely cause of birth defects.

Detection of abnormal chromosomes in fetal cells obtained from amniotic fluid or chorionic villus biopsy (see Chap. 56) may predict cardiac malformation as one component of the multisystem involvement that may exist in such syndromes as Down, Turner's, or trisomy 13-15 (D1) or 16-18 (E). Similarly, identification in such cells of the enzyme disorders observed in the mucopolysaccharidoses, homocystinuria, or type II glycogen storage disease may allow one to predict the ultimate presence of cardiac disease. Finally, immunization of children with rubella vaccine will avoid the effects of maternal rubella and its cardiac consequences.

Although fetal echocardiography may allow the identification of congenital heart disease, it is not yet clear if this modality will improve survivability.[17] [18] It is apparent, however, that a prenatal diagnosis of serious cardiac disease has resulted in a decision by some families to terminate pregnancies.

EMBRYOLOGY

NORMAL CARDIAC DEVELOPMENT.

Correlation of anatomical features of malformed hearts and embryonic cardiac morphology allows a developmental analysis of various anomalies.[19] Detailed accounts of the normal development of the cardiovascular system are provided elsewhere.[20] In brief, during the first month of gestation, the primitive, straight cardiac tube is formed, comprising the sinuatrium, the primitive ventricle, the bulbus cordis, and the truncus arteriosus in series, from cephalad to caudad. In the second month of gestation, this tube doubles over on itself to form two parallel pumping systems, each with two chambers and a great artery. The two atria develop from the sinuatrium, the AV canal is divided by the endocardial cushions into tricuspid and mitral orifices, and the right and left ventricles develop from the primitive ventricle and bulbus cordis. Differential growth of myocardial cells causes the straight cardiac tube to bear to the right, and the bulboventricular portion of the tube doubles over on itself, bringing the ventricles side by side. Migration of the AV canal to the right and of the ventricular septum to the left serves to align each ventricle with its appropriate AV valve. At the distal end of the cardiac tube, the bulbus cordis divides into a subaortic muscular conus and a subpulmonic muscular conus; the subpulmonic conus elongates and the subaortic conus resorbs, allowing the aorta to move posteriorly and connect with the left ventricle.

ABNORMAL DEVELOPMENT.

A host of anomalies may result from defects in this basic developmental pattern. Thus, double-inlet left ventricle is observed if the tricuspid orifice does not align over the right ventricle. The various types of persistent truncus arteriosus result from failure of the truncus to divide into the main pulmonary artery and aorta. Double-outlet anomalies of the right ventricle are produced by failure of either the subpulmonic or subaortic conus to resorb, whereas resorption of the subpulmonic instead of the subaortic conus may be central to transposition of the great arteries.

THE ATRIA.

The primitive sinuatrium is separated into right and left atria by the downgrowth from its roof of the septum primum toward the AV canal, thereby creating an inferior intraatrial ostium primum opening (Fig. 43-1) . Numerous perforations form in the anterosuperior portion of the septum primum as the septum secundum begins to develop to the right of the former. The coalescence of these perforations forms the ostium secundum. The septum secundum completely separates the atrial chambers except for a central opening--the fossa ovalis--which is covered by tissue of the septum primum, forming the valve of the foramen ovale.

Fusion of the endocardial cushions anteriorly and posteriorly divides the AV canal into tricuspid and mitral inlets (Fig. 43-2) . The inferior portion of the atrial septum, the superior portion of the ventricular septum, and portions of the septal leaflets of both the tricuspid and mitral valves are formed from the endocardial cushions. The integrity of the atrial septum depends on growth of the septum primum and septum secundum and proper fusion of the endocardial cushions. Atrial septal defects and various degrees of endocardial cushion defect are the result of developmental deficiencies of this process.

THE VENTRICLES.

Partitioning of the ventricles occurs as cephalic growth of the main ventricular septum results in its fusion with the endocardial cushions and the infundibular or conus septum. Defects in the ventricular septum may occur owing to a deficiency of septal substance; malalignment of septal components in different planes, preventing their fusion; or an overly long conus, keeping the septal components apart. Isolated defects probably result from the first

Figure 43-2 Frontal section through the heart of a 9-mm embryo *(A)* and 15-mm embryo *(B)*. At 9 mm, development of the cushions in the atrioventricular canal is noted, and the truncus and conus swellings are visible. At 15 mm, the conus septum is completed; note the septation in the atrial region. *(From Clark*

EB, Van Mierop LHS: Development of the cardiovascular system. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al [eds]: Moss' Heart Disease in Infants, Children, and Adolescents. 4th ed. Baltimore, © Williams & Wilkins, 1989.)

mechanism, whereas the latter two appear to generate the ventricular defects in tetralogy of Fallot and transposition complexes.

THE LUNGS.

These structures arise from the primitive foregut and are drained early in embryogenesis by channels from the splanchnic plexus to the cardinal and umbilicovitelline veins. An outpouching from the posterior left atrium forms the common pulmonary vein, which communicates with the splanchnic plexus, establishing pulmonary venous drainage to the left atrium. The umbilicovitelline and anterior cardinal vein communications atrophy as the common pulmonary vein is incorporated into the left atrium. Anomalous pulmonary venous connections to the umbilicovitelline (portal) venous system or to the cardinal system (superior vena cava) result from failure of the common pulmonary vein to develop or establish communications to the splanchnic plexus. Cor triatriatum results from a narrowing of the common pulmonary vein-left atrial junction.

THE GREAT ARTERIES.

The truncus arteriosus is connected to the dorsal aorta in the embryo by six pairs of aortic arches. Partition of the truncus arteriosus into two great arteries is a result of the fusion of tissue arising from the back wall of the vessel and the truncus septum. Rotation of the truncus coils the aorticopulmonary septum and creates the normal spiral relation between the aorta and pulmonary artery. Semilunar valves and their related sinuses are created by absorption and hollowing out of tissue at the distal side of the truncus ridges. Aorticopulmonary septal defect and persistent truncus arteriosus represent various degrees of partitioning failure.

Although the six aortic arches appear sequentially, portions of the arch system and dorsal aorta disappear at different times during embryogenesis (Fig. 43-3) . The first, second, and fifth sets of paired arches regress completely. The proximal portions of the sixth arches become the right and left pulmonary arteries, and the distal left sixth arch becomes the ductus arteriosus. The third aortic arch forms the connection between the internal and external carotid arteries, and the left fourth arch becomes the arterial segment between the left carotid and subclavian arteries; the proximal portion of the right subclavian artery forms from the right fourth arch. An abnormality in regression of the arch system in a number of sites can produce a wide variety of arch anomalies, whereas a failure of regression usually results in a double aortic arch malformation.

FETAL AND TRANSITIONAL CIRCULATIONS

Although the illness created by the presence of a cardiac malformation is almost always recognized only after an affected baby is born, important effects on the circulation have existed from early in pregnancy until the time of delivery. Thus, knowledge of the

changes in cardiocirculatory structure, function, and metabolism that accompany development is central to a systematic comprehension of congenital heart disease.

FETAL CIRCULATORY PATHWAYS.

Dynamic alterations occur in the circulation during the transition from fetal to neonatal life when the lungs take over the function of gas exchange from the placenta. The single fetal circulation consists of parallel pulmonary and systemic pathways (Fig. 43-4) in contrast to the two-circuit system in the newborn and adult, in whom the pulmonary vasculature exists in series with the systemic circulation. Prenatal survival is not endangered by major cardiac anomalies as long as one side of the heart can drive blood from the great veins to the aorta; in the fetus, blood can bypass the nonfunctioning lungs both proximal and distal to the heart.

Oxygenated blood returns from the placenta through the umbilical vein and enters the portal venous system. A variable amount of this stream bypasses the hepatic microcirculation and enters the inferior vena cava by way of the ductus venosus. Inferior vena caval blood flows from the ductus venosus, hepatic vein, and lower body venous drainage, which is summarily deflected to a significant extent across the foramen ovale into the left atrium. Almost all superior vena caval blood passes directly through the tricuspid valve, entering the right ventricle. Most of the blood that reaches the right ventricle bypasses the high-resistance, unexpanded lungs and passes through the ductus arteriosus into the descending aorta. The right ventricle contributes about 55 percent and the left 45 percent to the total fetal cardiac output. The major portion of blood ejected from the left ventricle supplies the brain and upper body, with lesser flow to the coronary arteries; the balance passes across the aortic isthmus to the descending aorta, where it joins with the large stream from the ductus arteriosus before flowing to the lower body and placenta.

FETAL PULMONARY CIRCULATION.

In fetal life, pulmonary arteries and arterioles are surrounded by a fluid medium, have relatively thick walls and small lumina, and resemble comparable arteries in the systemic circulation. The low pulmonary blood flow in the fetus (7 to 10 percent of the total cardiac output) is the result of high pulmonary vascular resistance. Fetal pulmonary vessels are highly reactive to changes in oxygen tension or in the pH of blood perfusing them as well as to a number of other physiological and pharmacological influences.

EFFECTS OF CARDIAC MALFORMATIONS ON THE FETUS.

Although fetal somatic growth may be unimpaired, the hemodynamic effects in utero of many cardiac malformations may alter the development and structure of the fetal heart and circulation.[22] Thus, total anomalous pulmonary venous connection in utero may result in underdevelopment of the left atrium and left ventricle, and premature closure of the foramen ovale may result in hypoplasia of the left ventricle. Moreover, postnatally, the caliber of the aortic isthmus may be reduced in the presence of lesions in utero that create left ventricular hypertrophy, such as aortic stenosis, and impede filling because of

reduced compliance of that chamber. It may also be reduced in the presence of a lesion that interferes with left ventricular filling directly (e.g., mitral stenosis) or indirectly by diverting a proportion of left ventricular output away from the ascending aorta while increasing right ventricular output and ductus arteriosus flow (e.g., AV septal defect with left ventricular-right atrial shunt or aortic or subaortic stenosis with VSD). Similarly, obstruction in utero to right ventricular outflow is associated with an increase in proximal aortic flow and diameter and almost never with aortic coarctation. Ebstein's malformation of the tricuspid valve is more commonly recognized in the fetus than ex utero. Death with severe hydrops in utero or early in postnatal life may account for a much lower frequency of this lesion in data gathered after birth. The anomaly, which produces fetal AV valvar regurgitation, a large right-to-left atrial shunt, and ineffective pulmonary flow compromising pulmonary vasculature development, is one of the most significant causes of fetal hydrops, heart failure, and loss. Similar tricuspid valve hemodynamic consequences can also occur in pulmonary atresia with intact ventricular septum.[17] [21] In these and other examples, it is important to recognize that malformations compatible with fetal survival may nonetheless result in abnormal development of the circulation in utero and also affect circulatory adjustments after birth.[23]

FUNCTION OF THE FETAL HEART.

Compared with the adult heart, the fetal and newborn heart is unique with respect to its ultrastructural appearance[24] its mechanical and biochemical properties,[25] [26] [27] [28] [29] [30] and autonomic innervation.[31] During late fetal and early neonatal development, there is maturation of the excitation-contraction coupling process[32] [33] and the biochemical composition of the heart's energy-utilizing myofibrillar proteins and of adenosine triphosphate and creatine phosphate energy-producing proteins.[29] Moreover, fetal and neonatal myocardial cells are small in diameter and reduced in density, so that the young heart contains relatively more noncontractile mass (primarily

Figure 43-3 Transformation of the aortic arches and dorsal aorta into the definitive vascular pattern is a process of fusion and segmental resorption of the paired first to sixth branchial arches with the paired dorsal aorta. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 398.)*

Figure 43-4 The fetal circulation; arrows indicate the directions of flow. A fraction of umbilical venous blood enters the ductus venosus and bypasses the liver. This relatively highly oxygenated blood flows across the foramen ovale to the left heart, preferentially perfusing the coronary arteries, head, and upper trunk. The output of the right ventricle flows preferentially across the ductus arteriosus and circulates to the placenta, as well as to the abdominal viscera and lower trunk. *(Courtesy of Dr. David Teitel.)*

mitochondria, nuclei, and surface membranes) than later in postnatal life. As a result, force generation and the extent and velocity of shortening are decreased, and stiffness and water content of ventricular myocardium are increased in the fetal and early newborn periods.

The diminished function of the young heart is reflected in its limited ability to increase cardiac output in the presence of either a volume load or a lesion that increases resistance to emptying.[34] Although functional integrity of efferent and afferent cardiac autonomic pathways exists early in life, fetal and newborn myocardium lacks the complete development of sympathetic but not cholinergic innervation. Thus, adaptation to cardiocirculatory stress in fetal or early newborn life may be less effective than in adulthood.

CHANGES AT BIRTH.

The fundamental change that normally occurs at birth is a division of the single parallel fetal circulation into separate, independent circulations. Inflation of the lungs at the first inspiration produces a marked reduction in pulmonary vascular resistance, owing partly to the sudden suspension in air of fetal pulmonary vessels previously supported by fluid media. The reduced extravascular pressure assists new vessels to open and already patent vessels to enlarge. The rapid decrease in pulmonary vascular resistance is related more importantly to vasodilatation owing to the increase in oxygen tension to which pulmonary vessels are exposed rather than to physical expansion of alveoli with gas. Defining the role of nitric oxide in the mediation of changes in pulmonary vascular tone in these events is of great interest.[35] Pulmonary arterial pressure falls, and pulmonary blood flow increases greatly. Systemic vascular resistance rises when clamping of the umbilical cord removes the low-resistance placental circulation. Increased pulmonary blood flow increases the return of blood to the left atrium and raises left atrial pressure, which in turn closes the foramen ovale.

The shift in oxygen dependence from the placenta to the lungs produces a sudden increase in arterial blood oxygen tension, which, in concert with alterations in the local prostaglandin milleu, initiates constriction of the ductus arteriosus.[36] Pulmonary pressure falls further as the ductus constricts. In healthy mature infants, the ductus arteriosus is profoundly constricted at 10 to 15 hours and is closed functionally by 72 hours, with total anatomical closure following within a few weeks by a process of thrombosis, intimal proliferation, and fibrosis. Preterm infants have a high incidence of persistent patency of the ductus arteriosus because of an immaturity of those mechanisms responsible for constriction. In surviving preterm infants, the ductus arteriosus spontaneously closes within 4 to 12 months of birth.

The ductus venosus, ductus arteriosus, and foramen ovale remain potential channels for blood flow after birth. Thus, persistent patency of the ductus venosus may mask the most marked signs of pulmonary venous obstruction in infants with total anomalous

pulmonary venous connection below the diaphragm. Similarly, lesions producing right or left atrial volume or pressure overload may stretch the foramen ovale and render incompetent the flap valve mechanism for its closure. Anomalies that depend on patency of the ductus arteriosus for preserving pulmonary or systemic blood flow remain latent until the ductus arteriosus constricts. A common example is the rapid intensification of cyanosis observed in infants with tetralogy of Fallot when the magnitude of pulmonary hypoperfusion is unmasked by spontaneous closure of the ductus arteriosus. Moreover, increasing evidence shows that ductal constriction is a key factor in the postnatal development of coarctation of the aorta. Finally, it should be recognized that because the ductus arteriosus is potentially patent after birth and the pulmonary resistance vessels are hyperreactive, hypoxic pulmonary vasoconstriction of diverse causes may result in a right-to-left shunt through the ductus.

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Pathological Consequences of Congenital Cardiac Lesions

CONGESTIVE HEART FAILURE

Although the basic mechanisms of cardiac failure, as outlined in Chapter 16 , are similar for all ages, pediatric cardiologists should clearly recognize that the common causes, time of onset, and often the approach to treatment vary with age.[37] [38] The development of fetal echocardiography has allowed the diagnosis of intrauterine cardiac failure.[21] [39] The cardinal findings of fetal heart failure are scalp edema, ascites, pericardial effusion, and decreased fetal movements. Although abnormalities in several organ systems may result in nonimmunological fetal hydrops, cardiac causes include a host of structural, functional, rhythm, and metabolic disturbances of the heart. Infants younger than 1 year and having cardiac malformations account for 80 to 90 percent of pediatric patients who develop congestive failure. Moreover, cardiac decompensation in an infant is a medical emergency necessitating immediate treatment if the patient is to be saved.

CAUSES OF HEART FAILURE.

In preterm infants, especially less than 1500-gm birth weight, persistent patency of the ductus arteriosus is the most common cause of cardiac decompensation, and other forms of structural heart disease are rare.[40] In full-term newborns, the earliest important causes of heart failure are the hypoplastic left heart and coarctation of the aorta syndromes, sustained tachyarrhythmia, cerebral or hepatic arteriovenous fistula, and myocarditis. Among the lesions commonly producing heart failure beyond age 1 to 2 weeks, when diminished pulmonary vascular resistance allows substantial left-to-right shunting, are VSD and atrioventricular septal defects, transposition of the great arteries, truncus arteriosus, and total anomalous pulmonary venous connection, often with pulmonary venous obstruction. Although heart failure usually is the result of a structural

defect or of myocardial disease, it should be recognized that the newborn myocardium may be severely depressed by such abnormalities as hypoxemia and acidemia, anemia, septicemia, marked hypoglycemia, hypocalcemia, and polycythemia. In older children, heart failure often is due to acquired disease (see Chap. 45) or is a complication of open-heart surgical procedures. In the acquired category are rheumatic and endomyocardial diseases, infective endocarditis, hematological and nutritional disorders, and severe cardiac arrhythmias.

CLINICAL MANIFESTATIONS IN THE INFANT.

The clinical expression of cardiac decompensation in infants consists of distinctive signs of pulmonary and systemic venous congestion and altered cardiocirculatory performance that resemble, but often are not identical to, those of older children or adults (Table 43-3) .[37] [41] These reflect the interplay between the hemodynamic burden and adaptive responses. Common symptoms and signs are feeding difficulties and failure to gain weight and grow, tachypnea, tachycardia, pulmonary rales and rhonchi, liver enlargement, and cardiomegaly. Less frequent manifestations include peripheral edema, ascites, pulsus alternans, gallop rhythm, wheezing, and inappropriate sweating. Pleural and pericardial effusions are exceedingly rare. The distinction between left and right heart failure is less obvious in infants than in older children or adults because most lesions that create a left ventricular pressure or volume overload also result in left-to-right shunting of blood through the foramen ovale and/or patent ductus arteriosus as well as pulmonary hypertension owing to elevated pulmonary venous pressures. Conversely, augmented

TABLE 43-3 -- FEATURES OF HEART FAILURE IN INFANTS

Poor feeding and failure to thrive
Respiratory distress--mainly tachypnea
Rapid heart rate (160 to 180 beats/min)
Pulmonary rales or wheezing
Cardiomegaly and pulmonary edema on radiogram
Hepatomegaly (peripheral edema unusual)
Gallop sounds
Color--ashen pale or faintly cyanotic
Excessive perspiration
Diminished urine output

filling or elevated pressure of the right ventricle in infants reduces left ventricular compliance disproportionately when compared with older children or adults and gives rise to signs of both systemic and pulmonary venous congestion.[37]

Fatigue and dyspnea on exertion express themselves as a feeding problem in infants. Characteristically, the respiratory rate in heart failure is rapid (50 to 100 breaths/min). In the presence of left ventricular failure, interstitial pulmonary edema reduces pulmonary compliance and results in tachypnea and retractions. Excessive pulmonary blood flow by way of significant left-to-right shunts may further decrease lung compliance. Moreover, upper airway obstruction may be produced by selective enlargement of cardiovascular structures. In patients with large left-to-right shunts and left atrial and main pulmonary artery enlargement, the left main stem bronchus may be compressed, resulting in emphysematous expansion of the left upper or lower lobe or left lower lobe collapse.[42] Respiratory distress with grunting, flaring of the alae nasi, and intercostal retractions is observed when failure is severe and especially when pulmonary infection precipitates cardiac decompensation, which often is the case. Under these circumstances, pulmonary rales may be due to the infection, failure, or both. A resting heart rate with little variability is also characteristic of heart failure. Hepatomegaly is common in infants in failure, although liver tenderness is uncommon. Cardiomegaly may be assessed roentgenographically, but it must be recognized that in normal newborn infants, the cardiac diameter may be as much as 60 percent of the thoracic diameter, and the large thymus gland in infants occasionally interferes with evaluation of heart size. Two-dimensional and Doppler echocardiography provide a reliable estimate of cardiac performance and chamber dimensions, and values may be compared with data derived from normal infants.[43] [44] [45]

Cardiac decompensation may progress with extreme rapidity in the first hours and days of life, producing a clinical picture of advanced cardiogenic shock and a profoundly obtunded infant. The presence of marked hepatomegaly and gross cardiomegaly usually allows distinction from noncardiac causes of diminished systemic perfusion.

CYANOSIS

Cyanosis is produced by reduced hemoglobin in cutaneous vessels in excess of approximately 3 gm/dl (see p. 1539). Peripheral cyanosis usually reflects an abnormally great extraction of oxygen from normally saturated arterial blood, commonly the result of peripheral cutaneous vasoconstriction. Central cyanosis is a result of arterial blood oxygen unsaturation, most often in patients with congenital heart disease caused by shunting of systemic venous blood into the arterial circuit. Infants especially (as compared with adults) may appear cyanotic when in heart failure because of both peripheral and central factors[46] ; the latter may include severe impairment of pulmonary function that commonly exists with alveolar hypoventilation, ventilation-perfusion inequality, or impaired oxygen diffusion.

In patients with central cyanosis owing to arterial oxygen unsaturation, the degree of cutaneous discoloration depends on the absolute amount of reduced hemoglobin, the magnitude of the right-to-left shunt relative to systemic flow, and the oxyhemoglobin saturation of venous blood. The last of these depends in turn on the tissue extraction of oxygen. Cyanosis commonly appears or intensifies with physical activity or exercise as the saturation of systemic venous blood declines concurrent with an increase in right-to-left shunting across a defect as peripheral vascular resistance decreases.

Oxygen transfer to the tissues is affected by shifts in the oxygen-hemoglobin dissociation relation, which may be altered by blood pH and levels of red blood cell 2,3-diphosphoglycerate concentration.

CLUBBING AND POLYCYTHEMIA/ERYTHROCYTOSIS.

Prominent accompaniments of arterial hypoxemia are polycythemia and clubbing of the digits. The latter is associated with an increased number of capillaries with increased blood flow through extensive arteriovenous aneurysms and an increase of connective tissue in the terminal phalanges of the fingers and toes. Polycythemia is a physiological response to chronic hypoxemia that stimulates erythrocytosis. The extremely high hematocrits observed in patients with arterial oxygen unsaturation cause a progressive increase in blood viscosity. Because the relationship is nonlinear between hematocrit and blood viscosity, relatively small increases beyond packed blood cell volumes of 60 percent result in large increases in viscosity. Also, the apparent viscosity of blood increases in the microcirculation, where lower shear rates exist, an increasingly important factor as the hematocrit exceeds 70 percent.

Both the hematocrit and the circulating whole blood volume are increased in polycythemia accompanying cyanotic congenital heart disease; the hypervolemia is the result of an increase in red blood cell volume. The augmented red blood cell volume provoked by hypoxemia provides an increased oxygen-carrying capacity and enhanced oxygen supply to the tissues. The compensatory polycythemia often is of such severity that it becomes a liability and produces such adverse physiological effects as hyperviscosity, cellular aggregation, and thrombotic lesions in diverse organs and a hemorrhagic diathesis.[47] In this regard, oral steroid contraceptives are contraindicated in adolescent cyanotic females because of the enhanced risk of cerebral thrombosis.

Management.

Red blood cell volume reduction and replacement with plasma or albumin (erythropheresis) lower blood viscosity and increase systemic blood flow and systemic oxygen transport; they thus may be helpful in the treatment of patients with severe hypoxic polycythemia (hematocrit
65 percent). A final hematocrit of 55 to 63 percent should be achieved; the higher level is necessary in patients with low initial oxygen saturation to avoid a severe reduction in arterial oxygen content. Acute phlebotomy without fluid replacement is contraindicated.

CEREBRAL AND PULMONARY COMPLICATIONS.

Cerebrovascular accidents and brain abscesses occur particularly in cyanotic patients with substantial arterial desaturation.[48] [49] *Cerebral thrombosis* is most common before age 2 years in severely cyanotic children, even in the presence of relatively low hematocrits, and occurs especially in a clinical setting in which oxygen requirements are raised by fever or, if blood viscosity is increased, dehydration.

Brain Abscess.

This is an important complication of cyanotic heart disease.[49] Such abscesses are rare before 18 months of age and commonly are of insidious onset marked by headache, low-grade fever, vomiting, and a change in personality. Seizures or paralysis less frequently herald the onset of a brain abscess. Abscess must be suspected in any cyanotic child with focal neurological signs. Morbidity and mortality are related inversely to oxygen saturation levels. Brain abscess is thought to occur in about 2 percent of the population with cyanotic congenital heart disease; a mortality rate of 30 to 40 percent often is related to delay in diagnosis and treatment.

Paradoxical Embolus.

This is a rare complication of cyanotic heart disease, usually observed only at necropsy.[50] Emboli arising in systemic veins may pass directly to the systemic circulation, because right-to-left intracardiac shunts allow venous blood to bypass the normal filtering action of the lungs.

Retinopathy.

Dilated tortuous vessels progressing to papiliedema and retinal edema occasionally are observed in cyanotic patients and appear to be related to decreased arterial oxygen saturation and/or to erythrocytosis but not to hypercapnia.

Hemoptysis.

This is an uncommon but major complication in cyanotic patients with congenital heart disease; it occurs most often in the presence of pulmonary vascular obstructive disease or in patients with an extensive bronchial collateral circulation or pulmonary venous congestion.[51] Massive hemoptysis almost always represents rupture of a dilated bronchial artery.

SQUATTING.

After exertion, patients with cyanotic heart disease, especially tetralogy of Fallot, typically assume a squatting posture to obtain relief from breathlessness.[52] Squatting appears to improve arterial oxygen saturation by increasing systemic vascular resistance, thereby diminishing the right-to-left shunt, and by the pooling of markedly desaturated blood in the lower extremities. In addition, systemic venous return, and therefore pulmonary blood flow, may increase.

HYPOXIC SPELLS.

Hypercyanotic or hypoxemic spells commonly complicate the clinical course in younger children with certain types of cyanotic heart disease, especially tetralogy of Fallot.[52] The

spells occur commonly in the morning and are characterized by anxiety, hyperpnea, and a sudden marked increase in cyanosis; they are the result of an abrupt reduction in pulmonary blood flow. Unless terminated, the hypercyanotic episodes may lead to convulsions and may even be fatal. The sudden reduction in pulmonary blood flow may be precipitated by fluctuations in arterial P_{CO_2} and pH, a sudden fall in

systemic or increase in pulmonary vascular resistance, or an acute increase in the severity of right ventricular outflow tract obstruction, either by augmented contraction of the hypertrophied muscle in the right ventricular outflow tract or by a decrease in right ventricular cavity volume owing to tachycardia.

Treatment.

This consists of oxygen administration, placing the child in the knee-chest position, and administration of morphine sulfate. Additional medications that may prove of value include intravenous administration of sodium bicarbonate to correct the accompanying acidemia, alpha-adrenoceptor stimulants such as phenylephrine hydrochloride (Neo-Synephrine) or methoxamine to raise peripheral resistance and diminish right-to-left shunting, and beta-adrenoceptor blocking agents, which reduce cardiac sympathetic tone, depress cardiac contractility directly, and increase ventricular volume by reducing heart rate.

ACID-BASE IMBALANCE

Disturbances in blood gas and acid-base equilibrium are noted particularly in infants with either congestive heart failure or cyanosis.[53] Large-volume left-to-right shunts, especially with pulmonary edema, may be associated with moderate respiratory acidemia and a lowering of arterial oxygen tensions, reflecting an increase in the alveolar-arterial oxygen tension gradient and ventilation-perfusion imbalance. Interference with carbon dioxide transport implies moderate to severe failure in these infants. Lesions associated with a reduced systemic cardiac output, such as severe coarctation of the aorta or critical aortic stenosis in infancy, often present as cardiac failure complicated by a severe metabolic acidemia and relatively high values of arterial oxygen tension. The latter finding, even in the presence of right-to-left shunting across a patent ductus arteriosus, is a result of diminished systemic perfusion and an elevated pulmonary-systemic blood flow ratio.

Respiratory acidemia and depressed levels of oxygen tension are observed in infants with obstruction to pulmonary venous return and right-to-left atrial shunting. Many infants with severe hypoxemia caused by lesions such as transposition of the great arteries or pulmonic atresia show metabolic acidemia and marked reductions in carbon dioxide tension secondary to hyperventilation, resulting from hypoxic stimulation of peripheral chemoreceptors.

IMPAIRED GROWTH

Impaired growth and physical development and delayed onset of adolescence are common features of many cyanotic and, to a lesser extent, acyanotic forms of congenital heart disease.[54] [55] Mental development seldom is affected. The severity of growth disturbance depends on the anatomical lesion and its functional effect. Most children with mild defects grow normally. Weight gain is commonly slower than linear growth in acyanotic patients with large left-to-right shunts, whereas in cyanotic congenital heart disease, height and weight usually parallel each other. Boys appear to be more retarded in growth than girls, especially in the second decade of life. Skeletal maturity (i.e., bone age) is delayed in cyanotic children in relation to the severity of hypoxemia.

In some children, prenatal factors such as intrauterine infection and chromosomal or other hereditary and nonhereditary syndromes are responsible for growth retardation. In other patients, extracardiac malformations may contribute to poor weight gain and linear growth. Additional explanations for the mechanisms of growth interference have implicated malnutrition as a result of anorexia and inadequate nutrient and caloric intake, hypermetabolic state, acidemia and cation imbalance, tissue hypoxemia, diminished peripheral blood flow, chronic cardiac decompensation, malabsorption or protein loss, recurrent respiratory infections, and endocrine or genetic factors. In some instances, the underdevelopment is influenced little by operative correction of the underlying cardiac anomaly.

Among factors that may be responsible for persistent growth retardation postoperatively are age at operation, hemodynamically significant residual lesions, and sequelae or complications of operation. As a general rule, it is unwise preoperatively to guarantee to the parents of a child with heart disease that surgery will result in accelerated growth and development.

PULMONARY HYPERTENSION (See also Chap. 53)

Pulmonary hypertension is a common accompaniment of many congenital cardiac lesions, and the status of the pulmonary vascular bed often is the principal determinant of the clinical manifestations, the course, and whether surgical treatment is feasible.[56] Increases in pulmonary arterial pressure result from elevations of pulmonary blood flow and/or resistance, the latter sometimes caused by an increase in vascular tone but usually the result of underdevelopment and/or obstructive, obliterative structural changes within the pulmonary vascular bed.[57] [58] [59]

Pulmonary vascular resistance normally falls rapidly immediately after birth, owing to onset of ventilation and subsequent release of hypoxic pulmonary vasoconstriction. Subsequently, the medial smooth muscle of pulmonary arterial resistance vessels thins gradually. This latter process often is delayed by several months in infants with large aorticopulmonary or ventricular communications, at which time levels of pulmonary vascular resistance are still somewhat elevated. In patients with high pulmonary arterial pressure from birth, failure of normal growth of the pulmonary circulation may occur, and

anatomical changes in the pulmonary vessels in the form of proliferation of intimal cells and intimal and medial thickening often progress, so that in an older child or adult vascular resistance ultimately may become fixed by obliterative changes in the pulmonary vascular bed. The causes of pulmonary vascular obstructive disease remain unknown, although increased pulmonary arterial blood pressure, elevated pulmonary venous pressure, polycythemia, systemic hypoxia, acidemia, and the nature of the bronchial circulation all have been implicated. Quite likely, injury to pulmonary vascular endothelial cells initiates a cascade of events that involve the release or activation of factors that alter the extracellular matrix, induce hypertrophy, cause proliferation of vascular smooth muscle cells, and promote connective tissue protein synthesis. Considered together, these may permanently alter vessel structure and function.[60] [61]

Many patients with pulmonary vascular obstruction have a cardiac anomaly that places them at particular risk early in life, precluding survival to adulthood. Patients at particularly high risk for the development of significant pulmonary vascular obstruction are those with certain forms of cyanotic congenital heart disease, such as complete transposition of the great arteries with or without VSD or patent ductus arteriosus, single ventricle without pulmonary stenosis, double-outlet right ventricle, and truncus arteriosus.[62] Other conditions in which pulmonary vascular obstruction appears to progress rapidly include large VSD, as well as the less common conditions of unilateral pulmonary artery absence, congenital left-to-right shunts in an environment of high altitude or in association with the Down syndrome of trisomy 21, and complete AV canal defects, even those unassociated with a chromosomal anomaly.

MECHANISMS OF DEVELOPMENT.

Intimal damage appears to be related to shear stresses because endothelial cell damage occurs at high-flow shear rates. A reduction in pulmonary arteriolar lumen size due to either thickened medial muscle or vasoconstriction increases the velocity of flow. Shear stress also increases as blood viscosity rises; therefore, infants with hypoxemia and high hematocrits as well as increased pulmonary blood flow are at increased risk of developing pulmonary vascular disease. In patients with left-to-right shunts, pulmonary arterial hypertension, if not present in infancy or childhood, may never occur or may not develop until the third or fourth decade or later. Once developed, intimal proliferative changes with hyalinization and fibrosis are not reversible by repair of the underlying cardiac defect. In severe pulmonary vascular obstructive disease, arteriovenous malformations may develop and predispose to massive hemoptysis.

Most vexing is the variability among patients with the same or similar cardiac lesions in both the time of appearance and rate of progression of their pulmonary vascular obstructive process. Although genetic influences may be operative (an example is the apparent acceleration of pulmonary vascular disease in patients with congenital heart disease and trisomy 21), evidence is now accumulating for important prenatal and postnatal modifiers of the pulmonary vascular bed that appear, at least in part, to be lesion dependent. Thus, a quantitative variability exists in the pulmonary vascular bed related to the *number,* not just the size and wall structure, of arterial vessels within the pulmonary circulation.[63] [64]

Modeling of the blood vessels occurs proximal to and within terminal bronchioles (preacinar and intraacinar vessels, respectively) continuously from before birth. The intraacinar vessels, in particular, increase in size and number from late fetal life throughout childhood, with minimal muscularization of their walls. The ensuing increase in the cross-sectional area of the pulmonary arterial circulation allows

the cardiac output to rise substantially without an increase in pulmonary arterial pressure. If, however, the presence of a cardiac lesion interferes with the normal growth and multiplication of these most peripheral arteries, the resulting elevation of pulmonary vascular resistance may first be related to failure of the Intraacinar pulmonary circulation to develop fully, and then secondarily to the morphological changes of obliterative vascular disease--medial thickening, intimal proliferation, hyalinization and fibrosis, angiomatoid and plexiform lesions, and ultimately, arterial necrosis.[59]

In essence, the morphometric framework adds an important dimension--that of growth and development of the pulmonary circulation--to the traditional view of pulmonary vascular obstructive disease occurring primarily as a result of anatomical changes in the individual pulmonary arterioles. Research attention currently focuses on the cellular and molecular biology of the vessel wall and abnormalities in endothelial cell-smooth muscle interactions in pulmonary hypertension.

ASSESSMENT OF THE PATIENT WITH PULMONARY HYPERTENSION.

It is important to understand the difficulties that exist with standard methods of assessing the severity of pulmonary vascular obstructive disease. Clinical and electrocardiographic (ECG) observations do not distinguish between reversible and irreversible elevations in pulmonary vascular resistance. Echocardiography and Doppler interrogation of the heart may enable one to diagnose the presence of pulmonary hypertension but do not provide an accurate estimate of pressure or a reliable calculation of pulmonary vascular resistance. The pulmonary systolic pressure is predicted from the velocity of tricuspid regurgitation using the modified Bernoulli equation, which is susceptible to error if the right atrial pressure is elevated. The mean pulmonary regurgitant velocity can also be relatively predictive of the mean pulmonary artery pressure. Thus, hemodynamic measurements at cardiac catheterization are the mainstay in assessing the pulmonary vascular bed, especially its reactivity. The premium on accuracy is high because the presence, degree, and reactivity of pulmonary vascular obstruction determine the feasibility and long-term outcome of operation. Surgery must not be offered to patients with severe, fixed pulmonary vascular obstruction, even when the cardiac defect is anatomically correctable. Such patients either do not survive operation or, if they do, are not benefited and more often than not are harmed.

The aims of hemodynamic study are to quantify and compare the pulmonary and

systemic flows and resistances and to determine the reactivity of the pulmonary vascular bed in patients with pulmonary hypertension. Because resistance to pulmonary blood flow cannot be measured directly, it is calculated from the ratio of pressure gradient to flow across the pulmonary bed according to Poiseuille's equation, which refers to steady flow of a newtonian fluid through straight, rigid tubes. There are potential errors in applying the equation and errors inherent in the methods of measurement. Furthermore, it is not possible in every patient to catheterize the pulmonary artery; when this is the case, pulmonary venous wedge pressures may be used, but they are not always reliable indicators of pulmonary artery pressure, and the moment of hemodynamic evaluation may not be representative of potentially variable states of the pulmonary circulation. Nonetheless, a practical index of pulmonary vascular resistance can be established from measurements of pulmonary and systemic arterial pressures and calculated flows. One can then determine whether administration of drugs or oxygen or nitric oxide reduces the pulmonary vascular resistance, implying that the resistance is not fixed and therefore may decrease or at least not progress after successful operation.[65] A reduction in calculated pulmonary vascular resistance in response to oxygen or nitric oxide inhalation or pharmacological intervention does not preclude coexisting anatomical pulmonary vascular disease but does imply a component of potentially reversible vasoconstriction contributing to the high resistance.

OTHER DIAGNOSTIC METHODS.

Because of the aforementioned shortcomings, additional methods have been developed to study the morphology of the small pulmonary arteries in patients with pulmonary hypertension. An example is the use of high-resolution magnification for *pulmonary wedge angiography* to determine the presence and extent of obstructive pulmonary vascular changes.[66] Pulmonary wedge angiograms, assessed quantitatively, appear to correlate well with both hemodynamic findings and histological observations of the structural state of the pulmonary vascular bed. Of additional interest is the current practical application of morphometric structural analyses that attempt to identify for operation patients whose postoperative pulmonary hemodynamics might be expected to improve, if not normalize.[67] Thus, preoperative or intraoperative *lung biopsy* has been proposed for patients with equivocal hemodynamic data to aid in determining whether to proceed with operation in reasonable anticipation of postoperative regression of elevated pulmonary vascular resistance.[68]

THE MORPHOMETRIC APPROACH.

Decisions on optimal timing of operations often are difficult because of the varying rates of development of pulmonary vascular disease in different patients with the same anomaly and because evaluation of pulmonary vascular resistance and reactivity in the catheterization laboratory is a less than perfect science. Preoperative lung biopsy using the Heath-Edwards criteria has enjoyed little popularity, especially because sampling errors may result from the scatter of different grades of lesion in different parts of the lung. Accordingly, it is attractive to seek an alternative method that would obviate these problems. In this regard, application of a morphometric approach holds promise because the described changes in pulmonary vessel morphological characteristics are more uniformly distributed throughout the lung and, importantly, lend themselves to

quantification.

Three abnormalities have been identified as anatomical markers of elevated pulmonary vascular resistance: (1) an excessive and premature extension of vascular smooth muscle into intraacinar pulmonary arteries, (2) failure of preacinar arterial wall thickness to regress normally, and (3) failure of pulmonary arteries to grow and proliferate normally during postnatal development. Frozen-section lung biopsy provides a firmer basis for judgment of whether reparative or palliative operation should proceed. The technique has proved useful in patients with univentricular hearts or tricuspid atresia in determining the feasibility of a Fontan procedure and in patients with lesions known to exhibit early and rapidly progressive pulmonary vascular disease such as complete transposition of great arteries, complete AV canal defect, and nonrestrictive VSD.[68] [69]

CLINICAL MANIFESTATIONS OF PULMONARY HYPERTENSION.

When this condition is associated with a large left-to-right shunt, the clinical manifestations reflect the specific malformation responsible. When pulmonary vascular resistance is elevated and a significant right-to-left shunt exists, the patient is cyanotic, and polycythemia and clubbing are noted. A dominant *a* wave in the jugular venous pulse may be seen, reflecting vigorous right atrial contraction caused by diminished compliance of the right ventricle. In some instances there are large systolic *c-v* waves, which suggest tricuspid regurgitation. A prominent right ventricular parasternal lift and palpable systolic expansion of the pulmonary artery are present. A soft pulmonary systolic ejection murmur preceded by an ejection sound and followed by a markedly accentuated pulmonic component of the second heart sound often is audible on auscultation; an early diastolic decrescendo blowing murmur of pulmonary regurgitation may be heard. If right ventricular failure and dilatation supervene, the systolic murmur of tricuspid regurgitation may be audible at the lower left sternal border. Right ventricular enlargement may be evident on the chest roentgenogram and ECG. The former examination also reveals a conspicuously enlarged pulmonary artery, prominent hilar pulmonary vascular markings, and attenuated peripheral vessels. The presence of pulmonary hypertension is suggested by analysis of Doppler waveforms of right and left ventricular ejection. The site of the underlying defect may be localized by means of two-dimensional and Doppler echocardiography and/or cardiac catheterization and angiocardiography. Pressures in the right side of the heart are essentially identical to systemic pressures in cyanotic patients if the shunt is at the ventricular or aorticopulmonary

levels, but they usually are lower than systemic pressures in patients with an intraatrial shunt. Efforts continue to identify a specific treatment for obstructive pulmonary vascular disease.[70] [71]

This fact underscores the importance of efforts to define the optimal age at operation to provide the highest probability of postoperative normalization of the pulmonary vascular

bed. It is important to emphasize that almost all congenital cardiovascular defects are amenable to surgical repair in infancy, and it is likely that the surgical art will progress to the point that virtually all patients with lesions associated with pulmonary hypertension will be operated on within the first 3 to 18 months of life. When this goal is reached without increased operative mortality, the incidence of postoperative pulmonary vascular obstruction may well achieve the status of a bygone concern.

OTHER CONSEQUENCES OF CONGENITAL HEART DISEASE

INFECTIVE ENDOCARDITIS (see also Chap. 47).

Infective endocarditis is uncommon before age 2 years and thereafter most often affects children with tetralogy of Fallot (especially after systemic-pulmonary anastomosis), VSD, aortic stenosis, and patent ductus arteriosus. Postsurgical patients with prosthetic heterograft or homograft valves or conduits are at particular risk. Infants and children with normal cardiac anatomy are at increased risk now that the use of central venous catheters is routine, and drug addiction in adolescents is an emerging risk factor.[72]

A causative organism can be isolated in about 90 percent of children, usually either alpha streptococci (usually *Streptococcus viridans*) or *Staphylococcus aureus,* although uncommon organisms may also be identified.[73] [74] [75] Fungal endocarditis is quite rare in the pediatric age group. Mortality appears to be highest when coagulase-positive *Staphylococcus* is the offending organism and when the endocarditis involves the left, rather than the right, side of the heart. Most recent data suggest 75 to 80 percent overall survival. Factors predisposing to endocarditis may be identified in about one-third of cases. These include cardiovascular surgery with infection during the perioperative period, respiratory tract infections, and ear, nose, throat, and dental procedures. Less often, contamination during a surgical procedure or cardiac catheterization or an infection involving the skin, genitourinary tract, or other organ system has been the cause.

Although routine antimicrobial prophylaxis is recommended for all children with congenital heart disease and for the majority of patients alter operative repair of the lesion,[74] [74A] it should be recognized that many different microbes are responsible for the disease and that an effective preventive approach ultimately may center on active immunization rather than antibiotics. Antibiotic prophylaxis currently is recommended for all dental procedures known to induce gingival or mucosal bleeding, including cleaning, oral trauma, and other procedures such as tonsillectomy, gastrointestinal surgery, genitourinary surgery, and incision and drainage of infected tissue (Table 43-4) . The risk of endocarditis is undoubtedly related both to the magnitude of bacteremia and to the type of underlying heart disease. Because infection on a prosthetic heart valve or conduit may be devastating, combinations of antibiotics given parenterally are advisable in these patients.

CHEST PAIN (see also Chap. 3).

Angina pectoris is an uncommon symptom of cardiac disease in infants and children,

occurring in association with anomalous pulmonary origin of a coronary artery or, occasionally, in association with severe aortic stenosis, pulmonic stenosis, or pulmonary hypertension owing to pulmonary vascular obstruction. Cardiac pain in infants with anomalous coronary artery usually takes the form of irritability and crying during feeding or straining at bowel movement. In children with severe or right ventricular outflow tract obstruction, chest pain commonly follows effort and is identical to angina observed in adults. Cardiac pain associated with *pulmonary vascular obstruction* may be anginal in nature but often is evanescent and pleuritic in type. Atypical forms of chest pain associated with the syndrome of *mitral valve prolapse* are much less usual in children than in adults. A sensation of chest discomfort or cardiac awareness frequently is interpreted as pain by the parents of children with cardiac arrhythmias. Careful questioning serves to identify palpitations rather than pain as the symptom and often elicits an additional history of anxiety, pallor, and sweating. Pain caused by *pericarditis* is commonly of acute onset and associated with fever, and it can be identified by specific physical, roentgenographic, and echocardiographic findings.

Most commonly, chest pain in children is *musculoskeletal* in origin and may be reproduced on upper extremity movement or by palpation; chest wall pain often is the result of *costochondritis.* [75] Finally,

TABLE 43-4 -- PROPHYLACTIC ANTIBIOTICS FOR PROTECTION FROM BACTERIAL ENDOCARDITIS

PROPHYLACTIC REGIMENS FOR DENTAL, ORAL, RESPIRATORY TRACT, OR ESOPHAGEAL PROCEDURES*
Standard General Prophylaxis for Patients at Risk
Amoxicillin: adults, 2.0 gm (children, 50 mg/kg) PO 1 hr before procedure.
Unable to Take Oral Medications
Ampicillin: adults, 2.0 gm (children, 50 mg/kg) IM or IV within 30 min before procedure.
Amoxicillin/Ampicillin/Penicillin-Allergic Patients
Clindamycin: Adults, 600 mg (children, 20 mg/kg) PO 1 hr before procedure.
or
Cephalexin* or cefadroxil : adults, 2.0 gm (children, 50 mg/kg) PO 1 hr before procedure.
or
Azithromycin or clarithromycin: Adults, 500 mg (children, 15 mg/kg) PO 1 hr before procedure.
Amoxicillin/Ampicillin/Penicillin-Allergic Patients Unable to Take Oral Medications
Clindamycin: adults, 600 mg (children, 20 mg/kg) IV within 30 min before procedure.
or

Cefazolin: adults, 1.0 gm (children, 25 mg/kg) IM or IV within 30 min before procedure.

PROPHYLACTIC REGIMENS FOR GENITOURINARY/GASTROINTESTINAL PROCEDURES

High-Risk Patients

Ampicillin plus gentamicin: ampicillin (adults, 2.0 gm; children, 50 mg/kg) plus gentamicin 1.5 mg/kg (for both adults and children, not to exceed 120 mg) IM or IV within 30 min before starting procedure. 6 hr later, ampicillin (adults, 1.0 gm; children, 25 mg/kg) IM or IV, or amoxicillin (adults, 1.0 gm; children, 25 mg/kg) PO.

High-Risk Patients Allergic to Ampicillin/Amoxicillin

Vancomycin plus gentamicin: vancomycin (adults, 1.0 gm; children, 20 mg/kg) IV over 1-2 hr plus gentamicin 1.5 mg/kg (for both adults and children, not to exceed 120 mg) IM or IV. Complete injection/infusion within 30 min before starting procedure.

Moderate-Risk Patients

Amoxicillin: adults, 2.0 gm (children, 50 mg/kg) PO 1 hr before procedure.

or

Ampicillin: adults, 2.0 gm (children, 50 mg/kg) IM or IV within 30 min before starting procedure.

Moderate-Risk Patients Allergic to Ampicillin/Amoxicillin

Vancomycin: adults, 1.0 gm (children, 20 mg/kg) over 1-2 hr. Complete infusion within 30 min before starting procedure.

Adapted from Prevention of Bacterial Endocarditis: Recommendations by the American Heart Association by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. JAMA 277:1794-1801, 1997. Circulation 96:358-366, 1997. Copyright 1997 American Medical Association.

*Follow-up dose no longer recommended.

Total children's dose should not exceed adult dose.

Cephalosporins should not be used in patients with immediate-type hypersensitivity reaction to penicillins.

children, like adults, may suffer chest pain of nonspecific form owing to *anxiety,* with or without hyperventilation; a history often is elicited of a family member or friend who had recently died of or suffered myocardial infarction.

SYNCOPE (see also Chap. 27).

Syncope is an unusual feature of heart disease in children; its presence suggests specific diagnoses, the most common being an arrhythmia. The symptom is observed in patients with long QT syndrome and in children with complete AV block that is less often

of congenital origin than a sequela of cardiac

operation. Syncope caused by abrupt episodes of either bradycardia or tachycardia occurs in association with the sick sinus syndrome. The latter is most commonly produced in children after surgical procedures that involve the region of the sinoatrial node, e.g., atrial septal defect closure or Mustard's venous switch procedure for transposition of the great arteries. Syncope is an occasional but ominous symptom if associated with severe aortic stenosis, pulmonary vascular obstruction, or a left atrial myxoma that transiently occludes left ventricular inflow.[76]

In children with an anatomically normal heart, transient episodes of vasovagally mediated hypotension and bradycardia (neurocardiogenic syncope) may be diagnosed by autonomic function testing and head-upright tilt-table testing (see Chap. 27). The latter is especially helpful in assessing the adequacy of prophylactic therapy, usually by volume expansion (e.g., salt and fludrocortisone), or by beta-adrenergic blockade or alpha-adrenergic agonist or serotonin reuptake inhibitor therapy.[77]

SUDDEN DEATH (see also Chap. 24).

The sudden infant death syndrome is not likely due to a cardiac cause but rather to pulmonary and/or central nervous system causes. In contrast to adults, children seldom die suddenly and unexpectedly of cardiovascular disease.[78] Arrhythmias, hypoxemia, and coronary insufficiency secondary to left ventricular outflow tract obstruction are the most frequent causes of death. Sudden death most often is reported in patients with postoperative heart disease or dilated cardiomyopathy. It is also observed in patients with aortic stenosis or hypertrophic obstructive cardiomyopathy, primary pulmonary hypertension, Eisenmenger's syndrome of pulmonary vascular obstruction, myocarditis, congenital complete heart block, primary endocardial fibroelastosis, anomalies of the coronary arteries, and cyanotic congenital heart disease with pulmonic stenosis or atresia. A relation exists between strenuous exercise and sudden death in patients with aortic stenosis or obstructive cardiomyopathy, thus providing justification for restricting patients with these lesions from gymnastic activities and strenuous competitive sports.[79]

Congenital long QT syndrome is most often inherited as an autosomal dominant trait and is associated with malignant arrhythmias. It is characterized by a prolonged Q-T interval in the surface ECG, syncope, seizures, and sudden death caused by ventricular tachyarrhythmias. On a molecular level, a great many mutations in four ion channel genes have thus far been identified in these patients[80] (see chaps. 23 and 25).

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The High-Risk Infant with Congenital Heart Disease

Without prompt recognition, accurate diagnosis, and treatment, about one-third of all infants born with congenital heart disease die in the first months of life. Heart failure and cyanosis are the two cardinal signs in high-risk infants with heart disease, and this section provides an approach to the management of each.

HEART FAILURE

Care of infants with heart failure must include careful consideration of the underlying structural or functional disturbance. The general aims of treatment are to achieve an increase in cardiac performance, augment peripheral perfusion, and decrease pulmonary and systemic venous congestion.[37] It must be emphasized, however, that under many conditions medical management cannot control the effects of the abnormal loads imposed by a host of congenital cardiac lesions. Under these circumstances, cardiac diagnosis and interventional catheter or operative intervention may be urgently required. Thus, initial therapy is aimed at stabilizing an infant's condition for diagnostic ultrasonography or hemodynamic or angiocardiographic study as soon as possible. In almost all situations, the decision to intervene surgically or to continue medical management requires a definitive anatomical diagnosis.

RESERVE MECHANISMS IN THE NEONATAL HEART

Pediatricians in particular should be aware of the important concept of cardiac reserve because it is in this regard that important differences exist between the young heart (of the preterm or newborn infant) and the fully developed heart of the older child, adolescent, and adult (Fig. 43-5) .

Clinicians have long recognized the unique fragility and lability of the neonatal circulation in response to disease states and various physiological stimuli. Moreover, it often is apparent that newborns may exhibit suboptimal therapeutic responses to drugs such as digitalis, which directly stimulate cardiac contractility. The age dependence of these observations has its basis in the reduced ability of the hearts of premature and full-term newborns, when compared with the hearts and circulation of older children or adults, to call on a functional reserve capacity to adapt to stress.[37] [81] [82]

Studies from our and other laboratories have shown that structural, functional, biochemical, and pharmacological properties of the young heart differ considerably from those of its older counterpart.[21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] The young heart contains fewer myofilaments to generate force with and to shorten during contraction. In addition, the chamber stiffness of the young heart's ventricles is greater than that later in life.

PRELOAD RESERVE.

Any increase in ventricular filling or volume in the small, young heart results in a disproportionately greater rise in

Figure 43-5 Schema of reduced cardiac reserve in fetal and newborn hearts compared with an adult's. In a newborn infant, resting cardiac muscle performance *(top panel)* is close to the peak of ventricular function because of limitations in diastolic, systolic, and heart rate reserve. Similarly, pump reserve *(bottom panel)* early in life is limited by these factors, as well as by a much higher resting cardiac output relative to body weight, compared with an adult.

ventricular wall tension or stress. Similarly, it takes a smaller increase in ventricular filling to reach the limits of assistance given to cardiac pump and muscle function by stretching the myofilaments; that is, *preload or diastolic reserve is limited.*

The young heart generates relatively less force; it cannot generate the same ventricular systolic pressure or wall tensions, or obtain the same stroke volume augmentation from any initial stretch, as can the older heart. With these facts in mind, it must be remembered that the oxygen consumption of a normal newborn is considerably higher than later in life; accordingly, a newborn at rest has a much higher cardiac output per square meter than a child or adult. Thus, even in the absence of stress, the young heart must function near peak performance just to satisfy the normal demands of the peripheral tissues. Because newborn cardiac performance at rest is so close to its celling, or limits of function, little *systolic reserve* is available to adapt to an acute or chronic stress such as pressure or volume load from an obstructive lesion or left-to-right

circulatory shunt, respectively, or asphyxia.

HEART RATE RESERVE.

This consists of the ability of the heart to change its rate of pumping to raise the level of cardiac output. In this regard, newborns also are limited because in this age group the intrinsic heart rate normally is high. In addition, heart failure per se raises the frequency of contraction even further, primarily as a result of high circulating levels of catecholamines. In this sense, a newborn's heart rate also is closer than a child's or adult's to its ceiling, or upper limits of effectiveness. Furthermore, increases in heart rate occur largely at the expense of diastolic filling time. Thus, at very rapid heart rates, there is a disproportionately diminished diastolic time and therefore diminished time for perfusion of the myocardium by its own coronary arterial system. In addition. rapid heart rates result in elevated myocardial energy expenditure and increased myocardial demand for oxygen. The sum of these considerations indicates that newborn *heart rate reserve* is reduced.

TREATMENT (see also Chap. 18).

Table 43-5 lists supportive and pharmacological measures in the treatment of newborns with heart failure. The supportive measures are designed to increase tissue oxygen supply, decrease tissue oxygen consumption, and correct metabolic abnormalities. Digitalis glycosides, preload reduction with certain diuretic agents, and afterload reduction with angiotensin-converting enzyme inhibitors provide the most important elements of medical therapy, but it is important to recognize that the

TABLE 43-5 -- TREATMENT OF CONGESTIVE HEART FAILURE

GENERAL INTERVENTIONS
Rest (occasional sedation)
Semi-Fowler's position
Temperature and humidity control
Oxygen
Decrease sodium load
Avoid aspiration
Treat infection, if present
SPECIFIC INTERVENTIONS
Preload manipulation
Move ventricular function curve up by volume infusion to increase venous return
Move ventricular function curve down with diuretics, venodilators
Afterload reduction
Facilitate ventricular emptying by reducing wall tension

Reduce blood viscosity
Drugs, arteriolar dilators, mechanical counterpulsation
Inotropic stimulation
Improve physical and metabolic milieu: pH, Pa_{O_2}, glucose, calcium, hemoglobin
Inotropic drugs: digitalis, catecholamines, dobutamine, dopamine, levodopa
Heart rate
Control rhythm disturbances with pacing, drugs
Other
Mechanical ventilation
Prostaglandin manipulation
Peritoneal dialysis
INTERVENTIONAL CATHETER-DIRECTED THERAPY or SURGERY (may include transplantation)

TABLE 43-6 -- DIURETIC AND DIGITALIS DOSAGES FOR INFANTS

PREPARATION	DOSAGE AND ROUTE OF ADMINISTRATION
Furosemide	IV, 1 mg/kg/dose; PO, 2-6 mg/kg/d
Ethacrynic acid	IV, 1 mg/kg/dose; PO, 2-3 mg/kg/d
Hydrochlorothiazide	PO 2-5 mg/kg/d
Spironolactone	PO 1-3 mg/kg/d
Triamterene	PO 2-4 mg/kg/d
Digoxin	
Elixir	0.05 mg/ml
Parenteral	0.10 mg/ml

AGE AND WEIGHT	DOSE AND ROUTE*	
	Acute Digitalization	Maintenance
Prematures <1.5 kg	10-20 mug/kg IV TDD: ½, ¼, ¼ of dose q8h	4 mug/kg/d IV (may increase to 4 mug/kg q12hr at age 1 mo)
1.5-2.5 kg	Same as above	4 mug/kg q12hr IV
Full-term newborns	30 mug/kg IV, TDD	4-5 mug/kg q12hr IV
Infants (1-12 mo)	35 mug/kg IV, TDD	5-10 mug/kg q12hr IV
>12 mo	40 mug/kg IV, TDD (maximum 1.0 mg)	5-10 mug/kg q12hr IV

Older children (>20 kg)	1.0-2.0 mg IV, TDD over 48 hr	0.125-0.250 mg IV qd
TDD=Total digitalizing dose.		

*PO=Oral dose approximately 20 percent greater than IV dose except in "older children." In older children, IV=oral dose.

dosage regimen of drugs administered to young patients must be adjusted to take into account the age and size of the patient and the maturity-dependent pharmacological properties of cardioactive drugs. Because this is especially true in early infancy, Table 43-6 provides the dosages of digoxin and diuretics commonly used for infants.

Digitalis and Diuretics.

Digoxin is the glycoside used exclusively to treat pediatric patients in most cardiac centers because it is readily absorbed, available in convenient dosage form, and excreted rapidly from the body. The efficacy and safety of digitalis remain topics of debate, although on balance, continued use is warranted. Premature infants are more sensitive to digitalis than are full-term newborns, who, in turn, are more sensitive than older infants. Infants absorb and excrete digoxin as well as adults do, and their relative distribution of the glycoside to different body tissues is also similar. The prevailing dose schedules for digoxin produce higher serum concentrations in infants than would be considered optimal for adults.[83] The basis for the higher digitalis requirement in infancy is unclear, although it may relate to an age-dependent alteration in the sensitivity of the myocardium per se to the glycosides. In this regard, infants tolerate higher serum digoxin concentrations than adults without developing signs of toxicity. In adults, the usual therapeutic concentrations of digoxin are less than 2 ng/ml blood, and toxicity commonly occurs above that level. In contrast, in infants, therapeutic levels of digoxin range from 1 to 5 ng/ml (mean = 3.5), and toxicity is associated with concentrations in excess of 3 ng/ml. Older children have therapeutic and toxic levels similar to those of adults.[84]

A restricted fluid intake (65 ml/kg/day) and a low-sodium diet (1 to 2 mEq/kg/day) should accompany diuretic therapy in the most seriously ill infants with heart failure. Furosemide is the agent of choice when the rapid elimination of excess salt and water is needed. Hydrochlorothiazide, occasionally in conjunction with spironolactone or triamterene to reduce potassium loss and sodium retention, is convenient for long-term therapy.

TABLE 43-7 -- DOSAGE REGIMENS: INOTROPIC AGENTS

DRUG	DOSE	COMMENTS
Epinephrine (Adrenalin)	0.05-1.0 mug/kg/min IV	May cause hypertension and cardiac arrhythmias; inactivated in alkaline solution
Isoproterenol (Isuprel)	0.05-0.5 mug/kg/min IV	May decrease coronary blood flow; results in peripheral and pulmonary vasodilation
Norepinephrine (Levophed)	0.05-0.5 mug/kg/min IV	Causes significant vasoconstriction
Dobutamine (Dobutrex)	2-10 mug/kg/min IV (max 40 mug/kg/min)	No direct effect on renal perfusion, little or no peripheral vasodilatation or tachycardia
Dopamine (Intropin)	2-20 mug/kg/min IV (max 50 mug/kg/min)	Significant renal vasodilatation
	2-5 mug/kg/min	Inotropic±heart rate acceleration
	5-8 mug/kg/min	Significant heart rate acceleration
	>8 mug/kg/min	±Vasoconstriction
	>10 mug/kg/min	Significant vasoconstriction
	15-20 mug/kg/min	
Levodopa	40-80 mg/kg/d PO; maximum single dose 1 gm q6h	Administer with pyridoxine 0.7 mg/kg/d (maximum 25 mg) and metoclopramide 0.1 mg/kg/dose, 1 hr before levodopa dose
	(Above dose/effect relations speculative in neonates)	
Amrinone	Dose schedule not well established for infants and children	May cause thrombocytopenia, hepatic and gastrointestinal disturbance, fever, and arrhythmias
	40-75 mug/kg/min IV for 2-3 min, then maintenance at 3-10 mug/kg/min; Dose not to exceed 10 mg/kg/24 hr	
Milrinone	Dose schedule not established for infants and children	See Amrinone
	Adults: bolus 50 mug/kg maintenance 0.375-0.75 mug/kg/min	

Modified from Friedman WF, George BL: New concepts and drugs in the treatment of congestive heart failure. Pediatr Clin North Am 31:1197, 1984.

Other Pharmacological Approaches.

These may prove to be of significant benefit in selected instances in which digitalis and diuretics are relatively ineffective. In situations in which cardiac decompensation is not the result of an obstructive lesion, catecholamines may be used temporarily to alleviate cardiac failure while the patient is awaiting more definitive operative treatment (Table 43-7) .[81] In infants with the coarctation of the aorta syndrome, in whom ductal constriction unmasks the aortic branch point, producing aortic narrowing, or with aortic arch interruption, heart failure may be reversed dramatically by intravenous infusion of prostaglandin E_1 (0.03 to 0.1 mg/kg/min), which results in dilatation of the ductus arteriosus and relief of the obstruction.[85] Conversely, in preterm infants in whom patent ductus arteriosus is responsible for profound cardiopulmonary deterioration, constriction of the ductus arteriosus may be accomplished by inhibition of prostaglandin synthesis with the nonsteroidal anti-inflammatory agent indomethacin (0.2 mg/kg intravenously).[86] [87]

Vasodilator therapy also is used in infants or children with heart disease in whom preload or afterload alterations may be expected to improve cardiac performance (Table 43-8) .[81] [88] Moreover, treatment of severe cardiac failure often requires combining inotropic and afterload-reducing agents (see Chap. 18). Combinations of dopamine, dobutamine, and nitroprusside have been used extensively and effectively in the pediatric population, primarily in the setting of low cardiac output after open-heart surgery.[89] [90] Use of oral afterload-reducing agents, e.g., hydralazine or captopril, in association with digoxin is worthwhile in the long-term therapy of outpatients with congestive cardiomyopathy and/or significant mitral or aortic regurgitation.[88]

Rapid developments in molecular biology have begun to revolutionize our understanding of cardiovascular regulation, both before and after birth and at all ages. As knowledge is gained about the mechanisms responsible for the variability of gene expression in the heart, it is apparent that the future holds the opportunity for clinicians to modify

TABLE 43-8 -- DOSAGE REGIMENS: VASODILATORS IN INFANTS AND CHILDREN

DRUG	DOSE AND ROUTE OF ADMINISTRATION	COMMENTS
Nitroglycerin	0.5-20 mug/kg/min IV (max 60 mug/kg/min IV)	Dosage schedule for IV and other routes of administration not well established for children
Hydralazine (Apresoline)	0.5 mg/kg/d PO q6-8hr (max 200 mg/d or 7 mg/kg/d)	May cause tachycardia, gastrointestinal symptoms, neutropenia, lupus-like syndrome
	1.5 mug/kg/min IV or 0.1-0.5 mg/kg/dose IV q6hr (max 2 mg/kg q6hr)	

Captopril (Capoten)	0.1-0.4 mg/kg/dose PO given q6-24hr as needed	May cause neutropenia/proteinuria
Enalopril (Vasotec)	0.1 mg/kg/24 hr PO; increase as needed over 2 wk (max 0.5 mg/kg/24 hr IV: 0.01 mg/kg/dose q8-24 hr)	
Nitroprusside (Nipride)	0.5-8 mug/kg/min IV	May result in thiocyanate or cyanide toxicity if used in high doses or for prolonged periods; light sensitive
Prazosin (Minipress)	1st dose: 5 mug/kg PO (max 25 mug/kg/dose q6hr)	Initial dose used to elevate hypotensive effects; orthostatic hypotension, attenuation of hemodynamic effects may occur
Modified from Friedman WF, George BL: New concepts and drugs in the treatment of congestive heart failure. Pediatr Clin North Am 31:1197, 1984.		

gene expression in ways that will importantly enhance the heart's ability to respond to both the heart failure state and those diseases that are responsible for the abnormalities leading to cardiac disease.[91]

CYANOSIS (See also p. 1617)

Cyanosis in infants often presents as a diagnostic emergency, necessitating prompt detection of the underlying cause. The schema in Figure 43-6 outlines a general approach to diagnosis. The cardiologist must distinguish between three types of cyanosis--peripheral, differential, and central--while recognizing that cyanosis may accompany diseases of the central nervous, hematological, respiratory, and cardiac systems.

PERIPHERAL CYANOSIS.

Peripheral cyanosis (normal arterial oxygen saturation and widened arteriovenous oxygen differences) usually indicates stasis of blood flow in the periphery. The level of reduced hemoglobin in the capillaries of the skin usually exceeds 3 gm/100 dl. The most prominent causes of peripheral cyanosis in newborns are autonomically controlled alterations in the cutaneous distribution of capillary blood flow (acrocyanosis) and septicemia associated with evidence of a low cardiac output, i.e., hypotension, weak pulse, and cold extremities. In many instances, peripheral cyanosis is clearly the result of a cold environment or high hemoglobin content. When cyanosis is caused by the former, vasodilatation produced by immersing the extremity in warm water for several minutes reverses the cyanosis.

CENTRAL CYANOSIS.

Oxygen unsaturation in central cyanosis may result from inadequately oxygenated pulmonary venous blood, in which case inhalation of 100 percent oxygen may diminish or clear the discoloration (discussed later). Conversely, in instances in which cyanosis is due to an intracardiac or extracardiac right-to-left shunt, pulmonary venous blood is fully saturated, and inhalation of 100 percent oxygen usually does not improve the infant's color. It is necessary to qualify the latter statement because oxygen may act directly in infants with elevated pulmonary vascular resistance to dilate the pulmonary blood vessels and thus reduce the magnitude of the venoarterial shunt. Central cyanosis also may be due to the replacement of normal by abnormal hemoglobin, as in methemoglobinemia.

Several factors influence the oxygen saturation produced at any given arterial P_{O_2} . These include temperature, pH, ratio of fetal to adult hemoglobin, and erythrocyte concentration of 2,3-diphosphoglycerate. For example, fetal hemoglobin has a higher affinity for oxygen than does adult hemoglobin and therefore would be more highly saturated at any given P_{O_2} . Thus, determination of the systemic arterial oxygen tension may provide a more accurate picture of the underlying pathophysiology than simply measuring the oxygen saturation.[46] [92]

DIFFERENTIAL CYANOSIS.

Differential cyanosis virtually always indicates the presence of congenital heart disease, often with patency of the ductus arteriosus and coarctation of the aorta as components of the abnormal anatomical complex. If the upper part of the body is pink and the lower part of the body blue, coarctation of the aorta or interruption of the aortic arch is probable, with oxygenated blood supplying the upper body and desaturated blood supplying the lower body by way of right-to-left flow through the ductus arteriosus. The latter also occurs in patients with patent ductus arteriosus and markedly elevated pulmonary vascular resistance. A patient with transposition of the great arteries and coarctation of the aorta with retrograde flow through a patent ductus arteriosus demonstrates the reverse situation, i.e., the lower part of the body is pink and the upper part blue. Simultaneous determinations of oxygen saturation in the temporal or right brachial artery and the femoral artery are helpful in confirming the presence of differential cyanosis.

Differentiating Between Pulmonary and Cardiac Causes of Cyanosis

The distinction between respiratory signs and symptoms arising from cyanotic cardiac disease and those associated with a primary pulmonary disorder is an important challenge to the cardiologist.[41] Upper airway obstruction precipitates cyanosis by producing alveolar hypoventilation owing to reduced pulmonary ventilation. Mechanical obstruction may occur from the nares to the carina, and the important diagnostic possibilities among congenital abnormalities are choanal atresia, vascular ring, laryngeal web, and tracheomalacia. Acquired causes include vocal cord paresis,

obstetrical injury to the cricothyroid cartilage, and

Figure 43-6 Flow chart for the evaluation of cyanotic infants. Tests to be done are listed at the left. The response to each of these tests leads along the line to the proper diagnostic category. CHD = congenital heart disease; CHF = congestive heart failure; CNS = central nervous system; Hct = hematocrit; PDA = patent ductus arteriosus; T/GA = transposition of great arteries; Coarct=coarctation; Rm=room. *(From Kirkpatrick SE, Friedman WF, Pitlick P, et al: Differential diagnosis of congenital heart disease in the newborn--University of California, San Diego, School of Medicine, and University Hospital, San Diego [Specialty Conference]. West J Med 128:127, 1978.)*

TABLE 43-9 -- ARTERIAL BLOOD GAS PATTERNS IN VARIOUS DISORDERS CAUSING CYANOSIS IN INFANTS

PATTERN	pH	P_{O_2}	P_{CO_2}	RESPONSE TO O_2	VENOUS pH	SUGGESTED CONDITION
1						Hyaline membrane or other pulmonary parenchymal disease
2						Hypoventilation
3	--		--		--	Venous admixture
4			--	--		Decreased or ineffective pulmonary blood flow
5			--	--		Systemic hypoperfusion

-- = no effect. For description of patterns, see pp. 1524 ff.

foreign body. Structural abnormalities in the lungs resulting from intrapulmonary disease are more frequently a basis for cyanosis among newborns than is upper airway obstruction. Hyaline membrane disease, atelectasis, or pneumonitis causing inflammation, collapse, and fluid accumulation in the alveoli results in reduction of the oxygenation of blood reaching the systemic circulation.

Successfully distinguishing among these various causes of cyanosis depends on interpretation of the respiratory pattern, the cardiac physical examination, evaluation of arterial blood gases (Table 43-9) , and interpretation of the ECG, chest radiograph, and echocardiogram.

RESPIRATORY PATTERNS.

The key to differential diagnosis at the bedside commonly is the proper evaluation of the pattern of respiration. Term infants normally exhibit a progressive reduction in respiratory rate during the first day of life from 60 to 70 breaths/min to 35 to 55 breaths/min. Moreover, mild intercostal retractions and minimal expiratory grunting disappear within several hours of birth. An increased depth of respiration in the presence of cyanosis but without other signs of respiratory distress often is associated with congenital cardiac disease in which inadequate pulmonary blood flow is the most important functional component.

Apnea.

The most important variations from normal respiratory patterns are apnea, bradypnea, and tachypnea. Intermittent apneic episodes are common in premature infants with central nervous system immaturity or disease. In addition, higher centers may be depressed as a result of severe hypoxemia, acidemia, or administration of pharmacological agents to mother or baby. The association of apneic episodes, lethargy, hypotonicity, and a reduction of spontaneous movement most often points to intracranial disease as an underlying cause.

Tachypnea.

Diverse conditions result in tachypnea in the newborn period. Tachypnea in the presence of intrinsic pulmonary disease with upper or lower airway obstruction usually is accompanied by flaring of the alae nasi, chest-wall retractions, and grunting. In contrast, tachypnea associated with intense cyanosis in the absence of obvious respiratory distress suggests the presence of cyanotic congenital heart disease. In general, highest respiratory rates (80 to 110 breaths/min) occur in association with primary lung disease, not heart disease. Initial chest radiography frequently is diagnostic, especially if the problem is aspiration, mucous plug, adenomatoid malformation, lobar emphysema, diaphragmatic hernia, pneumothorax, lung agenesis, pulmonary hemorrhage, or an abnormal thoracic cage configuration. Choanal atresia may be precluded by passing a feeding tube through the nares, and the more common types of esophageal atresia and tracheoesophageal fistula may be excluded by passing the tube farther into the stomach.

CARDIAC EXAMINATION.

Specific findings on cardiovascular examination may direct attention to a cardiac cause of cyanosis. Peripheral perfusion is poor in the presence of severe primary myocardial

disease or the hypoplastic left heart syndrome. In contrast, peripheral pulses are bounding and the dorsalis pedis and palmar pulses are easily palpable in infants with patent ductus arteriosus, truncus arteriosus, or aorticopulmonary window. A marked discrepancy between upper and lower extremity blood pressures helps to identify infants with coarctation of the aorta. Inspection and palpation of the precordium allow an overall estimate of cardiac activity. A thrill in the suprasternal notch and/or over the precordium occasionally may be felt in infants with patent ductus arteriosus, critical aortic stenosis, or coarctation of the aorta. Characterization of the second heart sound may be of help because it often is single in infants with a hypoplastic left heart complex, pulmonary atresia with or without an intact ventricular septum, or truncus arteriosus. Wide splitting of the second heart sound may occur in infants with total anomalous pulmonary venous return. Ejection sounds often are detectable in infants with persistent truncus arteriosus and occasionally with critical aortic or pulmonic stenosis. The presence of a third heart sound is normal, but a gallop rhythm may provide a clue to myocardial failure. Wide splitting of the first and second heart sounds may produce the characteristically rhythmic auscultatory cadence of Ebstein's anomaly of the tricuspid valve (see Chaps. 25 and 44). The presence of a cardiac murmur may point clearly to underlying cardiac disease, but the absence of a murmur does not preclude a cardiac malformation. Moreover, cardiac murmurs of specific anomalies often are atypical in the newborn period. However, certain cardiac murmurs such as the decrescendo holosystolic murmur of tricuspid regurgitation in Ebstein's anomaly or the transient tricuspid regurgitation of infancy may point clearly to an accurate diagnosis. Auscultation of the head and abdomen may detect the murmur of an arteriovenous malformation at those sites in infants who present with findings of severe heart failure.

BLOOD GAS AND pH PATTERNS.

Arterial blood gas analysis may be a reliable method of evaluating cyanosis, suggesting the type of altered physiology, and assessing responses to therapeutic maneuvers.[53] Specimens for blood gas analysis should be obtained in room air and in 100 percent oxygen. Stick capillary samples from the patient's warmed heel may be used, although determinations obtained by arterial puncture are preferable for evaluation of oxygenation because they are less susceptible to alterations in regional blood flow in critically ill infants. Sampling of right radial or temporal arterial blood is preferable because these sites are proximal to flow through a ductus arteriosus and do not reflect right-to-left ductal shunting, as would a sample from the descending aorta obtained by means of an umbilical artery catheter. A trial of continuous positive airway pressure may improve oxygenation in infants with either hyaline membrane disease or pulmonary edema.

Arterial blood gas patterns in various pathophysiological conditions are listed in Table 43-9 . Pattern 1 typically is observed in infants with ventilation-perfusion abnormalities resulting from primary respiratory disease, often associated with elevated pulmonary vascular resistance and venoarterial shunting across a patent foramen ovale or patent ductus arteriosus. Pulmonary hypoventilation with carbon dioxide retention produces pattern 2. In the presence of a lesion causing obligatory venous admixture, such as total anomalous

pulmonary venous connection (pattern 3), the response to oxygen may reflect an increase in pulmonary venous return secondary to a fall in pulmonary vascular resistance. Pattern 4 typically is seen in infants with a cardiac malformation that results in reduced pulmonary blood flow. Oxygen administration in these infants does not alter the arterial P_{O_2} . The alterations of pattern 5 are observed when systemic hypoperfusion is the principal hemodynamic problem. In these babies, the arteriovenous oxygen difference is high, and the acidemia may be progressive and unrelenting.

ELECTROCARDIOGRAM (see also Chap. 5).

ECG is less helpful in suggesting a diagnosis of heart disease in premature and newborn infants than in older children. Right ventricular hypertrophy is a normal finding in neonates, and the range of normal voltages is wide. However, specific observations can offer major clues to the presence of a cardiovascular anomaly. A counterclockwise, superiorly oriented frontal QRS loop with absent or reduced right ventricular forces suggests the diagnosis of tricuspid atresia. In contrast, when the QRS axis is normal but left ventricular forces predominate, the diagnosis of pulmonic atresia must be considered. The counterclockwise, superior QRS orientation also is observed in infants with an endocardiac cushion defect and in some with double-outlet right ventricle; right ventricular forces in these babies are increased.

The initial septal vector should be assessed from the ECG. Q waves often are not clearly seen in the lateral precordial leads in the first 72 hours of life. A leftward, posteriorly directed septal vector giving rise to Q waves in the right precordial leads is abnormal and suggests the presence of marked right ventricular hypertrophy, single ventricle, or inversion of the ventricles. T wave alterations may be seen on a normal neonatal ECG and may be of no particular consequence. By 72 hours of age, however, the T waves should be inverted in V_3 and V_1 and upright in the lateral precordium; persistently upright T waves in the right precordial leads are a sign of right ventricular hypertrophy. Depressed or flattened T waves in the lateral precordium may suggest subendocardial ischemia and a left heart outflow tract obstructive lesion, electrolyte disturbance, acidosis, or hypoxemia. An ECG pattern of myocardial infarction suggests a diagnosis of anomalous pulmonary origin of the coronary artery. Finally, rhythm disturbances such as complete heart block or supraventricular tachycardia (see Chap. 25) can be detected readily by ECG.

RADIOGRAPHIC EXAMINATION (see also Chap. 8).

Chest radiography often is useful in differentiating between respiratory and cardiac causes of cyanosis in the newborn period. Determination of a normal cardiac and abdominal situs aids in ruling out several kinds of complex cyanotic cardiac malformations associated with asplenia or polysplenia with abdominal heterotaxy and dextrocardia. The distinct appearance of pulmonary parenchymal disease, such as the classic reticulogranular pattern of hyaline membrane disease, may allow a specific

radiological diagnosis. In those premature infants with a large ductus arteriosus, the radiographic appearance often evolves from the typical findings of hyaline membrane disease to increased pulmonary vascular markings and finally to perihilar and generalized pulmonary edema.

Most important, the pediatric cardiologist depends heavily on the evaluation of pulmonary vascular markings to categorize neonatal congenital cardiac malformations according to function. In the presence of cyanosis, diminished pulmonary vascular markings call attention to the group of anomalies that includes tetralogy of Fallot, pulmonic stenosis with intact ventricular septum, pulmonic atresia, tricuspid atresia, and Ebstein's malformation of the tricuspid valve. Reduced pulmonary blood flow is responsible for the systemic arterial desaturation in these babies. Increased pulmonary vascular markings in cyanotic infants are associated with lesions in which an obligatory admixture of systemic venous and pulmonary venous blood occurs. The more common anomalies in this category include transposition of the great arteries, hypoplastic left heart syndrome, truncus arteriosus, and total anomalous pulmonary venous drainage.

As mentioned earlier, overall heart size in normal newborn infants is greater than in older children, and cardiothoracic ratios up to 0.60 are within normal limits. The thymus shadow occasionally obscures the cardiac silhouette and prohibits accurate estimation of heart size. An enlarged heart on x-ray examination suggests a cardiac disorder. However, in the presence of severe respiratory difficulties with an increase in carbon dioxide tension and a decrease in both pH and arterial oxygen tension, cardiomegaly may be only moderate. A right aortic arch suggests the presence of either tetralogy of Fallot or persistent truncus arteriosus. An ovoid heart with a narrow base associated with increased pulmonary vascular marking is typical of transposition of the great arteries. A boot-shaped heart with concavity of the pulmonary outflow tract suggests tetralogy of Fallot, pulmonic atresia, or tricuspid atresia.

LABORATORY STUDIES IN CONGENITAL HEART DISEASE

FETAL ECHOCARDIOGRAPHY (see also Chap. 7).

Ultrasound technology now allows examination of human fetal cardiac development and function in utero.[39] [93] [94] [95] Diagnostic-quality images of the fetal heart in utero can be obtained as early as 16 weeks of gestation. Cardiac structures are imaged primarily by cross-sectional echocardiography and augmented by a combination of range-gated pulsed Doppler ultrasonography, Doppler color flow imaging, and M-mode echocardiography. Analysis of the structure and function of the fetal heart during the second and third trimesters of pregnancy has allowed cardiologists to counsel prospective parents and, in a number of instances, to formulate management plans for pregnancy, delivery, and the immediate postnatal period. Using fetal echocardiography, major forms of congenital heart disease have been diagnosed in utero and cardiac rhythm abnormalities have been detected, permitting direct efforts at transplacental therapy. In particular, it has been established that a high incidence of cardiac pathology exists in the presence of nonimmune fetal hydrops. It appears clear that hydrops fetalis often represents end-stage fetal cardiac decompensation (Fig. 43-7) . AV

Figure 43-7 Fetal echocardiogram taken transabdominally through the uterus and the placenta shows a fetus lying with its head to the right hand side of the figure and demonstrates a pericardial (Peric) effusion (arrows). The right ventricle (RV), the aorta (AO), and the left atria (LA) are seen within the cardiac silhouette.

valve insufficiency often causes fetal right ventricular volume overload and systemic venous hypertension, leading to hydrops fetalis.

Pulsed Doppler and color flow mapping ultrasound examination of the fetus importantly supplement the echocardiographic findings in identifying the responsible defects, such as Ebstein's malformation of the tricuspid valve, atrial isomerism with AV septal defects, and the absent pulmonary valve and hypoplastic left heart syndromes.

Fetal cardiac ultrasonography is of special importance in analyzing disturbances of fetal cardiac rhythm, which usually are first suspected on the basis of auscultatory findings. Transabdominal ECG cannot identify atrial depolarization and is of limited value in the analysis of cardiac arrhythmias in utero. However, M-mode recordings of cardiac motion versus time allow conclusions about electrical events in the fetal heart, as they are reflected by the mechanical responses that are recorded echocardiographically. Supraventricular tachyarrhythmias are a common cause of nonimmune fetal hydrops (Fig. 43-8) . Detection is of practical use in the treatment of these patients because the arrhythmia is treatable with the use of various antiarrhythmic drugs, such as digoxin, procainamide, propranolol, and flecainide, administered to the mother and reaching the fetus transplacentally or, rarely, under sonographic guidance, by injecting drugs, such as amiodarone, into the umbilical vein.[96]

ECHOCARDIOGRAPHY IN THE NEONATE.

Echocardiography is of immense value in differentiating between heart disease and lung disease in newborns.[97] [97A] Indeed, it has become the standard for the diagnosis of virtually all cardiovascular malformations. A great many infants are now referred directly after ultrasound study for operative repair, without intervening cardiac catheterization. Echocardiographic diagnoses that often can be made with certainty include coarctation of the aorta, interruption of the aortic arch, patent ductus arteriosus, hypoplastic left heart syndrome, aortic valve stenosis, membranous and fibromuscular subvalvular aortic stenosis, aortic coarctation, hypertrophic cardiomyopathy, cor triatriatum, total anomalous

Figure 43-8 M-mode echocardiogram at 35 weeks' gestation, showing fetal supraventricular tachycardia

and pericardial effusion (PEff). The tracing, taken at the midventricular level, allows the heart rate to be calculated from atrioventricular valve (AVV) motion (250 beats/min). *(Courtesy of Dr. Charles Kleinman.)*

pulmonary venous connection, atrial septal defect, tricuspid atresia, Ebstein's anomaly of the tricuspid valve, valvular pulmonic stenosis, AV septal defect, single ventricle, double-outlet right ventricle, transposition of the great arteries, and patent ductus arteriosus. The echocardiogram provides suggestive and often conclusive evidence for tetralogy of Fallot, truncus arteriosus, and pulmonary atresia with an intact ventricular septum, as well as pulmonary atresia with a VSD and a patent ductus arteriosus.

Doppler ultrasonography (see Chap. 7) supplements the two-dimensional echocardiographic examination by its ability to quantify valve gradients, cardiac output, blood flow patterns in the cardiac chambers and great arteries, and often shunt size.[98] [99] For example, the pulmonary-systemic blood flow ratio can be calculated by multiplying the square of the ratio of the great vessel diameters by the ratio of the peak systolic flow velocities, the pulmonary variable being the numerator in each ratio. The coupling of Doppler ultrasonographic techniques with the two-dimensional echocardiogram, and the representation in color of abnormalities in flow, volume, and direction (see Chap. 7), greatly improve diagnostic accuracy. Magnetic resonance imaging (see Chap. 10) can also be useful.[99A]

DIAGNOSTIC CARDIAC CATHETERIZATION (see also Chap. 11).

If certain cardiac anomalies are identified by noninvasive studies or if a clear-cut differentiation cannot be made between cardiac and pulmonary disease, heart catheterization and angiocardiography may be necessary to define the underlying state precisely. However, fewer cardiac catheterizations have been performed in infants and children of all ages since the beginning of aggressive pursuit of preoperative diagnoses by noninvasive imaging modalities, particularly two-dimensional Doppler flow echocardiography.[99] [100] Hemodynamic study of newborn infants carries a small but distinct risk.[101] As a general rule, cardiac catheterization is not performed unless the information sought is central to treatment of the infant. Most infants with serious heart disease require therapeutic intervention, and thus catheterization should be performed only when surgical support is readily available. Cardiac catheterization is often performed in newborns who experience congestive heart failure in the first days after birth if the cause is an anatomical abnormality rather than an arrhythmia or a metabolic disturbance. Preferably, medical measures will have been instituted to stabilize the clinical state before a hemodynamic study is performed.

Some newborns with cyanotic congenital heart disease require prompt cardiac catheterization because of the considerable risk of rapid deterioration. Under these circumstances, hemodynamic and angiographic studies may not only provide the anatomical diagnosis required before emergency operation but also allow the opportunity for therapeutic maneuvers such as balloon atrial septostomy to facilitate intercirculatory mixing in patients with complete transposition of the great arteries or to augment interatrial shunting in patients with a restrictive patent foramen ovale and either tricuspid, pulmonic, or mitral atresia or total anomalous pulmonary venous connection. Selective intravenous infusion of low doses of prostaglandin E_1 (0.05 to 0.1 mug/kg/min)

has been used before and at cardiac catheterization for the emergency palliation of ductus-dependent cardiac lesions such as pulmonary atresia, aortic coarctation, and interruption of the aortic arch. Because a patent ductus arteriosus maintains pulmonary and systemic blood flow, respectively, in these infants, dilatation of the ductus with vasodilatory prostaglandins may retard their clinical deterioration. Thus, prostaglandin E_1 infusion has been shown to be an effective short-term measure to correct hypoxemia and acidemia and to improve the preoperative and intraoperative status of infants who require surgical relief of the congenital cardiac lesion that is causing pulmonary or systemic hypoperfusion.

THERAPEUTIC CATHETERIZATION (see also Chap. 38).

Balloon atrial septostomy was the first catheter intervention that proved useful in treating congenital heart disease, and it remains the standard initial palliation in infants with complete transposition of the great arteries unless the arterial switch operation is performed imminently.[102] Many additional transcatheter techniques are now used successfully to treat congenital heart disease. These include knife blade atrial septostomy; umbrella or coil closure of patent ductus arteriosus; self-expanding and centering Amplatzer occluding device, or buttoned or modified clamshell or umbrella device closure of atrial septal defect; balloon-expandable intravascular stents for peripheral pulmonary artery and selected postoperative stenoses; and balloon and coil embolization of large systemic pulmonary artery collateral vessels and arteriovenous fistulas.[103] [104] [105] Other procedures that have expanded the role of the cardiac catheter from a diagnostic tool to a therapeutic instrument include transvenous or transarterial pacemaker insertion and retrieval of foreign bodies from the cardiovascular system. Transluminal balloon angioplasty currently is used principally in pediatrics for dilation of pulmonic and aortic valve stenoses, native and recoarctation of the aorta, and peripheral pulmonary artery stenosis. Questions about transluminal angioplasty in native neonatal coarctation, tetralogy of Fallot, and congenital subaortic and mitral stenoses remain unresolved. Finally, electrode catheter radiofrequency ablative techniques for the treatment of tachycardias are now performed routinely in centers with pediatric electrophysiology programs.[106]

ELECTROPHYSIOLOGICAL STUDIES (see also Chap. 23).

The cardiac catheterization laboratory also is being used with increasing frequency to define the anatomical and physiological diagnoses of arrhythmias, thus facilitating an accurate prognosis and providing a rational basis for pharmacological, catheter ablation, or surgical treatment.[107] [108] [109] Catheter ablation approaches to tachyarrhythmias are now standard pediatric procedures (see Chaps. 23 and 25). The invasive electrophysiological approach provides unique information that cannot be obtained noninvasively. This includes determination of conduction times of individual components of the conducting system and measurement of refractory periods for structures such as the AV node, His bundle, and bundle branches. In addition, one can determine the

origin or anatomical circuit, sustaining mechanisms, and possible perturbations that terminate the arrhythmia. This last maneuver is particularly important because it may enable the planning of effective drug treatment. It also may determine the advisability of catheter ablation, pacemaker control, or surgical treatment of the rhythm disturbance.

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Specific Cardiac Defects

Many classifications of congenital cardiovascular lesions have been proposed on the basis of hemodynamic, anatomical, and radiographic factors. Although the groups overlap, the following arrangement of cardiac anomalies is used in this chapter: (1) communications between the systemic and pulmonary circulations without cyanosis (left-to-right shunts), (2) obstructing valvular and vascular lesions with or without associated right-to-left shunt, (3) abnormalities in the origins of the great arteries and veins (the transposition complexes), (4) malpositions of the heart and cardiac apex, and (5) miscellaneous anomalies.

LEFT-TO-RIGHT SHUNTS

Atrial Septal Defect (See also p. 1593)

MORPHOLOGY.

Atrial septal defect is one of the most commonly recognized congenital cardiac anomalies in adults but is very rarely diagnosed and even less commonly results in disability in infants.[110] The anatomical sites of interatrial defects are shown in Figure 43-9 . Defects of the sinus venosus type are high in the atrial septum near the entry of the superior vena cava and may be created by a deficiency in the wall that normally separates the pulmonary veins from the right lung and the superior vena cava and right atrium, thereby also resulting in partial anomalous pulmonary venous drainage.[111] The atrial septal defect most often involves the fossa ovalis, is midseptal in location, and is of the ostium secundum type. This type of defect is a true deficiency of the atrial septum and should not be confused with a patent foramen ovale. Embryologically, the left side of the atrial septum is derived from the septum primum, which possesses an

opening--the interatrial ostium secundum (see Fig. 43-1). The ostium secundum lies forward and superior to the position of the foramen ovale. The latter is formed by the septum secundum and occupies the right side of the atrial septum. Tissue of the septum primum lying to the left of the foramen ovale

Figure 43-9 Diagrammatic representation of open right atrium (RA) and right ventricle (RV) showing the position of the various types of interatrial communications. The superior vena cava (SVC), inferior vena cava (IVC), and right atrial appendage (RAA) define the areas of the right atrium. There are five potential spaces of interatrial communication. The classic ostium secundum (OS) atrial septal lies within the fossa ovalis. The second most frequent defect is an ostium primum (OP) atrial communication, followed by the superior vena caval type of sinus venosus (SV) defect lying posteriorly within the right atrium at the junction of the SVC and pulmonary veins. An IVC sinus venosus (SV) defect lies at the junction of the right atrium with the IVC. The last communication is through the coronary sinus (CS).

serves as a flap valve that usually becomes fused postnatally with the side of the foramen ovale, yielding an anatomically closed or sealed foramen. "Probe patency," or an incomplete seal of the foramen ovale, occurs in about 25 percent of adults. A widely patent foramen ovale may be considered an acquired form of atrial septal defect that occurs especially when a disproportion exists between the size of the foramen ovale and the effective length of its valve. Enlargement of the foramen ovale per se is commonly associated with obstructive lesions on the right side of the heart, whereas a short valve relative to the size of the foramen often attends large-volume left-to-right shunts in which left atrial dilatation is prominent.

Ostium primum atrial septal anomalies are a form of AV septal defect and are dealt with in the next section. Lutembacher's syndrome is a designation applied to the rare combination of atrial septal defect and mitral stenosis, which is almost invariably the result of acquired rheumatic valvulitis.[112] Ten to 20 percent of patients with ostium secundum atrial septal defect also have prolapse of the mitral valve as an associated anomaly.[113]

HEMODYNAMICS.

The magnitude of the left-to-right shunt through an atrial septal defect depends on the size of the defect, the relative compliance of the ventricles, and the relative resistance in both the pulmonary and the systemic circulation.[114] In patients with a small atrial septal defect or patent foramen ovale, the left atrial pressure may exceed the right by several millimeters of mercury, whereas the mean pressures in both atria are nearly identical when the defect is large. Left-to-right shunting occurs predominantly in late ventricular systole and early diastole with some augmentation during atrial contraction. The shunt results in diastolic overloading of the right ventricle and increased pulmonary blood flow. During the first few days and weeks of life, pulmonary resistance falls and systemic resistance rises, facilitating right ventricular emptying and impeding left ventricular

emptying; the left-to-right shunt rises. Early in infancy, left-to-right flow through even a large interatrial communication commonly is limited by both the reduced chamber compliance of the thick neonatal right ventricle and the elevated pulmonary and reduced systemic vascular resistance of the neonate. The pulmonary vascular resistance commonly is normal or low in older infants or children with atrial septal defect, and the volume load usually is well tolerated, even though pulmonary blood flow may be two to five times greater than systemic. A transient and small right-to-left shunt occurring with the onset of left ventricular contraction and especially during respiratory periods of decreasing intrathoracic pressure is common in patients with ostium secundum defect, even in the absence of pulmonary hypertension.

CLINICAL FINDINGS.

Patients with atrial septal defect usually are asymptomatic early in life, although occasional reports describe congestive heart failure and recurrent pneumonia in infancy.[110] Children with atrial septal defect may experience undue fatigue and exertional dyspnea. They tend to be somewhat underdeveloped physically and prone to respiratory infection. Atrial arrhythmias, pulmonary arterial hypertension, development of pulmonary vascular obstruction, and heart failure are exceedingly uncommon in the pediatric age range, in contrast to their common appearance in adults with atrial septal defect. In the former group, diagnosis often is entertained after detection of a heart murmur on routine physical examination prompts a more extensive cardiac evaluation. Small defects, less than 4 to 8 mm, have a modest probability of spontaneous closure.[115]

Physical Examination.

Common findings include a prominent right ventricular cardiac impulse and palpable pulmonary artery pulsation. The first heart sound is normal or split, with accentuation of the tricuspid valve closure sound. Increased flow across the pulmonic valve is responsible for a midsystolic pulmonary ejection murmur. After the normal postnatal decline in pulmonary vascular resistance, the second heart sound is split widely and is relatively fixed in relation to respiration in patients with normal pulmonary pressures and low pulmonary vascular impedance because of a delay in pulmonic valve closure. With pulmonary hypertension, the splitting interval is a function of the electromechanical intervals of each ventricle; wide splitting occurs with shortening of the left and/or lengthening of the right ventricular electromechanical interval.[116] If the shunt is large, increased blood flow across the tricuspid valve is responsible for a mid-diastolic rumbling murmur at the lower left sternal border. In patients with associated prolapse of the mitral valve, an apical holosystolic or late systolic murmur radiating to the axilla often is heard, but a midsystolic click may be difficult to discern. Moreover, left ventricular precordial overactivity usually is absent because mitral regurgitation is mild in most patients.

In teenage patients, the physical findings may be altered when an increase in pulmonary vascular resistance results in diminution of the left-to-right shunt. Both the pulmonary and the tricuspid murmurs decrease in intensity, whereas the pulmonic component of the second heart sound becomes accentuated and the two components

of the second heart sound may fuse; a diastolic murmur of pulmonic incompetence appears. Cyanosis and clubbing accompany development of a right-to-left shunt.

Electrocardiogram.

In patients with an ostium secundum defect, the ECG usually shows right-axis deviation, right ventricular hypertrophy, and rSR
or rsR
pattern in the right precordial leads with a normal QRS duration (Fig. 43-10 ; see also Fig. 44-1). It is not clear whether the delay in right ventricular activation is a manifestation of right ventricular volume overload or a true conduction delay in the right bundle branch and peripheral Purkinje system. An early notch (triphasic "crochetage") pattern on the R wave in inferior limb leads is as sensitive an indicator of atrial defect as incomplete right bundle branch block.[117] Left-axis

Figure 43-10 Typical electrocardiographic tracing in secundum atrial septal defect showing right-axis deviation, rSR
in the right pericordial leads, and right ventricular hypertrophy. *(Courtesy of Dr. Delores A. Danilowicz.)*

deviation of the P wave in the frontal plane (manifested by a negative P wave in lead III) suggests the presence of a sinus venosus rather than an ostium secundum type of atrial septal defect. Left-axis deviation and superior orientation and counterclockwise rotation of the QRS loop in the frontal plane suggest the presence of either an ostium primum defect or a secundum atrial septal defect in association with mitral valve prolapse. Prolongation of the PR interval may be seen with all types of atrial septal defects; the prolonged internodal conduction time may be related to both the increased size of the atrium and the increased distance for internodal conduction produced by the defect itself.[117]

Chest Roentgenogram (see Fig. 44-2).

This usually reveals enlargement of the right atrium and ventricle, dilatation of the pulmonary artery and its branches, and increased pulmonary vascular markings. Dilatation of the proximal portion of the superior vena cava occasionally is noted in patients with a sinus venosus defect. Left atrial dilatation is extremely rare but may be observed when significant mitral regurgitation exists.

Echocardiographic Features.

These include pulmonary arterial and right ventricular dilatation and anterior systolic (paradoxical) or "flat" interventricular septal motion if significant right ventricular volume overload is present.[98] The defect may be visualized directly by two-dimensional echo

imaging, particularly from a subcostal view of the interatrial septum (Fig. 43-11 ; also see Chap. 7). Transesophageal color-coded Doppler echocardiography and color flow provides excellent visualization of defects of the atrial septum.[118] [119] Associated mitral valve prolapse also may be identified by echocardiographic examination (see Chap. 7). Findings on ultrafast computed tomographic (CT) scanning are discussed in Chapter 10 .

Two-dimensional echocardiography, supplemented by conventional or color-coded Doppler flow and/or contrast echocardiography, has supplanted cardiac catheterization as the confirmatory test for atrial septal defect.[120] Cardiac catheterization is then used if inconsistencies exist in the clinical data or if significant pulmonary hypertension is suspected.

Cardiac Catheterization.

Diagnosis may be readily confirmed by passage of the catheter across the atrial defect. The site at which the catheter crosses, if high in the cardiac silhouette, may suggest a sinus venosus defect; if midseptal, a patent foramen ovale or ostium secundum defect; or, if low, a primum defect.[121] Serial determinations of the oxygen saturation or indicator dilution curve techniques may

Figure 43-11 Subcostal coronal view showing a secundum atrial septal defect between the left atrium (LA) and the right atrium (RA). The right upper pulmonary vein (PV) is seen entering the left atrium. This view is posterior to the major portion of the ventricles; the left ventricle (LV) is seen, but only a small portion of the right ventricle (unlabeled) is apparent. I = inferior; L = left; R = right; S = superior.

be used to estimate the magnitude of the shunt. In the absence of pulmonary hypertension, pressures on the right side of the heart often are normal, despite a large shunt. When a high oxygen saturation is found in the superior vena cava or when the catheter enters pulmonary veins directly from the right atrium, a sinus venosus defect is likely, and indicator dilution curves and selective angiography aid in identifying the number and location of the anomalous veins. *Partial anomalous pulmonary venous connection,* although usually associated with sinus venosus defect, may accompany secundum defects. Selective left ventricular angiography identifies prolapse of the mitral valve and allows assessment of the magnitude of mitral regurgitation that may be present in such patients.[128]

MANAGEMENT.

In contrast to adults, children with sinus venosus or secundum types of atrial septal defect seldom require treatment for heart failure or antiarrhythmic medications for atrial fibrillation or supraventricular tachycardia. Respiratory tract infections should be treated promptly. Although the risk of infective endocarditis is low, antibiotics should be administered prophylactically before dental procedures.

Operative or Transcatheter Repair.

This should be advised for all patients with uncomplicated atrial septal defects and evidence of significant left-to-right shunting, i.e., with pulmonary-systemic flow ratios exceeding about 1.5:1.0. Ideally, this should be carried out in those 2 to 4 years of age. Rarely, an atrial septal aneurysm is seen in association with a secundum-type atrial septal defect.[122] Such patients may experience spontaneous closure and may be monitored more conservatively until an older age before advising operation. Whether by median sternotomy or by minimally invasive transxiphoid techniques,[123] the defect is closed by suture or with a patch of prosthetic material with the patient on cardiopulmonary bypass. Earlier surgical repair is definitive treatment for the small number of infants and young children with significant symptoms or congestive failure. The surgical mortality rate is less than 1 percent, and results usually are excellent. Although the mitral valve may be examined directly at operation, it seldom is necessary in childhood to attempt plication or replacement of a ballooning or prolapsing mitral valve.

Operation should *not* be carried out in patients with small defects and trivial left-to-right shunts (pulmonary-systemic flow ratio
1.5:1.0) or in those with severe pulmonary vascular disease (pulmonary-systemic resistance ratio
0.7:1.0) without a significant left-to-right shunt.[124] Although still investigational, considerable experience exists with transcatheter closure by a variety of occluding devices using fluoroscopic or transesophageal echocardiographic imaging guidance[125] [126] [127] (Fig. 43-12) . Limitations include difficulties in centering the device, the size of the sheath delivery system, the need to have more than a 4-mm separation between the edges of the defect and other important cardiac structures, and the inability to close defects whose stretched diameter exceeds 22 mm.

Subtle evidence of left ventricular dysfunction may be observed preoperatively at cardiac catheterization in children with isolated large atrial septal defects but without overt left or right ventricular failure.[128] Thus, decreased left ventricular stroke volume and cardiac output have been observed in children with both low and normal left ventricular end-diastolic volumes. In routine catheterization studies carried out on patients whose atrial septal defects were closed during preadolescence or later, a residual reduced cardiac output response to intense upright exercise in the absence of residual shunts, arrhythmias, or pulmonary arterial hypertension has been observed.[129] Normal myocardial function is preserved in patients in whom the defects were closed in early childhood.[130]

Electrophysiological Abnormalities.

Intracardiac electrophysiological studies reveal a high incidence of intrinsic

Figure 43-12 Clamshell umbrella occlusion of an ostium secundum atrial septal defect. A long sheath is positioned in the left atrium *(A)*. *B,* The distal umbrella arms are opened in the left atrium and the umbrella and sheath are pulled back together to the atrial septum. *C,* The proximal set of arms is then delivered on the right atrial side of the atrial septum. The correct position of the device is confirmed by fluoroscopy, angiography, and echocardiography before the device is released. *(From Castaneda A, Jonas AR, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 136.)*

dysfunction of the sinoatrial and AV nodes, which persists after surgical repair. These intrinsic nodal abnormalities are more common in sinus venosus than in ostium secundum defects[131] but occur in both varieties. There also is evidence that the type of venous cannulation at the time of operative repair may contribute to the incidence and severity of arrhythmias observed at long-term follow-up.[132]

Atrioventricular Septal Defect (See also p. 1596)

AV septal defects account for 4 to 5 percent of congenital heart defects and comprise a range of malformations characterized by various degrees of incomplete development of the inferior portion of the atrial septum, the inflow portion of the ventricular septum, and the AV valves (see Figs. 43-1 and 44-3). These anomalies also have been called endocardial cushion defects and AV canal defects. The basic defect is a deficiency of the AV septum, which separates the left ventricular inlet from the right atrium; it causes anomalies that range in severity from a small ostium primum atrial defect to a complete AV septal malformation that also involves defects in the interventricular septum and the mitral and tricuspid valves. The latter often are abnormal to various degrees, with five or six leaflets of variable size present, and variability also in the completeness of their commissures. AV septal defects are often encountered in association with other congenital abnormalities, such as asplenia or polysplenia syndromes, trisomy 21 (Down syndrome), and Ellis-van Creveld syndrome of ectodermal dysplasia and polydactyly.

Ostium Primum Defect (Partial AV Canal)

Ostium primum atrial septal defects lie immediately adjacent to the AV valves, either of which may be deformed and incompetent. Most often, only the anterior or septal leaflet of the mitral valve is displaced, and it commonly is cleft; the tricuspid valve usually is not involved. A cleft often is considered to be present in the mitral valve, although it is likely that the valve is in fact a trileaflet structure, with the cleft representing an abnormal commissure. The interatrial defect often is large, and the size of the left-to-right interatrial shunt in these patients is controlled by the same factors that exist in patients with ostium secundum atrial septal defect. Moreover, the clinical features are quite similar and principally consist of right ventricular precordial hyperactivity, a wide and persistently split second heart sound, a right ventricular outflow tract systolic ejection murmur, and a mid-diastolic tricuspid flow rumble. The murmurs of AV valve regurgitation may be audible if either valve is significantly abnormal; however, serious

AV valve regurgitation usually is absent. In the occasional patient, mitral regurgitation is substantial and creates prominent signs of left ventricular overload.

Chest roentgenography usually reveals right atrial and ventricular cardiomegaly, prominence of the right ventricular outflow tract, and increased pulmonary vascular markings. The *ECG findings* (see Fig. 44-4) are characteristic and show a right ventricular conduction defect accompanied by left anterior division block, left-axis deviation, and superior orientation and counterclockwise rotation of the QRS loop in the frontal plane (see Chap. 5). Hemodynamic factors do not appear to be important in producing the characteristic ECG appearance. Rather, the superior QRS vector in patients with a shortened H-V interval appears to be related to early activation of the posterobasal left ventricular wall; in other patients with a normal conduction time between the bundle of His and the ventricles, the counterclockwise superior inscription of the frontal plane vector appears to be related to late activation of the anterolateral left ventricular wall.[133] A prolonged P-R interval is observed in many patients with an ostium primum atrial septal defect; prolonged internodal conduction may be related to displacement of the AV node in a posteroinferior direction in some patients and/or to the enlarged right atrium.

ECHOCARDIOGRAPHY.

Two-dimensional echocardiography is considered the standard for the diagnosis of all forms of AV septal defect (see Chap. 7). Important features include enlargement of both the right ventricle and the pulmonary artery, systolic anterior ventricular septal motion, prolonged mitral-septal apposition in diastole, and various abnormalities in mitral valve motion.[134] The defect is clearly visualized from the precordial apical and subxiphoid positions, with the latter views best demonstrating the relation between the atrial defect, the AV valves, and the interventricular septum (Fig. 43-13) . Doppler color flow enhances these relations. Interatrial septal tissue is absent in the region of the crest of the interventricular septum; the trileaflet configuration of the mitral valve also may be identified. The subxiphoid long-axis view of the left ventricular outflow tract exhibits the gooseneck deformity in a manner similar to that with a right anterior oblique left ventricular angiogram. Echocardiography is particularly useful for detecting and characterizing double-orifice mitral valve, an association in about 3 percent of patients with ostium primum atrial defect. It also allows detection of

Figure 43-13 *Top panel,* Transesophageal echocardiogram taken from a subcostal transgastric plane in a patient with tetralogy of Fallot and type C complete atrioventricular septal defect. A secundum atrial septal defect (upper smaller arrow) is also seen in the left panel, and the ostium primum component of the complete atrioventricular canal is seen below (larger lower arrow). The right frame shows the complete atrioventricular septal defect with the anterosuperior bridging leaflet (arrow) straddling between the left and right ventricles (LV, RV) without attaching to the interventricular septum. The left pulmonary artery (LP) is seen behind the ascending aorta (AO). *Bottom panel,* Four-chamber transesophageal plane demonstrates a communication above the anterior and bridging leaflets (ABL and PBL) in the right- and

left-hand frames, respectively. The small arrow indicates the typical position of an ostium primum atrial septal defect lying immediately below the rim of the atrial septum and above the valve tissue. LA = left atrium; RA = right atrium.

single left ventricular papillary muscle, hypoplasia of the left ventricle, and coarctation of the aorta, seen especially in symptomatic infants with an ostium primum atrial defect but without trisomy 21.[135] The *angiographic features* resemble those in the complete form of AV septal defect and are discussed later.

Complete AV Septal Defect

MORPHOLOGY.

The complete form of the AV septal defect includes, in addition to the ostium primum atrial septal defect, a VSD in the posterior basal inlet portion of the ventricular septum and a common AV orifice.[136] The common AV valve usually has six leaflets: left superior and inferior, left and right lateral, and right superior and inferior. The left and right superior leaflets together often are referred to as the "anterior" bridging leaflet. No attachment exists between the left superior and inferior leaflets and the right superior and inferior leaflets. The left superior leaflet may cross the crest of the ventricular septum to reside partially on the right ventricular side. A classification of complete AV canal defect into types A, B, and C reflects the variability and the degree of anterior leaflet bridging of the ventricular septum (see Fig. 43-13). Thus, in type A, the anterior leaflet is almost entirely committed to the left ventricle and is attached by chordae tendineae to the crest of the ventricular septum. In type C there is marked rightward displacement of the anterior bridging leaflet, which floats freely over the crest of the ventricular septum and is not attached to it by chordae tendineae. In type B, chordal attachments extend medially to an anomalous papillary muscle adjacent to the septum in the right ventricle.

A high incidence (about 35 percent) of additional cardiovascular lesions exists in patients with common AV canal. Principal among those associated with type C are tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries, and asplenia and polysplenia syndromes. Moreover, the type A complete AV septal anomaly commonly is seen in patients with Down syndrome.

The designation *unbalanced atrioventricular canal* is applied to the condition in which one ventricle is hypoplastic and the other receives most of the common AV valve. Subaortic obstruction may be due to abnormal features of the left side of the common AV valve or to hypoplasia of the left ventricle. The left-sided (mitral) component may also be the site of a potential form of double-orifice mitral stenosis postoperatively.

DIAGNOSIS.

Patients with common AV septal defects present clinically before age 1 year with a history of frequent respiratory infections and poor weight gain. Heart failure in infancy is extremely common. The *physical findings* are similar to those observed in patients with ostium primum atrial septal defect but may include as well the holosystolic, lower left sternal border murmur of an interventricular communication and/or the decrescendo, holosystolic apical murmur of mitral regurgitation. The ECG features of complete AV canal defects resemble those in the partial ostium primum variety of AV septal anomalies (see Fig. 43-10). *Radiographically,* the usual findings are generalized cardiomegaly and engorged pulmonary vessels.

Two-dimensional echocardiography is diagnostic (see Chap. 7).[134] Apical and subcostal views are used to determine the size of the septal defects, the commitment of valve tissue and chordal attachments to the ventricles, ventricular size, the magnitude of AV valve insufficiency, and the anatomy of the left ventricular outflow tract. The subcostal oblique coronal view is often best to evaluate the commitment of AV valve tissue to each ventricle. Patterns of shunting and the number and magnitude of regurgitant jets are best evaluated by using pulsed, continuous-wave, and color flow Doppler imaging. On *hemodynamic study,* patients with persistent common AV canal invariably have elevated pulmonary arterial pressures; after age 2 years, a significant number of these patients have progressively severe pulmonary vascular obstructive disease.

Diagnosis also is reliably established by selective left ventricular *angiocardiography* using rapid injection of relatively large quantities of contrast material.[137] The findings include an absence of the AV septum and a deficiency of the inlet portion of the ventricular septum, with elongation of the left ventricular outflow tract in relation to the inflow tract. The aortic valve is elevated and displaced anteriorly relative to the AV valves, changing the relation between the anterior components of the left AV valve and the aorta, which produces a pathognomonic gooseneck deformity seen angiographically in diastole.

MANAGEMENT.

In patients with complete AV canal, cardiac decompensation should be controlled initially. Even with an adequate response to medical therapy early in life, operation should be considered before age 6 months because infants with a complete form of the AV septal defect are at high risk of obstructive pulmonary vascular disease. The level of major shunting should be determined by echocardiographic-Doppler data, or less often during initial hemodynamic and angiographic studies, because if it is mainly at the ventricular level, pulmonary artery banding occasionally may be advised for intractable heart failure and failure to thrive. Often, however, there is a significant left ventricular-right atrial shunt either directly or indirectly by way of mitral regurgitation and left-to-right interatrial shunting, which will be unaffected by pulmonary artery banding and requires complete surgical correction.

Surgical Repair.

Operative repair of uncomplicated primum defects is, for the most part, simple and yields good results. Left AV valve regurgitation and subaortic stenosis can be late complications amenable to reoperation. In most centers, primary repair in patients who have intractable heart failure, growth failure, or severe pulmonary hypertension is the preferred approach at any age.[138] Mild to moderate regurgitation often persists after surgical repair, particularly if significant AV valve incompetence existed preoperatively.[139] Rarely, if left AV leaflet tissue is remarkably deficient or deformed, mitral valve replacement may be required. Advances in the surgical approach to complex forms of AV septal defects have greatly improved the outlook for patients born with this malformation.[140] [141] These include better reconstruction of the mitral valve (Fig. 43-14) and more precise preoperative detection of such anatomical features as additional muscular VSDs, malalignment

Figure 43-14 A suture technique is illustrated for repair of a cleft mitral valve *(A)*. Absolute alignment of the cleft in all its dimensions is of critical importance with placement of the sutures where the edges naturally coapt *(B)*. *C*, The cleft repair is accompanied by annuloplasty. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 174.)*

of the complete AV septum, and left ventricular hypoplasia. Operative improvement is primarily related to a clearer understanding of the anatomy of this complex lesion and to the ability to reconstruct the left AV valve, often by splitting of papillary muscles and shortening of chordae tendineae, with or without annuloplasty. Many surgeons prefer to close the septal defects with a single patch rather than separating ventricular and atrial patches. Suture placement is avoided in the region of the AV node and the bundle of His.

Figure 43-15 *A,* The four components of the ventricular septum viewed from the right ventricular side. I = inlet component, which extends from tricuspid annulus to attachments of the tricuspid valve; T = trabecular septum, which extends from the inlet out to the apex and up to the smooth-walled outlet; O = outlet septum or infundibular septum, which extends up to the pulmonary valve and membranous septum. *B,* The anatomical position of ventricular septal defects. a = outlet defect; b = papillary muscle of the conus; c = perimembranous defect; d = marginal muscular defects; e = central muscular defects; f = inlet defect; g = apical muscular defects. *(From Graham TP Jr, Gutgesell HP: Ventricular septal defects. In Emmanouilides GC, Riemenschneider TA, Allen HD, et al [eds]: Moss and Adams' Heart Disease in Infants, Children, and Adolescents. 5th ed. Baltimore, © Williams & Wilkins, 1994, p 724.)*

Ventricular Septal Defect **(See also p. 1595)**

MORPHOLOGY.

Among the most prevalent of cardiac malformations, defects of the ventricular septum occur commonly, both as isolated anomalies and in combination with other anomalies. The ventricular septum is made up of four compartments: the membranous septum, the inlet septum, the trabecular septum, and the outlet, or infundibular, septum. Defects result from a deficiency of growth or a failure of alignment or fusion of component parts. Defects most commonly are classified as occurring in or adjacent to one or more of the septal components (Fig. 43-15) . [142] [143]

The most common defects occur in the region of the membranous septum and are referred to as *paramembranous* or *perimembranous defects* because they are larger than the membranous septum itself and are associated with a muscular defect at a portion of their perimeter. They also are known as infracristal, subaortic, or conoventricular defects. These perimembranous defects also can be defined by their adjacent areas as inlet, trabecular, or outlet. A second type of defect is one with an entirely muscular rim. Such muscular defects also can be defined as inlet, trabecular, central, apical, marginal or Swiss cheese, or outlet and vary greatly in size, shape, and number. A third type of defect occurs when the outlet septum is deficient and commonly is referred to as supracristal, subpulmonary, outlet, infundibular, or conoseptal. Because the aortic and pulmonary valves are in fibrous continuity, this type of defect also may be referred to as doubly committed subarterial. A septal deficiency of the site of the AV septum characterizes defects called AV septal, AV canal, or inlet septal defects.

The other feature of any defect may be a malalignment of the septal components. Either the inlet or the outlet septum can be malaligned. Malalignment of the inlet septum produces either mitral or tricuspid valve override and/or straddle. Malalignment of the outlet septum can be to the right or the left of the trabecular septum; when to the left of the trabecular septum, the VSD is characteristic of tetralogy of Fallot, double-outlet ventricle, truncus arteriosus, and, in some cases, transposition of the great arteries.

ECHOCARDIOGRAPHY.

Two-dimensional and Doppler color flow mapping identify the type of defect in the ventricular septum (Fig. 43-16) .[144] [145] [146] Perimembranous VSDs are identified by septal dropout in the area adjacent to the septal leaflet of the tricuspid valve and below the right border of the aortic annulus. The subaortic or anterior malalignment type of VSD appears just below the posterior semilunar valve cusps, entirely superior to the tricuspid valve. The subpulmonary VSD appears as echo dropout within the outflow septum and extending to the pulmonary annulus. One or two of the aortic cusps may be seen to be protruding through the defect into the right ventricular outflow tract. The inlet AV septal-type of VSD extends from the fibrous annulus of the tricuspid valve into the muscular septum and often is entirely beneath the septal tricuspid leaflet. Muscular defects may appear anywhere throughout the ventricular septum and may be either large and single or small and multiple. Anatomical localization of all VSDs is facilitated by coupling two-dimensional ultrasound images (see Chap. 7) with a Doppler system and by superimposing a color-coded direction and velocity of blood flow on the real-time

images.

Figure 43-16 Four-chamber echocardiographic view in anatomical position demonstrates the ventricular septal defect (arrows within the left ventricular [LV] cavity). The tricuspid valve (TV) is adjacent to the ventricular septal defect and billows into the right ventricle (RV), a feature consistent with typical tricuspid tissue tags associated with perimembranous ventricular septal defect (formerly called ventricular septal aneurysm). LA = left atrium; RA = right atrium.

Pulmonary and systemic blood flow can be calculated from arterial velocity profiles and cross-sectional areas of the great vessels.[147] Calculation of pulmonary/systemic flow ratios is reasonably accurate. Detection of jets within the right ventricle allows determination of right ventricular pressure by subtracting the product using the Bernoulli equation, which gives the pressure difference, from the systemic systolic blood pressure. Continuous-wave Doppler has been helpful in determining the right ventricular pressure from tricuspid regurgitation, which is found fairly often with VSDs. Many other techniques of Doppler measurement have been used with varying success in efforts to determine pulmonary arterial pressure accurately.

PATHOPHYSIOLOGY.

The functional disturbance caused by a VSD depends primarily on its size and the status of the pulmonary vascular bed rather than on the location of the defect. A small VSD with high resistance to flow permits only a small left-to-right shunt. A large interventricular communication allows a large left-to-right shunt only if there is no pulmonic stenosis or high pulmonary vascular resistance because these factors also determine shunt flow. Resistance to left ventricular emptying also affects shunt flow because it is an important factor in determining left ventricular pressure. Large defects allow both ventricles to function hemodynamically as a single pumping chamber with two outlets, equalizing the pressure in the systemic and pulmonary circulations. In such patients, the magnitude of the left-to-right shunt varies inversely with pulmonary vascular resistance. The natural history of VSDs has a wide spectrum, ranging from spontaneous closure to congestive cardiac failure and death in early infancy. Within this spectrum are possible development of pulmonary vascular obstruction, right ventricular outflow tract obstruction, aortic regurgitation, and infective endocarditis.[148] [149] [150] [151]

Infants

It is unusual for a VSD to cause difficulties in the immediate postnatal period, although congestive heart failure during the first 6 months of life is a frequent occurrence. Early diagnosis is helpful to ensure more careful observation of the affected infant.[148] The examining physician usually suspects the diagnosis because of a harsh systolic murmur at the lower left sternal border. The ECG and chest roentgenogram findings are within normal limits in the immediate neonatal period because appreciable left-to-right shunting

occurs only after the pulmonary vascular resistance decreases as the pulmonary vessels lose their fetal characteristics. It is desirable to monitor these infants closely.

A VSD that either decreases in size or closes completely during the first year of life presents no problems to the practicing physician. Spontaneous closure occurs by age 3 years in about 45 percent of patients born with VSD; occasional patients, however, do not experience spontaneous closure until age 8 to 10 years or even later.[152] Closure is more common in patients born with a small VSD; nonetheless, about 7 percent of infants with a large defect and congestive heart failure early in life also may experience spontaneous closure. Partial rather than complete closure is common in patients with both large and small VSDs. Anatomically, reduction of the VSD often is based on adherence of the tricuspid valve to the defect, hypertrophy of septal muscle, or ingrowth of fibrous tissue. Rarely, closure of the VSD is the result of prolapse of an aortic cusp or infective endocarditis.[150] Some defects close when an aneurysm forms in the ventricular septum (see Fig. 43-16). On auscultation, a click may be heard in early systole as the aneurysm tenses toward the right; the septal aneurysm may be detected by echocardiography as an anterior systolic bulge in the right ventricular outflow tract. A persistent minute VSD is not life threatening unless infective endocarditis develops. With proper precautions (see Chap. 47), the incidence of this complication is less than 1 percent.

If a moderate or large defect maintains its size after birth, the net left-to-right shunt increases during the first month of life as pulmonary vascular resistance falls. *Physical examination* during this time usually reveals a thrill along the lower left sternal border, and the holosystolic murmur of flow across the interventricular defect is accompanied by a low-pitched diastolic rumble at the apex, reflecting increased flow across the mitral valve. *Chest roentgenograms* reveal increased pulmonary vascular markings; evidence of left or biventricular hypertrophy may be observed on the ECG. Infants with a large left-to-right shunt tend to fare poorly, with recurrent upper and lower respiratory tract infections, failure to gain weight, and congestive heart failure. Congestive heart failure may be severe and intractable despite intensive medical management.

MANAGEMENT.

We currently recommend primary intracardiac repair of the VSD at any age rather than surgical banding of the pulmonary artery[153] to reduce pulmonary blood flow and alleviate heart failure. An exception is made for the rare infant with multiple VSDs and a sievelike septum, who is at higher risk for complications after operative repair. Operation usually is deferred, along with debanding of the pulmonary artery, until the child reaches 3 to 5 years. Primary closure of the VSD, preferably through the right atrium, may be performed in infancy using cardiopulmonary bypass, profound hypothermia and cardiocirculatory arrest, or a combination of the two techniques. Mortality approaches zero in major centers if the defect is isolated and uncomplicated but approaches 10 percent if many anomalies are present.[154]

Fortunately, medical treatment often is successful in controlling congestive heart failure. Nevertheless, these infants should be referred for cardiac catheterization to evaluate pulmonary vascular resistance and to detect associated defects that may require

operation, such as patent ductus arteriosus and coarctation of the aorta.

Children

Beyond the first year of life, a variable clinical picture emerges in children with VSD.[148] [155] If a small defect is present, the child usually is asymptomatic, the ECG usually appears normal, and the chest roentgenogram shows normal or only a mild increase in pulmonary vascular markings. Effort intolerance and fatigue are associated with moderate left-to-right shunts. These children exhibit cardiomegaly with a forceful left ventricular impulse and a prominent systolic thrill along the lower left sternal border. The second heart sound normally is split, with moderate accentuation of the pulmonic component; a third heart sound and rumbling diastolic murmur that reflects increased flow across the mitral valve are audible at the cardiac apex. The characteristic murmur resulting from flow across the defect is harsh and holosystolic, is best heard along the third and fourth interspaces to the left of the sternum, and is widely transmitted over the precordium. A basal midsystolic ejection murmur due to increased flow across the pulmonic valve also may be heard. The ECG reveals left or combined ventricular hypertrophy, and the chest roentgenogram and CT scan (see Chap. 5) show cardiomegaly, left atrial enlargement, and vascular engorgement.

PULMONARY HYPERTENSION.

It is of utmost importance to identify patients who may develop irreversible pulmonary vascular obstructive disease (Eisenmenger's reaction).[155] [156] [157] [158] Retrospective analyses of children who develop this complication indicate that infants with systemic or near systemic pressures in the pulmonary artery at the time of initial hemodynamic study are most at risk. If early primary closure is not recommended, recatheterization before age 18 months and a second determination of pulmonary vascular resistance should be performed in these patients to decide whether surgical intervention is obligatory to prevent development of fixed obliterative changes in the pulmonary vessels.

Mechanisms.

It is likely that numerous factors are involved in the development of pulmonary vascular disease (see Chap. 53). The anatomically large VSD allows some or all of the systemic pressure to be transmitted to the pulmonary arteries, thereby retarding regression

of their muscular media. Medial hypertrophy in the first months of life is responsible for higher pulmonary vascular resistance than would be anticipated for the amount of pulmonary blood flow. The shearing forces created by the high velocity of flow through narrowed pulmonary arterioles cause endothelial damage that is progressive.

Although an elevation in left atrial pressure may contribute to the rise in pulmonary vascular resistance, it is not an essential factor because pulmonary venous pressures can be low in patients who later develop pulmonary vascular disease. Nonetheless, pulmonary venous hypertension also may contribute to pulmonary arterial vasoconstriction and thus to increased shear forces. In this same regard, pulmonary vasoconstriction enhancing the risk of pulmonary vascular obstruction also may be caused by hypoxia due to either high altitude or lung disease. At high altitudes, large VSDs have higher pulmonary vascular resistances and smaller shunts than at low altitudes.

Clinical Features.

If a child who previously had a loud murmur and thrill associated with poor growth suddenly has a growth spurt, fewer respiratory infections, and a diminution of the intensity of the cardiac murmur and disappearance of the thrill, he or she may be developing severe obliterative changes in the pulmonary vascular bed. An increase in intensity of the pulmonic component of the second heart sound, a reduction in heart size on the chest roentgenogram, and more pronounced right ventricular hypertrophy on the ECG also are noted. These changes occur because the increased pulmonary vascular resistance causes a decrease in the left-to-right shunt. If these changes are suspected, cardiac catheterization should be repeated; if they are confirmed, prompt surgical repair is indicated before an inoperable predominant right-to-left shunt ensues. If operation is performed before age 2 years, pulmonary vascular resistance may be expected to fall to normal levels.[158]

In older patients, the degree to which pulmonary vascular resistance is elevated before operation is a critical factor determining prognosis. If the pulmonary vascular resistance is one-third or less of the systemic value, progressive pulmonary vascular disease after operation is unusual. However, if a moderate-to-severe increase in pulmonary vascular resistance exists preoperatively, either no change or progression of pulmonary vascular disease is common postoperatively. Moreover, the presence of increased pulmonary vascular resistance results in a higher immediate postoperative mortality rate for surgical closure of VSD. These observations make it clear that a large VSD should be approached surgically very early in life when pulmonary vascular disease is still reversible or has not yet developed (Fig. 43-17) .

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION.

With time, the clinical picture changes in 5 to 10 percent of patients with VSD and a moderate to large left-to-right shunt early in life. It begins to resemble more closely the tetralogy of Fallot (see Chap. 44); i.e., subvalvular right ventricular outflow tract obstruction develops owing to progressive hypertrophy of the crista supraventricularis. Depending on the severity of the latter process, it ultimately may result in reduced blood flow and a right-to-left shunt across the VSD. As right ventricular outflow tract obstruction develops, the holosystolic murmur is replaced by the crescendo-decrescendo ejection systolic murmur of pulmonic stenosis, and the pulmonary closure sound becomes softer. Right ventricular hypertrophy is evident on

the ECG, and the chest roentgenogram shows a reduction in pulmonary vascular markings and a smaller heart size with a right ventricular configuration. Infundibular

Figure 43-17 Early and late postoperative changes of pulmonary artery pressure after closure of ventricular septal defects in infants. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 200.)*

hypertrophy may progress quite rapidly within the first year of life, but the typical evolution to a clinical picture of cyanotic tetralogy of Fallot often takes 1 to 4 years. In those infants who develop right ventricular outflow obstruction, the incidence of spontaneous closure or reduction in size of a VSD is low.

VENTRICULAR SEPTAL DEFECT WITH AORTIC REGURGITATION.

This well-described complication of VSD occurs in about 5 percent of patients.[159] It usually is noted after age 5 years when a physician detects the early diastolic blowing murmur and wide pulse pressure of aortic regurgitation while monitoring a patient with a VSD. The diagnosis is readily confirmed by Doppler echocardiography. In such patients, aortic regurgitation may become the predominant hemodynamic abnormality. It is of interest that VSD with aortic regurgitation is rare in Europe and the United States, with an incidence of about 4 percent of all cases of isolated VSD, whereas in Japan the incidence is substantially higher (about 10 percent). In the Japanese, in particular, aortic regurgitation is the result of herniation of an aortic leaflet (usually the right coronary) through a subpulmonic supracristal VSD. In these patients, closure of the VSD may be all that is required to relieve aortic regurgitation. In many patients, however, especially in the Western world, the VSD is below the infundibular septum (crista supraventricularis). Although aortic leaflet herniation, especially of the right or noncoronary cusp, may occur in some of these patients, aortic regurgitation often results from a primary abnormality of the valve, usually one defective commissure. In the latter situation, plication of the elongated leaflet may lessen but not abolish the aortic regurgitation; in some patients, prosthetic aortic valve replacement may be necessary to provide hemodynamic relief.

In most patients with VSD and aortic regurgitation, the VSD is small to moderate in size, and mild right ventricular outflow tract obstruction exists. The latter is caused by either subpulmonic infundibular stenosis or projection of the herniated aortic cusp into the right ventricular outflow tract. The distinction between types of VSD with aortic regurgitation usually can be made by two-dimensional and Doppler echocardiography and by selective left ventricular angiocardiography to define the site of the interventricular communication in combination with retrograde aortography to assess the anatomy and competence of the aortic valve.[160]

Management.

Treatment of patients with VSD and aortic regurgitation is controversial. In patients with a large, hemodynamically significant left-to-right shunt, repair of the VSD is indicated, but aortic regurgitation is repaired only if at least moderate aortic regurgitation exists. If

a supracristal VSD without aortic regurgitation is identified at cardiac catheterization in early childhood, a sensible argument for prophylactic closure of the VSD can be put forth to prevent the potential complication of aortic valve incompetence. In the presence of moderate or severe aortic regurgitation, valvuloplasty is preferred to valve replacement,[161] in recognition of the fact that the severity of aortic regurgitation may increase in subsequent years and that reoperation with valve replacement may be necessary. Operation should probably be deferred in asymptomatic patients with a subcristal VSD and an insignificant left-to-right shunt when aortic regurgitation is not severe. If the defect is supracristal in the same clinical setting, its closure may not alleviate the mild degree of aortic incompetence but may retard its progression.

OTHER FORMS OF VENTRICULAR DEFECT.

Unusual forms of VSD include numerous muscular defects and left ventricular-right atrial communications. Defects in the muscular ventricular septum frequently are several small fenestrations that produce a large net left-to-right shunt.[151] Their recognition is a necessary preliminary to successful operation because incomplete repair may result in postoperative cardiac failure and death. A shunt from the left ventricle to right atrium may occur with a VSD in the most superior portion of the ventricular septum because the tricuspid valve is lower than the mitral valve. The clinical, ECG, and radiological findings in these patients do not differ appreciably from those in patients with a simple VSD, although right atrial enlargement may provide a clue to correct diagnosis of left ventricular-right atrial communication.[162]

The pathophysiology of a single or common ventricle may resemble that of a large VSD, although these defects are dissimilar embryologically. The single chamber frequently is the morphological left ventricle; malposition of the great arteries is common. No cyanosis may be detectable if selective streaming and increased pulmonary blood flow rather than complete mixing occurs. Pulmonary hypertension invariably is present unless pulmonic stenosis exists. It is imperative to differentiate a single ventricle from a large VSD by echocardiography and angiography because the operative approaches to the former malformation require the atriopulmonary Fontan's connection.

MANAGEMENT.

It is rarely necessary to restrict the activities of a child with an isolated VSD. Infective bacterial endocarditis is always a threat, and antibiotic prophylaxis for dental procedures and minor surgery is indicated (see Table 43-4 , p. 1516). [163] Respiratory infections require prompt evaluation and treatment. These children should be seen at least once or twice yearly to detect changes in the clinical picture that suggest the development of pulmonary vascular obliterative changes.

SURGICAL TREATMENT.

When clinical findings suggest a moderate shunt but no pulmonary hypertension, elective hemodynamic evaluation should be undertaken before age 3 years. Of prime importance in the hemodynamic evaluation is determination of pressure and blood flow in the pulmonary artery.[164] Surgical treatment is not recommended for children who have normal pulmonary arterial pressures with small shunts (pulmonary-systemic flow ratios of less than 1.5 to 2.0:1).[165] In such patients, the remaining risk of infective endocarditis does not exceed the risk of operation. Moreover, although the inherent risk of operation is small, the possibility of postoperative heart block, infection, or other complications of operation and cardiopulmonary bypass dictates a conservative approach when the cardiac defect may be well tolerated for life.

In some centers, the use of intraoperative transesophageal echocardiography has provided accurate assessment of patch integrity and the presence of additional muscular defects after termination of cardiopulmonary bypass.[166] [167]

With larger shunts, elective operation may be advised before the child enters school, thus minimizing any subsequent distinction of these patients from their normal classmates. Total assessment of the psychosocial dynamics of the family and child is helpful in determining the proper age for elective operation in each patient.

Under investigation is transcatheter closure by umbrella or clamshell occluder devices inserted by crossing the ventricular defect to guide a venous catheter through a long sheath and, ultimately, placing the device across the ventricular septum from the right ventricular side.[168] [169] [170] The use of such devices is limited to defects in the apical muscular septum, well distanced from the semilunar and AV valves.

Complete heart block is the most significant surgically induced conduction system abnormality, occurring immediately after surgery in fewer than 1 percent of patients. Late-onset complete heart block occasionally is a problem, especially in the 10 to 25 percent of patients whose postoperative ECG findings show complete right bundle branch block with left anterior hemiblock. When the latter ECG pattern is observed in patients with transient complete heart block in the early postoperative period, electrophysiological studies should be conducted at postoperative cardiac catheterization. Patients presenting postoperatively with right bundle block and left anterior hemiblock appear to fall into two populations, defined by either peripheral damage to the conduction system or damage to the bundle of His or its proximal branches. The former has not been associated with transient postoperative complete heart block, and these patients usually have a benign course. Trifascicular damage may be demonstrated in the latter population by a prolonged H-V interval, which implies a higher risk of complete heart block later in life. Although prophylactic use of permanent pacemakers in asymptomatic patients with evidence of trifascicular damage is not currently recommended, this group certainly requires careful follow-up and continued study.

Treadmill exercise studies of patients who preoperatively had normal or only moderately elevated pulmonary vascular resistance and essentially normal postoperative cardiac catheterization data may uncover late abnormalities in circulatory function.[171] Despite

normal cardiac output at rest, an impaired cardiac output response to exercise is noted in some. Moreover, despite normal pulmonary arterial pressure at rest, markedly abnormal increases in pulmonary arterial pressure may be noted during exercise. These findings may be related to abnormal left ventricular function after closure of the VSD and/or to persistent pathological changes in the pulmonary arterioles or to abnormal pulmonary vascular reactivity.[172] A direct relation exists between age at operation and the magnitude of the pulmonary arterial pressure response to intense exercise, suggesting that early operation may prevent permanent impairment of the functional capacity of the myocardium and pulmonary vascular bed.

A child who has already developed pulmonary vascular obstruction and a net right-to-left shunt across the VSD may occasionally come to medical attention (see also p. 1614). Symptoms may consist of exertional dyspnea, chest pain, syncope, and hemoptysis; the right-to-left shunt leads to cyanosis, clubbing, and polycythemia. Little can currently be offered to this group of patients other than continuing support to the patient and family.

Patent Ductus Arteriosus (See also Chap. 44)

The ductus arteriosus normally exists in the fetus as a widely patent vessel connecting the pulmonary trunk and the descending aorta just distal to the left subclavian artery (see Fig. 43-4 , p. 1511). In a fetus, most of the output of the right ventricle bypasses the unexpanded lungs by way of the ductus arteriosus and enters the descending aorta, where it travels to the placenta, the fetal organ of oxygenation.

It was earlier assumed that during fetal life the ductus arteriosus is a passively open channel that constricted postnatally by means of undefined molecular mechanisms in response to the abrupt rise in arterial P_{O_2} accompanying the first breath of life.[173] Even in utero, the lumen of the ductus arteriosus may be influenced by vasoactive substances, particularly prostaglandins.[86] [87] [174] [175] [176] Thus, inhibition of prostaglandin synthesis causes profound constriction of the ductus arteriosus in the mammalian fetus that may be reversed by administration of vasodilatory E-type prostaglandins. Initial contraction and functional closure of the ductus arteriosus shortly after birth is related both to the sudden increase in the partial pressure of oxygen that accompanies ventilation and to changes in the synthesis and metabolism of vasoactive eicosanoids. Intimal proliferation and fibrosis proceed more gradually, so that anatomical closure may take as long as several weeks for completion.[177]

The ductus arteriosus is a unique structure after birth because its patency may, on the one hand, result in cardiac decompensation but may, on the other hand, provide the only life-sustaining conduit to preserve systemic or pulmonary arterial blood flow in the presence of certain cardiac malformations.[178] Appreciable left-to-right shunting across the patent ductus arteriosus frequently complicates the clinical course of infants born prematurely.[179] The ductal shunt has been implicated specifically in the deterioration of pulmonary function in infants with the respiratory distress syndrome; in these infants severe congestive heart failure often is unresponsive to digitalis and diuretics.[87]

A distinction should be made between patency of the ductus arteriosus in a *preterm*

infant, who lacks the normal mechanisms for postnatal ductal closure because of immaturity, and a full-term newborn, in whom patency of the ductus is a true congenital malformation, probably related to a primary anatomical defect of the elastic tissue within the wall of the ductus.[177] In the former circumstance, delayed spontaneous closure of the ductus may be anticipated if the infant does not succumb to the cardiopulmonary difficulties caused by the ductus itself or to some lethal complication of prematurity, such as hyaline membrane disease, intraventricular hemorrhage, or necrotizing enterocolitis. In a similar manner, some full-term newborns have persistent patency of the ductus arteriosus for weeks or months because their relative hypoxemia contributes to vasodilatation of the channel. In the latter category are infants born at high altitude; those born with congenital malformations causing hypoxemia, such as pulmonary atresia with or without VSD; or those born with malformations in which ductal flow supplies the systemic circulation, such as hypoplastic left heart syndrome, interruption of the aortic arch, or some examples of coarctation of the aorta syndrome.

In the clinical settings in which the ductus preserves pulmonary blood flow, the essentially inevitable spontaneous closure of the vessel is associated with profound clinical deterioration. The latter may be reversed medically within the first 4 to 5 days of life by infusion of prostaglandin E_1 intravenously. By dilating the constricted ductus arteriosus, a temporary increase occurs in arterial blood oxygen tension and oxygen saturation and correction of acidemia.[178] These infants can then undergo operative repair or a palliative systemic-pulmonary anastomosis, under more optimal circumstances. Pharmacological dilation of the ductus arteriosus also is effective in preoperative restoration of systemic blood flow and alleviation of heart failure, especially in infants with aortic coarctation or hypoplastic left heart syndrome, and in infants with complete transposition of the great arteries in whom intercirculatory mixing is augmented.

PREMATURE INFANTS.

In most, if not all, preterm infants less than 1500-gm birth weight, persistence of a patent ductus arteriosus is prolonged, and in about one-third of these infants a large aorticopulmonary shunt is responsible for significant cardiopulmonary deterioration.[180] [181] Radiographic, echocardiographic, and Doppler ultrasound signs of significant left-to-right shunting usually precede the appearance of physical findings suggesting ductal patency. A significant increase in the cardiothoracic ratio is seen on sequential roentgenograms, as well as increased pulmonary arterial markings progressing to perihilar and generalized pulmonary edema. Serial echocardiographic evaluations that demonstrate increases in left ventricular end-diastolic and left atrial dimensions, especially when correlated with the aforementioned radiographic signs, are highly suggestive of a large shunt. Two-dimensional and Doppler echocardiography directly visualize and define the flow characteristics of the ductus arteriosus with great accuracy.[182]

Clinical Findings.

These include bounding peripheral pulses, an infraclavicular and interscapular systolic murmur (occasionally a continuous murmur), precordial hyperactivity, hepatomegaly, and either multiple episodes of apnea and bradycardia or respiratory dependence. Cardiac catheterization carries a high risk in preterm infants and seldom is indicated unless the diagnosis is obscure.

Treatment.

Treatment of preterm infants with a patent ductus arteriosus varies with the magnitude of shunting and the severity of hyaline membrane disease because the ductus may contribute importantly to mortality in the respiratory distress syndrome. Intervention in an asymptomatic infant with a small left-to-right shunt is unnecessary because the patent ductus arteriosus almost invariably undergoes spontaneous closure and does not require late surgical ligation and division. Those infants who demonstrate unmistakable signs of a significant ductal left-to-right shunt during the course of the respiratory distress syndrome often are unresponsive to medical measures to control congestive heart failure and require closure of the patent ductus arteriosus to survive. These infants are best treated within the first 2 to 7 days of life by pharmacological inhibition of prostaglandin synthesis with indomethacin to constrict and close the ductus[179] [183] [184] [185] ; surgical ligation is required in the estimated 10 percent of infants who are unresponsive to indomethacin.[186] Early intervention is advised to reduce the likelihood of necrotizing enterocolitis and of bronchopulmonary dysplasia related to prolonged respirator and oxygen dependence. Less often, indications for pharmacological or surgical closure of the ductus consist of life-threatening episodes of apnea and bradycardia or a prolonged failure to gain weight and grow.

FULL-TERM INFANTS AND CHILDREN.

In full-term newborns and older infants and children, patency of the ductus arteriosus occurs particularly in girls and in the offspring of pregnancies complicated by first-trimester rubella. Although most frequent in isolated form, the anomaly may coexist with other malformations, particularly coarctation of the aorta, VSD, pulmonic stenosis, and aortic stenosis. Flow across the ductus is determined by the pressure relation between the aorta and the pulmonary artery and by the cross-sectional area and length of the ductus itself.[187] Pulmonary pressures most commonly are normal, and a persistent gradient and shunt from aorta to pulmonary artery exist throughout the cardiac cycle.

Physical examination reveals a characteristic thrill and a continuous machinery murmur, with a late systolic accentuation at the upper left sternal border. The left atrium and left ventricle enlarge to accommodate the increased pulmonary venous return, and flow murmurs across the mitral and aortic valves may be detected. With significant left-to-right shunting, the runoff of blood through the ductus causes a widened systemic pulse pressure and bounding peripheral pulses. The hemodynamic abnormality is

reflected in the ECG by left ventricular and occasionally left atrial hypertrophy, and in the chest roentgenogram by left atrial and ventricular enlargement, prominent ascending aorta and pulmonary artery, and pulmonary vascular engorgement (see Chaps. 8 and 44).

The clinical diagnosis may be difficult when the findings do not conform to the classic presentation. As mentioned earlier, disappearance of the diastolic component of the murmur is common in premature infants because pulmonary arterial diastolic pressures are higher at that age. In older patients, both heart failure and pulmonary hypertension are associated with a reduction in the pressure gradient across the ductus arteriosus and result in atypical systolic murmurs. When severe pulmonary vascular obstructive disease results in reversal of flow through the ductus and preferential shunting of unoxygenated blood to the descending aorta, the toes, rather than the fingers, may show cyanosis and clubbing.

Full-term infants with patent ductus arteriosus may survive for a number of years, although a large defect occasionally results in heart failure and pulmonary edema early in life. The leading causes of death in older children are infective endocarditis and heart failure. Beyond the third

Figure 43-18 *Top panel,* High parasternal view of a patent ductus arteriosus in the sagittal plane demonstrating the classic position of a ductus arteriosus (D) lying between the pulmonary trunk (PT) and the descending aorta (DAO). The transverse aorta (TAO) giving rise to vessels to the head and neck is seen lying above the pulmonary trunk. The left atrium (LA) is seen inferiorly. The pulmonary trunk appears continuous with a wide patent ductus into the descending aorta just above the origin of the left pulmonary artery (L). *Bottom panel,* Patent ductus arteriosus (PDA) in a conventional parasternal short-axis view arising from the main pulmonary artery (MPA). The left pulmonary artery lies immediately to the right of the ductus and the left pulmonary artery lies adjacent to the ascending aorta (AO). The ductus is continuous with the descending aorta (DAO). The AO lies between the MPA anteriorly, the right atrium (RA) and LA posteriorly, and the right pulmonary artery laterally to the left.

Figure 43-19 Transcatheter closure of a patient ductus arteriosus is illustrated using the Rashkind double-umbrella technique. The catheter approaches the ductus via a long sheath advanced from the femoral vein. The *right panel* shows expansion of the distal umbrella. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 136.)*

decade of life, severe pulmonary vascular obstruction has been known to cause aneurysmal dilatation, calcification, and rupture of the ductus.[188]

The patent ductus can be directly visualized by two-dimensional echocardiography (Fig. 43-18) ; range-gated pulsed Doppler echocardiography shows the characteristic flow abnormalities across the ductus, as well as a continuous flow disturbance in the

pulmonary artery. Cardiac catheterization may be indicated when additional lesions or pulmonary vascular obstruction is suspected.

Management.

In the absence of severe pulmonary vascular disease with predominant right-to-left shunting, the anatomical presence of a patent ductus usually is considered sufficient indication for closure. Ligation or division of the ductus carries a low risk, whether performed electively in an asymptomatic child or at any age if symptoms are present. The operative risk is reduced if heart failure can be compensated by medical measures before surgery. Operation should be deferred for several months in patients treated successfully for infective endarteritis because the ductus may remain somewhat edematous and friable. Rarely, when the infection does not subside with intensive antibiotic treatment, surgical ligation may be necessary to eradicate the infection.

Although strictly speaking still investigational, substantial experience exists with transcatheter closure of the patent ductus using various approaches, including coils, buttons, plugs, and umbrellas, with each occluder device introduced through a relatively large-diameter sheath from the femoral vein (Fig. 43-19) [189] [190] [191] [192] [193] [194] [195] (see Chap. 44). The approach is especially feasible in patients who weigh more than 10 kg and who have neither a long tubular ductus nor a ductus with a long, narrow aortic end. In experienced hands, initial occlusion is successful in 85 to 90 percent of patients; reocclusion adds 5 to 7 percent to the overall success rate. Potential complications in 5 to 10 percent of patients include embolization of the device, endocarditis, and hemolysis. Ductal closure by manually invasive surgery or thoracoscopy will undoubtedly undergo future evaluation.[196] [197]

Aorticopulmonary Septal Defect

Aorticopulmonary window or fenestration, partial truncus arteriosus, and aortic septal defect are other designations applied to this relatively uncommon anomaly. Septation of the aortopulmonary trunk occurs by fusion of the conotruncal ridges (see Fig. 43-2). The right and left sixth aortic arches, destined to become the pulmonary arteries, join the pulmonary artery to complete great artery development (see Fig. 43-5). Congenital defects between the ascending aorta and the pulmonary artery result from faulty development of this area during embryonic life. The typical aortopulmonary septal defect results because of incomplete fusion of the distal aortopulmonary septum.[198] Malalignment of the conotruncal ridges results in unequal partitioning of the aortopulmonary trunk, which may result in partial or complete fusion of the right pulmonary artery to the aorta.

The usual defect consists of a communication between the aorta and pulmonary artery just above the semilunar valves. Persistent patency of the ductus arteriosus is an associated lesion in 10 to 15 percent of cases. Less common accompanying cardiovascular lesions include VSD, aortic origin of the right pulmonary artery, aortic arch interruption, coarctation of the aorta, and right aortic arch. Aorticopulmonary septal defects usually are large and are accompanied by severe pulmonary arterial

hypertension and early-onset pulmonary vascular obstruction.

PHYSICAL EXAMINATION.

The pulses typically are bounding, like those of a large patent ductus arteriosus. The murmur, however, seldom is continuous, and a basal systolic murmur is most common. Cardiomegaly is present, and pulmonary hypertension is reflected in a loud and palpable sound of pulmonary valve closure. Aorticopulmonary septal defect should be suspected whenever a large shunt into the pulmonary artery is demonstrated at catheterization. Diagnosis of the anomaly and its distinction from patent ductus and persistent truncus arteriosus usually can be done by two-dimensional echocardiography. Identification of the aortopulmonary window and associated malformations may also employ hemodynamic study and selective angiocardiography with the injection of contrast material into the left ventricle and/or the root of the aorta (Fig. 43-20) . Although some patients may survive to adulthood with uncorrected aorticopulmonary

Figure 43-20 Aortic root injection of contrast material in the frontal view produces simultaneous opacification of the aorta and pulmonary artery through a large aorticopulmonary septal defect (arrow). *(Courtesy of Dr. Robert White.)*

septal defect, most die early in life unless surgical treatment is undertaken. Rarely, transcatheter closure by insertion of an occluding device may be feasible in infants with a small aortopulmonary window.[199] As a general rule, operative correction is indicated in all symptomatic infants when the diagnosis is made. Elective repair is advised at 3 to 6 months.[200] [201] Profound hypothermic total circulatory arrest or total cardiopulmonary bypass is required, and the defect is closed by way of a transaortic approach, usually with a prosthetic or xenograft pericardial patch.

Persistent Truncus Arteriosus

MORPHOLOGY.

Persistent truncus arteriosus is a rare but serious anomaly in which a single vessel forms the outlet of both ventricles and gives rise to the systemic, pulmonary, and coronary arteries.[202] The defect results from failure of septation of the embryonic truncus by the infundibular truncal ridges (see Fig. 43-4 , p. 1511). It is always accompanied by a VSD, frequently with a right-sided aortic arch. The VSD is due to the absence or underdevelopment of the distal portion of the pulmonary infundibulum. The truncal valve usually is tricuspid but is quadricuspid in about one-third of patients and rarely can be bicuspid. Truncal valve regurgitation and truncal valve stenosis are each seen in 10 to 15 percent of patients. There may be a single coronary artery,

displacement of the coronary ostia (usually the left ostium posteriorly), or a single posterior descending coronary artery arising from the right coronary or, less often, from the left circumflex artery, especially in patients with a single coronary artery.[203]

Truncus malformations can be classified either anatomically according to the mode of origin of pulmonary vessels from the common trunk or from a functional point of view, based on the magnitude of blood flow to the lungs. In the common type (type I) of truncus arteriosus malformation, a partially separate pulmonary trunk of variable length exists because of the presence of an incompletely formed aorticopulmonary septum. The pulmonary trunk usually is very short and gives rise to left and right pulmonary arteries. When the aorticopulmonary septum is absent, there is no discrete main pulmonary artery component, and both pulmonary artery branches arise directly from the truncus.

In type II, each pulmonary artery arises separately but close to the other from the posterior aspect of the truncus (Fig. 43-21) . In type III, each pulmonary artery arises from the lateral aspect of the truncus. Less commonly, one pulmonary artery branch may be absent, with collateral arteries supplying the lung that does not receive a pulmonary artery branch from the truncus. Truncus arteriosus malformation should not be confused with "pseudotruncus arteriosus," which is the severe form of tetralogy of Fallot with pulmonary atresia in which the single aorta arises from the heart accompanied by a remnant of atretic pulmonary artery.

HEMODYNAMICS.

Pulmonary blood flow is governed by the size of the pulmonary arteries and the pulmonary vascular resistance. In infancy, pulmonary blood flow is usually excessive because pulmonary vascular resistance is not greatly increased. Thus, despite an obligatory admixture of systemic and pulmonary venous blood in the common trunk, only minimal cyanosis is present. Rarely, pulmonary blood flow is restricted by hypoplastic or stenotic pulmonary arteries arising from the truncus. Pulmonary vascular obstruction usually does not restrict pulmonary blood flow before 1 year of age.[204]

CLINICAL FEATURES.

Infants with truncus arteriosus usually present with mild cyanosis coexisting with the cardiac findings of a large left-to-right shunt. Symptoms of heart failure and poor physical development usually appear in the first weeks or months of life. The most frequent physical findings include cardiomegaly, a systolic ejection sound accompanied by a thrill, a loud single second heart sound, a harsh systolic murmur, and a low-pitched mid-diastolic rumbling murmur and bounding pulses. Truncus arteriosus often is a measure of the *DiGeorge's syndrome* (see Table 43-2 (Table Not Available)); thus, facial dysmorphism, a high incidence of extracardiac malformations (particularly of the limbs, kidneys, and intestines), atrophy or absence of the thymus gland, T-lymphocyte deficiency, and predilection to infection also may be features of clinical presentation.[205] Evidence suggests that genetically induced embryonic abnormalities in the cardiac neural crest play a major part in creation of the cardiovascular malformation as well as

the other components of the syndrome[206] (see Chap. 56).

Truncal valve incompetence is suggested by the presence of a diastolic decrescendo murmur at the base of the heart. The physical findings are different if pulmonary blood flow is restricted by either high pulmonary vascular resistance or pulmonary arterial stenosis: Cyanosis is prominent, congestive failure is rare, and only a short systolic ejection may be audible, occasionally accompanied by continuous murmurs posteriorly of bronchial collateral flow.

Figure 43-21 *Top,* Subcostal coronal view of truncus arteriosus (Tr). The truncal valve lies above the ventricular septal defect (open arrow), which appears above the left ventricle (LV) and right ventricle (RV). The Tr is seen dividing into the transverse aortic arch (TAO), which gives rise to the vessels supplying the head and neck: the innominate artery (IA), the left carotid artery (LCA), and the left subclavian artery (LSA). *Bottom,* Doppler color flow image showing the superimposition of color flow into the truncus arteriosus, left pulmonary artery, transverse aorta, and branches to the head and neck.

ELECTROCARDIOGRAPHY AND RADIOGRAPHY.

Left ventricular hypertrophy alone or in combination with right ventricular hypertrophy is present electrocardiographically when a prominent left-to-right shunt exists; right ventricular hypertrophy is observed in patients with restricted pulmonary blood flow. The radiographic findings depend on the hemodynamic circumstances. Gross cardiomegaly with left or combined ventricular enlargement, left atrial enlargement, and a small or absent main pulmonary artery segment with pulmonary vascular engorgement are the usual radiographic features. A right aortic arch is common (25 to 30 percent of patients). When pulmonary blood flow is reduced, both heart size and pulmonary vascular markings are less prominent.

The *echocardiographic* features of truncus arteriosus (see Fig. 43-21) include a large truncal root overriding the ventricular septum and an outlet VSD. Additionally seen are

truncal valve abnormalities with a variable number of cusps and leaflets, often thickened with rolled edges, an increase in the right ventricular dimension, and mitral valve-truncal root continuity. Differentiation between truncus arteriosus and tetralogy of Fallot by ultrasonography may be difficult unless either the separate origin of the pulmonary arteries or a single trunk from the ascending portion of a single arterial root can he identified. The origin of the pulmonary arteries is detected from various imaging planes, including high short-axis views, scanning superiorly from the truncal valve, or from a subcostal view (see Fig. 43-21). Diagnosis should be suspected at cardiac catheterization if the catheter fails to enter the central pulmonary arteries from the right ventricle. Selective angiocardiography and retrograde aortography are necessary to establish a precise diagnosis and to reveal the common trunk arising from the heart and the origin of the pulmonary arteries from the truncus.[207]

The early fatal course as well as early development of pulmonary vascular obstructive disease in patients surviving infancy is responsible for the poor prognosis associated with truncus arteriosus. In infants and young children with large left-to-right shunts, surgical banding of one or both pulmonary arteries to reduce pulmonary flow has been used with little success. Corrective operation is indicated before age 3 months to avoid the development of severe pulmonary vascular obstructive disease.[208]

SURGICAL TREATMENT.

Operation consists of closure of the VSD, leaving the aorta arising from the left ventricle; the pulmonary arteries are excised from their truncus origin, and a valve-containing prosthetic conduit or aortic homograft valve conduit is used to establish continuity between the right ventricle and the pulmonary arteries (Fig. 43-22). Truncal valve insufficiency is a challenging problem and may require valve replacement or more moderate plastic repair to correct prolapse and improve central cusp coaptation. Important risk factors for perioperative death are severe truncal valve regurgitation, interrupted aortic arch, coronary artery anomalies, and age at operation greater than 100 days.[209] [210] Patients with only one pulmonary artery are especially prone to early development of severe pulmonary vascular disease but otherwise are not at increased risk from surgery.

With truncus arteriosus defects, the possible inequalities of pressure and flow between the two pulmonary arteries often make precise calculation of pulmonary resistance difficult. Corrective operation may be performed in patients with at least one adequate pulmonary artery having low distal pressure or arteriolar resistance. Conversely, significant systemic arterial desaturation in a patient with two pulmonary arteries and with neither pulmonary artery stenosis nor a previous pulmonary artery band signifies that high pulmonary vascular resistance exists and that the condition is probably inoperable. It is not yet clear how often and at what age the conduit between the right ventricle and pulmonary artery must be replaced with a larger prosthesis because of either growth of the patient, in whom a small conduit causes eventual obstruction, heterograft valve degeneration, or obstruction created by neointimal proliferation within a prosthetic conduit.[211] When operation is carried out within a conduit in the first year of life, conduit replacement often is required within 3 to 5 years.

Coronary Arteriovenous Fistula

Coronary arteriovenous fistula (see also Chap. 44) is an unusual anomaly that consists of a communication between one of the coronary arteries and a cardiac chamber or vein. The right coronary artery, or its branches, is the site of the fistula in about 55 percent of cases; the left coronary artery is involved in about 35 percent, and both coronary arteries in 5 percent. Connections between the coronary system and a cardiac chamber appear to represent persistence of embryonic intertrabecular spaces and sinusoids. Most of these fistulas drain into the right ventricle, right atrium, or coronary sinus; fistulous communication to the pulmonary artery, left atrium, or left ventricle is much less frequent. The shunt through the fistula most often is of small magnitude, and myocardial blood flow is not compromised.[212] Rarely, spontaneous closure may occur.

Potential complications include pulmonary hypertension and congestive heart failure if a large left-to-right shunt exists, bacterial endocarditis, rupture or thrombosis of the fistula or an associated arterial aneurysm, and myocardial ischemia distal to the fistula due to decreased coronary blood flow.

Most pediatric patients are asymptomatic and are referred because of a cardiac murmur that is loud, superficial, and continuous at the lower or midsternal border. The site of maximal intensity of the murmur is related to the site of drainage and usually is different from the second left intercostal space--the classic site of the continuous murmur of

Figure 43-22 Operative correction of truncus arteriosus, type III. The pulmonary arteries arise separately from the truncus. An anterior incision is made, and a segment of aorta containing the orifices of both pulmonary arteries is excised from the truncus *(a)*. The cuff of tissue containing the two pulmonary arteries is anastomosed to an extracardiac valved conduit *(b)*. Aortic continuity is restored by direct suture *(c)* or by interposing a preclotted graft *(d)*. The diagram does not show closure of the ventricular septal defect. *(From Stark J, deLaval M: Surgery for Congenital Heart Defects. New York, Grune & Stratton, 1983, p 420.)*

persistent ductus arteriosus--except when the fistula drains into the pulmonary artery or right ventricle. In the latter situation, the murmur is louder in diastole than in systole because of compression of the fistula by contracting myocardium. The ECG and chest roentgenogram findings often are normal and seldom show selective chamber enlargement or myocardial ischemia. A significantly enlarged feeding coronary artery can usually be detected by two-dimensional echocardiography. The entire course and site of entry of the AV fistula can be traced by combining two-dimensional echocardiography and Doppler color flow mapping and imaging techniques. The shunt entry site is characterized by a continuous turbulent systolic and diastolic flow pattern (see Chaps. 7 and 44). [212] [213] Multiplane transesophageal echocardiography also accurately defines the origin, course, and drainage site of the fistula.

Standard retrograde thoracic aortography, balloon occlusion angiography of the aortic root with a 45-degree caudal tilt of the frontal camera ("laid-back" aortogram),[214] or coronary arteriography can be used reliably to identify the size and anatomical features of the fistulous tract, which can be closed preferably by transcatheter coil embolization or suture obliteration in most cases.[215] [216] In the presence of a large left-to-right shunt and symptoms of heart failure, the decision to operate is clearly justified. The fistula most often is closed in asymptomatic patients to prevent future symptoms or complications, such as infective endocarditis. The prognosis after successful closure of a coronary artery-cardiac chamber fistula is excellent.

Anomalous Pulmonary Origin of the Coronary Artery

This rare malformation occurs in about 0.4 percent of patients with congenital cardiac

anomalies. In almost all patients, the left coronary artery originates from the posterior sinus of the pulmonary artery.[217]

In unusual cases that have been reported, the right coronary artery, or the entire coronary artery system, originates from the main pulmonary trunk. Embryologically, the distal coronary artery system is formed by 9 weeks from solid angioblastic buds that extend throughout the epicardium to form the major coronary artery branches. Proximally, the coronary network forms a ring around the truncus arteriosus, joining with coronary buds from the primitive aortic sinuses as the truncus partitions to form the great arteries. The varieties of anomalous pulmonary origin of the coronary artery are the result of displacement in this proximal process.

PATHOPHYSIOLOGY.

During fetal life, pulmonary artery pressure is slightly greater than aortic pressure, and perfusion of the left coronary artery is antegrade (Fig. 43-23 *A*). After birth, when pulmonary artery pressure falls below aortic pressure, perfusion of the left coronary artery from the pulmonary artery ceases, and the direction of flow in the anomalous vessel reverses. Blood flows from the aorta to the right coronary artery, then through collateral channels to the left coronary artery, and finally to the pulmonary artery (Fig. 43-23 *B*). In effect, the left coronary artery behaves as a fistulous communication between the aorta and pulmonary artery. If adequate collateral channels exist or develop between the two coronary artery circulations, total myocardial perfusion through the right coronary artery increases (Fig. 43-23 *C*). In 10 to 15 percent of patients, myocardial ischemia never develops because extensive intercoronary collaterals allow survival to adolescence or adulthood. In fact, if collateral blood flow is considerable, patients may develop the clinical manifestations of a large arteriovenous shunt and a continuous or diastolic murmur.

By far the most common clinical presentation is that of an infant who suffers a myocardial infarction and develops congestive heart failure.[218] The infant syndrome usually becomes manifested at age 2 to 4 months with angina-like symptoms that may be misinterpreted as colic. Feeding and defecation often are accompanied by dyspnea, irritability and crying, pallor, diaphoresis, and occasional loss of consciousness. Older children or adults usually present with a continuous murmur or with mitral regurgitation resulting from dysfunction of ischemic or infarcted papillary muscles. In some instances, the coronary anomaly is unsuspected until a previously well adolescent or adult experiences angina, heart failure, or sudden death.

DIAGNOSIS.

The diagnosis of anomalous origin of the coronary artery is supported by ECG demonstration of deep Q waves in association with ST segment alterations and T wave inversions in leads I, aV_L , V_5 , and V_6 (Fig. 43-24) . These findings greatly assist the differentiation of this anomaly from myocarditis and dilated cardiomyopathy.[219] Chest roentgenograms show moderate to severe enlargement of the left atrium and ventricle. Echocardiography with Doppler color flow mapping has replaced cardiac catheterization

as the standard method of diagnosis. The pulmonary

Figure 43-23 Anomalous origin of the left main coronary artery from the pulmonary artery. *A,* In a fetus, both right and left coronary arteries receive forward flow from their respective great arteries. *B,* Soon after birth, before collaterals are well developed, there may be an anterolateral infarct and slight retrograde flow from the left coronary artery to the pulmonary artery. *C,* After collaterals have enlarged, there is high flow in the enlarged right coronary artery and the collaterals and significant retrograde flow into the pulmonary artery. Dotted arrows indicate direction and approximate magnitude of flow in the right and left coronary arteries and the collaterals between them. PV = pulmonary vein; LA = left atrium; LAA = left atrial appendage; RA = right atrium; LMCA = left main coronary artery; LCx = left circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery. *(From Hoffman JIE: In Emmanouilides GC, Riemenschneider TA, Allen HD, et al [eds]: Moss and Adams' Heart Disease in Infants, Children, and Adolescents. 5th ed. Baltimore, © Williams & Wilkins, 1994, p 776.)*

Figure 43-24 Typical electrocardiogram of an infant with anomalous left coronary artery before *(above)* and after *(below)* ligation of the anomalous left coronary artery. Note the abnormal Q waves in I, AVL, and V_6 . *(Courtesy of Dr. Delores A. Danilowicz.)*

origin of the anomalous left coronary artery is visualized from long- or short-axis views. Color flow mapping demonstrates retrograde flow in the left coronary system and an abnormal flow jet from the left coronary artery into the pulmonary trunk. Moreover, detection of anterograde flow in the left coronary system helps to preclude the diagnosis.[221] Color flow mapping of the jet from the origin of the left coronary artery as it enters the pulmonary artery is diagnostic. Detection of anterograde diastolic flow in the left coronary system virtually precludes this diagnosis.[220] If the echocardiographic diagnosis is unequivocal, coronary arteriography or aortography is not required to make the diagnosis. The origin of the anomalous left coronary artery occasionally may be visualized echocardiographically from long- or short-axis views of the pulmonary artery.[221] Absence of the left coronary artery from its usual origin in the left sinus of Valsalva does not distinguish this lesion from single coronary artery. Color flow Doppler examination may also reveal associated mitral regurgitation. Ischemia or infarction is suggested by the echocardiographic findings of segmental wall motion abnormalities, particularly involving the anterolateral free wall of the left ventricle. Electron beam CT after intravenous contrast infection may accurately define the malformation (see Chap. 10). Stress thallium scintigraphy shows a characteristic defect of the anterolateral wall of the left ventricle. Positron emission tomography reveals both the perfusion defect and its metabolic consequences (Fig. 43-25).

Aortography or coronary angiography demonstrates the retrograde drainage of the coronary vessel into the pulmonary artery. It should be recognized that ventricular arrhythmias may complicate the course of hemodynamic study. The magnitude of shunting into the pulmonary artery may be determined by oximetry, indicator-dilution

curves, or angiography.

MANAGEMENT.

Medical treatment is indicated in infants with myocardial infarction for congestive heart failure, arrhythmias, and cardiogenic shock. In patients with a small left-to-right shunt or no shunt at all, the prognosis is exceedingly poor with conservative management, justifying an attempt to reestablish a two-coronary artery system. The *operations* that have been used include reimplanting the left coronary artery into the aortic root, surgically creating an aortopulmonary window and a tunnel to convey blood from the window across the back of the pulmonary trunk to the origin of the anomalous left coronary artery, with reconstruction of the anterior wall of the pulmonary trunk, and anastomosis of the left coronary artery with the subclavian artery or with the aorta by means of a graft.[222] [223] If clinical deterioration occurs in infants with a sizable left-to-right shunt into the pulmonary artery, simple ligation of the left coronary artery at its origin prevents retrograde flow

Figure 43-25 Positron emission tomography (PET) transaxial images depict myocardial perfusion and glucose metabolism in a 7-month-old infant with anomalous origin of the left coronary artery (LCA) from the pulmonary artery. The ammonia (NH_3) scan demonstrates hypoperfusion *(left panel)*, whereas the fluorodeoxyglucose scan shows increased glucose metabolism *(right panel)* in the anterior lateral left ventricular wall (arrows) in the region perfused by the LCA. Under fasting conditions, normal myocardium has minimal glucose (FDG) uptake, whereas in this figure, hypoperfused myocardium preferentially metabolizes glucose. The "mismatch" pattern in this figure indicates ischemic but viable myocardium. This patient underwent reimplantation of the LCA with subsequent complete recovery of cardiac function and normalization of PET perfusion and metabolism. RV = right ventricle; LV = left ventricle; IVS = interventricular septum.

and allows perfusion of the left ventricle with blood supplied through anastomoses with the right coronary artery. If medical management stabilizes the infant with significant intercoronary collaterals, operation may be postponed to allow the patient to grow, because increased size of the vessels enhances the likelihood of successful reimplantation or coronary arterial bypass surgery. The outcome of surgery and ultimate prognosis are significantly influenced by the degree of myocardial damage suffered preoperatively.[224] Uncommonly, it is necessary to consider aneurysmectomy or mitral valve replacement. Cardiac transplantation has been suggested as an option only if recovery of myocardial function is poor.

Aortic Sinus Aneurysm and Fistula

Congenital aneurysm of an aortic sinus of Valsalva, particularly the right coronary sinus, is an uncommon anomaly that occurs three times more often in males than in females. The malformation consists of a separation, or lack of fusion, between the media of the

aorta and the annulus fibrosis of the aortic valve.[225] The receiving chamber of the aorticocardiac fistula usually is the right ventricle, but occasionally, when the noncoronary cusp is involved, the fistula drains into the right atrium.

Five to 15 percent of aneurysms originate in the posterior or noncoronary sinus; seldom is the left aortic sinus involved. Associated anomalies are common and include bicuspid aortic valve, VSD, and coarctation of the aorta.

The deficiency in the aortic media appears to be congenital. Reports in infants are exceedingly rare[226] and are infrequent in children, because progressive aneurysmal dilatation of the weakened area develops but may not be recognized until the third or fourth decade of life, when rupture into a cardiac chamber occurs.

An *unruptured aneurysm* usually does not produce a hemodynamic abnormality, although pressure on the intracardiac conduction system by an unruptured aneurysm may be a rare cause of complete AV block; rarely, myocardial ischemia may be caused by coronary arterial compression. Rupture is often of abrupt onset, causes chest pain, and creates continuous arteriovenous shunting and volume loading of both right and left heart chambers, which results in heart failure. An additional complication is infective endocarditis, which may originate either on the edges of the aneurysm or on those areas in the right side of the heart that are traumatized by the jetlike stream of blood flowing through the fistula.

DIAGNOSIS.

The presence of this anomaly should be suspected in a patient with a history of chest pain of recent onset, symptoms of diminished cardiac reserve, bounding pulses, and a loud superficial continuous murmur accentuated in diastole when the fistula opens into the right ventricle, as well as a thrill along the right or left lower parasternal border. The *physical findings* can be difficult to distinguish from those produced by a coronary arteriovenous fistula. *Electrocardiography* shows biventricular hypertrophy, and chest roentgenography demonstrates generalized cardiomegaly. Two-dimensional and pulsed Doppler *echocardiographic* studies may detect the walls of the aneurysm and disturbed flow within the aneurysm or at the site of perforation, respectively.[227] *Transesophageal echocardiography* may provide more precise information than the transthoracic approach. *Cardiac catheterization* reveals a left-to-right shunt at the ventricular or, less commonly, the atrial level; the diagnosis may be established definitively by retrograde thoracic aortography (Fig. 43-26) .

MANAGEMENT.

Preoperative medical management consists of measures to relieve cardiac failure and to treat coexistent arrhythmias or endocarditis, if present. At operation, the aneurysm is closed and amputated, and the aortic wall is reunited with the heart, either by direct suture or with a prosthesis.[228] Every effort should be made to preserve the aortic valve in children because patch closure of the defect combined with prosthetic valve

replacement greatly enhances the risk of operation in small patients.

Figure 43-26 A retrograde aortogram shows the fistulous connection between the noncoronary sinus of Valsalva and the right ventricle (RV) (arrow). AO = aorta. *(Courtesy of Dr. Robert White.)*

VALVULAR AND VASCULAR LESIONS WITH OR WITHOUT RIGHT-TO-LEFT SHUNT

Aortic Arch Obstruction

The conventional anatomical and clinical divisions into preductal and postductal coarctation or infantile and adult types, respectively, are misleading because the anatomical localization is inaccurate and the age dependence of the clinical presentation does not hold true (i.e., the adult type often is seen in the first weeks of life). A spectrum of anatomical lesions exists, causing obstruction of the aortic arch or proximal portion of the descending aorta. These range from a localized coarctation or constriction of the lumen, most commonly located just distal to the origin of the left subclavian artery and closely related to the attachment of the ductus arteriosus with the aorta, to diffuse narrowing or interruption of a portion of the aortic arch. In this chapter, aortic arch obstruction is divided into three types: (1) localized juxtaductal coarctation, (2) hypoplasia of the aortic isthmus, and (3) aortic arch interruption. *Pseudocoarctation* is used synonymously with "kinking" or "buckling" of the aorta, which is a subclinical form of localized juxtaductal coarctation of the aorta.

Localized Juxtaductal Coarctation (See also p. 1600)

MORPHOLOGY.

This lesion consists of a localized shelflike thickening and infolding of the media of the posterolateral aortic wall opposite the ductus arteriosus; the wall of the aorta into which the ductus or ligamentum arteriosum inserts is not involved.[229] Juxtaductal coarctation occurs two to five times more commonly in males than in females, and there is a high degree of association with gonadal dysgenesis (Turner's syndrome) and bicuspid aortic valve.[230] Other common associated anomalies include VSD and mitral stenosis or regurgitation. The most important extracardiac anomaly is aneurysm of the circle of Willis.

PATHOGENESIS.

Juxtaductal coarctation is probably related to an abnormality in the pattern of ductus arteriosus blood flow in utero, which in turn may be the result of associated intracardiac

anomalies.[230] [231] Thus, in fetal life, blood flow through the aortic isthmus constitutes only 12 to 17 percent of the total cardiac output, whereas blood flow through the ductus arteriosus exceeds that across the aortic valve. The dorsal aortic wall directly opposite the ductus arteriosus resembles morphologically the apex of a normal branch point of the aorta if ductal flow pathways in utero diverge, with some flow directed cephalad into the aortic isthmus and the remainder proceeding into the descending aorta. The aortic branch point is identical histologically to the posterior shelf of juxtaductal aortic coarctation. A divergence of ductal flow is fostered by the presence of lesions in the fetus that create an imbalance between left and right ventricular outputs, with right-sided flow predominating (e.g., bicuspid aortic valve, mitral valve anomaly). In the absence of an anomaly fostering augmented ductal flow, a branch point may be created by an alteration in the angle at which the ductus arteriosus meets the aorta, pointing the ductal stream directly against the posterior aortic wall rather than obliquely down into the descending aorta. Cardiac anomalies that cause augmented ascending aortic blood flow (e.g., pulmonic atresia or stenosis, tetralogy of Fallot) prevent development of a branch point and indeed are almost never seen in association with juxtaductal coarctation of the aorta.

During fetal life, the posterior aortic shelf is not obstructive because blood may pass readily from the ascending aorta to the descending aorta by traversing the anterior aortic segment and the aortic end of the ductus arteriosus. Postnatally, however, when the ductus undergoes obliteration at its aortic end, the shelflike projection of the posterior aortic wall unmasks the obstruction to aortic flow (Fig. 43-27) . After pharmacological interventions that dilate the ductus arteriosus (prostaglandin E_1 infusion), the pressure difference may be obliterated across the site of coarctation because the fetal flow pattern is reestablished.[178] [232]

The pathogenesis of juxtaductal coarctation already described explains the prevalence of associated intracardiac anomalies that foster reduced ascending aortic flow and augmented ductus arteriosus flow in utero, as well as the absence of associated intracardiac anomalies in which the converse flow conditions exist in utero. The dependence of aortic obstruction on constriction of the ductus arteriosus postnatally explains the variable onset after birth of the clinical manifestations of coarctation, as well as the dramatic alleviation of the obstruction produced pharmacologically by dilatation of the ductus arteriosus.

CLINICAL FINDINGS.

The manifestations of juxtaductal coarctation of the aorta depend on the prominence of the posterolateral aortic shelf, which determines the intensity

Figure 43-27 Juxtaductal coarctation (COARCT) unmasked by constriction of the ductus arteriosus (DA). MPA = main pulmonary artery; D.Ao. = descending aorta; Ao.Isth. = aortic isthmus. *(Courtesy of Dr. Norman Talner.)*

of obstruction, and on the rapidity with which obstruction develops.

NEONATES AND INFANTS.

Rapid, severe obstruction in infancy is a prominent cause of left ventricular failure and systemic hypoperfusion. Substantial left-to-right shunting across a patent foramen ovale and pulmonary venous hypertension secondary to heart failure cause pulmonary arterial hypertension. Because little or no aortic obstruction existed during fetal life, the collateral circulation in the newborn period is often poorly developed. In these infants, peripheral pulses characteristically are weak throughout the body until left ventricular function is improved with medical management; a significant pressure difference then develops between the arms and the legs, allowing detection of a pulse discrepancy. Cardiac murmurs are nonspecific in infancy and commonly are derived from associated lesions.

The *ECG* shows the right-axis deviation and right ventricular hypertrophy; the *chest radiograph* shows generalized cardiomegaly and pulmonary arterial and venous engorgement. Two-dimensional and Doppler echocardiography provide an accurate noninvasive assessment of the anatomy and physiology in most patients. Hemodynamic study also allows delineation of the site and extent of aortic obstruction and detection of associated cardiac malformations. Most infants with early-onset severe heart failure respond poorly to medical management, and balloon angioplasty, surgical excision of the coarctation, or a subclavian flap angioplasty often is required. We prefer an operation consisting of excision of the area of coarctation and extended end-to-end repair or end-to-side anastomosis with absorbable sutures to allow remodeling of the aorta with time.[233]

Aortic obstruction may develop slowly in infants in whom the posterolateral aortic shelf is not prominent at birth and in whom ductus arteriosus constriction is gradual. In these babies, compensatory myocardial hypertrophy and an extensive collateral circulation have time to develop. If the obstruction does not intensify and cardiac failure does not occur by age 6 or 9 months, circulatory compensation is likely until adult life.

CHILDREN.

Most children with isolated juxtaductal coarctation are asymptomatic. Complaints of headache, cold extremities, and claudication with exercise may be noted, although attention usually is directed to the cardiovascular system by detection of a heart murmur of upper extremity hypertension on routine physical examination. Mechanical factors rather than those of renal origin play the primary role in the production of hypertension. Absent, markedly diminished, or delayed pulsations in the femoral arteries and a low or unobtainable arterial pressure in the lower extremities with hypertension in the arms are the basic clues to the diagnosis. A midsystolic murmur over the anterior chest, back, and spinous processes is most frequent, becoming continuous if the lumen is sufficiently narrowed to result in a high-velocity jet across the lesion throughout the cardiac cycle. Additional systolic and continuous murmurs over the lateral thoracic wall may reflect increased flow through dilated and tortuous collateral vessels.

ECG reveals left ventricular hypertrophy of various degrees, depending on the height of arterial pressure above the obstruction and the patient's age. Combined with right ventricular hypertrophy, this usually implies a complicated lesion. *Chest roentgenograms* (see Chaps. 8 and 44) can show a dilated left subclavian artery high on the left mediastinal border and a dilated ascending aorta. Indentation of the aorta at the site of coarctation and prestenotic and poststenotic dilatation (the "3" sign) along the left premediastinal shadow is almost pathognomonic. Poststenotic dilation also may be detected by indentation of the barium-filled esophagus. Notching of the ribs, an important radiographic sign, is due to erosion by dilated collateral vessels, increases with age, and usually becomes apparent between the 4th and 12th years of life. The aortic coarctation may be visualized directly by two-dimensional echocardiography from high parasternal or suprasternal notch views with short focused transducers and from the subxiphoid window with extended focal range transducers (Fig. 43-28) . Doppler examination reveals a flow disturbance and high-velocity jet at the site of obstruction and provides a reasonable estimate of the transcoarctation pressure gradient.[234] [235] CT, magnetic resonance imaging[235] [236] (Fig. 43-29 and Chap. 10), or cardiac catheterization and aortography (see Fig. 44-7 , p. 1601) also accurately localizes the site of

Figure 43-28 Aortic coarctation (Coarc) is visualized from the suprasternal notch. The aorta (Ao) can be traced from the ascending aorta (AAo). The aortic arch is somewhat narrowed, and the relationship of the left subclavian artery (LS) to the coarctation is identified clearly. LA = left atrium; PA = pulmonary artery; IA = innominate artery; LC = left carotid artery.

obstruction, determines the length of coarctation, and, particularly, identifies associated malformations. Preoperative catheterization is avoided for selected patients with typical clinical and two-dimensional and Doppler echocardiographic findings.[237] Intravascular ultrasonography provides interesting morphological images suitable especially for comparison with postoperative status.[238]

MANAGEMENT.

Controversy exists about the role of balloon angioplasty (see Chap. 38), with or without balloon-expandable stents, in the treatment of native coarctation, especially in neonates.[239] [240] [241] [241A] There is concern about residual pressure gradients, aneurysm formation, aortic dissection and rupture, and femoral arterial complications, especially late after angioplasty. It is clear that angioplasty can effectively reduce obstruction in many patients, albeit with an unpredictable late outcome.

An extended end-to-end anastomosis with resection of the aortic isthmus and ductal

tissue yields a low mortality and a low rate of recoarctation. It is now the procedure of

Figure 43-29 Three-dimensional computer reconstruction of magnetic resonance images in a child with discrete coarctation and numerous large collateral vessels, displayed in a lateral projection. Dilated brachiocephalic and internal mammary arteries are evident. *(Courtesy of Dr. W. James Parks, The Children's Heart Center, Emory University, Atlanta, GA.)*

choice at many centers.[242] Subclavian flap aortoplasty, particularly in neonates and infants, or surgical resection and end-to-end anastomosis of uncomplicated juxtaductal coarctation of the aorta can be accomplished with excellent results in most patients[243] ; some surgeons prefer an onlay patch across the site of obstruction. In children who are asymptomatic, it is preferable to delay surgery until age 4 to 6 years, at which time coarctation seldom recurs. Paradoxical hypertension of short duration often is noted in the immediate postoperative period, a phenomenon much less common after balloon angioplasty.[244] [245] [246] [247] A resetting of carotid baroreceptors and increased catecholamine secretion appears to be responsible for the initial phase of postoperative systemic hypertension, with a later, second phase of prolonged elevation of systolic and particularly diastolic blood pressure related to activation of the renin-angiotensin system. A necrotizing panarteritis of the small vessels of the gastrointestinal tract of uncertain cause occasionally complicates the course of recovery.

The risk of recurrent narrowing after repair of coarctation in infancy is 5 to 10 percent. Such narrowing is best detected by magnetic resonance imaging or Doppler ultrasonography.[235] This problem is treated most effectively by transcutaneous balloon angioplasty,[248] [248A] [249] which may be expected to markedly reduce but not entirely abolish the pressure differences across the site of recoarctation.

In those patients who survive the first 2 years of life, complications of juxtaductal coarctation are uncommon before the second or third decade. The chief hazards to patients with coarctation result from severe hypertension and include the development of cerebral aneurysms and hemorrhage, hypertensive encephalopathy, rupture of the aorta, left ventricular failure, and infective endocarditis. Systemic hypertension in the absence of residual coarctation has been observed in resting or exercise-stressed patients postoperatively and appears to be related to the duration of preoperative hypertension.[250] Lifelong observation is desirable because of the late onset of hypertension in some postoperative patients.[251]

Hypoplasia of the Aortic Arch

MORPHOLOGY.

The aortic isthmus, the portion of the aorta between the left subclavian artery and the ductus arteriosus, normally is narrowed in the fetus and newborn. The lumen of the aortic isthmus is about two-thirds that of the ascending and descending portions of the aorta until age 6 to 9 months, when the physiological narrowing disappears.[252] Pathological tubular hypoplasia of the aortic arch usually is noted in the aortic isthmus

and often is referred to as preductal or infantile coarctation of the aorta.[253] Associated major cardiac malformations occur in virtually all such infants and include large VSD, AV septal defect, transposition of the great arteries, the Taussig-Bing type of anomaly, and double-outlet right ventricle. The VSD most often is subpulmonary, lying within the substance of the infundibular septum. Thus, muscle persists between the aortic and pulmonary valve leaflets, and when it is displaced leftward, it produces subaortic stenosis. Persistent patency of the ductus arteriosus commonly coexists, and right-to-left flow across the ductus arteriosus usually provides filling of the descending aorta. The adequacy of blood flow to the lower body depends on the degree of aortic hypoplasia, the caliber of the ductus arteriosus, and the relationship between pulmonary and systemic vascular resistance. Substantial right-to-left shunting through a wide-open ductus arteriosus minimizes the arterial blood pressure difference between the upper and lower body.

CLINICAL FINDINGS.

Differential cyanosis of the toes and feet with normal color of the fingers and hands may be difficult to discern because intracardiac left-to-right shunting and pulmonary edema attenuate the differences in oxygen saturation in the ascending and descending aorta. Clinical deterioration is associated with ductal constriction or a decline in pulmonary vascular resistance. Moreover, the clinical presentation often is dictated by the hemodynamic effects of complex associated intracardiac malformations. Infants most often present with findings of a large left-to-right intracardiac shunt, pulmonary hypertension, and marked cardiac decompensation. Although tubular hypoplasia is detectable by two-dimensional echocardiography, cardiac catheterization may be required to evaluate the full extent of intracardiac and extracardiac lesions. Surgical repair of aortic

Figure 43-30 An extended repair of aortic coarctation is used in the presence of a hypoplastic aortic arch. The broken lines in the *left panel* delineate resection sites of the coarcted segment. In the *right panel,* the ductus arteriosus has been ligated and the incisions are extended to the undersurface of the aortic arch and onto the distal aorta. When the suture line is completed, the reconstruction of the arch is generally excellent. *(From Stark J, deLaval M: Surgery for Congenital Heart Defects. 2nd ed. Philadelphia, WB Saunders, 1994, p 292.)*

arch hypoplasia usually must be accompanied by operative palliation or correction of associated intracardiac lesions. An extended end-to-end anastomosis (Fig. 43-30) , classic or reversed subclavian flap angioplasty, patch aortography, and bypass grafting are among the operative approaches to correct long segment narrowing.[247] Recoarctation is common and often necessitates transcatheter balloon aortoplasty and/or a second operation later in life to relieve anastomotic stenosis.[247] [248]

AORTIC ARCH INTERRUPTION.

Aortic arch interruption is a rare and usually lethal anomaly; unless treated surgically, almost all infants die within the first month of life.[254] Interruptions distal to the left subclavian artery (type A) occur with almost equal frequency to interruptions distal to the left common carotid artery (type B); interruptions distal to the innominate artery (type C) are extremely uncommon. The right subclavian artery often is of variable origin, frequently arising from the descending aortic segment distal to the interruption. The clinical presentation resembles that in tubular hypoplasia or severe juxtaductal coarctation of the aorta with a patent ductus arteriosus.

Virtually all patients have associated intracardiac anomalies. A patent ductus arteriosus almost always connects the main pulmonary artery with the descending aorta. With rare exceptions, patients with interrupted aortic arch have either a VSD (80 to 90 percent of cases) or an aorticopulmonary window (10 to 20 percent). Because the ductus arteriosus provides lower body blood flow, its spontaneous constriction results in profound clinical deterioration. The latter may be temporarily ameliorated by prostaglandin E_1 infusion. The VSD most often is subpulmonary, lying within the substance of the infundibular septum. Thus, muscle persists between the aortic and pulmonary valve leaflets; when the muscle is displaced leftward, it produces subaortic stenosis.[255] Other complex intracardiac malformations, such as transposition of the great arteries, aortopulmonary window, and truncus arteriosus, are common.

CLINICAL FEATURES.

An association is frequent with the genetic 22q11 deletion of DiGeorge's syndrome, a constellation of cardiac, parathyroid, thymic, and facial anomalies attributed to disruption of the interaction of premigratory neural crest cells with endodermal pharyngeal pouch cells. In this syndrome, thymic hypoplasia or aplasia is accompanied by immunological and hypocalcemia problems.[256] [257] The major clinical problem is severe congestive heart failure as a consequence of volume overload of the left ventricle resulting from an associated intracardiac left-to-right shunt and of pressure overload imposed by systemic hypertension.

Management.

The perioperative clinical condition of most patients can be improved by intensive medical management with mechanical ventilation, inotropic support, and prostaglandin infusion. Various forms of palliative operative techniques have fair to poor results. There has been increasing success with complete primary repair in infancy as the procedure of choice.[258] Greater mortality is associated when a two-stage approach with initial arch repair and pulmonary artery banding is followed by later repair of the intracardiac lesion. Recurrent narrowing at the aortic suture line can be treated by balloon angioplasty or reoperation.

Congenital Valvular Aortic Stenosis (See also p. 1599)

MORPHOLOGY.

Congenital valvular aortic stenosis is a relatively common anomaly, estimated to occur in 3 to 6 percent of patients with congenital cardiovascular defects. However, it must be appreciated that the true incidence of the malformation is probably grossly underestimated because the congenital bicuspid aortic valve may be undetected in early life and becomes stenotic and of clinical significance only in adult life, at a time when it may be indistinguishable from the acquired forms of aortic stenosis. Congenital valvular aortic stenosis occurs much more frequently in males than in females, with the gender ratio approximating 4:1. Associated cardiovascular anomalies have been noted in as many as 20 percent of patients.[259] Patent ductus arteriosus and coarctation of the aorta occur most frequently with valvular aortic stenosis; all three of these lesions may coexist (see also Chap. 44).

The basic malformation consists of thickening of valve tissue with various degrees of commissural fusion. The valve most commonly is the bicuspid, with a single fused commissure and an eccentrically place orifice. A third commissure, incomplete or rudimentary, is sometimes apparent. Less commonly, the valve has three fused cusps with a stenotic central orifice. In some patients, the stenotic aortic valve is unicuspid and dome shaped, with no or one lateral attachment to the aorta at the level of the orifice. In infants and young children with severe aortic stenosis, the aortic valve ring may be relatively underdeveloped. This lesion forms a continuum with the hypoplastic left heart syndrome and the aortic atresia and hypoplasia complexes. Secondary calcification of the valve is extremely rare in childhood, but the dynamics of blood flow associated with the congenitally deformed aortic valve ultimately lead to thickening of the cusps and calcification in adult life. When the obstruction is hemodynamically significant, concentric hypertrophy of the left ventricular wall and dilatation of the ascending aorta occur.

HEMODYNAMICS (see also Chaps. 11 and 46).

The hemodynamic abnormalities produced by obstruction to left ventricular outflow are discussed in Chapter 46 . A peak systolic gradient exceeding 75 mm Hg in association with a normal cardiac output or an effective aortic orifice less than 0.5 cm^2 /m body surface area is considered to reflect critical or severe obstruction to left ventricular outflow.[259] The normal outflow orifice approximates 2.0 cm^2 /m body surface area; areas of 0.5 to 0.8 cm^2 /m^2 signify moderate obstruction; when the area is larger than 0.8 cm^2 /m^2 , the obstruction is considered to be mild.

The resting cardiac output and stroke volume usually are within normal limits. During exercise, most children with critical stenosis show an elevation of the cardiac output and an associated elevation in the transvalvular pressure gradient.[260] When left ventricular failure occurs, cardiac output decreases and left atrial, left ventricular end-diastolic, and

pulmonary vascular pressures increase.

Studies of left ventricular performance in children with aortic stenosis often reveal supernormal pump function, as

indicated by increases in ejection fraction and circumferential fiber shortening.[261] Despite high left ventricular systolic pressures, left ventricular wall stress appears to be lower than normal throughout systole, presumably because increases in wall thickness provide overcompensation for the pressure overload. Undoubtedly, a spectrum exists, from well-compensated patients at one end, who have supernormal pump function and normal contractile function, to patients with heart failure at the opposite end, who have both impaired pump function and a reduced contractile state.

While pressure overload hypertrophy can preserve systolic function, it can also result in abnormal left ventricular early diastolic filling.[262] Thus, clinical studies seeking to analyze the determinants of left ventricular filling by a separate assessment of dynamic (elastic recoil, ventricular relaxation rate, and atrial driving pressure) and static (chamber stiffness and left ventricular hypertrophy) determinants suggest that diastolic function most importantly varies according to the severity of left ventricular hypertrophy and systolic function. Studies of children suggest that hypertrophy is a more important factor than excessive wall stress and depressed ejection performance in accounting for abnormal diastolic filling.

The blood supply to the myocardium may be significantly compromised in infants and children with aortic stenosis, despite normal patency of the coronary arteries.[263] Coronary blood flow and arterial oxygen content are critical determinants of oxygen supply to the myocardium. Because intramyocardial compressive forces are greatest in the subendocardium, blood flow to that region of the left ventricle is entirely diastolic in the presence of elevated left ventricular systolic pressure. In patients with left ventricular outflow tract obstruction, coronary vasodilatation may give an inadequate response to an increase in the demands of the myocardium for oxygen at rest or with exercise. When subendocardial vessels are maximally dilated, the coronary artery driving pressure and the duration of diastole determine the magnitude of subendocardial flow. When the duration of systolic ejection lengthens across the stenotic orifice, diastole is shortened, especially at high heart rates. Moreover, a reduction occurs in coronary driving pressure if left ventricular end-diastolic pressure is high or if aortic diastolic pressure is low, e.g., with aortic regurgitation or heart failure. In patients with severe aortic stenosis, the redistribution of flow away from the subendocardium and the ischemia that results in that portion of ventricular muscle may be estimated by relating the diastolic pressure-time index (DPTI) (i.e., the area between the aortic and left ventricular pressures in diastole) to the systolic pressure-time index (SPTI) (a measure of myocardial oxygen demands). Inadequate subendocardial oxygen delivery has been shown to exist when the ratio [DPTI × arterial oxygen content/SPTI] falls below 10.[263]

NEONATES AND INFANTS

Reports exist of cardiac dysfunction and even nonimmunological fetal hydrops fetalis in association with severe aortic stenosis.[264] [265] [266] The hydrops can be the result of in utero left ventricular myocardial infarction or profound left ventricular systolic and diastolic dysfunction. Balloon dilation using coronary balloon catheters has been attempted via transabdominal echo-guided needle puncture of the fetal left ventricle. This approach is not established, and it is doubtful that it will become a management option.

Fortunately, isolated aortic valvular stenosis seldom causes symptoms in infancy.[267] This lesion, however, occasionally can be responsible for profound and intractable heart failure, even in fetal life. Despite normal coronary arterial anatomy, infarction of left ventricular papillary muscles may occur, resulting in an acquired form of mitral valvular regurgitation that intensifies the heart failure state. In addition, endocardial fibroelastosis may result from limited subendocardial oxygen delivery, and myocardial degeneration may be significant. Symptomatic infants with isolated valvular aortic stenosis are irritable, pale, and hypotensive and present with tachycardia, cardiomegaly, and pulmonary congestion manifested by dyspnea, tachypnea, subcostal retractions, and diffuse rales. Cyanosis may be observed secondary to pulmonary venous desaturation. The systolic murmur in infants often is atypical; it is best heard at the apex or along the lower left sternal border and may be confused with that caused by a VSD. In infants with heart failure, the murmur occasionally may be absent or extremely soft, becoming louder when myocardial contractility is improved with digitalis and other medical measures. Infants with heart failure frequently have a poor response to medical management.

The *ECG findings* may not be characteristic; left ventricular hypertrophy and/or strain as well as right atrial enlargement and right ventricular hypertrophy may be detected shortly after birth.[267] The latter signs of right heart involvement result from both pulmonary hypertension secondary to elevated left ventricular diastolic and left atrial pressures and from volume loading of the right ventricle caused by left-to-right shunting across the foramen ovale. Survival past the early neonatal period does not preclude subsequent difficulties, and clinical deterioration may recur with the onset of physiological anemia.

Management

Congenital aortic stenosis must be considered a medical emergency in a seriously ill newborn, and echocardiography, and sometimes cardiac catheterization and angiocardiography, may be indicated in the first 24 hours of life. Two-dimensional echocardiographic studies show a severe immobility of the aortic valve, with little or no systolic opening, poststenotic dilation of the aorta, left ventricular hypertrophy, right ventricular enlargement, and a severely disturbed Doppler-determined pattern of ascending aortic flow velocity. The echo-Doppler examination must also identify associated intracardiac and extracardiac anomalies, one of the most important of which

is severe aortic arch obstruction.

Dilation of the ductus arteriosus with prostaglandin E_1 infusion may provide transitional support of the systemic circulation. In many centers, expeditious balloon aortic valvuloplasty follows the echo-Doppler examination in infants who are unstable and markedly symptomatic.[268] [269] [270] [271] [272] A number of approaches have been reported for performing this procedure, including the use of a carotid artery cutdown, which thus far does not appear to result in any abnormalities of the carotid pulse or any neurological sequelae. A transumbilical technique of balloon valvuloplasty can be performed quickly, safely, and effectively with preservation of the femoral artery. Because of a high risk of iliofemoral artery complications in infants with the transfemoral route to valvuloplasty, when this route is used it is advisable to use double-balloon techniques to allow insertion of small valvuloplasty catheters. The complications of balloon valvuloplasty are related to the small size and young age of the patient. Accordingly, if arterial access is a problem, and in infants younger than 1 month, surgical valvotomy remains a satisfactory option. Open repair under direct vision is the preferred type of operation.

Hemodynamic findings in neonates and infants frequently include left-to-right shunting at the atrial level, elevated left atrial and left ventricular end-diastolic pressures, and a small pressure drop across the aortic valve as a result of markedly reduced cardiac output. Right-to-left shunting across a patent ductus arteriosus is encountered occasionally. The lesion may be distinguished from the hypoplastic left heart syndrome echocardiographically and angiographically by the presence of normal or enlarged left ventricular cavity and normal or dilated ascending aorta.[273] [274] Establishment of the diagnosis and prompt catheter valvuloplasty or surgical valvotomy are justified because prolonged periods of stabilization are uncommon with medical therapy. Poor myocardial performance resulting from endocardial fibroelastosis, subendocardial ischemia, reduced left ventricular compliance, and inadequate relief of obstruction with or without aortic insufficiency are some of the factors accounting for high mortality and morbidity after catheter-directed treatment or operation.

At the extreme end of the spectrum of critical valvar aortic stenosis in newborns are patients with many small left-sided structures; in these patients, the adverse effects of small inflow, outflow, and/or cavity size of the left ventricle appear to be cumulative.[274] It is in this group that traditional treatment by aortic valvuloplasty or valvotomy, which is a two-sided ventricle repair, may be less effective than a multistaged Norwood approach.[274] The latter consists of an initial single-ventricle repair in which the main pulmonary artery is anastomosed to the aorta with creation of a systemic-to-pulmonary arterial shunt, followed later by a Fontan-type operation that creates an atriopulmonary connection, with or without a prior superior cava-pulmonary connection. The single-ventricle repair results in functional sacrifice of the left ventricle and the right ventricle supporting the systemic circulation without a pulmonary ventricle.

CHILDREN

Congenital aortic stenosis may be responsible for severe obstruction to left ventricular outflow in the absence of clinical symptoms of diminished cardiac reserve that are so frequent in other forms of congenital heart disease.[275] Most children with congenital aortic stenosis grow and develop normally and are asymptomatic. Attention usually is called to these children when a murmur is detected on routine examination. When symptoms occur, those noted most commonly are undue fatigue, exertional dyspnea, angina pectoris, and syncope. Less often described are abdominal pain, profuse sweating, and epistaxis. A symptomatic child usually has critical stenosis. There is a distinct threat of sudden death in patients with severe obstruction[276] (see Chap. 26). Although the precise cause is poorly understood, ventricular arrhythmias, perhaps initiated by acute myocardial ischemia, are probably the most common inciting event. It has been speculated that an abrupt rise in intracavity left ventricular systolic pressure elicits a reflex hypotensive syncope that promotes acute ischemia and ventricular fibrillation. Bacterial endocarditis occurs in about 4 percent of patients with congenital valvular aortic stenosis.[277]

DIAGNOSIS

Physical Findings.

When the magnitude of obstruction is significant, a left ventricular lift usually is palpable, and a precordial systolic thrill often is palpated over the base of the heart with transmission to the jugular notch and along the carotid arteries; presystolic expansion often is palpable. The obstruction usually is mild if neither a left ventricular lift nor a thrill is present.

Opening of the aortic valve produces a systolic aortic ejection sound that typically is present at the cardiac apex when the valve is mobile, particularly in patients with mild to moderate stenosis. A delay in closure of the stenotic aortic valve leads to a single or a closely split second heart sound, and paradoxical splitting may be present. A fourth heart sound normally is associated with severe obstruction. A loud, harsh, rhomboid-shaped systolic murmur starts after completion of left ventricular isometric contraction and is best heard at the base of the heart. The murmur, like the thrill, radiates to the suprasternal notch and carotid vessel as well as to the apex. An early diastolic blowing murmur of aortic regurgitation is present in some patients, but unless the valve leaflets have been eroded by bacterial endocarditis, the regurgitation usually is not hemodynamically significant; uncommonly, in patients with a congenitally bicuspid valve, aortic regurgitation may be severe and may predominate.

Electrocardiography.

ECG signs of left ventricular hypertrophy tend to vary with the severity of obstruction, although a normal or near-normal ECG does not preclude severe aortic stenosis, and excessive left ventricular voltages may be observed in children with mild obstruction.[275]

The lack of close correlation between the ECG and the transvalvular pressure gradient emphasizes the potential hazard of relying on the ECG in patient care. The most reliable index of the severity of obstruction is the presence of a left ventricular "strain pattern," consisting of left ventricular hypertrophy combined with ST segment depressions and T wave inversion in the left precordial leads (Fig. 43-31) .

Roentgenography.

Overall heart size is normal or the degree of enlargement is slight in most children with congenital valvular aortic stenosis. Concentric left ventricular hypertrophy accompanies moderate or severe obstruction and is manifested by rounding of the cardiac apex in the frontal projection and posterior displacement in the lateral view.

Echocardiography.

Two-dimensional and Doppler echocardiography are the current methods of choice for defining the anatomy and the hemodynamic severity of valvular aortic stenosis.[278] [279] Real-time cross-sectional echocardiography reveals impaired mobility of cusp tissue, an alteration in the phasic movement of the aortic valve with reduced lateral and increased superior excursions of valve echoes, and an increase in the internal aortic root dimension beyond the level of the valve annulus.[259] Imaging of the valve must be performed many times in order to display the

Figure 43-31 Electrocardiogram in congenital aortic stenosis. This tracing shows left ventricular hypertrophy and the typical left ventricular "strain" pattern (V_6). *(Courtesy of Dr. Delores A. Danilowicz.)*

valve through the long axis of the left ventricular outflow tract and then through a plane parallel to the valve annulus. The long-axis view of the left ventricular outflow tract allows evaluation of the valve mobility and cusp separation; it is the best view for demonstrating doming of the aortic valve. The parasternal short-axis view bisects the face of the valve, demonstrating the anatomy of the commissures (Fig. 43-32) .

The echocardiogram also reveals associated left ventricular hypertrophy and the presence of endocardial fibroelastosis (seen as bright endocardial echoes). Further, measurements of mitral valve diameter, left ventricular enddiastolic dimension, and left ventricular cross-sectional area serve to distinguish those infants with critical aortic stenosis from those with a hypoplastic left ventricle.[274] Among these calculations suggesting the latter are an end-diastolic volume less than 20 ml/m^2 , an inflow dimension of 25 mm, a narrow ventricular aortic junction less than 5 mm, or a small mitral orifice less than 9 mm. Pulsed-wave Doppler echocardiography allows inspection of the pattern of flow velocity within the circulation. This technique detects the altered and disturbed turbulence of flow in patients with aortic stenosis. A highly accurate noninvasive approach to quantifying the severity of obstruction combines continuous-wave Doppler flow analysis with the cross-sectional echocardiographic determination of the area of the orifice.[280] A simplified Bernoulli equation uses the

measurement of the maximum velocity of the aortic jet and time-averaged pressure drop obtained from planimetry of the maximal velocity spectral reading. A simpler estimate of the transvalvular gradient (in mm Hg) may be calculated as four times the square of the peak Doppler velocity (m/sec).

The Doppler method records a peak instantaneous pressure difference, which may differ importantly from the gradient recorded by a cardiac catheter, which is a peak-to-peak pressure difference.[281] Doppler mean gradient is more

Figure 43-32 Standard short-axis view of aortic cusps in the closed position in a patient with a bicuspid aortic valve. *Left frame,* The right (R) and noncoronary (NC) left (L) cusps are seen within the aortic root. The arrows indicate the points of adherence of the cusps to the aortic wall. The right ventricle (RV) is seen anteriorly; the right atrium (RA), and left atrium (LA) are seen posteriorly. *Middle frame,* Same patient, with open valve leaflets in systole, shows fusion between the right and left coronary cusps. The fused raphe (arrow) between these cusps is typical of a bicuspid aortic valve. *Right frame,* Taken in systole from another patient with a bicuspid aortic valve, this frame demonstrates similar features but with a fused raphe (arrow) between the right and noncoronary cusps.

accurate than the instantaneous gradient when compared with the pressures found at cardiac catheterization. Management decisions often depend on estimation of the severity of obstruction, and all pressure gradient estimations depend on flow velocity across the valve, which may be confounded by low cardiac output or concomitant valvar regurgitation. Thus, an important argument can be made that the determination of the stenotic valve systolic area is often more important than calculation of a systolic gradient.[279] [280] [281]

The most widely accepted technique for correcting the gradient for flow is to use the continuity equation, which measures the flow velocity ratio across the aortic valve and therefore corrects for high and low flow rates. The continuity equation presumes that for flow in a series, the product of mean velocity and cross-sectional area is constant at all points in the flow circuit. In patients with aortic stenosis, the area of the left ventricular outflow tract is determined by two-dimensional echocardiography, the flow velocity of the outflow tract by pulsed-wave Doppler, and the flow velocity immediately above the valve by continuous-wave Doppler, all of which, taken together, allow determination of the valve area by the continuity equation: Aortic valve area: [(area)LVOT × V(LVOT)]/(V)AV (obtained by converting the diameter to area and assuming that it is circular); (V)LVOT = peak outflow tract velocity, and (V)AV = peak velocity across the aortic valve.

Transesophageal two-dimensional echocardiographic determination of aortic valve area has been applied in adults with aortic stenosis.[282] The approach offers considerably better resolution of cardiac anatomy than does conventional transthoracic two-dimensional echocardiography and may also prove to be more accurate in estimating pressure gradients and aortic valve areas. The approach is applicable to

older children but has not yet been reported in young children in sufficient detail to make specific recommendations.

Diagnostic Cardiac Catheterization

Cardiac catheterization is now rarely used to establish the site and severity of obstruction to left ventricular outflow because the malformation is readily diagnosed and the evaluation of the intensity of stenosis is accurate by echo-Doppler examination.[283] Instead, catheterization is undertaken when therapeutic interventional transcatheter balloon aortic valvuloplasty is indicated.

During the catheterization procedure, cardiac output is measured by the indicator-dilution, thermodilution, or Fick technique. Retrograde left heart catheterization allows withdrawal pressure recordings across the site of stenosis, and left ventricular angiocardiography can be carried out, permitting an evaluation of the size of the left ventricular cavity, the thickness of the wall, the competence of the mitral valve, the patency of the coronary arteries, and the diameter of the aortic root and ascending aorta. If aortic insufficiency is thought to be present, cineaortography is performed with injection of contrast material into the aortic root. The severity of aortic insufficiency can be assessed qualitatively by cineaortography and quantitatively by ventriculography, with calculation of regurgitant volume by subtraction of net forward flow (calculated by the Fick method) from angiographically determined total forward flow. The typical angiocardiographic features of valvar stenosis are thickening of the aortic cusps, poststenotic dilation of the ascending aorta, and, occasionally, a jet of contrast material entering the ascending aorta through a central or eccentric narrowed valve orifice (Fig. 43-33) . The leaflets of the bicuspid valve are domed in systole, and a central jet corresponds to the orifice of the stenotic valve. In contrast, the stenotic orifice of the unicommissural valve can be visualized by the systolic jet in contact with the posterior wall of the aorta, with leaflet tissue and valve motion seen only anteriorly.[259]

Balloon Valvuloplasty.

Balloon dilatation may be indicated in any infant or child who has a clinical diagnosis of aortic stenosis and in whom the clinical examination, roentgenogram, resting or exercise ECG, or Doppler echocardiogram suggests the possibility of severe obstruction.[284] Even in the absence of such findings, balloon valvuloplasty may be performed if symptoms that might be related to aortic stenosis exist, such as dizziness, fainting, or angina.

We prefer to catheterize the left side of the heart via a retrograde approach by femoral percutaneous puncture. The goals of the study are to analyze the severity of obstruction and assess the function of the left ventricle. In most centers, balloon valvuloplasty is recommended if the severity of the aortic stenosis would otherwise require surgical treatment--that is, a peak systolic pressure gradient exceeding 70 mm Hg measured in the basal state or a calculated effective orifice less than 0.5 cm^2/m^2 of body surface area. In the

Figure 43-33 *A,* Left ventricular angiocardiogram obtained by the transseptal method in a patient with congenital valvular aortic stenosis. Ao = poststenotic dilatation of the aorta; LV = left ventricle. Arrow denotes the thickened valve cusp. *B,* Selective angiocardiogram in a patient with discrete subvalvular stenosis (bottom arrow). Associated mitral regurgitation is evident from the reflux of contrast material into an enlarged left atrium (LA). The aortic valve (top arrow) is normal, and the right coronary artery is visualized. *(From Friedman WF, Kirkpatrick SE: Congenital aortic stenosis. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al: Moss' Heart Disease in Infants, Children, and Adolescents. 4th ed. Baltimore, © Williams & Wilkins, 1989.)*

presence of symptoms or left ventricular strain pattern on the ECG or an abnormal exercise ECG, there is less rigid regard to the hemodynamic assessment of the severity of stenosis. Further, some centers go forward with balloon valvuloplasty with peak systolic gradients greater than or equal to 50 mm Hg. There is general agreement that there be no significant aortic regurgitation (less than grade 2 of 4) and that other associated cardiac anomalies be absent, except aortic coarctation.

Balloon dilatation of the aortic valve began in the mid-1980s; truly long-term follow-up studies are not yet available. Early studies and our experience suggest that the diameter of the balloon should not exceed that of the aortic valve ring. Most centers prefer a balloon with a diameter 80 to 100 percent that of the aortic annulus or at least 1 mm smaller than it. The expected hemodynamic result is a reduction in the catheterization-measured peak-to-peak ejection gradient of about 60 to 70 percent. The appearance of aortic regurgitation or its progression is the major complication of valvuloplasty, although the aortic regurgitation is mild in the great majority of patients.[284] Significant aortic regurgitation appears to accompany the development of aortic valve prolapse, which is likely due to tearing of the valve cusp or its raphe or partial detachment of the valve from the valve ring, all of which undermine the support mechanism of the valve. In those patients whose balloon valvuloplasty has resulted in very significant aortic regurgitation, valve surgery may be required to either replace the valve or repair a tear in the valve. Other complications from balloon aortic valvuloplasty include bleeding, arrhythmias, cerebral vascular accidents, iliofemoral arterial complications, injury to the mitral valve, and, rarely beyond infancy, death.[284]

Natural History.

Congenital aortic stenosis frequently is a progressive disorder, even early in life, in a significant fraction of patients presenting initially with mild obstruction.[285] [286] [287] Thus, clinical deterioration may be anticipated because of an intensification in the severity of stenosis rather than the development of significant aortic regurgitation. Progression of obstruction usually is the result of the increase in cardiac output that occurs concurrently with increased body growth. Less often, a decrease in the area of the orifice is an added factor in the intensification of obstruction. The onset of symptoms or changes in the phonocardiogram or graphic pulse tracings, chest roentgenograms, ECGs, or vectorcardiograms cannot be depended on to indicate progressive obstruction in the

individual patient; Doppler echocardiography is most reliable.

MANAGEMENT.

A malformed aortic valve is a potential site of bacterial infection; antibiotic prophylaxis is recommended for all patients, regardless of the severity of obstruction. Strict avoidance of strenuous physical activity is advised if severe aortic stenosis is present. Participation in competitive sports also should probably be restricted in patients with milder degrees of obstruction. Digitalis should be administered to patients who have symptoms of diminished cardiac reserve and also should be considered for patients with left ventricular hypertrophy, even if they are not in heart failure.

Surgery.

Percutaneous balloon aortic valvuloplasty is a useful palliation to delay open valvulotomy, the Ross procedure (see below), or valve replacement. For those patients in whom balloon valvuloplasty is unsuccessful, operation is carried out under direct vision after institution of cardiopulmonary bypass, and the fused commissures are opened. When this is done precisely and judiciously, the commissural incision enlarges the valve orifice and does not result in significant aortic regurgitation.[288] When operation is performed in childhood, a mortality rate of less than 2 percent can be expected.[289] Among the factors influencing the indications, techniques, and results of operation are the patient's age, the nature of the valvar deformity, and the experience of the surgical team.

Long-term follow-up studies indicate that aortic valvotomy is a safe and effective means of palliative treatment with excellent relief of symptoms.[289] [290] Aortic insufficiency can occasionally be progressive and require valve replacement. Moreover, after commissurotomy, the valve leaflets remain somewhat deformed, and it is likely that further degenerative changes, including calcification, will lead to significant stenosis in later years.[259] Thus, prosthetic valve replacement is required in approximately 35 percent of patients within 15 to 20 years of the original operation. Because the valve is not rendered normal, antibiotic prophylaxis is indicated in postoperative patients, even if the systolic pressure gradient has been abolished. For those patients eventually requiring aortic valve replacement, the surgical options include replacement with a prosthetic aortic valve, an aortic homograft, or a pulmonary autograft in the aortic position. Accumulating evidence shows that the pulmonary autograft may ultimately be preferable to the aortic homograft for aortic reconstruction, and many surgeons

prefer the procedure to palliative surgical valvotomy as the initial operation of choice. In the pulmonary autograft, called the Ross procedure, the patient's pulmonary valve is removed and used to replace the diseased aortic valve, and the right ventricular outflow tract is reconstructed with a pulmnary valve allograft.[291] [292] [293] [294] We consider it likely that the Ross procedure will emerge as the approach of choice in the future. Neither

homografts nor autografts require anticoagulation. There is a finite incidence of valve degeneration of approximately 2 percent per patient per year with the former, whereas primary tissue failure has not been observed among pulmonary autografts.

Discrete Subaortic Stenosis (See also p. 1599)

This malformation accounts for 8 to 10 percent of all cases of congenital aortic stenosis and occurs twice as frequently in males as in females. The lesion consists of a membranous diaphragm or fibrous ring encircling the left ventricular outflow tract or a long fibromuscular narrowing just beneath the base of the aortic valve. Subaortic stenosis is rarely diagnosed in infancy, when it is usually the result of a malalignment VSD with deviation posteriorly of the outlet septum into the left ventricular outflow tract, often associated with coarctation of the aorta or interruption of the aortic arch.

Distinction of subvalvular from valvular aortic stenosis is extremely difficult by means of clinical findings alone.[259] Rarely, a systolic ejection sound is heard, and the diastolic murmur of aortic regurgitation is more common than it is in valvular aortic stenosis. Dilatation of the ascending aorta is common, but valvular calcification is not observed.

Echocardiography is useful in differentiating between valvular and subvalvular stenosis (see Chap. 7).[295] The criterion for diagnosis of the latter is demonstration of a localized subvalvar discrete ridge or long segment narrowing in the left ventricular outflow tract. Further, because of the possibility of recurrence of subvalvular aortic stenosis, careful postoperative follow-up echocardiography is required. Two-dimensional echocardiographic studies from the apical two-chamber and left parasternal and subxiphoid long-axis views demonstrate persistent, prominent echoes in the subaortic left ventricle in both systole and diastole (Fig. 43-34) . Doppler sampling proximal to the aortic valve shows increased flow velocity.[295] Most important, echocardiography also can identify hypertrophic subaortic stenosis when it coexists with fixed subaortic stenosis and can differentiate between the two forms of obstruction.

Definitive distinction between valvular and subvalvular obstruction is also provided by transesophageal Doppler echocardiography[296] and by recording pressure tracings as a catheter is withdrawn across the outflow tract and valve, or by localizing the site of obstruction with selective left ventricular angiocardiography (see Fig. 43-33).

Mild degrees of aortic valvular regurgitation commonly are observed in patients with discrete subaortic stenosis and appear to be caused by thickening of the valve and impaired mobility of the cusps secondary to the trauma created by the high-velocity jet passing through the subaortic diaphragm. Further deformation of these abnormal valve cusps by the vegetations of bacterial endocarditis often results in severe aortic regurgitation.

MANAGEMENT.

Because of the likelihood of both progressive obstruction and aortic regurgitation, the presence of even mild or moderate subaortic stenosis warrants consideration of elective

operation.[297] [298] [299] Reports describe transluminal balloon dilation for discrete subaortic stenosis, but it is unlikely that this palliative approach will be an acceptable alternative, since the relief of obstruction is not

Figure 43-34 Parasternal long axis (P Lax.) view of membranous subaortic stenosis. The ventricular septum (SEPT), right ventricle (RV), left ventricle (LV), and left atrium (LA), as well as the aorta (AO), are seen. The arrows indicate the attachments of the subvalvar membrane to the septum anteriorly and to the mitral valve posteriorly.

likely to be as complete or as long as in those patients undergoing surgical resection.

The risks of operation in patients with discrete subaortic stenosis and valvular aortic stenosis are essentially the same. Surgical treatment of discrete subaortic stenosis has evolved from simply excising the membrane or fibrous ridge to adding a generous ventricular myotomy and myectomy to the membranectomy.[300] Operation may be expected to improve the hemodynamic state substantially; it frequently is totally curative.

Evidence indicates that muscle resection combined with membrane excision lowers the risk of reoperation for recurrent subaortic stenosis.[301] Discrete membranous subaortic stenosis may tend to recur after operation, although we and others consider these recurrences to be often related, at least in part, to incomplete removal of the lesion at initial operation. Intraoperative echocardiography has been used as an adjunct to operation to enable immediate assessment of the adequacy of relieving obstruction. Studies have suggested that abnormal flow patterns may predispose to pathological proliferation of subvalvar aortic tissue, which reinforces the requirement that careful echocardiographic and surgical exploration of the outflow tract, even well below the subvalvar stenosis, be undertaken to detect and resect structures that cause turbulence.[302] For patients with recurrent obstruction, operation may consist of repeat resection plus creation of an outlet VSD extending up to but not across the aortic valve. This iatrogenic VSD is patched on the right side to further enlarge the subaortic area. For patients in whom the aortic valve cannot be repaired, the Ross pulmonary valve autograft procedure is used.[303]

UNCOMMON FORMS OF SUBAORTIC STENOSIS

COMBINED VALVULAR AND SUBVALVULAR STENOSIS.

In some patients, valvular and subvalvular aortic stenosis coexist with hypoplasia of the aortic valve ring and thickened valve leaflets, producing a tunnel-like narrowing of the left ventricular outflow tract. Additional findings often include a small ascending aorta. The subvalvular fibrous process usually extends onto the aortic valve cusps and almost always makes contact with the ventricular aspect of the anterior mitral leaflet at its base. The presence of "tunnel stenosis" may be suspected echocardiographically or angiographically from the appearance of the outflow tract and the aortic root. Operative treatment often is complicated by the need for an aortoventriculoplasty, consisting of

prosthetic or homograft replacement of the aortic valve as well as enlarging the aortic annulus, proximal aorta, and left ventricular outlet tract (the Kono-Rastan operation). The *modified* Kono-Rastan operation preserves the native aortic valve if the annulus is normal or near normal. Alternatively, a conal enlargement technique may be used.[304] [305]

Various anatomical lesions other than a discrete membrane or ridge may produce subaortic stenosis.[306] [307] [308] Among these are abnormal adherence of the anterior leaflet of the mitral valve to the left septal surface, and the presence in the left ventricular outflow tract of accessory endocardial cushion tissue. In some patients with an AV canal, the part of the ventricular septum that contributes to the wall of the left ventricular outflow tract is deficient, and the ventricular aspect of the anterior leaflet of the common AV valve is adherent to the posterior edge of the deficient septum, resulting in a narrow left ventricular outflow tract. Malalignment of the conoventricular septum, resulting in an inferior VSD, produces a leftward superior deviation and insertion of the conal septum, obstructing left ventricular outflow. In patients with a single ventricle and an outflow chamber, the bulboventricular foramen serves as a potential site of aortic outflow obstruction. Additionally, rarer causes of subaortic stenosis include redundant dysplastic left AV valve tissue in patients with congenitally corrected transposition of the great arteries and anomalous muscle bundles of the left ventricular outflow tract.

MUSCULAR SUBAORTIC STENOSIS.

A muscular type of subaortic stenosis may result from a convergence of all the mitral chordae into one or two fused papillary muscles; a "parachute" deformity of the mitral valve is produced, and it is often seen in association with supravalvular stenosis of the left atrium and coarctation of the aorta. In some of these patients, discrete membranous subvalvular aortic obstruction also has been noted.

In patients with VSD, muscular subaortic stenosis has been shown to develop after surgical banding of the pulmonary artery, possibly as a result of hypertrophy of the conal septum or crista supraventricularis encroaching on the left ventricular outflow tract above the septal defect.

Subaortic muscular hypertrophy secondary to diffuse involvement of the myocardium by glycogen storage disease (Pompe's disease) is an extremely rare cause of obstruction to left ventricular outflow. A positive family history, symptoms of muscle weakness, heart failure in infancy, and the characteristic ECG findings of a short PR interval, high-voltage QRS and T waves, and left ventricular hypertrophy warrant skeletal muscle biopsy or fibroblast culture, permitting an antemortem diagnosis.

The last, relatively uncommon form of subaortic stenosis to be mentioned occurs infrequently in patients with congenitally corrected transposition of the great arteries; in

these patients, an anomalous muscle bundle in the subaortic area of the arterial ventricle obstructs outflow.

Supravalvular Aortic Stenosis

Supravalvular aortic stenosis is a congenital narrowing of the ascending aorta that may be localized or diffuse, originating at the superior margin of the sinuses of Valsalva just above the levels of the coronary arteries.

The clinical picture of supravalvular obstruction usually differs in major respects from that observed in the other forms of aortic stenosis. Chief among these differences is the association of supravalvular aortic stenosis with idiopathic infantile hypercalcemia, a disease that occurs in the first years of life and may be associated with deranged vitamin D metabolism.[309] [310] [310A] [311] [312]

It is helpful to classify patients according to their clinical presentation into nonfamilial, sporadic cases with normal facies and intelligence; autosomal dominant familial cases with normal facies and intelligence; and the Williams syndrome with abnormal facial appearance and mental retardation (Fig. 43-35) . In contrast to the other forms of aortic stenosis, no gender predilection is noted in any of these three categories.

WILLIAMS SYNDROME.

The designations supravalvular aortic stenosis syndrome or Williams syndrome or Williams-Beuren syndrome[310] [310A] have been applied to the distinctive picture produced by coexistence of the cardiac and multiple-system disorders. Beyond infancy in these patients, a challenge with vitamin D or calcium loading tests unmasks abnormalities in the regulation of circulating 25-hydroxyvitamin D. Unanimity of opinion about the exact relation between Williams syndrome and calcium metabolism does not exist[311] [312] .

Infants with Williams syndrome often exhibit feeding difficulties, failure to thrive, and gastrointestinal problems in the form of vomiting, constipation, and colic. The entire spectrum of clinical manifestations includes auditory hyperacusis, inguinal hernia, a hoarse voice, and a typical personality that is outgoing and engaging. Other manifestations of this syndrome include mental retardation, "eifin facies" (see Fig. 43-32), narrowing of peripheral systemic and pulmonary arteries, strabismus, and abnormalities of dental development consisting of microdontia, enamel hypoplasia, and malocclusion[312A] .

Many medical conditions can complicate the course of Williams syndrome,[312B] including systemic hypertension, gastrointestinal problems, and urinary tract abnormalities. Particularly in an older child or adult, progressive joint limitation and hypertonia may become a problem. Adult patients are usually handicapped by their developmental disabilities.

Williams syndrome was previously considered to be nonfamilial. Interestingly, a number of families in which parent-to-child transmission of Wllliams syndrome has occurred

have now been identified. These are not families with autosomal dominant supravalvular aortic stenosis whose members are normal in appearance and intelligence. All of these families show a parent and child to be affected with Williams syndrome, including one instance of male-to-male transmission. This supports autosomal dominant inheritance as the likely pattern, with most cases of Williams syndrome probably occurring as the result of a new mutation. New information indicates that a genetic defect for supravalvular aortic stenosis is located in the same chromosomal subunit as elastin on chromosome 7.[312B] [313] Elastin is an important component of the arterial wall, but precisely how mutations in elastin genes cause the phenotypes of supravalvular aortic stenosis is not known for certain. The various aspects of Williams syndrome may represent a contiguous gene deletion syndrome (see Chap. 56).

FAMILIAL AUTOSOMAL DOMINANT PRESENTATION.

Most commonly, supravalvular aortic stenosis is a feature of the distinctive Williams syndrome described earlier.[312A] [312B] However, the aortic anomaly and peripheral

Figure 43-35 Typical elfin facies in three patients with supravalvular aortic stenosis. *(From Friedman WF, Kirkpatrick SE: Congenital aortic stenosis. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al: [eds]: Moss' Heart Disease in Infants, Children, and Adolescents. 4th ed. Baltimore, © Williams & Wilkins, 1989.)*

pulmonary arterial stenosis are also found in familial and sporadic forms *unassociated* with the other features of the syndrome. Thus, affected patients have normal intelligence and are normal in facial appearance. Genetic studies suggest that when the anomaly is familial, it is transmitted as autosomal dominant with variable expression. Some family members may have peripheral pulmonary stenosis either as an isolated lesion or in combination with the supravalvular aortic anomaly.

Linkage analyses in two unrelated families with autosomal dominant supravalvular aortic stenosis were performed. Linkage was identified between the supravalvular aortic stenosis phenotype and polymorphic markers on the long arm of chromosome 7. These findings indicate that the gene for supravalvular aortic stenosis is located in the same chromosomal subunit as elastin. Further, a family has been identified as having autosomal dominant supravalvular aortic stenosis and a balanced translocation, which disrupts the elastin gene and cosegregates with the disease in this family, also supporting the hypothesis that mutations in the elastin gene may cause supravalvular aortic stenosis.[314] Hemizygosity at the elastin locus is likely responsible for the vascular pathology in Williams syndrome, although it is unlikely that elastin deletions account for all features of the syndrome. Because the deletions responsible for Williams syndrome extend well beyond the elastin locus, it is probable that the syndrome is a contiguous gene disorder.

MORPHOLOGY.

Three anatomical types of supravalvular aortic stenosis are recognized, although some patients may have findings of more than one type. Most common is the hourglass type, in which marked thickening and disorganization of the aortic media produce a constricting annular ridge at the superior margin of the sinuses of Valsalva. The membranous type is the result of a fibrous or fibromuscular semicircular diaphragm with a small central opening stretched across the lumen of the aorta. Uniform hypoplasia of the ascending aorta characterizes the hypoplastic type.[315]

Because the coronary arteries arise proximal to the site of outflow obstruction in supravalvular aortic stenosis, they are subjected to the elevated pressure that exists within the left ventricle. These vessels often are dilated and tortuous, and premature coronary arteriosclerosis has been observed. Moreover, if the free edges of some or all of the aortic cusps adhere to the site of supravalvular stenosis, coronary artery inflow may be reduced. The formation of thoracic aortic aneurysms has been described in several patients.

CLINICAL FEATURES.

Patients with Williams syndrome are mentally retarded and resemble one another in their facial features. The typical appearance is similar to that of the elfin facies observed in the severe form of idiopathic infantile hypercalcemia and is characterized by a high prominent forehead, stellate or lacy iris patterns, epicanthal folds, underdeveloped bridge of the nose and mandible, overhanging upper lip, strabismus, and anomalies of dentition (see Fig. 43-35). Recognition of this distinctive appearance, even in infancy, should alert the physician to the possibility of underlying multisystem disease. In addition, a positive family history in a patient with a normal appearance and clinical signs suggesting left ventricular outflow obstruction should lead to the suspicion of either supravalvular aortic stenosis or hypertrophic obstructive cardiomyopathy.

Patients with supravalvular aortic obstruction appear to be subject to the same risks of unexpected sudden death [in some of whom myocardial infarction has been found at autopsy[316]] and endocarditis as those with valvular aortic stenosis. Studies of the natural history of the principal vascular lesions in these patients[317] --supravalvular aortic stenosis and peripheral pulmonary artery stenosis--indicate that the aortic lesion is usually progressive, with an increase in the intensity of obstruction related often to poor growth of the ascending aorta. In contrast, the patients with pulmonary branch stenosis, whether or not associated with the aortic lesion, tend to show no change or a reduction in right ventricular pressure with time.

With few exceptions, the major *physical findings* resemble those observed in patients with valvular aortic stenosis. Among these exceptions are accentuation of aortic valve closure due to elevated pressure in the aorta proximal to the stenosis, an infrequent systolic ejection sound, and the especially prominent transmission of a thrill and murmur into the jugular notch and along the carotid vessels. Found uncommonly is an early

diastolic, decrescendo, blowing murmur of aortic regurgitation caused by the fusion of one or more cusps to the area of stenosis. The narrowing of the peripheral pulmonary arteries that often coexists in these patients frequently produces a late systolic or continuous murmur that may help to distinguish this anomaly from valvular aortic stenosis. This differentiation is reinforced by the frequent finding of a significant disparity between the arterial pressures in the upper extremities in supravalvular aortic stenosis; the systolic pressure in the right arm tends to be the higher than in the left and occasionally exceeds that in the femoral arteries. The disparity in pulses may relate to the tendency of a jet stream to adhere to a vessel wall (Coanda effect) and selective streaming of blood into the innominate artery.[318] [319]

ECG usually reveals left ventricular hypertrophy when obstruction is severe. Biventricular or even right ventricular hypertrophy may be found if significant narrowing of peripheral pulmonary arteries coexists. Radiographically, in contrast to valvular and discrete subvalvular aortic stenosis, poststenotic dilation of the ascending aorta seldom is seen. The sinuses of Valsalva usually are dilated, and the ascending aorta and aortic arch appear small or of normal size.

Echocardiography is the most valuable technique for localizing the site of obstruction to the supravalvular area (Fig. 43-36) . Most often the sinuses of Valsalva are dilated, and the ascending aorta and arch appear small or of normal size. A useful ratio can be constructed of the measurements of the aortic annulus and the sinotubular junction, in which the latter is always less than the former in patients with supravalvular stenosis, a finding not present in normal persons.[320] Intraluminal ultrasound imaging has also been used to visualize the vascular pathology in Williams syndrome.[321] Doppler examination and retrograde aortic catheterization can determine the degree of hemodynamic abnormality.[322]

Because of the nature of the anatomical defect, we do not think that transcatheter balloon angioplasty,[323] with or without stenting, is an effective treatment option. For several reasons, depending primarily on the anatomical variant of the lesion, supravalvular aortic stenosis may be less amenable to operative treatment than either valvular or discrete subvalvular stenosis. The lumen of the aorta at the supravalvular level may be widened by the insertion of an oval- or diamond-shaped fabric prosthesis or pericardial symmetric aortoplasty in those patients with a normal or near-normal ascending aorta. If the aorta is markedly hypoplastic, however, this operation merely displaces the pressure gradient distally without abolishing the obstruction.

Figure 43-36 Supravalvar aortic stenosis is seen in a parasternal long-axis view. The constriction is distal to the sinuses of Valsalva in the ascending aorta (AAO). RV = right ventricle; LV = left ventricle; LA = left atrium.

Under these circumstances, repair may require replacement or widening of the entire

hypoplastic aorta with an appropriate prosthesis.[324] [325] [326] [327]

Hypoplastic Left Heart Syndrome

This designation is used to describe a group of closely related cardiac anomalies characterized by underdevelopment of the left cardiac chambers, atresia or stenosis of the aortic and/or the mitral orifices, and hypoplasia of the aorta.[327] These anomalies are an especially common cause of heart failure in the first week of life. The left atrium and ventricle often exhibit *endocardial fibroelastosis.* Pulmonary venous blood traverses a patent foramen ovale, and a dilated and hypertrophied right ventricle acts as the systemic, as well as pulmonary, ventricle; the systemic circulation receives blood by way of a patent ductus arteriosus (Fig. 43-37) (Figure Not Available) .

The diagnosis should be considered in infants, particularly boys, with the sudden onset of heart failure, systemic hypoperfusion, and nonspecific murmur. *ECG* frequently reveals right-axis deviation, right atrial and ventricular enlargement, and ST and T wave abnormalities in the left precordial leads. Chest roentgenography may show only slight enlargement shortly after birth, but with clinical deterioration there are marked cardiomegaly and increased pulmonary venous and arterial vascular markings. The *echocardiographic* findings usually are diagnostic (Fig. 43-38) . The aortic root is usually diminutive, less than 4 to 5 mm in diameter at the level of the sinuses of Valsalva and narrowed farther above. The left ventricle is frequently absent or is a small slit with a diminutive mitral valve. The endocardium is often thickened, consistent with endocardial fibroelastosis or papillary muscle infarction, features usually more suggestive of aortic stenosis. Indeed, distinction from the latter is pivotal to determine if a biventricular, rather than a Fontan, approach is feasible. Ultrasound study also determines the extent of patency of the interatrial communication; substantial restriction is predictive of

Figure 43-37 (Figure Not Available) Hypoplastic left heart with aortic hypoplasia, aortic valve atresia, and a hypoplastic mitral valve and left ventricle. RA = right atrium; RV = right ventricle; RC = right coronary artery; PA = pulmonary artery; PV = pulmonary vein; LC = left coronary artery; LV = left ventricle; AD = anterior descending coronary artery. *(From Neufeld HN, Adams P Jr, Edwards JE, et al: Diagnosis of aortic atresia by retrograde aortography. Circulation 25:278, 1962.)*

severe pulmonary edema and death. *Retrograde aortography* shows hypoplasia of the ascending aorta.

MANAGEMENT.

Medical therapy directed at cardiac decompensation, hypoxemia, and metabolic acidemia seldom prolongs survival beyond the first days of life.[328] Constriction of the patent ductus arteriosus and limited flow

Figure 43-38 *Left,* Four-chamber view of hypoplastic left heart syndrome demonstrating the right ventricle (RV) anteriorly, considerably larger than the diminutive left ventricle (LV) seen posteriorly. A small mitral valve (MV) separates the left atrium (LA) from the left ventricle. The apex of the heart is formed by the right ventricle. *Right,* Parasternal long-axis view demonstrating the discrepant relative sizes

between the right ventricle and the left heart chambers. The aorta (AO) is diminutive and measures approximately 4 mm in diameter. The larger pulmonary valve plate is seen anteriorly. A small platelike mitral valve (MV, dashed arrow) is seen between the left atrium and left ventricle.

through a restrictive patent foramen ovale are the principal factors responsible for early death. Prostaglandin E_1 infusion is effective in maintaining ductal patency.

SURGICAL TREATMENT.

Many centers are attempting staged surgical management in an effort to provide long-term palliation.[329] [330] The first stage, often referred to as *Norwood procedure,* consists of creating an unobstructed communication between the right ventricle and aorta and enlargement of the ascending aorta. The right ventricular-aortic connection has been accomplished with homograft or prosthetic conduits from the right ventricle or pulmonary trunk to the descending aorta, or by direct connection between the proximal pulmonary trunk and ascending aorta, which also enlarges the ascending aorta. Pulmonary blood flow and pressure are controlled by a tubed interposition systemic-pulmonary shunt to the distal pulmonary artery. The patent ductus arteriosus is ligated. A large interatrial communication also must be ensured in stage 1 to allow free access of pulmonary venous blood to the tricuspid valve.

Most surgeons prefer to perform a stage 2 modified superior vena cava-pulmonary artery shunt (bidirectional Glenn operation) or a hemi-Fontan procedure as an intermediate step before a Fontan correction (stage 3). In some centers, the preferred operation is cardiac transplantation.[331] [332] Stenting of the ductus arteriosus can be used as an ambulatory bridge to transplantation.[333]

Congenital Aortic Regurgitation

Congenital aortic valve regurgitation is a rare isolated congenital cardiac lesion.[334] [345] Aortic regurgitation most often occurs in association with congenital valvular aortic stenosis in which the valve commissures are fused, inhibiting cusp mobility; subvalvular aortic stenosis in which the aortic ring is dilated and the valve cusps are deformed; coarctation of the aorta when the aortic ring is dilated and the aortic valve is bicuspid; VSD; and endocardial fibroelastosis. Aortic valve regurgitation may accompany various complex cardiac anomalies and also may accompany aortic sinus aneurysm or be secondary to dilatation of the ascending aorta in patients with Marfan syndrome, Turner syndrome, cystic medial necrosis, or osteogenesis imperfecta, in which the aortic lesions are manifestations of the underlying connective tissue disorder.

Severe aortic regurgitation also may occur through channels other than the aortic valve.[336] Thus, aortic-left ventricular tunnel is a rare anomaly that must be distinguished from congenital aortic valve regurgitation, because the approach to management of the former usually does not include consideration for prosthetic valve replacement. The

aortic-left ventricular tunnel is an abnormal channel beginning in the ascending aorta above the right coronary orifice and ending in the left ventricle below the right aortic cusp. The channel usually passes behind the right ventricular infundibulum and through the ventricular septum.

Echocardiography, Doppler studies, and aortography combine to establish a precise diagnosis. Exercise testing[337] and magnetic resonance velocity mapping[338] are useful to assess the severity of the lesion. In infants and children with congenital aortic regurgitation, the severity of regurgitation increases with time, and valve replacement rather than plication is almost always necessary to correct the lesion. Operation should be deferred until symptoms, signs, and noninvasive assessment dictate its necessity.[339] Conversely, closure of an aortic-left ventricular communication is advisable before progressive dilation of the aortic annulus creates secondary changes in the aortic valve itself, which may necessitate aortic valve replacement.

Pulmonary Vein Atresia and Stenosis

Pulmonary vein atresia is a rare anomaly in which the pulmonary veins do not connect with the heart or with a major systemic vein. The lesion is incompatible with life, but infants may survive for days, probably because communications exist between the pulmonary veins and the bronchial or esophageal veins and allow limited egress for pulmonary venous blood. Pulmonary vein stenosis may occur as a focal stenosis at the atrial junction or generalized hypoplasia of one or more pulmonary veins. The incidence of associated cardiac malformations is extremely high, including atrial septal defect, tetralogy of Fallot, tricuspid and mitral atresia, and endocardial cushion defect. The severe pulmonary vein obstruction imposed by pulmonary vein abnormalities causes severe cyanosis, congestive cardiac failure, and early death. Focal stenosis of one or more pulmonary veins at the atrial junction, recognized by two-dimensional echocardiography, magnetic resonance imaging, or angiography, may be relieved surgically. Results of transcutaneous balloon angioplasty have been disappointing.

Cor Triatriatum

In this malformation, failure of resorption of the common pulmonary vein results in a left atrium divided by an abnormal fibromuscular diaphragm into a posterosuperior chamber receiving the pulmonary veins and an anteroinferior chamber giving rise to the left atrial appendage and leading to the mitral orifice.[340] The communication between the divided atrial chambers may be large, small, or absent, depending on the size of the opening in the subdividing diaphragm, which determines the degree of obstruction to pulmonary venous return. Elevations of both pulmonary venous pressure and pulmonary vascular resistance result in severe pulmonary artery hypertension.

The diagnosis is established by two-dimensional or transesophageal echocardiography[341] [342] ; cardiac catheterization and angiography are necessary only if major associated cardiac anomalies are suspected. The obstructive membrane is visualized in the parasternal long- and short-axis and four-chamber (Fig. 43-39) views and can be distinguished from a supravalvular mitral ring[343] by its position superior to the left atrial appendage, which forms part of the distal chamber. Also present are

diastolic fluttering of the mitral leaflets and high-velocity flow detected by Doppler examination in the distal atrial chamber and at the mitral orifice.

The diagnosis should be suspected at cardiac catheterization if the pulmonary arterial wedge pressure is higher than a simultaneous left atrial pressure. The diagnosis also may be established by visualizing the obstructing lesion angiographically. Although rare, the malformation is important to recognize because it may be easily correctable at operation.[344]

Congenital Mitral Stenosis

Anatomical types of mitral stenosis include the parachute deformity of the valve, in which shortened chordae tendineae converge and insert into a single large papillary muscle; thickened leaflets with shortening and fusion of the chordae tendineae; an anomalous arcade of obstructing papillary muscles; accessory mitral valve tissue; and a supravalvular circumferential ridge of connective tissue arising at the base of the atrial aspect of the mitral leaflets.[345] [346] Associated cardiac defects are common, including endocardial fibroelastosis, coarctation of the aorta, patent ductus arteriosus, and left ventricular outflow tract obstruction. Two-dimensional echocardiography, combined with Doppler studies, often provides a complete analysis of the anatomy and function of congenital left ventricular inflow lesions.[346] The clinical and hemodynamic consequences of isolated congenital mitral stenosis are similar to those of acquired mitral obstruction, with modifications imposed by coexisting anomalies.

The prognosis is poor; symptoms attributable to pulmonary vein obstruction usually begin in infancy, and the majority of patients expire before age 1 year unless catheter balloon dilation or operation is successful.[347] [348] Conduit bypass of the mitral valve and prosthetic valve replacement are required if a reparative operation is not possible.[349] [350] The use of a porcine bioprosthesis is contraindicated because of its rapid degeneration in an infant or young child.

Figure 43-39 Echocardiograms demonstrating the membrane (M) of cor triatriatum. The apical four-chamber view *(top panel)* shows the membrane lying within the left atrial chamber. The atrial appendage is distal to the membrane, and the pulmonary veins drain into the proximal portion. The parasternal long-axis view *(center panel)* shows the membrane posterior to the aortic root (Ao) and mitral valve, dividing the left atrium into two chambers. In the parasternal short-axis view *(bottom panel)*, the membrane is within the left atrium close to the posterior aortic root. RA = right atrium; RV = right ventricle; LV = left ventricle.

Congenital Mitral Regurgitation

The syndrome of *mitral valve prolapse* is discussed in Chapter 46 . This condition usually is quite benign in children.[351] [352] However, occasional difficulties exist with

infective endocarditis, arrhythmias, atypical chest pain, and sudden death. *Isolated congenital mitral regurgitation* of hemodynamic significance is an unusual lesion in infants and children.

MORPHOLOGY.

Congenital malformations of the mitral valve producing insufficiency most often are encountered in association with endocardial cushion defect, congenitally corrected transposition of the great arteries, endocardial fibroelastosis, anomalous pulmonary origin of the coronary artery, congenital subaortic stenosis, hypertrophic obstructive cardiomyopathy, and coarctation of the aorta. Mitral valve dysfunction also is common in various metabolic disorders (e.g., the mucopolysaccharidoses), primary and secondary cardiomyopathies, connective tissue disease (e.g., rheumatoid arthritis, Marfan's syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum), and rheumatic and nonrheumatic inflammatory diseases of the myocardium.[353]

The various anatomical lesions that result in isolated congenital mitral regurgitation include prolapse of one or both mitral leaflets, cleft or perforated mitral leaflet, inadequate leaflet tissue, double orifice of the mitral valve, anomalous insertion of chordae tendineae (anomalous mitral arcade), redundant leaflet tissue, displacement inferiorly of the ring of the inferior leaflet into the left ventricle, and abnormal length of the chordae tendineae.

CLINICAL FINDINGS.

The clinical, echocardiographic, and hemodynamic findings in patients with isolated congenital mitral incompetence resemble those observed in acquired mitral regurgitation. Mitral annuloplasty (which is preferred) and prosthetic valve replacement are procedures reserved for infants and children who are at least moderately symptomatic despite comprehensive medical treatment, often with repeated episodes of pulmonary infection or with cardiac failure with anorexia and retarded growth and development.[353] Operative candidates are shown by echocardiographic, Doppler, hemodynamic, and angiographic studies to have pulmonary hypertension, a regurgitant fraction in excess of 50 percent, and a marked increase in left ventricular end-diastolic volume.

Pulmonary Arteriovenous Fistula

Abnormal development of the pulmonary arteries and veins in a common vascular complex is responsible for this rare congenital anomaly (see also Chap. 44). A variable number of pulmonary arteries communicate directly with branches of the pulmonary veins; in some cases, the fistula receives systemic arterial branches.[354] Most patients have an associated Weber-Osler-Rendu syndrome; additional associated problems include bronchiectasis and other malformations of the bronchial tree, as well as absence of the right lower lobe. Venoarterial shunting depends on the extent of the fistulous communications and may result in cyanosis and secondary polycythemia. Paradoxical

emboli and brain abscess may cause major neurological deficits.

Patients with hereditary hemorrhagic telangiectasis often are anemic owing to repeated blood loss and may have less obvious cyanosis. Systolic and continuous murmurs are audible over areas of the fistula. Rounded opacities of various sizes in one or both lungs on chest roentgenogram may suggest the presence of the lesion. Pulmonary angiography reveals the site and extent of the abnormal communication. Unless the lesions are widespread throughout both lungs, surgical treatment aimed at removing the lesions with preservation of healthy lung tissue commonly is indicated to avoid the complications of massive hemorrhage, bacterial endocarditis, and rupture of arteriovenous aneurysms. Pulmonary arteriovenous fistulas may also be acquired and the result of surgical creation of cavopulmonary shunts.[355]

Transcatheter balloon or plug or coil occlusion embolotherapy may prove to be the therapeutic procedure of choice.[356]

Peripheral Pulmonary Artery Stenosis

Stenosis of the pulmonary artery may occur as single or numerous lesions located anywhere from the main pulmonary trunk to the smaller peripheral arterial branches.[357] Associated defects are observed in most patients and include pulmonic valvular stenosis, VSD, tetralogy of Fallot, and supravalvular aortic stenosis.

ETIOLOGY.

The most important cause of significant pulmonary artery stenoses producing symptoms in newborns is intrauterine rubella infection.[358] Diagnosis is facilitated in these infants by finding elevations of the IgM fraction and rubella antibody titer. Other cardiovascular malformations commonly found in association with congenital rubella include patent ductus arteriosus, pulmonic valve stenosis, and atrial septal defect. Generalized systemic arterial stenotic lesions also may be a feature of the rubella embryopathy, often involving large and medium-sized vessels such as the aorta and coronary, cerebral, mesenteric, and renal arteries. Cardiovascular lesions are but one manifestation of intrauterine rubella infection because cataracts, microphthalmia, deafness, thrombocytopenia, hepatitis, and blood dyscrasias also are common. Thus, the clinical picture in infants with rubella syndrome depends on the severity of the cardiovascular lesions and the associated abnormalities of other organs and systems.

Peripheral pulmonary stenosis also often is associated with supravalvular aortic stenosis in patients with the familial form of the latter anomaly or in patients with Williams syndrome.

MORPHOLOGY.

Obstruction within the pulmonary arterial tree may be classified into four types: (1) stenosis of the main pulmonary trunk or the main left or right branch; (2) narrowing at the bifurcation of the pulmonary artery, extending into both right and left branches; (3) numerous sites of peripheral branch stenosis; and (4) a combination of main and peripheral stenosis. Pulmonary artery obstruction may be produced by localized narrowing, diffuse constrictions, or, rarely, a membrane or diaphragm. Poststenotic dilatation is usual when the stenosis is localized but may be absent or minimal with elongated constriction. It should be recognized that a physiological branch pulmonary artery stenosis often is present in normal newborns in whom both right and left main pulmonary arteries are small and arise almost perpendicular from a large main pulmonary artery.[359] The branch vessels increase in size with growth and become less angulated in their takeoff from the main pulmonary artery.

CLINICAL FINDINGS.

The degree of obstruction is the principal determinant of clinical severity; the type of obstruction determines the feasibility of direct surgical relief. The clinical features vary; most infants and children are asymptomatic.[360] An ejection systolic murmur heard at the upper left sternal border and well transmitted to the axillae and back is most common. The presence of an ejection sound suggests that pulmonic valve stenosis coexists. The pulmonic component of the second heart sound may be slightly accentuated but occasionally is extremely loud if multiple peripheral stenoses exist. A continuous murmur is audible, especially in patients with main or branch stenosis and particularly if an associated cardiovascular anomaly produces increased pulmonary blood flow. ECG shows right ventricular hypertrophy when obstruction is severe; left-axis deviation with counterclockwise orientation of the frontal QRS vector is common in the rubella syndrome and when the lesion coexists with supravalvular aortic stenosis. Mild or moderate stenosis usually produces normal findings on chest roentgenogram; detectable differences in vascularity between regions of the lungs or dilated pulmonary artery segments are uncommon. When obstruction is bilateral and severe, right atrial and ventricular enlargement may be observed.

Diagnosis.

This is confirmed by observing pressure gradients within the pulmonary arterial system at cardiac catheterization; digital subtraction and/or selective pulmonary angiography defines the exact location, extent, and distribution of the lesion (Fig. 43-40) . Mild to moderate unilateral or bilateral stenosis does not require surgical relief; numerous stenotic areas are not amenable to correction, even with intraoperative balloon angioplasty. Well-localized obstruction of severe degree in the main pulmonary artery or its

Figure 43-40 Right ventricular angiocardiogram showing numerous sites of peripheral pulmonic stenosis and poststenotic dilatation of the peripheral pulmonic arteries.

major branches may be alleviated by percutaneous transcatheter balloon angioplasty (see Chap. 38),[361] often accompanied by endovascular stent implantation[362] [363] or with a patch graft or bypassed with a tubular conduit. The natural history of peripheral pulmonary stenosis is not clear. Obstruction may increase by discrepant growth between a stenotic area and normal portions of the pulmonary artery tree, or as a result of an increase in cardiac output, especially during adolescence. Rarely, hypertrophy of right ventricular infundibular muscle is progressive and results in hypercyanotic spells.

Pulmonic Stenosis with Intact Ventricular Septum (See also p. 1602)

Valvular pulmonic stenosis, resulting from fusion of the valve cusps during mid- to late intrauterine development, is the most common form of isolated right ventricular obstruction and occurs in about 7 percent of patients with congenital heart disease. Hypertrophy of the septal and parietal bands narrowing the right ventricular infundibulum often accompanies the pulmonic valve lesion, especially if it is severe. Fused cusps of varying thickness and rigidity form a fibrous dome in the severest forms. Pulmonic valve dysplasia, especially common in patients with Noonan's syndrome (see Chap. 56), produces obstruction in the absence of adherent leaflets because leaflets are thickened, rigid, and myxomatous and are limited in their lateral movement because of the presence of tissue pads within the pulmonic valve sinuses.[364]

NEONATES AND INFANTS.

The clinical presentation and course of circulation in a newborn with pulmonic stenosis depends on the severity of obstruction and the degree of development of the right ventricle and its outflow tract, the tricuspid valve, and the pulmonary arterial tree. The greater the degree of pulmonic valve stenosis, the more closely the manifestations resemble those observed with pulmonary atresia and intact ventricular septum. Severe pulmonic stenosis is characterized by cyanosis caused by right-to-left shunting through the foramen ovale, cardiomegaly, and diminished pulmonary blood flow in the absence of persistent patency of the ductus arteriosus. Hypoxemia and metabolic acidemia rather than right ventricular failure are the main clinical disturbances in symptomatic neonates and can be alleviated temporarily by infusion of prostaglandin E_1 to dilate the ductus arteriosus and increase pulmonary blood flow. Distinction of these babies from those with tetralogy of Fallot or tricuspid or pulmonary atresia usually is possible because infants with tetralogy usually do not have roentgenographic evidence of cardiomegaly; infants with tricuspid and pulmonary atresia show a preponderance of left ventricular forces by ECG, in contrast to the right ventricular hypertrophy usually observed with critical pulmonic stenosis in the absence of right ventricular hypoplasia.

Combined two-dimensional echocardiographic and continuous-wave Doppler examination (see Chap. 7) characterizes the anatomical valve abnormality and its severity and has essentially eliminated the requirement for cardiac catheterization and

angiographic studies to establish a precise diagnosis (Fig. 43-41) .[365] [366]

Balloon Valvuloplasty.

Balloon dilatation of the pulmonary valve is the therapeutic procedure of choice,[365] [366] [367] [368] [369] [370] but a pulmonary valvotomy and systemic-to-pulmonary arterial shunt may be necessary in infants with underdevelopment of the right ventricular cavity.[371] In this group, success has been achieved by modification of balloon valvuloplasty with predilation initially using a coronary dilatation catheter to facilitate introduction of a definitive balloon catheter. Transcatheter balloon valvuloplasty can be expected to reduce but not abolish the pressure difference in neonates with mobile doming valves. Sustained relief of the severe obstruction is usual, and so is good growth of the right ventricle. This approach is of lesser efficacy in those patients with dysplastic valves and is contraindicated if valve dysplasia is associated with annular hypoplasia.[372]

CHILDREN.

The clinical profile of patients with valvular pulmonic stenosis beyond infancy usually is distinctive.[373] The severity of obstruction is the most important determinant of the clinical course. In the presence of a normal cardiac output, a peak systolic transvalvular pressure gradient between 50 and 80 mm Hg or a peak systolic right ventricular pressure between 75 and 100 mm Hg is considered to be indicative of moderate stenosis; levels below and above that range are classified as mild and severe, respectively. Most patients with mild pulmonic stenosis are asymptomatic, and the condition is discovered during routine examination. In patients with more significant obstruction, the severity of stenosis may increase with time. Progression

Figure 43-41 Right ventriculogram in an infant with critical pulmonic stenosis shows the thickened, nonmobile pulmonic valve (arrow) in the lateral projection *(left)*. Both the lateral and frontal *(right)* projections show regurgitation of contrast material across the tricuspid valve into the right atrium (ra), with subsequent shunting across the foramen ovale to the left atrium (la). rv = right ventricle; pa = pulmonary artery. *(Courtesy of Dr. Norman Talner).*

may be relative and reflect disproportional physical growth of the patient, infundibular narrowing due to progressive hypertrophy of the right ventricular outflow tract, or fibrosis of the valve cusps. Symptoms, when present, vary from mild exertional dyspnea and mild cyanosis to signs and symptoms of heart failure, depending on the degree of obstruction and the level of myocardial compensation. Exertional fatigue, syncope, and chest pain are related to an inability to augment pulmonary blood flow during exercise in some patients with moderate or severe obstruction.

PHYSICAL EXAMINATION.

The severity of obstruction often is suggested by the physical findings. Right ventricular hypertrophy reduces compliance of that chamber, and a forceful right atrial contraction is necessary to augment right ventricular filling. Prominent *a* waves in the jugular venous pulse, a fourth heart sound, and, occasionally, presystolic pulsations of the liver reflect a vigorous atrial contraction and suggest the presence of severe stenosis. Cardiomegaly and a right ventricular parasternal lift accompany moderate or severe obstruction. A systolic thrill is palpable along the upper left sternal border in all but the mildest forms of stenosis. The first heart sound is normal and is followed by a systolic ejection sound at the upper left sternal edge produced by sudden opening of the stenotic valve; an ejection sound is not heard in patients with pulmonic valve dysplasia. The ejection sound typically is louder during expiration; when it is inaudible or occurs less than 0.08 second from the onset of the Q wave on ECG, severe obstruction is suggested. Right ventricular ejection is prolonged in patients with moderate or severe stenosis, and the sound of pulmonic valve closure is delayed and soft. The characteristic feature of valvular pulmonic stenosis on auscultation is a harsh, diamond-shaped systolic ejection murmur heard best at the upper left sternal border. The systolic murmur becomes louder and its crescendo occurs later in systole, obscuring the aortic component of the second sound with more severe degrees of valvular obstruction because these patients have a greater prolongation of right ventricular systole. The holosystolic decrescendo murmur of tricuspid regurgitation may accompany severe pulmonic stenosis, especially in the presence of congestive heart failure. Cyanosis, reflecting venoarterial shunting through a patent foramen ovale, is absent with mild stenosis and infrequent with moderate obstruction. Cyanosis may not be apparent in patients with severe obstruction if the atrial septum is intact.

ELECTROCARDIOGRAPHY.

This technique may be helpful in assessing the degree of obstruction to right ventricular output.[374] In mild cases, the ECG often appears normal, whereas moderate and severe stenoses are associated with right-axis deviation and right ventricular hypertrophy. In the latter patients between ages 2 and 20 years, an estimate of right ventricular pressure can be made by multiplying the height of the R wave in lead V_{4R} or V_1 by 5. A tall QR wave in the right precordial leads with T wave inversion and ST segment suppression (right ventricular "strain") reflects severe stenosis. When an rSR pattern is observed in lead V_1 (20 percent of patients), lower right ventricular pressures are found than in patients with a pure R wave of equal amplitude. High-amplitude P waves in leads II and V_1 indicating right atrial enlargement are associated with severe stenosis.

CHEST ROENTGENOGRAPHY.

In patients with mild or moderate pulmonic stenosis, chest roentgenography often shows a heart of normal size and normal pulmonary vascularity (see Chap. 8). Poststenotic dilatation of the main and left pulmonary arteries often is evident. Right

atrial and right ventricular enlargement are observed in patients with severe obstruction and resultant right ventricular failure. The pulmonary vascularity may be reduced in patients with severe stenosis, right ventricular failure, and/or a venoarterial shunt at the atrial level.

ECHOCARDIOGRAPHY.

Reliable localization of the site of obstruction and assessment of its severity are obtained by combined continuous-wave or pulsed-wave Doppler and two-dimensional echocardiography[375] (see Chap. 7 and Fig. 43-42). The latter usually shows prominent pulmonary valve echoes with restricted systolic motion as well as poststenotic dilation of the main pulmonary artery and its branches. In contrast to these findings in classic valvular pulmonic stenosis, patients with a dysplastic valve show thickened and immobile leaflets with hypoplasia of the pulmonary valve annulus and absent poststenotic dilatation of the pulmonary artery. Parasternal and subcostal views are required to detect most accurately maximal pulmonary artery blood flow velocity, which is converted to a pressure difference across the valve using a modified Bernoulli equation (pressure difference [mm Hg] = 4 × the squared peak Doppler velocity [m/sec]) (Fig 43-42). A semiquantitative estimation of pulmonary and tricuspid regurgitation can be

Figure 43-42 *A,* Severe valvular pulmonic stenosis seen from a parasternal short-axis view. The thickened pulmonary valve can be seen lying between the right ventricular outflow tract (RVO) and a dilated pulmonary artery (PA). The arrows are at the annulus of the pulmonary valve; the thickened, domed valve can be identified clearly. LV = left ventricle; AO = aorta; LA = left atrium. *B,* Doppler ultrasound from the subcostal (SC) transducer position. The velocity signal is approximately 3.8 m/sec at its height; predicted peak gradient (PGRAD) is 58 mm Hg, predicted mean gradient (MnGRAD) is 34 mm Hg.

obtained. The peak systolic velocity of the tricuspid regurgitant jet provides a reliable indirect measurement of the severity of obstruction because the reverse gradient between the right ventricle and right atrium allows derivation of the ventricular peak systolic pressure. The constant value of 14 is used for right atrial pressure in the calculation.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY.

These techniques are now used only rarely to establish or preclude other diagnostic possibilities. The usual indication for cardiac catheterization is to provide definitive therapy for the lesion. Cardiac catheterization, however, may also localize the site of obstruction, evaluate its severity, and document the coexistence of additional cardiac malformations. The resting cardiac output usually is normal, even in cases of severe stenosis, and most children show the ability to increase cardiac output with exercise.[376]

Right ventricular dysfunction occurs especially when venoarterial shunting is significant and produces systemic arterial desaturation. In patients with critical stenosis, care must be taken during hemodynamic study that the cardiac catheter does not dangerously occlude the stenotic valve opening. The angiographic appearance of a typical valvular pulmonic stenosis differs from that of a dysplastic valve. The former is thickened and domed during systole, returning to normal configuration in diastole. Poststenotic dilatation of the main pulmonary trunk and sometimes of the left pulmonary artery is usual. The leaflets of the dysplastic valve are not fused anatomically but are thickened and immobile, creating little change in the angiographic picture during the cardiac cycle. Moreover, a small annulus and narrow sinuses of Valsalva are common accompaniments of valve dysplasia. With either type of valve, systolic narrowing of the right ventricular infundibulum usually is associated with moderate or severe obstruction.

NATURAL HISTORY.

Mild and moderate pulmonic valve stenoses have a generally favorable course; uncommonly, progression occurs in the severity of obstruction, particularly in infancy.[377] Serial hemodynamic studies reveal unchanged pressure gradients over 4- to 8-year intervals in three-fourths of patients. Equal percentages of the remainder have an increase or a decrease in the severity of obstruction; significant increases in the pressure gradient occur especially in children with a gradient in excess of 50 mm Hg at initial examination.[373]

MANAGEMENT.

Percutaneous transluminal balloon valvuloplasty (see Chap. 38) is the initial procedure of choice in patients with typical pulmonary valve stenosis and moderate to severe degrees of obstruction (Fig. 43-43). [372] This approach provides palliative improvement with the great likelihood that the improvement is permanent. In these same patients, *surgical relief* also can be accomplished at extremely low risk.[378] The valve is approached through an incision in the pulmonary arterial trunk, and resection of infundibular muscle, if necessary, may be accomplished through the pulmonic valve. Reoperation or subsequent balloon valvuloplasty is seldom required. In patients with a dysplastic valve, in whom transcatheter valvuloplasty is ineffective, the thickened valve tissue is removed and a patch often is required to widen the annulus and proximal main pulmonary artery. In children with mild pulmonic valve stenosis, prophylaxis against infective endocarditis is recommended; these patients need not restrict their physical activities. After relief of stenosis, cardiac performance as judged by exercise testing improves in children in whom postoperative resolution of right ventricular hypertrophy is expected. In contrast, myocardial fibrosis can explain a lack of improvement in adults.[379]

Pulmonic Atresia with Intact Ventricular Septum

MORPHOLOGY.

This anomaly is an uncommon and highly lethal cause of neonatal cyanosis that may

respond well to aggressive medical and surgical treatment.[380] [381] In almost all infants, the pulmonic valve is atretic; in the majority, both the valve ring and the main pulmonary artery are hypoplastic. The right ventricular infundibulum may occasionally be atretic or extremely narrowed. Right ventricular cavity size and configuration span the spectrum from a diminutive right ventricular chamber, often with tricuspid stenosis, to a large right ventricle, frequently with tricuspid regurgitation (Fig. 43-44) . In most infants, the right ventricle is hypoplastic, and sinusoidal communications

Figure 43-43 Right ventriculogram (RV) in the lateral projection *(top left)* from a patient with valvular pulmonic stenosis. The pulmonary valve (PV) is thickened and domes in systole. Poststenotic dilatation of the pulmonary artery (PA) is seen. At the *top right,* successful balloon valvuloplasty shows almost complete disappearance of the stenotic waist (arrow). The *bottom panel* shows the pre- *(left)* and post- *(right)* valvuloplasty hemodynamics, showing a reduction from moderately severe to mild pulmonic stenosis. AO = aorta. *(Courtesy of Dr. Thomas G. DiSessa.)*

exist in half the patients between the right ventricular cavity and the coronary circulation.[382] [383]

The intramyocardial sinusoids may end blindly or communicate with coronary arteries. Further, these communications may be numerous and may feed both the left and right coronary systems, or they may be fed via a single dilated vessel. The proximal coronary arteries in some patients may be atrophic, proximal to a communication between the sinusoids and the distal coronary artery, particularly

Figure 43-44 Pulmonic atresia with intact ventricular septum. With a competent tricuspid valve, the right ventricular chamber is diminutive *(A)*; significant tricuspid regurgitation is associated with a normal or large right ventricular cavity *(B)*. VC = vena cava; RA = right atrium; RV = right ventricle; PT = pulmonary trunk; PV = pulmonary vein; LA = left atrium; LV = left ventricle; Ductus A. = ductus arteriosus; LPA = left pulmonary artery; RPA = right pulmonary artery; LPV = left pulmonary vein. *(From Edwards JE: Congenital malformations of the heart and great vessels. In Gould SE [ed]: Pathology of the Heart. 2nd ed, 1960. Courtesy of Charles C Thomas, Publisher, Ltd., Springfield, Illinois.)*

Figure 43-45 Right ventricular angiocardiogram in the frontal projection in a 1-day-old infant with an atretic pulmonic valve (arrow). The cavity of the right ventricle (RV) is small and eccentrically shaped. *(Courtesy of Dr. Robert Freedom.)*

in hearts with severe hypoplasia of the right ventricle. In these circumstances, the distal coronary vessels are supplied by communications with the right ventricle, and the coronary circulation therefore is right ventricle dependent. In this group, decompression of the right ventricle by a surgical procedure would be associated with a high risk of myocardial ischemia and death.[384] [385]

Because the pulmonic valve is imperforate and completely obstructed, systemic venous blood returning to the heart bypasses the right ventricle through an interatrial communication. Right ventricular output does not contribute to the effective cardiac output and is proportional to the magnitude of tricuspid regurgitation and the size and extent of the sinusoidal communications with the coronary arterial tree. The blood supply to the lungs is derived from the bronchial circulation and from flow through a persistently patent ductus arteriosus. The size and patency of the ductus arteriosus are critical determinants in postnatal survival; ductus closure results in death. Reduced pulmonary blood flow by way of a partially constricted ductus arteriosus results in profound hypoxemia, tissue hypoxia, and metabolic acidemia.

DIAGNOSIS.

The diagnosis is suggested by roentgenographic findings of pulmonary hypoperfusion and the ECG observation of a normal QRS axis, absent or diminished right ventricular forces, and/or dominant left ventricular forces. In the minority of infants with marked tricuspid regurgitation, the right ventricle and right atrium are massively enlarged. The echocardiogram in the usual infant shows a small right ventricular cavity and diminutive or absent pulmonic valve echoes.[386] Doppler examination shows continuous retrograde flow to the pulmonary artery and/or its branches through a patent ductus arteriosus, which usually is narrow and tortuous. Only if tricuspid valve echoes are imaged by ultrasound examination can tricuspid atresia be distinguished from pulmonic atresia.

Although the diagnosis of this entity can be made by echocardiography, angiocardiography is required to assess treatment options because key determinants are the identification and nature of ventriculocoronary connections, which are not well characterized by echocardiography. Cardiac catheterization is usually performed on an emergency basis. Because survival depends on patency of the ductus arteriosus, intravenous infusion of prostaglandin E_1 , (0.05 to 0.1 mug/kg/min) may dramatically reverse clinical deterioration and improve arterial blood gases and pH. The usual hemodynamic findings are right atrial and right ventricular hypertension, with right ventricular pressure often greater than systemic pressure, and a massive right-to-left interatrial shunt. Selective angiocardiography establishes the diagnosis and allows evaluation of the degree of separation between the right ventricular infundibular and pulmonary trunk, the size of the right ventricular cavity and the pulmonary arteries (Fig. 43-45) , the anatomy and function of the tricuspid valve, and the anatomical and functional details of the coronary circulation.

MANAGEMENT.

Initial stabilization is usually required in infants, necessitating infusion of prostaglandin

E_1 to dilate the ductus arteriosus and measures to correct metabolic acidosis. The rare infant with membranous pulmonary atresia may be a candidate for balloon valvotomy. Initial surgical considerations focus on whether the patient is a candidate for a biventricular or univentricular (Fontan) repair (Fig. 43-45) .[384] [387] [388] [389] The angiographic delineation of coronary artery anatomy determines the feasibility of early decompression of the right ventricle, because this approach is contraindicated when there are ventriculocoronary connections with part or all of the coronary circulation right ventricle dependent. Patients in this latter group cannot undergo operation that decompresses the right ventricle and are ultimately candidates for a lateral tunnel Fontan procedure, after initial palliation by balloon atrial septostomy followed by a systemic-pulmonary artery shunt.[390]

At the other end of the spectrum, babies with only mild hypoplasia of the right ventricle and tricuspid valve are candidates for a transventricular closed pulmonary valvotomy, followed later by balloon angioplasty or repeat surgical valvotomy. Ultimately, the size of the tricuspid valve and right ventricle, and occasionally the presence of coronary artery obstructive lesions in association with right ventricle to coronary artery fistulas, will dictate whether patients will be candidates for two-ventricle repair or whether a less corrective procedure such as the Fontan operation will be the most definite surgical option.[387] In infants with moderate right ventricular hypoplasia, a biventricular repair is preferred, often using a homograft valve in the outflow tract. In this group, the smaller the size of the right ventricle and tricuspid valve, the more likely a partial biventricular repair will be necessary, relieving the outflow tract obstruction with insertion of a valve, coupled with a bidirectional cavopulmonary (Glenn) shunt to ensure obligatory pulmonary blood flow.

Intraventricular Right Ventricular Obstruction

Infundibular pulmonic stenosis with an intact ventricular septum and the presence of anomalous muscle bundles are the two principal causes of intraventricular right ventricular obstruction (Fig. 43-46) .[391]

SUBPULMONIC INFUNDIBULAR STENOSIS.

This anomaly usually occurs at the proximal portion of the infundibulum and consists of a fibrous band at the junction of the right ventricular cavity and outflow tract. The clinical manifestations, course, and prognosis of infundibular stenosis are similar to those of valvular stenosis, although the former diagnosis is suggested by the absence of a systolic ejection

Figure 43-46 Intraventricular right ventricular obstruction. The right ventricular inflow (RVI) and outflow (RVO) tracts are separated by bands (arrowheads), creating intraventricular right ventricular obstruction. PA = pulmonary artery.

sound and a systolic murmur lower along the left sternal border. Doppler echocardiography, withdrawal pressure tracings, and selective right ventricular angiocardiography permit localization of the site of obstruction and assessment of its extent and severity. Surgical treatment consists of resection of the fibrotic narrowed area and hypertrophied muscle. It may occasionally be necessary to widen the outflow tract with a pericardial or prosthetic patch.

ANOMALOUS MUSCLE BUNDLES.

A two-chambered right ventricle is formed by right ventricular obstruction due to anomalous muscle bundles; most of the patients have an associated malalignment or perimembranous VSD, and about 5 percent have subaortic stenosis.[392] Aberrant hypertrophied muscle bands, occasionally in association with a VSD, traverse the right ventricular cavity, extending from its anterior wall to the crista supraventricularis and/or the portion of the adjacent interventricular septum. The anomalous pyramid-shaped muscle mass obstructs blood flow through the body of the right ventricle and produces a proximal high-pressure inflow chamber and a distal low-pressure chamber. Thus, this type of obstruction is distinguishable from that in tetralogy of Fallot, in which hypertrophied infundibular muscle protrudes into but does not cross the cavity of the right ventricle.

The clinical, ECG, and chest roentgenographic findings resemble those observed in pulmonic valvular or subvalvular infundibular obstruction, although the systolic thrill and murmur may be displaced lower along the left sternal border. Progressive obstruction occurs in some patients. The diagnosis may be established by two-dimensional echocardiography.[393] Selective right ventricular angiocardiography provides the most accurate diagnosis and reveals a filling defect in the midportion of the right ventricle; this defect often does not change significantly with systole and diastole.

Management.

The treatment for anomalous muscle bundles consists of surgical removal.[394] In the absence of preoperative recognition of the anomaly, the surgeon should be alerted to the correct diagnosis by the presence of a dimple during contraction on the ordinarily smooth anterior surface of the right ventricle and/or the inability to view the tricuspid valve through a longitudinal ventriculotomy because of the presence of the abnormal muscle mass.

Tetralogy of Fallot

DEFINITION.

The overall incidence of this anomaly approaches 10 percent of all forms of congenital

heart disease, and it is the most common cardiac malformation responsible for cyanosis after 1 year of age. The four components of this malformation are (1) VSD, (2) obstruction to right ventricular outflow, (3) overriding of the aorta, and (4) right ventricular hypertrophy. The basic anomaly is the result of an anterior deviation of the septal insertion of the infundibular ventricular septum from its usual location in the normal heart between the limbs of the trabecular septum. The interventricular malalignment defect usually is large, approximating the aortic orifice in size, and is located high in the septum just below the right cusp of the aortic valve, separated from the pulmonic valve by the crista supraventricularis. The aortic root may be displaced anteriorly and straddle or override the septal defect, but as in a normal heart, it lies to the right of the origin of the pulmonary artery. In most cases, no dextroposition of the aorta exists; overriding of the aorta is a phenomenon secondary to the subaortic location of the VSD.

HEMODYNAMICS.

The degree of obstruction to pulmonary blood flow is the principal determinant of the clinical presentation.[395] The site of obstruction is variable[396] ; infundibular stenosis is the only major obstruction in about 50 percent of patients and coexists with valvular obstruction in another 20 to 25 percent (Fig. 43-47) . Supravalvular and peripheral pulmonary arterial narrowing may be observed, and unilateral absence of a pulmonary artery (usually the left) is found in a small number of patients. Circulation to the abnormal lung is accomplished by bronchial and other collateral arteries.[397] [398] Atresia of the pulmonic valve, infundibulum, or main pulmonary artery is occasionally referred to as "pseudotruncus arteriosus." True truncus arteriosus with absent pulmonary arteries (type 4) differs from

Figure 43-47 Tetralogy of Fallot with infundibular and valvular pulmonic stenosis. The arrows indicate direction of blood flow. A substantial right-to-left shunt exists across the ventricular septal defect. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; Ao = aorta; PA = pulmonary artery.

tetralogy of Fallot, in which pulmonary artery branches are present but are fed by a patent ductus arteriosus and/or bronchial arteries (see Fig. 43-50). A right-sided aortic knob, aortic arch, and descending aorta occur in about 25 percent of patients with tetralogy of Fallot. The coronary arteries may have surgically important variations[399] : The anterior descending artery may originate from the right coronary artery; a single right coronary artery may give off a left branch that courses anterior to the pulmonary trunk; a single left coronary artery may give off a right branch that crosses the infundibulum of the right ventricle. Enlargement of the infundibulum branch of the right coronary artery often presents a problem with respect to a right ventriculotomy.

Associated cardiac anomalies exist in about 40 percent of patients. Major associated cardiac anomalies include patent ductus arteriosus, numerous (usually muscular) VSDs, and complete AV septal defects. Localized single or multiple peripheral pulmonary arterial stenotic lesions are common; rarely, the right or left pulmonary artery may arise anomalously from the ascending aorta. Infrequently, aortic valve regurgitation results

from aortic cusp prolapse. Associated extracardiac anomalies are present in 20 to 30 percent of patients.

The relation between the resistance of blood flow from the ventricles into the aorta and into the pulmonary vessels has a major role in determining the hemodynamic and clinical picture.[400] Thus, the severity of obstruction to right ventricular outflow is of fundamental significance. When right ventricular outflow tract obstruction is severe, the pulmonary blood flow is markedly reduced, and a large volume of unsaturated systemic venous blood is shunted from right to left across the VSD. Severe cyanosis and polycythemia occur, and symptoms and sequelae of systemic hypoxemia are prominent. At the opposite end of the spectrum, the term "acyanotic" or "pink" tetralogy of Fallot often is used to describe an interventricular communication and a milder degree of obstruction to right ventricular outflow with little or no venoarterial shunting. In many infants and children, the obstruction to right ventricular outflow is mild but progressive, so that early in life pulmonary exceeds

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systemic blood flow and the symptoms resemble those produced by a simple VSD.

CLINICAL MANIFESTATIONS.

Few children with tetralogy of Fallot remain asymptomatic or acyanotic (see Chap. 44). Most are cyanotic from birth or develop cyanosis before age 1 year. In general, the earlier the onset of systemic hypoxemia, the more likely the possibility that severe pulmonary outflow tract stenosis or atresia exists. Dyspnea with exertion, clubbing, and polycythemia is common. When resting after exertion, children with tetralogy characteristically assume a squatting posture. The latter may be obvious even in infancy; many cyanotic infants prefer to lie in a knee-chest position. Spells of intense cyanosis related to a sudden increase in renoarterial shunting and a reduction in pulmonary blood flow most often have their onset between 2 and 9 months of age and constitute an important threat to survival.[401] [402] The attacks are not restricted to patients with severe cyanosis; they are most common in the morning after awakening and are characterized by hyperpnea and increasing cyanosis that progresses to limpness and syncope and occasionally terminates in convulsions, a cerebrovascular accident, and death.

Physical Examination.

This reveals variable degrees of underdevelopment and cyanosis. Clubbing of the terminal digits may be prominent after the first year of life. The heart is not hyperactive or enlarged; a right ventricular impulse and systolic thrill often are palpable along the left sternal border. An early systolic ejection sound that is aortic in origin may be heard at the lower left sternal border and apex; the second heart sound is single, the pulmonic component rarely being audible. A systolic ejection murmur is produced by flow across the narrowed right ventricular infundibulum or pulmonic valve. The intensity and duration

of the murmur vary inversely with the severity of obstruction--the opposite of the relation that exists in patients with pulmonic stenosis and an intact ventricular septum. Polycythemia, decreased systemic vascular resistance, and increased obstruction to right ventricular outflow may all be responsible for a decrease in intensity of the murmur; with extreme outflow tract stenosis or pulmonic atresia and during an attack of paroxysmal hypoxemia, no murmur or only a very short, faint murmur may be detected. A continuous murmur faintly audible over the anterior or posterior chest reflects flow through enlarged bronchial collateral vessels. A loud continuous murmur of flow through a patent ductus arteriosus occasionally may be heard at the upper left sternal border.

LABORATORY EXAMINATIONS.

The *ECG* ordinarily shows right ventricular and, less frequently, right atrial hypertrophy. In a patient with acyanotic tetralogy, combined ventricular hypertrophy may be noted initially, progressing to right ventricular hypertrophy as cyanosis develops. *Roentgenographic* examination characteristically reveals a normal-sized boot-shaped heart (coeur en sabot) with prominence of the right ventricle and a concavity in the region of the underdeveloped right ventricular outflow tract and main pulmonary artery. The pulmonary vascular markings are typically diminished, and the aortic arch and knob may be on the right side; the ascending aorta usually is large. A uniform, diffuse, fine reticular pattern of vascular markings is noted in the presence of prominent collateral vessels.

Echocardiography.

Findings include aortic enlargement, aortic-septal discontinuity, and aortic overriding of the ventricular septum.[403] Two-dimensional echocardiography (see Chap. 7) shows the right ventricular outflow tract to be narrowed and in a more horizontal orientation than normal. The main pulmonary artery and its branches are mildly to severely hypoplastic. The usual ventricular septal malalignment defect lies superior to the tricuspid valve and immediately below the aortic valve cusps. These findings are best displayed in views of the long axis of the right ventricular outflow tract, which are the subxiphoid short axis and the high transverse parasternal echo windows. Echo views that show the anteroposterior coordinates best indicate the overriding of the aorta; these are the parasternal long-axis, apical two-chamber, and subxiphoid views (Fig. 43-48) . The echocardiographic examination also reveals the origin of the main pulmonary artery from the right ventricle, as well as continuity of the main pulmonary artery with its right and left branches, and is accurate for diagnosing coronary abnormalities,[404] [405] although the latter are identified best by angiography. Delineation or complex pulmonary vascular abnormalities may require combined angiography and advanced CT[406] (see Chaps. 10 and 11). Combined angiography and three-dimensional CT has been shown to be useful for assessing systemic-to-pulmonary collaterals. The demonstration of mitral-semilunar valve continuity helps to distinguish tetralogy from double-outlet right ventricle with pulmonic stenosis, in which discontinuity of the mitral valve echo and the aortic cusp echo is a critical feature.

Cardiac Catheterization and Angiocardiography (Fig. 43-49) .

Despite the accuracy of noninvasive approaches, many centers still consider invasive study necessary to confirm the diagnosis; assess the magnitude of right-to-left shunting; provide details of additional muscular VSDs, if present; evaluate the architecture of the right ventricular outflow tract, pulmonic valve, and annulus and the morphology and caliber of the main branches of the pulmonary arteries; and analyze the anatomy of the coronary arteries. *Axial cineangiography,* using the sitting-up projection, greatly facilitates evaluation of the pulmonary outflow tract and arteries.[137] Preoperative assessment of tetralogy with pulmonic atresia must include delineation of the arterial supply to both lungs by selective catheterization and visualization of bronchial collateral arteries with late serial filming; pulmonary arteries may be opacified only after the bronchial collateral arteries have cleared of contrast material (Fig. 43-50) . A patient with pulmonic atresia should not be ruled out as a candidate for surgical correction unless an inadequate pulmonary arterial supply to the lungs is clearly demonstrated.[397] Rarely, injection of contrast through a catheter in the pulmonary venous capillary wedge position is required to assess the possibility that anatomical pulmonary arteries are present. CT may visualize central pulmonary arteries when conventional angiography cannot.

MANAGEMENT.

Among the factors that may complicate the management of tetralogy are iron deficiency anemia,

Figure 43-48 Tetralogy of Fallot in a parasternal long-axis (PLAx) view, which demonstrates the aorta overriding the ventricular septum (Sept). RV = right ventricle; RVO = right ventricular outflow tract; LV = left ventricle; LA = left atrium; AO = aorta; AAO = ascending aorta.

Figure 43-49 Lateral view of a right ventriculogram in a child with tetralogy of Fallot showing simultaneous opacification of the pulmonary artery (PA) and aorta (Ao). PV = pulmonic valve; VSD = ventricular septal defect; RV = right ventricle.

infective endocarditis, paradoxical embolism, polycythemia, coagulation disorders, and cerebral infarction or abscess. Paroxysmal hypercyanotic spells may respond quickly to oxygen, placing the child in the knee-chest position, and morphine. If the spell persists, metabolic acidosis develops from prolonged anaerobic metabolism, and infusion of sodium bicarbonate may be necessary to interrupt the attack. Vasopressors, beta-adrenoceptor blockade, or general anesthesia occasionally may be necessary.[402]

Total Surgical Correction.

This operation is advisable ultimately for almost all patients with tetralogy of Fallot. Early definitive repair, even in infancy, is currently advocated in most centers that are experienced in intracardiac surgery in infants.[407] [408] [409] Successful early correction appears to prevent the consequences of progressive infundibular obstruction and acquired pulmonic atresia, delayed growth and development, and complications secondary to hypoxemia and polycythemia with bleeding tendencies. The anatomy of the right ventricular outflow tract and the size of the pulmonary arteries, rather than the age or size of the infant or child, are the most important determinants in assessing candidacy for primary repair; a transannular patch may be used in infants with severe outflow narrowing.[410] Marked hypoplasia of the pulmonary arteries is a relative contraindication for early corrective operation.

Figure 43-50 Selective systemic collateral bronchial arteriogram demonstrates gull-wing configuration of the hypoplastic right pulmonary artery (rpa) and left pulmonary artery (arrows) in a patient with tetralogy of Fallot and pulmonic atresia. *(Courtesy of Dr. Robert Freedom.)*

Palliative Surgery.

When marked hypoplasia of the pulmonary arteries exists, a palliative operation designed to increase pulmonary blood flow is recommended and usually consists in the smallest infants of a systemic-pulmonary arterial anastomosis.[411] A transventricular infundibulectomy or valvulotomy is an alternative palliative procedure that may be considered. Balloon dilatation of the pulmonary valve may afford palliation in selected infants.[412] Total correction can then be carried out at a lower risk later in childhood. The palliative procedures relieve hypoxemia caused by diminished pulmonary blood flow and reduce the stimulus to polycythemia. Because pulmonary venous return is augmented, the left atrium and ventricle are stimulated to enlarge their capacity in anticipation of total correction. In the most severe forms of tetralogy of Fallot with pulmonic atresia, the goals of operation include establishment of nonstenotic continuity between the right ventricle and pulmonary arteries, closure of the intracardiac shunt, and interruption of surgically created shunts or major collateral arteries to the lungs. Transcatheter coil occlusion of significant aorta-pulmonary collateral vessels as well as of modified Blalock-Taussig shunts and ascending aorta to pulmonary artery interposition grafts can be used before corrective operation.[413] [414] When atresia is confined to the infundibulum or pulmonic valve, repair may be accomplished by infundibular resection and reconstruction of the outflow tract with a pericardial patch. If a long segment of pulmonary arterial atresia exists, a valve-containing conduit is inserted from the right ventricle to the distal pulmonary artery.[415] The presence of a single pulmonary artery in the hilus of either lung is a prerequisite for repair of pulmonic atresia. Prior unifocalization to incorporate several systemic to pulmonary artery collaterals into a neopulmonary artery may be required in selected patients.[416] A conduit also may be necessary in less severe forms of right ventricular outflow tract obstruction when an

anomalous coronary artery crosses the right ventricular outflow tract.

Postoperative Complications.

Various complications are common in the postoperative period after palliative or corrective operation. Mild to moderate left ventricular decompensation may be secondary to the sudden increase in pulmonary venous return; various degrees of pulmonic valvular regurgitation increase right ventricular cavity size further. Patients with progressive pulmonary insufficiency and severe right ventricular dilatation are candidates for prosthetic pulmonary valve insertion.[417]

Bleeding problems are common, especially in older polycythemic patients (see Chap. 44). Complete right bundle branch block or the pattern of left anterior hemiblock often is seen, but disabling dysrhythmias are infrequent.[418] [419] Restricted pulmonary arterial flow is the greatest

cause of early and late mortality and poor late results.[420] After convalescence from intracardiac repair, symptoms of hypoxemia and severe exercise intolerance are relieved even in the presence of some residual right ventricular outflow tract obstruction, pulmonic valve incompetence, and/or cardiomegaly. However, cardiovascular performance at rest or during exercise may remain below normal,[421] [422] [423] and major complications, such as trifascicular block, complete heart block, ventricular arrhythmias, and sudden death, may rarely occur many years after surgical treatment.[419]

Late ventricular arrhythmias are rare in patients with successful early correction of the malformation unless complex or numerous operations were performed. Because widespread use of ambulatory ECG monitoring has resulted in greater detection of ventricular arrhythmias, usually isolated ventricular extrasystoles or nonsustained tachycardia, some have suggested that the asymptomatic patients in this category should have pharmacological suppression of their arrhythmias. It would appear that both ventricular depolarization and repolarization abnormalities contribute to the pathogenesis of ventricular arrhythmias after repair of the anomaly (see Chaps. 25 and 44). Most studies, however, do not support the use of potentially dangerous long-term antiarrhythmic treatment for asymptomatic postoperative patients, and a large-scale long-term follow-up study is indicated before prophylactic therapeutic options can be established definitively (see Chap. 23).

Congenital Absence of the Pulmonic Valve

PATHOLOGY AND PATHOGENESIS.

In the majority of cases of this rare malformation, the lesion is associated with a VSD, a narrowed obstructive annulus of the pulmonic valve, and marked aneurysmal dilatation of the pulmonary arteries. The combination of anomalies often is referred to as tetralogy

of Fallot with absent pulmonic valve. The obstructing lesion principally consists of underdeveloped, primitive valve tissue within a hypoplastic annulus; infundibular obstruction and the VSD do not differ from classic tetralogy of Fallot. Reports indicate that deletion within chromosome 22 is common in patients with this anomaly.[424]

The massively dilated pulmonary arteries often are the major determinant of the clinical course because they frequently result in upper airway obstruction and severe respiratory distress in infancy.[425] Smaller intrapulmonary bronchi may also be compressed by abnormally branching distal pulmonary arteries, and in some cases the number of bronchial generations or alveolar multiplications is reduced.[426] Poststenotic pulmonary artery aneurysms develop in utero, and their size and location appear to be related to the magnitude of pulmonic regurgitation in fetal life, the orientation of the right ventricular infundibulum to the right or left, and the size of the ductus arteriosus.[427]

CLINICAL AND LABORATORY FINDINGS.

The *clinical* features often are distinctive, with an early onset of severe respiratory distress caused by tracheobronchial compression accompanied by a systolic ejection and a widely transmitted low-pitched, decrescendo diastolic murmur at the upper left sternal border. In the absence of pulmonary complications, cyanosis is commonly mild. *Roentgenographically,* the heart is moderately enlarged; hyperinflated lung fields are observed, with large hilar densities representing the aneurysmally dilated pulmonary arteries. The *echocardiographic* features are similar to those seen in classic tetralogy of Fallot, in addition to massive dilatation of the main pulmonary artery and branch pulmonary arteries. Remnants of pulmonary cusps may be visible. Right ventricular dilatation is produced by significant pulmonary regurgitation; the latter is identified by retrograde diastolic flow in the pulmonary arteries and right ventricle at Doppler examination. These findings may be detected before birth (Fig. 43-51) . Definitive diagnosis is established by cardiac catheterization and selective angiocardiography. Magnetic resonance imaging is a complementary diagnostic modality and is particularly useful for demonstrating bronchial morphology and the severity of bronchial obstruction.[428]

NATURAL HISTORY AND MANAGEMENT.

Prognosis is related to the intensity of upper airway obstruction; pulmonary complications are the usual cause of death in infancy. If survival beyond infancy is accomplished, the respiratory symptoms usually diminish, probably because of maturational changes in the structure of the tracheobronchial tree. The surgical approach in infancy often is unsatisfactory; various procedures have been attempted, ranging from aneurysmorrhaphy to pulmonary artery suspension to transection and reanastomosis of pulmonary artery segments to homograft insertion.[429] Also suggested are ligation of the main pulmonary artery and creation of a systemic-pulmonary shunt, as well as primary repair of the VSD with pulmonary arterial plication. In older patients, the stenotic annulus

Figure 43-51 Two-dimensional *(top panel)* and Doppler *(lower panel)* echocardiogram of a 30-week-gestation fetus with tetralogy of Fallot and an absent pulmonary valve. The pulmonary artery (PA) is aneurysmally dilated, and the right ventricle (RV) is also dilated. The arrow points to the stenotic pulmonary valve annulus. Pulmonary valve leaflets are not detectable. The Doppler study at the level of the pulmonary valve annulus demonstrates to-and-fro flow with increased forward velocity in systole. LV = left ventricle. *(Courtesy of Dr. James C. Huhta.)*

may be widened with a patch and the VSD closed. It seldom is necessary to replace the pulmonic valve.

Tricuspid Atresia

MORPHOLOGY.

This anomaly is characterized by absence of the tricuspid orifice, an interatrial communication, hypoplasia of the right ventricle, and the presence of a communication between the systemic and pulmonary circulations, usually a VSD.[430] Thus formed is a univentricular AV connection, consisting of a left-sided mitral valve between the morphological left atrium and left ventricle. Unequal division of the AV canal by fusion of the right-sided endocardial cushions has been proposed as the embryological fault. Patients may be subdivided into those with normally related great arteries (70 to 80 percent of cases) and those with dextro- or D-transposition of the great arteries; further classification depends on the presence of pulmonic stenosis or atresia and the absence or size of the VSD (Fig. 43-52) . Additional cardiovascular malformations often are present, especially in patients with D-transposition of the great arteries, and include persistent left superior vena cava, patent ductus arteriosus, coarctation of the aorta, and juxtaposition of the atrial appendages.

PATHOPHYSIOLOGY.

The association with other cardiac malformations determines whether or not pulmonary blood

Figure 43-52 *A,* Tricuspid atresia with normally related great arteries, a small ventricular septal defect, diminutive right ventricular chamber, and narrowed outflow tract. *B,* An example of tricuspid atresia and complete transposition of the great arteries in which the left ventricular chamber is essentially a common ventricle, with the aorta arising from an infundibular component (RV) of the common ventricle. VC = vena cava; RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; LPV = left pulmonary vein; LPA = left pulmonary artery; PT=pulmonary trunk. *(Modified from Edwards JE, Burchell HB: Congenital tricuspid atresia: Classification. Med Clin North Am 33:1177, 1949.)*

flow is decreased, normal, or increased and therefore the degree of systemic hypoxemia.[431] The clinical picture usually is dominated by symptoms resulting from

greatly diminished pulmonary blood flow with severe cyanosis. Cyanosis results from an obligatory admixture of systemic and pulmonary venous blood in the left atrium, and its intensity primarily depends on the magnitude of pulmonary blood flow. Heart failure, rather than cyanosis, is the predominant problem in infants with torrential pulmonary blood flow, which results when D-transposition of the great arteries, a VSD, and an unobstructed pulmonary outflow tract coexist. If these patients survive infancy, they are at risk for pulmonary vascular obstructive disease; a favorable response to pulmonary arterial banding is common early in life.

CLINICAL FEATURES.

The diagnosis is easily established in the vast majority of infants with tricuspid atresia and pulmonary hypoperfusion. The *ECG* findings of left-axis deviation, right atrial enlargement, and left ventricular hypertrophy in a cyanotic infant strongly suggest tricuspid atresia. *Echocardiography* reveals a small or absent right ventricle, large left ventricle, and absent tricuspid valve echoes (Fig. 43-53 ; see also Chap. 7); further, it may demonstrate the relation of the great arteries unless pulmonic atresia is present. Color flow and pulsed Doppler echocardiography reveal the abnormal flow patterns; apical and subxiphoid cross-sectional views best reveal the atretic tricuspid orifice. Seen *roentgenographically* are diminished pulmonary vascular markings and a concavity in the region of the cardiac silhouette usually occupied by the main pulmonary artery. The right atrial shadow may be prominent unless left-sided juxtaposition of the atrial appendages exists, which produces a straight and flattened right heart border.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY.

The right ventricle cannot be entered directly from the right atrium. When the great arteries are related normally, pulmonary blood flow is found to be derived from shunting through a VSD or by way of a patent ductus arteriosus; the latter and the bronchial collaterals are the source of pulmonary flow if the ventricular septum is intact. In complete transposition, the pulmonary artery fills directly from the left ventricle and the aorta indirectly through a VSD and the hypoplastic right ventricle. Because complete admixture exists in the left atrium of pulmonary and systemic venous return, the degree of systemic arterial hypoxemia depends on the pulmonary-systemic flow ratio. Right atrial angiography does not opacify the right ventricle unless by way of a VSD. Selective left ventricular *angiography* permits identification of the hypoplastic right ventricle, the size and location of the VSD, the type of pulmonary obstruction, the relation between the great arteries, and the size of the distal pulmonary arterial tree.

MANAGEMENT.

Balloon atrial septostomy in those infants with a restrictive interatrial communication and palliative operations designed to increase pulmonary blood flow (systemic arterial--or venous--pulmonary artery anastomosis) are capable of producing clinical improvement of significant duration in patients with diminished blood flow.[431]

Functional correction of the anomaly has been accomplished in children older than 12

months by an intraatrial cavopulmonary baffle (lateral tunnel Fontan) (Fig. 43-54) or connection of the left pulmonary artery to the superior vena cava and inferior vena cava to the right pulmonary artery.[432] An adjustable snare around the atrial septal defect or a fenestrated cavocaval baffle with later transcatheter closure appears to prevent acute increases in systemic venous pressure, improve cardiac output, and enhance surgical survival.[433] [434] In patients with tricuspid atresia and complete transposition of the great arteries, subaortic obstruction can be anticipated when the VSD becomes restrictive, also referred to as an obstructive bulboventricular foramen. In most patients, the subaortic tissue must be resected, or preferably, a main pulmonary artery to ascending aorta anastomosis (Damus-Stansel-Kaye procedure) is performed at the time of the Fontan operation.[435] Candidates for these corrective procedures must have normal pulmonary vascular resistance and a mean pulmonary artery pressure less than 15 mm Hg, pulmonary arteries of adequate size, pulmonary vascular resistance less than 3 units/m, and good left ventricular function.[436] The postoperative period usually is characterized transiently by a superior vena cava syndrome with right heart failure, edema, ascites, and hepatomegaly. Long-term results have been generally good, but late management issues after Fontan operation are concerned with ventricular dysfunction,

Figure 43-53 Apical four-chamber views of a patient with tricuspid atresia. In these views, the right atrium (RA) and left atrium (LA) can be seen above, and the small right ventricle (RV) and large left ventricle (LV) can be seen below. *Top,* Diastole with the mitral valve in the open position. Note the intense tissue echoes from the right atrioventricular groove between the right atrium (RA) and right ventricle (RV), indicating absence of the tricuspid valve. The descending aorta (DAO) can be identified posterior to the left atrium (LA). *Bottom,* Doppler color flow map of the same patient taken toward end-systole, showing the passage of blood across the ventricular septal defect (arrow).

atrial ventricular valve regurgitation, atrial arrhythmia, cyanosis, thromboembolism, and protein-losing enteropathy.[437] [438] Late postoperative exercise studies show subnormal exercise tolerance.[439] Late atrial arrhythmias can be a consequence of adverse preoperative hemodynamic function or the type of surgical correction (see Chap. 25).[440]

Ebstein Anomaly of the Tricuspid Valve (See also p. 1603)

This malformation is characterized by a downward displacement of the tricuspid valve into the right ventricle due to anomalous attachment of the tricuspid leaflets (Fig. 43-55 ; see also (Fig. 44-8 (Figure Not Available)).[441] Case-control studies suggest that maternal exposure in the first trimester to lithium carbonate, used in the management of manic-depressive psychosis, is associated with a greatly increased risk of this anomaly in exposed offspring.[442] Tricuspid valve tissue is dysplastic, and a variable portion of the septal and inferior

Figure 43-54 Fontan operation by total cavopulmonary connection. *Top,* The pulmonary trunk has been divided close to the pulmonary valve, and both ends have been closed. The right atrium is opened, and a pump sump sucker is placed across the foramen orale and into the left atrium (not shown). Marking stitches are placed at the proposed site of transection of the superior vena cava (SVC) and at the proposed sites of the two longitudinal incisions on the superior and inferior aspects of the right pulmonary artery (RPA). *Middle,* The anastomosis is made between the distal end of the divided superior vena cava and the incision in the superior aspect of the right pulmonary artery. The cardiac end of the superior vena cava is rarely enlarged; anastomosis is made to an incision in the inferior aspect of the right pulmonary artery. *Bottom,* A tunnel is created from a cylinder of either Dacron, Gore-Tex, or pericardium connecting the inferior vena cava (IVC) to the atrial orifice of the superior vena cava. The right pulmonary veins drain behind the tunnel. Ao=aorta. *(From Kirklin, JW, Barratt-Boyes BG: Cardiac Surgery. 2nd ed. New York, Churchill Livingstone, 1993, p 1068.)*

Figure 43-55 Anatomical specimen of Ebstein's anomaly of the tricuspid valve, cut in the same plane as an apical four-chamber echocardiographic view (see Fig. 43-56). The septal and anterior leaflets of the tricuspid valve (SLTV, ALTV) are displaced into the right ventricle (RV), producing a large atrialized right ventricle (ARV). VS = ventricular septum; RA = right atrium; LA = left atrium; MV = mitral valve; LV = left ventricle. *(Courtesy of Dr. Thomas DiSessa.)*

cusps adheres to the right ventricular wall some distance away from the AV junction. Because of the abnormally situated tricuspid orifice, a portion of the right ventricle lies between the AV ring and the origin of the valve, which is continuous with the right atrial chamber. This proximal segment is "atrialized," and a distal, functionally small ventricular chamber exists. The degree of impairment of right ventricular function depends primarily on the extent to which the right ventricular inflow portion is atrialized and on the magnitude of tricuspid valve regurgitation.

CLINICAL MANIFESTATIONS.

These are variable because the spectrum of pathology varies widely and because of the presence of associated malformations. [443] [444] If the tricuspid valve is severely deformed, neonatal heart failure or even fetal hydrops and intrauterine death may occur.[445] At the other end of the spectrum, patients with a mildly deformed tricuspid valve may remain symptom free well into adulthood. The severity of symptoms also depends on the presence or absence of associated malformations. An interatrial communication consisting of a patent foramen ovale or an ostium secundum atrial septal defect is present in more than half the cases. The most common important associated defect is pulmonic stenosis or atresia. Other coexistent anomalies may include an ostium primum type of atrial septal defect and VSD alone or in combination with other lesions. The Ebstein lesion commonly is observed in association with congenitally corrected transposition of the great arteries, in which the tricuspid valve is in the left AV orifice. The usual manifestations in infancy are cyanosis, a cardiac

murmur, and severe congestive heart failure. The magnitude of tricuspid regurgitation in neonates is enhanced because the pulmonary vascular resistance is normally high early in life.[446] In this regard, newborn infants with Ebstein anomaly and massive tricuspid regurgitation must be distinguished by two-dimensional and Doppler echocardiography from those with organic pulmonary atresia and the presence of elevated perinatal pulmonary vascular resistance.

The tricuspid regurgitation in infants with Ebstein anomaly may lessen substantially, and cyanosis may disappear early in life as pulmonary vascular resistance falls, only to occur at a later age when right ventricular dysfunction and/or paroxysmal arrhythmias develop. In some infants with Ebstein malformation, cyanosis is suddenly intensified as the degree of pulmonary hypoperfusion is unmasked by spontaneous closure of a patent ductus arteriosus.[447]

Beyond infancy, the onset of symptoms is insidious; the most common complaints are exertional dyspnea, fatigue, and cyanosis. About 25 percent of patients suffer episodes of paroxysmal atrial tachycardia. A prominent systolic pulsation of the liver and a large *v* wave in the jugular venous pulse accompany the systolic thrill and murmur of tricuspid regurgitation. Wide splitting of the first and second heart sounds and prominent third and fourth heart sounds may produce a characteristically rhythmic auscultatory cadence with a triple, quadruple, and quintuple combination of sounds.

LABORATORY FINDINGS.

The ECG abnormalities commonly fall into two categories--those with a right bundle branch block pattern and those with a Wolff-Parkinson-White (WPW) pattern (see Chap. 25). The ECG presentation in the latter is always from a right-sided accessory pathway, resembling left bundle branch block with predominant S waves in the right pericardial leads. The presence of a WPW pattern increases the risk of supraventricular paroxysmal tachycardia (WPW syndrome).[448] The ECG most often shows giant P waves, a prolonged PR interval (in the absence of WPW), and prolonged terminal QRS depolarization, producing variable degrees of right bundle branch block. These distinctive findings help to distinguish Ebstein's anomaly from other forms of right ventricular dysplasia (see Chaps. 25 and 48), whose presenting problem often is an arrhythmia. *Roentgenographic* studies (see Chap. 8) usually demonstrate an enlarged right atrium, a small right ventricle, and a pulmonary artery with reduced pulsations; the pulmonary vascularity can be reduced if a large right-to-left shunt is present.

Echocardiographic Findings.

Echocardiography clearly defines the features of Ebstein malformation.[449] The apical four-chamber plane shows the downward displacement of the attachment of the septal leaflet of the tricuspid valve, a finding overemphasized in the literature. The most important valvar displacement is that of the posterior or mural leaflet of the tricuspid valve, which is not well seen in the four-chamber view but rather in the subcostal view in infants and smaller children and in the parasternal long-axis or apical two-chamber view in older children and adults (Fig. 43-56) . Subcostal echocardiography also defines the dysplasia of the leaflets of the valve, the right atrial dilatation, and the displacement of

the entire tricuspid valve into the right ventricle. An additional challenge posed by the malformation, especially important for operative repair, is to determine whether the valvular attachment of the anterosuperior tricuspid leaflet is attached to the underlying myocardium. Echocardiographic identification of the chordae tendineae informs the surgeon of the need for freeing the valve during annuloplasty.

Doppler color flow imaging defines the degree of tricuspid regurgitation. Mapping determines the magnitude of regurgitation and the site of origin well within the body of the right ventricle. In addition, the presence of valvular stenosis (or nonopening) is determined by Doppler, particularly in neonates in whom patent ductus arteriosus supported systemic pressure may hold the pulmonary valve leaflets shut, simulating pulmonary atresia. The faint detection of pulmonary regurgitation by Doppler flow mapping aids differentiation of these two entities.

Invasive Study.

These are rarely necessary. When *cardiac catheterization* is performed, the intracavitary ECG recorded just proximal to the tricuspid valve shows a right ventricular type of complex, while the pressure recorded is that of the right atrium. A right-to-left atrial shunt is normally present. The hemodynamic findings depend on the degree of tricuspid regurgitation. The cardiac muscle is unusually irritable, and a high incidence of significant arrhythmias during catheterization has been noted. Selective right ventricular *angiocardiography* shows the position of the displaced tricuspid valve, the size of the right ventricle, and the configuration of the outflow portion of the right ventricle.

MANAGEMENT.

Ebstein anomaly may be compatible with a relatively long and active life, with most patients surviving into the third decade of life[450] (see Chap. 44). In

Figure 43-56 Apical four-chamber view of Ebstein's malformation in anatomical orientation. The left atrium (LA) and right atrium (RA) are seen above, and the right ventricle (RV) and left ventricle (LV) are seen below. Arrows point to the anterior leaflet of the tricuspid valve (AL) and septal leaflet (SL). The space between the septal attachment of the tricuspid valve and the mitral valve arrows is enlarged. This area between the true right atrium and the atrioventricular valve indicates the area of atrialized right ventricle.

symptomatic infants with severe cardiomegaly, the initial surgical approach is similar to that in patients with tricuspid atresia, creating a systemic pulmonary shunt, and at a later age the Fontan approach, which necessitates suture or pericardial patch closure of the tricuspid valve. Consideration may be given in some of these patients to creating a bidirectional Glenn shunt from the superior vena cava to the pulmonary arteries, to

divert systemic venous return from the right atrium and to increase pulmonary blood flow. In older patients, significant benefit has resulted from reconstruction of the tricuspid valve, closure of the atrial septal defect, plication of the free wall of the right ventricle, posterior tricuspid annuloplasty, and a reduction in right atrial size.[443] [455] Because late results of this latter approach are encouraging, we now recommend operation for all symptomatic patients and even asymptomatic patients if their heart size is increasing significantly.[451] [452] [453] [454] Some surgeons have sought to minimize postoperative tricuspid regurgitation by inserting a bioprosthetic valve if tricuspid valve tissue is inadequate for a good result.[456] In patients with a preexcitation syndrome (see Chap. 25) that is producing life-threatening rhythm disturbances, the accessory conduction pathways are either catheter ablated or surgically divided (see Chap. 23).[457]

TRANSPOSITION COMPLEXES

The term *transposition* identifies a group of malformations that have in common an abnormal relation between the cardiac chambers and great arteries. In this chapter the term is used to include both anomalous insertion of the pulmonary veins and cardiac malpositions.

Complete Transposition of the Great Arteries (See also p. 1609)

MORPHOLOGY.

This is a common and potentially lethal form of heart disease in newborns and infants.[458] The malformation consists of the origin of the aorta arising from the morphological right ventricle and that of the pulmonary artery from the morphological left ventricle. With rare exceptions, there is no fibrous continuity between the aortic and mitral valves. The origin of the aorta usually is to the right and anterior to the main pulmonary artery but may be lateral to it. Thus, dextro- or D-transposition is a term often used interchangeably with complete transposition. In other classifications, the anomaly is described as concordant AV and discordant ventriculoarterial connections. The embryogenesis of complete transposition of the great arteries is controversial. The consensus is that the ventricular origins of the great arteries are reversed after development of a straight rather than a spiral infundibulotruncal septum. Transposition appears to result from a transfer of the pulmonary artery, instead of the aorta, from the heart tube's outlet zone to the left ventricle.[459] The latter can result from maldevelopment of the infundibulum or from a combination of both infundibulum maldevelopment and truncal malseptation; the former results if the subpulmonary rather than the subaortic infundibulum is absorbed.

The anatomical arrangement results in two separate and parallel circulations. Some communication between the two circulations must exist after birth to sustain life; otherwise, unoxygenated systemic venous blood is directed inappropriately to the systemic circulation and oxygenated pulmonary venous blood is directed to the pulmonary circulation. Almost all patients have an interatrial communication (Fig. 43-57 ; see also Fig. 44-17 (Figure Not Available)). Two-thirds have a patent ductus arteriosus, and about one-third have an associated VSD. Complete transposition occurs

more frequently in the offspring of diabetic mothers and more often in males than in females. Without treatment, about 30 per cent of these infants die within the first week of life, 50 percent within the first month, 70 percent within 6 months, and 90 percent

Figure 43-57 Complete transposition of the great arteries. Intercirculatory mixing occurs only at the atrial level. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; Ao = aorta; PA = pulmonary artery.

within the first year.[458] Those who live beyond infancy have, as a general rule, either an isolated large atrial septal defect or a single ventricle, or VSD and pulmonic stenosis. Current aggressive medical and surgical approaches to this group of patients have transformed the prognosis for an infant with this malformation from hopeless to very good.

HEMODYNAMICS.

The *clinical course* is determined by the degree of tissue hypoxia, the ability of each ventricle to sustain an increased workload in the presence of reduced coronary arterial oxygenation, the nature of the associated cardiovascular anomalies, and the anatomical and functional status of the pulmonary vascular bed.[460] A bidirectional shunt is always present because continuous unidirectional shunting would result in progressive depletion of the circulating volume in either the pulmonary or the systemic vascular bed.

A major determinant of the systemic arterial oxygen saturation is the amount of blood exchanged between the two circulations by intercirculatory shunts. The net volume of blood passing left to right from the pulmonary to the systemic circulation represents the anatomical left-to-right shunt and is in fact the effective systemic blood flow (i.e., the amount of oxygenated pulmonary venous return reaching the systemic capillary bed). Conversely, the volume of blood passing right to left from the systemic to the pulmonary circulation constitutes the anatomical right-to-left shunt and is in fact the effective pulmonary blood flow (i.e., the net volume of unsaturated systemic venous return perfusing the pulmonary capillary bed).

The net volume exchange between the two circulations per unit time is equal. The magnitude of the intercirculatory mixing volume is modified by the number of intercirculatory communications that exist, the presence of associated obstructive intracardiac and extracardiac anomalies, the extent of the bronchopulmonary circulation, and the relation between pulmonary and systemic vascular resistance. For example, in newborns with an intact ventricular septum and a constricted or closed patent ductus arteriosus, inadequate mixing through a small patent foramen ovale often is the cause of severe hypoxemia. If a large interatrial communication or a VSD exists, systemic arterial oxygen saturation is influenced more importantly by the pulmonary-systemic

blood flow relation than by the adequacy of mixing; augmented pulmonary blood flow produces a higher systemic arterial saturation if the left ventricle can sustain a high-output state without the intervention of congestive heart failure and pulmonary edema. The systemic arterial oxygen saturation is low, despite adequate intercirculatory mixing sites, if pulmonary blood flow is reduced by left ventricular outflow tract obstruction or increased pulmonary vascular resistance.

Pulmonary Vascular Changes.

Infants with complete transposition of the great arteries are particularly susceptible to the early development of *pulmonary vascular obstructive disease.*[460] Moderately severe morphological alterations develop in the pulmonary vascular bed by the age of 6 to 12 months in many infants and by 2 years in almost all patients with an associated large VSD or large patent ductus arteriosus in the absence of obstruction to left ventricular outflow. Advanced pulmonary vascular disease is also noted within this same time frame in 15 to 30 percent of patients without a patent ductus arteriosus and with an intact ventricular septum. Systemic arterial hypoxemia, increased pulmonary blood flow, and pulmonary hypertension contribute to the development of pulmonary vascular obstruction in these patients, as they do in other forms of congenital heart disease. Among the additional factors implicated in the accelerated and more widespread pulmonary vascular obstruction found in patients with complete transposition is the presence of extensive bronchopulmonary anastomotic channels, which enter the pulmonary vascular bed proximal to the pulmonary capillary bed; thus, oxygen tension is reduced at the precapillary level, causing pulmonary vasoconstriction.[461]

Beyond the early neonatal period, many patients have an abnormal distribution pattern of pulmonary blood flow, with preferential flow to the right lung. The asymmetrical distribution of pulmonary blood flow in these individuals results from an abnormal rightward inclination of the main pulmonary artery in the transposition malformation that favors flow from the main to the right pulmonary artery. Persistently increased pulmonary blood flow to the right lung would be expected to contribute to pulmonary vascular obstructive changes within the lung; in the left pulmonary vascular bed, thrombotic changes may occur because of the combination of reduced flow and polycythemia. Finally, it should be recognized that a prenatal alteration in pulmonary vascular smooth muscle may exist because blood perfusing the fetal lungs in complete transposition of great arteries has a higher than normal P_{O_2} and may serve to dilate pulmonary vessels in utero. Postnatally, such vessels may have an enhanced capacity to constrict in response to vasoactive stimuli and suffer anatomical, obliterative changes.

CLINICAL FINDINGS.

Average birth weight and size of infants born with complete transposition of the great arteries are greater than normal. The usual clinical manifestations are dyspnea and cyanosis from birth, progressive hypoxemia, and congestive heart failure. Early in postnatal life, the clinical manifestations and course are influenced principally by the magnitude of intercirculatory mixing. The most severe cyanosis and hypoxemia are observed in infants who have only a small patent foramen ovale or ductus arteriosus

and an intact ventricular septum and in whom mixing is inadequate, or in those infants with relatively reduced pulmonary blood flow because of left ventricular outflow tract obstruction.[462] With a large persistent patent ductus arteriosus or a large VSD, cyanosis may be minimal and heart failure is the usual dominant problem after the first few weeks of life.[458] It should be recognized that a patent ductus arteriosus is present in about half of newborn infants with transposition, although it closes functionally and anatomically soon after birth in almost all cases. If the ductus arteriosus remains open, better mixing of the venous and arterial circulations usually is at the expense of pulmonary artery hypertension.[463]

Cardiac murmurs are of little diagnostic significance and are absent or insignificant in about 30 to 50 percent of infants with complete transposition of the great arteries and an intact ventricular septum. In infants with a large persistent patent ductus arteriosus, fewer than half exhibit physical signs typical of ductus arteriosus, such as continuous murmur, bounding pulses, or a prominent mid-diastolic rumble. Moreover, *differential cyanosis* caused by reversed pulmonary-to-systemic shunting across the ductus arteriosus is difficult to detect because of generalized arterial desaturation. In those infants with a large VSD, a pansystolic murmur usually emerges within the first 7 to 10 days of life. In newborns with transposition and severe pulmonic stenosis or atresia, the clinical findings are similar to those in infants with tetralogy of Fallot.

ELECTROCARDIOGRAPHY AND ROENTGENOGRAPHY.

The most usual *ECG findings* include right-axis deviation, right atrial enlargement, and right ventricular hypertrophy, reflecting that the right ventricle is the systemic pumping chamber. Combined ventricular hypertrophy may be present in those patients with a large VSD and elevated pulmonary blood flow. Isolated left ventricular hypertrophy is encountered rarely in patients with a VSD and a hypoplastic right ventricle, in many of whom the tricuspid valve is displaced abnormally and straddles a VSD. In the first days of life, the chest radiograph may appear normal, particularly

in infants with an intact ventricular septum. Thereafter, roentgenographic findings often are highly suggestive of the diagnosis,[464] and consist of (1) progressive cardiac enlargement in early infancy; (2) a characteristic oval or egg-shaped cardiac configuration in the anteroposterior view, and a narrow vascular pedicle created by superimposition of the aortic and pulmonary artery segments; and (3) increased pulmonary vascular markings (Fig. 43-58) . A right aortic arch is seen in about 4 percent of infants with an intact ventricular septum and 11 percent of infants with VSD.

CT scanning and magnetic resonance imaging (see Chap. 10) are also capable of establishing the diagnosis.

ECHOCARDIOGRAPHY.

Two-dimensional echocardiography is the procedure of choice in the diagnosis of complete transposition of the great arteries and the detection of significant associated cardiac anomalies[465] (Figs. 43-59 and 43-60 ; see also Fig. 44-21). Indeed, prenatal detection, leading to early management, favorably modifies neonatal morbidity and mortality.[465] Postnatally, in sagittal cross sections, the aorta is observed to ascend retrosternally, in contrast to the normal posterior sweep of the pulmonary artery. With transverse short-axis cross-sectional imaging, the diagnosis is confirmed by demonstrating that the anterior great artery (the aorta) is to the right of the posterior great artery (pulmonary) or that the two arteries are visualized side by side (see Fig. 43-59). Moreover, from subcostal views (see Fig. 43-60), the course of the two great arteries may be traced to delineate their ventricle of origin, demonstrating that the anterior rightward vessel (aorta) originates from the right ventricle and the posterior leftward vessel (pulmonary artery) originates from the left ventricle (see Fig. 43-60). In addition, echocardiography allows sensitive demonstration of the proximal coronary artery position, branching, and course. The intramural proximal course of a coronary artery has also been recognized.[467] [468] Echocardiography also readily identifies associated defects. VSDs may be localized to the membranous, AV, and trabecular muscular septa, and malalignment types of VSDs may be identified if the infundibular septum is shifted either anteriorly or posteriorly.[469] A subaortic obstruction may be created by anterior shifting of the infundibular septum, whereas a posterior shift may narrow the subpulmonary area. The nature of left ventricular outflow tract obstruction may be further identified as a fixed obstruction caused by a fibromuscular ridge or as a dynamic obstruction caused by deviation of the interventricular

Figure 43-58 Chest roentgenogram in a 4-day-old infant with complete transposition of the great arteries showing an oval-shaped heart with a narrow base and increased pulmonary vascular markings.

Figure 43-59 *Top,* A two-dimensional echocardiographic short-axis scan demonstrates normal great artery relations. The right ventricular outflow tract (RVO) wraps around the aorta (AO) in a clockwise direction. The pulmonic valve (PV) is to the left of the aortic valve. *Bottom,* Parasternal short-axis (P S AX) view showing the aorta (AO) anteriorly and the pulmonary artery (PA) posteriorly bifurcating into its left and right branches (arrow). LA = left atrium; RA = right atrium; TV = tricuspid valve.

septum toward the left ventricular cavity and the apposition between a thickened interventricular septum and systolic anterior motion of the mitral valve.

Ultrasound imaging has become a standard procedure to guide catheter placement and manipulation during balloon atrial septostomy[470] and to assess the anatomical adequacy of the septostomy. Because echocardiography so clearly delineates the arterial transposition, the coronary arteries, and associated anomalies, many infants may proceed to surgery without prior cardiac catheterization.

The major abnormal hemodynamic findings include right ventricular pressure at systemic levels and either a high or low left ventricular pressure, depending on pulmonary blood flow, pulmonary vascular resistance, and the presence or absence of left ventricular outflow tract obstructive lesions. Oxygen saturation in the aorta is lower than that in the pulmonary artery. Application of the Fick principle to the calculation of pulmonary and systemic blood flow rates in these patients is an important source of error. Assumed values of oxygen consumption are unreliable in severely hypoxemic infants.

Figure 43-60 Composite subcostal views of transposition of the great arteries. *Top,* Subcostal coronal view showing the main pulmonary artery (MPA) arising directly from the left ventricle (LV) and dividing into the right (R) and left (L) pulmonary arteries. The right atrium (RA) and right ventricle (RV) lie adjacent in this view to the liver. *Middle,* The scan plane has been rotated 90 degrees clockwise (note the change in spatial orientation and the position of the spine). The thymus (TH) is seen anteriorly, and the innominate vein (IV) lies anterior to the aortic arch (indicated by arrows, respectively). The right ventricle (RV) lies anteriorly above the diaphragm and behind the thymus and gives rise to the aorta (AO), its arch, and the descending aorta (DAO). The main pulmonary artery (PA) lies in the crux of the aortic arch. *Bottom,* An intermediate subcostal view, lying oblique in a plane between the top two panels. The entire ventriculoarterial connection is imaged in this plane, showing the right ventricle connecting to the aortic arch, a small ventricular septal defect indicated by the small arrow, and the pulmonary artery (PA) arising from the left ventricle (LV). The left atrium (LA) can be seen below the pulmonary artery.

Moreover, because systemic and particularly pulmonary arteriovenous oxygen differences may be quite reduced, small errors in oxygen saturation values result in large errors in flow calculations. Furthermore, because bronchial collaterals enter the pulmonary circuit at the precapillary level, a true mixed pulmonary artery saturation cannot be sampled; pulmonary blood flow is therefore overestimated when one uses a sample from the central pulmonary artery, and pulmonary vascular resistance values often are underestimated.

Infants who have simple, complete transposition of the great arteries and who present in the first few weeks of life to a center prepared to correct the anomaly by the arterial switch operation (discussed later) often are taken to the operating room shortly after two-dimensional echocardiography and Doppler examination are performed.[21] In these cases, transcatheter balloon atrial septostomy is not performed unless a delay is expected in taking the patient to the operating room. In essentially all other patients, under echocardiographic or fluoroscopic guidance at cardiac catheterization, balloon septostomy is the initial approach to the patient.

The diagnostic portion of the cardiac catheterization allows confirmation of the anatomical derangement of the great arteries and establishes the presence of

associated lesions; in newborns, unless prompt arterial switch repair is planned, it should always be accompanied by a palliative balloon atrial septostomy, which serves to enlarge the interatrial communication and improve oxygenation. In older neonates, usually beyond age 3 weeks, thickening of the atrial septum may preclude satisfactory balloon septostomy. In those instances, transcatheter blade septostomy is the preferred approach to palliation. Two-dimensional echocardiography, with or without fluoroscopy, may be used as the imaging mode for both balloon and blade creation of an atrial septal defect.[471] Subcostal four-chamber and sagittal views image cardiac anatomy and catheter position during the procedure, substantially reducing radiation dose.

Both the diagnostic and the palliative procedures can be performed by percutaneous entry into the femoral vein, umbilical vein catheterization, or direct cutdown into the femoral or saphenous vein. The catheter passes easily across the foramen ovale into the left atrium and left ventricle and may be manipulated into the pulmonary artery by means of a flow-directed balloon-guided catheter or by manipulation of a standard catheter bent in the form of a J loop within the left ventricle, with the tip pointed posteriorly to the pulmonary artery. When a large VSD is present, the catheter can often be manipulated directly across it from the right ventricle into the pulmonary artery.

ANGIOGRAPHY.

This is diagnostic and demonstrates that the anteriorly placed aorta arises from the right ventricle and that the posteriorly placed pulmonary artery in continuity with the mitral valve arises from the left ventricle. The status of the ductus arteriosus and the site and size of a VSD can be well visualized by angiography. Interventricular defects posterior and inferior to the crista supraventricularis occur in about half of these patients; less often, the defects are anterior and superior to the crista supraventricularis or are of the AV septal type.[472] Various lesions may be

identified as the cause of left ventricular outflow tract obstruction, including ventricular septal hypertrophy with systolic anterior movement of the mitral valve, discrete or tunnel fibromuscular subpulmonic stenosis, valvular and supravalvular stenosis, and, rarely, an aneurysm of the membranous ventricular septum or redundant tricuspid valve tissue protruding through a VSD.

Both angiographic and echocardiographic imaging may be required to detect the coronary arterial patterns seen in patients with complete transposition of the great arteries.[467] [468] [473] [474] In the majority, the left coronary artery originates in the left sinus and the right coronary artery originates in the posterior sinus, with a single ostium above both the left and the posterior sinus. In almost 20 percent of patients, the left circumflex artery arises as a branch of the right coronary artery; a single coronary artery is present in about 6 percent; in 3 to 4 percent of patients, either the right coronary and anterior descending arteries originate in the left sinus, with the left circumflex originating in the posterior sinus, or two ostia are present above one sinus, one giving rise to the right and

the other to the left coronary artery. To avoid the danger of excision during transfer of the coronary arteries as part of the arterial switch corrective operation, the intramural course of the left coronary artery or the left anterior descending coronary artery should be identified, a finding in up to 5 percent of patients. An intramural course should be assumed when the vessel has an aberrant origin from the right sinus or when it is in intimate relationship with the commissure between the right and left sinuses and courses between the great arteries.

MANAGEMENT

Medical Treatment.

This often is of limited help but should be vigorous because both functional and anatomical corrections of the malformation achieve good results. Conservative measures include the use of oxygen, digitalis, diuretics, iron (if an associated iron-deficiency anemia is present), and intravenous sodium bicarbonate for severe hypoxemic metabolic acidosis. Dilatation of the ductus arteriosus by prostaglandin E_1 in the early neonatal period both augments pulmonary blood flow and enhances intercirculatory mixing.

Atrial Septostomy.

Creation or enlargement of an interatrial communication is the simplest procedure for providing increased intracardiac mixing of systemic and pulmonary venous blood; this is preferably achieved by rupturing the valve of the foramen ovale by balloon catheter during transseptal catheterization of the left side of the heart (Rashkind procedure) or by blade septostomy. Surgical atrial septectomy seldom is required. The balloon should be inflated to a diameter of about 15 mm before pull-back to the right atrium. Salutary results consist of a fall in left atrial pressure, equalization of mean left and right atrial pressures, and an increase in the systemic arterial oxygen saturation. When the foramen ovale is stretched by the balloon without accomplishing rupture of the septum primum valve of the fossa ovalis, the improvement in oxygenation is short lived. Infusion or reinfusion intravenously of prostaglandin E_1 (0.05 to 0.1 mg/kg/min) has been shown to improve systemic oxygenation temporarily in the latter situation by dilating the ductus arteriosus and thereby facilitating intercirculatory mixing. Although balloon atrial septostomy usually is successful in stabilizing the infant's condition and allowing survival in the neonatal period, the initial rise in systemic arterial oxygen saturation to 65 to 75 percent often is not sustained beyond 6 to 9 months of age.

SURGICAL TREATMENT

The development of *corrective operations* for infants born with transposition of the great arteries has greatly improved prognosis.[475] It has also been suggested that prenatal detection of the anomaly reduces neonatal morbidity and mortality.

ARTERIAL SWITCH OPERATION.

A one-stage anatomical correction is the approach of choice in major centers that care for infants with congenital heart disease.[475] [476] [477] [478] [479] In this operation, both coronary arteries are transposed to the posterior artery; the aorta and pulmonary arteries are transected, contraposed, and anastomosed (Jatene operation) (Fig. 43-61 ; see also Fig. 44-18 (Figure Not Available)). The arterial switch anatomical correction may be complicated by coronary ostial stenosis, acquired supravalvular aortic and/or pulmonary stenosis, and pulmonic and/or aortic incompetence. The major advantages of the arterial switch procedure, when compared with the atrial switch procedure, are restoration of the left ventricle as the systemic pump and the potential for long-term maintenance of sinus rhythm.[480]

Within the first month of life or rarely two,[477] the arterial switch operation may be performed as a single-stage repair. In such patients, the origin and branching patterns of the coronary arteries are reliably defined preoperatively by two-dimensional echocardiography. One of the main limiting factors for success in the arterial switch procedure is proper relocation of the coronary arteries. Thus, it is particularly important to know the precise variations in coronary arterial anatomy. In approximately 5 percent of the patients, the arteries follow an intramural course, requiring reroofing to allow coronary transfer.[458] Most centers consider that in infants beyond age 1 month it is necessary to prepare the left ventricle to withstand the systemic pressure that is produced after switching the great arteries, because if the ventricular septum is intact, left ventricular pressure and left ventricular wall thickness diminish normally in relation to the postnatal reduction in pulmonary artery pressure. In these infants, a two-stage approach is used, the first of which consists of banding the pulmonary artery; the arterial switch is performed soon thereafter, in some centers as early as 1 to 2 weeks later.[481]

In the unusual infant with an intact ventricular septum and a significant patent ductus arteriosus, an early neonatal arterial switch corrective operation with closure of the ductus is indicated. The optimal management of a large VSD is a one-stage intraarterial switch anatomical correction as early in life as possible.

In some patients, after early arterial repair of transposition of the great arteries, abnormally enlarged bronchial arteries are identified at postoperative catheterization, and they explain continuous murmurs or persistent cardiomegaly. When these vessels are large enough to produce a volume load to the systemic ventricle, catheter-directed coli embolization is indicated.[482] Follow-up studies after the arterial switch operation have demonstrated good left ventricular function

Figure 43-61 Complete transposition of the great arteries, corrected by a modified arterial switch operation *(a)*. The aorta and pulmonary artery are transected, and the orifices of the coronary arteries are excised with a rim of adjacent aortic wall *(b)*. The aorta is brought under the bifurcation of the pulmonary artery, and the proximal pulmonary artery and the aorta are anastomosed without necessitating graft interposition. The coronary arteries are transferred to the pulmonary artery *(c)*. The mobilized pulmonary artery is directly anastomosed to the proximal aortic stump *(d)*. *(From Stark J, deLaval M: Surgery for*

Congenital Heart Defects. New York, Grune & Stratton, 1983, p 379.)

and normal exercise capacity.[483] [484] Potential sequelae of the operation include supravalvular pulmonary stenosis (which may be treated by either reoperation or balloon angioplasty), supravalvular aortic stenosis, and neoaortic regurgitation, usually mild. Long-term patency and growth of the coronary arteries appear satisfactory.[485] [486] [487] Infants with transposition of the great arteries plus a VSD and left ventricular outflow tract obstruction may require a systemic-pulmonary artery anastomosis when a pronounced diminution in pulmonary blood flow exists. A later corrective procedure for these patients bypasses the left ventricular outflow obstruction and uses an intracardiac ventricular baffle connecting the left ventricle to the aorta and an extracardiac prosthetic conduit between the right ventricle and the distal end of a divided pulmonary artery (Rastelli procedure).[488] An alternative approach (Lecompte procedure) couples an intraventricular tunnel and the arterial switch operation, avoiding the use of an extracardiac conduit.[489]

ATRIAL (VENOUS) SWITCH OPERATION.

This correction, by either the Mustard or Senning techniques, diverts systemic venous return into the left ventricle through the mitral valve and thence through the left ventricle and pulmonary artery, while the pulmonary venous blood is diverted through the tricuspid and right ventricle to the aorta. Because midterm results of atrial switch procedures disclosed numerous problems involving late right ventricular failure, tricuspid insufficiency, and arrhythmias, most centers have abandoned the use of the atrial switch approach in favor of the more anatomical arterial switch operation.[490] [491] [492] [493] [494] [495] [496]

After physiological correction by atrial switch, postoperative complications are directly related to the intraatrial repair (shunts across the intraatrial patch and obstruction to either systemic or pulmonary venous return or both). There is a high incidence of early and late postoperative dysrhythmias that are more likely to have their basis in injury to the sinoatrial node and/or its arterial supply than in disruption of internodal tracts or damage to the AV node.[491] Tricuspid regurgitation is a less common complication of operation and may in some patients be related to a preexisting abnormality of the tricuspid valve, whereas in most it is related to right ventricular dysfunction. Although assessment of right ventricular contractility is difficult, the right ventricular pump function appears to be impaired before Mustard operation and does not return to normal after successful surgery.[496] It seems likely that the right ventricle can perform as a systemic pumping chamber for the duration of a normal life span.[492]

In patients with significant pulmonary vascular obstructive disease, the risk associated with definitive repair (anatomical correction or intraatrial baffle and closure of the ventricular septal defect) is great. In this group of patients, a "palliative" Mustard or Senning procedure leaving the ventricular septal defect open often provides good,

short-term, symptomatic improvement by increasing arterial oxygen tension and reducing the stimulus to progressive polycythemia.[497]

Congenitally Corrected Transposition of the Great Arteries (See also p. 1612)

This term is applied to two distinctly different anomalies: anatomically corrected transposition or malposition of the great arteries and physiologically corrected levo- or L-transposition of the great arteries.

DEFINITION.

Invariably, the term *congenitally corrected l*-transposition is applied to the heart in which a functional correction of the circulation exists by virtue of the relation between the ventricles and great arteries.[499] [500] Corrected or L-transposition occurs when the primitive cardiac tube loops to the left instead of to the right during embryogenesis. The anatomical right ventricle comes to lie on the left and receives oxygenated blood from the left atrium; this blood is ejected into an anteriorly placed, left-sided aorta. The anatomical left ventricle lies to the right and connects the right atrium to a posteriorly placed pulmonary artery. Thus, there are both ventriculoarterial and AV discordant connections, with ventricular inversion. This arrangement of the great arteries and ventricles (in contrast to the uncorrected, complete, or D-transposition) permits functional correction, so that systemic venous blood passes into the pulmonary trunk while arterialized pulmonary venous blood flows into the aorta. In a heart with congenitally corrected transposition, the venae cavae and coronary sinus drain into a right atrium that is normal in position and structure.

MORPHOLOGY.

Anatomically corrected malposition of the great arteries is a rare form of congenital heart disease in which the great arteries are abnormally related to each other and to the ventricles but arise, nonetheless, above the anatomically correct ventricles.[498] Because of this, the term *malposition* rather than *transposition* is preferable. The anomaly results from either leftward looping of the ventricular segment of the embryonic heart tube in the situs solitus heart or from rightward looping in the situs inversus heart. In this unusual malformation, the aorta is anterior and to the left (levo- or L-malposition) and the pulmonary artery is posteromedial and to the right, presumably because of a subaortic conus that causes mitral-aortic discontinuity.

When no other defect exists, the circulation proceeds normally. When an associated lesion prompts ochocardiographic examination, the diagnosis is indicated by the finding of AV concordance in association with wide mitral-aortic discontinuity with an anteriorly placed aorta. At cardiac catheterization, the diagnosis of the abnormal relation between the great arteries may be made by biplane angiocardiography. Anomalies commonly associated with anatomically corrected malposition of the great arteries include VSD, left juxtaposition of the atrial appendages, tricuspid atresia or stenosis, and valvular and subvalvular pulmonic stenosis.

PHYSIOLOGY.

Venous blood flows from the right atrium, designated as the "venous atrium," across an AV valve that has the structure of a normal mitral valve and into the right-sided "venous ventricle" (Fig. 44-22) (Figure Not Available) . The venous ventricle, however, has the morphological characteristics of a normal left ventricle; i.e., its interior lining is trabeculated, it has no crista supraventricularis, and the AV valve is in continuity with the posteriorly placed semilunar valve. It ejects blood into the pulmonary trunk, which arises posterior to the ascending aorta. Oxygenated blood returns from the lungs to the left atrium, which is normal in position and structure; from there it flows into the left-sided "arterial ventricle" across an AV valve that has the structure of a normal tricuspid valve. The interior lining of the arterial ventricle has the morphological characteristics of a normal right ventricle (i.e., it has coarse trabeculations and a crista supraventricularis), and the tricuspid AV valve is not in continuity with the anteriorly placed semilunar valve. The arterial ventricle ejects blood into the aorta, which arises anterior to the pulmonary trunk. In addition to inversion of the cardiac ventricles, there is inversion of the conduction system and coronary arteries. Commonly associated anatomical lesions include atrial and ventricular septal defects, often accompanied by valvular or subvalvular pulmonary stenosis; single ventricle with an outlet chamber with or without pulmonic stenosis; left AV valve regurgitation, usually because of an Ebstein's malformation of the left-sided tricuspid valve; and abnormalities of visceral and atrial situs.[499]

CLINICAL MANIFESTATIONS.

The clinical presentation, course, and prognosis of patients with congenital functionally corrected transposition vary, depending on the nature and severity of the complicating intracardiac anomalies. [500] Patients in whom corrected transposition exists as an isolated anomaly present no functional alterations and have no symptoms.[501] Asymptomatic children with an increase in the size of the systemic ventricle, due to significant left-to-right shunting or tricuspid regurgitation, usually develop symptoms of systemic ventricular dysfunction by the third or fourth decade.[500] [501] [502] [503] The natural history of the anomaly and the ability of the right ventricle to perform systemic work are determined primarily by the nature and severity of the associated cardiac defects.[502]

The *physical findings* in congenitally corrected transposition are those of the associated lesions with two exceptions: (1) a single accentuated second heart sound usually is present in the second left intercostal space, representing closure of the aortic valve lying lateral and anterior to the pulmonic valve; and (2) there is a high incidence of cardiac dysrhythmias.

LABORATORY EXAMINATION.

Because of the inversion of the heart's conduction system, the *ECG* can provide important clues in the diagnosis. An abnormal direction of initial (septal) depolarization from right to left causes leftward, anterior, and superior orientation of the initial QRS

forces and reversal of the precordial Q wave pattern (Q waves are present in the right precordial leads and absent in the left). Two AV nodes, one posterior and one anterior, are present in some patients.[504] In addition to inversion of the conduction system, the His bundle is elongated because of the greater distance between the AV node and the base of the ventricular septum. The His bundle is located beneath

the pulmonic valve in the position of mitral pulmonary continuity; thus, it is subject to significant excursions during mitral valve closure. The anterior "accessory" AV node may be connected directly with an aberrantly located penetrating portion of the His bundle. This arrangement may be a causal factor in the arrhythmias and AV conduction disturbances commonly observed in these patients. First-degree AV block occurs in about 50 percent and complete AV block occurs in 10 to 15 percent of patients. Other degrees of AV dissociation may be observed, as well as paroxysmal supraventricular tachycardia and ventricular extrasystoles. In some patients, Kent bundle connections provide the anatomical substrate for preexcitation.[504]

Roentgenographic examination characteristically reveals absence of the normal pulmonary artery segment and a smooth convexity of the left supracardiac border produced by the displaced ascending aorta (see Chap. 8). The latter may be visualized by radionuclide scintillation scans of the central circulation. The main pulmonary trunk is medially displaced and absent from the cardiac silhouette; the right pulmonary hilus often is prominent and elevated compared with the left, producing a right-sided waterfall appearance.

Two-dimensional echocardiography seeks to identify the morphology of each ventricle by defining the characteristics of the inflow and outflow tracts and papillary and trabecular muscle morphology, ventricular shape, and great artery position.[505] By tracing the great arteries back to their ventricles of origin in subxiphoid and parasternal short-axis planes, one would find that the anterior leftward great artery (the aorta) arises from the left-sided ventricle and is not in continuity with the left-sided AV valve. The great arteries exit the heart in parallel fashion; the position, origin, and branching pattern of the great arteries are observed in subxiphoid and suprasternal views, and the anteroposterior and right-left positions of the great arteries can be seen from the parasternal short-axis view. Because the ventricular septum lies in the anteroposterior plane parallel to the echo beam, it may not be visualized from a left parasternal view. In apical-basal or subxiphoid four-chamber echocardiographic views, the right and left ventricular morphology and the inverted position of the AV valves may be ascertained correctly. The latter views also demonstrate the level of attachment of the AV valves and allow detection of inferior displacement of the left-sided tricuspid valve when Ebstein's anomaly coexists.

At *cardiac catheterization,* the diagnosis should be suspected when the venous catheter enters a posterior and midline main pulmonary trunk. Retrograde arterial catheter passage establishes the typical position of the ascending aorta at the upper left cardiac border. Hemodynamic abnormalities depend on the lesions associated with corrected

transposition. Selective *angiocardiography* allows visualization of the transposed great arteries and morphological differentiation of the two ventricles (Fig. 43-62) . The ventricles usually lie side by side, with the ventricular septum oriented in an anteroposterior direction. Selective aortography demonstrates the inverted coronary arterial pattern that is invariably present in corrected transposition. The competence of the left AV valve may be determined by injection of contrast material into the arterial ventricle.[506] When a left-sided Ebstein's malformation exists, the leaflets are displaced distal to the true valve annulus. The level of the annulus may be determined by visualization of the circumflex branch of the left coronary artery, which courses posteriorly in the AV groove.

Specific problems have attended operative repair of the lesions associated with congenitally corrected transposition, owing primarily to the course of the conduction AV system and the coronary arterial pattern.[507] [508] The inversion of the coronary arterial system occasionally may limit and preclude an incision into the venous ventricle, thereby interfering with exposure of intracardiac defects in the usual manner. The disadvantage in approaching intracardiac anomalies using an incision in the morphological right ventricle is that this is the systemic ventricle. When significant pulmonary stenosis exists within a VSD, a valved extracardiac conduit often is a required part of the surgical repair. Surgical risks are especially high in patients in whom significant regurgitation exists from the arterial ventricle to the arterial atrium. In these patients, annuloplasty or, more usually, valve replacement is required. In all operative approaches, if complete heart block has been present intermittently or permanently preoperatively or intraoperatively, permanent epicardial atrial and ventricular pacemaker leads are implanted.

The disappointing results with traditional techniques of repair have led to more anatomical forms of surgical correction in which the morphological left ventricle supports the systemic circulation, rather than leaving the morphological right ventricle and tricuspid valve in the systemic circulation. Thus, the so-called double-switch procedure promises to decrease the development and significance of tricuspid valve regurgitation as well as the incidence of surgical complete heart block. In this procedure, an arterial switch operation establishes ventriculoarterial concordance and the systemic and pulmonary venous returns are rerouted by either the Mustard or Senning technique. If a VSD is present, it can be closed in the usual manner. When pulmonary stenosis is present in association with a ventricular defect, the performance of an arterial switch procedure is precluded, but the left ventricle can be routed to the aorta via a prosthetic baffle within the right ventricle to channel the VSD to the aortic valve. The outflow tract of the right ventricle can then be reconstructed by placement of a conduit from the right ventricle to the pulmonary artery bifurcation, and a venous switch procedure completes the operation.

Double-Outlet Right Ventricle

MORPHOLOGY.

Other designations applied to this lesion include origin of both great arteries from the right ventricle, partial transposition, complete transposition of the aorta and levoposition

of the pulmonary artery, complete dextroposition of the aorta, and the Taussig-Bing complex. This is an extremely heterogeneous category of malformations in which an abnormal relation exists between the aorta and the pulmonary trunk, which arise wholly or in large part from the right ventricle.[509]

DEFINITIONS.

A uniform definition or classification of double-outlet right ventricle does not exist. To some, double-outlet right ventricle means origin of one great artery and at least 50 percent of the other over the right ventricle; others require the presence of bilateral conus muscle between both great arteries and the AV annulus. One or both great arteries may arise from an infundibular chamber; there may be considerable variability in the amount of subarterial conus muscle. Thus, the semilunar valves may lie side by side, or with the pulmonary valve more anterior and superior, or with a more anterior and superior aortic valve. Commonly, neither semilunar valve is in fibrous continuity with either AV valve, and a VSD is usually present and represents the only outlet from the left ventricle. The VSD is of the malalignment type because the infundibular septum is positioned abnormally.

When the amount of conus muscle beneath the two great arteries varies, the VSD commonly is positioned beneath the more posterior semilunar valve, which in fact usually overrides the interventricular septum through this VSD. The amount of conus muscle underneath the valve determines the position of the semilunar root in relation to the ventricles below. Thus, double-outlet right ventricle resides within the spectrum of conotruncal abnormalities ranging from tetralogy of Fallot to transposition of the great arteries. The VSD occasionally extends beneath both great arteries and is referred to as doubly committed. In some instances, the VSD is remote from both great arteries, or is considered uncommitted, in which case the defect often lies in the inlet or muscular portion of the interventricular septum.

ASSOCIATED LESIONS.

More than half of patients with double-outlet right ventricle have associated anomalies of the right AV valves.[509] [510] Mitral atresia associated with a hypoplastic left ventricle is common; less often observed are tricuspid stenosis, Ebstein's anomaly of the tricuspid valve, complete AV septal defect, and overriding or straddling of either AV valve. Aortic coarctation may be associated with double-outlet right ventricle, particularly when the subaortic area is narrowed by malalignment of the infundibular septum. Double-outlet right ventricle also may be a component of the many cardiovascular anomalies of the splenic dysgenesis or heterotaxy syndromes. An increased incidence of the anomaly occurs in infants with the trisomy 18 syndrome.

The pathological features in most patients include side-by-side pulmonic and aortic valves and discontinuity between the mitral and aortic valves. The latter exists because muscular infundibulum is usual beneath both semilunar valves. The VSD may be remote from or closely related to one or both semilunar valves (Fig. 43-63) . When the interventricular defect is subpulmonic, with or without a straddling pulmonary trunk, the complex is designated Taussig-Bing. In most patients, the interventricular septal defect

is below the crista supraventricularis and is subaortic in location. Least often, the defect either

Figure 43-62 Congenitally corrected (levo-)transposition of the great arteries in a 4-year-old boy. *A,* Anteroposterior ventriculogram in left-sided ventricle with mesocardia. The morphological right ventricle (RV) is left sided, indicating an L-ventricular loop (inverted ventricles in situs solitus). The aorta (AO) originates above the morphological right ventricle and is thus transposed and in classic levo-transposition. *B,* Lateral ventriculogram in left-sided ventricle (same frame as *A)*. The aorta originates anteriorly above the morphological right ventricle (RV). *C,* Anteroposterior ventriculogram in right-sided morphological left ventricle (LV). The transposed pulmonary artery (PA) arises from this ventricle, and the ventricular septum appears intact. Pulmonic valve thickening is also evident. The aorta *(A)* is to the left of the pulmonary artery. Note that the ventricular septum in the L-ventricular loop is visualized best in the anteroposterior views. *D,* Lateral ventriculogram in right-sided ventricle (same frame as *C)*. The pulmonary artery is posterior to the aorta, and supravalvular pulmonic narrowing is seen. *(From Freedom RM, Harrington DP, White RI Jr, et al: The differential diagnosis of levo-transposed or malposed aorta: An angiocardiographic study. Circulation 50:1040, 1974.)*

is remote from both semilunar valves (uncommitted) or underlies both (doubly committed).

CLINICAL MANIFESTATIONS.

The clinical and physiological picture is determined by the size and location of the VSD and the presence or absence of pulmonic stenosis. In the Taussig-Bing form of double-outlet right ventricle, the malformation resembles physiologically and clinically complete transposition with VSD and pulmonary hypertension. When the VSD is subaortic, the stream of blood from the left

Figure 43-63 Double-outlet right ventricle with side-by-side relation of great arteries is illustrated in both panels. *A,* A subaortic ventricular septal defect below the crista supraventricularis favors delivery of left ventricular blood to the aorta. *B,* Subpulmonary location of the ventricular septal defect above the crista favors streaming to the pulmonary trunk. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 446.)*

ventricle is directed preferentially to the aorta. Thus, there may be little or no detectable cyanosis, and these patients usually clinically resemble those with an isolated large VSD and pulmonary hypertension.

The most important determinant of the natural history in both these types of

double-outlet right ventricle is the progression of pulmonary vascular obstruction. In contrast, when there is pulmonary outflow tract obstruction, which often is severe and found commonly in these patients in whom the VSD is subaortic, clinical findings are similar to those of cyanotic tetralogy of Fallot. In some patients, especially without pulmonic stenosis, the ECG shows a superiorly oriented counterclockwise frontal plane QRS loop in addition to right ventricular hypertrophy.[511] The pattern appears to result from relative hypoplasia of the anterosuperior left bundle and preferential activation of the posteroinferior left ventricular wall. The presence of the latter ECG pattern in patients with double-outlet right ventricle should alert one to the possibility of a coexistent AV septal defect or abnormality of the mitral valve.

DIAGNOSIS.

Two-dimensional *echocardiography* may reliably distinguish double-outlet right ventricle from other lesions causing cyanosis, such as tetralogy of Fallot and transposition of the great arteries.[512] [513] The three key imaging features are origin of both great arteries from the anterior right ventricle, mitral-semilunar valve discontinuity, and absence of left ventricular outflow other than the VSD. The relative anteroposterior positions of the great arteries can be determined from the parasternal short-axis view. The parasternal long-axis view shows the position of the more posterior semilunar root relative to the interventricular septum and anterior mitral leaflet and is the best view for demonstrating the presence of subarterial conus muscle. Subxiphoid views best demonstrate the position of both great arteries over the ventricles. Each great artery is displayed on long- and short-axis subxiphoid sweeps.

In reporting echocardiographic results, it is imperative to state each component's anatomical feature, i.e., the position of both great arteries, the presence and amount of infundibulum under each semilunar valve, the anatomy of both subpulmonary and subaortic outflow tracts, the position and size of the associated VSD, and the presence of all other associated lesions, particularly AV valve anomalies and coarctation of the aorta.

In each of the different types of double-outlet right ventricle, precise delineation of the malformation also depends on careful angiocardiographic analysis. The diagnosis can be established with confidence when the angiographic findings include simultaneous opacification of both great vessels from the right ventricle, aortic and pulmonic valves at the same transverse level, and separation of the aortic valve from the aortic leaflet of the mitral valve by the crista supraventricularis (Fig. 43-64) . The position of the VSD and the relation between the great arteries must be defined to plan surgical procedures appropriately.

Experience is growing with the application of transesophageal echocardiograpy in analyzing the complex anatomical and spatial relationships encountered in double-outlet right ventricle, requiring a biplane or multiplane format for adequate assessment.

SURGICAL TREATMENT.

The goals of operative treatment are to establish left ventricle-to-aorta continuity, create adequate right ventricle-to-pulmonary continuity, and repair associated lesions.[510] Because of the complexity of intracardiac repair of these anomalies, many centers prefer to give palliation to infants, attempting reparative surgery after the age of 1 to 2 years. In double-outlet right ventricle with subaortic VSD, repair is accomplished by creating an intraventricular baffle that conducts left ventricular blood to the aorta. When the VSD is subpulmonic, repair is accomplished by closure of the VSD and arterial switch.[510] [514] When the VSD is doubly committed, i.e., both subaortic and subpulmonic, operation consists of creating an intraventricular baffle that conducts left ventricular blood to the aorta. The type of double-outlet right ventricle in which the VSD is remote and uncommitted to either semilunar orifice may be approached by a venous switch operation, permitting the right ventricle to eject into the aorta, followed by placement of a conduit between the left ventricle and the pulmonary trunk. Alternatively, some patients may be candidates for a cavopulmonary shunt or a modified Fontan procedure, particularly if additional findings include a common AV orifice, hypoplastic ventricles, a straddling tricuspid valve, or a straddling mitral valve.[515]

Double-Outlet Left Ventricle

One of the rarest cardiac anomalies consists of the origin of both great arteries from the morphological left ventricle. Conal musculature or an infundibulum usually is absent or deficient beneath the orifices of both semilunar valves.[516] The spectrum of associated malformations is broad. VSD and valvular or subvalvular pulmonic stenosis has been present in most patients. Supportive diagnostic information is provided by magnetic resonance imaging. Echocardiographic[517] and angiocardiographic assessment of the spatial relations of the origins of the great arteries are essential to an accurate diagnosis and to evaluating the possibility of operative repair. In most patients, the latter consists of closure of the VSD and placement of a right ventricle-pulmonary artery conduit.

Figure 43-64 Simultaneous opacification of both great arteries from a right ventricular injection of contrast material in a patient with double-outlet right ventricle (RV). The aortic and pulmonic valves are at the same transverse level. AO = aorta; PA = pulmonary artery. *(Courtesy of Dr. Robert White.)*

Total Anomalous Pulmonary Venous Connection

This anomaly has been estimated to account for 1 to 3 percent of all cases of congenital heart disease and 2 percent of deaths therefrom in the first year of life.[518] The anomaly is the result of persistence during embryogenesis of communications between the pulmonary portion of the foregut plexus and the cardinal or umbilicovitelline system of veins, resulting in the connection of all the pulmonary veins either to the right atrium directly or to the systemic veins and their tributaries. Because all venous blood returns

to the right atrium, an interatrial communication is an integral part of this malformation. Additional major cardiac malformations occur in about 30 percent of patients. Among these are common atrium, atrial isomerism, single ventricle, truncus arteriosus, and anomalies of the systemic veins. Extracardiac malformations, particularly of the alimentary, endocrine, and genitourinary systems, are present in 25 to 30 percent of cases.

MORPHOLOGY.

The anatomical varieties of total anomalous pulmonary venous connection may be subdivided, depending on the level of the abnormal drainage (Fig. 43-65). Table 43-10 provides average figures of the distribution of the sites of anomalous connection.[578] The anomalous connection usually is supradiaphragmatic and to the left brachiocephalic vein, right atrium, coronary sinus, or superior vena cava. In about 13 percent, particularly in males, the distal site of connection is below the diaphragm. In this situation, a common trunk originates from the confluence of pulmonary veins and descends in front of the esophagus, penetrating the diaphragm through the esophageal hiatus. The anomalous trunk then connects into the portal vein or one of its tributaries, the ductus venosus, or, rarely, to one

Figure 43-65 Anatomical types of total anomalous pulmonary venous return: supracardiac, in which the pulmonary veins drain either via the vertical vein to the anomalous vein *(A)* or directly to the superior vena cava with the orifice close to the orifice of the azygos vein *(B)*. *C,* Drainage directly into the right atrium or into the coronary sinus. *D,* Infracardiac drainage via a vertical vein into the portal vein or the inferior vena cava. *(From Stark I, deLeval M: Surgery for Congenital Heart Defects. 2nd ed. Philadelphia, WB Saunders, 1994, p 330.)*

TABLE 43-10 -- SITE OF CONNECTION IN TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

Connection to right atrium	15%
Connection to common cardinal system	
(Right) superior vena cava	11%
Azygos vein	1%
Connection to left common cardinal system	
Left innominate vein	36%
Coronary sinus	16%
Connection to umbilicovitelline system	
Portal vein	6%
Ductus venosus	4%
Inferior vena cava	2%

Hepatic vein	1%
Multiple sites	7%
Unknown	1%

of the hepatic veins. In rare cases, various combinations of anomalous connection occur, with drainage to several levels.

HEMODYNAMICS.

The physiological consequences and, accordingly, the clinical picture depend on the size of the interatrial communication and on the magnitude of the pulmonary vascular resistance. When the interatrial communication is small, systemic blood flow is markedly limited.[519] Right atrial and systemic venous pressures are elevated, and hepatic enlargement and peripheral edema are present. The size of the interatrial communication also is an important determinant in the development in utero and postnatally of the left atrium and left ventricle. Left atrial cavity size usually is somewhat reduced, whereas left ventricular volumes may be reduced or normal. The magnitude of pulmonary blood flow and therefore the ratio of oxygenated to unoxygenated blood that returns to the right atrium are a function of pulmonary vascular resistance. The arterial oxygen saturation, which ranges from markedly reduced to normal values, is inversely related to the pulmonary vascular resistance. In this regard, in most patients, the principal determinant of pulmonary pressures and resistance is related less to augmented pulmonary blood flow and pulmonary arteriolar vascular obstruction than to the presence and intensity of pulmonary venous obstruction.[520] [521]

Obstruction to pulmonary venous return and pulmonary venous hypertension are invariably present in patients with infradiaphragmatic anomalous pulmonary venous connection and in many with a subdiaphragmatic pathway. In the former type, pulmonary venous obstruction results from the length and narrowness of the common pulmonary venous trunk, compression at the esophageal hiatus of the diaphragm, constriction at the subdiaphragmatic site of insertion, or pulmonary venous return that must pass first through the portal-hepatic circulation before returning to the right atrium. When venous obstruction occurs in supradiaphragmatic types of drainage, constriction may exist at the entrance site of the anomalous veins into the systemic venous circulation, and/or the anomalous venous channel may be kinked or situated abnormally and compressed between the left pulmonary artery and left bronchus.[520] The presence of a small, restrictive patent foramen ovale occasionally results in pulmonary venous obstruction. Pulmonary vascular obstructive disease is rare during infancy, although exceptions have been reported. In patients without pulmonary venous obstruction, the risk of developing Eisenmenger reaction is comparable with that in patients with an atrial septal defect.

CLINICAL MANIFESTATIONS.

The majority of patients with total anomalous pulmonary venous connection have symptoms during the first year of life, and 80 percent die before age 1 year if left

untreated.[518] The few who remain asymptomatic have a relatively good prognosis; once the condition is detected, operation may be elected later in

childhood. Symptomatic infants with total anomalous pulmonary venous connection present with signs of heart failure and/or cyanosis. Infants with pulmonary venous obstruction present with the early onset of severe dyspnea, pulmonary edema, cyanosis, and right heart failure. Cardiac murmurs often are not prominent. In the unobstructed forms of total anomalous pulmonary venous connection, the characteristic physical findings include right ventricular precordial overactivity and minimal cyanosis unless congestive heart failure intervenes. Multiple heart sounds often are audible, consisting of a first heart sound followed by an ejection sound; a fixed, widely split second heart sound with an accentuated pulmonic component; and a third and often a fourth heart sound. A soft systolic ejection murmur is usual along the left sternal border, and a mid-diastolic murmur of flow across the tricuspid valve commonly is audible at the lower left sternal border.

LABORATORY FINDINGS.

The *ECG* shows right-axis deviation and right atrial and right ventricular hypertrophy. *Roentgenograms* of the chest reveal increased pulmonary blood flow; the right atrium and ventricle are dilated and hypertrophied, and the pulmonary artery segment is enlarged (Fig. 43-66) . In addition, the specific site of anomalous connection may cause a characteristic appearance of the cardiac silhouette. Thus, in patients with total anomalous pulmonary venous connection to the left brachiocephalic vein, the superior vena cava on the right, left brachiocephalic vein superiorly, and vertical vein on the left produce a cardiac shadow that resembles a snowman or figure eight. The upper right cardiac border may be prominent when the anomalous connection is to the right superior vena cava.

Echocardiography demonstrates marked enlargement of the right ventricle and a small left atrium.[522] The objective of ultrasound imaging in these patients is to confirm the clinical diagnosis and to locate the site of connection of the common pulmonary vein. Doppler flow and color mapping enhance the capability of identifying all the pulmonary veins and their drainage sites and help to assess the presence of obstruction within individual pulmonary veins and along the vertical vein.[523] [524] An echo-free space representing the common pulmonary venous chamber may occasionally be seen to lie behind the left atrium on ultrasound examination. The use of echocardiography has supplanted cardiac catheterization in preoperative diagnosis in patients without atrial isomerism or single-ventricle hearts. Diagnostic echocardiographic findings include an absence of pulmonary

Figure 43-66 Chest roentgenogram in an infant with total anomalous pulmonary venous connection

below the diaphragm shows normal overall heart size but a diffuse pattern of pulmonary venous hypertension in both lung fields.

vein connections and a small left atrium in the presence of right-to-left bulging of the septum primum at the foramen ovale. Positive diagnosis is made by identifying pulmonary venous connection to the systemic veins, coronary sinus, or right atrium rather than to the left atrium. All four pulmonary veins and their connections must be identified to diagnose mixed types accurately. There is no standard echocardiographic method for tracing pulmonary venous pathways because of their diverse anatomical positions, although transesophageal studies can importantly assist in this regard.[524]

An infradiaphragmatic total anomalous pulmonary venous connection usually connects to the portal venous system but can connect to the hepatic veins. Doppler is used to distinguish between the abdominal vessels. Thus, the flow pattern in the inferior vena cava is phasic, nearly continuous, and toward the heart, in contrast to flow in the descending aorta, which has a laminar profile in systole in a direction away from the heart. Flow in the common pulmonary vein resembles that of the inferior vena cava except that its direction is away from the heart. Although not often used, especially in infants, magnetic resonance imaging may also delineate the site of connections of the various types of total anomalous pulmonary venous return.

At *cardiac catheterization,* those patients found to have systemic arterial saturations below 70 percent and pulmonary artery pressure at or above systemic levels are likely to have pulmonary venous obstruction. Variations in oxygen saturation in the systemic venous circulation may be helpful. In the subdiaphragmatic type, a step-up may not be apparent in inferior vena caval oxygen saturations obtained by way of femoral vein cannulation because of the contribution of highly oxygenated renal venous blood to the caval stream. In contrast, sampling of the hepatic or portal vein by way of a catheter inserted through the umbilical vein yields diagnostically higher oxygen saturations, indicating anomalous return to those vessels. If the cardiac catheter can be manipulated directly into the anomalous trunk through its site of connection, selective injection of contrast material into the common channel provides anatomical definition of the pulmonary venous tree. If the pulmonary veins cannot be entered directly, selective right and left main pulmonary artery injection of contrast material often is more helpful than is injection into a main pulmonary artery because many infants have a persistent patent ductus arteriosus through which the contrast agent flows right to left. Moreover, the drainage from both lungs must be outlined clearly to preclude a mixed type of anomalous venous drainage. Pulmonary venous obstruction may be detected by noting a pressure difference between the pulmonary artery wedge pressure and the right atrium.

MANAGEMENT.

Corrective surgery for sick infants should be performed as soon as possible, usually on the basis of two-dimensional and Doppler echocardiography, avoiding the additional stress of invasive diagnostic study. Before age 1 month, survival greater than 75 percent is anticipated. Infants with the worst prognosis are those in whom individual pulmonary vein sizes are smallest, which are measurements that can be made

preoperatively by echocardiogram. Unless a child has pulmonary vascular disease, results of operation for total anomalous pulmonary venous connection in patients beyond infancy are generally good.[525] [526] The procedure consists of creating an anastomosis between the common pulmonary venous channel and left atrium and closing the atrial defect and the anomalous venous pathway. Improved results of operation in infancy require that postoperative pulmonary venous hypertension be averted by construction of a generally large anastomosis with or without enlargement of the left atrium. Normal hemodynamics and cardiac function have been demonstrated after surgical correction.

Partial Anomalous Pulmonary Venous Connection

In this condition, one or more of the pulmonary veins, but not all, are connected to the right atrium or to one or more of its venous tributaries. An atrial septal defect, particularly one of the sinus venosus type, commonly accompanies this anomaly; the usual connection involves the veins of the right upper and middle lobes and the superior vena cava.[518] Exclusive of atrial septal defects, major additional cardiac malformations occur in about 20 percent of patients: these include VSD, tetralogy of Fallot, and various complex anomalies.

In the absence of associated anomalies, the physiological disturbance is determined by the number of anomalous veins and their site of connection, the presence and size of an atrial septal defect, and the state of the pulmonary vascular bed.[527] In the usual patient with isolated partial pulmonary venous connection, the hemodynamic state and physical findings are similar to those in atrial septal defect. Rarely, venous drainage of the right lung is into the inferior vena cava. This condition often is associated with hypoplasia of the right lung, dextroposition of the heart, pulmonary parenchymal abnormalities, and anomalous system supply to the lower lobe of the right lung from the abdominal aorta or its main branches. This complex has been designated the *scimitar syndrome* because of the characteristic roentgenographic finding of a crescent-like shadow in the right lower lung field that is produced by the anomalous venous channel.[528]

Transesophageal echocardiography is highly diagnostic of partial anomalous pulmonary venous connection and can obviate catheterization and angiography.[524] At *cardiac catheterization,* partial anomalous pulmonary venous connection to the coronary sinus, azygos vein, or superior vena cava may be identified by careful and frequent oximetry sampling. Oximetry is of limited value when the anomalous connection is to the inferior vena cava because of both reduced flow through the right lung and the contribution to the vena caval stream of highly oxygenated blood from the renal veins. Selective angiography is most helpful in cases in which the anomalous veins connect far away from the right atrium. Surgical repair offers definitive therapy at low risk if pulmonary vascular obliterative disease has not yet developed.

Malpositions of the Heart and Cardiac Apex

Positional anomalies of the heart are conditions in which the cardiac apex is located in the right side of the chest (dextrocardia) or is centrally located (mesocardia), or in which the heart is in its normal location in the left side of the chest but the position of the viscera is abnormal (isolated levocardia). Such hearts commonly are abnormal with respect to chamber localization and great artery attachments: associated complex intracardiac and extracardiac lesions are common.

Problems of terminology abound in the literature describing these complex cardiac anomalies, although sensible and uniform systems of classification are available.[529] [530]

ANATOMICAL FEATURES.

Defining the cardiac anatomy in instances of cardiac malposition requires a description of three cardiac segments--the visceroatrial situs, the ventricular loop, and the conotruncus (the atria, ventricles, and great arteries, respectively). In addition to defining positional interrelation, the description of the malposed heart also must include the connections of the ventricles to the atria and great arteries as well as chamber identification, both morphologically and functionally.

DIAGNOSIS.

To accomplish accurate diagnosis may require a synthesis of findings from noninvasive tests such as two-dimensional echocardiography, CT, and magnetic resonance imaging,[531] as well as hemodynamic and cineangiographic findings obtained at cardiac catheterization. Expert echocardiographers analyze, separately and independently of adjacent segments, each cardiac segment (atria, AV canal, ventricles, infundibulum, and great arteries) in terms of both situs and alignments.[532] [533]

In general, the determination of the body situs indicates the position of the atria. The visceral situs usually can be determined by the location of the stomach bubble and liver on a routine roentgenogram and of the inferior vena cava by means of echocardiography or the position of a cardiac catheter or by means of a CT or venous or radioisotope angiocardiogram. Atrial anatomy is best investigated noninvasively by using subxiphoid long- and short-axis and apical four-chamber echocardiographic views. Venous contrast injections may be useful to define systemic venous connections.

Situs solitus is the normal arrangement of viscera and atria, with the right atrium right sided and the left atrium left sided. Situs solitus is further characterized by a trilobed right lung and eparterial bronchus (i.e., the right upper lobe bronchus passes above the right pulmonary artery), a bilobed left lung and hyparterial bronchus (i.e., the left bronchus passes below the left pulmonary artery), the major lobe of the liver on the right, a left-sided stomach and spleen, and right-sided venae cavae. *Situs inversus* is a mirror image of normal. *Situs ambiguus* or visceral heterotaxy refers to an anatomically uncertain or indeterminate body configuration. The latter often is seen in association

with congenital asplenia, which resembles bilateral right-sidedness (right isomerism), and congenital polysplenia, which resembles bilateral left-sidedness (left isomerism).[530] [531] [532] [533] [534] [535]

ASPLENIA (RIGHT ISOMERISM).

Cardiac anomalies commonly associated with asplenia include anomalous systemic venous connection, atrial septal or complete endocardial cushion defect, common ventricle, transposition of the great arteries, severe pulmonic stenosis or atresia, and anomalous pulmonary venous connection usually infradiaphragmatic or to the superior vena cava-atrium junction. Polysplenia (left isomerism) commonly is associated with absence of the hepatic portion of the inferior vena cava with azygos continuation, bilateral superior venae cavae, anomalous pulmonary venous connection, and atrial septal defect (either ostium secundum or endocardial cushion). Pulmonic stenosis and double-outlet right ventricle are each observed in about 25 percent of cases. It is important to recognize these complex syndromes to distinguish them from forms of cyanotic heart disease that may be more amenable to corrective surgical therapy. In many of these patients, improvement results from palliation by modifications of the Fontan procedure, despite anomalies of systemic and pulmonary venous return in association with single ventricle anatomy.[536] [537] Diagnosis is suggested by a symmetrical liver shadow roentgenographically and, in asplenia, by the presence of Howell-Jolly and Heinz bodies in red blood cells demonstrated on blood smear, and it is confirmed by a negative or abnormal radioactive spleen scan.

Once the type of visceral situs is defined, it is necessary to describe the bulboventricular loop. The primitive cardiac tube normally bends to the right (D-loop), and thus the anatomical right ventricle is brought to the right of the anatomical left ventricle. An L-loop brings the morphological right ventricle left-sided relative to the morphological left ventricle. The L-loop is normal in the presence of situs inversus, but in situs solitus it is synonymous with inverted ventricles.

VENTRICULAR MORPHOLOGY.

The number, morphology, and size of the ventricles can be ascertained by using various echocardiographic views. The morphological features of each ventricle also can be identified angiographically. The anatomical right ventricle is equipped with a tricuspid valve, is highly trabeculated, and contains the septal band of the single papillary muscle; its infundibulum lies anterior to and superiorly beyond the outlet of the left ventricle. The anatomical right ventricle usually connects with whichever of the two great arteries is the more anterior. The anatomical left ventricle is smooth walled and contains an outlet that lies posterior to the right ventricular infundibulum; its entrance is guarded by a bicuspid mitral valve, the anterior leaflet of which is normally in continuity with elements of the semilunar valve at its outlet. On echocardiographic examination, the insertion of the AV valves assists identification of the ventricle. The tricuspid valve is more apically situated than the mitral valve and is attached to the ventricular septum by papillary muscles, whereas the mitral valve is not. The right ventricular apical musculature is coarse and contains a moderator band of muscle.

GREAT ARTERIES.

The great arteries are described in terms of their positional interrelations and their ventricular connections. Each outflow tract and semilunar valve should be examined in both long- and short-axis echocardiographic views.[533] The ventriculoarterial alignments may be determined by direct visualization from the subxiphoid window. The relation between the great arteries can best be demonstrated noninvasively using parasternal short-axis echocardiographic views, which display the semilunar roots. The aortic arch and brachiocephalic arteries are seen well using suprasternal notch views. The pulmonary artery is seen from high parasternal or suprasternal notch short-axis sections. The ventricular attachments may be normal or may form the anomalies of double-outlet right or left ventricle or transposition. The arterial interrelations are described as D(dextro), in which the ascending aorta sweeps toward the right and lies to the right of the main pulmonary artery; L(levo), in which the ascending aorta sweeps toward the left and lies to the left of the main pulmonary artery; or A(antero), which is the rare situation in which the aorta lies directly in front of the pulmonary artery. The D, L, and Adescriptions of the aorticopulmonary artery interrelations should not be confused with the D- or L-loop designation of the ventricular interrelations.[530]

Using segmental sets composed of descriptive units of visceroatrial situs/ventricular loop/great artery relations greatly simplifies expression of the type of cardiac anatomy present in cardiac malposition. For example, the normal heart in a patient with situs inversus and dextrocardia is referred to as inversus/Lloop/Lnormal; complete transposition of the great arteries in a patient with situs inversus is referred to as inversus/Lloop/Ltransposition; functionally corrected transposition in a patient with situs solitus is referred to as solitus/Lloop/Ltransposition; dextrocardia and functionally corrected transposition is designated solitus/Dloop/Dtransposition with dextrocardia.

After the cardiac chambers are diagnosed functionally (arterial and venous), the positional and morphological relations are understood, and the presence of associated anomalies is established, the principles of medical and surgical treatment apply to these cardiac malpositions as they do to normally located hearts.[536]

OTHER CONDITIONS

Congenital Pericardial Defects

Isolated pericardial defects (see Chap. 50) are rare. They most commonly occur in males and usually are left sided, although they may be right sided, diaphragmatic, or total.[538] The anomaly is produced by deficient formation of the pleuropericardial membrane or, if diaphragmatic, defective formations of the septum transversum. Associated congenital anomalies of the heart and lungs occur in about 30 percent of cases. Most patients with the isolated defect are asymptomatic. Nonspecific anterior

chest pain may be the result of torsion of the great arteries due to absence of the stabilizing forces of the left pericardium.

With complete absence of the left pericardium, a conspicuous apical impulse may be noted to be shifted leftward to the anterior or midaxillary line. ECG changes may be related to levoposition of the heart; a leftward displacement of the QRS transition in the precordial leads and vertical or right-axis deviation are usual. The diagnosis may be suggested by chest roentgenograms. With complete left pericardial absence, the heart is levo-posed, and the aortic knob, pulmonary artery, and ventricles form three prominent left heart border convexities.

A partial left pericardial defect may be suspected on the basis of various degrees of prominence of the pulmonary artery and/or the left atrial appendage. Echocardiographic findings often mimic those observed in patients with right ventricular volume overload (enlarged right ventricle and abnormal ventricular septal motion), probably owing to the altered cardiac position and motion with the thorax.[539] Other echocardiographic clues include lateral extension of the left atrial appendage as it herniates through the pericardial defect; this is best seen in short-axis views. The anomaly can be definitively diagnosed by CT or magnetic resonance imaging.[540] Cardiac catheterization is of little diagnostic value.

Complete absence of the left pericardium requires no treatment. Partial defects, however, may impose serious risks, including herniation and strangulation of the ventricles or left atrial appendage with left-sided defects or the possibility of a superior vena cava obstructive syndrome with right-sided defects.[541] In the diaphragmatic type, cardiac compression by abdominal contents requires surgical repair. Partial left or right defects may be closed with a patch of mediastinal pleura.

Single Atrium

Single or common atrium is a rare, isolated defect. The anomaly consists of an absent atrial septum, usually with a cleft in the anteromedial leaflet of the mitral valve and, occasionally, with a cleft tricuspid valve as well. The lesion may be one component of the Ellis-van Creveld syndrome (see Table 43-2 (Table Not Available)) or of the complex cardiac anomalies in patients with asplenia or polysplenia.

Single atrium may be suspected clinically by the presence of cardiac murmurs of an atrial septal defect and mitral regurgitation associated with mild cyanosis, roentgenographic evidence of cardiac enlargement and increased pulmonary blood flow, and ECG features of AV septal defect. An absence of echoes from any part of the atrial septum is the essential feature of two-dimensional echocardiographic examination, which also may show a cleft anterior mitral leaflet, increased right ventricular end-diastolic dimension, paradoxical ventricular septal motion, and a dilated, pulsatile pulmonary trunk. Angiographically, the absence of the atrial septum produces a large, globe-shaped single atrial structure. Selective left ventricular angiocardiography shows the characteristic gooseneck appearance seen in the various forms of AV septal defect. In the absence of pulmonary vascular obstructive disease, surgical correction is

indicated by means of a prosthetic patch.

Single Ventricle (Univentricular Atrioventricular Connection)

Hearts with univentricular AV connection constitute a family of complex lesions in which both AV valves or a common AV valve open into a single ventricular chamber.[542] Terminology is varied, and the anomaly often is referred to as a double-inlet, single, or common ventricle, which is imprecise but useful shorthand for the entity. The definition excludes examples of tricuspid or mitral atresia. Single ventricle is almost always accompanied by abnormal great artery positional relations; the incidence of L-malposition of the great arteries is about equal to that of D-malposition. Associated anomalies are common and include, in particular, pulmonic valvular or subvalvular stenosis, subaortic stenosis, total or partial anomalous pulmonary venous connection, and coarctation of the aorta.

MORPHOLOGY.

In about 80 percent of patients, the single ventricle morphologically resembles a left ventricular chamber that is separated from an infundibular outlet chamber by a bulboventricular septum.[543] The opening is variously called the bulboventricular foramen and VSD. The infundibular chamber is considered to represent developmentally the outflow tract of the right ventricle. The usual AV connection is transposition; when the heart is left sided, the connection is usually L-transposition, whereas it is usually D-transposition when the heart is right sided. When the great arteries are malposed, the infundibulum lying anteriorly at the basal position of the single ventricle communicates with the aorta and may be in one of two positions: noninverted (D-malposition), when it is situated at the right basal aspect of the heart, or inverted (L-malposition), when it is located at the left base of the heart. In the unusual situation in which the great arteries are normally related, the infundibulum communicates with the pulmonary trunk.[542] *Double-inlet left ventricle* is a term used synonymously to describe the most frequently encountered single ventricular chamber that has the anatomical characteristics of the left ventricle. Less commonly, the single ventricular chamber resembles a right ventricle (double-inlet right ventricle) or contains features suggestive of both ventricles or neither one; the latter two situations occasionally have been designated common ventricle and single ventricle of the primitive type, respectively.

CLINICAL FINDINGS.

Depending on the associated anomalies, the clinical presentation of single ventricle mimics other conditions in which cyanosis and decreased or increased pulmonary blood flow coexist, e.g., tetralogy of Fallot or tricuspid atresia in the former instance or complete transposition of the great arteries and double-outlet right ventricle in the latter. The *ECG* in double-inlet left ventricle without inversion of the infundibulum (D-malposition) usually shows features of left ventricular hypertrophy. with infundibular inversion (L-malposition) the electrical forces are directed anteriorly and rightward, as they are in ventricular inversion without associated defects. In patients with the more primitive types of common or single ventricle, a repetitious rS pattern is seen in all the

precordial ECG leads. *Chest roentgenographic* findings resemble those observed in patients with complete (dextro-) transposition of the great arteries or functionally corrected (levo-) transposition of the great arteries without features distinctive of single ventricle.

ECHOCARDIOGRAPHY.

Two-dimensional and Doppler echocardiography are extremely important to demonstrate ventricular anatomy and to recognize associated intra- and extracardiac anomalies (Fig. 43-67) . A segmental approach should be used for accurate and complete echocardiographic evaluation. Thus, precise details are required of the basic anatomy of atrial and visceral situs, location of the cardiac apex, the extracardiac course of the great arteries, and systemic and pulmonary venous connections.

In those patients in whom two separate AV valves communicate with the single ventricular chamber, *echocardiography* (see Chap. 7) suggests the correct diagnosis when echoes are visualized from the two valves without an intervening interventricular septum. In the absence of ventricular septal echoes when the two valves are not visualized simultaneously, they may be identified separately with a careful long-axis sweep of the ventricle. It is possible to detect the presence of a small outflow chamber anterior to the AV valves by using subcostal or parasternal short-axis views and a plane orthogonal to the long-axis plane (see Fig. 43-63).

The single ventricle with a single AV valve is suspected when the excursion of echoes from the single valve located posteriorly in the

Figure 43-67 Echo images of a double-inlet left ventricle type of univentricular heart. *Top,* Subcostal coronal view shows the right atrium (RA) giving rise to a tricuspid valve guarding entry into a main chamber (M CH) of left ventricular morphology from which the pulmonary artery (PA) arises. The arrow indicates the small ventricular septal defect (bulboventricular foramen) entering into an outflow chamber (O CH), which gives rise to the aorta (AO). *Middle,* Orthogonal subcostal sagittal equivalent to the top frame. The left atrium (LA) is seen above the main chamber of left ventricular morphology (V). The arrows indicate the origin of the left and right atrioventricular valves within the same ventricular chamber. The pulmonary artery (PA) arises from the main chamber, and the long narrow bulboventric ular foramen is shown to enter the outlet chamber (O Ch.), with its connection to the aorta. *Bottom,* Apical four-chamber view shows the right atrium (RA) and the left atrium (LA) with their corresponding valves (arrows) entering into the common large ventricle (V).

ventricular chamber is of large amplitude. Enhanced assessment of the AV valve in patients with single ventricle is provided by Doppler echocardiography.[544] Magnetic resonance imaging provides valuable information complementary to echocardiographic study. Selective ventriculography is necessary to delineate with certainty the anatomical type of single ventricle and to diagnose the associated great artery interrelations and the presence or absence of additional lesions.

SURGICAL TREATMENT.

Modifications of Fontan approach are generally applied to patients with all types of anatomical and functional single ventricle.[545] [546] [547] Surgical outcome is related to the creation of an unobstructed pathway from the systemic veins to the pulmonary arteries, low pulmonary vascular resistance, and a compliant, well-functioning ventricle. In most centers, Fontan procedure is divided into two stages, an initial superior vena cava-pulmonary artery anastomosis (bidirectional Glenn shunt or hemi-Fontan procedure: Fig. 43-68), followed later by completion of the Fontan procedure directing flow from the inferior vena cava to the amalgamation of the superior vena cava and the branch pulmonary arteries. At first-stage operation, prior systemic-pulmonary shunts are eliminated and any areas of distortion or narrowing of the pulmonary arteries are repaired, particularly if a prior pulmonary artery banding was performed to limit pulmonary blood flow.

At our center, the complete Fontan procedure is accompanied by placement of a snare around the atrial septal defect to control its size postoperatively,[548] whereas in other centers, fenestrations in the atrial baffle may be used.[549] [550] [551] [552] These procedures appear to reduce significantly postoperative morbidity from pericardial effusions and significantly improve survival. Results of early bidirectional cavopulmonary shunting in young infants are encouraging. The objective of this approach early in life is to yield a more suitable Fontan candidate while reducing ventricular volume overload and repeated palliative procedures. Subaortic stenosis, a common occurrence in patients with univentricular heart and malposed great arteries, occurs as a result of a restrictive bulboventricular foramen (VSD) or as a consequence of ventricular hypertrophy from a previous pulmonary banding operation.

The *Damus-Kaye-Stansel operation,* consisting of anastomosis of the pulmonary artery to the ascending aorta, is a generally successful approach to this problem.[552] After operation, all patients need continued close surveillance.[553] [554] [555] [556] Complications include thromboembolic phenomena and atrial arrhythmias. Survivors generally lead active lives with exercise levels less than normal but relevant to ordinary daily life.

VASCULAR RINGS

MORPHOLOGY.

The normal development of the aortic arch system is described earlier (see Fig. 43-3). The term *vascular ring* is used for those aortic arch or pulmonary artery malformations that exhibit an abnormal relation with the esophagus and trachea, causing compression, dysphagia, and/or respiratory symptoms.[557] The most common and serious vascular ring is produced by a double aortic arch in which both the right and left fourth embryonic aortic arches persist. In the most common type of double aortic arch, there is a left ligamentum arteriosum or ductus arteriosus and both arches are patent, the right being larger than the left. A right aortic arch with a left ductus or ligamentum arteriosum connecting the left pulmonary artery and the upper part of the descending aorta and

with an anomalous right subclavian artery arising from the left descending aorta are additional important vascular ring arrangements.

Figure 43-68 A bidirectional cavopulmonary artery shunt with patch occlusion of the superior vena cava right atrial junction (hemi-Fontan procedure) using direct cannulation of the superior and inferior venae cavae and a single arterial cannula. The main pulmonary artery is shown divided and oversewn, but in some cases it may be allowed to remain patent. Connections are made between both ends of the divided superior vena cava and the pulmonary artery. A subsequent Fontan operation involves only removal of the patch at the junction of the superior vena cava and the right atrium and placement of the intraatrial baffle to divert the inferior vena caval blood up to the superior vena cava orifice. *(From Castaneda A, Jonas RA, Mayer JE Jr, et al: Cardiac Surgery of the Neonate and Infant. Philadelphia, WB Saunders, 1994, p 263.)*

The latter anomaly frequently exists in cases of tetralogy of Fallot and otherwise uncomplicated coarctation of the aorta. An unusual cause of tracheal compression is the vascular sling created by an anomalous left pulmonary artery that arises from a rightward, elongated pulmonary trunk and courses between the trachea and esophagus before it branches normally within the left lung.[558] This arrangement commonly is associated with other cardiac and extracardiac anomalies.

CLINICAL FINDINGS.

The symptoms produced by vascular rings depend on the tightness of anatomical constriction of the trachea and esophagus and consist principally of respiratory difficulties, cyanosis (associated especially with feeding), stridor, and dysphagia. The ECG appears normal unless associated cardiovascular anomalies are present. The barium esophagogram is a useful screening procedure. Prominent posterior indentation of the esophagus is observed in the common vascular ring arrangements, although the pulmonary artery vascular sling produces an anterior indentation. Unusual and rare aortic arch anomalies may create rings that impinge on the trachea but do not compress the esophagus and are detected not by this simple radiographic procedure but rather by bronchoscopy. Selective contrast angiography delineates the anatomy of the aorta and its branches or the course of the main pulmonary arteries. CT and magnetic resonance imaging offer excellent imaging alternatives.[559]

MANAGEMENT.

The severity of symptoms and the anatomy of the malformation are the most important factors in determining treatment. Patients, particularly infants, with respiratory obstruction require prompt surgical intervention. Operative repair of the double aortic arch requires division of the minor arch (usually the left).[560] A reported 10 to 20 percent operative mortality is related, in part, to problems in postoperative respiratory care, especially when there is coexistent residual anatomical tracheal narrowing. Patients with

a right aortic arch and a left ductus or ligamentum arteriosum require division of the ductus or ligamentum and/or ligation and division of the left subclavian artery, which is the posterior component of the ring. Video-assisted thoracoscopy holds promise as an alternative to open thoracotomy for management.[561] Operation seldom is indicated for patients with an aberrant right subclavian artery derived from a left aortic arch and left descending aorta. In patients with a pulmonary artery vascular sling, operation consists of detachment of the left pulmonary artery at its origin and anastomosis to the main pulmonary artery directly or by way of a conduit of its proximal end brought anterior to the trachea.[560] Some patients with persistent respiratory symptoms require postoperative evaluation of residual anatomical obstruction, tests of pulmonary function, and bronchodilator therapy.[562]

CONGENITAL ARRHYTHMIAS

This classification refers to arrhythmias that are present in infancy, whose causes, when known, relate to a structural malformation or defect of the conduction system or to an acquired prenatal condition such as myocarditis, hypoxia acidosis, or transplacental passage of a drug or substance from mother to fetus. In these latter examples, the substrate for the postnatal expression of the rhythm disturbance existed before birth and the arrhythmia is therefore designated congenital. Complete heart block and supraventricular and ventricular tachycardias are the most common important congenital arrhythmias.[563] The electrophysiological and ECG features of these arrhythmias are discussed elsewhere (see Chaps. 23 and 25).

Congenital Complete Heart Block

The AV node and the His bundle originate during fetal development as separate structures and later join together. Anatomical studies have shown the basic lesion in congenital complete heart block to consist of discontinuity between the atrial musculature and the AV node or the His bundle, if the AV node is absent. The anatomical interruption occasionally can be situated between the AV node and the main His bundle or within the bundle itself.[564] No cause is known for the vast majority of cases of congenital heart block in infants, who usually have otherwise anatomically normal hearts. However, fetal myocarditis, idiopathic hemorrhage and necrosis involving conduction tissue, and degeneration and fibrosis related in some instances to the transplacental passage of anti-SSA/Ro-SSB/La antibodies and other immune complexes from mothers with systemic lupus erythematosus all are entities capable of causing congenital heart block.[565] It is not clear if medical treatment in high-risk pregnancies aimed at reducing antibody titers will modify immunopathologic damage to the fetus. Less often, congenital heart block can be associated with various forms of congenital heart disease, the most common malformation being congenitally corrected transposition of the great arteries.[566]

Detection of consistent fetal bradycardia (heart rate 40 to 80 beats/min) by auscultation, fetal echocardiography (Fig. 43-69) , or electronic monitoring allows anticipation of the correct diagnosis. A newborn, especially with a ventricular

Figure 43-69 M-mode recording taken from the four-chamber fetal reference image shown in the lower right corner. The image is inverted, with the M-mode reference from fetal left ventricle (LV) through to the right atrium. In the M-mode, the ventricle is seen above (V) and the atrium (A) is seen below. The ventricular rate is approximately 48 beats/min, whereas the atrial rate is approximately 150 beats/min. There were no structural cardiac abnormalities. The mother had lupus erythematosus.

rate less than 50 beats/min and atrial rate in excess of 150 beats/min, is at highest risk; the presence of an associated cardiovascular anomaly greatly lessens the chances of survival. Treatment is not required for asymptomatic infants. Digitalization is recommended for infants in congestive heart failure, irrespective of complete heart block. Isoproterenol and other sympathomimetic drugs and atropine do not have permanent or beneficial effect. Congestive heart failure and Stokes-Adams attacks require pacemaker treatment at any age, including transvenous or transatrial placement of endocardial leads in older children or permanent epicardial pacemaker insertion in infants and small children.[567] [568] Various problems can be anticipated after pacemaker implantation related to growth of the patient, which stresses the electrical lead system; the fragility of the lead system in a physically active young patient; and the limited life span of the pulse generator. Patients who have congenital complete heart block and who survive infancy usually remain asymptomatic until late in childhood or adolescence.[569]

Supraventricular Tachycardia

Paroxysmal tachycardia of supraventricular origin can have its origin in utero or in the immediate postnatal period. The most frequent arrhythmias producing symptoms are paroxysmal supraventricular tachycardia with or without ventricular preexcitation, atrial flutter, and junctional tachycardia. The arrhythmia can cause intrauterine cardiac failure and hydrops fetalis[570] [571] ; its detection and persistence prenatally should prompt consideration of administration of digitalis or, if that fails, of propranolol, quinidine, flecainide, or amiodarone to the mother if amniocentesis indicates surfactant deficiency and fetal lung immaturity, because early delivery is not indicated if the baby will have hyaline membrane disease. Experience with antiarrhythmic drugs, delivered by umbilical venous infusion, is limited.[96] Cesarean delivery or induced labor may be indicated if the fetus is close to term. No cause is recognized for the disorder in the majority of infants. Transplacental passage of long-acting thyroid stimulators (LATSs) and immune gamma-2-globulin from hyperthyroid mothers, hypoglycemia, and Ebstein's anomaly of the tricuspid valve occasionally are causative. WPW syndrome (see Chaps. 23 and 25) is present in 10 to 50 percent of infants with supraventricular tachycardia.[572] Symptoms produced by the tachyarrhythmia after birth are subtle and often remain undetected until signs of heart failure have been present for 24 to 36 hours. Conversion to normal sinus rhythm usually is accomplished by administration of digitalis or adenosine, direct-current cardioversion, transesophageal atrial pacing, or a diving reflex elicited by covering the face with an ice-cold wet washcloth for 4 to 5 seconds.[573] [574] [575] [576] [577] Conversion should be followed by digitalization on a prophylactic basis. Common practice consists

of digitalis treatment for 9 to 12 recurrence-free months followed by its abrupt cessation.[578] Recurrence of tachycardia, particularly in those infants with ventricular preexcitation, is not uncommon; maintenance of normal rhythm may require administration, alone or in combination, of digitalis, phenytoin sodium, flecainide, sotalol, and amiodarone.[573] The rate of recurrence falls substantially between ages 2 and 10 years, with a slight rise during adolescence. In general, the prognosis is excellent.

ELECTROPHYSIOLOGICAL STUDIES.

Beyond infancy, patients whose condition is refractory to medical treatment are candidates for electrophysiological catheter evaluation, which facilitates differentiation of a causative ectopic anatomical focus within the atria from accessory conduction pathways (see Chap. 23).[579] [580] If the tachyarrhythmia is refractory to pharmacological therapy, it should be treated definitively by radiofrequency catheter ablation of accessory pathways (see Chaps. 23 and 25). This procedure has become the primary treatment modality for most symptomatic rhythm disturbances in children. The results are excellent, with success exceeding 90% and very low complication rates.[576] [580] [581] Among the advantages of this approach is that successful ablation represents a cure; the heart is left structurally normal, and the cause of the arrhythmia is eliminated. Further, the need for antiarrhythmic agents with the concomitant risk of side effects or proarrhythmia is eliminated.

ATRIAL FLUTTER (see Chaps. 23 and 25).

Uncommonly, atrial flutter is the cause of supraventricular tachycardia,[582] especially in newborn infants with hydrops fetalis, whose intrauterine tachyarrhythmia

is an alternation between supraventricular tachycardia with WPW syndrome and atrial flutter. Another common clinical setting for atrial flutter is in infants younger than 6 months with an otherwise normal heart, who show frequent premature atrial complexes. In infants, classic flutter waves may not be present on a surface ECG or rhythm strip; detection may require recordings of transesophageal atrial electrograms. Acute treatment with electrical conversion or transesophageal overdrive pacing effectively terminates the rhythm disturbance.[583] If synchronized direct-current electrocardioversion is used, standby pacing should be available; if overdrive pacing is used, the same pacing catheter can be used to pace the heart in the event of asystole. Long-term drug treatment with digitalis, digitalis plus quinidine, or amiodarone may uncommonly be required.

Junctional automatic tachycardia is characterized by a narrow QRS complex and AV dissociation, with the ventricular rate faster than the normal atrial rate. Ventricular dysfunction and congestive heart failure occur early, and the rhythm disturbance usually is not convertible to sinus rhythm by any medical treatment. When the latter falls and because sudden death is a risk, catheter ablation can be used to eliminate the

tachycardia focus. Pacemaker implantation may be necessary if heart block results (see Chap. 25).

VENTRICULAR TACHYCARDIA.

Ventricular tachycardia is defined as three or more consecutive premature ventricular complexes (see Chap. 25). The definition, however, falls to identify a high-risk group. Infants or children who meet this criterion but seldom require treatment and seem to be at little risk have no symptoms and no evidence of anatomical heart disease. Potentially serious ventricular tachycardia in the newborn is associated with QT prolongation, mitral valve prolapse, and Marfan's syndrome. In these settings, the tachycardia is potentially life threatening and always merits treatment.[563]

Numerous genes causing long QT syndrome have been identified, confirming that the defects occurs in a transmembrane ion channel in most patients (see Chaps. 23 and 25).[584] The two most effective treatments are beta blockade and high thoracic left sympathectomy, which reduce the incidence of syncope and sudden death without affecting the QT interval. Trials of gene-specific therapy directed at the involved ion channel may be anticipated in the future.[584] Implantable defibrillators can be life saving in patients at risk for torsades de pointes and ventricular fibrillation.

The treatment of ventricular tachycardia (see Chap. 23) consists of intravenous administration of lidocaine, followed by direct-current electrical cardioversion. In the absence of QT prolongation but in the presence of mitral prolapse or other cardiac abnormalities, long-term treatment should be undertaken of multiform premature ventricular complexes, couplets, or ventricular tachycardia. In infants and children unresponsive to conventional or investigational antiarrhythmic drugs, consideration should be given to pacemaker implantation, cardiac sympathetic denervation, and perhaps implantation of a defibrilator.[585]

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PATHOLOGICAL CONSEQUENCES

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Chapter 44 - Congenital Heart Disease in Adults

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Adult patients with congenital heart defects are a growing patient population.[1] [1A] [1B] There are about 1 million affected Americans in the year 2000, compared with an estimated 300,000 in 1980, and 1.4 million are anticipated in 2020. About half of these patients are at significant risk of premature mortality, reoperation, or future complications of their conditions and their treatments.

One of the special challenges in this field is that there are about 100 separate main diagnostic groups. Each patient may have one or more of such diagnoses. The cardiologist may meet these patients in the office, the emergency department, the hospital, or the diagnostic laboratories. Dealing appropriately with these patients is a challenge. For many patients, especially those with "high-risk conditions," the preferred method is to have them seen by an expert. At present, there are not enough such individuals or facilities to make this possible. The cardiologist may then need access to educational material as a reminder of the anatomy, the clinical issues, the treatments, and expected residua and sequelae for the specific patient needing informed attention.[2]

This chapter has been written for the practicing cardiologist to provide the essential

information to draw on when seeing such patients. The information here is fully compatible with the only existing expert recommendations for the care of adult patients with congenital cardiac defects.[2] These and further guidelines are/will be available on the Internet at www.cachnet.org and at www.library.utoronto.ca/nevilthomas/. For congenital cardiac defects not included in this chapter, such as anomalous origin of coronary arteries,[2A] see Chapter 43 .

GENERAL PRINCIPLES

All patients should have been taught in adolescence about their condition, their future outlook, and the possibility of further surgery and complications, and they also should have been advised about their responsibilities in ensuring self-care and professional surveillance. This is not always the case, and staff in adult clinics may have to take the patient through this process. Patients may wish to continue their own education through Internet sites or to join a chat line or listserver.

Some of the most important data in the files of adult patients with congenital heart defects are prior operative reports. Heart catheterization reports may be important as well. These should all be obtained. They may be invaluable when clinical questions arise. Those patients believed to be at significant risk of future complications, future surgery, and premature death should be monitored life long.

Congenital heart disease in the adult is not a simple continuation of the childhood experience. The patterns of many lesions change in adult life. Arrhythmias are more frequent and of a different character. Cardiac chambers often enlarge, and ventricles tend to develop systolic dysfunction. Bioprosthetic valves, prone to quick failure in childhood, last longer when implanted at an older age. The patient is planning or involved in a career and may need advice on types of work to avoid. The comorbidities that tend to develop in adult life often become an important factor needing attention.

As a result, the needs of these patients are often best met by a physician or a team familiar with both pediatric and adult cardiology issues. Surgery and interventional catheterization procedures should usually be performed at centers with adequate surgical and institutional volumes of congenital heart cases at any age.[3] Diagnostic heart catheterizations, electrophysiological studies, and even magnetic resonance imaging (MRI)[3A] and other imaging of complex cases are best done where qualified staff have relevant training, experience, and equipment. Patient care in the ideal world should be multidisciplinary. Skilled cardiology and echocardiography skills are essential, but other individuals with special training, experience, and interest should also be accessible. This includes nurses, reproductive health staff, mental health professionals,[3B] anesthesiologists, medical imaging technicians, respiratory consultants, and others. Beyond the issues raised by individual lesions, these patients may also wish to have normal sex lives and to have children.

Pregnancy

Many female patients will need confirmation that they can safely carry a pregnancy. The literature offers guidance for certain lesions,[3] but, for many, certain principles can be

reasonable guides.[4] Maternal risks for pregnancy include pulmonary hypertension, obstructive lesions, ventricular dysfunction, heart failure, and ascending aortic aneurysms (mainly in patients with Marfan syndrome). In severe cases, termination and sometimes sterilization may be recommended to protect the mother. Fetal risks are high in the presence of maternal cyanosis and medication exposure (e.g., warfarin and angiotensin-converting enzyme [ACE] inhibitors).

Delivery should usually be vaginal unless there is an obstetrical reason for cesarean section. Women at moderate and high risk for pregnancy should usually be evaluated

and treated in a high-risk pregnancy unit. The staff in such units will know how to obtain templates for the management of specific patients with lesions of concern.

Patients will wish advice on contraception and on recurrence risks of congenital heart disease in their offspring. Referral to a geneticist may be helpful. As a rule, the recurrence risk is 3 to 4 percent, compared with the risk in the general population of 0.8 percent (range, 0.5-1.2 percent).[5] [6] In some patients, such as those with chromosome 22 microdeletion or Marfan syndrome, the risk is 50 percent.

Cardiac Arrhythmias (see also Chap. 25)

These are a major clinical challenge in adult congenital heart patients. They are the most frequent reason for emergency department visits/admissions. They are usually chronically recurrent and may worsen or become less responsive to treatment with time.[7] Treatment options are often limited and of limited efficacy.

Atrial flutter and, to a lesser degree, atrial fibrillation are most common. Atrial flutter tends to reflect right atrial, and atrial fibrillation left atrial, abnormalities. Atrial flutter in such patients is often atypical in appearance and behavior and is better called intraatrial reentrant tachycardia. We will use the simpler term. Recognition of atrial flutter may be difficult, and the observer will need to be vigilant in recognizing 2:1 conduction masquerading as sinus rhythm. Recurrence is likely and should not be assumed to represent failure of the management strategy. The conditions in which atrial flutter is most likely are Mustard/Senning repairs of transposition of the great arteries (TGA),[8] [9] repaired or unrepaired atrial septal defects (ASDs), repaired tetralogy of Fallot, Ebstein's anomaly of the tricuspid valve, and Fontan operation. Atrial flutter may reflect hemodynamic deterioration in patients who have had Mustard/Senning, tetralogy of Fallot, or Fontan repairs. Its arrival is usually associated with more symptoms and functional limitation.

The pharmaceutical agents most commonly used in therapy are warfarin, beta blockers, amiodarone, sotalol, propafenone, and digoxin. As a rule, patients with good ventricular function can receive sotalol or propafenone, whereas those with depressed ventricular function should receive amiodarone. Other therapies, including pacemakers, ablative

procedures, and innovative surgery, are being both applied and refined. Sustained ventricular tachycardia or ventricular fibrillation occur less often, usually in the setting of ventricular dilation and scarring. Although sudden death is common in several conditions, the mechanism is poorly understood.

SPECIFIC CARDIAC DEFECTS

Atrial Septal Defect (See also Chap. 43)

ASDs are the most common congenital cardiac malformation first diagnosed in adults.

ANATOMY.

Four types of ASDs occur: ostium primum, ostium secundum, sinus venosus, and coronary sinus. Ostium primum is discussed later (see Atrioventricular Septal Defect). Ostium secundum defects occur from either excessive resorption of the septum primum or from deficient growth of the septum secundum and are occasionally associated with anomalous pulmonary venous drainage (<10 percent). Sinus venosus/superior vena cava (SVC) type defect occurs inferior to the orifice of the SVC, giving rise to an SVC connected to both atria and always associated with anomalous pulmonary venous drainage (usually from the right lung). Sinus venosus/inferior vena cava (IVC) type defects abut the junction of the IVC, inferior to the fossa ovalis. Coronary sinus septal defects are rare and arise from an opening in the wall of the distal portion of the coronary sinus, allowing left-to-right atrial shunting (see Fig. 43-9). In any type of ASD, the degree of left-to-right atrial shunting depends on the size of the defect and the relative diastolic filling properties of the two ventricles. Any condition causing reduced left ventricular compliance (e.g., systemic hypertension, cardiomyopathy or myocardial infarction) or increased left atrial pressure (e.g., mitral stenosis and/or regurgitation) will tend to increase the left-to-right shunt.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

A significant shunt (Qp/Qs > 1.5/1.0) probably causes symptoms over time, and symptomatic patients become progressively more limited as they age. Effort dyspnea is seen in about 30 percent of patients by the third decade and over 75 percent of patients by the fifth decade. Supraventricular arrhythmias (atrial fibrillation or flutter) and right-sided heart failure develop by age 40 in about 10 percent of patients. The development of pulmonary hypertension, although probably not as common as originally thought, can occur at an early age. Life expectancy is probably reduced, although not nearly as severely as was quoted in an early article. Data regarding the natural history of ASD should be interpreted carefully because much of the data relates predominantly to sicker patients and the follow-up information was often inadequate.[10]

CLINICAL MANIFESTATIONS.

The most common symptoms are exercise intolerance (dyspnea and fatigue) and palpitations (usually from atrial fibrillation, less often atrial flutter or sick sinus

syndrome). Paradoxical embolism resulting in transient ischemic attack or cerebrovascular accident can call the diagnosis to attention. Right ventricular failure can be the presenting symptom in older patients. The presence of cyanosis should alert one to the possibility of shunt reversal and Eisenmenger syndrome (see p. 1614) or, alternatively, to a prominent eustachian valve directing IVC flow to the left atrium through a secundum or sinus venosus/IVC ASD. On examination, there is "left atrialization" of the jugular venous pressure (a wave=v wave). A hyperdynamic right ventricular impulse can be felt at the left sternal border at the end of expiration or in the subxiphoid area on deep inspiration. A dilated pulmonary artery trunk can be palpated in the second left intercostal space. A wide and fixed split S_2 is the auscultatory hallmark of ASD. A systolic ejection murmur, usually grade 2, is best heard at the second left intercostal space, and a mid-diastolic rumble, from increased flow through the tricuspid valve, can be present at the left lower sternal border. When right ventricular failure ensues, a holosystolic murmur of tricuspid regurgitation is usual.

DIAGNOSTIC TESTING

Electrocardiogram.

Sinus rhythm or atrial fibrillation/flutter may occur. The QRS axis is normal or rightward in secundum ASD (see Fig. 43-10). Negative P waves in the inferior leads indicate a low atrial pacemaker and are often seen in sinus venosus/SVC type defects, which are located in the area of the sinoatrial node rendering it deficient. Partial to complete right bundle branch block can prolong the QRS duration (Fig. 44-1).

Chest Radiography.

The classic radiographic features are cardiomegaly (from right atrial and ventricular enlargement), dilated central pulmonary arteries with pulmonary plethora indicating increased pulmonary flow, and a small aortic knuckle (Fig. 44-2) .

Echocardiography (see Figs. 7-81 and 43-11).

Transthoracic echocardiography (TTE) documents the type(s) and size (defect diameter) of the ASD(s) and the direction(s) of the shunt and perhaps can determine the presence or absence of anomalous pulmonary venous return. The functional importance of the defect can be estimated by the size of the right ventricle, the presence or absence of right ventricular volume overload (paradoxical motion of the septum), and the calculation of pulmonary artery blood flow

Figure 44-1 Typical electrocardiogram of a sinus venosus atrial septal defect of the superior vena cava

type showing low atrial rhythm, mild right-axis deviation, and right bundle branch block.

relative to systemic blood flow (Qp/Qs). Indirect measurement of the pulmonary artery pressure can be obtained from the Doppler velocity of the tricuspid regurgitation jet. Transesophageal echocardiography (TEE) permits better visualization of the interatrial septum and may be required when device closure is contemplated or assessment of pulmonary venous drainage is incomplete (see Fig. 43-11).

Catheterization.

Cardiac catheterization may be required when the hemodynamic significance of an ASD is questioned or when assessment of pulmonary artery pressures and resistances is needed.

Open-Lung Biopsy.

Open-lung biopsy should only be considered when the reversibility of the pulmonary hypertension is uncertain from hemodynamic data (see section on Eisenmenger syndrome).

INDICATIONS FOR INTERVENTION.

Hemodynamically "nonsignificant" ASDs (Qp/Qs<1.5) do not require closure, with the possible exception of trying to prevent paradoxical emboli.[11] "Significant" ASDs (Qp/Qs > 1.5, or ASDs associated with right ventricular volume overload) require closure when symptoms are present.[12] [13] [14] In the absence of symptoms, indications for closure are somewhat controversial. In patients younger than age 40 years, "significant" ASDs should probably be closed, although this practice has been challenged by some.[15] The proper therapeutic strategy for asymptomatic patients > 40 years old with "significant" ASDs is still disputed. For patients with pulmonary hypertension (pulmonary artery pressure [PAP] > two thirds of systemic arterial blood pressure [SABP], or pulmonary arteriolar resistance more than two thirds of systemic arteriolar resistance), closure can be recommended if there is a net left-to-right shunt of at least 1.5:1, evidence of pulmonary artery reactivity when challenged with a pulmonary vasodilator (e.g., oxygen or nitric oxide), or evidence on lung biopsy that pulmonary arterial changes are potentially reversible (see Chap. 53).

Transvenous pacing should be avoided when possible in patients with ASDs, because paradoxical emboli can occur. For the same reason, venous thromboemboli from any site are potential sources of systemic emboli. If a source of paradoxical embolism is found, anticoagulation and/or ASD closure may be recommended.

INTERVENTIONAL OPTIONS AND OUTCOMES

Device Closure.

The use of devices to close ASDs percutaneously under fluoroscopy and TEE guidance[16] is gaining popularity. Indications for device closure are the same as for surgical closure but selection criteria are stricter. This technique is available mainly for patients with single secundum ASD with a stretched diameter of less than 50 percent of the diameter of the biggest available device and with adequate septal margin for proper device support. Anomalous pulmonary venous drainage or proximity of the defect to the atrioventricular (AV) valves, coronary sinus, or systemic venous drainage precludes the use of this technique. It is a safe and effective procedure in experienced hands, with major complications (e.g., device embolization, atrial perforation) occurring in less than 1 percent of patients and echo closure achieved in 85 percent or more of patients. Using "older" devices, silent residual shunts, more than half of which are trivial or mild, are still seen in 19 to 53 percent of patients at 6 to 12 months' follow-up.[17] Long-term follow-up data are not available.[17] Notwithstanding, device closure can be attractive to a patient wishing to avoid the consequences of surgery (general anesthesia, pain, and a scar) or to a patient believed to be at high surgical risk (see Fig. 43-12).

Surgery.

Surgical closure of ASDs can be performed by primary suture closure or using an autologous pericardial

Figure 44-2 Chest radiograph in an adult with ostium secundum atrial septal defect. Arrows point to the enlarged right and left pulmonary arteries. Note the increase in peripheral pulmonary perfusion.

or synthetic patch. The procedure is usually performed through a midline sternotomy, but the availability of an inframammary or minithoracotomy approach to a typical secundum ASD should be made known to potentially interested patients. Surgical mortality in the adult without pulmonary hypertension should be less than 1 percent with a low morbidity related mainly to the development of perioperative arrhythmias (atrial flutter/fibrillation or junctional rhythm).[12] [18] Surgical closure of an ASD improves functional status and exercise capacity in symptomatic patients[12] and improves survival, especially when patients are operated on at an earlier age.[13] [15] The incidence of late congestive heart failure is probably also reduced.[13] However, surgical closure of ASD does not prevent atrial fibrillation/flutter or stroke[13] especially when patients are operated on after the age of 40 years.[12] The role of a concomitant Cox/Maze procedure (see Chaps. 23 and 25) in patients older than the age of 40 years with a prior history of atrial flutter/fibrillation is unclear.[19] Patients with persistent atrial fibrillation should undergo anticoagulation.

Follow-Up.

Patients who have had surgical or device repair as adults, with or without elevated pulmonary artery pressures at the time of operation, patients with atrial arrhythmias preoperatively or postoperatively, and patients with ventricular dysfunction preoperatively should remain under long-term cardiology surveillance.

Isolated Ventricular Septal Defect (see also Chap. 43)

Ventricular septal defects (VSDs) are the second most common congenital malformation of the heart, accounting for approximately 20 percent of all congenital cardiac malformations. Surgical repair of large defects and spontaneous closure of smaller defects during childhood decrease the overall incidence of VSDs in adulthood.

ANATOMY.

The ventricular septum is composed of a muscular septum that can be divided into three major components (inlet, trabecular, and outlet) and a small membranous septum lying just underneath the aortic valve. VSDs are classified into three main categories according to their location and margins. *Muscular* VSDs are bordered entirely by myocardium and can be trabecular, inlet, or outlet in location. *Membranous* VSDs often have inlet, outlet, or trabecular extension and are bordered in part by fibrous continuity between the leaflets of an AV valve and an arterial valve. *Doubly committed subarterial* or *outlet* VSDs are situated in the outlet septum and are bordered by fibrous continuity of the aortic and pulmonary valves (see Fig. 43-15). In this section, we will deal with VSDs occurring in isolation from major associated cardiac anomalies.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

A *restrictive* VSD is defined as a defect that produces a significant pressure gradient between the left ventricle and the right ventricle, is accompanied by a small (<1.5/1.0) shunt, and does not cause significant hemodynamic derangement. A *moderately restrictive* VSD is accompanied by a moderate shunt (Qp/Qs=1.5-2.5/1.0) and will pose a hemodynamic burden on the left ventricle. This will lead to left atrial and ventricular dilation and dysfunction as well as a variable increase in pulmonary vascular resistance. Important atrial arrhythmias and, less often, ventricular arrhythmias can occur. A large or *nonrestrictive* VSD results initially in left ventricular volume overload early in life with a progressive rise in pulmonary artery pressure. In turn, this leads to higher pulmonary vascular resistance and eventually irreversible pulmonary vascular changes and systemic pulmonary pressures, the so-called Eisenmenger syndrome (see p. 1614).

Spontaneous closure of a perimembranous VSD (from tricuspid leaflet tissue apposition) or of a small muscular VSD during adulthood is uncommon (<10 percent). Small VSDs pose an ongoing and relatively high risk of endocarditis.[20] Perimembranous or outlet VSDs can be associated with progressive aortic valve regurgitation due to prolapse of the aortic cusp(s) into the defect. Late development of subaortic and subpulmonary stenosis has also been reported.[21]

CLINICAL MANIFESTATIONS.

Most adult patients with a small *restrictive* VSD are asymptomatic. Physical examination reveals a harsh or high-frequency holosystolic murmur, usually grade 3 to 4/6, heard with maximal intensity at the left sternal border in the third or fourth intercostal space. Patients with a *moderately restrictive* VSD often present with dyspnea in adult life. Physical examination typically reveals a displaced cardiac apex with a similar holosystolic murmur as well as an apical diastolic rumble and third heart sound (S_3) at the apex from the increased flow through the mitral valve. Patients with large *nonrestrictive* VSDs are discussed in the section on Eisenmenger syndrome.

DIAGNOSTIC TESTING

Electrocardiogram.

The ECG mirrors the size of the shunt and the degree of pulmonary hypertension. Small *restrictive* VSDs usually produce a normal tracing. *Moderate-sized* VSDs produce a broad, notched P wave characteristic of left atrial overload as well as signs of left ventricular volume overload, namely, deep Q and tall R waves with tall T waves in lead V_5 and V_6, and often atrial fibrillation. Large VSDs will produce right ventricular hypertrophy with right axis deviation (see section on Eisenmenger syndrome, p. 1614).

Chest Radiography.

The chest radiograph reflects the magnitude of the shunt as well as the degree of pulmonary hypertension. A moderate-sized shunt causes signs of left ventricular dilation with some pulmonary plethora. A large-sized shunt will over time produce pulmonary hypertension with enlarged central pulmonary arteries and peripheral pruning (see section on Eisenmenger syndrome, p. 1614).

Echocardiography (see also Chap. 43).

TTE can identify the location, size, and hemodynamic consequences of the VSD as well as any associated lesions (aortic regurgitation, right ventricular outflow tract obstruction [RVOTO], or left ventricular outflow tract obstruction [LVOTO]).

INDICATIONS FOR INTERVENTION.

The presence of a significant VSD (the symptomatic patient; Qp/Qs > 1.5/1.0; pulmonary artery systolic pressure > 50 mm Hg; increased left ventricular and left atrial size, or deteriorating left ventricular function) in the absence of irreversible pulmonary hypertension warrants surgical closure.

If severe pulmonary hypertension is present (defined as pulmonary arteriolar resistance

greater than two thirds of systemic arteriolar resistance), surgical closure can be safely undertaken if there is a net left-to-right shunt of at least 1.5/1.0, strong evidence of pulmonary reactivity when challenged with a pulmonary vasodilator (oxygen, nitric oxide), or lung biopsy evidence that pulmonary artery changes are reversible.

Other relative indications for VSD closure include the presence of a perimembranous or outlet VSD with more than mild aortic regurgitation and a history of endocarditis, especially if recurrent.[22]

INTERVENTIONAL OPTIONS

Surgery.

Surgical closure, by direct suture closure or with a Dacron patch, has been used for over 50 years with low perioperative mortality--even in adults--and a very high closure rate.[6]

Device Closure.

Successful transcatheter device closure of trabecular (muscular) and perimembranous VSDs has been reported.[23] Trabecular VSDs have proven more amenable to this technique because of their relatively straightforward anatomy and muscular rim to which the device attaches

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well. The closure of perimembranous VSDs is technically more challenging and should be considered experimental.

INTERVENTIONAL OUTCOMES.

For patients with good to excellent functional class and good left ventricular function before surgical closure, life expectancy after surgical correction is close to normal. The risk of progressive aortic regurgitation is markedly reduced after surgery, as is the risk of endocarditis, unless a residual VSD persists. Intraventricular conduction disturbances are slightly increased after surgical closure and may be responsible for the slight increase in risk of sudden death encountered in this patient population.[24]

FOLLOW-UP.

Yearly cardiac evaluation is suggested for patients with associated cardiac lesions (RVOTO, LVOTO, aortic regurgitation) not undergoing surgical repair, Eisenmenger syndrome patients, and adults with significant atrial or ventricular arrhythmias. Cardiac surveillance is also recommended for patients who had late repair of moderate or large defects, which are often associated with left ventricular impairment and elevated

pulmonary artery pressure at the time of surgery. Residual patch or device leaks are seldom hemodynamically important but can predispose to endocarditis. Maintenance of good dental hygiene and antibiotic prophylaxis in these patients is very important.

Atrioventricular Septal Defect (see also Chap. 43)

Unlike secundum ASDs, unoperated atrioventricular septal defects (AVSDs) are seldom first diagnosed in adults.

ANATOMY.

AVSDs comprise a spectrum of anomalies caused by abnormal development of the endocardial cushions, which may give rise to partial, intermediate, or complete AVSDs (Table 44-1) . In AVSD, the AV valves are fundamentally abnormal, being derived from five leaflets (a right anterosuperior leaflet, a right inferior leaflet, a superior bridging leaflet, an inferior bridging leaflet, and a left mural leaflet). This arrangement may result in separate but

TABLE 44-1 -- DEFINITIONS OF TYPES OF ATRIOVENTRICULAR SEPTAL DEFECTS (AVSD)

PARTIAL AVSD
Ostium primum ASD
Two separate AV valves
"Cleft" left AV valve
Intact ventricular septum
Rarely, no ASD with only a "cleft" in the left AV valve
Associated anomalies: Down syndrome (<10%), unroofed coronary sinus, left superior vena cava, and patent ductus arteriosus
INTERMEDIATE AVSD
Primum ASD
Restrictive VSD
Separate, abnormal AV valves
COMPLETE AVSD
Contiguous primum ASD
Nonrestrictive VSD
Common AV valve
Rastelli type A: Superior bridging leaflet with a cleft with chordal attchment to the crest of the ventricular septum
Rastelli type B: Superior bridging leaflet with a cleft with chordal attachment to a papillary muscle in the right ventricle

Rastelli type C: Superior bridging leaflet without a cleft and with no chordal attachment. The superior bridging leaflet is therefore "free floating." Associated anomalies include Down syndrome (>90%).

ASD=Atrial septal defect; *AV*=atrioventricular; VSD=ventricular septal defect.

Figure 44-3 Right- and left-sided atrioventricular valve in normal heart *(A),* partial atrioventricular septal defect *(B),* and complete atrioventricular septal defect *(C).* Rastelli type A: Superior bridging leaflet (RSL and LSL) has a cleft with ventricular septal attachment. Rastelli type B: Superior bridging leaflet has a cleft with right papillary muscle attachment. Rastelli type C: Superior bridging leaflet has no cleft and no attachment. TV=tricuspid valve; MV=mitral valve; AL=anterior leaflet; PL=posterior leaflet; SL=septal leaflet; RSL=right superior (bridging) leaflet; RLL=right lateral (anterosuperior) leaflet; RIL=right inferior (bridging) leaflet; LSL=left superior (bridging) leaflet; LLL=left lateral (mural) leaflet; LIL=left inferior (bridging) leaflet. *(From Kirklin JW, Barratt-Boyes BG: Cardiac Surgery. 2nd ed. New York, Churchill Livingstone, 1993.)*

abnormal right and left AV valves (primum and intermediate AVSD) or a common valve (complete AVSD) (Fig. 44-3) . The left AV valve is invariably abnormal, having a "cleft" at the conjunction of the superior and inferior bridging leaflets. Rarely, a double orifice left (mitral) AV valve is also encountered. The "unwedged" anteriorly located aorta, coupled to an apically displaced left AV valve (at the same level as the right AV valve), gives rise to an elongated left ventricular outflow tract, often characterized as a "gooseneck deformity." AVSD may occur in association with Down syndrome, tetralogy of Fallot, and other forms of complex congenital heart disease, including univentricular hearts.

NATURAL HISTORY OF THE UNOPERATED PATIENT

Partial and Intermediate AVSD.

Patients with partial and intermediate AVSDs have a course similar to that of patients with large secundum ASDs, with the caveat that symptoms may appear sooner when significant mitral regurgitation occurs through the cleft left AV valve. Patients are usually asymptomatic until their third or fourth decade, but progressive symptoms related to congestive heart failure, atrial arrhythmias, complete heart block, and variable degrees of pulmonary hypertension develop in virtually all of them by the fifth decade.

Complete AVSD.

Most patients with complete defects have had surgical repair in infancy. Some patients may have had palliative surgery in the past with pulmonary artery bands and have variable degrees of pulmonary vascular obstructive disease. When presenting de novo, most adults have established pulmonary vascular disease (see Eisenmenger Syndrome). Patients with Down syndrome have a propensity to develop pulmonary hypertension at an even earlier age than do other patients with AVSD.

Clinical Manifestations.

Clinical presentation depends on the presence and size of the ASD, on the VSD, and on the competence of the left AV valve. A large left-to-right shunt gives rise to symptoms of heart failure (dyspnea or fatigue on exertion) or, worse, pulmonary vascular disease (exertional syncope, cyanosis). Severe chronic left or right AV valve insufficiency leads to pulmonary congestion, hepatic congestion, and peripheral edema. Palpitations from atrial arrhythmias are very common. Down syndrome is seen in 35 percent of patients with AVSD. Almost all have the complete form. Cardiac findings on physical examination for patients with partial AVSD are similar to those of patients with secundum ASD, with the important addition of a prominent left ventricular apex and holosystolic murmur when significant left AV valve regurgitation is present. The murmur of left AV valve regurgitation can sometimes be heard radiating to the left sternal border if the regurgitant jet is directed into the right atrium (the Gerbode defect). Intermediate AVSDs resemble partial AVSD with the addition of a holosystolic VSD murmur heard best at the left sternal border, sometimes difficult to differentiate from a left AV valve regurgitant murmur. Complete AVSDs have a single first heart sound (S_1) (common AV valve), a mid-diastolic murmur from augmented AV valve inflow, and findings of pulmonary hypertension and/or a right-to-left shunt.

DIAGNOSTIC TESTING

Electrocardiogram.

Because of the posteriorly located AV node and hence the closer proximity of the left posterior fascicle, most patients have first-degree AV block and left-axis deviation from late left anterior fascicular depolarization. Complete AV block and/or atrial fibrillation/flutter can be present in older patients. Partial or complete right bundle branch block is usually associated with right ventricular dilation (Fig. 44-4) .

Chest Radiography.

Cardiomegaly and pulmonary plethora are the rule with an enlarged left atrium commonly present.

Echocardiography.

Echocardiography is essential to document the type of AVSD; assess the magnitude and direction of intracardiac shunting, the degree of AV valve regurgitation, the presence/absence of subaortic stenosis; and estimate pulmonary artery pressure (Fig. 43-13) . The lack of "offsetting" between the left and right AV valves (the right AV valve being apically displaced in normal hearts) is readily seen in the four-chamber view and is the echocardiographic hallmark of AVSD (Fig. 44-5) . TEE may be needed to further

define the underlying anatomy of the defect (Rastelli type, see Table 44-1) and associated lesions (e.g., double orifice mitral valve) if unclear after TTE.

Cardiac Catheterization.

Heart catheterization to determine the severity of pulmonary vascular disease, the presence and magnitude of intracardiac shunts, and the severity of subaortic stenosis may be necessary. The typical "goose neck" deformity of the left ventricular outflow tract is readily demonstrated on angiography.

Open-Lung Biopsy.

This should only be considered when the reversibility of the pulmonary hypertension is uncertain from the hemodynamic data (see Eisenmenger Syndrome, p. 1614).

INDICATIONS FOR INTERVENTION.

The patient with an unoperated or newly diagnosed AVSD and significant hemodynamic defects, manifested by atrial arrhythmias and impaired ventricular function or right ventricular volume overload, requires surgical repair. Equally, patients with symptoms, reversible pulmonary hypertension, or significant

Figure 44-5 Transesophageal echocardiogram of intermediate atrioventricular septal defect illustrates the lack of offsetting between the left-sided and right-sided atrioventricular valves. Single arrow points at the primum atrial septal defect; double arrows point at the restrictive ventricular septal defect. RA\m4\right atrium; LA\m4\left atrium; RV\m4\right ventricle; LV\m4\left ventricle.

Figure 44-4 Typical electrocardiogram of partial atrioventricular septal defect shows first-degree atrioventricular block, left-axis deviation, and complete right bundle branch block.

subaortic obstruction (peak gradient of at least 50 mm Hg at rest) require surgical intervention.

INTERVENTIONAL OPTIONS

Partial AVSD.

Pericardial patch closure of the primum ASD with concomitant suture (±annuloplasty) of the "cleft" left AV valve is usually performed. When "mitral" valve repair is not possible, "mitral" valve replacement may be necessary.

Intermediate/Complete AVSD.

The "staged approach" (pulmonary artery banding followed by intracardiac repair) has been supplanted by primary intracardiac repair. The goals of intracardiac repair are ventricular and atrial septation with adequate mitral and tricuspid reconstruction. Both "single" and "double" patch techniques to close atrial and ventricular septal defects have been described with comparable results.[25] "Tricuspidization" of the left AV "mitral" valve (making a trileaflet left AV valve) at the time of surgery has been advocated by some,[26] [27] but a bileaflet repair is preferred by most. [28] [29] Patch augmentation of the tissue-deficient "bridging leaflets" forming the mitral valve is sometimes performed.[30] Occasionally, left AV valve replacement is necessary when valve repair is not possible. In patients with complete heart block, endocardial transvenous pacing should be avoided when intraatrial or intraventricular communications are present, because paradoxical emboli may occur.

INTERVENTIONAL OUTCOMES.

Surgical mortality in adults with partial AVSDs varies between 0 and 6 percent with 5- and 10-year survivals of 87 percent and 72 percent, respectively.[31] [32] [32A] The worst outcome occurs in patients with pulmonary arterial hypertension, severe AV valve regurgitation,

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and an enlarged heart.[32B] Improvement in functional class after surgical repair is the rule.[31] [32] Postoperative complications include patch dehiscence or residual septal defects (1 percent), the development of complete heart block (3 percent), late atrial fibrillation/flutter, left AV valve dysfunction, and progressive or de novo subaortic stenosis. Recurrent left AV valve regurgitation is the principal cause of late morbidity after surgical repair of AVSDs, necessitating reoperation in at least 10 percent of patients.[28] [29] [31] [32] [32A] [32B] [33] Left AV stenosis from overly zealous cleft suturing may occur. The development or progression of subaortic stenosis after AVSD surgery occurs in about 5 percent of cases.[34] The morphological features of AVSD (the long, narrow left ventricular outflow tract) promote actual or potential subaortic stenosis. Subaortic stenosis can be discrete or tunnel-like, and surgical repair is often necessary. An operation tailored to the underlying cause of obstruction has been advocated because of the high risk of recurrence after surgical resection[34] (see Subaortic Stenosis, p. 1599).

FOLLOW-UP.

All patients require periodic follow-up by a cardiologist because of the possibility of progressive AV valve regurgitation (or stenosis), the development of subaortic stenosis, significant atrial arrhythmias, or progression of the commonly present first-degree AV block. Particular attention should be paid to those patients with pulmonary hypertension,

severe AV valve regurgitation, and an enlarged heart.

Patent Ductus Arteriosus (see also Chap. 43)

The incidence of isolated persistent patency of the ductus arteriosus has been estimated at 1:2000 to 1:5000 births, or about 10 to 12 percent of all varieties of congenital heart disease.

ANATOMY.

The ductus arteriosus derives from the left sixth primitive aortic arch and connects the proximal left pulmonary artery to the descending aorta, just distal to the left subclavian artery. Occasionally, the ductus fails to close at birth and presents as a potential clinical problem.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Physiological consequences of a patent ductus arteriosus (PDA) depend on the degree of left-to-right shunting, which is determined by both the size of the duct and the difference between systemic and pulmonary vascular resistances.[35] A small ductus accompanied by a small shunt does not cause significant hemodynamic derangement but may predispose to endarteritis, especially if accompanied by an audible murmur.[2] A moderate-sized duct and shunt pose a volume load on the left atrium and ventricle with resultant left ventricular dilation and dysfunction and eventual atrial fibrillation. A large duct results initially in left ventricular volume overload, with a progressive rise in pulmonary artery pressure leading to high pulmonary vascular resistance and eventually irreversible pulmonary vascular changes and systemic pulmonary pressures (see Eisenmenger Syndrome, p. 1614).

CLINICAL MANIFESTATIONS.

Patients with *silent* PDAs are asymptomatic, and the PDAs are detected by nonclinical means, usually echocardiography. A small audible duct usually causes no symptoms but may rarely present as an endovascular infection. Physical examination reveals a grade 1-2 continuous murmur, peaking in late systole, and best heard in the first or second left intercostal space. Patients with a moderate-sized duct may present with dyspnea or palpitations from atrial arrhythmias. A louder

Figure 44-6 Short-axis left parasternal transthoracic echocardiogram of systolic flow traveling toward the pulmonary valve (arrow) in the main pulmonary artery from a patent ductus arteriosus. RV\m4\right ventricle; RA\m4\right atrium; AV\m4\aortic valve; PV\m4\pulmonary valve; MPA\m4\main pulmonary artery; LPA\m4\left pulmonary artery; RPA\m4\right pulmonary artery.

continuous "machinery" murmur in the first or second left intercostal space is typically accompanied by a wide systemic pulse pressure from aortic diastolic runoff into the

pulmonary trunk and signs of left ventricular volume overload, such as a displaced left ventricular apex and sometimes a left-sided S_3 . With a moderate degree of pulmonary hypertension, the diastolic component of the murmur disappears, leaving a systolic murmur. Adults with a large uncorrected PDA eventually present with Eisenmenger syndrome physiology (see p. 1614).

DIAGNOSTIC TESTING

Electrocardiogram.

The ECG reflects the size and degree of shunting occurring through the duct. A small duct produces a normal ECG. A moderate-sized duct may show left ventricular volume overload with broad, notched P waves together with deep Q waves, tall R waves, and peaked T waves in V_5 and V_6 . A large duct produces findings of right ventricular hypertrophy (see Eisenmenger syndrome, p. 1614).

Chest Radiography.

A small duct produces a normal chest radiograph. A moderate-sized duct causes moderate cardiomegaly with left-sided heart enlargement and increased pulmonary perfusion. A large duct produces right ventricular hypertrophy and enlarged central pulmonary arteries with peripheral pruning (see Eisenmenger syndrome, p. 1614).

Echocardiography.

This will determine the presence, size, and degree of shunting and the physiological consequences of the shunt. Suprasternal and parasternal short-axis views will best identify the duct. In the absence of Eisenmenger physiology, color flow Doppler shows a jet that travels on the lateral wall of the main pulmonary artery toward the pulmonary valve in systole and diastole (Fig. 44-6 ; see also Fig. 43-18). Direction and timing of the flow as well as the Doppler-derived gradient obtained from the jet provide estimates of the pulmonary artery pressure.

INDICATIONS FOR INTERVENTION.

Closure of a clinically detectable PDA, in the absence of irreversible pulmonary hypertension, is usually recommended to avoid its associated morbidity and premature mortality. The risk of endarteritis in a patient with a *silent* PDA is considered negligible, and closure of such ducts is not recommended for that reason.[2] In the presence of pulmonary hypertension (PAP > two thirds of SAP, or pulmonary arteriolar resistance > two thirds of systemic arteriolar resistance), PDA closure should be carried out if there is a net pulmonary/systemic blood flow greater than 1.5/1.0, evidence of pulmonary artery reactivity when challenged with a pulmonary vasodilator (e.g., oxygen, nitric oxide), or lung biopsy evidence that pulmonary arterial changes are potentially reversible (Heath-Edwards grade II or less). Contraindications to ductal closure include irreversible

pulmonary hypertension or active endarteritis.[2]

INTERVENTIONAL OPTIONS AND OUTCOMES

Transcatheter Treatment.

Over the past 20 years, the efficacy and safety of transcatheter device closure for ducts less than 8 mm has been established,[36] [37] [38] with complete ductal closure achieved in more than 85 percent of patients by 1 year after device placement at a mortality rate of less than 1 percent. The avoidance of general anesthesia, thoracotomy, postoperative pain, and prolonged convalescence makes transcatheter closure a very attractive modality. In centers with appropriate resources and experience, transcatheter device occlusion should be the method of choice for ductal closure (see Chap. 43 , Fig. 43-19).

Surgical Treatment.

Surgical closure, by ductal ligation and/or division, has been performed for over 50 years with a marginally greater closure rate than device closure but somewhat greater morbidity and mortality. Immediate clinical closure (no shunt audible on physical examination) is achieved in more than 95 percent of patients.[39] Surgical mortality in adults is 1.0 to 3.5 percent and relates to the presence of pulmonary artery hypertension and the difficult

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ductal morphology (calcified or aneurysmal) often seen in adults. Surgical closure of a duct should be reserved for patients with larger ducts (> 8 mm diameter) or at centers without access to interventional expertise. Emerging procedures such as muscle-sparing minithoracotomy and video-assisted thoracoscopic surgery may further broaden therapeutic surgical choices in the future.

FOLLOW-UP.

Patients with a silent PDA do not require follow-up. Patients with device occlusion or after surgical closure should be examined periodically for possible recanalization. Silent residual shunts may be found by TTE. The risk of late endarteritis from a clinically silent residual shunt after device implantation or surgical closure is unclear,[40] [41] and the clinical management of such patients remains problematic. Until long-term follow-up data become available, it may be prudent to continue antibiotic endocarditis prophylaxis in such patients.[36] [40] [41]

Bicuspid Aortic Valve (see also Chap. 43)

The bicuspid aortic valve remains the most common congenital malformation of the

heart (1-2 percent of the population). This lesion accounts for approximately half the cases of surgically important isolated aortic stenosis in adults.

ANATOMY.

A bicuspid aortic valve consists of two cusps, often of unequal size, the larger usually containing a false raphe. There is a male preponderance of 4:1. It usually occurs in isolation but is associated with other abnormalities in 20 percent, the most common being coarctation of the aorta and PDA. There is also a high prevalence of aortic root enlargement in patients with bicuspid aortic valve that occurs irrespective of altered hemodynamics or age.[42] [42A] [42B]

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Patients with a bicuspid aortic valve may not experience any problems, although there is always the risk of endocarditis. Mild aortic stenosis from bicuspid aortic valve commonly progresses as the patient ages, but the rate is variable.[43] Late aortic stenosis from calcification of the valve in the sixth decade is common. Other patients can develop aortic regurgitation, aneurysmal aortic root dilation, and possibly aortic dissection.[44]

DIAGNOSTIC TESTING

Electrocardiogram.

The ECG ranges from normal to showing marked left ventricular hypertrophy from severe aortic stenosis or regurgitation. (see Fig. 43-31).

Chest Radiography.

Dilation of the ascending aorta is common. Valvar calcification can sometimes be detected. The left ventricle is enlarged in proportion to the degree of aortic regurgitation.

Echocardiography.

This permits identification of the bileaflet aortic valve and quantification of the severity of obstruction and/or regurgitation. It also provides information on left ventricular size and function as well as aortic root size. Concomitant defects such as coarctation or dissection of the aorta should be sought (see Fig. 43-32).

INDICATIONS FOR INTERVENTION.

Bicuspid aortic valves require intervention for stenosis when symptoms (exertional dyspnea, angina, presyncope or syncope) are present. Intervention for asymptomatic "critical" aortic stenosis (valve area<0.6 cm^2) is debatable. Patients with moderate or severe regurgitation associated with deteriorating ventricular function, a dilating

ventricle, or symptoms are surgical candidates. Prophylactic surgery for proximal aortic dilation (> 55 mm) seems better than waiting for the aorta to dissect or rupture, although there is no agreement on the diameter at which referral for surgery is appropriate.

INTERVENTIONAL OPTIONS.

Bicuspid aortic stenosis can be treated with balloon valvuloplasty if the valve is noncalcified.[45] Other treatment options include open aortic valvotomy or valve replacement using a mechanical valve, a biological valve, or a pulmonary autograft. The pulmonary autograft (Ross procedure), introduced by Donald Ross in 1967, consists of replacing the aortic valve with the patient's pulmonary valve and implanting a homograft in the pulmonary position. The advantages of this procedure--avoidance of anticoagulation and much reduced risk of thromboembolism--need to be weighed against the greater technical complexity of the procedure, the risk of early and late autograft dysfunction, and homograft failure.[46] [47] The choice of intervention depends on the availability and skills of the team involved and the preference of the patient. Aortic valve repair has been reported for aortic regurgitation from a prolapsing aortic valve leaflet. Short-term results are promising, but long-term data are awaited.[48]

FOLLOW-UP.

All patients, treated and untreated, require skilled follow-up, the frequency being determined by the severity of the pathology.

Subaortic Stenosis (see also Chap. 43)

ANATOMY.

Subvalvar LVOTO can be either *discrete* (most common) or *tunnel* shaped. Discrete obstruction is due to a membranous ridge or fibromuscular narrowing partially or completely encircling the left ventricular outflow tract beneath the base of the aortic valve.[49] Tunnel-like obstruction is produced by a fibromuscular channel that involves a long segment of the left ventricular outflow tract and is usually associated with a small aortic root. Rarely, abnormal insertion of the mitral valve or an accessory mitral leaflet will cause subvalvar obstruction. Subvalvar LVOTO can also be seen after repair of AVSD (see p. 1596). The concurrence of subvalvar LVOTO, coarctation, and mitral stenosis (parachute mitral valve and supramitral ring) is known as Shone syndrome. VSD is sometimes associated with subvalvar LVOTO.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Subvalvar LVOTO, discrete or tunnel-like, usually progresses at variable rate, resulting in left ventricular hypertrophy and the development of symptoms.[50] It is often associated with progressive aortic regurgitation (up to 60 percent of cases) from a bicuspid aortic valve or an otherwise normal valve damaged by the subvalvar jet of blood. Aortic regurgitation in this setting is seldom more than moderate. These patients

are particularly vulnerable to endocarditis.

CLINICAL MANIFESTATIONS.

Patients can be asymptomatic or can present with angina, syncope, or heart failure. On examination, the pulse pressure may be diminished if the obstruction is severe. A_2 may be normal or diminished depending on the severity of the stenosis. A systolic ejection murmur may be heard at the mid-left sternal edge in cases of tubular stenosis and in the second right intercostal space in cases of discrete stenosis. A blowing diastolic murmur from concomitant aortic regurgitation is often present. A systolic ejection click is not present in subvalvar aortic stenosis, and the systolic murmur does not radiate to the carotid arteries.[51]

DIAGNOSTIC TESTING

Electrocardiogram.

Left ventricular hypertrophy may be present.

Chest Radiography.

An inconspicuous cardiac silhouette and ascending aorta are the rule unless LVOTO is associated with a bicuspid aortic valve (see bicuspid valve/ascending aortopathy) or significant aortic regurgitation.

Echocardiography.

Two-dimensional echocardiography permits identification of the morphology of the obstruction and any associated anomalies (e.g., bicuspid aortic valve, VSD, coarctation, or mitral inflow obstruction).[52] The severity

of LVOTO can be determined by continuous-wave Doppler and the severity of aortic regurgitation by Doppler and color flow imaging.

Angiography.

An angiogram to assess the severity of obstruction may be needed when noninvasive means are not adequate.

INDICATIONS FOR INTERVENTION.

Whereas patients with symptomatic subvalvar LVOTO require intervention, indications for intervention in asymptomatic patients are less well defined. A resting peak-to-peak angiographic gradient greater than 50 mm Hg as well as progressive or moderate to severe aortic regurgitation have been used as criteria for intervention.[6] Some advocate earlier relief of subvalvar obstruction to minimize early aortic valve damage and prevent progressive regurgitation.[53]

INTERVENTIONAL OPTIONS

Surgical.

For discrete obstruction, membranectomy with concomitant myomectomy or myotomy is usually performed. For tunnel-like obstruction, the left ventricular outflow tract often requires surgical augmentation using the modified Konno procedure (aortoventriculoplasty with aortic valve sparing).[54] In patients with significant aortic stenosis or moderate/severe aortic regurgitation, the Konno procedure (aortoventriculoplasty with aortic valve replacement) or the Konno-Ross procedure (aortoventriculoplasty with pulmonary autograft)[55] for younger patients or those with a contraindication to anticoagulation should be performed. Left ventricular apex-to-aorta valved conduits, bypassing the LVOTO, have been used in the past, but the long-term durability is unacceptable and the procedure has largely been abandoned.

Transcatheter.

Transluminal balloon dilation of discrete subaortic stenosis has been described with good short- and intermediate-term results,[56] but long-term data have not been reported. At present, a surgical approach is still recommended.

INTERVENTIONAL OUTCOMES.

Complications related to surgery include complete AV block, creation of VSD, or mitral valve regurgitation from intraoperative damage to the mitral valve apparatus. Long-term complications include recurrence of fibromuscular subvalvar LVOTO (up to 20 percent), particularly with tunnel-like obstruction or following isolated membranectomy for discrete obstruction. Clinically important aortic regurgitation is also not uncommon (up to 25 percent of patients).

FOLLOW-UP.

Particular attention should be paid to patients with recurrent subvalvar stenosis or patients with an associated bicuspid aortic valve or progressive aortic regurgitation because they are most likely to require eventual surgery. Patients with bioprosthetic aortic valves in the aortic position (after the Konno procedure) or the pulmonic position (after the Konno-Ross procedure) need close follow-up. Reoperation is required in up to 25 percent of patients in the 20 years[57] [58] after surgical repair. Endocarditis prophylaxis

should be used for prosthetic valves or in the presence of any residual lesions.

Coarctation of the Aorta (see also Chap. 43)

This left-sided obstructive lesion occurs most frequently in males, with a sex ratio approaching 3:1.

ANATOMY.

Coarctation of the aorta is a narrowing usually in the region of the ligamentum arteriosum (see Fig. 43-27). It may be discrete or associated with hypoplasia of the aortic arch and isthmus. The specific anatomy, severity, and degree of hypoplasia proximal to the coarctation are highly variable. "Complex" coarctation is used to describe coarctation in the presence of other important intracardiac anomalies (e.g., VSD, LVOTO, and mitral stenosis) and is usually detected in infancy. "Simple" coarctation refers to coarctation in the absence of such lesions. It is the most common form detected de novo in adults. Associated abnormalities include bicuspid aortic valve in 50 to 85 percent of cases, intracranial aneurysms (most commonly of the circle of Willis), and acquired intercostal artery aneurysms. One definition of "significant" coarctation is one with a gradient greater than 20 mm Hg across the coarctation site at angiography with or without proximal systemic hypertension. A second definition of "significant" coarctation requires the presence of proximal hypertension in the company of echocardiographic or angiographic evidence of aortic coarctation. Of note, if there is an extensive collateral circulation, there may be minimal or no pressure gradient and acquired aortic atresia.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

A significant coarctation causes a pressure load proximally with consequent left ventricular hypertrophy and ultimately heart failure. Most patients will develop systemic hypertension, typically during childhood, and are at risk of premature coronary artery disease. The mean survival of patients with untreated coarctation is 35 years, with 75 percent mortality by 50 years of age.[59] Death in patients who do not undergo repair is usually due to heart failure (usually beyond 30 years of age), coronary artery disease, aortic rupture/dissection, concomitant aortic valve disease, infective endarteritis/endocarditis, or cerebral hemorrhage.[59]

CLINICAL MANIFESTATIONS.

Patients may be asymptomatic or present with minimal symptoms of epistaxis, headache, leg weakness on exertion, or more serious symptoms of congestive heart failure, angina, aortic stenosis, aortic dissection, or unexplained intracerebral hemorrhage. Leg claudication is rare unless there is concomitant abdominal aortic coarctation (Somerville J, personal communication, 1998). A thorough clinical examination reveals upper limb systemic hypertension as well as a differential systolic blood pressure of at least 10 mm Hg (brachial > popliteal artery pressure). Radial-femoral pulse delay is evident unless significant aortic regurgitation coexists.

Auscultation may reveal an interscapular systolic murmur emanating from the coarctation site and a widespread crescendo-decrescendo systolic murmur throughout the chest wall from intercostal collateral arteries. Fundoscopic examination can reveal "corkscrew" tortuosity of retinal arterioles. [60]

DIAGNOSTIC TESTING

Electrocardiogram.

Left ventricular hypertrophy is common. Concomitant left atrial enlargement may be present.

Chest Radiography.

Prestentotic and poststenotic dilation of the aorta gives the "3 sign" appearance on a chest radiograph. Rib notching appearing as sclerotic scalloping on the inferior surface of ribs number 3 through 8 from dilated intercostal arteries may be present, usually bilaterally, unless the left or right subclavian artery arises aberrantly below the coarctation, giving rise to unilateral right-sided or left-sided rib notching, respectively.

Echocardiography.

The coarctation site can be visualized from the suprasternal view and its severity assessed by Doppler mode (see Fig. 43-28). A peak gradient greater than 20 mm Hg, especially if accompanied by continuous forward flow during diastole in the descending or abdominal aorta, suggests significant aortic coarctation. In addition, the echocardiographer should evaluate other cardiac lesions--notably aortic, mitral, or subaortic abnormality and the status of left ventricular function.

Angiography.

Angiography with hemodynamic measurements can be done to assess the location, type, and severity of coarctation and to determine the presence/absence of collaterals or aneurysm formation. Associated stenoses in other great vessels (carotids and subclavian arteries) can also be detected by this modality. Coronary angiography should be performed if surgery is planned because of the risk of premature coronary artery disease in these patients.

Magnetic Resonance Imaging (MRI).

MRI (two-dimensional and velocity mapping) provides as good anatomical and hemodynamic details as angiography and may obviate the need for angiography, unless

coronary artery disease needs to be excluded.

INDICATIONS FOR INTERVENTION.

All patients with significant coarctation or re-coarctation (arm > leg systolic pressure difference
10 mm Hg; radial-femoral pulse delay; peak transcoarctation gradient > 20 mm Hg at angiography) including those with long-standing hypertension (regardless of age), whether symptomatic or asymptomatic, warrant intervention to reduce or eliminate the gradient.[59]

INTERVENTIONAL OPTIONS

Surgical.

Surgical techniques include end-to-end repair, subclavian flap plasty, patch repair, interposed graft, or bypass graft and varies according to the underlying anatomy of the coarctation.[61] Patients with significant aortic valve stenosis may also require valve surgery that may or may not be done at the same time as coarctation repair. If lesions are operated on separately, the more severe lesion should be dealt with first.

Transcatheter.

Balloon dilation with or without stent insertion in patients with native coarctation and re-coarctation has been performed with good immediate and medium-term results in children and adolescents.[62] [63] [64] However, it should still be considered experimental in the adult population and should only be performed in centers and by individuals with expertise in this domain (Fig. 44-7) .

INTERVENTIONAL OUTCOMES

Surgical.

After surgical repair of simple coarctation, the obstruction is usually relieved with minimal mortality (<1 percent). Paraplegia due to spinal cord ischemia is uncommon (0.4 percent) and may occur in patients who do not have well-developed collateral circulation. The prevalence of recoarctation reported in the literature varies widely, from 7 to 60 percent depending on the definition used, the length of follow-up, and the age at surgery.[65] The appropriateness of the surgical repair for a given anatomy is probably the main factor dictating the chance of recoarctation, rather than the type of surgical repair itself.[66] True aneurysm formation at the site of coarctation repair is also a well-recognized entity with a reported incidence between 2 and 27 percent.[67] Aneurysms are particularly common after Dacron patch aortoplasty and usually occur in the native aorta opposite the patch. Late dissection at the repair site is rare but false aneurysms, usually at the suture line, can occur.

Prior hypertension resolves in up to 50 percent of patients but may recur later in life, especially if the intervention is performed at an older age. In some of these patients this may be "essential hypertension," but a hemodynamic basis should be sought and blood pressure control attained. Systolic hypertension is also common with exercise and may be related to residual arch hypoplasia or more likely to increased renin and catecholamine activity from residual functional abnormality of the precoarctation vessels.[69] [70] Late cerebrovascular events occur, notably in those patients undergoing repair as adults and in those with residual hypertension. Endocarditis/endarteritis can occur at the coarctation site or on intracardiac lesions; and if this occurs at the coarctation site, embolic manifestations are restricted to the legs.

Long-term follow-up after surgical correction of coarctation of the aorta still reveals an increased incidence of premature cardiovascular disease and death.

Transcatheter.

After balloon dilation, aortic dissection, restenosis, and aneurysm formation at the site of coarctation have all been documented.[62] [63] [64] These complications may well be reduced if stents are used. The significance of aneurysm formation is unknown,[68] and longer-term data are needed.

FOLLOW-UP.

All patients should have follow-up every 1 to 3 years. Particular attention should be directed toward residual hypertension, heart failure, or intracardiac disease, such as an associated bicuspid aortic valve, which can become stenotic or regurgitant later in life, or an ascending aortopathy (due to cystic medial necrosis) sometimes seen in the presence of bicuspid aortic valve. Complications at the site of repair such as restenosis and aneurysm formation should also be sought using clinical examination, chest radiography, echocardiography, or, preferably, MRI.[68A] Patients with Dacron patch repair should probably undergo an MRI or spiral computed tomographic (CT) examination every 3 to 5 years or so to detect subclinical aneurysm formation. Hemoptysis from a leaking/ruptured aneurysm is a serious complication requiring immediate investigation

Figure 44-7 Angiograms of coarctation of the thoracic aorta *(A)* and transcatheter stent placement in the treatment of coarctation of the aorta *(B).*

and surgery. New or unusual headaches should raise the possibility of berry aneurysm. Endocarditis prophylaxis is recommended for any residual turbulent flow.

Right Ventricular Outflow Tract Obstruction (see also Chap. 43)

Right ventricular outflow tract obstruction (RVOTO) can occur at supravalvar, valvar, and subvalvar levels.

ANATOMY.

Supravalvar RVOTO seldom occurs in isolation. It may occur in tetralogy of Fallot, Williams syndrome, Noonan syndrome, VSD, or arteriohepatic dysplasia (Alagille syndrome) (Table 44-2) . *Branch* pulmonary artery stenosis may occur in the setting of congenital rubella syndrome and tetralogy of Fallot. *Subvalvar* (infundibular) RVOTO usually occurs in combination with other lesions, particularly ventricular septal defect, as part of tetralogy of Fallot, or in association with subaortic stenosis. The "*double-chambered right ventricle*" is different from infundibular RVOTO. It consists of a midcavity obstruction, often from a prominent moderator band, and may be associated with a small VSD. *Valvar* RVOTO (pulmonic stenosis) is the most common form of RVOTO. It is almost always congenital in origin. It usually occurs as an isolated anomaly but it can be part of a syndrome (see Table 44-2). Typically, the stenotic pulmonic valve is a thin, pliable, dome-shaped structure, with a narrow opening at its apex. In 15 percent of cases, the stenotic valve is dysplastic with thickened and immobile cusps. The severity of stenosis is classified by the level of the peak systolic pressure gradient (Table 44-3) .

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Supravalvar RVOTO can progress in severity and should be monitored. *Subvalvar* (infundibular and double-chamber) RVOTO often progresses in severity, causing worsening right ventricular hypertrophy, symptoms, and critical gradients requiring surgical repair. Patients with trivial and mild *valvar* RVOTO rarely become worse with time. [71] Moderate valvar RVOTO can progress in 20 percent of unoperated

TABLE 44-2 -- SYNDROMES ASSOCIATED WITH PULMONARY VALVE STENOSIS

Williams Syndrome

Cardiac: Pulmonary stenosis, pulmonary artery stenosis, supravalvar aortic stenosis

CNS: Mental retardation, "cocktail personality"

Facies: Small chin, large mouth, upturned and blunt nose, wide-set eyes, broad forehead, baggy cheeks, and malformed teeth

Other: Infantile hypercalcemia, short stature

Noonan Syndrome

Cardiac: Dysplastic pulmonary stenosis, hypertrophic cardiomyopathy, atrial septal defect

CNS: Mental retardation (1 in 3 patients)

Facies: Short webbed neck, low-set ears, low posterior hair line, high-arched palate, micrognathia, eye abnormality (ptosis/hypertelorism)

Other: Short stature; thoracic, penile, and testicular abnormality

Congenital Rubella

Cardiac: Pulmonary stenosis, pulmonary artery stenosis, patent ductus arteriosus

CNS: Mental retardation, hypotonia, hearing loss

Facies: Cataracts, retinopathy

Alagille Syndrome

Cardiac: Pulmonary stenosis, pulmonary arterial stenosis

Facies: Prominent overhanging forehead, deep-set eyes, small pointed chin

TABLE 44-3 -- HEMODYNAMIC SEVERITY GRADING FOR RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION (PEAK GRADIENT)

Trivial	<25 mm Hg
Mild	25-49 mm Hg
Moderate	50-79 mm Hg
Severe or critical	>80 mm Hg

patients, especially as adults because of calcification of the valve, and may require intervention.[71] Some of these patients can also become symptomatic, particularly in later life, because of atrial arrhythmias resulting from right ventricular pressure overload and tricuspid regurgitation. Patients with severe valvar RVOTO will have had valvotomy (balloon or surgical) to survive to adult life. Long-term survival in patients with repaired pulmonic valvar stenosis is similar to that of the general population, with excellent to good functional class at long-term follow-up in the vast majority of patients.[71]

CLINICAL MANIFESTATIONS.

Patients with isolated mild to moderate RVOTO of any type are usually asymptomatic. Patients with severe RVOTO may present with exertional fatigue, dyspnea, lightheadedness, and chest discomfort (right ventricular angina). Physical examination may reveal a prominent jugular a wave, a right ventricular lift, and possibly a thrill in the second left interspace. Auscultation reveals a normal S_1 , a split second heart sound (S_2) with a diminished pulmonic component (P_2) (unless the obstruction is supravalvular in which case the intensity of the P_2 does not change), and a systolic ejection murmur best heard in the second left intercostal space. When the pulmonic valve is thin and pliable, a systolic ejection click, which decreases on inspiration, is heard. As the severity of stenosis progresses, the interval between the S_1 and the systolic ejection click becomes shorter, the S_2 becomes widely split, the P_2 diminishes or disappears (but remains the same if the obstruction is supravalvular), and the systolic ejection murmur lengthens

and peaks later in systole, often extending beyond the aortic component of the S_2 (A_2). An ejection click seldom occurs with dysplastic pulmonic stenosis or subvalvar or supravalvar RVOTO. Typically, the systolic murmur of subvalvar stenosis is located lower on the left chest (third to fifth intercostal space) and that of supravalvular stenosis (pulmonary artery/branches stenosis) has a wide thoracic distribution. Mild cyanosis may be present when a patent foramen ovale or ASD permits right-to-left shunting.

DIAGNOSTIC TESTING

Electrocardiogram.

A peaked P wave consistent with right atrial overload and evidence of right ventricular hypertrophy may be present.

Chest Radiography.

Dilation of the main and left pulmonary arteries is the radiographic hallmark of valvar pulmonary stenosis. Pulmonary valvar calcification occasionally is seen. Dilation of the pulmonary trunk is not a feature of subvalvar and supravalvar RVOTO. Peripheral pulmonary vascular markings may be diminished when RVOTO is severe.

Echocardiography.

Echocardiography is useful to document the level(s) of obstruction and quantitate the severity (see Fig. 43-42). Associated abnormalities such as ASD, PDA, VSD, and tetralogy of Fallot can be identified.

Diagnostic Catheterization.

Cardiac catheterization can be useful to assess the hemodynamics and severity of obstruction as well as to delineate the extent and site of pulmonary artery branch stenoses.

INDICATIONS FOR INTERVENTION.

Intervention is recommended when the peak gradient across the right ventricular outflow tract is more than 50 mm Hg at rest[2] [72] or when the patient is symptomatic. Intervention may be indicated

occasionally for other reasons (e.g., a person with a lesser degree of obstruction who wishes to play vigorous sports, scuba dive, or become pregnant). An associated ASD should be closed at the time of intervention.

INTERVENTIONAL OPTIONS

Balloon Valvuloplasty.

Balloon valvuloplasty is the treatment of choice for valvar RVOTO. It is a highly effective procedure that can be carried at low risk.[73]

Surgical Valvotomy.

Surgical valvotomy may be required for pulmonary stenosis when the valve is calcified or dysplastic.[74] Pulmonary valvectomy or pulmonary valve replacement is seldom performed.

Relief of peripheral pulmonary stenosis can be accomplished by balloon dilation with or without stent placement.

Relief of obstruction in a double-chambered right ventricle is accomplished by surgical resection of right ventricular muscle bands.

INTERVENTIONAL OUTCOMES

Balloon Valvuloplasty.

The prognosis and outcomes of pulmonic valvuloplasty compare favorably with those of surgical valvotomy.[75] A 55 to 75 percent immediate reduction in transvalvular gradient is the rule, and usually the benefit persists at up to 9 years of follow-up. After pulmonic valvuloplasty, dynamic RVOTO from residual subvalvular hypertrophy is sometimes seen but usually regresses by 3 to 12 months and can be treated with a beta blocker in the meantime.[76] Severe pulmonic regurgitation as a consequence of valvuloplasty is rare. The results of balloon dilation for dysplastic pulmonary valves are less satisfactory.[74]

Surgical Valvotomy.

The long-term results of surgical pulmonary valvotomy are well known and excellent. Relief of valvar RVOTO is usually permanent, but residual obstruction can progress. Significant pulmonary regurgitation is reportedly more frequent after surgery and can become severe enough to warrant re-intervention.

Subvalvar and supravalvar RVOTO seldom recur after adequate intervention.

FOLLOW-UP.

Patients with moderate or greater RVOTO require annual monitoring because

intervention or re-intervention may be required. After intervention, severe pulmonic regurgitation associated with reduced exercise capacity, arrhythmias, or evidence of deteriorating right ventricular function may necessitate pulmonary valve replacement.

Ebstein Anomaly (see also Chap. 43)

ANATOMY.

Ebstein anomaly results from apical displacement of the septal, posterior, or (rarely) anterior leaflet of the tricuspid valve, resulting in "atrialization" (functioning as an atrial chamber) of the inflow tract of the right ventricle and consequently a variably small functional right ventricle (Figs. 7-89 , and 44-55). Varying degrees of tricuspid regurgitation (or in exceptional cases tricuspid stenosis) result from this abnormal tricuspid leaflet morphology with consequent further right atrial enlargement. Infundibular dilation can also be present. Associated anomalies include patent foramen ovale or ASD in approximately 50 percent of patients, accessory conduction pathways in 25 percent, and, occasionally, varying degrees of RVOTO, VSD, coarctation of the aorta, PDA, or mitral valve disease.

Natural History of the Unoperated Patient.

The natural history of patients with Ebstein anomaly depends on its severity.[77] Adults with Ebstein anomaly can remain asymptomatic throughout their life if the anomaly is mild--survival to the ninth decade has been reported. With moderate tricuspid valve deformity and dysfunction, patients will usually develop symptoms during late adolescence or young adult life.

Figure 44-8 (Figure Not Available) Diagrammatic representation of Ebstein anomaly. RA=right atrium; RV=right ventricle; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

Clinical Manifestations.

Most adult patients present with exercise intolerance (dyspnea and fatigue), palpitations of supraventricular origin, or cyanosis from a right-to-left shunt at the atrial level.[1] Occasionally, a paradoxical embolus resulting in a transient ischemic attack or cerebrovascular accident can call attention to the diagnosis. End-stage right-sided cardiac failure from severe tricuspid regurgitation and right ventricular dysfunction is possible. Sudden death (presumed to be arrhythmic in nature) is known to occur.[78] Physical examination reveals an unimpressive jugular venous pressure because of the large and compliant right atrium and atrialized right ventricle, a widely split S_1 with a loud tricuspid component (the "sail sound"), a widely split S_2 from the right bundle branch block, and a right-sided S_3 . A holosystolic murmur increasing on inspiration from tricuspid regurgitation is best heard at the lower left sternal border. Cyanosis from a right-to-left shunt at the atrial level may or may not be present.[79]

DIAGNOSTIC TESTING

Electrocardiogram.

The ECG presentation of Ebstein anomaly varies widely. Low voltage is typical. Peaked P waves in lead II and V_1 reflect right atrial enlargement. The PR interval is usually prolonged, but a short PR interval and a delta wave from early activation through an accessory pathway can be present. An rsr
pattern consistent with right ventricular conduction delay is typically seen in lead V_1 (Fig. 44-9) . Atrial flutter and fibrillation are common. Alternatively, the ECG may be normal.

Chest Radiography.

A rightward convexity from an enlarged right atrium and atrialized right ventricle coupled with a leftward convexity from a dilated infundibulum give the heart a "water bottle" appearance on a chest radiograph. Cardiomegaly, highly variable in degree, is the rule. The aorta and the pulmonary trunk are inconspicuous. The pulmonary vasculature is usually normal to reduced.

Echocardiography.

The diagnosis of Ebstein anomaly can often be made by echocardiography. Apical displacement of the septal leaflet of the tricuspid valve by 8 mm/m^2 or more, combined with an elongated sail-like appearance of the anterior leaflet, confirms the diagnosis[80] (Figs. 44-10 , 7-90 , and 43-56). The size of the atrialized portion of the right ventricle (identified between the tricuspid annulus and the ventricular attachment of the tricuspid valve leaflets)

Figure 44-9 Electrocardiogram typical of Ebstein anomaly. Accessory pathway exemplified by the short PR interval, delta wave, and wide QRS complex. Note the peaked P wave in V_2 representing right atrial overload.

and the systolic performance of the functional right ventricle can be determined. The degree of tricuspid regurgitation (and more rarely stenosis) can be assessed. Associated defects such as ASDs as well as the presence and direction of shunting can also be identified.

Angiography.

Heart catheterization is required mainly when concomitant coronary artery disease is suspected. When performed, selective right ventricular angiography shows the extent of tricuspid valve displacement, the size of the functional right ventricle, and configuration of its outflow tract.

INDICATIONS FOR INTERVENTION.

Indications for intervention include deteriorating functional capacity (NYHA Class III), progressive cyanosis, right-sided heart failure, and the occurrence of paradoxical emboli. Recurrent supraventricular arrhythmias not controlled by medical or ablation therapy (see Chap. 23) and asymptomatic cardiomegaly (cardiothoracic ratio > 65 percent) are relative indications.[78] [81]

INTERVENTIONAL OPTIONS.

Tricuspid valve repair when feasible is preferable to tricuspid valve replacement. The feasibility of tricuspid valve repair depends primarily on the experience and skill of the surgeon, as well as on the adequacy of the anterior leaflet of the tricuspid valve to form a monocusp valve.[81] [82] Tricuspid valve repair is possible when the edges of the anterior leaflet of the tricuspid valve are not severely tethered down to the myocardium and when the functional right ventricle is of adequate size (>35 percent of the total right ventricle). If the tricuspid valve cannot be repaired, valve replacement with either a bioprosthetic or mechanical tricuspid valve is necessary. It is controversial whether the atrialized portion of the right ventricle should be plicated at the time of surgery to reduce the risk of atrial arrhythmias. For "high-risk" patients (those with severe tricuspid regurgitation, an inadequate functional right ventricle [because of size or function], and/or chronic supraventricular arrhythmias), a bidirectional cavopulmonary connection can be added to reduce right ventricular preload (see Glen procedure, Chap. 43).[83] Occasionally, a Fontan operation may be the best option in patients with tricuspid stenosis and/or hypoplastic right ventricle (see Fontan operation, p. 1607). Concomitant right atrial maze procedure at the time of surgery should be considered in patients with chronic atrial flutter/fibrillation.[84] If an accessory pathway is present, it should be mapped and obliterated either at the time of surgical repair or preoperatively in the catheter laboratory (see Chaps. 23 and 25). An atrial communication, if present, should be closed.

INTERVENTIONAL OUTCOMES.

With satisfactory valve repair, with or without plication of the atrialized right ventricle or bidirectional cavopulmonary connection, the medium-term prognosis is excellent.[81] [82] Late arrhythmias can occur. With valve replacement, results are less satisfactory. Valve re-replacement may be necessary because of a failing bioprosthesis or thrombosed mechanical valve. Long-term anticoagulation with mechanical valves is mandatory.

Complete heart block after tricuspid valve replacement can occur.

FOLLOW-UP.

All patients with Ebstein anomaly should have regular follow-up, the frequency dictated by the severity of their disease. Particular attention should be paid to patients with cyanosis, cardiomegaly, worsening right ventricular function, and important atrial arrhythmias. Patients with tricuspid regurgitation after tricuspid valve repair need close follow-up, as do patients with recurrent atrial arrhythmias, degenerating bioprostheses, or dysfunctional mechanical valves.

Figure 44-10 Four-chamber view, transthoracic echocardiogram of Ebstein anomaly. Multiple arrows point at the apically displaced tricuspid valve. RA=right atrium; ARV=atrialized right ventricle; RV=functional right ventricle; LA=left atrium; MV=mitral valve; LV=left ventricle.

Tetralogy of Fallot (see also Chap. 43)

Tetralogy of Fallot is the most common form of cyanotic congenital heart disease after 1 year of age, with an incidence approaching 10 percent of all forms of congenital heart disease.

ANATOMY.

The defect is due to anterocephalad deviation of the outlet septum resulting in four features: (1) nonrestrictive VSD; (2) overriding aorta (but<50 percent); (3) RVOTO, which may be infundibular, valvar, or (usually) a combination of both, with or without supravalvar or branch pulmonary artery stenosis; and (4) consequent right ventricular hypertrophy. The so-called pentalogy of Fallot also has an ASD. Accompanying features can include additional VSDs, anomalous coronary arteries, right-sided aortic arch, PDA, aortic root dilation, aortic regurgitation, and aortopulmonary collaterals (Figs. 44-11 (Figure Not Available) and 43-47).

NATURAL HISTORY OF THE UNOPERATED PATIENT.

To reach adulthood, most patients will have had surgery, either palliative or, more commonly, reparative. A few patients however will present as adults with uncorrected tetralogy of Fallot. Natural survival into the fourth decade is rare (approximately 3 percent).

SURGICAL PROCEDURES.

These are usually done in childhood.

Palliation.

Palliative procedures in tetralogy of Fallot serve to increase pulmonary blood flow. The types of palliative procedures include the Blalock-Taussig shunt (classic or modified--subclavian artery to pulmonary artery end-to-side shunt or interposition graft), Waterston shunt (ascending aorta to right pulmonary artery shunt), Potts shunt (descending aorta to left pulmonary artery shunt), or a central interposition tube graft (see shunt procedure, Chap. 43). The Brock procedure (infundibular resection), pulmonary valvotomy, or right ventricle to pulmonary artery conduit without VSD closure or with fenestrated closure were occasionally performed.

Repair.

Reparative surgery involves closing the VSD with a Dacron patch and relieving the RVOTO. The latter

Figure 44-11 (Figure Not Available) Diagrammatic representation of tetralogy of Fallot. 1, Pulmonary stenosis; 2, ventricular septal defect; 3, overriding aorta; 4, right ventricle hypertrophy. RA=right atrium; RV=right ventricle; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

Figure 44-12 (Figure Not Available) Diagrammatic representation of the surgical repair of tetralogy of Fallot. Patch closure of ventricular septal defect (1); right ventricular outflow/main pulmonary artery outflow patch (transannular patch) (2). RA=right atrium; RV=right ventricle; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

may involve resection of infundibular muscle and insertion of a right ventricular outflow tract or transannular patch--a patch across the pulmonary valve annulus that disrupts the integrity of the pulmonary valve and causes important pulmonary regurgitation (Fig. 44-12) (Figure Not Available) . Occasionally, the pulmonic valve is replaced with a pericardial monocusp valve. When an anomalous coronary artery crosses the right ventricular outflow tract and precludes transection of the latter, an extracardiac conduit is placed between the right ventricle and pulmonary artery, bypassing the RVOTO. A patent foramen ovale or secundum ASD is closed. Additional treatable lesions such as muscular VSDs, PDA, and aortopulmonary collaterals should also be addressed at the time of surgery or in the catheterization laboratory.

CLINICAL MANIFESTATIONS

Unoperated.

The pathophysiology varies depending on the degree of RVOTO. With mild obstruction, the presentation is of increased pulmonary blood flow and minimal cyanosis, the so-called pink, or acyanotic, tetralogy of Fallot. This is a rare presentation in adults.

Progressive cyanosis from worsening RVOTO along with cerebrovascular accidents, endocarditis, supraventricular arrhythmias, and aortic regurgitation are the most common presenting features. On physical examination, the length and loudness of the systolic murmur are inversely related to the severity of the RVOTO. As the RVOTO increases toward occlusion, the right ventricular blood flow is directed through the VSD into the aorta and the pulmonic stenosis murmur becomes shorter and softer.[85] P_2 is faint and delayed in patients with mild cyanosis and inaudible with severe cyanosis. An ejection sound from aortic dilation and a diastolic murmur from consequent aortic regurgitation can be heard. Central cyanosis and clubbing are present to varying degrees.

Palliated.

Progressive cyanosis with its complications (see p. 1608) can result from worsening RVOTO, gradual stenosis and occlusion of palliative aorto-pulmonary shunts, or development of pulmonary hypertension (sometimes seen after Waterston or Potts shunts). Left ventricular dilation and failure from long-standing left-to-right shunting can also occur. On physical examination, central cyanosis

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and clubbing invariably are present. Continuous murmurs should be sought to assess shunt patency.

Repaired.

After intracardiac repair, over 85 percent of patients are asymptomatic on follow-up. Palpitations from atrial and ventricular tachycardias, with or without dizziness or syncope, and dyspnea from progressive right ventricular dilation secondary to chronic pulmonary regurgitation or severe residual RVOTO occur in 10 to 15 percent of patients at 20 years after initial repair.[86] An ascending aortic aneurysm and progressive aortic regurgitation from a dilated aortic root can also be present. Physical examination may reveal a parasternal right ventricular lift from right ventricular dilation, a normal S_1 , but a soft and delayed P_2 with a low-pitched diastolic murmur from pulmonary regurgitation at the left sternal border. A systolic ejection murmur from RVOTO, a high-pitched diastolic murmur from aortic regurgitation, and a holosystolic murmur from a VSD patch leak can also be heard.

DIAGNOSTIC TESTING

Electrocardiogram

Unoperated.

Right ventricular hypertrophy with right-axis deviation is the rule. Right bundle branch block can be present.

Palliated.

A prominent R wave in V_5 to V_6 can be present and represents left ventricular hypertrophy.

Repaired.

Complete right bundle branch block after repair is the rule. QRS width reflects the degree of right ventricular dilation[87] (Fig. 44-13) .

Figure 44-13 Electrocardiogram of tetralogy of Fallot after surgical repair. Note the wide right bundle branch block (160 msec). First-degree atrioventricular block is also present.

Chest Radiography

Unoperated.

The distinctive "coeur en sabot" or "boot-shaped heart" configuration results from a small main pulmonary artery and a hypertrophied right ventricle coupled to a small to normal-sized left ventricle. Pulmonary vascularity is reduced. A right-sided aortic arch in present in 25 percent.

Palliated.

Increased pulmonary blood flow with rib notching on the side of the shunt (Blalock-Taussig) or evidence of unilateral pulmonary hypertension (Waterston or Potts shunt) may be seen.

Repaired.

Cardiomegaly from right ventricular dilation can be present, along with dilation of the ascending aorta.

Echocardiography

Unoperated.

The malaligned, nonrestrictive VSD and overriding aorta (<50 percent override) are readily identified in the left parasternal long-axis or four-chamber views. Additional muscular VSDs should be sought on two-dimensional and color flow Doppler. The presence and degree of RVOTO (infundibular, valvar, and/or pulmonary arterial stenosis) are best assessed using two-dimensional and Doppler modes (see Figs. 7-86 and 43-48).

Palliated.

Aortopulmonary shunts can be detected from a suprasternal view, by color flow and Doppler mode, as turbulent flow entering the right or left pulmonary artery.

Repaired.

Residual pulmonary stenosis and regurgitation, residual VSD, right and left ventricular sizes and function, aortic root size, and the degree of aortic regurgitation should be assessed (Fig. 44-14) .

Catheterization

Unrepaired/Palliated.

Cardiac catheterization should be performed before surgical repair in patients in whom the presence of an anomalous coronary artery, significant aortopulmonary collaterals, additional muscular VSDs, peripheral pulmonary artery stenosis, and pulmonary hypertension have not been excluded by other modalities.

Repaired.

Complete heart catheterization including coronary angiography (for patients with risk factors for coronary artery disease) should be done if surgical re-intervention is planned or when adequate assessment of the hemodynamics is not obtainable by noninvasive means.

INDICATIONS FOR INTERVENTION

Unoperated.

For unoperated adults, surgical repair is still recommended because the results are gratifying and the operative risk is comparable to pediatric series (provided there is no serious coexisting morbidity).[88]

Palliated.

Palliation was seldom intended as a permanent treatment strategy, and most of these patients should undergo surgical repair. In particular, palliated patients with increasing cyanosis and erythrocytosis (from gradual shunt stenosis or development of pulmonary hypertension), left ventricular dilation, or aneurysm formation in the shunt should undergo intracardiac repair with takedown of the shunt unless irreversible pulmonary hypertension has developed.

Repaired.

The following situations *may* warrant intervention after repair: a residual VSD with a shunt greater than 1.5/1.0; residual pulmonary stenosis with right ventricular pressure two thirds or more of systemic pressure (either the native right ventricular outflow or valved conduit if one is present); or free pulmonary regurgitation associated with important right ventricular enlargement and/or dysfunction, exercise intolerance, or sustained arrhythmias. The development of major cardiac arrhythmias, most commonly atrial flutter/fibrillation or sustained ventricular tachycardia, usually reflects hemodynamic deterioration and should be treated accordingly.[87] Surgery is necessary for significant aortic regurgitation associated with symptoms

Figure 44-14 Transthoracic echocardiogram of severe pulmonary regurgitation as exemplified by the broad base, nonturbulent flow in diastole (arrow) originating from as far as the right and left pulmonary arteries. RVOT\m4\right ventricular outflow tract; AV\m4\aortic valve; MPA\m4\main pulmonary artery; LPA\m4\left pulmonary artery; RPA\m4\right pulmonary artery.

Figure 44-15 Modifications of the Fontan operation. *A,* Direct atriopulmonary connection (1) for tricuspid valve atresia (2); ventricular septal defect, oversewn (3); patch closure of atrial septal defect (4). RA=right atrium; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.) B,* Extracardiac conduit made of a Dacron graft bypassing the right atrium, connecting the inferior vena cava to the inferior aspect

of the right pulmonary artery. Superior vena cava is anastomosed to the superior aspect of the right pulmonary artery. *(From Marcelletti C: Inferior vena cava-pulmonary artery extracardiac conduit: A new form of right heart bypass. J Thorac Cardiovasc Surg 100:228-232, 1990.)*

and/or progressive left ventricular dilation and perhaps for aortic root enlargement of 55 mm or more in diameter.[89] Rapid enlargement of a right ventricular outflow tract aneurysm or evidence of infection or false aneurysm needs surgical attention.

INTERVENTIONAL OPTIONS

Surgery.

Reoperation is necessary in 10 to 15 percent of patients after reparative surgery over a 20-year follow-up, mainly due to long-term complications of the RVOT.[86] For persistent RVOTO, resection of residual infundibular stenosis or placement of an RV outflow or transannular patch, with or without pulmonary arterioplasty, can be performed. Occasionally, an extracardiac valved conduit may be necessary. Pulmonary valve replacement (either homograft or xenograft) often is used to treat severe pulmonary regurgitation. Concomitant tricuspid valve annuloplasty may be performed for moderate or severe tricuspid regurgitation. Concomitant cryoablation should be performed at the time of surgery for patients with either preexisting atrial or ventricular arrhythmias.[86] [90]

Interventional.

Significant branch pulmonary artery stenosis can be managed with balloon dilation and usually stent insertion.

INTERVENTIONAL OUTCOMES.

The overall survival of patients who have had initial operative repair is excellent, provided the VSD has been closed and the RVOTO has been relieved. A 25-year survival of more than 94 percent has been reported.[91] [95] [97] Pulmonary valve replacement for chronic pulmonary regurgitation or RVOTO after initial intracardiac repair can be done safely with a mortality rate of 1 percent.[97] Pulmonic valve replacement, when performed for significant pulmonary regurgitation, leads to an improvement in functional class and may lead to improvement in right ventricular dimension and function.[93] [93A] Death, however, can occur from congestive heart failure or can be sudden, presumably arrhythmic, from either ventricular tachycardia or complete heart block. Ventricular tachycardia can arise at the site of the right ventriculotomy, from VSD patch suture lines, or from the right ventricular outflow tract. Patients at high risk for sudden death include those with right ventricular dilation and a QRS duration of 180 milliseconds or more on their ECG.[87] [94] The reported incidence of sudden death is approximately 5 percent, which accounts for approximately one third of late deaths over 20 years of follow-up.[91] [95]

FOLLOW-UP.

All patients should have expert cardiology follow-up every 1 to 2 years.[96] [97]

Post-Fontan Procedure

SURGICAL PROCEDURES.

Since its description for the surgical management of tricuspid atresia in 1971, the Fontan procedure has become the definitive palliative surgical treatment when a biventricular repair is not feasible (e.g., for pulmonary atresia with intact ventricular septum or univentricular hearts). The principle is diversion of the systemic venous return directly to the pulmonary arteries without passing through a subpulmonary ventricle. Over the years, many modifications of the original procedure have been described and performed, namely, direct atriopulmonary connection (Fig. 44-15 *A*), total cavopulmonary connection (see Chap. 43 , Fig. 43-54), and extracardiac tunnel/conduit (see Fig. 44-15 *B*). Fenestration (5 mm diameter) of the Fontan circuit into the left atrium is sometimes performed at the time of surgery in "high-risk" patients, permitting right-to-left shunting and decompression of the Fontan circuit. A right atrium to right ventricular conduit for tricuspid atresia is sometimes performed when right ventricular size and function are adequate.

FONTAN POSTOPERATIVE HISTORY.

Patient selection is of utmost importance and has a major impact on clinical outcome. Long-term survival in "ideal candidates" (see Table 44-4) [98] is 81 percent at 10 years,[99] compared with 60 to 71 percent in "all comers."[100] Death occurs mostly from congestive heart failure and atrial arrhythmias. The Fontan procedure remains a palliative, not curative, procedure.

CLINICAL MANIFESTATIONS.

The majority of patients (
90 percent) present with functional Class I to II at 5 years follow-up after a Fontan procedure.[99] [101] Progressive deterioration of functional status with time is the rule.[99] [100] Supraventricular arrhythmias such as atrial tachycardia, flutter, and fibrillation are common. Physical examination in an otherwise uncomplicated patient will reveal an elevated,

TABLE 44-4 -- IDEAL CANDIDATES FOR THE FONTAN PROCEDURE

Preoperative mean pulmonary artery pressure 15 mm Hg
Pulmonary resistance 4 units/m^2
Pulmonary artery-aortic diameter ratio 0.75

Systemic ventricular ejection fraction	60%
Systemic atrioventricular regurgitation	mild

usually nonpulsatile jugular venous pulse (10 cm above the sternal angle, needed to provide the hydrostatic pressure to drive cardiac output through the pulmonary circulation), a quiet apex, a normal S_1 , and a single S_2 (the pulmonary artery having been tied off). A heart murmur should not be present, and its identification suggests the presence of systemic AV valve regurgitation or subaortic obstruction. Generalized edema may be a sign of protein-losing enteropathy (see Protein-Losing Enteropathy).

DIAGNOSTIC TESTING

Electrocardiogram.

Sinus rhythm, atrial flutter, junctional rhythm, or complete heart block may be present. The QRS complex reflects the basic underlying cardiac anomaly. In patients with tricuspid atresia, left-axis deviation is the norm. In patients with univentricular hearts, the conduction pattern varies widely and depends on the morphology and relative position of the rudimentary chamber.

Chest Radiography.

Mild bulging of the right lower heart border from a dilated right atrium is often seen in patients with atriopulmonary connection. A prominent inferior vena cava is sometimes visualized (Somerville J, personal communication, 1998).

Echocardiography.

The presence or absence of right atrial stasis, thrombus, patency of a fenestration, and Fontan circuit obstruction should be sought. SVC/IVC biphasic and pulmonary artery triphasic flow pattern that varies with respiration suggests unobstructed flow in the Fontan circuit, whereas a mean gradient between the Fontan circuit and the pulmonary artery of 2 mm Hg or more may represent significant obstruction. Assessment of the pulmonary venous flow pattern is important in detecting pulmonary vein (PV) obstruction (right PV > left PV) sometimes caused by an enlarged right atrium (often 80 by 60 mm or so in adults with atriopulmonary connections). Concomitant assessment of systemic ventricular function and AV valve regurgitation can be readily accomplished. TEE may be required if there is inadequate visualization of the Fontan anastomosis or to exclude thrombus in the right atrium.[102]

Diagnostic Catheterization.

Complete heart catheterization is advised if surgical re-intervention is planned or if adequate assessment of the hemodynamics is not obtained by noninvasive means.

MRI.

MRI may be needed as a complement to or replacement for TEE and sometimes even heart catheterization if the Fontan circuit cannot be assessed otherwise.

COMPLICATIONS AND SEQUELAE

Arrhythmia.

Atrial flutter/fibrillation is common (15-20 percent at 5 years follow-up)[103] [104] and increases with duration of follow-up.[103] [105] Atrial flutter/fibrillation carries significant morbidity, can be associated with profound hemodynamic deterioration, and needs prompt medical attention (see later). The combination of atrial incisions and multiple suture lines at the time of Fontan surgery combined with increased right atrial pressure and size probably explains the high incidence of atrial arrhythmias in such patients. Patients at greater risk for atrial tachyarrhythmias are those who were operated on at an older age, with poor ventricular function, systemic AV valve regurgitation, or increased pulmonary artery pressure.[103] [105] It has been suggested that the exclusion of the right atrium from elevated systemic venous pressure (as in total cavopulmonary connection [TCPC] or extracardiac conduit) leads to a decrease in the incidence of atrial arrhythmias.[106] [107] This apparent benefit may, however, be due exclusively to the shorter length of follow-up in this group of patients.[103] Sinus node dysfunction and complete heart block can occur and require pacemaker insertion (see later).

Thrombosis and Stroke.

The reported incidence of thromboembolic complications in the Fontan circuit varies from 6 to 25 percent, depending on the diagnostic method used and the length of follow-up.[108] Thrombus formation may relate to the presence of supraventricular arrhythmias, right atrial dilation, right atrial "smoke," and the presence of artificial material used to construct the Fontan circuit[112] (Fig. 44-16) . Accordingly, a similar incidence of thrombus formation had been reported for all types of Fontan circuits.[107] Systemic arterial embolism in patients with and without a fenestrated Fontan has also been reported. Protein C deficiency has been reported in these patients and may explain in part their propensity to thromboembolism.[108] [109]

Protein-Losing Enteropathy.

Protein-losing enteropathy, defined as severe loss of serum protein into the intestine, occurs in 4 to 13 percent of patients after a Fontan procedure.[110] Patients present with

generalized edema, ascites, pleural effusion, or chronic diarrhea.[110] Protein-losing enteropathy is thought to result principally from chronically elevated systemic venous pressure causing intestinal lymphangiectasia with consequent loss of albumin, protein, lymphocytes, and immunoglobulin into the gastrointestinal tract. The diagnosis is confirmed by finding low serum albumin and protein, low plasma alpha$_1$ -antitrypsin level and lymphocyte counts, and, most important, a high alpha$_1$ -antitrypsin stool clearance. It carries a dismal prognosis, with a 5-year survival of 46 to 59 percent.[110]

Right Pulmonary Vein Compression/Obstruction.

Right pulmonary vein obstruction/compression can occur from the enlarged right atrium or atrial baffle bulging into the left atrium and can lead to increased pulmonary artery pressure with further dilation of the right atrium.

Fontan Obstruction.

Stenosis/partial obstruction of the Fontan connection leads to exercise intolerance, atrial tachyarrhythmias, and right-sided heart failure. Sudden total obstruction can present as sudden death.

Ventricular Dysfunction and Valvar Regurgitation.

Progressive deterioration of systemic ventricular function, with or without progressive AV valve regurgitation, is common. Patients with morphological systemic right ventricles tend to fare less well than those with morphological left ventricles.

Hepatic Dysfunction.

Mildly raised hepatic transaminase levels from hepatic congestion are frequent but seldom clinically important.

Cyanosis.

Worsening cyanosis may relate to worsening of ventricular function, the development of venous collateral

Figure 44-16 Transesophageal echocardiogram of a large thrombus located in the right atrium of a patient with a right atrium to pulmonary artery Fontan connection. RA=right atrium.

channels draining to the left atrium, or the development of pulmonary arteriovenous

malformations (especially if a classic Glenn procedure (see Chap. 43) remains as part of the Fontan operation).

TREATMENT OPTIONS

Arrhythmias.

Atrial tachyarrhythmias are very difficult to manage, and should quickly raise the thought of long-term warfarin therapy. When atrial flutter/fibrillation are present, an underlying hemodynamic cause should *always* be sought, and, in particular, evidence for obstruction of the Fontan circuit needs to be sought. Prompt attempts should be made to restore sinus rhythm. Antiarrhythmic medications, alone or combined with an antitachycardia pacing device, and radiofrequency catheter ablation techniques have had limited success.[111] Surgical conversion from an atriopulmonary Fontan to a total cavopulmonary connection with concomitant atrial cryoablation therapy at the time of surgery has been reported with good short-term success.[112] [112A] Pacemaker insertion for sinus node dysfunction and/or complete heart block may be necessary. Endovenous ventricular pacing through the coronary sinus is possible, but epicardial AV sequential pacing should be employed whenever possible.[113]

Anticoagulant Therapy.

The use of prophylactic long-term anticoagulation is contentious.[114] It is recommended that patients with a history of documented arrhythmias, fenestration in the Fontan connection, or spontaneous contrast ("smoke") in the right atrium on echocardiography be anticoagulated. For established thrombus, thrombolytic therapy versus surgical removal of the clot and conversion of the Fontan circuit have been described.

Protein-Losing Enteropathy.

Treatment modalities include a low-fat, high-protein, medium-chain triglyceride diet to reduce intestinal lymphatic production; albumin infusions to increase intravascular osmotic pressure; and/or the introduction of diuretics, afterload reducing agents, and positive inotropic agents to lower central venous pressure. Catheter-based interventions such as balloon dilation of pathway obstruction or creation of an atrial fenestration[115] as well as surgical interventions from conversion or takedown of the Fontan circuit to cardiac transplantation[116] have also been advocated. Newer treatment modalities include subcutaneous heparin,[117] octreotide treatment,[118] and prednisone therapy. [119]

Right Pulmonary Vein Compression/Obstruction.

When hemodynamically significant, Fontan conversion to a total cavopulmonary connection or extracardiac conduit may be recommended.[120] [121]

Fontan Obstruction.

Surgical revision for obstructed right atrium-pulmonary artery, SCV/IVC-pulmonary artery, or right atrium-right ventricle connection is recommended. Alternatively, balloon angioplasty with or without stenting may be used when appropriate and feasible.

Ventricular Failure and Valvar Regurgitation.

ACE inhibitors are of unproven benefit and do not appear to enhance exercise capacity.[122] Patients with systemic AV valve regurgitation may require AV valve repair or replacement. Cardiac transplantation should also be considered.

Cyanosis.

In the setting of a fenestrated Fontan, surgical or preferably transcatheter closure of the fenestration can be attempted. Pulmonary arteriovenous fistulas from a classic Glenn may be improved by surgical conversion to a bidirectional Glenn connection.[123]

FOLLOW-UP.

Close and expert follow-up is recommended with particular attention to ventricular function and systemic AV valve regurgitation. The development of atrial tachyarrhythmia should instigate a search for possible obstruction at the Fontan anastomosis, right pulmonary vein obstruction, or thrombus within the right atrium.

Complete Transposition of the Great Arteries (see also Chap. 43)

ANATOMY.

In patients with complete TGA, the connections between the atria and ventricles are concordant and the connections between ventricles and great arteries are discordant. Consequently, the pulmonary and systemic circulations are connected in parallel rather than the normal in-series connection. In one circuit, systemic venous blood passes to the right atrium, the right ventricle, and then to the aorta. In the other, pulmonary venous blood passes through the left atrium and ventricle to the pulmonary artery. The aorta arises from the morphological right ventricle and usually lies anterior and to the right of the pulmonary artery, whereas the pulmonary artery arises from the morphological left ventricle (Fig. 44-17 (Figure Not Available) and see Fig. 43-57). This situation is incompatible with life unless mixing of the two circuits occurs.

Approximately two thirds of patients have no major associated abnormalities ("simple" transposition) and one third have associated abnormalities ("complex" transposition). The most common associated abnormalities are VSD and pulmonary/subpulmonary stenosis.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Survival before surgical repair is dependent on mixing of the circulations at one level or another, whether natural (VSD, ASD, PDA) or by intervention (Blalock-Hanlon atrial septectomy or Rashkind balloon atrial septostomy). Unoperated (simple) transposition is a lethal condition, with 90 percent mortality by 1 year. Nearly all patients seen as adults will have had surgical intervention (atrial switch, arterial switch, or Rastelli operation--see later), with the exception perhaps of patients with a large VSD who may survive into adulthood without intervention and present with pulmonary vascular disease.

SURGICAL PROCEDURES

Atrial Switch.

The most common surgical procedure in patients who are currently adults is the atrial switch operation. Patients will have had either a Mustard or a Senning procedure. Blood is redirected at the atrial level using a

Figure 44-17 (Figure Not Available) Diagrammatic representation of complete transposition of the great arteries. RA=right atrium; RV=right ventricle; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

baffle made of Dacron or pericardium (Mustard operation) or atrial flaps (Senning operation), achieving physiological correction. Systemic venous return is diverted through the mitral valve into the subpulmonary morphological left ventricle, and the pulmonary venous return is rerouted through the tricuspid valve into the subaortic morphological right ventricle. By virtue of this repair, the morphological right ventricle is left to support the systemic circulation (Fig. 44-18) (Figure Not Available) .

Arterial Switch.

The atrial switch operation has gradually been supplanted by the arterial switch operation (Jatene) since the late 1970s, but few of these patients have yet become adults. Blood is redirected at the great artery level by switching the aorta and pulmonary arteries (often using the Lecompte maneuver) such that the morphological left ventricle becomes the subaortic ventricle and supports the systemic circulation and the morphological right ventricle becomes the subpulmonary ventricle (see Chap. 43 , Fig. 43-61). The coronary arteries, with a sleeve of surrounding tissue, are translocated to the proximal neoaorta (formerly the proximal pulmonary artery), with the loss of tissue from the former coronary ostia of the neopulmonary artery (formerly the aorta) made good with pericardial patches.

Rastelli Procedure.

Patients (<10 percent of all TGA patients) who have VSD and pulmonary/subpulmonary stenosis may have been corrected by the Rastelli operation. This procedure consists of redirecting the blood at the ventricular level with the left ventricle tunneled to the aorta through the VSD and a valved conduit placed from the right ventricle to the pulmonary artery. By virtue of this procedure, the left ventricle supports the systemic circulation.

Palliative Atrial Switch.

Uncommonly, in patients with a large VSD and established pulmonary vascular disease, a palliative atrial switch operation will be done to improve oxygenation. The VSD is left open or enlarged at the time of atrial baffle surgery. These patients resemble patients

Figure 44-18 (Figure Not Available) Diagrammatic representation of atrial switch surgery (Mustard/Senning procedure). Superior vena cava (SVC) and inferior vena cava (IVC) blood is redirected into the morphological left ventricle (LV), which pumps blood into the pulmonary artery (PA), whereas the pulmonary venous blood flow is rerouted to the morphological right ventricle (RV), which empties into the aorta (Ao). RA=right atrium; LA=left atrium; 1=transposition of the great arteries; 2=atrial baffles; 3=pulmonary vein blood flow through tricuspid valve to RV; 4=IVC and SVC blood flow through mitral valve to LV. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

with Eisenmenger VSDs and should be managed as such (see p. 1614).

POSTOPERATIVE CLINICAL PICTURE

Atrial Switch.

After atrial baffle surgery, most patients who reach adulthood are in NYHA Classes I and II.[124] [125] Over 25 years of follow-up, some will present with symptoms of congestive heart failure (2-15 percent) despite objective evidence of moderate or severe systemic right ventricular dysfunction in up to 40 percent of patients.[129] [129A] [130] [131] More than mild systemic tricuspid regurgitation is present in 10 to 40 percent,[125] exacerbating right ventricular dysfunction. Palpitations or near-syncope/syncope from rhythm disturbances is common. Atrial flutter occurs in 20 percent of patients by age 20,[9] [124] [125] [126] and progressive sinus node dysfunction is seen in half of the patients by that time.[9] [125] [126] These rhythm disturbances are thought to be a consequence of direct and indirect atrial and sinus node damage at the time of atrial baffle surgery.

Shortened life expectancy is the rule with 70 to 80 percent survival at 20 to 30 years follow-up.[8] [9] [124] Patients with "complex" TGA in general fare much worse than "simple" TGA.[89] [91] Sudden cardiac death is the clinical presentation in about 5 percent of these patients[8] [9] [127] and may relate to systemic right ventricular dysfunction,[8] [125] the presence of atrial flutter,[8] [128] and pulmonary hypertension.[125] Significant pulmonary vascular disease can develop over time and relates to older age at the time of atrial switch operation, particularly in patients with a substantial VSD, as well as in those with

long-standing left-to-right shunts through a baffle leak. Rarely, cyanosis can be the presenting symptom due to atrial baffle leak with right-to-left shunting. Superior vena cava or inferior vena cava baffle obstruction often goes undetected because collateral drainage through the azygos vein prevents systemic venous congestion. Pulmonary baffle obstruction causes elevated pulmonary artery pressure, and patients can present with dyspnea and pulmonary venous congestive features. Physical examination of a patient whose condition is otherwise uncomplicated reveals a right ventricular parasternal lift, a normal S_1 , a single S_2 (P_2 is not heard because its posterior location), a holosystolic murmur from tricuspid regurgitation if present (best heard at the left lower sternal border, but not increasing with inspiration), and a right-sided S_3 when severe systemic ventricular dysfunction is present.

Arterial Switch.

Data on clinical presentation in adults who have undergone the arterial switch procedure are lacking, because most patients have not yet reached adulthood. Clinical arrhythmia promises to be less of a problem in this group of patients.[129] Concerns about the development of supra-neopulmonary artery stenosis, ostial coronary artery disease, and progressive neoaortic valve regurgitation remain to be addressed over the long term.[129A] Cardiac examination in uncomplicated patients is normal.

Rastelli Procedure.

Progressive right ventricular to pulmonary artery conduit obstruction can cause exercise intolerance or right ventricular angina. Left ventricular tunnel obstruction can present as dyspnea or syncope. Physical examination in uncomplicated patients reveals, in contrast to atrial switches, no right ventricular lift, an ejection systolic murmur from the conduit, and two components to the S_2 .

DIAGNOSTIC TESTING

Electrocardiogram.

Atrial flutter, sinus bradycardia, or junctional rhythm, in the absence of a right atrial overload pattern, with evidence of right ventricular hypertrophy and right axis deviation is characteristically present in patients after the atrial switch procedure (Fig. 44-19) . The ECG is typically normal in patients after the arterial switch procedure. The ECG typically shows right bundle branch block after a Rastelli procedure.

Chest Radiography.

On the posteroanterior film, a narrow vascular pedicle with an oblong cardiac silhouette ("egg on its side") is typically seen in patients after the

Figure 44-19 Electrocardiogram of a patient with complete transposition of the great arteries after an atrial switch procedure. Note the atrial flutter at 200 beats/min, the right ventricular hypertrophy, and the right-axis deviation. There is an incidental ventricular premature beat.

atrial switch procedure (Fig. 44-20) . On the lateral view, the anterior aorta is seen to fill the retrosternal air space. For the arterial switch, normal mediastinal borders are present despite the Lecompte maneuver. After the Rastelli procedure, the chest radiograph is normal unless the conduit becomes calcified or a nonhomograft prosthesis is employed.

Echocardiography.

After the atrial switch procedure, parallel great arteries are the hallmark of TGA. They are best visualized from a long parasternal view (running side-by-side) or from a short parasternal view (seen en face, with the aorta anterior and rightward) (Fig. 44-21) . Qualitative assessment of systemic right ventricular function, the degree of tricuspid regurgitation, and the presence or absence of subpulmonic left ventricular obstruction (dynamic or fixed) is possible. Assessment of baffle leak or obstruction is best done using color and Doppler flow imaging. Normal baffle flow should be phasic in nature and varies with respiration, with a peak velocity less than 1 m/sec.[130] After arterial switch, neoaortic valve regurgitation, supra-neopulmonary valve stenosis, and segmental wall motion abnormality from ischemia due to coronary ostial stenosis should be sought. In patients who have undergone the Rastelli operation, left ventricular to aorta tunnel obstruction as well as right ventricular to pulmonary artery conduit degeneration (stenosis/regurgitation) must be sought.

Diagnostic Cardiac Catheterization.

Diagnostic cardiac catheterization may be required for assessing the presence or severity of systemic/pulmonary baffle obstruction, baffle leak, and pulmonary hypertension; coronary ostial stenosis; or tunnel or conduit obstruction when not diagnosed by noninvasive means.

INDICATIONS FOR RE-INTERVENTION.

After the atrial switch procedure, severe symptomatic right ventricular dysfunction *may* warrant surgical treatment in the form of

Figure 44-20 Chest radiograph of an adult with complete transposition of the great arteries after a Mustard procedure. Note the narrow mediastinum with the "egg-on-its-side" configuration of the cardiac

silhouette.

"two-stage arterial switch" procedure (see Two-Stage Arterial Switch)[131] [132] [133] or cardiac transplantation. Tricuspid valve replacement can be performed for severe systemic (tricuspid) AV valve regurgitation providing right ventricular function is adequate.[128] Baffle leak resulting in a significant left-to-right shunt (>1.5/1.0), any right-to-left shunt, or symptoms requires surgical or transcatheter closure. SVC or IVC pathway obstruction may require intervention. SVC stenosis

Figure 44-21 Left parasternal transthoracic echocardiogram of a patient with complete transposition of the great arteries shows the typical arrangement of the great arteries in parallel. AO=aorta; AV=aortic valve; RVOT=right ventricular outflow tract; PA=pulmonary artery; PV=pulmonary valve; LV=left ventricle; MV=mitral valve.

is usually benign, whereas IVC stenosis may be life threatening. Balloon dilation of SVC or IVC stenosis is an option, but success is limited in adults. Pathway obstruction after the Senning operation is usually more amenable to balloon dilation and stenting. Pulmonary venous obstruction, although usually seen early and reoperated on in childhood, may present in adulthood. Consideration for the "two-stage arterial switch" procedure in these patients is warranted (see Two-Stage Arterial Switch).[134] [135] Symptomatic bradycardia warrants permanent pacemaker implantation, whereas tachyarrhythmias may require catheter ablation, antitachycardia pacemaker device, or medical therapy. After an atrial switch, transvenous pacing leads must traverse the upper limb of the baffle to enter the morphological left ventricle. Active fixation is required because coarse trabeculation is absent in the morphological left ventricle. Transvenous pacing should be avoided in patients with residual intracardiac communications because paradoxical emboli can occur.

After an arterial switch procedure, significant RVOTO at any level (peak gradient > 50 mm Hg or RV/LV pressure ratio >0.6) may require surgical or catheter augmentation of the right ventricular outflow tract. Myocardial ischemia from coronary artery obstruction may require coronary artery bypass grafting, preferably with arterial conduits. Significant neoaortic valve regurgitation[136] may warrant aortic valve replacement. In patients who have had the Rastelli operation, significant right ventricle-to-pulmonary artery conduit stenosis (peak gradient<50 mm Hg) or significant regurgitation necessitates conduit replacement. Subaortic obstruction across the left ventricle-to-aorta tunnel necessitates left ventricle-to-aorta baffle reconstruction. A significant residual VSD (shunt > 1.5/1.0) may require surgical closure.[137] Patients with clinical deterioration and a palliative atrial switch should be considered for lung or heart-lung transplantation.

INTERVENTIONAL OPTIONS

Medical Therapy.

The role of afterload reduction with ACE inhibitors to preserve systemic right ventricular function is as yet unknown. In light of the effects of these drugs on dysfunctional systemic left ventricles, it seems logical to assume that similar beneficial effects on systemic right ventricles may occur.

Two-Stage Arterial Switch.

Patients with symptomatic, severe systemic (right) ventricular dysfunction with or without severe systemic (tricuspid) AV valve regurgitation, following an atrial switch procedure, may require consideration of a conversion procedure to an arterial switch ("two-stage arterial switch") or heart transplantation. The "two-stage arterial switch" or "switch-conversion" procedure consists of banding the pulmonary artery in the first stage, to induce morphological pulmonary left ventricular hypertrophy and "train" the left ventricle to support systemic pressure. Once left ventricular systolic pressure is more than 75 percent of systemic pressure and the left ventricular mass is considered adequate, in the second stage, the atrial baffles and the pulmonary band are taken down, the atrial septum is reconstructed, and the great arteries are switched, leaving the morphological left ventricle as the systemic ventricle. This procedure, however, is still experimental in adults, with little data available to assess its short- and long-term efficacy.[133]

Cardiac Transplantation.

Heart transplantation should be considered as an alternative, given its relatively good 5- to 10-year survival.[7]

FOLLOW-UP.

Regular follow-up by physicians with special expertise in adult congenital heart disease is recommended.

Atrial Switch.

Serial follow-up of systemic right ventricular function is warranted. Echocardiography, radionuclide angiography, and MRI can be used.[138] [139] ACE inhibitors are often recommended empirically for moderate to severe right ventricular dysfunction and may be helpful to all atrial switch patients. Asymptomatic baffle obstruction should be sought with echocardiography or MRI. Regular Holter monitoring is recommended to diagnose unacceptable bradyarrhythmias or tachyarrhythmias.

Arterial Switch.

Regular follow-up with echocardiography is recommended.

Rastelli Procedure.

Regular follow-up with echocardiography is warranted given the inevitability of conduit degeneration over time.

Congenitally Corrected Transposition of the Great Arteries (see also Chap. 43)

ANATOMY.

Congenitally corrected TGA is a rare condition, accounting for less than 1 percent of all congenital heart disease. In congenitally corrected TGA, the connections of both the atria to ventricles and of the ventricles to the great arteries are discordant. Systemic venous blood passes from the right atrium through a mitral valve to the left ventricle and then to the right-sided posteriorly located pulmonary artery. Pulmonary venous blood passes from the left atrium through a tricuspid valve to the right ventricle and then to an anterior, left-sided aorta (Fig. 44-22) (Figure Not Available) . The circulation is thus "physiologically" corrected but the morphological right ventricle supports the systemic circulation. Associated anomalies occur in up to 95 percent of patients and consist of VSD (75 percent), pulmonary or subpulmonary stenosis (75 percent), and left-sided (tricuspid and often "Ebstein-like") valve anomalies (>75 percent).[140]

Because of the inherently abnormal conduction system (anterior origin of the AV node and anterior course of the His bundle [anterior to the pulmonary artery and down the morphological left ventricular side of the septum]), 5 percent of patients with congenitally corrected TGA are born with congenital complete heart block. Congenitally corrected transposition may exist in the setting of univentricular heart.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Patients with no associated abnormalities ("isolated" congenitally corrected TGA) can survive until the seventh or eighth

Figure 44-22 (Figure Not Available) Diagrammatic representation of congenitally corrected transposition of the great arteries. AV and VA discordance (1). Note intact ventricular septum (2). RA=right atrium; RV=right ventricle; LA=left atrium; LV=left ventricle; Ao=aorta; PA=pulmonary artery. *(From Mullins CE, Mayer DC: Congenital Heart Disease: A Diagrammatic Atlas. New York, Wiley-Liss, 1988.)*

decade and can go unrecognized until cardiac problems arise.[141] Progressive systemic (tricuspid) AV valve regurgitation and systemic (right) ventricular dysfunction tend to occur from the fourth decade onward, whereas atrial tachyarrhythmias are more

common from the fifth decade onward.[142] In addition to those born with congenital complete heart block, acquired complete AV block continues to develop at a rate of 2 percent per year. Patients with associated anomalies (VSD, pulmonary stenosis, left-sided [tricuspid] valve anomaly) often have undergone surgical palliation (systemic-to-pulmonary artery shunt for cyanosis) or repair of the associated anomalies (see surgical procedures).

SURGICAL PROCEDURES

"Classic" Repair.

VSD patch closure for hemodynamically significant VSD, left ventricular to pulmonary artery valved conduit insertion for significant pulmonary valvar or subvalvar stenosis, and systemic tricuspid valve replacement for significant regurgitation may have been performed. VSD patch closure is carried out with a particular attention to avoid the anterior conduction system (coursing anterior to the VSD). In isolated pulmonary/subpulmonary stenosis, direct enlargement of the outflow tract and valve is seldom possible and a pulmonary (morphological left) ventricle to pulmonary artery conduit is required. Patients who have undergone this "classic" repair continue to have a morphological right ventricle supporting the systemic circulation.

CLINICAL MANIFESTATIONS

Unoperated.

Patients with no associated defects (1 percent of all such patients) can be asymptomatic until late adulthood. Dyspnea, exercise intolerance from developing congestive heart failure, and palpitations from supraventricular arrhythmias may arise in the fifth or sixth decade. Patients with well-balanced VSD/pulmonary stenosis can present with paradoxical emboli or cyanosis, especially if pulmonary stenosis is severe. Physical examination of a patient whose condition is otherwise uncomplicated reveals a somewhat more medial apex due to the side-by-side orientation of the two ventricles. The A_2 is often palpable in the second left intercostal space due to the anterior and leftward location of the aorta. A single S_2 (A_2) is heard, with P_2 being silent due to its posterior location. The murmur of an associated VSD or of left AV valve regurgitation may be heard. The murmur of pulmonary stenosis will radiate upward and to the right given the rightward direction of the main pulmonary artery. If there is complete heart block, cannon a waves with an S_1 of variable intensity are present.

"Classic" Repair.

The majority of patients are in functional Class I at 5 to 10 years after surgery[143] [144] despite the common development of tricuspid regurgitation and systemic right ventricular dysfunction after surgical repair (>30 percent of patients at 3 years after surgery).[143] [145] [146] Dyspnea, exercise intolerance, and palpitations from supraventricular arrhythmia can occur in the fourth decade.[147] Complete heart block may complicate surgery in an additional 25 percent.[6] [7] [8] [144] [145] [146] Physical

examination reflects the basic cardiac malformation with or without residual coexisting anomalies.

DIAGNOSTIC TESTING

Electrocardiogram.

Complete AV block can be present in up to 40 percent of adults. A delta wave from a left-sided accessory bypass tract (associated with "Ebstein-like" anomaly of the left-sided AV valve) can be seen. The presence of Q wave in leads V_1 and V_2 combined with an absent Q wave in leads V_5 and V_6 is typical and reflects the initial right-to-left septal depolarization occurring in the setting of "ventricular inversion" (Fig. 44-23) . This should not be mistaken for evidence of previous anterior myocardial infarction.

Chest Radiography.

Because of the unusual position of the great vessels (pulmonary artery to the right and aorta to the left), the pulmonary trunk is inconspicuous and an abnormal

Figure 44-23 Electrocardiogram of a patient with congenitally corrected transposition of the great arteries. Note the presence of Q wave in V_1 and the absence of Q wave in V_{5-6} . Low atrial rhythm and left-axis deviation are also present.

bulge along the left side of the cardiac contour reflects the left-sided ascending aorta rising to the aortic knuckle. A shallow indentation or "septal notch" can be seen above the left hemidiaphragm reflecting the apical portion of the interventricular groove (Fig. 44-24) .

Echocardiography.

Echocardiography permits the identification of the basic malformation as well as any associated anomalies. The morphological pulmonary left ventricle is characterized by its smooth endocardial surface and is guarded by a bileaflet AV (mitral) valve with no direct septal attachment. The morphological systemic right ventricle is recognized by its apical trabeculation and moderator band and is guarded by a trileaflet apically displaced AV valve (tricuspid valve) with direct attachment to the septum (Fig. 44-25) . "Ebstein-like" malformation of the left (tricuspid) AV valve is defined by excessive (>8 mm/m^2) apical displacement of the left (tricuspid) AV valve, with or without dysplastic features.

Diagnostic Cardiac Catheterization.

This may be required to assess the hemodynamic significance or consequences of associated anomalies.

INDICATION FOR INTERVENTION OR RE-INTERVENTION.

If moderate or severe systemic (tricuspid) AV valve regurgitation develops, valve replacement is usually required. Left AV valve replacement should be performed before systemic right ventricular function deteriorates, namely at an ejection fraction of 45 percent or more.[148] When tricuspid regurgitation is associated with poor systemic (right) ventricular function, the "double switch" procedure (see Double Switch Procedure) should perhaps be considered.[131] [149] [150] [151] [152]

Patients with end-stage symptomatic heart failure should be referred for cardiac transplantation. The presence of a hemodynamically significant VSD (Qp/Qs > 1.5:1.0) or residual VSD with significant native or postsurgical (conduit) pulmonary outflow tract stenosis (peak gradient >50 mm Hg) may require surgical correction. Left AV valve replacement at the time of VSD and pulmonary stenosis surgery should be considered if concomitant left AV valve regurgitation is present.[153] Complete AV block may require pacemaker implantation for symptoms, progressive or profound bradycardia, poor exercise heart rate response, or cardiac enlargement. The optimal pacing modality is DDD. Active fixation electrodes are required, owing to the lack of apical trabeculation in the morphological pulmonary left ventricle. Transvenous pacing should be avoided if there are intracardiac shunts because paradoxical emboli may occur. Epicardial leads are preferred under these circumstances.[154]

INTERVENTIONAL OPTIONS

Medical Therapy.

ACE inhibitor therapy for patients with systemic ventricular dysfunction is recommended. The role of afterload reduction with an ACE inhibitor to preserve systemic right ventricular function is as yet unknown. The results of clinical trials are awaited.

Classic Repair.

Tricuspid valve replacement for significant regurgitation is preferable to tricuspid valve repair. Valve repair is usually unsuccessful because of the abnormal, often "Ebstein-like" anatomy of the valve.

Double Switch Procedure.

This procedure has been successfully performed in children. It should be considered for patients with severe tricuspid regurgitation and systemic ventricular dysfunction. Its purpose is to relocate the left ventricle into the systemic circulation and the right

ventricle into the pulmonary circulation, achieving "anatomical" correction. An atrial switch procedure (Mustard or Senning) together with either an arterial switch procedure (when pulmonary stenosis is not present, see Chap. 43) or a Rastelli-type repair, the so-called Ilbawi procedure (left ventricle tunneled to aorta and right ventricular to pulmonary artery valved conduit when VSD and pulmonary stenosis are present), can be performed after adequate left ventricular

Figure 44-24 Chest radiograph of a patient with congenitally corrected transposition of the great arteries. Note the left-sided ascending aorta (AO), transvenous pacemaker and mechanical left-sided (tricuspid) atrioventricular valve, and enlarged right atrium.

Figure 44-25 Transthoracic echocardiographic picture of a patient with congenitally corrected transposition of the great arteries. *A,* Single arrow points to the normally apically displaced left-sided tricuspid valve. Double arrows point to the left-sided right ventricular trabeculations. RA=right atrium; MV=mitral valve; LV=right-sided morphologic left ventricle; LA=left atrium; TV=tricuspid valve; TR=tricuspid regurgitation; RV=left-sided morphologic right ventricle.

retraining, leaving the regurgitant tricuspid valve and failing right ventricle on the pulmonary side.

Cardiac Transplantation.

Patients with deteriorating systemic (right) ventricular function should be treated aggressively with medical therapy but may need to be considered for transplantation.

INTERVENTIONAL OUTCOMES

"Classic" Repair.

After "classic" surgical repair, median survival of patients reaching adulthood is 40 years.[143] [144] [145] [147] [155] Usual causes of death are sudden (presumed arrhythmic) or, more commonly, progressive systemic right ventricular dysfunction with systemic (tricuspid) AV valve regurgitation. The major predictor of poor outcome is the presence of left AV (tricuspid) valve regurgitation.[155] Reoperation is common (15-25 percent), with left AV valve replacement usually being the primary reason.[143] [144] [146] [147]

Double Switch Procedure.

Data in adults using the "double switch" procedure is lacking, and this procedure should be considered experimental in this patient population.

FOLLOW-UP.

All patients should have at least annual cardiology follow-up with an expert in the care of adult patients with congenital cardiac defects. Regular assessment of systemic (tricuspid) AV valve regurgitation by serial echocardiographic studies and systemic ventricular function by echocardiography, MRI, or radionuclide angiography should be done. Holter recording may be useful if paroxysmal atrial arrhythmias or transient complete AV block is suspected.

Eisenmenger Syndrome (see also Chaps. 43 and 53)

DEFINITION.

Eisenmenger syndrome, a term coined by Paul Wood, is defined as pulmonary vascular obstructive disease that develops as a consequence of a large preexisting left-to-right shunt such that pulmonary artery pressures

approach systemic levels and the direction of the flow becomes bidirectional or right to left. Congenital heart defects that can result in Eisenmenger syndrome include "simple" defects such as ASD, VSD, and PDA as well as more "complex" defects such as AVSD, truncus arteriosus, aortopulmonary window, and univentricular heart. The high pulmonary vascular resistance is usually established in infancy (by age 2 years, except in ASD) and sometimes is present from birth.

NATURAL HISTORY OF THE UNOPERATED PATIENT.

Patients with defects that allow free communication between the pulmonary and systemic circuits at the aortic or ventricular levels usually have a fairly healthy childhood and gradually become progressively cyanotic during their second or third decade. Exercise intolerance (dyspnea and fatigue) is proportional to the degree of hypoxemia or cyanosis. In the absence of complications, these patients generally have an excellent to good functional capacity up to their third decade[156] [157] and thereafter usually experience a slowly progressive decline in their physical abilities. Most patients survive to adulthood,[157] [158] with a reported 77 percent and 42 percent survival rate at 15 and 25 years of age.[157]

Complications from Eisenmenger syndrome tend to occur from the third decade onward. Congestive heart failure, the most serious complication, usually occurs after age 40.[156] The most common modes of death are sudden death (30 percent), congestive heart failure (25 percent), and hemoptysis (15 percent). Pregnancy, perioperative mortality after noncardiac surgery, and infectious causes (brain abscesses and endocarditis) account for most of the remainder.[156] [157]

CLINICAL MANIFESTATIONS.

Patients can present with the following complications: those related to their cyanotic state (see p. 1617); palpitations in nearly half the patients (atrial fibrillation/flutter--35 percent, ventricular tachycardia--10 percent); hemoptysis in about 20 percent; pulmonary thromboembolism, angina, syncope, and endocarditis in about 10 percent; and congestive heart failure.[156] Hemoptysis is usually due to bleeding bronchial vessels or pulmonary infarction. Physical examination reveals central cyanosis and clubbing of the nail beds. Patients with Eisenmenger PDA can have pink nail beds on the right (± left) hand and cyanosis and clubbing of both feet (± the left hand), so-called "differential cyanosis." This occurs because venous blood shunts through the ductus and enters the aorta distal to the right subclavian artery. The jugular venous pressure in Eisenmenger syndrome patients can be normal or elevated--especially with prominent v waves when tricuspid regurgitation is present. Signs of pulmonary hypertension--a right ventricular heave, palpable and loud P_2 , and a right-sided S_4 --are typically present. In many patients, a pulmonary ejection click and a soft and scratchy systolic ejection murmur, attributable to dilation of the pulmonary trunk, and a high-pitched decrescendo diastolic murmur of pulmonary regurgitation (Graham Steelle) are audible. Peripheral edema is absent until right-sided heart failure ensues.

DIAGNOSTIC TESTING

Electrocardiogram.

Peaked P waves consistent with right atrial overload and evidence of right ventricular hypertrophy with right axis deviation are the rule. Atrial arrhythmias can be present (Fig. 44-26) .

Chest Radiography.

Dilated central pulmonary arteries with "pruning" of the peripheral pulmonary vasculature are the radiographic hallmarks of Eisenmenger syndrome (Fig. 44-27) . Pulmonary artery calcification may be seen and is diagnostic of long-standing pulmonary hypertension. Eisenmenger syndrome due to VSD or PDA usually has a normal or slightly increased cardiothoracic ratio. Eisenmenger syndrome due to an ASD typically has a large cardiothoracic ratio due to right atrial and ventricular dilation, along with

Figure 44-26 ECG of a patient with Eisenmenger syndrome due to a VSD. Note the peaked P wave in lead II, right ventricular hypertrophy, and right-axis deviation.

an inconspicuous aorta. Calcification of the duct may be seen in Eisenmenger PDA.

Echocardiography.

The intracardiac defect should be seen readily along with bidirectional shunting. Evidence of pulmonary hypertension will be found. Assessment of pulmonary right ventricular function adds prognostic value.

Catheterization.

Cardiac catheterization not only provides direct measurement of the pulmonary artery pressure, documenting the existence of severe pulmonary hypertension, but also may allow assessment of reactivity of the pulmonary vasculature. Administration of pulmonary arterial vasodilators (O_2 , nitric oxide, prostaglandin I_2) can discriminate between patients in whom surgical repair is contraindicated and those with reversible pulmonary hypertension who may benefit from surgical repair. Radiographic contrast material may cause hypotension and worsening cyanosis and should be used cautiously.

Open-Lung Biopsy.

Open-lung biopsy should only be considered when the reversibility of the pulmonary hypertension is uncertain from the hemodynamic data. An expert opinion will determine the severity of the changes, usually using the Heath-Edwards classification.

INDICATIONS FOR INTERVENTION.

The underlying principle of clinical management in patients with Eisenmenger syndrome is to avoid any factors that may destabilize the delicately balanced physiology. In general, an approach of nonintervention is recommended. The main interventions, therefore, are directed toward preventing complications (e.g., flu shots to reduce the morbidity of respiratory infections) or to restore the physiological balance (e.g., iron replacement for iron deficiency; antiarrhythmic management of atrial arrhythmias; digoxin and diuretics for right-sided

Figure 44-27 Typical chest radiograph of a patient with Eisenmenger syndrome due to a ventricular septal defect. Note the enlarged central pulmonary arteries and the peripheral pruning of the pulmonary vasculature. *A,* Posteroanterior view. LPA=left pulmonary artery; RPA=right pulmonary artery.

heart failure). As a general rule, the first episode of hemoptysis should be considered an indication for hospital admission and investigation. Bed rest should be implemented; and, although usually self-limiting, each such episode should be regarded as potentially

life threatening, and a treatable cause sought. When patients are severely incapacitated from severe hypoxemia or congestive heart failure, the main intervention available is lung (plus repair of the cardiac defect) or heart-lung transplantation. This is generally reserved for individuals without contraindications who are thought to have a 1-year survival of less than 50 percent. Such assessment is fraught with difficulty because of the unpredictability of the time course of the disease and the risk of sudden death.

Noncardiac surgery should be performed only when absolutely necessary because of its high associated mortality.[156] [159] Eisenmenger syndrome patients are particularly vulnerable to alterations in hemodynamics induced by anesthesia or surgery, such as minor decrease in systemic vascular resistance that can increase right-to-left shunting and possibly potentiate cardiovascular collapse. Local anesthesia should be used whenever possible. Avoidance of prolonged fasting and especially dehydration, the use of antibiotic prophylaxis when appropriate,[160] and careful intraoperative monitoring (sometimes with an arterial line ± a central venous line to allow early detection of sudden pressure and volume changes during surgery) are recommended. [159] [161] The choice of general versus epidural-spinal anesthesia is controversial. An experienced cardiac anesthetist with an understanding of Eisenmenger syndrome physiology should administer anesthesia. Additional risks of surgery include excessive bleeding, postoperative arrhythmias, and deep venous thrombosis with paradoxic emboli. An "air filter" or "bubble trap" should be used for any intravenous lines. Early ambulation is recommended.[159] [161] Postoperative care in an intensive care unit setting is optimal.

INTERVENTIONAL OPTIONS AND OUTCOMES

Oxygen.

In a small prospective nonrandomized study of 15 children with pulmonary vascular disease, chronic administration of oxygen (12 hours a day for up to 5 years) resulted in an increased survival in the treatment group (n=9).[162] The impact of supplemental oxygen on survival in adult patients with Eisenmenger syndrome has never been studied, and its role is unclear. Chronic oxygen therapy can perhaps help raise oxygen saturation and reduce symptoms, but this should be counterbalanced with the potential effect of mucosal dehydration and increased incidence of epistaxis. Supplemental oxygen during commercial air travel is often recommended, but the scientific basis for this recommendation is lacking.[163]

Transplantation.

Lung transplant may be undertaken in association with repair of existing cardiovascular defect(s). Alternatively, heart-lung transplantation may be required if the intracardiac anatomy is not correctable. The outcome of transplantation in these patients is generally less satisfactory than for transplant recipients without Eisenmenger syndrome. The 1-year survival rate for adults undergoing lung transplantation with primary intracardiac repair is 70 to 80 percent, and less than 50 percent of patients are alive 4 years after transplantation.[164] [165] The outcome after heart-lung transplantation is not better, with a 1-year survival rate of 60 to 80 percent and a 10-year survival rate of less than 30 percent.[164] These options, however sobering, may be relatively attractive to individuals

who are confronting death and have an intolerable quality of life.

INVESTIGATIONAL THERAPY

Calcium Channel Blockers.

The chronic use of nifedipine in a small group of patients with Eisenmenger syndrome demonstrated a small but significant increase in exercise tolerance[166] and a decrease in pulmonary vascular resistance, especially in children.[167] This therapy is still considered investigational and should only be prescribed in a clinical research setting.

ACE Inhibitors.

Data available on a highly selected group of 10 patients with cyanotic congenital heart disease showed no change in oxygen saturation despite a subjective improvement in functional capacity.[168] Proponents of the use of ACE inhibitors in these patients argue that, by decreasing systemic vascular resistance, one improves the cardiac output and thus oxygen delivery. The counter argument is that these agents are potentially dangerous because they lower systemic vascular resistance without changing pulmonary vascular resistance and lead to an increase in right-to-left shunting. The use of this medication remains highly experimental and again should only be administered within the boundaries of a study trial guided by rigorous monitoring.

Prostacyclin.

A recent study of chronic prostacyclin administration in such patients showed improvement in hemodynamics (lower pulmonary vascular resistance and increased cardiac output) and a somewhat increased exercise capacity.[169] Further research in this field is needed before recommendations on the use of prostaglandins in these patients can be made.

Pulmonary Artery Banding.

Pulmonary artery banding in one patient with biopsy-proven irreversible pulmonary vascular changes led to regression of pulmonary vascular changes, which made surgical closure of the defects possible.[170] Further data regarding this revolutionary practice are awaited.

FOLLOW-UP.

Patient education is critical. Avoidance of over-the-counter medications, dehydration, smoking, high-altitude exposure, and excessive physical activity should be stressed. Avoidance of pregnancy is of paramount importance (see Chap. 65). Annual flu shots and use of endocarditis prophylaxis together with proper skin hygiene (avoidance of nail biting) are recommended. A yearly assessment of complete blood cell count and uric acid, creatinine, and ferritin levels should be done to monitor treatable causes of

deterioration.

Medical Management of Cyanotic Congenital Heart Disease

PATHOPHYSIOLOGY OF CYANOSIS.

Patients with cyanotic congenital heart lesions, either unoperated or palliated, have chronic hypoxemia as a result of persistent systemic venous to arterial shunting. Ensuing physiological adaptive mechanisms to enhance oxygen delivery include, among others, an increase in red blood cell mass to improve systemic oxygen transport. Erythropoietin production is stimulated as a result of exposure of renal oxygen sensors to hypoxemia. Red blood cell production is enhanced, oxygen content (hemoglobin×O_2 saturation) increases, and oxygen delivery (cardiac output×O_2 saturation) is reestablished, albeit at the cost of a higher hematocrit. Erythrocytosis, in the setting of chronic cyanotic congenital heart disease, is thus an adaptive physiological mechanism.[171]

HYPERVISCOSITY SYNDROME.

Symptoms of hyperviscosity include headaches, altered mentation, visual disturbances, tinnitus, paresthesias, fatigue, dizziness, and myalgias.[171] These symptoms can be mild, moderate, or severe. They usually present in patients with an elevated hematocrit (>65 percent) or can present at a hematocrit less than 65 percent if the patient is iron deficient. The patient usually experiences the same hyperviscosity symptoms each time (e.g., headache, visual disturbances, fatigue), and they must be relieved by phlebotomy to qualify as hyperviscosity symptoms.

An increased hematocrit level, in the absence of symptoms, does not constitute an indication for phlebotomy. Repeated phlebotomy under these circumstances will lead to iron deficiency, and perhaps cerebral arterial events. Dehydration secondary to excessive heat, illness, fever, diarrhea, or vomiting can be the cause of hyperviscosity symptoms and should be managed appropriately with volume replacement.

If dehydration or iron deficiency is not the cause of hyperviscosity symptoms, phlebotomy becomes the treatment of choice. Removal of 500 ml of blood over 30 to 45 minutes preceded by or simultaneous with a 500- to 1000-ml volume replacement with normal saline (or dextran for patients with congestive heart failure) can usually be performed in an outpatient setting. The goal of phlebotomy is symptom control. The patient having phlebotomy is at risk of iron deficiency. As a rule, iron supplementation should be prescribed.

IRON DEFICIENCY AND REPLACEMENT.

Iron deficiency is an important and common finding in cyanotic adults. The etiology can be multifactorial and includes excessive bleeding from hemoptysis, epistaxis, or excessive menses, but by far the most distressing cause is inappropriate phlebotomy. Microcytosis from iron deficiency results in an increase in whole blood viscosity because microspheres are much less deformable than the normal biconcave disc-shaped iron-replete red blood cell.

In contrast to normocytic erythrocytosis, which seldom causes symptoms at hematocrit levels less than 65 percent, iron deficiency can present as hyperviscosity symptoms at hematocrit levels well below 65 percent. The treatment of choice in this case is iron repletion and not phlebotomy. If iron deficiency is confirmed, supplemental iron should be administered until a rise in hematocrit is registered, or until the iron-replete state has been achieved. Intravenous iron preparations are an alternative for patients intolerant of oral iron supplementation.[171]

HEMOSTATIC ABNORMALITIES.

Hemostatic abnormalities have been documented in cyanotic patients with erythrocytosis.[171] Any bleeding tendency is usually mild and superficial, leading to easy bruising, petechiae, or mucosal bleeding. However, at times, bleeding can be moderate, with epistaxis or hemoptysis, or can even be life threatening, particularly in the postoperative setting. An increase in prothrombin time (PT) and partial thromboplastin time (PTT) from decreased levels of factors V, VII, VIII, and X, from quantitative and qualitative platelet disorders, and from increased fibrinolytic activity have all been described.

The management of a bleeding diathesis can be subdivided into two clinical categories: spontaneous bleeding and perioperative prevention. Spontaneous, superficial bleeding usually is self-limited. Avoidance of aspirin, nonsteroidal antiinflammatory drugs, and heparin is an important prophylactic measure. The treatment of severe spontaneous bleeding is dictated by the specific hemostatic disturbances. Platelet transfusions, fresh-frozen plasma, vitamin K, and cryoprecipitate have all been used.

It is recommended that cyanotic patients facing major surgery undergo prophylactic phlebotomy if the hematocrit level is greater than 65 percent to minimize hemostatic abnormalities intraoperatively and postoperatively. Isovolumetric phlebotomy of 500 ml can be performed every 24 hours until the hematocrit levels decrease below 65 percent. Blood that has been withdrawn should be kept for autologous transfusion if needed.

CEREBROVASCULAR EVENTS.

Cerebrovascular events including stroke secondary to thrombosis or embolus have been recognized as a complication of cyanosis in adults with congenital heart disease. The risk of stroke caused by cerebral arterial thrombosis has usually been seen in patients with iron deficiency and not iron-replete erythrocytosis.[172] [173] Cerebral hemorrhage can occur due to hemostatic defects and is most often observed after the

use of often dangerous anticoagulant therapy. Patients with right-to-left shunts can also be at risk for paradoxical emboli. Focal brain injury can provide a nidus for brain abscess if bacteremia supervenes. Brain abscess patients can present with headaches with fever and focal neurological findings or seizures.[174] It follows from the previous discussion that prophylactic phlebotomy has no place in the prevention of cerebral arterial thrombosis. Avoidance of microcytosis is of paramount importance.[172] [173] Meticulous attention should be paid to the use of air filters in peripheral intravenous lines to avoid paradoxical emboli through a right-to-left shunt.[174] Anticoagulants should usually be avoided in chronically cyanotic cardiac patients. In the uncommon patient with atrial fibrillation or a mechanical prosthesis, a risk-benefit dilemma must be addressed.

RENAL DYSFUNCTION.

Renal dysfunction can present as proteinuria, hyperuricemia, and, rarely, overt renal failure.[175] Hyperuricemia, commonly observed in patients with cyanotic congenital heart disease, is caused mainly by increased reabsorption of uric acid rather than by overproduction from erythrocytosis. Fortunately, urate nephropathy, uric acid nephrolithiasis, and gouty arthritis are rare. Asymptomatic hyperuricemia need not be treated. Acute gouty arthritis responds to intravenous colchicine. Corticosteroid therapy is a viable alternative. Nonsteroidal antiinflammatory drugs should be avoided, given the baseline hemostatic anomalies in these patients. Symptomatic hyperuricemia and chronic gouty arthritis can be treated with probenecid or sulfinpyrazone, which are uricosuric agents, or with allopurinol, which decreases uric acid production. Most diuretics are relatively contraindicated because they reduce renal tubular secretion of uric acid and may aggravate existing hyperuricemia.

ARTHRALGIA.

Hypertrophic osteoarthropathy is thought to be the mechanism responsible for the arthralgias affecting up to one third of patients with cyanotic congenital heart disease. In patients with right-to-left shunting, megakaryocytes released from the bone marrow can bypass the lung. The entrapment of megakaryocytes in the systemic arterioles and capillaries induces the release of platelet-derived growth factor, promoting local cell proliferation.

New osseous formation with periostitis ensues and gives rise to arthralgia and bony pain.[175] Arthralgias can be managed with salsalate, a nonacetylated analog of aspirin. This medication does not appear to interfere with platelet function and, therefore, is an ideal antiinflammatory medication for patients with bleeding tendencies.

FOLLOW-UP.

Patients with cyanotic congenital heart disease should be followed regularly by experts.

Hemoglobin levels, mean corpuscular volume, ferritin, renal function, and uric acid should be checked at least annually to avoid treatable causes of deterioration. Annual flu shots are recommended. Avoidance of unnecessary phlebotomies and anticoagulant therapy is key. Smoking is to be strongly discouraged because it impairs oxygen-carrying capacity and worsens oxygen delivery.

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Chapter 45 - Acquired Heart Disease in Children

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The purpose of this chapter is to review cardiac diseases acquired in childhood. Congenital cardiac defects are discussed in Chapters 43 and 44 , while neurological diseases that affect the heart are described in Chapter 71 . Here we focus on cardiomyopathies, Kawasaki disease, hypertension, and hyperlipidemias.

CARDIOMYOPATHIES (see also Chap. 48)

This diverse group of disorders has historically been understood to represent "heart muscle diseases of unknown etiology,"[1] clearly excluding secondary processes such as hypertension, ischemic heart disease, and valvar and congenital heart disease. In addition, the World Health Organization definition also specifically excluded myocardial disease related to a known systemic disorder. Clinical practice does not concur with these exclusions, and secondary forms of cardiomyopathy are referred to as "anthracycline cardiomyopathy," "infectious cardiomyopathy," and other descriptive terms. Even etiologies that were intended to be specifically excluded have been incorporated under names such as "ischemic cardiomyopathy" and "cardiomyopathy of overload," a term that embodies the clinically familiar concept of load-induced myocyte

dysfunction. Cardiomyopathy is now more familiarly taken to imply a disease process involving the heart muscle that results in intrinsic myocardial dysfunction, subcategorized as primary and secondary forms. Classification of the cardiomyopathies as dilated, hypertrophic, and restrictive has fared the test of time somewhat better, although this terminology clearly has problems as well. The mixture of morphology and physiology inherent within this classification is unquestionably problematic because many overlapping cases are encountered. Furthermore, it is clear that the same etiology can be manifested as dilated cardiomyopathy (DCM) in some patients and as hypertrophic cardiomyopathy (HCM) in others and that individual patients can transition between the two. Although this effort at categorization is merely a general, descriptive approach that cannot be relied on for unambiguous classification, it nonetheless provides a clinically useful framework and will be used in this presentation.

Dilated Cardiomyopathy (see also Chap. 48)

DCM has numerous etiologies, clinical manifestations, and outcomes that vary depending on both the pathogenesis and host response. Multiple associations have been described in children, but most cases remain idiopathic. Although the true frequency of the various causes of DCM is currently unknown, improved methods of diagnosis have enabled determination of the cause for a progressively larger proportion of the previously idiopathic cases. Between one-third and one-half of cases are thought to be familial.[2] Inflammatory heart disease caused by viral myocarditis or an abnormal immunologic response to viral infection is believed to be a common cause, but problems in confirming this diagnosis beyond the acute stage have hampered determination of the true incidence. Progress in molecular identification of viral presence in diseased human heart tissue[3] has created new opportunities to define the relationship between viral infections and myocarditis.

It is generally assumed clinically that the primary functional change at the myofiber level in DCM is depression of contractile function. Despite how commonly this assumption is believed, several groups have shown that isolated cardiac muscle harvested from patients with end-stage heart failure is capable of normal force-generating capacity under ideal conditions and low stimulation frequencies,[4] even when force generation deteriorates at higher stimulation frequencies.[5] In contrast, diastolic abnormalities are a constant property of failing heart muscle.[6] The molecular event or events that account for myocardial failure remain elusive, although many metabolic abnormalities have been described. Numerous abnormalities often coexist, and their relative importance is not known. Although most investigators have sought a single final pathway to contractile dysfunction, this approach may not be correct. Since DCM appears as the end result of many quite different processes, it is likely that numerous metabolic disturbances may have contractile dysfunction as the final common manifestation. Clarification of the disease-specific pathogenesis of contractile failure has no doubt been hampered by our very limited ability to determine etiology.

Clinical Features and Diagnostic Evaluation

Regardless of the underlying cause of the ventricular dysfunction, the congestive cardiomyopathies have a similar mode of expression. Older children experience

exercise intolerance, dyspnea on exertion, tachycardia, palpitations, abdominal distention, syncope or near-syncope, and occasionally, cardiovascular collapse and sudden death. Although many symptoms parallel those seen in adults, primary complaints of peripheral edema and paroxysmal nocturnal dyspnea are uncommon in children. Infants are generally recognized on the basis of respiratory distress, abdominal distention, and poor feeding, but occasionally the process is subacute and failure to thrive is present at the time of diagnosis. Secondary cardiomyopathies can manifest a broad spectrum of noncardiac abnormalities, depending on the nature of the primary disorder.

PHYSICAL FINDINGS.

Physical findings depend on the severity of clinical compromise. Patients with mild ventricular dysfunction can have reduced exercise capacity but no

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abnormal physical findings. Congestive heart failure is nearly always accompanied by tachypnea and tachycardia. Peripheral cyanosis is noted only in the presence of severe compromise. Peripheral pulses are often weak and can be difficult to palpate because of narrow pulse pressure and occasionally hypotension. Cool extremities and poor capillary refill can be noted, particularly in infants. Intercostal retractions are a common finding in infants and young children, but in contrast to adults, pulmonary auscultation rarely reveals rales, even when frank pulmonary edema is present on chest radiographs. Wheezing can be heard at all ages because of attenuated airway relaxation, a process that appears to result from the generalized desensitization of beta-adrenergic receptors that is characteristic of congestive heart failure.[7] Hepatomegaly is a seminal finding and can be massive in infants but changes rapidly in response to therapy. Neck vein distention and peripheral edema are almost never observed in infants but become more common with age. The cardiac impulse is often displaced laterally and is frequently diffuse. Gallop rhythm with a third heart sound is common, as is a murmur of mitral regurgitation.

LABORATORY DATA.

Cardiomegaly, pulmonary venous congestion, pulmonary edema, atelectasis, and pleural effusions are common radiographic findings. The electrocardiogram (ECG) shows sinus tachycardia in most patients. Nonspecific ST-T wave changes and left ventricular hypertrophy are noted in about half of patients,[8] with atrial and right ventricular hypertrophy in 25%. Just under 50% of patients have arrhythmias on initial evaluation, including atrial fibrillation and flutter, ventricular ectopic beats, and nonsustained ventricular tachycardia on Holter recording. DCM must be differentiated from tachycardia-induced cardiomyopathy, a process that can have similar features but responds to arrhythmia control with complete recovery.[9]

Echocardiography.

Diagnostic findings on echocardiography are a dilated left ventricle with diminished systolic performance. Dysfunction is global, although moderate regional variation in wall motion is usually present. Quantitative assessment of systolic and diastolic functional parameters and ventricular morphology is diagnostically and prognostically useful. Pericardial effusions are frequent. Intracardiac thrombi have been reported in as many as 23% of children, although rarely in infants.[10] Color flow and spectral Doppler examinations are useful for assessment of mitral regurgitation, as well as diastolic function. The echocardiogram is equally critical for excluding valvar and structural cardiac disease. Anomalous origin of the left main coronary artery from the pulmonary artery can be reliably recognized through the combined use of imaging and color flow Doppler.[11]

Cardiac Catheterization.

This procedure is performed primarily for endomyocardial biopsy. Occasionally, the possibility of a coronary anomaly remains in doubt, in which case coronary arteriography is mandatory. Assessment of hemodynamics is rarely useful for patient management unless the clinical findings are discrepant from the echocardiographic findings, but hemodynamic evaluation has important prognostic implications and is needed if organ transplantation is considered. Biopsy findings in idiopathic DCM are nonspecific and demonstrate myocyte hypertrophy and variable amounts of fibrosis without evidence of inflammatory infiltrates. The primary importance of biopsy is detection of known causes of DCM, including histological or polymerase chain reaction evidence of myocarditis, infiltrative or mitochondrial disorders, cytoskeletal protein defects,[12] and endocardial fibroelastosis (EFE).[10] Numerous rare disorders can be diagnosed only by tissue analysis. A finding of inflammatory heart disease justifies a delay in consideration of transplantation because myocarditis in children is generally associated with a more favorable prognosis,[10] including the potential for complete recovery. The safety of transvenous biopsy has been amply demonstrated, and extensive experience in its use has been gained through routine application in cardiac transplant recipients. The highest risk is noted in infants,[13] in whom perforation by the stiff biopsy catheters is a recognized complication. However, this patient group is exactly the one in which the results can be most helpful, with the risk-benefit ratio shifted in favor of the test, even in this age group.

DIFFERENTIAL DIAGNOSIS.

In children and infants with DCM the differential diagnosis is complex because of the imposing array of possible rare disorders. An ordered and logical algorithm for diagnostic evaluation based on standard and widely available laboratory screening tests has been published[14] and has led to targeted specific testing for particular disorders of metabolism. This field is rapidly evolving as new enzymatic disorders are recognized and must be incorporated within this algorithm.[14A] [14C] Certain disorders, such as the mitochondrial disorders,[15A] [15C] can be particularly difficult to diagnose because of tissue-selective and heterogeneous expression related to either tissue-specific

isoenzyme or to unbalanced segregation of mutated and wild-type mitochondrial DNA. The defect is biochemically manifested when a certain threshold of mutated mitochondrial DNA is reached. The situation is rendered even more complex by the age-dependent accumulation of mitochondrial DNA deletions that appear to have no causal relation to DCM.[16]

Treatment

In the absence of an identifiable cause, treatment is supportive, nonspecific, and targeted at controlling the symptoms of congestive heart failure. The severity of clinical compromise determines the level of support needed. Critically ill children will generally require mechanical ventilation and inotropic support. Management at centers that have extracorporeal membrane oxygenator and ventricular assist device support available is advised for these patients. Some patients can experience sufficient recovery within a period of days to permit withdrawal of mechanical myocardial support, and the method can at times be used as a bridge to transplantation.[17] Once the patient is stabilized, or in patients who are not critically compromised at the time of initial assessment, oral therapy with digoxin, angiotensin-converting enzyme (ACE) inhibitors, and diuretics remains the mainstay of treatment. Recent data in adults indicate a 30% reduction in deaths when spironolactone is included in the diuretic scheme.[18] This medication is well tolerated in children, and despite the absence of specific data in this age group, these results are fairly compelling for its use. No consensus has been reached regarding which of these agents to institute first in children who do not require multidrug therapy, but asymptomatic ventricular dysfunction is often managed with ACE inhibitors alone because of the absence of significant reported risk.

Arrhythmias are common in children with DCM,[8] and their management is not substantially different from that of adults. Data concerning the utility of ventricular stimulation protocols are rare in children, but the available data suggest that it is useful in risk stratification but not clearly effective in guiding therapy.[19] Intermittent infusion of inotropes such as dobutamine, a common practice in the management of children with severe chronic congestive heart failure, has been based on practice in adult clinics. Although the results in adult studies are mixed, with some trials reporting that survival can be adversely affected, most studies continue to note symptomatic improvement.[20] Intermittent inotrope infusion appears to be a reasonable alternative to achieve stabilization and symptom control in patients awaiting transplantation.

Carnitine deficiency and disorders of carnitine transport can result in DCM and HCM, and in some cases, dietary carnitine supplementation can lead to dramatic cardiac and clinical improvement. In an attempt to avoid delays in ther

apy, it is not uncommon for clinicians to initiate empirical carnitine supplementation prior to biochemical confirmation of this disorder. In fact, cardiomyopathy is not a prominent feature of myopathic carnitine deficiency, in which skeletal muscle weakness and

recurrent metabolic crises dominate. In addition to potentially obscuring diagnostic evaluation, other inborn errors of metabolism have been described that are manifested as DCM but deteriorate rapidly in response to carnitine supplementation.[21] Plasma carnitine concentrations and fatty acid metabolism byproducts should be evaluated in all infants with cardiomyopathy of unknown etiology, but empirical therapy is not advised.

Children with DCM are at risk for intracardiac thrombus formation and systemic embolization. Intracardiac thrombi were seen in 46 to 84 percent of children at autopsy, but their relationship to premorbid findings is unclear since one of these studies documented no intracardiac thrombi during life.[22] Clinical series report the presence of intracardiac thrombi in 0 to 23 percent.[10] [22] [23] Comparison of these studies indicates an age-related trend toward a higher incidence, but none of the series have been large enough to draw firm conclusions. Guidelines for antithrombotic therapy are derived from and parallel those in adults.

Mitral valve regurgitation is common in DCM and in some instances can be moderate or more pronounced in severity. Clinical improvement in symptoms, ventricular function, and survival after mitral valvuloplasty has, however, been reported in patients with DCM.[24] [25] The repair represents a form of afterload reduction, with a fall in wall stress consequent to ventricular remodeling. In patients with moderate to severe mitral regurgitation associated with DCM, valve repair should be seriously considered, but valve replacement generally entails excessive risk.

Several forms of therapy are currently investigational in children. Two recent large and favorable experiences with beta blockers in adults with congestive heart failure[26] [26A] have not been adequately replicated in children. There is ample theoretical justification for their use, and preliminary results in children have been reported,[27] but data on risk-benefit analysis, appropriate dosing schedule, and patient selection criteria are limited. The combination of an ACE inhibitor and beta blocker has been found to result in a synergistic effect in adult patients with asymptomatic dysfunction,[28] an issue that has not been addressed in children. Trials of angiotensin II receptor antagonist[29] use in children have not been reported. Early reports of potential benefits of growth hormone therapy in adults with DCM[30] have not been confirmed in children. Patients with DCM often have markedly asynchronous ventricular activation resulting in a diminished peak force of contraction.[30A] Biventricular DDD pacing with optimized atrioventricular synchrony can improve ventricular performance and has been tried as a therapeutic modality in several small series of adult patients.[31] [31A] Again, no data are available in children. The recent advent of ventricular volume reduction surgery as a means of afterload reduction in patients with end-stage DCM has been attempted in a few children,[32] but the numbers are too few to draw any conclusions. This procedure improves systolic function at the expense of further impairing diastolic function,[33] [33A] with an unpredictable net impact on overall cardiac function. Infants and children with DCM have a marked dominance of systolic dysfunction with less evidence of diastolic dysfunction than is generally noted in adult studies, thus suggesting that they might indeed benefit from this procedure.

Predictors of Outcome

Negative predictors of outcome in children with DCM include the severity of dysfunction, spherical ventricular shape, coexistence of right ventricular dysfunction, familial cardiomyopathy, tissue diagnosis of EFE, persistent cardiomegaly, and persistent congestive heart failure. Tissue diagnosis of myocarditis has been associated with a better outcome. Ventricular size and mass at initial evaluation have not been found to be predictive of outcome. Younger age at diagnosis has been reported to be associated with a better outcome by some groups,[34] has been associated with a worse outcome by other groups,[35] and in other series has not been found to be a significant factor.[36] One motivation for defining factors predictive of outcome is to facilitate early recommendation for cardiac transplantation. It is therefore disturbing that so little agreement has been found in the many studies to date. Given the heterogeneity of the disorder itself and the small number of patients included in many series, it is likely that the patient samples are quite dissimilar. Entry criteria have also varied substantially among these studies, with specific inclusion of myocarditis in some but exclusion in others. Many of the variables are likely to have a real association with outcome, but the relationship is weak. The fact that commonly used measures of ventricular performance are only weakly predictive of survival severely limits their utility in decisions concerning transplantation.

OUTCOME.

Survival statistics for infants (Fig. 45-1) and older children (Fig. 45-2) with idiopathic DCM have varied, with 1-, 2-, 5-, and 10-year survival rates of 41 to 94 percent, 20 to 88 percent, 34 to 86 percent, and 52 to 84 percent, respectively, having been reported. In those who survive, nearly half have full normalization of ventricular function, 25 percent have improved but abnormal function, and 25percent have persistently severely depressed function.[37] Recovery of function is generally complete within the first year, but occasional patients experience continued late improvement.[10] [38]

Infective Myocarditis (see also Chap. 48)

Myocardial inflammatory diseases are an important cause of DCM in children. Myocarditis cannot be reliably distinguished from other forms of DCM on clinical grounds alone because both the acute and chronic forms have symptoms and functional consequences related to the severity of ventricular dysfunction. A significant number of cases of myocarditis have manifestations that are subclinical and associated with ECG changes or arrhythmias, and in a significant number the myocarditis can be occult or cause sudden death.[39] Nearly all the organisms that cause common infectious illnesses in children can also cause myocarditis,[40] although fewer have been associated with the manifestations of DCM. In addition, myocarditis can occur as a hypersensitivity or toxic reaction and is associated with a number of important systemic diseases such as rheumatic fever.

Management of myocarditis is similar to management of other forms of DCM in that etiology-specific therapy is not generally available. Considerable evidence indicates that the immune response and autoimmunity may play a central role in the acute and chronic myocardial damage,[41] thus suggesting a role for immunosuppressive therapy. Small,

uncontrolled trials of corticosteroid therapy in children with evidence of myocarditis[42] [43] have reported favorable outcomes. Similar to trials of these and other immunosuppressive agents in adults, these uncontrolled studies in a disease with a high rate of spontaneous resolution are impossible to interpret. In some centers, administration of high-dose intravenous gamma globulin to children with findings indicative of acute myocarditis has led to improved survival and more rapid recovery of function.[44]

Endocardial Fibroelastosis (see also Chap. 48)

Diffuse thickening of the left ventricular endocardium secondary to proliferation of fibrous and elastic tissue is an

Figure 45-1 Survival in infants with idiopathic dilated cardiomyopathy. *Chen (1990):* Chen S, Nouri S, Balfour I, et al: Clinical profile of congestive cardiomyopathy in children. J Am Coll Cardiol 15:189, 1990; *Griffin (1988):* Griffin ML, Hernandez A, Martin TC, et al: Dilated cardiomyopathy in infants and children. J Am Coll Cardiol 11:139, 1988; *Matitiau (1994):* Matitiau A, Perez-Atayde A, Sanders SP, et al: Infantile dilated cardiomyopathy: Relation of outcome to left ventricular mechanics, hemodynamics, and histology at the time of presentation. Circulation 90:1310, 1994.

uncommon but nonspecific response to a variety of inciting agents. The finding was at one time thought to represent a specific disease, but as emphasized by Lurie,[45] it is now clear that EFE represents a final common pathway for many different myocardial stressors. An association with mumps virus infection has been suspected for many years, a theory supported by detection of the mumps virus genome in the myocardium of infants and children.[46] This proposed etiology for a significant proportion of cases is further supported by the observed fall in EFE incidence coincident with implementation of widespread vaccination. Despite the reduction in frequency, this histological finding continues to be reported in association with a wide variety of cardiac diseases, including prenatal and postnatal left ventricular outflow tract obstruction, numerous other forms of congenital heart disease, and many forms of DCM and HCM, as well as being a focal finding in adults with various cardiac disorders.[47] Among the various associations, no single theme emerges, which supports the interpretation that EFE represents a nonspecific tissue response. The pathophysiology of the response is of interest inasmuch as it can provide clues to pathways of injury shared by various diseases.

Figure 45-2 Survival in children with idiopathic dilated cardiomyopathy. *Akagi (1991):* Akagi T, Benson LN, Lightfoot NE, et al: Natural history of dilated cardiomyopathy in children. Am Heart J 121:1502, 1991; *Arola (1998):* Arola A, Tuominen J, Ruuskanen O, et al: Idiopathic dilated cardiomyopathy in children: Prognostic indicators and outcome. Pediatrics 101:369, 1998; *Burch (1994):* Burch M, Siddiqi SA, Celermajer DS, et al: Dilated cardiomyopathy in children: Determinants of outcome. Br Heart J 72:246, 1994; *Chen (1990):* Chen S, Nouri S, Balfour I, et al: Clinical profile of congestive cardiomyopathy in

children. J Am Coll Cardiol 15:189, 1990; *Friedman (1991):* Friedman RA, Moak JP, Garson A Jr: Clinical course of idiopathic dilated cardiomyopathy in children. J Am Coll Cardiol 18:152, 1991; *Griffin (1988):* Griffin ML, Hernandez A, Martin TC, et al: Dilated cardiomyopathy in infants and children. J Am Coll Cardiol 11:139, 1988; *Taliercio (1985):* Taliercio CP, Seward JB, Driscoll DJ, et al: Idiopathic dilated cardiomyopathy in the young: Clinical profile and natural history. J Am Coll Cardiol 6:1126, 1985; *Wiles (1991):* Wiles HB, McArthur PD, Taylor AB, et al: Prognostic features of children with idiopathic dilated cardiomyopathy. Am J Cardiol 68:1372, 1991.

Clinically, more than 80 percent of cases occur in the first year of life, with features dependent on which form of the disease is manifested. Most patients have a dilated ventricle with increased wall thickness and depressed systolic function. The clinical manifestations of the dilated form are similar to findings in other types of DCM. Rarely, patients have a contracted form characterized by a small left ventricle and a clinical picture of restrictive cardiomyopathy. The diagnosis of EFE is most commonly made at autopsy. Although EFE is often suspected on echocardiography (see Chap. 7) when the ultrasound signal from the endocardial surface is unusually strong, echocardiography has not been found to be a reliable diagnostic technique.[48] EFE can be recognized on endomyocardial biopsy, and despite greater involvement of the left ventricle in many patients, the diagnosis can frequently be confirmed on right ventricular biopsy. An autopsy series found that most patients with EFE had right ventricular involvement, although to a lesser extent than on the left,[49] but the diagnostic accuracy of endomyocardial biopsy of the right ventricle has not been systematically tested. The purpose of the diagnosis is primarily for prognosis since in some clinical situations the finding of EFE has been associated with a poor outcome. For example, in case series of DCM, EFE is often identified as one of the risk factors for death.[10] [23] Nevertheless, in a group of patients with idiopathic EFE, the 4-year survival rate was 77 percent, which is not worse than rates reported in other forms of DCM.

Doxorubicin Cardiomyopathy (see Chaps. 48 and 69)

The anthracycline antibiotics include a number of valuable antitumor agents, with doxorubicin (Adriamycin) in particular having the broadest spectrum of antitumor activity of the available cancer chemotherapeutic agents. Thousands of children have received doxorubicin over the past 30 years for several of the most common pediatric oncological disorders, including acute lymphocytic leukemia. A dramatic improvement in long-term survival after childhood cancer has occurred during the same time interval. As a result, late residua from therapy often represent the most important clinical problem for these patients. Among these residua is doxorubicin-associated cardiomyopathy, the consequences of which continue to unfold as the length of follow-up increases. The magnitude of this problem has escalated to the point that for many pediatric centers, doxorubicin cardiomyopathy accounts for the majority of cases of DCM.

CLINICAL FEATURES.

Clinically, the most significant problems relate to a chronic, dose-related

cardiomyopathy. Historically, cardiomyopathy was manifested by left ventricular dysfunction, elevated filling pressure, and reduced cardiac output 2 to 4 months after completion of therapy. The myocardial insult is often delayed for a period after the last dose of the drug because of a time delay in the full cytotoxic effect of the drug, with a mean latency between 3 and 8 weeks. More recently, new onset of congestive heart failure has been described in patients years after completion of therapy.[50] As a group, these patients manifest a low incidence of depressed contractility. The dominant abnormality is elevated afterload related to inadequate hypertrophy in the absence of significant dilation.[50] [51] Total cumulative dose, age at the time of doxorubicin therapy, and duration since completion of therapy each relate to the incidence of cardiac abnormalities. Excess afterload is a particular risk for young children; it appears gradually and is manifested as inadequate myocardial growth when compared with the rate of somatic growth. This form of doxorubicin-mediated cardiac injury appears to represent impaired growth capacity of the myocardium, a problem of particular importance to a small child.

Numerous clinical studies have identified certain factors that place patients at increased risk for the adverse cardiac effects of doxorubicin. Patients younger than 4 years have an increased risk.[50] Females are at higher risk on a dose-matched basis.[52] [53] Mediastinal irradiation increases toxicity,[54] although the effect is not marked. However, the factor that has been consistently found to bear the strongest relationship to the incidence of cardiotoxicity is the total cumulative dose. The relationship between the total cumulative dose of doxorubicin and symptomatic cardiotoxicity is nonlinear, with an inflection point somewhere between 400 and 600 mg/m[2] . For example, in one study the incidence of cardiomyopathy was 7 percent in subjects who received less than 550 mg/m[2] , but it increased to 18 percent in the group that received 700 mg/m[2] .[55] Although some variation is seen in the dose at which the incidence of congestive heart failure has been observed to rise, this general pattern has been observed in the numerous studies that have examined it.

PREVENTION.

Recognition of the dose-related nature of early-onset congestive heart failure has resulted in nearly universal limitation of the cumulative dose to less than 350 to 450 mg/m[2] , which successfully reduces this complication to 1 percent or less. Although late toxicity also appears to be dose related, doses as low as 90 to 220 mg/m[2] still represent a measurable risk,[50] [51] with no "safe" dose having been demonstrated. In addition to uniform dose reduction for all patients, alternative means of toxicity reduction that have been reported include dosing regimens designed to reduce peak serum levels (such as continuous infusion), coadministration of agents aimed at providing cardioprotection, and programmed dose reduction as dictated by one of several monitoring programs. Numerous agents with the potential to reduce doxorubicin cardiotoxicity have been tried in animal and human trials, but at present the most promising is dexrazoxane (ICRF-187). Dexrazoxane has a plausible mechanism of action (iron chelation),[56] evidence of reduced early and late toxicity in animals, and promising early results in clinical trials in children.[57]

Cardiac monitoring programs that attempt to detect cardiotoxicity on an individual basis,

thereby permitting individual dosing regimens and dose reduction in patients with evidence of cardiac injury, are both widely used and highly contentious.[58] [59] Although the means used to detect myocardial injury has varied from study to study, in other regards the monitoring programs that have been recommended are quite similar. The basic approach is to evaluate patients periodically during doxorubicin therapy and to delay or discontinue treatment with the drug in patients with abnormal test results. It is generally agreed that the onset of congestive heart failure justifies cessation of doxorubicin therapy. However, the more typical scenario is a patient who has received some fraction of the intended cumulative dose of doxorubicin, at which time an asymptomatic drop in left ventricular function is detected. For patients treated by set protocols, if the fall in function exceeds some predefined criteria, cessation of anthracycline therapy is advised. This approach is advocated to minimize adverse cardiac outcomes.[58] However, opponents of published criteria voice concern that the impact of these programs on overall outcome has not been addressed.[59] Fundamentally, it is important to recognize that administration of anthracyclines is intrinsically a compromise between cancer cure and cardiac injury such that any reduction in the total cumulative dose decreases the antitumor effect. Even a reduction in cumulative dose from 270 to 180 mg/m[2] has been shown to have a detectable impact on the cancer cure rate.[51] Similarly, cardiotoxicity is a progressive phenomenon, with mild but detectable injury even at very low doses.[50] [51] Evaluation of the success of any cardiac monitoring program must include a decision regarding what severity of cardiac injury is unacceptable to achieve the desired antitumor effect. At

perhaps the most simplistic level, dose reduction in response to a monitoring program should result in verifiable net improvement in survival. However, at present the benefits of serial cardiac assessment for doxorubicin-induced cardiomyopathy as a means of dose adjustment remain enticing but unproven.

Hypertrophic Cardiomyopathy (see Chap. 48)

HCM is defined as the presence of ventricular hypertrophy without an identifiable hemodynamic cause such as hypertension, valvular heart disease, catecholamine-secreting tumors, hyperthyroidism, or any other condition that could secondarily stimulate cardiac hypertrophy. It is clear that HCM represents a heterogeneous group of disorders, and this diversity is more apparent in childhood than at any other age. These disorders can be subdivided into primary and secondary forms, where the primary form is a familial disorder ("familial HCM") typically devoid of findings outside of the heart. Secondary forms include diseases such as Friedreich ataxia, where ventricular hypertrophy is common but not the dominant clinical manifestation (see Chap. 71) , and others such as glycogenosis type IX, in which a systemic disorder has primarily or exclusively cardiac manifestations.

Familial Hypertrophic Cardiomyopathy

CLINICAL DESCRIPTION.

In about half of affected patients, it is possible to elicit a history of another family member with familial HCM or a family history of sudden death at a young age. Although many young patients are asymptomatic, the full spectrum of symptoms associated with this disease can be present from early childhood. Limitation of exercise capacity because of either dyspnea or chest pain is often the primary and most disabling symptom in familial HCM. As a group, exercise performance is impaired, even when asymptomatic patients are included.[60] Chest pain, which is an extremely unusual finding in most forms of heart disease in children, is common in children with familial HCM and can have characteristics of angina; however, the chest pain is often atypical in that it occurs at rest, has a variable threshold of onset, and is at times prolonged. Infants with familial HCM often have clinical features more typical of congestive heart failure, with a history of tachypnea, hepatomegaly, and poor feeding and growth. Palpitations are common in adults but rarely noted by children. Syncope occurs in 15 to 25 percent of adult subjects. Although syncope is less common in childhood, it is strongly associated with the risk of sudden death.

PHYSICAL FINDINGS.

Most children and young adults are remarkably healthy, with a frequent predilection for athletics. Although many physical findings have been described in this disease, most relate to dynamic ventricular outflow obstruction and are absent in subjects without obstruction. Therefore, a completely normal physical examination in a healthy patient who may be quite athletic does not exclude the presence of this potentially fatal disorder, an observation that has led some observers to suggest echocardiographic screening as part of an evaluation prior to sports participation. The apical and parasternal cardiac impulses are often augmented but rarely displaced. Hepatomegaly is common in infants but is generally not seen beyond this age. In the presence of outflow obstruction, a bisferious carotid pulse can be encountered that corresponds to the "spike-and-dome" aortic pulse contour of patients with dynamic outflow obstruction. Parasternal and carotid systolic thrills are frequent in patients with left or right ventricular outflow obstruction. The murmur of dynamic left ventricular outflow obstruction can be noted, and it rises in intensity with physiological maneuvers that lower preload or afterload or increase contractility. Very loud systolic murmurs are usually found in subjects with subpulmonary stenosis, which is more common in infants and children. The murmur of mitral regurgitation is frequent in patients with subaortic stenosis, although difficult to separate from the outflow murmur. Aortic regurgitation can be heard but is less commonly encountered than in discrete subaortic stenosis.

ELECTROCARDIOGRAM AND HOLTER RECORDING.

Although the vast majority of patients with familial HCM and obstruction to left ventricular outflow have an abnormal ECG, about 25 percent of patients without obstruction have a normal ECG. The most common abnormalities are left ventricular hypertrophy, ST segment and T wave abnormalities, and abnormal Q waves. Atrial fibrillation develops in approximately 15 percent of adults with familial HCM but is

unusual in children. Symptomatic ventricular tachycardia on Holter recording or induced at electrophysiology study appears to identify a high-risk subgroup.[61] Although syncope is a risk factor for sudden death,[62] the presence of asymptomatic ventricular tachycardia on Holter recording is not a risk factor.[63] In children, ventricular arrhythmias on Holter recording are less frequent than in adults.

ECHOCARDIOGRAM.

The echocardiogram permits noninvasive assessment of ventricular size, wall thickness, systolic and diastolic function, outflow obstruction, and valvar insufficiency. Localized hypertrophy of the anterior septum is seen in 10 to 15 percent of patients, and 20 to 35 percent of patients have involvement of both anterior and posterior portions of the septum. At least 50 percent of patients have involvement of the anterolateral free wall in addition to the septum. The incidence of isolated involvement of the posterior and apical portions of the septum or anterolateral free wall without hypertrophy of the anterior septum is as much as 20 percent. The reported incidence of concentric hypertrophy is quite variable but can be as much as 20 percent. The anatomical pattern has not proved to be predictive of outcome but is a primary determinant of outflow obstruction and is an important factor in surgical planning.[64]

EXERCISE TESTING.

Quantitative assessment of functional capacity is useful for documenting clinical status, as well as for objectively assessing the response to therapeutic interventions. High-grade arrhythmias are elicited in some patients and have a negative prognostic implication. A hypotensive response to exercise appears to represent a risk for sudden death,[65] but more definitively, a normal exercise blood pressure response identifies a low-risk cohort.[66] Children and young adults with thallium scintigraphic evidence of ischemia have been reported to be at increased risk of sudden death.[67] Unfortunately, ECG changes with exercise are an unreliable marker of ischemia because they occur with equal frequency in patients with and without inducible ischemia.

CATHETERIZATION.

The hemodynamic findings in familial HCM depend on the presence or absence of obstruction. The right ventricle can be involved, particularly in infants and children, and can demonstrate outflow gradients and elevated diastolic pressure. In infants, the septum often impinges on right ventricular outflow, and right ventricular cavity obliteration in systole can be noted. Myocardial bridges, i.e., muscle bands overlying epicardial coronary arteries, are congenital and sufficiently common (having been observed in 20 to 66 percent of hearts) that they are considered an anatomical variant rather than a congenital anomaly.[68] Despite angiographic evidence of systolic compression of the underlying coronary artery, little evidence supports the hypothesis that myocardial bridges can be associated with ischemia. Compression of the coronary artery by myocardial bridges has been detected angiographically in 30 percent of adults with familial HCM,[69] with no evidence of adverse impact on outcome. In a recent provocative report of a relationship between sudden death and the presence of myocardial bridging in children with familial HCM, Yetman and associates suggested

that surgical unroofing of the coronary artery can prevent sudden death.[70] These authors describe delayed diastolic filling of the affected coronary artery as a mechanism for ischemia. It is unclear why myocardial bridges would have a greater impact on children than has been described in adults, so further confirmation is required before myocardial bridging can be accepted as an adverse risk factor worthy of surgical intervention.

DIFFERENTIAL DIAGNOSIS.

Ultimately, the diagnosis of familial HCM depends on molecular identification of the offending gene or the abnormal gene product. Until this test is available on a commercial basis, reliance on current, less than perfect diagnostic tools is necessary. Although echocardiographic identification of hypertrophy is the primary diagnostic modality in current clinical use, familial HCM with an associated risk of sudden death can be present even in the absence of hypertrophy. Surprisingly, when a genotyped population is investigated, the usual ECG and echocardiographic criteria accurately detect disease in only 83 percent of adults and only 50 percent of children.[71] Under these circumstances, the need for alternative diagnostic modalities is apparent. Endomyocardial biopsy is useful for excluding other causes of HCM, including mitochondrial disorders and storage diseases, and is therefore recommended in infants and young children. However, the

primary histological abnormality of focal myocardial disarray is not unique to familial HCM and cannot be reliably detected on biopsy specimens.

Although isolated case reports have described HCM in association with many disorders, in a number of disorders HCM is seen with sufficient frequency to indicate that it is an intrinsic element of the disease (Table 45-1) . Patients with Friedreich ataxia have a 25 to 50 percent incidence of HCM, with clinical characteristics quite different from those of familial HCM (see also Chap. 71) . HCM is seen in up to 20 to 30 percent of patients with Noonan syndrome,[72] with findings similar to those in familial HCM. Although the risk of congestive heart failure is more common than in familial HCM, there is also at least some risk of sudden death.[73] Infants of diabetic mothers and neonates exposed to corticosteroids often have transient biventricular hypertrophy, sometimes with outflow tract obstruction and occasionally causing symptoms. Finally, many genetic disorders are often accompanied by cardiac hypertrophy. Generally, HCM in infants is associated with unique problems in the differential diagnosis. In various series, diseases other than familial HCM have accounted for 30 to 70 percent of HCM cases in patients younger than 2 years.[73] Hypertrophy with depressed function is rare in familial HCM and highly suggestive of a metabolic or mitochondrial disorder.[74] Myocardial biopsy is often necessary to distinguish among these disorders, is recommended in all patients younger than 2 years, and can be particularly helpful in children with symmetrical hypertrophy or depressed function who have no family history of familial HCM.[74] Mitochondrial disorders present a particular problem in diagnosis because of variable

and often tissue-specific involvement.

Differentiation between physiological hypertrophy secondary to athletic participation and pathological hypertrophy in familial HCM is a frequent and important problem in children and young adults. The cardiac response to chronic, intense exercise has been well characterized and includes dilation and hypertrophy with preservation of myocardial contractility. The hypertrophic response is most intense in sports that elicit a marked rise in blood pressure during exercise, such as rowing, wrestling, and power lifting. Wall thickness greater than 13 mm, as occasionally found in athletes, and the not infrequent

TABLE 45-1 -- CONDITIONS OTHER THAN FAMILIAL HYPERTROPHIC CARDIOMYOPATHY ASSOCIATED WITH HYPERTROPHIC CARDIOMYOPATHY

Syndromes
Beckwith-Wiedemann syndrome
Cardiac-facial-cutaneous syndrome
Costello syndrome
Friedreich ataxia
Lentiginosis (LEOPARD syndrome)
Noonan syndrome
Secondary forms
Anabolic steroid therapy and abuse
Infant of diabetic mother
Prenatal and postnatal corticosteroid therapy
Metabolic disorders
Carnitine deficiency (carnitine palmitoyltransferase II deficiency, carnitine-acylcarnitine translocase deficiency)
Fucosidosis type 1
Glycogenoses types II, III, and IX (Pompe disease, Forbes disease, phosphorylase kinase deficiency)
Glycolipid lipidosis (Fabry disease)
I cell disease
Lipodystrophy, total
Mannosidosis
Mitochondrial disorders (multiple forms)
Mucopolysaccharidoses types I, II, and V (Hurler syndrome, Hunter syndrome, Scheie syndrome)
Selenium deficiency

LEOPARD=lentigenes (multiple), electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness.

occurrence of mild left ventricular hypertrophy in patients with familial HCM result in a significant incidence of diagnostic ambiguity. ECG has not been particularly helpful in differentiation because of the frequent presence of ECG abnormalities in athletes.[75] Echocardiographic and clinical features that increase the probability of familial HCM include (1) a family history of HCM or early sudden death, (2) significant regional differences in hypertrophy, (3) diastolic dysfunction, (4) abnormal ultrasonic myocardial reflectivity, (5) absence of deconditioning-induced regression of hypertrophy, and (6)

abnormalities in coronary flow reserve.[76] Ultimately, differentiation by available techniques is simply not possible in some subjects.

MANAGEMENT

The therapeutic options available in children are not fundamentally different from those in adults (see Chap. 48) . Although safety data from small series are available for most of these alternatives, no sufficiently large studies have independently addressed efficacy in infants or children. Chest pain and dyspnea are often relieved by propranolol, but improved exercise capacity is seen less often, and side effects such as fatigue and depression are often encountered. Calcium channel blockers can also reduce dyspnea and chest pain, and an increase in exercise capacity usually occurs. Although older patients with congestive heart failure can be intolerant of these drugs, pediatric tolerance has been excellent, even in neonates.[73] While several retrospective studies report a reduced risk of sudden death,[73] [77] [78] definitive controlled trials to support this finding are not available.

Each of the several interventions used to reduce outflow obstruction in adults with familial HCM and subaortic stenosis (surgery, asynchronous pacing, and septal ablation) are also available to children, but additional technical considerations affect the risk-benefit ratio. Often, clinicians attach too much significance to the presence or absence of outflow obstruction, as discussed by Criley.[79] Outflow obstruction is present in less than half of patients with familial HCM and is not predictive of outcome, with symptomatic patients without obstruction faring more poorly than those who have gradients. The magnitude of outflow obstruction is unrelated to the occurrence of ventricular tachycardia or risk of sudden death. Surgical or pharmacological reduction in the outflow gradient in symptomatic patients is usually associated with a reduction in symptoms, although the incidence of sudden death is not improved. In general, dynamic outflow obstruction is not a negative prognostic factor, and interventions aimed at reducing the gradient are justified only inasmuch as symptomatic benefit can be anticipated.

SEPTAL MYOTOMY-MYECTOMY.

In symptomatic HCM with subaortic stenosis, this procedure results in symptomatic improvement in nearly all patients despite the fact that symptoms are generally not correlated with the presence and degree of obstruction. Results in children have been similar to those reported in adults.[80] Although occasional studies have reported improved survival, most have documented no change. Consequently, surgery should be considered for relief of symptoms in patients with intractable and debilitating symptoms in spite of maximum medical therapy. Intervention based on gradient alone cannot be recommended.

ASYNCHRONOUS VENTRICULAR PACING.

This technique has emerged as an effective method of symptomatic treatment in some patients with left ventricular outflow tract obstruction.[81] Studies in small cohorts of

children with outflow obstruction who were symptomatic despite medical therapy have reported symptomatic improvement, reduced outflow obstruction, and improved exercise tolerance.[82] [83] Controlled studies in adults found that only about 60 percent of patients improved, in two-thirds of these the benefit appeared to reflect a placebo effect, and an adverse effect on symptoms was seen in 5 percent.[84] Pacemaker implantation is associated with a significant incidence of complications,[85] particularly in growing children. Based on current information, dual-chamber pacing can be considered as an alternative to surgical or transcatheter septal reduction in patients with obstructive HCM who are symptomatic despite maximum medical therapy.

EXERCISE RESTRICTION.

Avoidance of strenuous exercise is generally recommended for patients with familial HCM. The rationale for this restriction is based on the observations that sudden death is the usual cause of death in familial HCM and has a higher than expected association with exercise,[86] and that familial HCM is believed to be the most common cause of sudden death in young, competitive athletes.[87] Nevertheless, the basis for this recommendation has several serious weaknesses.[88] The true incidence of familial HCM in athletes who experience sudden death is uncertain since genetic confirmation was not available and diagnosis was based on morphological criteria that cannot unequivocally differentiate familial HCM from physiological hypertrophy. It is clear that some patients with familial HCM tolerate intense, competitive athletic participation without symptoms or sudden death.[89] Population studies have documented the

Figure 45-3 Survival in infants with hypertrophic cardiomyopathy. *Maron (1982):* Maron BJ, Tajik AJ, Ruttenberg HD, et al: Hypertrophic cardiomyopathy in infants: Clinical features and natural history. Circulation 65:7, 1982; *Moran (1998):* Moran AM, Colan SD: Verapamil therapy in infants with hypertrophic cardiomyopathy. Cardiol Young 8:310, 1998.

apparent paradox that although patients with coronary artery disease who regularly participate in low- and high-level exertion have a transient increase in the risk for sudden death during intense exercise, these individuals experience an overall reduction in the risk for sudden death (see Chap. 26) .[90] In addition, patients who do not exercise regularly have an exaggerated risk of sudden death during exercise. Studies have not been conducted to determine whether athletic participation increases the overall risk for sudden death; it has not been shown that survival is improved in those who do not exercise, nor is the level of exercise that represents a safe limit known. Detraining and social stigmatization are particularly difficult problems for an adolescent who is excluded from the usual school activities and peer interactions. Competitive team sports elicit an emotional overlay that appears to increase the risk associated with the sport itself, in addition to demanding more intense exercise. Certain activities such as weightlifting are associated with high levels of circulating catecholamines that can predispose to arrhythmias and elicit a marked stimulus to eccentric cardiac hypertrophy. However,

little evidence indicates that moderate aerobic-type exercise is a significant risk in these patients, and it does provide measurable hemodynamic and psychological benefits.

RISK STRATIFICATION.

Many prognostic factors for sudden death have been reported, but few have been confirmed. It is likely that the availability of genotyping will permit genetic risk stratification (see Fig. 48-11) (Figure Not Available) , but at present, four major risk factors have been identified: a family history of sudden death, exercise-induced hypotension, syncope, and symptomatic nonsustained ventricular tachycardia on Holter recording. Patients free of all risk factors are considered to be at low risk, and interventions (other than for symptoms such as chest pain or exercise intolerance) are not indicated. With two or more risk factors or with syncope alone in children, risk is considered high and aggressive management such as with an implantable cardioverter-fibrillator is recommended (see Chaps. 23 , 24 , and 25). No consensus has been reached on management of intermediate-risk patients. Additional negative prognostic factors such as evidence of ischemia on exercise thallium testing, marked QT dispersion, and myocardial bridging can also be useful in management decisions for these patients.[91]

CLINICAL COURSE.

The clinical course of familial HCM is highly age dependent. HCM in infancy appears to carry a worse prognosis than in older age groups. Symptomatic infants generally manifest congestive heart failure and cyanosis and have been reported to have a particularly poor

Figure 45-4 Survival in children with hypertrophic cardiomyopathy. *Maron (1976):* Maron BJ, Henry WL, Clark CE, et al: Asymmetric septal hypertrophy in childhood. Circulation 53:9, 1976; *McKenna (1984):* McKenna WJ, Deanfield JE: Hypertrophic cardiomyopathy: An important cause of sudden death. Arch Dis Child 59:971, 1984; *Yetman (1998):* Yetman AT, Hamilton RM, Benson LN, et al: Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. J Am Coll Cardiol 32:1943, 1998.

outlook, with 9 of 11 dying within the first 5 years in one series[92] and 10 of 19 dying in the first year of life in another.[93] However, some series have noted survival not dissimilar to that in older children, with reported survival rates of 100 percent at 6 years[94] and 85 percent at 12 years,[73] probably representing differences related to small series and the numerous etiologies of HCM in this age group. The reported survival in several series of HCM in infants (Fig. 45-3) and older children (Fig. 45-4) illustrate the diversity of results in these several series. Ventricular hypertrophy can develop during childhood or adolescence, and ECG abnormalities can precede its appearance, but new appearance in a previously normal adult has not been described. The severity of hypertrophy can progress during periods of accelerated somatic growth,

particularly during adolescence,[95] whereas in adults, progression does not appear to be a feature of the disease. Importantly, the increase in magnitude of hypertrophy that is sometimes seen does not have prognostic importance and does not justify an alteration in management.[96] Regression of hypertrophy is not generally considered a characteristic of the disease, although it has occasionally been reported in children.[97]

Systolic function is nearly always normal or hyperdynamic and generally does not change over time unless transition to a thin-walled congestive cardiomyopathy occurs, a transformation rarely observed during childhood[97] and invariably associated with a grim prognosis. In patients with obstruction, the pressure gradient is also generally stable in adult subjects, although progression does occur in children and adolescents.[98] Sudden death in patients referred to tertiary care centers is seen annually in 3 to 5 percent of adults and 6 to 8 percent of children.[99] Recent population studies indicate a much lower annual mortality (0.1 to 1 percent), which indicates a major referral bias in these statistics.[100] Asymptomatic adults appear to be at even lower risk,[101] although a similar relationship to symptoms has not been demonstrated in children. While improved survival has been reported with medical and surgical interventions, the studies are invariably retrospective and usually rely on historical controls. Definitive evidence of improved survival with any available therapy has not yet appeared.

Restrictive Cardiomyopathy (see also Chap. 48)

Restrictive cardiomyopathy is the least common form of cardiomyopathy and is quite rare among children. With the exception of occasional case reports, only four series in children with a total of 36 patients (8 patients in each of three studies[102] [103] [104] and 12 in the other[105]) have appeared. Clinical characteristics have been similar to those in adults, with a pattern of normal ventricular size and function, severe elevation in diastolic filling pressure, and marked atrial dilation. Numerous secondary causes of restrictive cardiomyopathy have been described in adults, but the pediatric cases have been uniformly idiopathic despite tissue analysis in nearly all, although several cases were familial. Differentiation from many of the secondary causes, such as myocardial noncompaction (persistence of embryonic or "spongy" myocardium[106]), can be made on morphological criteria. Tissue analysis is generally undertaken given the dismal prognosis of the disease and the desire to exclude any potentially treatable disorder. Methods of differentiation between restrictive cardiomyopathy and constrictive pericarditis have not been specifically investigated in children, primarily because constrictive pericarditis is virtually never encountered in children. The most striking characteristic of the reports in children has been the uniformly poor prognosis, with a 1-year survival rate of approximately 50 percent in all four series. Survival therefore appears to be even more limited than has been described in adults. Anticoagulation is recommended because a 25 percent incidence of thromboembolism has been seen in children. Therapy is otherwise nonspecific and usually of very limited benefit. The onset of irreversible elevation in pulmonary vascular resistance can occur within 1 to 4 years in these patients, and early cardiac transplantation is therefore recommended to avoid the need for heart and lung transplantation.[105]

KAWASAKI DISEASE

Kawasaki disease is an acute vasculitis of unknown etiology that occurs predominantly in infants and young children. Kawasaki first described the illness in Japanese in l967,[107] but the entity is now recognized in both endemic and community-wide epidemic forms in children of all races throughout the world. Features of Kawasaki disease include fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15 to 25 percent of untreated children with the disease and may lead to myocardial infarction, sudden death, or chronic coronary artery insufficiency.[108] In the United States, acquired heart disease in children is now caused more commonly by Kawasaki disease than by acute rheumatic fever (see Chap. 66) .[109] The cause of Kawasaki disease remains unknown.

Clinical Features

The clinical criteria put forth in Kawasaki's first English language description of the disease are still in use today.[107] A child with Kawasaki disease must have fever lasting 5 or more days without another reasonable explanation and satisfy at least four of the following criteria: (1) bilateral, nonexudative conjunctival injection; (2) at least one of the following: mucous membrane changes, injected or fissured lips, injected pharynx, or "strawberry tongue"; (3) at least one of the following extremity changes: erythema of the palms or soles, edema of the hands or feet, or periungual desquamation; (4) polymorphous exanthem; and (5) acute nonsuppurative cervical lymphadenopathy (at least one node 1.5 cm or larger in diameter). An additional category of "atypical Kawasaki disease" includes patients with only four criteria and coronary artery abnormalities by echocardiography.[110] None of the clinical features of Kawasaki disease is pathognomonic. For this reason, the diagnosis of Kawasaki disease requires exclusion of other illnesses that might mimic its clinical features, including streptococcal and staphylococcal toxin-mediated illness; infection with adenovirus, enterovirus, and measles; and systemic allergic reactions to various medications. Many symptoms and signs apart from the diagnostic criteria are frequently present in children with Kawasaki disease and include arthralgias, arthritis, urethritis, aseptic meningitis, diarrhea, vomiting, and abdominal pain.

The conventional diagnostic criteria should be viewed as guidelines; they are especially useful in preventing overdiagnosis but may result in failure to recognize incomplete forms of illness. Signs and symptoms of Kawasaki disease may be particularly subtle or absent in infants younger than 6 months, a subgroup at high risk for coronary lesions. The frequent occurrence of coronary artery involvement among children with incomplete criteria suggests that echocardiography should be performed in all children with prolonged, unexplained fever and some signs of Kawasaki disease.

Cardiac Findings

CORONARY ARTERY ABNORMALITIES.

Coronary artery ectasia or aneurysms occur in 15 to 25 percent of children

with Kawasaki disease who do not receive treatment with intravenous gamma globulin (IVIG) in the acute phase.[111] [112] Dilatation of coronary arteries (Japanese Ministry of Health criteria)[113] may be detected by echocardiography beginning 7 days after the first appearance of fever, with the coronary diameter usually peaking around 4 weeks after illness onset. In general, clinical and laboratory indices of greater inflammation are associated with a higher likelihood of aneurysm development.

MYOCARDITIS.

Myocarditis has been demonstrated in autopsy and myocardial biopsy studies to be a universal feature of early Kawasaki disease. With high-dose IVIG treatment, myocardial function improves rapidly, i.e., within days, in patients with acute Kawasaki disease.[114] When myocardial dysfunction occurs after the acute phase of the disease, it is usually secondary to ischemia or infarction, with or without mitral regurgitation.

With the use of endomyocardial biopsy, myocardial abnormalities have been detected in all time periods after disease onset; their severity was unrelated to the presence of coronary artery abnormalities. In addition, electron microscopic examination of endomyocardial biopsy specimens has demonstrated histological abnormalities late after Kawasaki disease.[115] Assessment of the full impact of Kawasaki disease on heart function and structure must await the follow-up of these children into later adult life.

VALVAR REGURGITATION.

Mitral regurgitation may result from transient papillary muscle dysfunction, myocardial infarction, or valvulitis. Kato and colleagues reported mitral regurgitation in 1.0 percent of patients in their series.[116] The appearance of mitral regurgitation after the acute stage is usually secondary to myocardial ischemia, although late-onset valvulitis unrelated to ischemia has been documented.

Aortic regurgitation has been documented angiographically by Nakano and colleagues in approximately 5 percent of children with Kawasaki disease and was attributed to valvulitis.[117] Others have observed a much lower incidence of aortic regurgitation in the acute phase.[116] Late-onset aortic regurgitation has been reported as a rare finding after Kawasaki disease and may be associated with the need for aortic valve replacement.

Laboratory Data

GENERAL TESTS.

Laboratory findings in acute Kawasaki disease reflect the marked degree of systemic inflammation. Common initial findings include anemia, leukocytosis with a left shift, elevation of acute phase reactants, and mild elevation of liver transaminase levels. Thrombocytosis usually peaks in the third to fourth week after the onset of fever. Urinalysis may reveal the presence of white cells on microscopic examination. Since the white cells are mononuclear rather than polymorphonuclear, the dipstick test for nonspecific esterase activity (i.e., neutrophil enzyme) is usually negative. Examination of cerebrospinal fluid reveals a mild mononuclear cell pleocytosis with normal glucose and normal to mildly elevated protein.[118]

ELECTROCARDIOGRAPHY.

The ECG in acute Kawasaki disease may show mild abnormalities consistent with myocarditis, most commonly a prolonged PR interval and nonspecific ST and T wave changes.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY.

Two-dimensional echocardiography has high sensitivity and specificity for proximal vessels of the right and left coronary arterial trees (see Chap. 7) . The initial echocardiogram should be obtained as soon as the diagnosis of Kawasaki disease is suspected.[110] Longitudinal echocardiographic follow-up should begin 10 to 14 days after the onset of illness, when early coronary dilation will first be noticed in the majority of children in whom aneurysms are destined to develop. In the absence of significant coronary dilation, cardiac ultrasound may be repeated approximately 6 to 8 weeks after illness onset. Follow-up of patients with coronary dilation should be adapted to their clinical course and the severity of their lesions.

Echocardiographers often find it difficult to reach an agreement on the exact configuration and extent of any given coronary artery lesion as seen by two-dimensional echocardiography. In 1984, the Japanese Ministry of Health established criteria for coronary artery abnormalities in Kawasaki disease.[113] These criteria classify coronary arteries as abnormal if the internal lumen diameter is greater than 3 mm in children younger than 5 years or greater than 4 mm in children at least 5 years of age, if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment, or if the coronary artery lumen is clearly irregular. Current statistics on the prevalence of coronary dilation secondary to Kawasaki disease are based on these criteria. Recently, de Zorzi and colleagues showed, in patients with Kawasaki disease whose coronary arteries are classified as "normal" by Japanese Ministry of Health criteria, that body surface area-adjusted coronary dimensions are larger than expected in the acute, convalescent, and late phases.[119] Thus, the Japanese Ministry of Health criteria may underestimate the true prevalence of coronary dilation following Kawasaki disease. Figure 45-5 *A* to *C* depicts normal left main, left anterior descending, and right coronary artery size, respectively, according to body surface area.

CORONARY ARTERIOGRAPHY.

Selective coronary arteriography can provide definitive delineation of coronary artery anatomy. This technique is especially useful for visualization of coronary artery stenoses or distal coronary artery lesions that are difficult to define by two-dimensional echocardiography.

Based on the coronary artery classification system used in the Coronary Artery Surgery Study,[120] Takahashi and colleagues defined coronary artery aneurysms imaged at angiography as either localized or extensive.[121] Localized aneurysms, i.e., confined to one arterial segment, are further classified as either fusiform (spindle shaped) or saccular (showing abrupt transition from the normal to the dilated state, e.g., spherical, dumbbell shaped, triangular, or sack-like). Extensive aneurysms involve more than one segment and may be either ectatic (uniformly dilated) or segmented (having multiple dilated segments joined by normal or stenotic segments). Coronary aneurysms in early Kawasaki disease usually occur in the proximal segments of the major coronary vessels; aneurysms that occur distally are almost always associated with proximal coronary abnormalities.

Aneurysms can also occur in arteries outside the coronary system, most commonly the subclavian, brachial, axillary, iliac, or femoral vessels and occasionally the abdominal aortic and renal arteries.[112] For this reason, abdominal aortography and subclavian arteriography are often performed in patients undergoing coronary arteriography for Kawasaki disease.

Treatment

ASPIRIN.

Aspirin has been a standard therapy for Kawasaki disease because of its antiinflammatory and antithrombotic effects, but it does not reduce the prevalence of coronary artery aneurysms.[122] Therapy with aspirin is usually initiated at the time of initial assessment in a dose of 80 to 100 mg/kg/day divided into four doses. Once fever has resolved, the dose is lowered to an antiplatelet regimen of 3 to 5 mg/kg/day orally for up to 6 to 8 weeks. For children in whom coronary aneurysms develop, aspirin (with or without anticoagulation or other antiplatelet agents) may be continued indefinitely.

INTRAVENOUS GAMMA GLOBULIN THERAPY.

Although its exact mechanism of action remains unknown, IVIG administered in the acute phase of Kawasaki disease reduces the prevalence of coronary artery abnormalities.[122] [123] Patients should be treated with IVIG 2 gm/kg in a single

Figure 45-5 Mean and 95% prediction limits for size of the left main coronary artery *(A),* left anterior descending coronary artery *(B),* and proximal right coronary artery *(C)* according to body surface area for children younger than 18 years, as derived from 152 normal children at Children's Hospital, Boston.

infusion, together with aspirin.[110] Ideally, this therapy should be instituted within the first 10 days of illness (optimally by day 7 of illness), but it should be administered after the 10th day of illness to any child with persistent fever[124] or with aneurysms and ongoing signs of inflammation. Even when treated with high-dose IVIG regimens within the first 10 days of illness, however, approximately 5 percent of children with Kawasaki disease experience at least transient coronary artery dilation, and giant aneurysms develop in 1 percent.[125] Most experts recommend retreatment with IVIG 2 gm/kg in patients with persistent or recrudescent fever 48 to 72 hours after initial therapy.

CORTICOSTEROIDS.

The subgroup of patients with Kawasaki disease resistant to IVIG therapy is at greatest risk for the development of coronary artery aneurysms and long-term sequelae of the disease.[126] [127] Although one early study showed a detrimental effect of steroid use in Kawasaki disease,[128] others have suggested that steroids may be beneficial in the prevention of coronary artery aneurysms.[129] [130] Further studies are needed to assess the risks and benefits of steroid administration in Kawasaki disease.

OTHER THERAPIES DURING THE ACUTE PHASE.

High-dose pentoxifylline, a vasodilator and inhibitor of platelet aggregation and neutrophil activation, has been shown in one study to reduce the incidence of coronary artery aneurysms.[131] Case reports suggest that plasmapheresis may produce dramatic improvement in severe Kawasaki disease[132] ; however, it is a technically complex intervention in young children and should be reserved for those who remain desperately ill despite multiple doses of IVIG and intravenous methylprednisolone.

ANTITHROMBOTIC THERAPY.

Paradoxically, the risk of coronary artery thrombosis is greatest *after* the acute phase subsides, when well-established coronary vasculitis occurs concomitantly with marked elevation of the platelet count and a hypercoagulable state. As above, low-dose aspirin (3 to 5 mg/kg/day given as a single dose) is the mainstay of antithrombotic therapy in Kawasaki disease. Other antiplatelet agents, such as clopidogrel or dipyridamole, may be substituted for aspirin when salicylates are contraindicated. For children without evidence of coronary artery ectasia or aneurysms, antiplatelet therapy is usually discontinued approximately 2 months after illness onset.

Children with coronary artery abnormalities require long-term antithrombotic therapy, usually with low-dose aspirin. The risk of coronary thrombosis and myocardial infarction is especially great in children with rapidly increasing coronary dimensions or with giant aneurysms during the subacute phase.[133] [134] During this period, some investigators advocate treatment with systemic heparin, together with an antiplatelet agent. For chronic antithrombotic therapy, therapeutic options include antiplatelet therapy with aspirin, with or without dipyridamole or another inhibitor of antiplatelet aggregation; anticoagulant therapy with warfarin; or a combination of anticoagulant and antiplatelet therapy, usually warfarin plus aspirin. No prospective data

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exist to guide the clinician in choosing the optimal regimen. The most common regimen for patients with giant aneurysms is low-dose aspirin together with warfarin, with the international normalized ratio maintained at 2.0:2.5. Some physicians substitute low-molecular-weight heparin for warfarin, although this therapy requires subcutaneous injections twice daily.

THROMBOLYTIC THERAPY.

Despite the use of antithrombotic agents, myocardial infarction secondary to thrombotic occlusion of coronary aneurysms can develop in some children, especially those with giant aneurysms. Sometimes, coronary artery thrombus can be detected in asymptomatic patients by two-dimensional echocardiography. Because no large trials of thrombolytic therapy have been performed in children, the choice of thrombolytic agent for the treatment of infants and children with coronary thrombosis is derived from studies in adults with coronary thrombosis. Although effective in adults, the use of immediate coronary angioplasty has not been reported in children with Kawasaki disease and coronary artery thrombosis.

SURGICAL MANAGEMENT.

Surgical management in Kawasaki disease consists primarily of coronary artery bypass grafts for obstructive lesions.[134A] However, indications for coronary bypass graft procedures in children have not been established. Such surgery should be considered when reversible ischemia is present on stress-imaging tests, the myocardium to be perfused through the graft is still viable, and no appreciable lesions are present in the artery peripheral to the planned graft site.

The earliest coronary artery bypass operations in children with Kawasaki disease were performed with autologous saphenous veins or veins obtained from parents. However, the late results with this technique have been relatively unsatisfactory, especially in very young children. Kitamura and coworkers reported improved results with the use of internal mammary artery grafts in pediatric patients.[135] The diameter and length of internal mammary grafts increase with the general somatic growth of the child, as

opposed to the tendency of saphenous vein grafts to shorten somewhat over time. In children younger than 7 years, the arterial graft patency rate 90 months after surgery was 70 percent. Children who were older than 8 years at the time of coronary arterial grafting appeared to have even better long-term patency than seen in younger children; by 90 months after surgery, the arterial graft patency rate was 84 percent. Of note, 8 years after internal mammary artery grafting to the left anterior descending coronary artery, 98.7 percent of patients in the series of Kitamura and colleagues were still alive.

INTERVENTIONAL CARDIAC CATHETERIZATION TECHNIQUES.

Although results over the first decade after surgery are encouraging, graft patency in later adult life after coronary artery bypass grafting in childhood is still unknown. When it is preferable to delay the time until surgery, percutaneous transluminal coronary angioplasty (PTCA) may be performed in the stenotic coronary arteries of children with Kawasaki disease[136] [137] (Fig. 45-6) . PTCA is not as effective in patients with Kawasaki disease as in adults with atherosclerotic coronary artery disease because the stenotic lesions in long-term Kawasaki disease are very stiff and often associated with marked calcifications, especially many years after illness onset. The relatively high balloon pressures necessary under these circumstances can lead to late aneurysm formation.[137] Intravascular ultrasound imaging has been found to be a useful tool for evaluating internal morphology before and after PTCA.[136] Once calcification and stenosis have become severe, rotational ablation techniques may be necessary for the success of coronary angioplasty.

CARDIAC TRANSPLANTATION.

Cardiac transplantation has been performed in a small number of patients with severe ischemic heart disease resulting from Kawasaki disease.[138]

Figure 45-6 Left coronary arteriograms. *A,* Localized stenosis can be seen at a site just proximal to the aneurysm of the left anterior descending artery. *B,* The stenosis was dilated by conventional percutaneous transluminal coronary angioplasty (PTCA). *C,* Follow-up angiography performed 13 months after the initial PTCA revealed no significant restenoses. Pre=pre-PTCA; POST=post-PTCA. (From Ino T, Akimoto K, Ohkubo M, et al: Application of percutaneous transluminal angioplasty to coronary arterial stenosis in Kawasaki disease. Circulation 93:1711, 1996. By permission of the American Heart Association, Inc.)

This procedure should be considered only for individuals with severe, irreversible myocardial dysfunction and coronary lesions for which interventional catheterization procedures or coronary artery bypass is not feasible.

Clinical Course

REGRESSION AND EVOLUTION OF CORONARY LESIONS.

Coronary artery lesions resulting from Kawasaki disease change dynamically with time.

Angiographic resolution 1 to 2 years after disease onset has been observed in approximately half to two-thirds of vessels with coronary aneurysms.[121] [139] The likelihood of resolution of the aneurysm appears to be determined in large measure by the initial

size of the aneurysm, with smaller aneurysms having a greater likelihood of regression.[133] Takahashi and coauthors reported other factors positively associated with regression of aneurysms, including age younger than 1 year, saccular (rather than fusiform) aneurysm morphology, and aneurysm location in a distal coronary segment.[121] Vessels that do not undergo apparent resolution of abnormalities may show persistence of aneurysmal morphology, development of stenosis or occlusion, or abnormal tortuosity.

PATIENTS WITH PERSISTENT CORONARY ARTERY ABNORMALITIES.

Whereas aneurysm size tends to diminish over time, stenotic lesions secondary to marked myointimal proliferation are frequently progressive.[112] In the series of Kato and coworkers, stenotic lesions were recognized within 2 years from disease onset in about half of the patients in whom coronary stenoses ultimately developed, but the prevalence of stenosis continued to rise almost linearly over time.[139] Kamiya and colleagues have also reported a steady increase in the presence of coronary artery stenoses with increasing duration since illness onset; the highest rate of progression to stenosis occurred among patients whose aneurysms were large.[140]

The worst prognosis occurs in children with so-called giant aneurysms, i.e., those with a maximum diameter greater than 8 mm.[141] In these aneurysms, thrombosis is promoted by sluggish blood flow within the massively dilated vascular space, together with frequent development of stenotic lesions at the proximal or distal end of the aneurysms.

Myocardial infarction caused by thrombotic occlusion in an aneurysmal and/or stenotic coronary artery is the principal cause of death in Kawasaki disease.[111] The highest risk of myocardial infarction occurs in the first year after disease onset, and most fatal attacks are associated with obstruction either in the left main coronary artery or in both the right main and left anterior descending coronary arteries.[111] Serial stress tests and myocardial imaging are mandatory in the management of patients with Kawasaki disease and significant coronary artery disease to determine the need for coronary angiography and for surgical or transcatheter intervention.

Late cardiac sequelae of Kawasaki disease may first become apparent in adulthood. Burns and associates identified 74 patients in the English and Japanese literature with Kawasaki disease in childhood whose first symptoms of coronary artery disease occurred in young adulthood.[142] A history of a Kawasaki-like illness in childhood should be sought in patients with coronary aneurysms in the absence of generalized atherosclerotic disease. However, adult patients may be unable to recall an illness that

occurred so early in life.

PATIENTS WITH SPONTANEOUS REGRESSION OF ANEURYSMS.

Approximately half of vascular segments with coronary artery aneurysms show angiographic regression of the aneurysms. This regression usually occurs by myointimal proliferation, although more rarely the mechanism of regression can be organization and recanalization of a thrombus. Pathological examination reveals fibrous intimal thickening despite normal coronary artery diameter. Similarly, transluminal (intravascular) ultrasound of regressed coronary aneurysms shows marked symmetrical or asymmetrical myointimal thickening.[143] Regressed coronary artery aneurysms not only are histopathologically abnormal but also show reduced vascular reactivity.[144] [144A]

KAWASAKI DISEASE WITHOUT DETECTABLE CORONARY LESIONS.

Although coronary artery aneurysms produce the most serious sequelae of Kawasaki disease, vascular inflammation during the acute stage of the illness is diffuse. Generalized endothelial dysfunction has been suggested by the observation that plasma 6-ketoprostaglandin F_1 remains generally undetectable over an observation period of 8 weeks after the onset of Kawasaki disease.[145] In addition, Kawasaki disease produces altered lipid metabolism that persists beyond clinical resolution of the disease.[146] Histological data concerning the long-term status of coronary arteries in children who never had demonstrable abnormalities are few and difficult to interpret.[147]

Some investigators in Japan have studied coronary physiology in the population without aneurysms. Among children with a history of Kawasaki disease but with normal epicardial coronary arteries, Muzik and colleagues found lower myocardial flow reserve and higher total coronary resistance than in normal controls.[148] Children without a history of coronary aneurysms have also been reported to have abnormal endothelium-dependent brachial artery reactivity.[149] Data are conflicting regarding impairment in long-term endothelium-dependent relaxation of the epicardial coronary arteries among children with Kawasaki disease in whom coronary artery dilation was never detected.[150] [151]

From a purely clinical perspective, children without known cardiac sequelae during the first month after diagnosis of Kawasaki disease appear to return to their previous, usually excellent state of health, without signs or symptoms of cardiac impairment.[139] Meaningful knowledge about long-term myocardial function, late-onset valvar regurgitation, and coronary artery status in this population must await their careful surveillance over the coming decades.

SYSTEMIC HYPERTENSION

Hypertension is well recognized as a major risk factor for cardiovascular disease, including stroke, myocardial infarction, congestive heart failure, and renal failure. Because the precursors of these processes are likely to arise early in life, evaluation and treatment of pediatric hypertension are important. Estimates of significant

hypertension in childhood have ranged from 0.26 to 2.0 percent.[152] The most common causes of hypertension change during childhood, with secondary causes of hypertension predominating in the youngest patients and those in whom systemic hypertension is the most severe. For many years, pediatricians focused solely on identification and treatment of secondary forms of hypertension, such as renal parenchymal disease and renal artery stenosis.[152] With recommendations for routine measurement of blood pressure during well-child visits to the pediatrician, as well as the publication of national norms for blood pressure in children, essential hypertension has been increasingly recognized, especially in adolescents with mild to moderate elevation of blood pressure. Children with higher blood pressure are more likely to have first-degree relatives with histories of hypertension, and the tracking correlation of blood pressure from childhood into young adult life is relatively high. Nonetheless, the sensitivities and predictive values for childhood blood pressure are only modest as a screening test for adult blood pressure.[153]

DEFINITION.

The distribution of blood pressure in the normal pediatric population is shown in Tables 45-2 and 45-3 . The National High Blood Pressure Education Program has recommended that blood pressure between the 90th and 95th percentiles be considered high-normal or borderline hypertension. Hypertension is defined as average systolic or diastolic blood pressure greater than or equal to the 95th percentile for sex, age, and height on at least three separate occasions. Thus, elevation of blood pressure must be sustained to establish a diagnosis of hypertension. Ideally, blood pressure should be measured with a standard sphygmomanometer, blood pressure cuff, and stethoscope. Many centers currently use automated oscillometric blood pressure monitoring devices for ease of use and elimination of interobserver variability. In addition, 24-hour ambulatory

TABLE 45-2 -- BLOOD PRESSURE LEVELS FOR THE 90TH AND 95TH PERCENTILES OF BLOOD PRESSURE FOR BOYS AGED 1 TO 17 YEARS BY PERCENTILES OF HEIGHT

AGE (yr)	BLOOD PRESSURE PERCENTILE*	SYSTOLIC BLOOD PRESSURE BY PERCENTILE OF HEIGHT (mm Hg)							DIASTOLIC BLOOD PRESSURE BY PERCENTILE OF HEIGHT (mm Hg)				
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%
1	90th	94	95	97	98	100	102	102	50	51	52	53	54
	95th	98	99	101	102	104	106	106	55	55	56	57	58
2	90th	98	99	100	102	104	105	106	55	55	56	57	58
	95th	101	102	104	106	108	109	110	59	59	60	61	62
3	90th	100	101	103	105	107	108	109	59	59	60	61	62

	95th	104	105	107	109	111	112	113	63	63	64	65	66
4	90th	102	103	105	107	109	110	111	62	62	63	64	65
	95th	106	107	109	111	113	114	115	66	67	67	68	69
5	90th	104	105	106	108	110	112	112	65	65	66	67	68
	95th	108	109	110	112	114	115	116	69	70	70	71	72
6	90th	105	106	108	110	111	113	114	67	68	69	70	70
	95th	109	110	112	114	115	117	117	72	72	73	74	75
7	90th	106	107	109	111	113	114	115	69	70	71	72	72
	95th	110	111	113	115	116	118	119	74	74	75	76	77
8	90th	107	108	110	112	114	115	116	71	71	72	73	74
	95th	111	112	114	116	118	119	120	75	76	76	77	78
9	90th	109	110	112	113	115	117	117	72	73	73	74	75
	95th	113	114	116	117	119	121	121	76	77	78	79	80
10	90th	110	112	113	115	117	118	119	73	74	74	75	76
	95th	114	115	117	119	121	122	123	77	78	79	80	80
11	90th	112	113	115	117	119	120	121	74	74	75	76	77
	95th	116	117	119	121	123	124	125	78	79	79	80	81
12	90th	115	116	117	119	121	123	123	75	75	76	77	78
	95th	119	120	121	123	125	126	127	79	79	80	81	82
13	90th	117	118	120	122	124	125	126	75	76	76	77	78
	95th	121	122	124	126	128	129	130	79	80	81	82	83
14	90th	120	121	123	125	126	128	128	76	76	77	78	79
	95th	124	125	127	128	130	132	132	80	81	81	82	83
15	90th	123	124	125	127	129	131	131	77	77	78	79	80
	95th	127	128	129	131	133	134	135	81	82	83	83	84
16	90th	125	126	128	130	132	133	134	79	79	80	81	82
	95th	129	130	132	134	136	137	138	83	83	84	85	86
17	90th	128	129	131	133	134	136	136	81	81	82	83	84
	95th	132	133	135	136	138	140	140	85	85	86	87	88

From National Heart, Lung and Blood Institute: Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. Pediatrics 98:649, 1996. Copyright American Academy of Pediatrics 1996.

*Blood pressure percentile was determined by a single measurement.

Height percentile was determined by standard growth curves.

blood pressure monitoring has been used when "white coat" hypertension is suspected and for management of known hypertension.[154] [155] [155A]

EVALUATION.

Evaluation of an asymptomatic child or adolescent with hypertension should focus on potential etiologies. The family history should be carefully probed for hypertension, premature cardiovascular disease, and renal disease, medical conditions, or drugs. In adolescents, the possibility of substance abuse should always be considered. The physical examination should be directed toward signs of definable causes of hypertension, as well as toward its sequelae.

Many adolescents whose blood pressure is at or just greater than the 95th percentile have family histories of hypertension and are overweight, but they have an otherwise negative history and physical examination.[152] For such patients, a work-up that includes urinalysis, urine culture, and electrolyte, serum creatinine (noting that normal values vary according to age), and blood urea nitrogen levels may be sufficient.[156] Such patients would also usually benefit from a lipid profile to exclude other risk factors for premature cardiovascular disease.[152] When children or adolescents with borderline high blood pressure are not obese and have no family history of hypertension, renal Doppler ultrasound provides a first-line screen for renovascular hypertension, parenchymal integrity, and hydronephrosis.

For patients in whom blood pressure is well above the 95th percentile, secondary causes of hypertension should be pursued aggressively, with targeting of conditions believed to be most likely on the basis of age (Table 45-4) or targeting of findings on initial assessment. Most children with secondary hypertension (60 to 80 percent) have renal parenchymal disease,[156] commonly reflux nephropathy, pyelonephritis, and obstructive uropathy. Less common renal etiologies include glomerulonephritis, nephrotic syndrome, congenital renal dysplasia, renal damage following hemolytic-uremic syndrome, and polycystic disease.[156] Renal parenchymal disease can be assessed with imaging studies, including renal ultrasonography, voiding cystourethrography, or renal scintiscanning.

Renovascular hypertension has been reported in 8 to 10 percent of children with secondary hypertension.[156] [157] In such patients, hypertension may be caused by stenosis of a main renal artery or by segmental renal artery stenoses in one or both kidneys.[156] Methods of evaluation of renovascular hypertension vary in different centers and include renal scanning before and after captopril challenge, intravenous digital subtraction angiography, captopril radionuclide renography, Doppler sonography, computed tomographic angiography, and magnetic resonance angiography. Conventional angiography and intraarterial digital subtraction angiography remain the gold standard for the diagnosis of renovascular hypertension and should be considered for children with severe, persistent hypertension without other findings, greatly elevated

plasma renin activity, a bruit, or a solitary kidney and severe hypertension.[156]

TABLE 45-3 -- BLOOD PRESSURE LEVELS FOR THE 90TH AND 95TH PERCENTILES OF BLOOD PRESSURE FOR BOYS AGED 1 TO 17 YEARS BY PERCENTILES OF HEIGHT

AGE (yr)	BLOOD PRESSURE PERCENTILE*	SYSTOLIC BLOOD PRESSURE BY PERCENTILE OF HEIGHT (mm Hg)							DIASTOLIC BLOOD PRESSURE BY PERCENTILE OF HEIGHT (mm Hg)				
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%
1	90th	97	98	99	100	102	103	104	53	53	53	54	55
	95th	101	102	103	104	105	107	107	57	57	57	58	59
2	90th	99	99	100	102	103	104	105	57	57	58	58	59
	95th	102	103	104	105	107	108	109	61	61	62	62	63
3	90th	100	100	102	103	104	105	106	61	61	61	62	63
	95th	104	104	105	107	108	109	110	65	65	65	66	67
4	90th	101	102	103	104	106	107	108	63	63	64	65	65
	95th	105	106	107	108	109	111	111	67	67	68	69	69
5	90th	103	103	104	106	107	108	109	65	66	66	67	68
	95th	107	107	108	110	111	112	113	69	70	70	71	72
6	90th	104	105	106	107	109	110	111	67	67	68	69	69
	95th	108	109	110	111	112	114	114	71	71	72	73	73
7	90th	106	107	108	109	110	112	112	69	69	69	70	71
	95th	110	110	112	113	114	115	116	73	73	73	74	75
8	90th	108	109	110	111	112	113	114	70	70	71	71	72
	95th	112	112	113	115	116	117	118	74	74	75	75	76
9	90th	110	110	112	113	114	115	116	71	72	72	73	74
	95th	114	114	115	117	118	119	120	75	76	76	77	78
10	90th	112	112	114	115	116	117	118	73	73	73	74	75
	95th	116	116	117	119	120	121	122	77	77	77	78	79
11	90th	114	114	116	117	118	119	120	74	74	75	75	76
	95th	118	118	119	121	122	123	124	78	78	79	79	80
12	90th	116	116	118	119	120	121	122	75	75	76	76	77
	95th	120	120	121	123	124	125	126	79	79	80	80	81

13	90th	118	118	119	121	122	123	124	76	76	77	78	78	
	95th	121	122	123	125	126	127	128	80	80	81	82	82	
14	90th	119	120	121	122	124	125	126	77	77	78	79	79	
	95th	123	124	125	126	128	129	130	81	81	82	83	83	
15	90th	121	121	122	124	125	126	127	78	78	79	79	80	
	95th	124	125	126	128	129	130	131	82	82	83	83	84	
16	90th	122	122	123	125	126	127	128	79	79	79	80	81	
	95th	125	126	127	128	130	131	132	83	83	83	84	85	
17	90th	122	123	124	125	126	128	128	79	79	79	80	81	
	95th	126	126	127	129	130	131	132	83	83	83	84	85	

From National Heart, Lung and Blood Institute: Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. Pediatrics 98:649, 1996. Copyright American Academy of Pediatrics 1996.

*Blood pressure percentile was determined by a single reading.

Height percentile was determined by standard growth curves.

Coarctation of the aorta (see Chap. 43) , a common cause of hypertension in the first year of life, is present in one-third of infants with hypertension but accounts for only 2 percent of cases of secondary hypertension in childhood and adolescence.[156] This cause of hypertension is easily detected on physical examination by careful measurement of upper and lower extremity blood pressures, together with palpation of radial and femoral pulses. Since 80 percent of patients with coarctation have an associated bicuspid aortic valve, physical examination often includes a constant early systolic ejection click at the apex and base. A soft early to midsystolic ejection murmur is frequently heard over the left lateral aspect of the chest, and older children with collateral circulation may have continuous murmurs over the back. The diagnosis of coarctation of the aorta may be confirmed by two-dimensional echocardiography or, in an older child or adolescent, by magnetic resonance imaging (MRI). After the coarctation is repaired, a residual gradient may either remain or recur, sometimes necessitating late procedures such as balloon dilation or stenting of the aorta. Some patients require chronic antihypertensive medication after adequate repair of coarctation.

More rarely, hypertension can be caused by endocrine disorders.[158] Pheochromocytoma alone causes approximately 0.5 to 2.0 percent of cases of secondary hypertension in children.[159] Most children with pheochromocytoma (88 percent) have sustained rather than episodic hypertension, and many have extraadrenal or multiple tumors (31 and 32 percent, respectively).[156] Elevation of urinary catecholamine levels in a 24-hour urine collection or elevation of plasma

catecholamines points to a diagnosis of pheochromocytoma (or other types of neural crest tumor). Definitive diagnosis is made with MRI (T_2 weighted or gadolinium-labeled diethylenetriaminepentaacetic acid [DTPA] enhanced) or with meta-iodobenzylguaninine (MIBG) scanning.[156] [160] [161] Pheochromocytomas are removed surgically, after the hypertension is controlled.[159] [162] [163] Other endocrine causes of secondary hypertension (e.g., excess glucocorticoids or mineralocorticoids, hyperthyroidism) may be pursued if the history, physical examination, or screening tests are suggestive.

Hypertension may rarely be associated with abnormalities of the central nervous system (CNS). These abnormalities may be primary (e.g., brain tumors, familial dysautonomia) or secondary (e.g., hypercalcemia or lead poisoning). Because hypertension of CNS origin may have a fulminant manifestation, CNS-mediated causes of hypertension should always be considered by the clinician.[156] [164]

MANAGEMENT.

All children with blood pressure consistently above the 90th percentile should be introduced to nonpharmacological therapies, including a diet rich in fruits, vegetables, and low-fat dairy products, reduced intake

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TABLE 45-4 -- MOST COMMON CAUSES OF SECONDARY HYPERTENSION, BY AGE

AGE GROUP	CAUSE
Newborn	Renal artery or venous thrombosis Renal artery stenosis Congenital renal abnormalities Coarctation of the aorta Bronchopulmonary dysplasia
First year	Coarctation of the aorta Renovascular disease Renal parenchymal disease Iatrogenic (medication, volume) Tumor
Infancy to 6 yr	Renal parenchymal disease Renovascular disease Coarctation of the aorta Endocrine causes* Iatrogenic* Essential hypertension*

Age 6-10 yr	Renal parenchymal disease Renovascular disease Essential hypertension Coarctation of the aorta Endocrine causes* Iatrogenic*
Age 12-18 yr	Essential hypertension Iatrogenic Renal parenchymal disease* Endocrine causes* Coarctation of the aorta*

From Swinford RD, Ingelfinger JR: Evaluation of hypertension in childhood diseases. In Barratt TM, Avner ED, Harmon WD (eds): Pediatric Nephrology. 4th ed. Baltimore, Lippincott Williams & Wilkins, 1999, p 1007.

*Uncommon for category.

of saturated fat,[165] and for obese children, weight modification. Children and their families should also be counseled regarding the benefits of aerobic physical activity and the hazards of smoking.[152] Treatment with medications should be instituted for patients with severe hypertension or evidence of end-organ damage (e.g., increased left ventricular mass by two-dimensional echocardiography). In addition, pharmacological treatment of hypertension should be guided by the presence of other cardiovascular risk factors (e.g., childhood diabetes, chronic renal disease).

When drugs are prescribed for children and adolescents with hypertension, the goal is to reduce blood pressure to below the 95th percentile for age, gender, and height.[152] Drug therapy should aim at prescribing the simplest regimen with the fewest adverse side effects. All antihypertensive medications should be individualized to the patient's medical history (including the etiology of the hypertension), severity of hypertension, response to therapy, and occurrence of side effects.[152] Thiazide diuretics and beta blockers have been used for years in children and adolescents and continue to have a role in the treatment of hypertension. Since publication of the Report of the Second Task Force on Blood Pressure Control in Children in 1987,[166] newer antihypertensive agents have come into common use in pediatric patients. These medications include ACE inhibitors and calcium channel blockers.[167] Use of the other classes of antihypertensive agents (e.g., central alpha-adrenergic agonists, alpha-adrenergic blocking drugs, direct vasodilators) is only rarely indicated in pediatric cardiology practice. Long-term clinical trials have not examined the benefits and risks of antihypertensive therapy in children and adolescents. Until such data are available, when choosing the optimal antihypertensive medication, physicians should draw on the adult experience.

HYPERLIPIDEMIAS (see also Chaps. 30 , 31 , 32 , and 33)

Abnormalities in plasma lipoproteins are an important cause of premature coronary artery disease. Because epidemiological and pathological observations have introduced the concept that the process of atherosclerosis begins early in life and progresses to cardiovascular morbidity and mortality in later life, efforts to prevent clinical disease have centered around the modification of plasma lipid concentrations in childhood and adolescence.[168]

RATIONALE FOR LIPID MODIFICATION IN CHILDHOOD.

The rationale for modification of cholesterol in childhood is based on postmortem and epidemiological data. In 1953, Enos and colleagues first reported that postmortem examination showed advanced lesions in the coronary arteries of young American soldiers killed in the Korean war.[169] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, a multiinstitutional study of atherosclerosis in 15- to 34-year-old males and females, demonstrated that the conditions predicting risk of coronary heart disease in adults are also associated with the extent and severity of atherosclerosis in youth.[170] Recently, this group reported on the ubiquity of fatty streaks in the abdominal aortas and the frequency of fibrous plaques in the aortas and coronary arteries in the 15- to 19-year-old age group.[171] Other autopsy studies have shown that antemortem low-density lipoprotein (LDL) and total cholesterol are highly associated with aortic fatty streaks in subjects aged 7 to 24 years.[172] Recently, Berenson and associates reported that serum concentrations of total cholesterol, triglycerides, LDL cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were strongly associated with the extent of lesions in the aorta and coronary arteries at autopsy in young persons who died of various causes, principally trauma.[173] Among these subjects, greater numbers of cardiovascular risk factors were directly associated with increased severity of asymptomatic coronary and aortic atherosclerosis.[173]

Epidemiological investigations in children across and within different populations have provided further evidence of the importance of cholesterol in pediatrics. In cross-population studies, children from countries with a high incidence of coronary artery disease in adults have higher cholesterol levels than do children from countries where adults have a low incidence of coronary artery disease. Within populations, elevated levels of total cholesterol and LDL-C in children have been associated with coronary artery disease in their adult relatives. In a study of the progeny of individuals with premature coronary artery disease, half had abnormal lipid profiles.[174]

The importance of monitoring lipid levels in childhood is further supported by evidence that children and adolescents with severe dyslipidemia are more likely than the general population to have abnormal lipid profiles as they grow older. Furthermore, long-term prospective studies have shown a strong association between cholesterol levels in young adult life and later risk of cardiovascular disease.[175]

SCREENING FOR DYSLIPIDEMIAS.

The distribution of fasting lipid and lipoprotein levels in children and adolescents is

displayed in Table 45-5 . The value of selective versus universal screening strategies for hyperlipidemia in childhood has been controversial. The National Cholesterol Education Program (NCEP) has advocated a selective screening strategy in which high-risk children older than 2 years are targeted for cholesterol screening.[176] High-risk children are defined as those whose parents or grandparents, at 55 years of age or younger, underwent diagnostic coronary arteriography and were found to have coronary atherosclerosis or suffered a documented myocardial infarction, angina pectoris, peripheral vascular disease, cerebrovascular

TABLE 45-5 -- FASTING LIPID AND LIPOPROTEIN LEVELS (mg/dl) IN CHILDREN BY AGE

	MALES			FEMALES		
	5%	**50%**	**95%**	**5%**	**50%**	**95%**
Cholesterol						
0-4 yr	114	155	203	112	156	200
5-9 yr	121	160	203	126	164	205
10-14 yr	119	158	202	124	160	201
15-19 yr	113	150	197	120	158	203
Triglycerides						
0-4 yr	29	56	98	34	64	112
5-9 yr	30	56	101	32	60	105
10-14 yr	32	66	125	37	75	131
15-19 yr	37	78	148	39	75	132
HDL cholesterol						
5-9 yr	38	56	74	36	53	73
10-14 yr	37	55	74	37	52	70
15-19 yr	30	46	63	35	52	74
LDL cholesterol						
5-9 yr	63	93	129	68	100	140
10-14 yr	64	100	140	68	97	132
15-19 yr	62	94	130	59	96	137

HDL=high-density lipoprotein; LDL=low-density lipoprotein.

disease, or sudden cardiac death; those whose parent(s) have a total cholesterol level of 240 mg/dl or higher; those for whom the health history of a parent or grandparent is unknown; or those whose personal health includes risk factors (e.g., diabetes). In such a selective screening strategy, adult cardiologists should refer the children of their patients with premature atherosclerotic cardiovascular disease for cholesterol testing and follow-up.

Some experts continue to recommend universal screening based on the observation that almost half of children with elevated cholesterol levels would be missed if screening were performed only on children with a positive family history.[177] [178] Moreover, a family history does not selectively identify the most severely affected children.[178] The relationship of parental history to children's lipid profiles appears to be associated with race.[177] Specifically, the Bogalusa Heart Study found that white children with a parental history of heart attack or diabetes were significantly more likely than black children to have elevated levels of total cholesterol and LDL-C, whereas in black children, a parental history of cardiovascular disease was more likely to be associated with low levels of HDL-C than in white children. Only 40 percent of white children and 21 percent of black children with elevated levels of LDL-C had a parent with a history of vascular diseases.[173]

The NCEP formulated recommendations for the management of hypercholesterolemia in children.[176] When children or adolescents have a documented history of premature cardiovascular disease in a parent or grandparent, the initial test should be a fasting lipoprotein analysis. Random screening in the nonfasting state should always include both a total cholesterol and HDL-C level because total cholesterol alone is a poor screening test in childhood.[179]

SECONDARY CAUSES.

Dyslipidemia most commonly results from a combination of genetic and dietary factors, but it can also be secondary to other systemic disorders. Indeed, the lipid profile can be affected by the use of medications and by endocrine and metabolic disorders, obstructive liver disease, or renal disease. Viral and bacterial infections, so common in childhood, can have profound effects on the lipid profile in the month after the onset of infection. In the first year of life, the most common causes of secondary hyperlipidemia are congenital biliary atresia and glycogen storage disease. Endocrine disorders (e.g., hypothyroidism and diabetes mellitus) and renal disease are the most common secondary causes later in childhood. Especially in adolescents, exogenous causes, such as medications, smoking, or alcohol, can affect the lipid profile. Secondary causes are usually evident from a careful review of the medical history and use of medications, together with a physical examination. When a secondary cause is not apparent, it may be appropriate to measure blood levels of thyroid-stimulating hormone, perform liver function tests, and obtain a urinalysis.

MANAGEMENT.

Because atherosclerosis is a continuous process throughout life, expert panels have suggested guidelines to reduce the risk of cardiovascular disease beginning in childhood. With the rationale that symptomatic adult coronary heart disease might be prevented or retarded by lowering of the LDL-C level in childhood and adolescence, the NCEP published guidelines for detection and management of childhood hyperlipidemia in a 1991 Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.[176] The NCEP expert panel recommended initial nonpharmacological intervention in hyperlipidemic children, including diet modification. To lower the average population cholesterol levels, a so-called prudent diet was recommended for all children older than 2 years. In addition to providing adequate nutrients and calories to maintain ideal body weight, this diet restricts total fat calories to 30 percent or less, saturated fat calories to 40 percent or less, and cholesterol intake to 300 mg/day or less. Indeed, the long-term safety, efficacy, and acceptability of lower fat diets in high-risk pubertal children have been demonstrated in the Dietary Intervention Study in Children (DISC).[180]

In children with severe familial hyperlipidemia, LDL-C rarely decreases by more than 15 percent with diet management alone. The NCEP guidelines recommended pharmacological therapy with bile acid sequestrants (cholestyramine or colestipol) for children older than 10 years who despite diet modification had an LDL-C level of 190 mg/dl or higher or a level of 160 mg/dl or higher with a family history of premature cardiovascular disease or with two other cardiovascular disease risk factors. Tonstad and coworkers studied 72 children in a randomized, placebo-controlled trial of cholestyramine and found only modest reductions (<20 percent) in LDL-C.[181] Furthermore, the inconvenience and unpalatability of bile acid sequestrants have limited the compliance and hence the usefulness of these agents in later childhood and adolescence.[182] In the pediatric population, alternative therapies with nicotinic acid are also poorly tolerated,[182] [183] and fibric acid derivatives have been associated with significant transaminase elevations.[181]

Since formulation of the NCEP guidelines, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have become the most widely used cholesterol-lowering agents in adults and have been shown to be effective in reducing mortality and morbidity from coronary heart disease in both primary and secondary prevention trials. In children, investigations of the use of HMG-CoA reductase inhibitors have included both early observational studies[182] [184] and short-term therapeutic trials in heterozygous familial dyslipidemias. In a placebo-controlled study, Knipscheer and colleagues treated 72 patients aged 8 to 16 years with pravastatin in doses ranging from 5 to 20 mg/day.[185] LDL-C fell by 23 to 32 percent and no adverse effects were observed. Lambert and associates performed a multicenter 8-week trial in which 69 adolescent boys (weight >27 kg) were randomized to four doses of lovastatin ranging from 10 to 40 mg/day after a 4-week placebo period; LDL-C was reduced 21 to 36 percent in a dose-response relationship.[186] Increases in HDL-C and apolipoprotein A1 were also observed. Neither serious clinical adverse events nor important elevations in

serum

transaminases or creatine kinase values were found. Most recently, in a randomized, placebo-controlled trial in 132 adolescent boys aged 10 to 17 years with familial hyperlipidemia, Stein and coauthors reported that lovastatin was effective in lowering LDL-C.[187] Comprehensive clinical and biochemical data on growth, hormonal, and nutritional status indicated no significant differences between the groups treated with lovastatin and placebo. Although HMG-CoA reductase inhibitor treatment of hyperlipidemic children and adolescents has been demonstrated to have short-term safety and efficacy in lowering the serum lipid profile, it is unknown whether such treatment affects preclinical disease in this age group.

Antioxidant vitamins may also have a role in the treatment of dyslipidemic children and adolescents. In a recent study in children with familial hyperlipidemia, impaired brachial vasoreactivity was improved after therapy with vitamin E and vitamin C.[188]

ASSESSMENT OF PRECLINICAL ATHEROSCLEROSIS.

Assessment of the effect of treatment of hyperlipidemia in childhood on vascular health is hampered by the long latency until occurrence of clinical disease. Therefore, the effects of therapies on preclinical markers of atherosclerosis are important. Methods of assessment of preclinical atherosclerosis that have been demonstrated to relate to risk factors in children include brachial artery flow-mediated dilation,[189] [189A] carotid intimal-medial thickness,[190] [191] and coronary artery calcification on electron beam computed tomography.[192]

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Infective Cardiomyopathy

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Chapter 46 - Valvular Heart Disease

EUGENE BRAUNWALD

Mitral Stenosis

ETIOLOGY AND PATHOLOGY

The predominant cause of mitral stenosis (MS) is rheumatic fever[1] (see Chap. 66) , and rheumatic involvement is present in 99 percent of stenotic mitral valves excised at the time of mitral valve replacement.[2] Approximately 25 percent of all patients with rheumatic heart disease have pure MS, and an additional 40 percent have combined MS and mitral regurgitation (MR).[3] [4] [5] Two thirds of all patients with rheumatic MS are female.

Rheumatic fever results in four forms of fusion of the mitral valve apparatus leading to stenosis: (1) commissural, (2) cuspal, (3) chordal, and (4) combined.[3] [4] [5] Thickening of the commissures alone occurs in 30 percent of patients, of the cusps alone in 15 percent, and of the chordae tendineae alone in 10 percent; in the remaining patients, thickening of more than one of these structures is involved. Characteristically, mitral valve cusps fuse at their edges, and fusion of the chordae tendineae results in thickening and shortening of these structures. The leaflets exhibit fibrous obliteration

and revascularization. The stenotic mitral valve is typically funnel-shaped, and the orifice is frequently shaped like a "fish mouth" or buttonhole, with calcium deposits in the valve leaflets sometimes extending to involve the valve ring, which may become quite thick (Fig. 46-1) . The thickened leaflets may be so adherent and rigid that they cannot open or shut, reducing or rarely even abolishing the first heart sound (S_1) and leading to combined MS and MR. When rheumatic fever results exclusively or predominantly in contraction and fusion of the chordae tendineae, with little fusion of the valvular commissures, dominant MR results.[6]

A debate continues about whether the anatomical changes in severe MS result from a smoldering rheumatic process or whether, once the valve has been deformed by the initial episode, the constant trauma produced by the turbulent blood flow leads to progressive fibrosis, thickening, and calcification of the valve apparatus.[7] Probably both processes are involved. Enlargement of the left atrium and resultant elevation of the left main stem bronchus, calcification of the left atrial wall, development of mural thrombi, and obliterative changes in the pulmonary vascular bed (see Chap. 53) may all result from chronic rheumatic MS.

Far less frequently, MS is congenital in etiology, and this form is observed almost exclusively in infants and young children (see Chap. 43) . Very rarely, MS is a complication of malignant carcinoid, systemic lupus erythematosus, rheumatoid arthritis,[8] the mucopolysaccharidoses of the Hunter-Hurler phenotype,[9] Fabry disease, and Whipple disease. Amyloid deposits may occur on rheumatic valves and contribute to the obstruction to left atrial emptying.[10] Methysergide therapy is an unusual but documented cause of MS.[11] Atrial septal defect is associated with MS, generally of rheumatic origin, in Lutembacher syndrome (see Chap. 43) . Obstruction to left atrial outflow may be caused by a left atrial tumor, particularly myxoma (see Chap. 49) ; ball-valve thrombus in the left atrium (usually associated with MS)[12] ; infective endocarditis with large vegetations; and a congenital membrane in the left atrium, i.e., cor triatriatum (see Chap. 43) . These conditions may simulate MS. Although calcification of the mitral annulus usually causes MR, MS may result when subvalvular or intravalvular extension is extensive.

PATHOPHYSIOLOGY

In normal adults, the cross-sectional area of the mitral valve orifice is 4 to 6 cm^2 . When the orifice is reduced to approximately 2 cm^2 , which is considered to represent *mild* MS, blood can flow from the left atrium to the left ventricle only if propelled by a small, although abnormal, pressure gradient. When the mitral valve opening is reduced to 1 cm^2 , which is considered to represent *critical* MS,[13] a left atrioventricular pressure gradient of approximately 20 mm Hg (and, therefore, in the presence of a normal left ventricular diastolic pressure, a mean left atrial pressure of approximately 25 mm Hg) is required to maintain normal cardiac

Figure 46-1 Rheumatic mitral stenosis. *A,* Moderate valvular changes including diffuse leaflet fibrosis, commissural fusion, and chordal thickening and fusion. In another patient, an atrial view (*B*) and subvalvular and aortic aspects (*C*) show prominent subvalvular involvement; severe subvalvular distortion is evident (arrow). *D,* Severe rheumatic mitral stenosis with specimen shown in apical four-chamber echocardiographic view, demonstrating small left ventricle (lv) and enlarged left atrium (la), right ventricle (rv), and right atrium (ra). Note the calcified stenotic valve (arrow) and prominent subvalvular changes (double arrows). *(A and D from Schoen FJ, St. John Sutton M: Contemporary issues in the pathology of valvular heart disease. Hum Pathol 18:568, 1987.)*

output at rest (Fig. 46-2 ; see also Fig. 11-14) . The elevated left atrial pressure, in turn, raises pulmonary venous and capillary pressures, resulting in exertional dyspnea. The first bouts of dyspnea in patients with MS are usually precipitated by exercise, emotional stress, sexual intercourse, infection, or atrial fibrillation, all of which increase the rate of blood flow across the mitral orifice and result in further elevation of the left atrial pressure.[14] [15]

In order to assess the severity of obstruction of the mitral valve (and, for that matter, of any valve), both the transvalvular pressure gradient and the transvalvular flow rate must be measured (see Chap. 11) .[16] The latter is a function not only of the cardiac output but also of the heart rate. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of cardiac output, tachycardia augments the transmitral valvular pressure gradient and elevates left atrial pressures further.[17] This explains the sudden occurrence of dyspnea and pulmonary edema in previously asymptomatic patients with MS who develop atrial fibrillation with a rapid ventricular rate. It also accounts for the equally rapid improvement in these patients when the ventricular rate is slowed by cardiac glycosides, beta-blocking agents, and/or heart-rate-slowing calcium antagonists, even when the transvalvular flow rate per minute remains constant. Hydraulic considerations dictate that at any given orifice size the transvalvular pressure gradient is a function of the square of the transvalvular flow rate.[18] Thus, a doubling of flow rate quadruples the pressure gradient, so that a stress such as exercise in patients with moderate or severe MS causes a marked elevation of left atrial pressure.[19] Pregnancy, hypervolemia, and hyperthyroidism all increase mitral valve flow and thereby the transvalvular pressure gradient.

Atrial contraction augments the presystolic transmitral valvular gradient by approximately 30 percent in patients with MS. Withdrawal of atrial transport when atrial fibrillation develops reduces cardiac output by about 20 percent.

Although the Gorlin formula (see Chap. 11) has been the benchmark for evaluating stenotic valvular orifices since 1951,[18] there is increasing evidence that valvular orifices are not rigid and that, in fact, as transvalvular flow increases, the orifice becomes distended. Accordingly, it has been proposed that stenosis can also be expressed as valvular resistance, the quotient of the mean transvalvular pressure gradient and the mean transvalvular flow.[20]

Figure 46-2 Schematic relationship of left ventricular, aortic, and pulmonary arterial wedge (PAW) pressures. Note that the higher the left atrial *v* wave, the earlier the pressure crossover and the earlier the mitral valve (MV) opening. The higher left atrial end-diastolic pressure with severe mitral stenosis (MS) also results in later closure of the mitral valve. PAW pressures are shown in severe mitral regurgitation (MR), mitral stenosis (MS), and normal (NL). The left ventricular diastolic pressure in mitral stenosis rises slowly, denoting the absence of a rapid filling wave.*(From Braunwald E, Turi ZG: Pathophysiology of mitral valve disease. In Wells FC, Schapiro LM [eds]: Mitral Valve Disease. London, Butterworths, 1996.)*

Intracardiac and Intravascular Pressures

LEFT ATRIAL AND RIGHT HEART PRESSURES.

In patients with MS and sinus rhythm, mean left atrial pressure is elevated, and the left atrial pressure pulse generally exhibits a prominent atrial contraction (*a*) wave and a gradual pressure decline after mitral valve opening (*y* descent). In patients with mild to moderate MS without elevated pulmonary vascular resistance, pulmonary arterial pressure may be normal or only minimally elevated at rest but rises during exercise. However, in patients with severe MS and those in whom the pulmonary vascular resistance is significantly increased, pulmonary arterial pressure is elevated when the patient is at rest. In very rare patients with extremely elevated pulmonary vascular resistance, pulmonary arterial pressure may exceed systemic arterial pressure. Further elevations of left atrial and pulmonary vascular pressures occur during exercise and/or tachycardia. With moderately elevated pulmonary arterial pressure (systolic pressure 30 to 60 mm Hg), right ventricular performance is usually maintained.[21] However, a greater elevation of pulmonary arterial pressure represents a serious impedance to emptying of the right ventricle. During exercise, patients with MS and severe pulmonary hypertension commonly fail to exhibit normal elevation of the right ventricular ejection fraction.

LEFT VENTRICULAR DIASTOLIC PRESSURE.

This pressure is normal in patients with isolated MS; however, coexisting MR, aortic valve lesions, systemic hypertension, ischemic heart disease, and cardiomyopathy may all be responsible for elevations of left ventricular diastolic pressure. In approximately 85 percent of patients with isolated MS, the left ventricular end-diastolic volume is within the normal range, whereas it is reduced in the remaining patients.[22] In approximately 25 percent of patients with isolated MS, the ejection fraction and other ejection indices of systolic performance (see Chap. 15) are below normal, most likely resulting in part from chronic reduction in preload and elevated afterload.[23] Regional hypokinesis is common,[24] perhaps caused by extension of the scarring process from the mitral valve into the adjacent posterior basal myocardium or by associated ischemic heart disease. Leftward displacement of the interventricular septum secondary to more rapid early filling of the right ventricle may be responsible for a reduction of left ventricular

compliance (left ventricular stiffening).[25] The left ventricular mass is normal or slightly reduced.[22]

The bulk of available evidence suggests that other than the posterior basal myocardium, left ventricular contractility is normal or only slightly impaired in the majority of patients with isolated MS.[26] Most patients with MS have a normal elevation of ejection fraction and a reduction of end-systolic volume during exercise.[27] Associated ischemic heart disease may, however, be responsible for myocardial dysfunction.[28]

PULMONARY HYPERTENSION.

Pulmonary hypertension in patients with MS results from (1) passive backward transmission of the elevated left atrial pressure; (2) pulmonary arteriolar constriction, which presumably is triggered by left atrial and pulmonary venous hypertension (reactive pulmonary hypertension); and (3) organic obliterative changes in the pulmonary vascular bed, which may be considered to be a complication of longstanding and severe MS[29] (see Chap. 53) . In time, severe pulmonary hypertension results in right-sided heart failure, with dilatation of the right ventricle and its annulus and secondary tricuspid and sometimes pulmonic regurgitation. These changes in the pulmonary vascular bed may also exert a protective effect; the elevated precapillary resistance makes the development of symptoms of pulmonary congestion less likely by tending to prevent blood from surging into the pulmonary capillary bed and damming up behind the stenotic mitral valve, although this protection occurs at the expense of a reduced cardiac output. In patients with severe MS, pulmonary vein-bronchial vein shunts occur.[30] Their rupture may cause hemoptysis. Patients with severe MS manifest a reduction in pulmonary compliance, an increase in the work of breathing, and a redistribution of pulmonary blood flow from the base to the apex.

CLINICAL AND HEMODYNAMIC FEATURES.

At any given severity of stenosis, the clinical picture is dictated largely by the levels of cardiac output and pulmonary vascular resistance. The response to a given degree of mitral obstruction may be characterized at one end of the hemodynamic spectrum by a normal cardiac output and a high left atrioventricular pressure gradient or, at the opposite end of the spectrum, by a markedly reduced cardiac output and low transvalvular pressure gradient. Thus, in some patients with moderately severe MS (mitral valve area=1.0 to 1.5 cm^2), cardiac output at rest may be normal and rises normally during exertion. In these patients, the high transvalvular pressure gradient causes marked elevation of left atrial and pulmonary capillary pressures. This leads to severe pulmonary congestion during exertion. In contrast, in the majority of patients with severe MS, cardiac output rises subnormally during exertion, thus reducing the pulmonary venous pressure and the severity of symptoms of pulmonary congestion more than would be the case if the cardiac output rose normally. In patients with severe MS (mitral valve area
1.0 cm^2), particularly when pulmonary vascular resistance is elevated, cardiac output is usually depressed at rest and may fail to rise at all during exertion. These patients frequently have severe weakness and fatigue secondary to a low cardiac output.

LEFT ATRIAL CHANGES.

The combination of mitral valve disease and atrial inflammation secondary to rheumatic carditis causes (1) left atrial dilatation, (2) fibrosis of the atrial wall, and (3) disorganization of the atrial muscle bundles. The last leads to disparate conduction velocities and inhomogeneous refractory periods. Premature atrial activation, due either to an automatic focus or to reentry, may stimulate the left atrium during the vulnerable period and thereby precipitate atrial fibrillation. The development of this arrhythmia correlates independently with the severity of the MS and the height of the left atrial pressure.[31] Atrial fibrillation is often episodic at first, but then becomes more persistent. Atrial fibrillation per se causes diffuse atrophy of atrial muscle, further atrial enlargement,[32] and further inhomogeneity of refractoriness and conduction. These changes, in turn, lead to irreversible atrial fibrillation.

CLINICAL MANIFESTATIONS

History

The principal symptom of MS is exertional dyspnea, largely the result of reduced pulmonary compliance. Dyspnea may be accompanied by cough and wheezing. Vital capacity is reduced, presumably owing to the presence of engorged pulmonary vessels and interstitial edema. Patients who have critical obstruction to left atrial emptying and dyspnea with ordinary activity (New York Heart Association [NYHA] Class III) generally have orthopnea as well and are at risk of experiencing attacks of frank pulmonary edema. The latter may be precipitated by effort, emotional stress, respiratory infection, fever, sexual intercourse, pregnancy, or atrial fibrillation with a rapid ventricular rate or other tachyarrhythmia. Indeed, pulmonary edema may be caused by any condition that increases flow across the stenotic mitral valve, either by increasing total cardiac output or by reducing the time available for blood flow across the mitral orifice to occur. In patients with a markedly elevated pulmonary vascular resistance, right ventricular function is often impaired.[33]

HEMOPTYSIS.

Wood has differentiated between several kinds of *hemoptysis* complicating MS.[14]

1. Sudden hemorrhage (previously called "pulmonary apoplexy"). Although the hemorrhage is often profuse, it is only rarely life-threatening.[34] It results from the rupture of thin-walled, dilated bronchial veins,[30] usually as a consequence of a sudden rise in left atrial pressure. With persistence of pulmonary venous hypertension, the walls of these veins thicken appreciably. This form of hemoptysis tends to disappear as MS progresses.

2. Blood-stained sputum associated with attacks of paroxysmal nocturnal dyspnea.
3. Pink, frothy sputum characteristic of acute pulmonary edema with rupture of alveolar capillaries.
4. Pulmonary infarction, a late complication of MS associated with heart failure.
5. Blood-stained sputum complicating chronic bronchitis. The edematous bronchial mucosa in patients with chronic MS increases the likelihood of chronic bronchitis, which is a common complication of MS, particularly in Great Britain.

CHEST PAIN.

A small percentage, perhaps 15 percent, of patients with MS experience chest discomfort that is indistinguishable from angina pectoris.[14] This symptom may be caused by severe right ventricular hypertension secondary to the pulmonary vascular disease or by concomitant coronary atherosclerosis.[28] Rarely, chest pain may be secondary to coronary obstruction caused by coronary embolization.[35] In many patients, however, a satisfactory explanation for the chest pain cannot be uncovered even after complete hemodynamic and angiographic studies.

SYSTEMIC EMBOLISM.[36] [36A]

Before the advent of surgical treatment, this serious complication of MS developed in at least 20 percent of patients at some time during the course of their disease.[37] Before the era of anticoagulant therapy and surgical treatment, approximately 25 percent of all fatalities in patients with mitral valve disease were secondary to systemic embolism. The tendency for development of systemic embolization correlates directly with the patient's age and the size of the left atrial appendage and inversely with the cardiac output; 80 percent of patients with MS in whom systemic emboli develop are in atrial fibrillation. When embolization occurs in patients in sinus rhythm, the possibility of transient atrial fibrillation or underlying infective endocarditis should be considered. There is no simple correlation between the incidence of embolism on the one hand and the size of the mitral orifice on the other. Indeed, embolism may be the first symptom of MS and may occur in patients with mild MS even before the development of dyspnea.

Because thrombi are found in the left atrium at operation in only a minority of patients with a history of recent embolism, it is likely that only fresh clots are discharged. Approximately half of all clinically apparent emboli are found in the cerebral vessels. Coronary embolism may lead to myocardial infarction and/or angina pectoris, and renal emboli may be responsible for the development of systemic hypertension. Emboli are recurrent and multiple in approximately 25 percent of patients who develop this complication. Rarely, massive thrombosis develops in the left atrium, resulting in a pedunculated ball-valve thrombus, which may suddenly aggravate obstruction to left atrial outflow when a specific body position is assumed or may cause sudden death.[12] Similar consequences occur in patients with free-floating thrombi in the left atrium. These two conditions are usually characterized by variability in the physical findings, often on a positional basis. They are very hazardous and require surgical treatment, often as an emergency.

INFECTIVE ENDOCARDITIS (see also Chap. 47) .

This complication tends to occur *less frequently* on rigid, thickened, calcified valves and is therefore more common in patients with mild MS than those with severe MS.

OTHER SYMPTOMS.

Compression of the left recurrent laryngeal nerve by a greatly dilated left atrium, enlarged tracheobronchial lymph nodes, and a dilated pulmonary artery may cause hoarseness (Ortner syndrome).[38] A history of repeated hemoptysis is common in patients with pulmonary hemosiderosis. Systemic venous hypertension, hepatomegaly, edema, ascites, and hydrothorax are all signs of severe MS with elevated pulmonary vascular resistance and right-sided heart failure.

Physical Examination[39] [40]

Patients with severe MS, a low cardiac output, and systemic vasoconstriction may exhibit the so-called *mitral facies,* characterized by pinkish-purple patches on the cheeks.[14] The *arterial pulse* is usually normal, but in patients with a reduced stroke volume, the pulse may be small in volume. The *jugular venous pulse* usually exhibits a prominent *a* wave in patients with sinus rhythm (see Fig. 4-5) and elevated pulmonary vascular resistance. In patients with atrial fibrillation, the *x* descent of the jugular venous pulse disappears, and there is only one crest, a prominent *v* or *c-v* wave, per cardiac cycle. *Palpation* of the cardiac apex usually reveals an inconspicuous left ventricle; the presence of either a palpable presystolic expansion wave or an early diastolic rapid filling wave speaks strongly against serious MS. A readily palpable, tapping S_1 suggests that the anterior mitral valve leaflet is pliable. When the patient is in the left lateral recumbent position, a diastolic thrill of MS may be palpable at the apex. Often a right ventricular lift is felt in the left parasternal region in patients with pulmonary hypertension. A markedly enlarged right ventricle may displace the left ventricle posteriorly and produce a prominent apex beat that can be confused with a left ventricular lift. A loud pulmonic closure sound (P_2) may be palpable in the second left intercostal space in patients with MS and pulmonary hypertension.

AUSCULTATION.

The auscultatory features of MS (Fig. 46-3; see also Figs. 4-16 *B* and 4-34) include an accentuated S_1 with prolongation of the Q-S_1 interval, correlating with the level of the left atrial pressure. Accentuation of S_1 occurs when the mitral valve leaflets are flexible. [41] It is caused, in part, by the rapidity with which left ventricular pressure rises at the time of mitral valve closure as well as by the wide closing excursion of the leaflets.[42] Marked calcification and/or thickening of the mitral valve leaflets reduces the amplitude of S_1 , probably because of diminished motion of the leaflets. As pulmonary arterial pressure rises, P_2 at first becomes accentuated and widely transmitted and can often be readily heard at both the mitral and the aortic areas. With further elevation of pulmonary arterial

pressure,

Figure 46-3 The classic auscultatory signs of MS in patients in sinus rhythm. These include a presystolic murmur, a loud S_1 , an opening snap (OS), and a mid-diastolic murmur (DR, low-pitched, decrescendo diastolic rumble). These signs may be accentuated or at times may only be heard by placing the patient in the left lateral decubitus position. These signs are helpful in assessing the severity of MS; as MS becomes more severe, the S_2 -OS interval is shortened, and the length of the mid-diastolic rumble is increased. *(From Kawanishi DT, Rahimtoola SH: Mitral stenosis. In Rahimtoola SH [ed]: Valvular Heart Disease. Atlas of Heart Diseases, vol. 11. Braunwald E, series ed. Philadelphia, Current Medicine, 1997, pp 8.1-8.24.)*

splitting of S_2 narrows because of reduced compliance of the pulmonary vascular bed, and this shortens the "hangout interval." Finally, S_2 becomes single and accentuated. Other signs of severe pulmonary hypertension include a nonvalvular pulmonic ejection sound that diminishes during inspiration, owing to dilatation of the pulmonary artery; a systolic murmur of tricuspid regurgitation; a Graham Steell murmur of pulmonic regurgitation; and an S_4 originating from the right ventricle. An S_3 originating from the left ventricle is absent in patients with MS unless significant mitral or aortic regurgitation coexists.

The *opening snap* (OS) of the mitral valve is caused by a sudden tensing of the valve leaflets after the valve cusps have completed their opening excursion. The OS occurs when the movement of the mitral dome into the left ventricle suddenly stops.[42] It is most readily audible at the apex, using the diaphragm of the stethoscope. The OS can usually be differentiated from P_2 because the OS occurs later, unless right bundle branch block is present. The mitral valve cannot be totally rigid if it produces an OS, which is usually accompanied by an accentuated S_1 . Calcification confined to the tip of the mitral valve leaflets does not preclude an OS, although calcification of both the body and the tip does. The mitral OS follows A_2 by 0.04 to 0.12 second; this interval varies inversely with the left atrial pressure.[41] A short A_2 -OS interval is a reliable indicator of severe MS.

The Diastolic Murmur of MS.

This murmur is a low-pitched, rumbling murmur, best heard at the apex, with the bell of the stethoscope and with the patient in the left lateral recumbent position. When this murmur is soft, it is limited to the apex, but when louder, it may radiate to the left axilla or the lower left sternal area. Although the intensity of the diastolic murmur is not closely related to the severity of stenosis, the *duration* of the murmur is a guide to the severity of mitral valve narrowing. The murmur persists for as long as the left atrioventricular pressure gradient exceeds approximately 3 mm Hg. The murmur usually commences immediately after the OS. In mild MS, the early diastolic murmur is brief, but in the

presence of sinus rhythm it resumes in presystole. In severe MS, the murmur is holodiastolic.

The *diastolic rumbling murmur* of MS may be masked by the presence of a thick chest wall, pulmonary emphysema, and a low cardiac output with a low flow rate across the mitral valve. This murmur may be sharply localized and thus missed unless palpation is used to detect the apex of the left ventricle and to pinpoint the area at which auscultation should be carried out. In so-called "silent" MS, there is usually marked right ventricular enlargement. Consequently, the right ventricle occupies the cardiac apex, the left ventricle is rotated posteriorly, and cardiac output is reduced, so that the murmur either is not audible at all or can be heard only in the mid- or posterior axillary line. Auscultation of the murmur is facilitated by placing the patient in the left lateral position and auscultating during expiration after having the patient do a few sit-ups, walk up a flight of stairs, or other maneuvers described later.

DYNAMIC AUSCULTATION (See also Chap. 4) .

The diastolic murmur and OS of MS are often reduced during inspiration and augmented during expiration,[39] [40] which is the opposite of what occurs when these findings are secondary to tricuspid stenosis (see p. 1690). During inspiration, the A_2 -OS interval widens, and three sequential sounds (A_2 , P_2 , and OS) may be audible. Sudden standing and the resultant reduction of venous return lower the left atrial pressure and widen the A_2 -OS interval; this maneuver is useful in distinguishing an A_2 -OS combination from a split S_2 , which narrows on standing. In contrast, the A_2 -OS interval is significantly narrowed during exercise as left atrial pressure rises. The diastolic rumbling murmur of MS is reduced during the strain of a Valsalva maneuver and in any condition in which transmitral valve flow rate declines. Amyl nitrite inhalation, coughing, isometric or isotonic exercise, and sudden squatting are all useful in accentuating a faint or equivocal murmur of MS.

DIFFERENTIAL DIAGNOSIS.

The *Carey-Coombs murmur* of acute rheumatic fever is a sign of active mitral valvulitis and can be confused with the murmur of MS. The Carey-Coombs murmur is a soft early diastolic murmur, usually varies from day to day, and is higher pitched than the diastolic rumbling murmur of established MS. In pure, severe MR--indeed in any condition in which flow across a nonstenotic mitral valve is increased--there may also be a short diastolic murmur following an S_3 . *Left atrial myxoma* may produce auscultatory findings similar to those in rheumatic valvular MS (see Chap. 49) .

A high-frequency early systolic murmur is audible along the lower left sternal border in one-third of patients with MS. This should be distinguished from the apical (often holosystolic or late systolic) murmur of MR. In addition, a *pansystolic murmur of tricuspid regurgitation* and an S_3 originating from the right ventricle may be audible in the 4th intercostal space in the left parasternal region in patients with severe MS. These signs, which are secondary to pulmonary hypertension, may be confused with the

findings of MR. However, the inspiratory augmentation of the

murmur and of the S_3 and the prominent *v* wave in the jugular venous pulse aid in establishing that the murmur originates from the tricuspid valve. A high-pitched decrescendo diastolic murmur along the left sternal border in patients with MS and pulmonary hypertension is usually due to aortic regurgitation but occasionally represents a Graham Steell murmur of pulmonary regurgitation. The latter, when present, characteristically increases during inspiration.

LABORATORY EXAMINATION

ELECTROCARDIOGRAPHY (See also Chap. 5) .

The electrocardiogram (ECG) is relatively insensitive for detecting mild MS, but it does show characteristic changes in moderate or severe obstruction.[43] Left atrial enlargement (P-wave duration in lead II
0.12 sec and/or a P-wave axis between +45 and -30 degrees) is a principal ECG feature of MS and is found in 90 percent of patients with significant MS and sinus rhythm.[44] The ECG signs of left atrial enlargement correlate more closely with left atrial volume than with left atrial pressure and often regress following successful valvotomy.[14] Atrial fibrillation usually develops in the presence of preexisting ECG evidence of left atrial enlargement and is related to the size of the chamber, the extent of fibrosis of the left atrial myocardium, the duration of atriomegaly, and the age of the patient.

Whether or not there is ECG evidence of right ventricular hypertrophy depends largely on the height of right ventricular systolic pressure. Approximately half of all patients with right ventricular systolic pressures between 70 and 100 mm Hg manifest the ECG criteria for right ventricular hypertrophy, including both a mean QRS axis greater than 80 degrees in the frontal plane and an R:S ratio greater than 1.0 in lead V_1 . Other patients with this degree of pulmonary hypertension have no frank evidence of right ventricular hypertrophy, but the R:S ratio fails to increase from the right to the midprecordial leads. When right ventricular systolic pressure is greater than 100 mm Hg in patients with isolated or predominant MS, ECG evidence of right ventricular hypertrophy is found quite consistently.

The *QRS axis in the frontal plane* correlates roughly with the severity of valve obstruction and with the level of pulmonary vascular resistance in patients with pure MS. Thus, a mean frontal axis between 0 and +60 degrees suggests that the mitral valve area is greater than 1.3 cm^2 , whereas an axis of more than 60 degrees suggests that the valve area is less than 1.3 cm^2 . In patients in whom pulmonary vascular resistance exceeds 650 dyne-sec·cm^{-5} , the mean axis is usually greater than +110 degrees. In patients whose pulmonary artery systolic pressure approaches systemic levels, the

mean axis averages +150 degrees.[45]

RADIOLOGICAL FINDINGS (See also Figs. 8-7 *B* and 8-25) .

Although their cardiac silhouette may be normal in the frontal projection, patients with hemodynamically significant MS almost invariably have evidence of left atrial enlargement on the lateral and left anterior oblique views. Extreme left atrial enlargement rarely occurs in pure MS; when it is present, MR is usually severe. Enlargement of the pulmonary artery, right ventricle, and right atrium (as well as the left atrium) is commonly seen in patients with severe MS. Occasionally, calcification of the mitral valve is evident on the chest roentgenogram, but, more commonly, fluoroscopy is required to detect valvular calcification.

Radiological changes in the lung fields indirectly reflect the severity of MS. Interstitial edema, an indication of severe obstruction, is manifested as Kerley B lines (dense, short, horizontal lines most commonly seen in the costophrenic angles). This finding is present in 30 percent of patients with resting pulmonary arterial wedge pressures less than 20 mm Hg and in 70 percent of patients with pressures greater than 20 mm Hg. Severe, longstanding mitral obstruction often results in Kerley A lines (straight, dense lines up to 4 cm in length running toward the hilum) as well as the findings of pulmonary hemosiderosis and rarely of parenchymal ossification. Pulmonary edema is seldom evident.

ANGIOGRAPHY.

Angiograms exposed in the right and left anterior oblique projections afford the best views of the mitral valve. Although contrast material should ideally be injected into the left atrium, it is often possible to achieve good visualization of the left side of the heart by injecting a large volume of contrast material into the main pulmonary artery. Such angiograms provide an assessment of left atrial size, may demonstrate thickening and reduced motion of the valve leaflets, and outline large intraluminal thrombi.[46] Left ventriculography makes possible simultaneous assessment of left ventricular contractile function and of the subvalvular mitral apparatus. However, echocardiography has largely superseded angiography in the evaluation of patients with MS or suspected MS.

ECHOCARDIOGRAPHY (See also Chap. 7) .

This is now the cornerstone of the diagnostic assessment of patients with MS. Two-dimensional transthoracic or transesophageal

Figure 46-4 Two-dimensional transthoracic parasternal short-axis view of the mitral valve orifice during diastole, demonstrating the echocardiographic method of mitral valve area calculation. The innermost border of the mitral orifice was planimetered with the use of a light-pen system to obtain the area (in cm^2). *(Reproduced with permission from Smith MD et al: Comparative accuracy of two-dimensional echocardiography and Doppler pressure half-time methods in assessing severity of mitral stenosis in patients with and without prior commissurotomy. Circulation 73:100, 1986. Copyright 1986 American*

Heart Association.)

echocardiograms of a thickened, calcified, stenotic rheumatic valve demonstrate increased acoustic impedance and fusion of the mitral valve leaflets and poor leaflet separation in diastole (Fig. 46-4) . The leaflets fail to close normally in mid-diastole and may not reopen widely during atrial contraction when sinus rhythm is present. The left atrium is usually enlarged, and in isolated MS the left ventricular cavity is normal or reduced in size. Two-dimensional echocardiography (see Figs. 7-47 , 7-48 , 7-49 , 7-50 , 7-51 , and 7-52) may be helpful in recognizing left atrial thrombus preoperatively and in assessing mitral valve calcification and left ventricular contractility.[47] With progressive thickening and fibrosis of the leaflets, the orifice becomes fixed and can then often be imaged directly and measured. Two-dimensional echocardiography also provides information on the pliability of the leaflets, the extent of valvular calcification, thickening of the subvalvular apparatus, and fusion and retraction of the chordae tendineae, as well as calcification of the mitral annulus. This technique allows determination of left ventricular size and function and can also evaluate the aortic valve. The two-dimensional echocardiogram is helpful in determining whether the patient with MS is a suitable candidate for balloon mitral valvuloplasty (see p. 1651). Transesophageal two-dimensional echocardiography provides images of the mitral valve that are superior to those obtained by transthoracic imaging and is more sensitive in detecting left atrial thrombus. Pedunculated and free-floating thrombi are also usually readily detected by this technique. Transesophageal echocardiography is necessary when the transthoracic signal is inadequate.

Doppler echocardiography is the most accurate noninvasive technique available for quantifying the severity of MS[47] (see Fig. 7-51) and for estimating pulmonary arterial pressure.[48] [49] Color flow Doppler imaging can enhance the accuracy of the Doppler data by determining whether MR, aortic regurgitation, and other valvular abnormalities coexist. The pulmonary arterial pressure also can be estimated from the tricuspid regurgitation velocity signal.

In a patient with MS, a detailed echocardiographic examination, including two-dimensional echocardiography (transthoracic or transesophageal), a Doppler study, and color flow Doppler imaging, can usually provide sufficient information to develop a therapeutic plan without the need for cardiac catheterization (see below).[50]

MANAGEMENT

Medical Treatment

Patients with MS due to rheumatic heart disease should receive penicillin prophylaxis for beta-hemolytic streptococcal infections and prophylaxis for infective endocarditis (see Chaps. 47 and 66) . Anemia and infections should be treated promptly and aggressively in patients with valvular heart disease. Adolescents and young adults with

severe valvular heart disease should be advised to avoid entering occupations requiring strenuous exertion. Asymptomatic patients with moderate MS should be reevaluated yearly.[51] Heavy exertion is contraindicated in symptomatic patients.

In symptomatic patients with mitral valve disease, considerable improvement occurs with the administration of oral diuretics and the restriction of sodium intake. Digitalis glycosides do not alter the hemodynamics and usually do not benefit patients with MS and sinus rhythm,[52] but these drugs are of value in slowing the ventricular rate in patients with atrial fibrillation and in treating patients with right-sided heart failure. Hemoptysis is managed by measures designed to reduce pulmonary venous pressure, including sedation, assumption of the upright position, and aggressive diuresis. Beta-blocking agents and rate-slowing calcium antagonists may increase exercise capacity by reducing heart rate in patients with sinus rhythm[53] and especially in patients with atrial fibrillation.

Anticoagulant therapy is helpful in preventing venous thrombosis and pulmonary embolism in patients who have experienced one or more previous pulmonary embolic episodes; in patients who are at high risk of systemic embolization, i.e., with persistent or transient atrial fibrillation (especially elderly patients > 70 years of age); and in those with previous systemic emboli. Treatment with warfarin, to maintain the international normalized ratio (INR) between 2.0 and 3.0, is indicated.[54] However, no firm evidence exists that anticoagulant therapy reduces the incidence of pulmonary or systemic embolism in patients in sinus rhythm in whom such episodes have not previously occurred.

TREATMENT OF ARRHYTHMIAS.

Frequent premature atrial contractions often presage atrial fibrillation. The administration of antiarrhythmic agents (see Chap. 23) may be effective in preventing this complication. However, once atrial fibrillation has developed, these agents may be ineffective in restoring sinus rhythm because of the pathological changes that occur in the atrium secondary to the arrhythmia itself. After electrical cardioversion, sinus rhythm can often be maintained with antiarrhythmic agents, especially in young patients with mild MS but without marked left atrial enlargement who have been in atrial fibrillation less than 6 months and who are maintained on adequate doses of quinidine.

Immediate treatment of atrial fibrillation should include intravenous heparin followed by oral warfarin. The ventricular rate should be slowed with intravenous digoxin and a beta-blocking agent or rate-slowing calcium antagonist. An effort should be made to reestablish sinus rhythm by a combination of pharmacological treatment and cardioversion. If cardioversion is planned in a patient who has had atrial fibrillation for more than 24 hours before the procedure, anticoagulation with warfarin for more than three weeks is indicated. Alternatively, if a transesophageal echocardiogram shows no atrial thrombus, immediate cardioversion can be carried out using intravenous heparin.[55] Paroxysmal atrial fibrillation and repeated conversions, spontaneous or induced, carry the risk of embolization. In patients who cannot be converted or maintained in sinus rhythm, digitalis should be used to maintain the ventricular rate at rest at approximately 60 beats/min. If this is not possible, small doses of a beta-blocking

agent, such as atenolol (25 mg daily), may be added. Multiple repeat cardioversions are *not* indicated if the patient fails to sustain sinus rhythm while on adequate doses of an antiarrhythmic. Patients with chronic atrial fibrillation who undergo open mitral valve repair or replacement may undergo the Cox maze procedure (atrial compartment operation). More than 80 percent of patients undergoing this procedure can be maintained in sinus rhythm postoperatively[56] and can regain normal atrial function.[57]

NEED FOR CATHETERIZATION.

There has been considerable debate concerning the need for routine cardiac catheterization in determining whether valvotomy is indicated.[51] A careful clinical evaluation and noninvasive assessment, particularly using two-dimensional and Doppler echocardiography, can provide sufficient information to permit an informed decision in the majority of patients. Preoperative catheterization is recommended for the following patients with MS: (1) patients who have a discrepancy between clinical and echocardiographic findings; hemodynamic measurements during exercise are often useful in these patients; (2) patients who have associated chronic obstructive pulmonary disease in whom it is important to determine the contribution of MS to the symptoms; (3) patients in whom left atrial myxoma should be excluded; (4) patients who have angina pectoris or angina-like chest pain in whom associated coronary artery disease must be excluded; and (5) men over 40 years of age and women over 50 years of age who have risk factors for coronary artery disease or a positive stress test and in whom surgery is planned; it is important to ascertain whether or not bypass grafting is indicated for those patients at risk of having coexisting coronary artery disease. Critical narrowing of one or more coronary vessels occurs in approximately 25 percent of all adults with severe MS. This finding is more common in men over 45 years of age who have angina and risk factors for coronary artery disease.[28]

Natural History

The development of effective surgical treatment has obscured our understanding of the natural history of MS (Fig. 46-5) and, for that matter, of all valvular lesions. Although few meaningful data are available, it appears that in temperate zones, such as the United States and Western Europe, patients who develop acute rheumatic fever have an asymptomatic period of approximately 15 to 20 years before symptoms of MS develop. It then takes approximately 5 to 10 years for most patients to progress from mild disability (i.e., early NYHA Class II) to severe disability (i.e., NYHA Class III or IV). The progression is much more rapid in patients in tropical and subtropical areas,[58] in Polynesians, and in Alaskan Inuit. Both economic and genetic conditions may play a role. In India, critical MS may be present in children as young as 6 to 12 years old. In North America and Western Europe, however, symptoms develop

Figure 46-5 Schematic representation of the subsequent life history after the initial development of symptoms in a large group of patients with mitral stenosis. The colored solid circles and colored lines indicate a surgical procedure. The dashed lines represent estimated survival of patients who are not receiving the surgical procedure. MC = mitral commissurotomy; MVR = mitral valve replacement; TA = tricuspid annuloplasty; AVR = aortic valve replacement. *(From Kirklin JW, Barratt-Boyes BG [eds]:*

more slowly and occur most commonly between the ages of 45 and 65.[51] Two echocardiographic studies have reported hemodynamic progression in patients with MS who had not undergone surgery[59] [60] ; there was considerable interpatient variability, but on average the mitral valve area decreased by 0.09 cm^2 /yr.

In the *presurgical era,* Olesen found 62 percent 5-year survival rates and 38 percent 10-year survival rates among medically treated patients with MS in NYHA Class III but only 15 percent 5-year survival rates among patients in Class IV.[61] Among asymptomatic patients with MS treated medically, 40 percent deteriorated or died within 10 years. Among mildly symptomatic patients (NYHA Class II), the comparable number was 80 percent.[62] In medically treated patients with MS or with combined MS and MR, Munoz and associates found a 45 percent 5-year survival rate.[63] In a comparable group of patients who underwent mitral valvotomy, the 5-year survival rate was substantially better. Horstkotte et al. reported a 5-year survival rate of 44 percent in patients with symptomatic MS who refused valvotomy (Fig. 46-6) . [64]

Valvotomy

Indications

Patients with MS who are asymptomatic or minimally symptomatic frequently remain so for years. However, once moderate symptoms develop (NYHA Class II), if the stenosis is not relieved mechanically, the disease may progress relatively rapidly, as already discussed (Table 46-1) . Valvotomy (percutaneous balloon mitral valvuloplasty [BMV] or surgical valvotomy) should therefore be carried out in symptomatic patients with moderate to severe MS (i.e., a mitral valve orifice area < approximately 1.0 cm^2 /m^2 body surface area [BSA] or <1.5 to 1.7 cm^2 in normal-sized adults). It is also indicated in patients with mild stenosis (orifice area 1.0 to 1.5 cm^2 /m^2 who are symptomatic during ordinary activity and who develop pulmonary arterial systolic pressures exceeding 60 mm Hg or mean pulmonary capillary wedge pressures exceeding 25 mm Hg during exercise.[51]

Treatment must be individualized. For instance, mechanical relief of obstruction might well be deferred in a retired, mildly symptomatic, sedentary septuagenarian with a mitral valve orifice of 0.8 cm^2 /m^2 BSA. On the other hand, a 30-year-old laborer whose family's economic well-being depends on his continued physical exertion might be an excellent candidate for mechanical relief of obstruction, although his mitral valve orifice size is 1.2 cm^2 /m^2 BSA. Some years ago, I saw a 33-year-old woman with MS who

Figure 46-6 Natural history of 159 patients with isolated mitral stenosis (open circles) or mitral

regurgitation (open triangles) who were not operated upon (even though the operation was indicated) compared with patients treated with valve replacement for mitral stenosis (solid circles) or mitral regurgitation (solid triangles). The expected survival rate in the absence of mitral valve disease is indicated by the upper curve (dashed line). *(From Horstkotte D, Niehues R, Strauer BE: Pathomorphological aspects, aetiology, and natural history of acquired mitral valve stenosis. Eur Heart J 12(Suppl):55-60, 1991.)*

had had hemoptysis and pulmonary edema during the second trimester of a pregnancy 2 years previously. She then became asymptomatic but wished to have another child. Hemodynamic study showed a pulmonary artery wedge pressure of 17 mm Hg and a mitral orifice area of 1.7 cm^2/m^2 BSA. This patient underwent prophylactic BMV

TABLE 46-1 -- APPROACHES TO MECHANICAL RELIEF OF MITRAL STENOSIS

APPROACH	ADVANTAGES	DISADVANTAGES
Closed surgical valvotomy	Inexpensive	No direct visualization of valve
	Relatively simple	Only feasible with flexible, noncalcified valves
	Good hemodynamic results in selected patients	
		Contraindicated if MR>2+
	Good long-term outcome	Surgical procedure with general anesthesia
Open surgical valvotomy	Visualization of valve allows directed valvotomy	Best results with flexible, noncalcified valves
	Concurrent annuloplasty for MR is feasible	Surgical procedure with general anesthesia
Valve replacement	Feasible in all patients regardless of extent of valve calcification or severity of MR	Surgical procedure with general anesthesia
		Effect of loss of annular-papillary muscle continuity on LV function
		Prosthetic valve
		Chronic anticoagulation
Balloon mitral valvotomy	Percutaneous approach	No direct visualization of valve
	Local anesthesia	Only feasible with flexible, noncalcified valves
	Good hemodynamic results in selected patients	
		Contraindicated if MR>2+
	Good long-term outcome	

LV=left ventricular; MR=mitral regurgitation.

From Otto CM: Valvular Heart Disease. Philadelphia, WB Saunders, 1999, p 261.

because it was deemed that another pregnancy would have resulted in serious symptoms. However, there is no evidence that valvotomy improves the prognosis of patients with no or only slight functional impairment. Therefore, valvotomy is *not* ordinarily indicated in patients who are entirely asymptomatic. Because of the high rate of recurrence, mechanical relief of obstruction is also indicated in patients with MS who have had a previous systemic embolism, even if they are otherwise asymptomatic and even though there is no *definitive* evidence that the incidence of recurrent emboli will be significantly reduced. Anticoagulants should be administered to such patients up to the time of the procedure.

Balloon Mitral Valvotomy (See also Chap. 38)

This percutaneous technique consists of advancing a small balloon flotation catheter across the interatrial septum (after transseptal puncture), enlarging the opening, advancing a large (23 to 25 mm) hourglass-shaped balloon (the Inoue balloon), and inflating it within the orifice. Alternatively, two smaller (12 to 18 mm) balloons may be employed.[65] Commissural separation and fracture of nodular calcium appear to be the mechanisms responsible for improvement in valvular function. In several series, the hemodynamic results of BMV have been quite favorable (Fig. 46-7) , with reduction of the transmitral pressure gradient from an average of approximately 18 mm Hg to 6 mm Hg, a small (average 20 percent) increase in cardiac output, and an average doubling of the calculated mitral valve area from 1.0 to 2.0 cm^2 . Although the double-balloon technique may result in a slightly greater valve opening, the clinical outcomes of the two approaches are similar.[66] Improvement in exercise tolerance has paralleled the favorable hemodynamic changes.

Results are especially impressive in younger patients without valvular thickening or calcification. Elevated pulmonary vascular resistance declines rapidly, although usually not completely.[67] [67A] The reported mortality rate has ranged from 1 to 2 percent. Complications include cerebral emboli and cardiac perforation, each in approximately 1

Figure 46-7 Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after balloon mitral valvotomy in a patient with severe mitral stenosis. *(Courtesy of Raymond G. McKay, M.D.)*

Figure 46-8 Determination of echocardiographic score. Leaflet rigidity, thickening, calcification, and the amount of subvalvular disease are graded 0 to 4, depending on the severity of the abnormality. The sum

of the four factors equals the echocardiographic score. *(From Block PC: Mitral balloon valvotomy: Why, when and how? Cardiol Rev 2:19, 1994.)*

percent of patients, and the development of MR severe enough to require operation in another 2 percent (approximately 15 percent develop lesser, but still undesirable, degrees of MR). Approximately 5 percent of patients are left with a small residual atrial septal defect, but this closes or decreases in size in the majority. Rarely, the defect is large enough to cause right-sided heart failure. Results are surgeon-dependent and patients should be referred to experienced teams.[68] [69] [69A]

The indications for BMV are the same as those for valvotomy (discussed below). A combination of significant symptoms and documented MS generally serves as the indication. Detailed two-dimensional and Doppler echocardiographic studies are indicated before a decision is made. Left atrial thrombus must be excluded by echocardiography.

An echocardiographic scoring system developed by Wilkins and colleagues[70] has been found to be particularly valuable in patient selection and has been widely adopted. Leaflet rigidity, leaflet thickening, valvular calcification, and subvalvular disease are each scored from 0 to 4 (Fig. 46-8) . Rigid, thickened valves with extensive subvalvular fibrosis and calcification lead to suboptimal results. A score of 8 or less is usually associated with an excellent immediate and long-term result, whereas scores exceeding 8 are associated with less impressive results (Fig. 46-9) , including the risk of development of MR.[71] Fluoroscopically visible calcium[72] and coexisting MR[73] are additional important predictors of an adverse outcome.[72] Transesophageal echocardiography provides a precise assessment of mitral valve structure and function and evaluation of accompanying MR and left atrial thrombus (a contraindication to BMV).[74] It also provides an accurate assessment of outcome. Three-dimensional echocardiography has also been found to be useful in assessing indications for BMV.[75] The findings on echocardiography affect the outcome of both open and closed surgical valvotomy in a similar manner. A trial in which patients with severe MS were randomized to undergo either BMV or open surgical valvotomy resulted in similar clinical results from the two techniques. Indeed, after 3 years, mitral valve area was greater in the balloon catheter-treated group.[76] In patients with favorable anatomical findings, survival without functional disability or need for surgery or repeat BMV

Figure 46-9 Event-free survival after balloon mitral valvotomy for 736 patients enrolled in the Balloon Valvuloplasty Registry who were stratified by baseline echocardiographic morphology score: less than 8 (solid line), 8 to 12 (short-dashed line), or more than 12 (long-dashed line); P < 0.0001. *(From Dean LS, Mickel MC, Bonan R, et al: Four-year follow-up of patients undergoing percutaneous balloon mitral commissurotomy: A report from the National Heart, Lung and Blood Institute Balloon Valvuloplasty Registry. J Am Coll Cardiol 28:1452, 1996.)*

is 70 percent at 7 years.[77] [78] [79] Excellent results have also been reported in children[80]

and adolescents[81] in developing nations, where patients tend to be younger. These young patients usually have quite pliable valves, which are ideal for BMV.[82]

Percutaneous BMV is the procedure of choice in patients who have symptomatic, hemodynamically severe stenosis with an echocardiographic score of 8 or less and without left atrial thrombus.[69] The lower cost and morbidity are obvious advantages. BMV can also be the initial procedure in patients with symptomatic, severe MS and less favorable valves (echocardiographic score > 8 and/or dense calcification on fluoroscopic examination).[65] [72] However, the failure rate is considerable in these patients, and they may require surgical treatment, most often mitral valve replacement. BMV also has acceptable results in patients with accompanying mild or moderate aortic regurgitation[74] [83] and in those with mitral restenosis after surgical valvotomy.[84] It may also be used in patients with less favorable valves who are unsuitable for surgery because of very high risk.[85] These include very elderly, frail patients; patients with associated severe ischemic heart disease; patients in whom MS is complicated by pulmonary, renal, or neoplastic disease; women of childbearing age in whom valve replacement is undesirable; and pregnant women with MS.[86] [87] BMV is contraindicated in patients with severe mitral or aortic regurgitation and should probably not be used in patients with stenotic bioprosthetic valves.[85]

Because the cost of the balloon catheter is deemed high in countries with restricted financial resources, a reusable metallic valvulotome has been devised. Early results are at least as good as those achieved with balloon catheters.[88]

Surgical Valvotomy

Three operative approaches are available for the treatment of rheumatic MS: (1) closed mitral valvotomy using a transatrial or transventricular approach[89] [90] [91] ; (2) open valvotomy, i.e., valvotomy carried out under direct vision with the aid of cardiopulmonary bypass; and (3) mitral valve replacement (see Table 46-1) .

CLOSED MITRAL VALVOTOMY.

This procedure is performed without cardiopulmonary bypass but with the aid of a transventricular dilator. It is an effective operation, provided that MR, atrial thrombosis, or valvular calcification is not serious and that chordal fusion and shortening are not severe. Echocardiography is useful in selecting suitable candidates for this procedure by identifying patients without valvular calcification or dense fibrosis. If possible, closed mitral valvotomy should be carried out with "pump standby"; if the surgeon is unable to achieve a satisfactory result, the patient can be placed on cardiopulmonary bypass and the valvotomy carried out under direct vision or the valve replaced.

On average, the mitral valve area is increased by 1.0 cm^2 , with only 20 to 30 percent of patients requiring mitral valve replacement within 15 years.[92] In one large series,[90] the hospital mortality rate was 1.5 percent, and 0.3 percent of patients developed severe MR. Marked symptomatic improvement occurred in 86 percent of survivors. The actuarial survival rate was 89.5 percent after 18 years. Patients undergoing closed

valvotomy for restenosis had a 6.7 percent mortality rate. Long-term follow-up has shown that the results are best if the operation is carried out before chronic atrial fibrillation and/or heart failure has occurred, but complication rates are higher when valves are calcified and/or severely thickened.[89]

Closed mitral valvotomy is rarely used in the United States today, having been replaced by BMV, which is of similar effectiveness in patients who are candidates for closed mitral valvotomy. Closed mitral valvotomy is more popular in developing nations, where the expense of open-heart surgery and even of balloon catheters for BMV is an important factor and where patients with mitral valve disease are younger and therefore have more pliable valves. But even in these nations, closed mitral valvotomy is being displaced by BMV.

OPEN VALVOTOMY.

Most surgeons in North America and Western Europe now prefer to carry out *direct-vision* or *open valvotomy.*[92] [93] [94] This operation is most frequently performed in patients with MS whose mitral valves are too distorted or calcified for BMV. Cardiopulmonary bypass is established, and in order to obtain a dry, quiet heart, body temperature is usually lowered, the heart is arrested, and the aorta is occluded intermittently. Thrombi are removed from the left atrium and its appendage, and the latter is often amputated in order to remove a potential source of postoperative emboli. The commissures are incised, and, when necessary, fused chordae tendineae are separated, the underlying papillary muscle is split, and the valve leaflets are debrided of calcium. Mild or even moderate MR may be corrected. Left atrial and ventricular pressures are measured after bypass has been discontinued to confirm that the valvotomy has, in fact, been effective. When it has not been effective, another attempt can be made. When repair is not possible--most commonly owing to severe distortion and calcification of the valve and subvalvular apparatus with accompanying regurgitation that cannot be corrected--mitral valve replacement should be carried out (see p. 1653).[95] In patients with atrial fibrillation, conversion to sinus rhythm is done at the completion of the operation. In a series of open mitral valve reconstructive procedures for MS at Brigham and Women's Hospital, the actuarial probability of survival at 10 years was 95 percent. The annual reoperation rate was 1.7 percent.[93] A survival rate of 75 percent over 20 years after surgical repair of MS has been reported.[96]

The mortality rate after mitral valvotomy, whether open or closed, ranges from 1 to 3 percent, depending on the condition of the patient and the skill and experience of the surgical team.[93] Five-year survival rates are 90 to 96 percent, and event-free survival rates are 72 to 94 percent.[96] [97] In general, open valvotomy provides better hemodynamic relief of mitral valve obstruction than does the closed procedure,[94] [98] and the risk of dislodging thrombi from the atrium or calcium from the mitral valve is also less.[93] Left atrial size, the need for mitral or tricuspid annuloplasty, and the presence of left atrial thrombus are all "risk factors" for a less than optimal outcome after open mitral

valvotomy. [95] Although a contemporary control series of medically and surgically treated patients is not available (nor is it likely ever to be), valvotomy appears to prolong survival substantially in patients with MS (see Fig. 46-6) .

MITRAL RESTENOSIS.

Mitral valvotomy, whether percutaneous or operative and whether open or closed, is *palliative* rather than curative, and even when successful, this procedure merely "turns the clock back." (The generally more effective open valvotomy turns the clock back further than does the closed valvotomy or BMV.) Thus, successful valvotomy does not result in a normal mitral valve but rather in one resembling the valve as it existed perhaps a decade earlier. Because the valve is not normal postoperatively, turbulent flow usually persists in the paravalvular region, and the resultant trauma may well play a role in restenosis. These changes are analogous to the gradual development of obstruction in a congenitally bicuspid aortic valve and are *not* usually the result of recurrent rheumatic fever.

On clinical grounds alone, i.e., based on the reappearance of symptoms, the incidence of "restenosis" has been estimated to range widely (from 2 to 60 percent).[99] Approximately 10 percent of patients who have undergone surgical mitral valvotomy require reoperation within 5 years, but that number increases to 60 percent by 10 years.[100] Recurrence of symptoms is usually *not* due to restenosis but may be due to one or more of the following conditions: (1) an inadequate first operation with residual stenosis; (2) the presence or development of MR, either at operation or as a consequence of infective endocarditis; (3) the progression of aortic valve disease; and (4) the development of coronary artery disease. True restenosis occurs in less than 20 percent of patients who are followed for 10 years.[51] In a study of 18 patients who had undergone successful surgical valvotomy in whom the size of the mitral orifice was estimated using two-dimensional echocardiography, no change in the mitral valve area occurred over a 10- to 14-year period in 13 patients (72 percent), whereas in true restenosis developed in 5 patients (28 percent).[100] Others have estimated the rate of true restenosis to be approximately 10 percent within 6 years.[101]

Thus, in properly selected patients, mitral valvotomy, however performed--balloon angioplasty, closed or open valvotomy--is a low-risk procedure that results in a significant increase in the size of the mitral orifice and favorably alters the clinical course of an otherwise progressive disease. Pulmonary arterial pressure falls promptly and decisively when mitral obstruction is effectively relieved.[102] [103] The majority of patients maintain clinical improvement for 10 to 15 years of follow-up. When a second procedure is required because of symptomatic deterioration, the valve is usually calcified and more seriously deformed than at the time of the first operation, and adequate reconstruction may not be possible. Accordingly, mitral valve replacement (MVR) is often necessary at that time.

INDICATIONS FOR MITRAL VALVE REPLACEMENT.

This procedure is often required in patients with combined MS and moderate or severe MR; in those with extensive commissural

TABLE 46-2 -- OPERATIVE MORTALITY RATES FOLLOWING VALVE REPLACEMENT AND REPAIR

OPERATIVE CATEGORY	NUMBER	OPERATIVE MORTALITY (%)
AVR (isolated)	26,317	4.3
MVR (isolated)	13,936	6.4
Multiple valve replacement	3,840	9.6
AVR+CAB	22,713	8.0
MVR+CAB	8,788	15.3
Multiple valve replacement+CAB	1,424	18.8
AVR+any valve repair	938	7.4
MVR+any valve repair	1,266	12.5
Aortic valve repair	26,597	5.9
Mitral valve repair	4,167	3.0
Tricuspid valve repair	144	13.9
AVR+aortic aneurysm repair	1,723	9.7

AVR=aortic valve replacement; CAB=coronary artery bypass; MVR=mitral valve replacement.

Modified from Jamieson WRE, Edwards FH, Schwartz M, et al: Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Ann Thorac Surg 67:943, 1999.

calcification, severe fibrosis, and subvalvular fusion; and in those who have undergone previous valvotomy. The operative mortality rate following isolated MVR ranges from 3 to 8 percent in most centers and averaged 6.4 percent in the large database of 13,936 such operations for patients with MS and/or MR reported in the Society of Thoracic Surgeons National Database[104] (Table 46-2) . As described later (see p. 1701), mechanical deterioration of bioprosthetic valves may occur. Also, the hazards of lifelong anticoagulant treatment in patients with mechanical prostheses must be considered. Therefore, the threshold for operation should be higher in patients in whom preoperative evaluation suggests that valve replacement may be required than in patients in whom valvotomy alone appears to be indicated.

MVR is indicated in two groups of patients with MS whose valves are not suitable for valvotomy: (1) those with a mitral valve area less than 1.5 cm^2 in NYHA Class III or IV;

and (2) those with severe MS (mitral valve area <1.0 cm^2), NYHA Class II, and severe pulmonary hypertension (pulmonary artery systolic pressure >70 mm Hg).[51] Since the operative mortality risk may be quite high (10 to 20 percent) in patients in NYHA Class IV, operation should be carried out before patients reach this stage if possible. On the other hand, such patients should not be denied operation unless they have comorbid conditions that preclude surgery or a satisfactory outcome. (The results of MVR are discussed on p. 1663).

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Mitral Regurgitation

ETIOLOGY AND PATHOLOGY

The mitral valve apparatus involves the mitral leaflets *per se,* chordae tendineae, papillary muscles, and mitral annulus. Abnormalities of any of these structures may cause MR.[104A] The major causes of MR include rheumatic heart disease, infective endocarditis, collagen-vascular disease, cardiomyopathy, and ischemic heart disease (Table 46-3) . The mitral valve prolapse syndrome, an important cause of MR, is discussed in a separate section (see p. 1665). A less common cause is use of certain appetite suppressant drugs.

ABNORMALITIES OF VALVE LEAFLETS.

MR due to predominant involvement of the valve leaflets occurs in patients with chronic rheumatic heart disease. However, in contrast to MS, this lesion is more frequent in men than in women. It is a consequence of shortening, rigidity, deformity, and retraction of one or both mitral valve cusps and is associated with shortening and fusion of the chordae tendineae and papillary muscles. Infective endocarditis can cause MR by perforating valve leaflets (see Chap. 47) ; vegetations can prevent leaflet coaptation, and valvular retraction during the healing phase of endocarditis can cause MR. Destruction of the mitral valve leaflets can also occur

TABLE 46-3 -- CAUSES OF ACUTE AND CHRONIC MITRAL REGURGITATION

ACUTE
Mitral Annulus Disorders
Infective endocarditis (abscess formation)
Trauma (valvular heart surgery)
Paravalvular leak due to suture interruption (surgical technical problems or infective endocarditis)
Mitral Leaflet Disorders
Infective endocarditis (perforation or interfering with valve closure by vegetation)
Trauma (tear during percutaneous balloon mitral valvotomy or penetrating chest injury)
Tumors (atrial myxoma)
Myxomatous degeneration
Systemic lupus erythematosus (Libman-Sacks lesion)
Rupture of Chordae Tendineae
Idiopathic, e.g., spontaneous
Myxomatous degeneration (mitral valve prolapse, Marfan syndrome, Ehlers-Danlos syndrome)
Infective endocarditis
Acute rheumatic fever
Trauma (percutaneous balloon valvotomy, blunt chest trauma)
Papillary Muscle Disorders
Coronary artery disease (causing dysfunction and rarely rupture)
Acute global left ventricular dysfunction
Infiltrative diseases (amyloidosis, sarcoidosis)
Trauma
Primary Mitral Valve Prosthetic Disorders
Porcine cusp perforation (endocarditis)
Porcine cusp degeneration
Mechanical failure (strut fracture)
Immobilized disc or ball of the mechanical prosthesis
CHRONIC
Inflammatory
Rheumatic heart disease

Systemic lupus erythematosus
Scleroderma
Degenerative
Myxomatous degeneration of mitral valve leaflets (Barlow click-murmur syndrome, prolapsing leaflet, mitral valve prolapse)
Marfan syndrome
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Calcification of mitral valve annulus
Infective
Infective endocarditis affecting normal, abnormal, or prosthetic mitral valves
Structural
Ruptured chordae tendineae (spontaneous or secondary to myocardial infarction, trauma, mitral valve prolapse, endocarditis)
Rupture or dysfunction of papillary muscle (ischemia or myocardial infarction)
Dilatation of mitral valve annulus and left ventricular cavity (congestive cardiomyopathies, aneurysmal dilatation of the left ventricle)
Hypertrophic cardiomyopathy
Paravalvular prosthetic leak
Congenital
Mitral valve clefts or fenestrations
Parachute mitral valve abnormality in association with:
Endocardial cushion defects
Endocardial fibroelastosis
Transposition of the great arteries
Anomalous origin of the left coronary artery
Data from Jutzy KR, Al-Zaibag M: Acute mitral and aortic valve regurgitation. In Al-Zaibag M, Duran CMG (eds): Valvular Heart Disease. New York, Marcel Dekker, 1994, pp 345-382 (top portion); and Haffajee CI: Chronic mitral regurgitation. In Dalen JE, Alpert JS (eds): Valvular Heart Disease. 2nd ed. Boston, Little, Brown and Co, 1987, p 112 (lower portion).

in patients with penetrating and nonpenetrating trauma (see Chap. 51) .

ABNORMALITIES OF THE MITRAL ANNULUS

Dilatation.

In a normal adult, the mitral annulus measures approximately 10 cm in circumference. It is soft and flexible, and contraction of the surrounding left ventricular muscle during systole causes the annular constriction that contributes importantly to valve closure. MR secondary to dilatation of the mitral annulus can occur in any form of heart disease characterized by dilatation of the left ventricle, especially dilated cardiomyopathy. Left ventricular submitral aneurysm has been reported as a cause of annular MR in sub-Saharan Africa. It appears to be due to a congenital defect in the posterior portion of the annulus. Diagnosis by transesophageal echocardiography[105] and surgical repair have been reported.

Calcification.

Idiopathic (degenerative) calcification of the mitral annulus is one of the most common cardiac abnormalities found at autopsy; in most hearts it is of little functional consequence. However, when severe, it may be an important cause of MR,[106] and, in contrast to MR secondary to rheumatic fever, it is more common in women than in men. The development of degenerative calcification of the mitral annulus is accelerated by systemic hypertension, aortic stenosis, and diabetes, as well as by an intrinsic defect in the fibrous skeleton of the heart, as occurs in the Marfan and Hurler syndromes. In these two syndromes, the mitral annulus is not only calcified but also dilated, further contributing to MR. The incidence of mitral annular calcification is also increased in patients who have chronic renal failure with secondary hyperparathyroidism.[107] The annulus may also become thick, rigid, and calcified secondary to rheumatic involvement; when this process is severe, it also can interfere with valve closure.

With severe annular calcification, a rigid, curved bar or ring of calcium encircles the mitral orifice (see Fig. 8-20) , and calcific spurs may project into the adjacent left ventricular myocardium.[108] The calcification may immobilize the basal portion of the mitral leaflets, preventing their normal excursion in diastole and coaptation in systole, and aggravating the MR that results from loss of the normal sphincteric action of the mitral ring. Rarely, obstruction to left ventricular filling may occur when severe calcification encroaches on or protrudes into the mitral orifice. In patients with severe calcification, the conduction system may be invaded by calcium, leading to atrioventricular and/or intraventricular conduction defects.[108] Calcification of the aortic valve cusps is an associated finding in approximately 50 percent of patients with severe mitral annular calcification, but this rarely causes aortic stenosis. Occasionally, calcific deposits extend into the coronary arteries.

ABNORMALITIES OF THE CHORDAE TENDINEAE.

Such abnormalities are important causes of MR. Lengthening and rupture of the chordae tendineae are cardinal features of the mitral valve prolapse syndrome (see p. 1666). The chordae may be congenitally abnormal; rupture may be spontaneous ("primary")[109] or may occur as a consequence of infective endocarditis, trauma,

rheumatic fever, or, rarely, osteogenesis imperfecta or relapsing polychondritis.[110] In most patients, no cause for chordal rupture is apparent other than increased mechanical strain. Chordae to the posterior leaflet rupture more frequently than those to the anterior leaflet. Patients with idiopathic rupture of mitral chordae tendineae frequently exhibit pathological fibrosis of the papillary muscles. It is possible that the dysfunction of the papillary muscles may cause stretching and ultimately rupture of the chordae tendineae. Chordal rupture may also result from acute left ventricular dilatation, regardless of the cause. Depending on the number of chordae involved in rupture and the rate at which rupture occurs, the resultant MR may be mild, moderate, or severe and acute, subacute, or chronic.

INVOLVEMENT OF THE PAPILLARY MUSCLES.

Diseases of the left ventricular papillary muscles are a frequent cause of MR.[111] Because these muscles are perfused by the terminal portion of the coronary vascular bed, they are particularly vulnerable to ischemia, and any disturbance in coronary perfusion may result in papillary muscle dysfunction. When ischemia is transient, it results in temporary papillary muscle dysfunction and may cause transient episodes of MR that are sometimes associated with attacks of angina pectoris. When ischemia of papillary muscles is severe and prolonged, it causes papillary muscle dysfunction and scarring, as well as chronic MR. The posterior papillary muscle, which is supplied by the posterior descending branch of the right coronary artery, becomes ischemic and infarcted more frequently than does the anterolateral papillary muscle; the latter is supplied by diagonal branches of the left anterior descending coronary artery and often by marginal branches from the left circumflex artery as well. Ischemia of the papillary muscles is caused most commonly by coronary atherosclerosis, but it may also occur in patients with severe anemia, shock, coronary arteritis of any cause, or an anomalous left coronary artery. MR occurs frequently in patients with healed myocardial infarcts[112] and is caused by dyskinesis of the left ventricular myocardium at the base of a papillary muscle. MR has been reported in patients who are taking certain appetite suppressant drugs.[112A]

Left ventricular dilatation of any cause, including ischemia, can alter the spatial relationships between the papillary muscles and the chordae tendineae and thereby result in MR.[113] Although *necrosis of a papillary muscle* is a frequent complication of myocardial infarction, [114] frank rupture is far less common; the latter is usually fatal because of the extremely severe MR that it produces (see Chap. 35) . However, rupture of one or two of the apical heads of a papillary muscle results in a lesser degree of MR and thus makes survival possible, usually following surgical therapy (see Chap. 35) .

Some degree of MR is found in approximately 30 percent of patients with coronary artery disease who are being considered for coronary artery bypass surgery. In these patients, MR is secondary to ischemic damage to the papillary muscles and/or dilatation of the mitral valve ring. In most of these patients, MR is mild; however, in the small percentage with severe MR (3 percent in one large series of patients with coronary

artery disease proved by coronary arteriography), it is associated with a poor prognosis.[115] The incidence and severity of regurgitation vary inversely with the left ventricular ejection fraction and directly with the left ventricular end-diastolic pressure. MR occurs in approximately 20 percent of patients following acute myocardial infarction and, even when mild, is associated with a higher risk of adverse outcomes.[112]

Various other disorders of the papillary muscles may also be responsible for the development of MR (see Table 46-3) . These include congenital malposition of the muscles; absence of one papillary muscle, resulting in the so-called parachute mitral valve syndrome; and involvement or infiltration of the papillary muscles by a variety of processes, including abscesses, granulomas, neoplasms, amyloidosis, and sarcoidosis.

Other causes of MR, discussed in greater detail elsewhere, include mitral valve prolapse (see p. 1665), obstructive cardiomyopathy (see Chap. 48) , the hypereosinophilic syndrome,[116] endomyocardial fibrosis,[117] trauma affecting the leaflets[118] and/or papillary muscles[119] (see Chap. 51) , Kawasaki disease[120] (see Chap. 45) , left atrial myxoma (see Chap. 49) , and various congenital anomalies, including cleft anterior leaflet[121] and ostium secundum atrial septal defect (see Chap. 43) .[122]

PATHOPHYSIOLOGY

Because the regurgitant mitral orifice is functionally in parallel with the aortic valve, the impedance to ventricular emptying is reduced in patients with MR. Consequently, MR enhances left ventricular emptying. Almost 50 percent of the regurgitant volume is ejected into the left atrium before the aortic valve opens. The volume of MR flow depends on a combination of the instantaneous size of the regurgitant orifice and the (reverse) pressure gradient between the left ventricle and the left atrium.[19] [123] [124] [125] Both the orifice size and the pressure gradient are labile. Left ventricular systolic pressure, and therefore the left ventricular-left atrial gradient, depends on systemic vascular resistance,[123] and in patients in whom the mitral annulus has normal flexibility, the cross-sectional area of the mitral annulus may be altered by many interventions. Thus, increase of both preload and afterload and depression of contractility increase left ventricular size and enlarge the mitral annulus and thereby the regurgitant orifice.[125] When ventricular size is reduced by treatment with positive inotropic agents, diuretics, and particularly vasodilators, the volume of regurgitant flow declines, as reflected in the height of the *v* wave in the left atrial pressure pulse and in the intensity and duration of the systolic murmur. Pharmacological reductions of systemic vascular resistance and left ventricular filling pressure reduce the volume of regurgitant flow by means of a reduction in the regurgitant orifice area.[126] Conversely, left ventricular dilatation, regardless of cause, may increase MR.

LEFT VENTRICULAR COMPENSATION.

The left ventricle initially compensates for the development of *acute* MR in part by emptying more completely and in part by increasing preload, i.e., by use of the Frank-Starling principle. As regurgitation, particularly severe regurgitation, becomes chronic, the left ventricular end-diastolic volume increases and the end-systolic volume

returns to normal. By means of the Laplace principle (which states that myocardial wall tension is related to the product of intraventricular pressure and radius), the increased ventricular end-diastolic volume increases wall tension to normal or supranormal levels in the so-called chronic compensated stage of severe MR.[127] The resultant increase in left ventricular end-diastolic volume and mitral annular diameter may create a vicious circle in which "MR begets more MR." In patients with chronic MR, both left ventricular end-diastolic volume and mass are increased; i.e., typical volume overload (eccentric) hypertrophy develops. The degree of hypertrophy is usually proportionate to the degree of left ventricular dilatation, so that the ratio of left ventricular mass to end-diastolic volume is normal (see Fig. 16-5) . The eccentric ventricular hypertrophy that accompanies the elevated end-diastolic volume of chronic MR is secondary to new sarcomeres laid down in parallel. A shift to the right (greater volume at any pressure) occurs in the left ventricular diastolic pressure-volume curve in patients with chronic MR (Fig. 46-10 *C*). With decompensation chamber stiffness increases, raising the diastolic pressure at any volume[128] (see Fig. 46-10 *D*).

In most patients with severe primary MR, compensation is maintained for years, but ultimately the prolonged hemodynamic overload leads to myocardial decompensation. End-systolic volume, preload, and afterload all rise, whereas ejection fraction and stroke volume decline. A depressed ratio of phosphocreatine/adenosine triphosphate has been reported in patients with MR and severe decompensation.[129] It is not clear whether this is the cause or a marker of heart failure in these patients.

In canine experiments which compared the *acute* effects of equally severe MR and aortic regurgitation (AR) on the left ventricle, left ventricular end-diastolic pressure, volume, and radius increased with

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Figure 46-10 Left ventricular diastolic pressure-volume relationships in volume overload. *A,* A moderate acutely applied volume overload from MR. There is modest chamber enlargement at end-diastole with little increase in end-diastolic pressure and a leftward shift of the diastolic pressure-volume relationship due to a smaller end-systolic chamber size achieved from the hyperdynamic chamber performance. *B,* A major upward shift represents a higher pressure for a wide range of chamber volumes. This is acute pericardial restraint and a right-left ventricular interaction effect. These two mechanisms come into play when the acute MR is so severe that the total intrapericardial volume increases to the point of stretching the noncompliant pericardial sac. *C,* This is the classic rightward shift of compensated volume overload lesions--mitral, tricuspid, and aortic regurgitation being the most common (red line). With little change in wall thickeness, the chamber is greatly enlarged, with myocardial cell slippage allowing a reduction in chamber stiffness and growth of the pericardium allowing increased intracavitary volumes to exist with a normal low pericardial pressure. *D,* Chamber stiffness increases when decompensation occurs in volume overload (red line). Often the myocardium has become myopathic and fibrotic. End-diastolic pressure volume and end-systolic volume have risen. ×1 = end-systolic pressure and volume; ×2 = end-diastolic pressure and volume in the normal subject.

both lesions, but far *less so* with MR.[130] Peak left ventricular wall tension rose markedly when AR was induced but either did not change greatly or actually declined with MR.

Because *acute* MR reduces both late systolic ventricular pressure and radius, left ventricular wall tension declines markedly (and proportionately to a greater extent than left ventricular pressure), permitting a reciprocal increase in both the extent and the velocity of myocardial fiber shortening. The ratio of wall thickness to ventricular radius is lower and the fractional shortening of myocardium is greater in patients with MR than in those with AR.[131] Thus, the reduced left ventricular afterload allows a greater proportion of the contractile energy of the myocardium to be expended in shortening than in tension development and explains how the left ventricle can adapt to the load imposed by MR.

A large volume of induced experimentally MR produces only slightly increased myocardial oxygen consumption (MV_{O_2}) because myocardial fiber shortening, which is elevated in patients with MR, is not one of the principal determinants of MV_{O_2}.[132] One of these determinants, mean left ventricular wall tension, may actually be reduced in patients with MR, whereas the other two, contractility and heart rate, may be little affected. These experimental observations correlate with the low incidence of clinical manifestations of myocardial ischemia in patients with severe MR compared with the much higher incidence occurring in those with aortic stenosis and AR, conditions in which MV_{O_2} is augmented.

ASSESSMENT OF MYOCARDIAL CONTRACTILITY IN MITRAL REGURGITATION.

Because the ejection phase indices of myocardial contractility are inversely correlated with afterload, patients with early MR (with reduced left ventricular afterload) often exhibit elevations in ejection phase indices of myocardial contractility, such as ejection fraction (EF), fractional fiber shortening (FS), and velocity of circumferential fiber shortening (VCF).[133] However, by the time patients become seriously symptomatic, EF, FS, and mean VCF have usually declined to *normal* or *below normal* levels. As MR persists, the reduction in afterload, which increases myocardial fiber shortening and the earlier-mentioned ejection phase indices, is opposed by the impairment of myocardial function characteristic of severe chronic diastolic overload. However, even in patients with overt heart failure secondary to MR, the EF and FS may be only modestly reduced.[133A] Therefore, *normal* values for the ejection phase indices of myocardial performance in patients with acute MR may actually reflect impaired myocardial function,[134] whereas moderately reduced values (e.g., EF of 40 to 50 percent) generally signify severe, often irreversible, impairment of contractility. An EF of less than 35 percent in patients with severe MR usually represents advanced myocardial dysfunction; such patients are high operative risks and may not experience marked improvement following mitral valve replacement (see p. 1663).[127]

END-SYSTOLIC VOLUME.

Preoperative myocardial contractility is an important determinant of the risk of operative death, of cardiac failure perioperatively, and of the level of left ventricular function postoperatively. Therefore, it is not surprising that the end-systolic pressure/volume (or stress/dimension) relation has emerged as a useful index for evaluating left ventricular function in patients with MR.[135] Indeed, the simple measurement of end-systolic volume

has been found to be more useful as a predictor of outcome than the EF, end-diastolic volume, or end-diastolic pressure.[136] Patients with severe MR who had a normal preoperative end-systolic volume (<40 ml/m^2) retained normal left ventricular function postoperatively, whereas a marked increase in the end-systolic volume (>80 ml/m^2) signified a high perioperative mortality rate and residual left ventricular dysfunction. An end-systolic volume of 55 ml/m^2 appears to discriminate between patients who do well after surgical correction (<55 ml/m^2) and those who are at risk of irreversible dysfunction (>55 ml/m^2). Patients with MR and a modest increase in end-systolic volume (40 to 80 ml/m^2) usually tolerate operation satisfactorily but may have reduced left ventricular function postoperatively.

A closely related variable, the end-systolic diameter, determined by echocardiography, is a reliable noninvasive predictor of outcome (survival without severe heart failure) following mitral valve replacement. The outcome is excellent until the end-systolic diameter exceeds approximately 45 mm or 26 mm/m^2 (Fig. 46-11) . [137]

HEMODYNAMICS.

Effective (forward) *cardiac output* is usually depressed in severely symptomatic patients with MR, whereas *total* left ventricular output (the sum of forward and regurgitant flow) is usually elevated until quite late in the patient's course. The cardiac output achieved during exercise, not the regurgitant volume, is the principal determinant of functional capacity.[138] The atrial contraction (*a*) wave in the left atrial pressure pulse is usually not as prominent in MR as in MS, but the *v* wave is often much taller (see Fig. 11-5) because it is inscribed during ventricular systole, when the left atrium is being filled with blood from the pulmonary veins as well as from the left ventricle. Occasionally, backward transmission of the tall *v* wave into

Figure 46-11 The probability of postoperative death or persistence of severe heart failure in patients with mitral regurgitation plotted against preoperative echocardiographic end-systolic diameter. As end-systolic diameter exceeded 45 mm, the incidence of a poor postoperative outcome increased abruptly. *(Reproduced with permission from Wisenbaugh T, et al: Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. Circulation 89:191, 1994. Copyright 1994 American Heart Association.)*

the pulmonary arterial bed may result in an early diastolic "pulmonary arterial *v* wave."[139] In patients with pure MR, the *y* descent in the pulmonary capillary pressure pulse is particularly rapid as the distended left atrium empties rapidly during early diastole. However, in patients with combined MS and MR, the *y* descent is gradual. Although a left atrioventricular pressure gradient persisting throughout diastole signifies the presence of significant associated MS, a brief early diastolic gradient may occur in patients with isolated, severe MR as a result of the rapid flow of blood across a normal-sized mitral orifice early in diastole.[140]

LEFT ATRIAL COMPLIANCE

The compliance of the left atrium (and pulmonary venous bed) is an important determinant of the hemodynamic[141] and clinical picture in patients with severe MR. Three major subgroups of patients with severe MR based on left atrial compliance have been identified[130] [142] [143] (Fig. 46-12) and are characterized as follows:

NORMAL OR REDUCED COMPLIANCE.

In this subgroup, there is little enlargement of the left atrium but marked elevation of the mean left atrial pressure, particularly of the *v* wave,[144] [145] and pulmonary congestion is a prominent symptom. Severe MR usually develops acutely, as occurs with rupture of the chordae tendineae, infarction of one of the heads of a papillary muscle, or perforation of a mitral leaflet as a consequence of trauma or endocarditis. In patients with acute MR, the left atrium initially operates on the steep portion of its pressure-volume curve with a marked rise in pressure for a small increase in volume. Sinus rhythm is usually present; after the passage of weeks or a few months, the left atrial wall becomes hypertrophied, is capable of contracting vigorously, and facilitates left ventricular filling. The thicker atrium is less compliant than normal, which further increases the height of the *v* wave. Thickening of the walls of the pulmonary veins and proliferative changes in the pulmonary arteries, as well as marked elevations of pulmonary vascular resistance and pulmonary artery pressure, usually develop over the course of 6 to 12 months after the onset of acute, severe MR.

MARKEDLY INCREASED COMPLIANCE.

At the opposite end of the spectrum from patients in the first group are those with severe, longstanding MR with massive enlargement of the left atrium and normal or only slightly elevated left atrial pressure.[143] The atrial wall contains only a small remnant of muscle surrounded by fibrous tissue. Longstanding MR in these patients has altered the physical properties of the left atrial wall and thereby displaced the atrial pressure-volume curve to the right, allowing a normal or almost normal pressure to exist in a greatly enlarged left atrium. Pulmonary arterial pressure and pulmonary vascular resistance may be normal or only slightly elevated at rest. Atrial fibrillation and a low cardiac output are almost invariably present.[143]

MODERATELY INCREASED COMPLIANCE.

This, the most common subgroup, consists of patients between the ends of the spectrum represented by the first and second groups. These patients have severe, chronic MR and exhibit variable degrees of enlargement of the left atrium, associated with significant elevation of the left atrial pressure.

CLINICAL MANIFESTATIONS

History

The nature and severity of symptoms in patients with chronic MR are functions of its severity, rate of progression, the level of pulmonary arterial pressure, and the presence of associated valvular, myocardial, or coronary artery disease.

Figure 46-12 Diagram depicting the two extremes of the spectrum in pure mitral regurgitation. When severe mitral regurgitation appears suddenly in individuals with previously normal or near-normal hearts (top), the left atrium (LA) is relatively small and the high pressure within it is reflected back into the pulmonary vessels and right ventricle (RV). The anatomical indicator of this latter physiological event is severe hypertrophy of the left atrial and right ventricular walls and marked intimal proliferation and medial hypertrophy of the pulmonary arteries (PA), arterioles, and veins (PV). At the other extreme, in patients with severe chronic mitral regurgitation (bottom), the left atrial cavity is of giant size and its wall is thin. It is thus able to "absorb" the left ventricular (LV) pressure without reflecting it back into the pulmonary vessels or right ventricle. As a consequence, pulmonary vessels remain normal, and the right ventricular wall does not thicken. PT = pulmonary trunk; RA = right atrium. *(From Roberts WC, et al: Nonrheumatic valvular cardiac disease. A clinicopathologic survey of 27 different conditions causing valvular dysfunction. In Likoff W [ed]: Cardiovascular Clinics. Vol. 5, No. 2, Valvular Heart Disease. Philadelphia, F.A. Davis Co, 1973, p 403.)*

Because symptoms usually do not develop in patients with chronic MR until left ventricular decompensation occurs, the time interval between the initial attack of rheumatic fever (if one has occurred) and the development of symptoms tends to be longer in these patients than in those with MS and often exceeds two decades. Hemoptysis and systemic embolization are less common in patients with isolated or predominant MR than in those with MS. The development of atrial fibrillation affects the course adversely but perhaps not as dramatically as in MS. On the other hand, chronic weakness and fatigue secondary to a low cardiac output are more prominent features in MR.

The majority of patients with MR of rheumatic origin have only mild disability, unless regurgitation progresses as a result of chronic rheumatic activity, infective endocarditis, or rupture of the chordae tendineae. However, the indolent course of MR may be deceptive. By the time that symptoms secondary to a reduced cardiac output and/or pulmonary congestion become apparent, serious and sometimes even irreversible left ventricular dysfunction may have developed.

In patients with severe, chronic MR who have a greatly enlarged left atrium and relatively mild left atrial hypertension (patients with increased left atrial compliance [second subgroup], described earlier), pulmonary vascular resistance does not usually rise markedly. Instead, the major symptoms, fatigue and exhaustion, are related to the depressed cardiac output. Right-sided heart failure, characterized by congestive hepatomegaly, edema, and ascites, is prominent in patients with acute MR, elevated

pulmonary vascular resistance, and pulmonary hypertension. Angina pectoris is rare unless coronary artery disease coexists.

NATURAL HISTORY.

This is variable and depends on a combination of the volume of regurgitation, the state of the myocardium, and the cause of the underlying disorder. Asymptomatic patients with mild primary MR usually remain in a stable state for many years.[146] Severe regurgitation develops in only a small percentage of these patients, most commonly because of intervening infective endocarditis or rupture of the chordae tendineae. Regurgitation tends to progress more rapidly in patients with connective tissue diseases, such as the Marfan syndrome, than in those with chronic MR of rheumatic origin. Acute rheumatic fever is a frequent cause of isolated, severe MR in adolescents in developing nations, and these patients often have a rapidly progressive course.

Because the natural history of severe MR has been altered greatly by surgical intervention, it is difficult now to predict the course of patients who receive medical therapy alone. However, in an unselected group of patients with MR who were treated medically before surgical treatment of severe MR became commonplace, approximately 80 percent survived 5 years and almost 60 percent survived 10 years after the diagnosis was established.[147] Patients with combined MS and MR had a poorer prognosis, with only 67 percent surviving 5 years and 30 percent surviving 10 years after diagnosis. Munoz and colleagues[63] found that medically treated patients with severe MR had a 5-year survival rate of 45 percent, whereas Horstkotte and associates[64] reported a 5-year survival of only 30 percent in patients who were candidates for but who declined operation (see Fig. 46-6) .

Physical Examination

Palpation of the arterial pulse is helpful in differentiating aortic stenosis from MR, both of which may produce a prominent systolic murmur at the base of the heart. The carotid arterial upstroke is sharp in severe MR[148] and delayed in aortic stenosis; the volume of the pulse may be normal or reduced in the presence of heart failure. The cardiac impulse, like the arterial pulse, is brisk and hyperdynamic. It is displaced to the left, and a prominent left ventricular filling wave is frequently palpable. Systolic expansion of the enlarged left atrium may result in a late systolic thrust in the parasternal region, which may be confused with right ventricular enlargement.

AUSCULTATION.

With severe, chronic MR due to defective valve cusps, S_1 , produced by mitral valve closure, is usually diminished. Wide splitting of S_2 is common and results from the shortening of left ventricular ejection and an earlier A_2 as a consequence of reduced resistance to left ventricular outflow. In patients with MR who have severe pulmonary hypertension, P_2 is louder than A_2 . The abnormal increase in the flow rate across the mitral orifice during the rapid filling phase is often associated with an S_3 , which should

not be interpreted as a feature of heart failure in these patients.

The *systolic murmur* is the most prominent physical finding; it must be differentiated from the systolic murmur of aortic stenosis, tricuspid regurgitation, and ventricular septal defect. In most patients with severe MR, the systolic murmur commences immediately after the soft S_1 and continues beyond and may obscure the A_2 because of the persisting pressure difference between the left ventricle and left atrium after aortic valve closure. The holosystolic murmur of chronic MR is usually constant in intensity, blowing, high-pitched, and loudest at the apex with radiation to the left axilla and left infrascapular area; however, radiation toward the sternum or the aortic area may occur with abnormalities of the posterior leaflet. The murmur shows little change even in the presence of large beat-to-beat variations of left ventricular stroke volume, as occur in atrial fibrillation. This contrasts with most midsystolic (ejection) murmurs, such as in aortic stenosis, which vary greatly in intensity with stroke volume and therefore with the duration of diastole.[149] There is little correlation between the intensity of the systolic murmur and the severity of MR. Indeed, in patients with severe MR due to left ventricular dilatation, acute myocardial infarction, or paraprosthetic valvular regurgitation, or in those who have marked emphysema, obesity, chest deformity, or a prosthetic heart valve, the systolic murmur may be barely audible or even absent, a condition referred to as "silent MR."[150]

The murmur of MR may be holosystolic, late systolic, or early systolic. When the murmur is confined to late systole, the regurgitation is usually mild and may be secondary to prolapse of the mitral valve or to papillary muscle dysfunction. These causes of MR are frequently associated with a normal S_1 because initial closure of the mitral valve cusps may be unimpaired. The late systolic murmur of papillary muscle dysfunction is particularly variable; it may become accentuated or holosystolic during acute myocardial ischemia and often disappears when ischemia is relieved. The response of a mid- to late systolic murmur to a number of maneuvers, as described on page 1668 , helps to establish the diagnosis of mitral valve prolapse. When the left atrial *v* wave is markedly elevated in acute MR, the murmur may diminish or disappear in late systole as the reverse pressure gradient declines (see Fig. 4-29) . A short, low-pitched diastolic murmur following S_3 may be audible in patients with severe MR, even without accompanying MS.

DYNAMIC AUSCULTATION.

The holosystolic murmur of rheumatic MR varies little during respiration. However, sudden standing and amyl nitrite inhalation usually diminish the murmur (Table 46-4) , whereas squatting augments it. The murmur is reduced during the strain of the Valsalva maneuver and shows a left-sided response (i.e., a transient overshoot that occurs six to eight beats following release of the strain). The murmur of MR is usually intensified by isometric exercise, differentiating it from the systolic murmurs of valvular aortic stenosis and hypertrophic obstructive cardiomyopathy, both of which are reduced by this intervention. The murmur of MR caused by left ventricular dilatation *decreases* in intensity and duration following

TABLE 46-4 -- EFFECT OF VARIOUS INTERVENTIONS ON SYSTOLIC MURMURS

INTERVENTION	HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY	AORTIC STENOSIS	MITRAL REGURGITATION	MITRAL VALVE PROLAPSE
Valsalva				or
Standing		or unchanged		
Handgrip or squatting		or unchanged		
Supine position with legs elevated		or unchanged	Unchanged	
Exercise		or unchanged		
Amyl nitrite				
Isoproterenol				

= Markedly increased.

Modified from Paraskos JA: Combined valvular disease. In Dalen JE, Alpert JS (eds): Valvular Heart Disease. 2nd ed. Boston, Little, Brown and Co, 1987, p 365.

effective therapy with cardiac glycosides, diuretics, rest, and particularly vasodilators.

DIFFERENTIAL DIAGNOSIS.

The holosystolic murmur of MR resembles that produced by a ventricular septal defect. However, the latter is usually loudest at the sternal border rather than the apex and is usually accompanied by a parasternal, rather than an apical, thrill. The murmur of MR may also be confused with that of tricuspid regurgitation, which is usually heard best

along the left sternal border, is augmented during inspiration, and is accompanied by a prominent *v* wave and *y* descent in the jugular venous pulse.

When the chordae tendineae to the posterior leaflet of the mitral valve rupture, the regurgitant jet is often directed anteriorly, so that it impinges on the atrial septum adjacent to the aortic root and causes a systolic murmur that is most prominent at the base of the heart. This murmur can be confused with that of aortic stenosis. On the other hand, when the chordae tendineae to the anterior leaflet rupture, the jet is usually directed to the posterior wall of the left atrium, and the murmur may be transmitted to the spine or even to the top of the head.[151]

Patients with rheumatic disease of the mitral valve exhibit a spectrum of abnormalities, ranging from pure MS to pure MR. The presence of an S_3 , a rapid left ventricular filling wave and left ventricular impulse on palpation, and a soft S_1 all favor predominant MR. In contrast, an accentuated S_1 , a prominent opening snap (OS) with a short A_2 -OS interval, and a soft, short systolic murmur all point to predominant MS. Elucidation of the predominant valvular lesion may be complicated by the presence of a holosystolic murmur of tricuspid regurgitation in patients with pure MS and pulmonary hypertension; this murmur may sometimes be heard at the apex when the right ventricle is greatly enlarged and may therefore be mistaken for the murmur of MR.

LABORATORY EXAMINATION

ELECTROCARDIOGRAPHY.

The principal ECG findings are left atrial enlargement[44] [152] and atrial fibrillation. ECG evidence of left ventricular enlargement occurs in about one-third of patients with severe MR. Approximately 15 percent of patients exhibit ECG evidence of right ventricular hypertrophy, a change that reflects the presence of pulmonary hypertension of sufficient severity to counterbalance the hypertrophied left ventricle of MR.

RADIOLOGICAL FINDINGS (see Fig. 8-18 *D*).

Cardiomegaly with left ventricular enlargement, and particularly with left atrial enlargement, is a common finding in patients with chronic, severe MR.[153] However, there is little correlation between left atrial size and pressure. Interstitial edema with Kerley B lines is frequently seen in patients with acute MR or with progressive left ventricular failure.

In patients with combined MS and MR, overall cardiac enlargement and particularly left atrial dilatation are prominent findings. However, it is often difficult to determine which lesion is predominant from the plain chest roentgenogram because distinguishing between right and left ventricular enlargement may not be possible. Predominant MS is suggested by relatively mild cardiomegaly (principally straightening of the left cardiac border) and significant changes in the lung fields, whereas predominant MR is more likely when the heart is greatly enlarged and the changes in the lungs are relatively

inconspicuous. Chronic MR is almost always the dominant lesion when the left atrium is aneurysmally dilated. *Calcification of the mitral annulus,* an important cause of MR in the elderly, is most prominent in the posterior third of the cardiac silhouette. The lesion is best visualized on chest films exposed in the lateral or right anterior oblique projections, in which it appears as a dense, coarse, C-shaped opacity (see Fig. 8-20) .

ECHOCARDIOGRAPHY (See also Chap. 7) .

In patients with severe MR, *two-dimensional echocardiography* shows enlargement of the left atrium and left ventricle, with increased systolic motion of both chambers. The underlying cause of the regurgitation, e.g., rupture of chordae tendineae, mitral valve prolapse (see Fig. 7-57) , a flail leaflet[154] (see Figs. 7-55 and 7-56) , vegetations (see Chap. 47) , and left ventricular dilatation (see Fig. 7-54) can often be determined on the transthoracic echocardiogram. It may also show calcification of the mitral annulus as a band of dense echoes between the mitral apparatus and the posterior wall of the heart.[155] This technique is also useful for estimating the hemodynamic consequences of MR[155A] [155B] ; in patients with left ventricular dysfunction, end-diastolic and end-systolic volumes are increased and the ejection fraction and shortening rate may decline.

Doppler echocardiography in MR characteristically reveals a high-velocity jet in the left atrium during systole. The severity of the regurgitation is a function of the distance from the valve that the jet can be detected (see Fig. 7-53) and the size of the left atrium. Both color flow Doppler imaging and pulsed techniques correlate well with angiographic methods in estimating the severity of MR.[156] Other methods of assessing the severity of MR include measurement of the area of the mitral jet (
8 cm^2 indicates severe MR). However, color flow jet areas are significantly influenced by the cause of the regurgitation and jet eccentricity, thus limiting the accuracy of this approach.[157] The vena contracta, defined as the narrowest cross-sectional areas of the regurgitant jet as mapped by color flow Doppler echocardiography, predicts the severity of MR[158] [159] [160] (Fig. 46-13) . Reversal of flow in the pulmonary veins during systole[161] and a high peak mitral inflow velocity[162] are also useful signs of severe MR.

Transesophageal echocardiography (see Fig. 7-55) is superior to transthoracic echocardiography in assessing the detailed anatomy of the regurgitant mitral valve. Therefore, this technique is useful when the transthoracic image is suboptimal and when determining whether valve repair is feasible or whether MVR is necessary.[163] [164] Also, angiographic grading of MR correlates better with color flow mapping obtained by the transesophageal than by the transthoracic technique.[165] Three-dimensional transthoracic echocardiography and three-dimensional color Doppler[166] have also been reported to help elucidate the mechanism of MR.

RADIONUCLIDE ANGIOGRAPHY (see also Chap. 9) .

Gated blood pool nuclear imaging or first-pass angiography may reveal an increased end-diastolic volume; the regurgitant fraction can be estimated from the ratio of left ventricular to right ventricular stroke volume. In patients with MR and impaired left ventricular function, the ejection fraction fails to rise normally during exercise. Radionuclide angiograms are useful for interval follow-up. Progressive increases in

ventricular end-diastolic and/or end-systolic volume often suggest that surgical treatment is necessary (discussed later).

Figure 46-13 Linear regression plot showing good correlation between biplane vena contracta width and regurgitant volume. *(From Hall SA, Brickner E, Willen DL, et al: Assessment of mitral regurgitation severity by Doppler color flow mapping of the vena contracta. Circulation 95:636, 1997.)*

LEFT VENTRICULAR ANGIOCARDIOGRAPHY.

The prompt appearance of contrast material in the left atrium following its injection into the left ventricle indicates the presence of MR.[167] The injection should be rapid enough to permit left ventricular opacification but slow enough to avoid the development of premature ventricular contractions, which can induce spurious regurgitation.

The regurgitant volume can be determined from the difference between the total left ventricular stroke volume, estimated by angiocardiography, and the simultaneous measurement of the effective forward stroke volume by the Fick method. In patients with severe MR, the regurgitant volume may approach, and in rare instances may even exceed, the effective forward stroke volume. Qualitative but clinically useful estimates of the severity of MR may be made by cineangiographic observation of the degree of opacification of the left atrium and pulmonary veins following the injection of contrast material into the left ventricle.

The cause of the regurgitation (e.g., prolapse of the mitral valve) and a flail leaflet can often be distinguished by angiography. MR secondary to rheumatic heart disease is characterized angiographically by a central regurgitant jet and by thickened leaflets that exhibit reduced motion. In regurgitation due to other causes, particularly dilatation or calcification of the mitral annulus or ruptured chordae tendineae and papillary muscles, the systolic jet may be eccentric, and the valves consist of thin filaments that display excessive motion.

MAGNETIC RESONANCE IMAGING.

This study (see Fig. 10-24) is the most accurate technique for measuring regurgitant flow and provides measurements that correlate well with quantitative Doppler imaging.[168] [169] It is also the most accurate noninvasive technique that can provide measurement of ventricular end-diastolic and end-systolic volumes and ventricular mass.

Acute Mitral Regurgitation

The causes of acute MR are shown at the top of Table 46-3 . They are diverse and represent acute manifestations of disease processes that may, under other circumstances, cause chronic MR. Especially important causes of acute MR are infective endocarditis with disruption of valve leaflets or rupture of chordae tendineae, ischemic dysfunction or rupture of a papillary muscle, and malfunction of a prosthetic valve.

One major hemodynamic difference between acute and chronic MR derives from the differences in left atrial compliance, as discussed on page 1657 and as illustrated in Figure 46-12 . Acute, severe MR causes a marked reduction of forward stroke volume, a slight reduction of end-systolic volume, and an increase in end-diastolic volume. Patients who develop acute, severe MR usually have a normal-sized left atrium (normal or reduced left atrial compliance [first subgroup], see p. 1657). The left atrial pressure rises abruptly, which often leads to pulmonary edema, marked elevation of pulmonary vascular resistance, and right-sided heart failure.

Because the *v* wave is markedly elevated in patients with acute, severe MR, the reverse pressure gradient between the left ventricle and left atrium declines at the end of systole, and the murmur may be decrescendo rather than holosystolic, ending well before A_2 (see Fig. 4-29) . It is usually lower pitched and softer than the murmur of chronic MR. A left-sided S_4 is frequently found.[130] Pulmonary hypertension, which is common in patients with acute MR, may increase the intensity of P_2 and the murmurs of pulmonary and tricuspid regurgitation, and a right-sided S_4 may also develop. In patients with severe, acute MR, a *v* wave (late systolic pressure rise) in the pulmonary artery pressure pulse (see Fig. 11-5) may rarely cause premature closure of the pulmonary valve, an early P_2 , and paradoxical splitting of S_2 . Acute MR, even if severe, often does not increase overall cardiac size, as seen on the chest roentgenogram, and may produce only mild left atrial enlargement despite marked elevation of left atrial pressure. In addition, the echocardiogram may show little increase in the internal diameter of either the left atrium or the left ventricle, but increased systolic motion of the left ventricle is prominent.

MANAGEMENT

Medical Treatment

This includes all of the measures used in the treatment of cardiac dysfunction, as outlined in Chapter 18 . Afterload reduction is of particular benefit in the management of both the acute and the chronic forms of MR.[170] [171] By reducing the impedance to ejection into the aorta, the volume of blood regurgitating into the left atrium is reduced. In addition, decreasing left ventricular volume reduces the regurgitant orifice.[172] Mean left atrial pressure and, in particular, the elevated *v* wave both decline. Afterload reduction with intravenous nitroprusside may be lifesaving in patients with acute MR due to rupture of the head of a papillary muscle that occurs during an acute myocardial infarction. It may permit stabilization of the patient's condition and thereby allow coronary arteriography and surgery to be performed with the patient in optimal

condition. In patients with acute MR who are hypotensive, an inotropic agent such as dobutamine should be administered with the nitroprusside. Intraaortic balloon counterpulsation may be necessary to stabilize the patient as preparations for surgery are made.

When surgical treatment is contraindicated in patients with severe, chronic MR, chronic afterload reduction with an angiotensin converting enzyme inhibitor[170] [171] [173] [173A] or oral hydralazine may improve the clinical status. However, definitive randomized trials documenting the efficacy of these agents are not available. In addition to diuretics, digitalis glycosides are indicated in patients with severe MR

Figure 46-14 Schematic representation of the concept of optimal timing of valve replacement surgery. Early surgery yields low operative mortality and preservation of ventricular function. However, because of a finite postoperative risk of prosthesis-associated complications (the major determinant of the slope of the postoperative survival curve in either early or optimally timed surgery), postoperative risk exceeds that of pure medical treatment at this early phase of the disease. In contrast, if surgery is done too late, operative mortality is increased and ventricular function may progressively deteriorate after surgery. Thus, following late surgery, postoperative survival is primarily determined by both prosthesis-associated complications and congestive heart failure. Optimal timing of surgery balances the risks of maintaining medical management with the new risks associated with postoperative complications. With optimally timed surgical intervention, operative mortality is relatively low, ventricular function is almost completely preserved, and postoperative risk is determined, as in early surgery, predominantly by the risk of prosthesis-associated complications. *(From Schoen FJ, St. John Sutton M: Contemporary issues in the pathology of valvular disease. Hum Pathol 18:568, 1987.)*

and clinical evidence of heart failure and are particularly helpful in patients with established atrial fibrillation. The latter should also receive anticoagulants. As do all patients with valvular lesions, patients with MR require appropriate prophylaxis to prevent infective endocarditis (see Chap. 47) .

Surgical treatment should be considered for patients with functional disability despite optimal medical management and/or for patients with only mild symptoms but with progressively deteriorating left ventricular function as documented by noninvasive studies. Two-dimensional or transesophageal echocardiography with Doppler echocardiography and color flow Doppler imaging provide detailed assessment of mitral valve structure and function. However, left heart catheterization, left ventricular angiocardiography, and coronary arteriography are indicated for the following: (1) in evaluating a discrepancy between echocardiographic findings and the clinical picture; (2) in detecting and assessing the severity of any associated valvular lesions; and (3) in determining the presence and assessing the extent of coronary artery disease.

Surgical Treatment

Without surgical treatment, the prognosis for patients with MR and heart failure is poor

(see Fig. 46-6) . When operative treatment is being considered, the chronic and often slowly but relentlessly progressive nature of MR must be weighed against the immediate risks and long-term uncertainties attendant upon surgery, especially mitral valve replacement (MVR) (Fig. 46-14) . Surgical mortality depends on the patient's clinical and hemodynamic status (particularly the function of the left ventricle); on the presence of comorbid conditions such as renal, hepatic, or pulmonary disease; and on the skill and experience of the surgical team[104] (see Table 46-2) . The decision to replace or to reconstruct the valve (Fig. 46-15) is of critical importance. Replacement involves the operative risk, as well as the risks of thromboembolism and anticoagulation in patients receiving mechanical prostheses, of late valve deterioration in patients receiving bioprostheses (see p. 1696), and of late

Figure 46-15 Valve repair techniques for quadrilateral resection of the posterior leaflet of the mitral valve. *(From Cohn LH, DiSesa VJ, Couper GS, et al: Mitral valve repair for myxomatous degeneration and prolapse of the mitral valve. J Thorac Cardiovasc Surg 98:987, 1989.)*

mortality, especially in patients with associated coronary artery disease who require coronary artery bypass grafting (see Table 46-2) . Surgical mortality does not depend significantly on *which* of the currently used tissue or mechanical valve prostheses is selected.

The reconstructive procedure consists of annuloplasty, often with the use of a rigid (Carpentier) or a flexible prosthetic (Duran) ring (Fig. 46-16) or with reconstruction of the valve[174] [175] [176] [177] [177A] [178] [179] (see Fig. 46-15) . Prolapsed valves causing severe MR are usually treated with resection of the prolapsing segment and plication of the annulus (see p. 1671). Replacing,[180] reimplanting, elongating, or shortening of chordae tendineae; splitting the papillary muscles; and repairing the subvalvular apparatus have been successful in selected patients with pure or predominant MR.[175] Reconstruction of the mitral valve is most often successful in (1) children and adolescents with pliable valves; (2) adults with MR secondary to mitral valve prolapse[18] ; (3) annular dilatation; (4) papillary muscle secondary to ischemia, dysfunction, or rupture; or (5) chordal rupture and perforation of a mitral leaflet due to infective endocarditis. These procedures are less likely to be successful in older patients with the rigid, calcified, deformed valves of rheumatic heart disease or those with severe subvalvular chordal thickening and major loss of leaflet substance. Many of the latter patients require MVR, which is also usually the procedure of choice for patients with badly scarred mitral valves who have previously undergone MVR. Young patients in developing countries who have severe rheumatic MR in the absence of active carditis may undergo successful repair.

Ischemic MR following acute myocardial infarction may be managed by reattaching the papillary muscle to adjacent myocardium or by valve replacement. Ischemic MR secondary to severe annular dilatation may be treated by direct or ring annuloplasty.[176]

[177] [177A] Episodic MR due to transient ischemia is often eliminated by coronary revascularization, whereas severe, chronic MR secondary to fibrotic infarcted papillary muscle usually requires valve replacement.

Although MVR with a mechanical or bioprosthesis has been used successfully in treating MR for almost four decades,[181] there has been some dissatisfaction with the results of this operation. First, left ventricular function often deteriorates following this procedure, contributing to early and late mortality and late disability. The increase in afterload

Figure 46-16 Insertion of an annuloplasty ring. *(Reproduced with permission from Galloway AC, Colvin SB, Baumann FG, et al: Current concepts of mitral valve reconstruction for mitral insufficiency. Circulation 78:1087, 1988. Copyright 1989 American Heart Association.)*

Figure 46-17 Preoperative (PRE) and postoperative (POST) left ventricular (LV) ejection fractions for patients undergoing MVR with chordae tendineae severed (open squares) or with chordae tendineae preserved (closed circles). MVR with chords severed resulted in decreased ejection fraction, but MVR with chords preserved did not.
, $P < 0.05$ for comparing PRE and POST status with chords severed. *, No significant difference with chords preserved. *(From Rozich JD et al: Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation; mechanisms for differences in postoperative ejection performance. Circulation 86:1718, 1992.)*

consequent to abolishing the low impedance leak was first believed to be responsible, but now it is clear that the loss of annular-chordal-papillary muscle continuity interferes with left ventricular function in patients who have undergone MVR. This does not occur after mitral valve reconstruction.[180] Indeed, animal experiments have shown convincingly that the normal function of the mitral valve apparatus "primes" the left ventricle for normal contraction and that contraction is prevented when operation causes discontinuity of this apparatus. There is evidence from animal experiments[182] and from human patients[183] [184] [185] that preservation of the papillary muscle and its chordal attachments to the mitral annulus is beneficial to postoperative left ventricular function, after both mitral valve reconstruction and in MVR (Fig. 46-17) . Thus, preservation of these tissues, whenever possible, is now considered a critical feature of MVR.[186]

A second disadvantage of MVR results from the prosthesis itself. This includes thromboembolism or hemorrhage associated with mechanical prostheses, late mechanical dysfunction of bioprostheses, and the risk of infective endocarditis with all prostheses (see p. 1697). For these reasons, increasing efforts are being made to reconstruct the mitral valve whenever possible, especially in patients with isolated or predominant MR.[187] [188] [189] [190] These procedures have been widely employed in Europe since the early 1960s and are now frequently being used by surgeons in the United States as well. The Society of Thoracic Surgeons National Database Committee reported a 3 percent mortality rate in 4167 patients undergoing isolated mitral valve

repair[104] (see Table 46-2) .

Intraoperative transesophageal color flow Doppler mapping is extremely useful in assessing the adequacy of mitral valve repair. In the minority of patients with persistent severe MR in whom the operative results are unsatisfactory, the problem can usually be corrected immediately, or, if necessary, the valve can be replaced. Left ventricular outflow tract obstruction due to systolic anterior motion of the

mitral valve occurs in 5 to 10 percent of patients following mitral valve repair. The causes are not clear; but they may include excess valvular tissue with severe leaflet redundancy and/or an interventricular septum bulging into a small left ventricle.[191] [192] These complications may also be recognized intraoperatively by transesophageal echocardiography. Treatment with volume loading and beta-blocking agents is often helpful. The obstruction usually disappears with time; if it does not, reoperation and re-repair or MVR may be necessary.

Progressive decrease in the prevalence of rheumatic heart disease (involving severely damaged valves that often are not suitable for reconstructive surgery) and a simultaneous increase in degenerative causes of MR (including mitral valve prolapse and rupture of chordae tendineae) as well as in ischemic MR are increasing the number of patients in whom reconstruction is carried out.[193] In many centers in the United States, approximately two-thirds of all patients requiring operation for pure or predominant MR now receive reconstructive procedures, and the remainder undergo MVR. However, mitral valve repair is technically a more demanding procedure than is MVR, with a distinct learning curve for the surgeon. Furthermore, some regurgitant valves, particularly those that are thickened, severely deformed, calcified, and partly stenotic, are not suitable for reconstruction, and patients with these valves require MVR.[193A] [193B]

Minimally invasive surgical techniques (Fig. 46-18) utilizing a small, low, asymmetrical sternotomy or anterior thoracotomy[194] and percutaneous cardiopulmonary bypass,[195] [195A] although quite demanding technically, have been found to be less traumatic and can be employed for both valve repair and replacement. This approach has been reported to reduce cost, improve cosmetic results, and shorten the recovery time.[196] However, it also is technically difficult and is successfully performed by only a minority of cardiac surgeons.

SURGICAL RESULTS.

Mortality rates of 3 to 9 percent are now common in many centers for patients with pure or predominant MR (NYHA Class II or III) who undergo elective isolated MVR.[137] [197] [198] The Society of Thoracic Surgeons National Database Committee reported an overall operative mortality rate of 6.4 percent in 13,936 patients undergoing isolated MVR; this compares with 4.3 percent for isolated aortic valve replacement and 3 percent for

isolated mitral valve repair. The combination of MVR and repair of another valve was associated with a mortality rate of 12.5 percent and of MVR with coronary artery bypass grafting of 8 percent. The mortality rate is higher (up to 25 percent) in older patients with severe left ventricular dysfunction, especially when MR is secondary to myocardial ischemia, when pulmonary or renal function is impaired, or when the operation must be carried out as an emergency. Age *per se* is no barrier to successful surgery; MVR can be performed in patients older than 75 years of age if their general health status is adequate; however, surgery in these patients has a higher risk than in younger patients.[184]

Surgical treatment substantially improves survival in patients with symptomatic MR. Preoperative factors such as age less than 60 years, NYHA Class II, a cardiac index exceeding 2.0 liters/min/m^2 , a left ventricular end-diastolic pressure less than 12 mm Hg, and a normal ejection fraction and end-systolic volume all correlate with excellent immediate and long-term survival rates. Both preoperative end-systolic diameter (see Fig. 46-11) and ejection fraction (Fig. 46-19) are important predictors of short-term and long-term outcome. Excellent survival is observed in patients with end-systolic diameters less than 45 mm and ejection fractions of 60 percent or more. Intermediate outcomes are seen in patients with end-systolic diameters between 45 and 52 mm and ejection fractions between 50 and 60 percent. Poor outcomes are associated with values beyond these limits.

A large proportion of operative survivors have improved clinical status, quality of life, and exercise tolerance following valve replacement or repair. Severe pulmonary hypertension is reduced, and left ventricular end-diastolic volume and mass decrease. Depressed contractile function improves, especially if the papillary muscles and chordal attachment to the annulus remain intact. However, patients with MR who have marked left ventricular dysfunction preoperatively sometimes remain symptomatic with a depressed ejection fraction despite a technically satisfactory surgical procedure. Indeed, progressive left ventricular dysfunction and death from heart failure may occur in adults. Recovery of left ventricular function is much better in children.[199] Long-term survival in patients with predominant MR who undergo MVR may be poorer than in those with pure MS or with mixed stenotic and regurgitant lesions, presumably because left ventricular dysfunction may be quite advanced and largely irreversible by the time patients with pure MR develop serious symptoms.[200] Ten-year survival was 76 percent in patients in NYHA-Class I or II versus 48 percent in patients in Class III or IV.[200] Thus, every effort should be made to operate on patients before they develop serious symptoms. However, even though operating on patients with MR is clearly desirable before they develop marked left ventricular dysfunction[201] and despite the limitations of the results of surgical treatment, operation is still indicated in the majority of these patients because conservative therapy has little to offer.

The cause of MR also plays an important role in the outcome following surgical treatment.[202] In patients in whom mitral dysfunction is secondary to ischemic heart disease, the 5-year survival rate is about 40 percent, whereas in patients with rheumatic MR it is approximately 75 percent. Occlusive coronary artery disease coexisting with, but not the primary cause of, mitral dysfunction requires simultaneous coronary artery bypass grafting and mitral valve repair or replacement and is associated with decreased perioperative and long-term postoperative survival (Fig. 46-20) . However, some

improvement resulting from mitral valve repair or replacement can be expected even in patients with MR secondary to ischemic heart disease who did not respond to medical treatment and now have congestive heart failure, as long as the cardiac index exceeds 1.8 liters/min/m^2 and the ejection fraction is greater than 30 percent. When left ventricular dysfunction is more severe, however, the risk of perioperative death becomes very high.[203]

SURGICAL TREATMENT OF ACUTE MITRAL REGURGITATION.

Emergency surgical treatment may be required for patients with acute left ventricular failure caused by acute MR secondary to myocardial infarction and rupture of the head of a papillary muscle, by trauma to the mitral valve, or by infective endocarditis. Emergency surgery is associated with higher mortality rates than is elective surgery for chronic MR. However, unless patients with acute, severe MR and heart failure are treated aggressively, a fatal outcome is almost certain. If patients with MR secondary to acute myocardial infarction can be stabilized by medical treatment, it is preferable to defer operation until 4 to 6 weeks after the infarction. Vasodilator treatment may be useful during this period. However, medical management should not be prolonged if multisystem (renal and/or pulmonary) failure develops. Intraaortic balloon counterpulsation may be required to stabilize the patient preoperatively. Surgical mortality rates are also higher in patients with acute MR and refractory heart failure (NYHA Class IV), in those in whom a previously implanted prosthetic valve must be replaced because of thromboembolism or valve dysfunction, and in those with active infective endocarditis (of either a natural or a prosthetic valve). Despite the higher

Figure 46-18 *A,* Minimally invasive right parasternal incision: A 5- to 7-cm incision is made, resecting a small portion of the third and fourth costal cartilages. Cannulation of the groin vessels (femoral artery and vein) has been performed frequently but has been revised to allow for minimal wound and vascular complications. The groin incision is placed parallel to the groin crease and is only 5 cm long. The artery and vein are exposed, and, after heparinization, the vein is cannulated using a pursestring and a 25- to 27-French wire reinforced Biomedicus catheter over a wire and then a dilator. The arterial cannula may be introduced by a small transverse cut downward. *B,* With the minimally invasive approach, a right atrial incision is used after exclusion of both the inferior and the superior vena cava, and the valve is approached through the septum (insert). *C,* When the right atrium is incised, an incision is made in the atrial septum through the fossae ovalis. Retraction sutures, on both the right atrium and the atrial septum, of 2-0 silk, are then used to elevate the septum and to keep the left atrium open. The mitral valve will then be exposed (insert). *(From Byrne JG, et al: Minimally invasive direct access mitral valve surgery. Semin Thorac Cardiovasc Surg 11:212, 1999.)*

surgical risks, the efficacy of early operation has been established in patients with infective endocarditis complicated by medically uncontrollable congestive heart failure and/or recurrent emboli (see Chap. 47) . Because fungal endocarditis responds poorly to medical management, the practice now is to recommend valve replacement in these patients *before* the onset of heart failure or embolization.

INDICATIONS FOR OPERATION.

The threshold for surgical treatment of MR is declining for several reasons. These include the reductions in operative mortality, the improvements in both mitral valve reconstructive procedures and procedures involving prosthetic valves, and the recognition of the poor long-term results in many patients whose MR is corrected only after a long history of impaired

Figure 46-19 Graph of the late survival of of patients who underwent surgical correction of MR according to preoperative echocardiographic ejection fraction (EF). *(Reproduced with permission from Enriquez-Sarano M, et al: Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation 90:833, 1994. Copyright 1994 American Heart Association.)*

left ventricular function, atrial fibrillation, or pulmonary hypertension.

A detailed echocardiographic examination should be carried out to assess the likelihood that mitral valve repair, rather than replacement, is possible. In addition, the difference in outcome between these procedures should be weighed when deciding whether or not to proceed. Asymptomatic patients (NYHA Class I) should be considered for mitral valve reconstruction only if they have left ventricular dysfunction (ejection fraction 60 percent and/or left ventricular end-systolic diameter 45 mm). Class I patients with normal left ventricular function should be followed clinically and by echocardiography every 6 to 12 months. Rarely, they *may* be considered for operation if atrial fibrillation or pulmonary hypertension is present. At times, a careful history and performance of an exercise test often reveal that these patients are not truly asymptomatic. [204] [205] Patients with severe MR who are asymptomatic, who perform well on an exercise test, and who have excellent ventricular function (ejection fraction > 70 percent, end-systolic diameter <40 mm, end-systolic volume <40 ml/m^2) can be followed by echocardiography every 6 to 12 months. However, operation may be considered even in asymptomatic patients if they are less than 70 years of age, if they are likely to be candidates for mitral valve repair, and if ventricular function (as reflected by end-systolic diameter and ejection fraction) shows *progressive* deterioration. If valve replacement is likely to be necessary, a higher threshold for clinical and hemodynamic impairment should be employed than if valve reconstruction is contemplated. Because of the higher operative mortality, older patients (>75 years of age) should, in general, undergo surgery only if they are symptomatic.

Patients with severe MR and moderate or severe symptoms (NYHA Classes II, III, and IV) should generally be considered for surgery. One exception is a patient in whom echocardiography suggests that MVR will be required and

Figure 46-20 Plots of overall survival compared for repair and replacement groups for patients who had (left) or did not have (right) associated coronary artery bypass grafting (CABG). Note that the outcome is better with repair than with replacement in both groups and that the outcome is worse in patients who underwent CABG and MVR. *(From Enriquez-Sarano M, Schaff HV, Orszulak TA, et al: Valve repair improves the outcome of surgery for mitral regurgitation: A multivariate analysis. Circulation 91:1022, 1995.)*

whose ejection fraction is less than 30 percent. Because of the high risk of operation in these patients, medical therapy is usually advised, but the outcome is poor in any event. However, when mitral valve repair appears possible, even patients with serious left ventricular dysfunction may be considered for operation.[206] [207] [208]

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Mitral Valve Prolapse Syndrome

ETIOLOGY AND PATHOLOGY

DEFINITION.

The mitral valve prolapse (MVP) syndrome has been given many names, including the systolic click-murmur syndrome, Barlow syndrome, billowing mitral cusp syndrome, myxomatous mitral valve syndrome, floppy valve syndrome, and redundant cusp syndrome.[209] [210] [211] [212] [213] It is a variable clinical syndrome that results from diverse pathogenic mechanisms of one or more portions of the mitral valve apparatus, valve leaflets, chordae tendineae, papillary muscle, and valve annulus. The MVP syndrome is one of the most prevalent cardiac valvular abnormalities and was

previously thought to affect as much as 5 to 10 percent of the population.[212] It now appears likely that overdiagnosis occurred in many individuals, perhaps because of the absence of rigorous echocardiographic criteria. Using such criteria (to be discussed), a community-based study showed that MVP syndrome occurred in only 2.4 percent of the population.[202] The syndrome is twice as frequent in females as in males. However, serious MR occurs more frequently in elderly males with MVP than in young females with this disorder.

Normally, the mitral valve billows slightly into the left atrium, and an exaggerated finding should be termed "billowing mitral valve." A "floppy valve" is regarded as an extreme

form of billowing. MR occurs when the leaflet edges of the valve do not coapt. With chordal rupture, the prolapsed mitral valve is "flail." Obviously, these conditions blend into one another, and it is often difficult to distinguish among them.

Perloff and coworkers have proposed specific clinical criteria for the diagnosis of MVP.[213] They have divided the findings into three groups (Table 46-5) : (1) major criteria, the presence of one or more of which establishes the diagnosis of MVP; (2) minor criteria, the presence of which cannot be discounted and should raise the suspicion of MVP but which by themselves are not sufficient to establish the diagnosis; and (3) other findings not shown in Table 46-5 , which, although often present in patients with MVP, are nonspecific. Superior displacement of the mitral valve leaflets by more than 2 mm above the annulus is an important diagnostic criterion.[202] In addition, Marks and colleagues emphasized the importance of systolic displacement of one or both mitral leaflets into the left atrium in

TABLE 46-5 -- DIAGNOSTIC CRITERIA IN MITRAL VALVE PROLAPSE

MAJOR CRITERIA
Auscultation
Mid- to late systolic clicks and late systolic murmur or "whoop" alone or in combination at the cardiac apex
Two-dimensional echocardiogram
Marked superior systolic displacement of mitral leaflets (2 mm above annulus) with coaptation point at or superior to annular plane
Mild to moderate superior systolic displacement of mitral leaflets with:
Chordal rupture
Doppler mitral regurgitation
Annular dilatation
Echocardiogram plus auscultation
Mild to moderate superior systolic displacement of mitral leaflets with:
Prominent mid- to late systolic clicks at the cardiac apex
Apical late systolic or holosystolic murmur in the young patient
Late systolic "whoop"
MINOR CRITERIA
Auscultation
Loud S_1 with an apical holosystolic murmur
Two-dimensional echocardiogram
Isolated mild to moderate superior systolic displacement of the posterior mitral leaflet
Moderate superior systolic displacement of both mitral leaflets
Echocardiogram plus history of:

Mild to moderate superior systolic displacement of mitral leaflets with:

Focal neurologic attacks or amaurosis fugax in the young patient

First-degree relatives with major criteria

Modified from Perloff JK, Child JS, Edwards JE: New guidelines for the clinical diagnosis of mitral valve prolapse. Am J Cardiol 57:1124, 1986.

the *parasternal view* in the two-dimensional echocardiogram in the diagnosis of MVP.[214] Such an approach avoids overdiagnosis, which may occur with posterior bowing of the mitral valve on M-mode echocardiography and even in the four-chamber view on two-dimensional echocardiography.

ETIOLOGY.

Most frequently, MVP occurs as a primary condition that is not associated with other diseases.[211] However, it has also been reported to be associated with many conditions.[212] [215] [216] [217] [218] [219] [220] [221] [222] [223] [224] [225] [226] [227] [227A] [228] [229] MVP occurs quite commonly in heritable disorders of connective tissue that increase the size of the mitral leaflets and apparatus, including Marfan syndrome (see Chap. 56) , Ehlers-Danlos syndrome [224] (see Chap. 56) , osteogenesis imperfecta, pseudoxanthoma elasticum,[225] periarteritis nodosa, myotonic dystrophy,[218] von Willebrand disease,[217] hyperthyroidism,[216] and congenital malformations such as Ebstein anomaly of the tricuspid valve, atrial septal defect of the ostium secundum variety, the Holt-Oram syndrome, and hypertrophic cardiomyopathy.[51] There may be a higher incidence of MVP in patients with an asthenic habitus[226] and various congenital thoracic deformities, including "straight back syndrome," pectus excavatum, and a shallow chest.[220] [222] These associations have not been proved using rigorous echocardiographic criteria, and, with the exception of connective tissue disorders, it is not clear how many of these are chance associations.

PATHOLOGY (Fig. 46-21) .

Findings include myxomatous proliferation of the mitral valve, in which the spongiosa component of the valve (i.e., the middle layer of the leaflet composed of loose, myxomatous material) is unusually prominent,[227] [227A] and the quantity of acid mucopolysaccharide is increased. Electron microscopy shows a haphazard arrangement of cells with disruption and with fragmentation of collagen fibrils (Fig. 46-22) . The concordance between inadequate production of type III collagen and echocardiographic findings of MVP in patients with type IV Ehlers-Danlos syndrome suggests that this collagen abnormality may be responsible in patients with this syndrome.[228] Although the majority of patients with MVP exhibit myxomatous degeneration of the valve, postinflammatory changes may also be responsible for prolapse.[229]

In mild cases, the valvular myxoid stroma is enlarged on histological examination, but the leaflets are grossly normal. However, with increasing quantities of myxoid stroma, the leaflets become grossly abnormal, redundant, and prolapsed. Regions of endothelial

disruption are common and are possible sites of endocarditis or thrombus formation.[230] The severity of MR depends on the extent of the prolapse. The cusps of the mitral valve, the chordae tendineae, and the annulus may all be affected by myxomatous proliferation. Degeneration of collagen within the central core of the chordae tendineae is primarily responsible for chordal rupture, which often occurs and may intensify the severity of MR. Increased chordal tension resulting from the enlarged area of the valve cusps may play a contributory role.[231] Myxomatous changes in the annulus may result in annular dilatation and calcification, contributing to the severity of MR.

Myxomatous proliferation, although most commonly affecting the mitral valve, has also been described in the tricuspid, aortic, and pulmonic valves, particularly in patients with the Marfan syndrome, and may lead to regurgitation of these valves as well as the mitral valve.

The MVP syndrome can coexist with rheumatic MS, and it may develop following mitral valvotomy. *Ischemic heart disease* and MVP are both common disorders and sometimes coexist. MVP may also occur secondary to papillary muscle dysfunction. In some patients, MVP has been documented to develop for the first time *following* myocardial infarction.[232] It has been proposed that MVP may *cause* myocardial ischemia by increasing tension on the base of the involved muscle. During systole, the tips of the papillary muscles move basally instead of apically.

CLINICAL MANIFESTATIONS

The MVP syndrome appears to exhibit a strong hereditary component[209] [232] and in some patients is transmitted as an

Figure 46-21 *A,* Myxomatous mitral valve, atrial view, from a patient with severe mitral regurgitation. The surface area of the valve is increased, with increased folding of the valve surface. The widths of the anterior leaflet (AL) and the posterior leaflet (PL) are almost equal. Individual scallops of the posterior leaflet are enlarged and redundant. *B,* Comparison of an excised myxomatous mitral valve from a patient who had severe mitral regurgitation (top) with a normal mitral valve from a patient who died of noncardiac causes (bottom), showing the increased surface area of both anterior leaflets (AL) and posterior leaflets (PL) of the myxomatous valve with enlarged and redundant posterior leaflet scallops, enlarged mitral annulus, and elongated chordae tendineae. PCS = posteromedial commissural scallops; MS = middle scallop; ACS = anterolateral commissural scallop. *(From Boudoulas H, Wooley CF: Mitral valve prolapse and the mitral valve prolapse syndrome. In Yu P, Goodwin J [eds]: Progress in Cardiology. Philadelphia, Lea and Febiger, 1986.)*

autosomal dominant trait with varying penetrance. The clinical presentations of the MVP syndrome are diverse.[213] The condition has been observed in patients of all ages and in both sexes. Despite the overestimation of the prevalence in the population referred to earlier, MVP is the most common cause of isolated MR requiring surgical treatment in the United States.[211] Echocardiographic evidence of MVP has been found in more than

90 percent of patients with the Marfan syndrome[233] and in many of their first-degree relatives.

History

A large majority of patients with MVP are asymptomatic and remain so throughout their lives[234] (Fig. 46-23) . In many cases, otherwise asymptomatic patients with MVP suffer from undue anxiety, perhaps precipitated by their having been informed of the presence of heart disease. Boudoulas and colleagues have called attention to an "MVP syndrome" with a characteristic systolic nonejection click and various nonspecific symptoms, such as fatigability, palpitations, postural orthostasis, and neuropsychiatric symptoms, as well as symptoms of autonomic dysfunction.[235] How, and even whether, these symptoms relate to the presence of MVP is not clear. It has been suggested that many of the symptoms are related to dysfunction of the autonomic nervous system, with increased excretion of catecholamines that occurs frequently in the MVP syndrome.[236] [237]

Patients may complain of syncope, presyncope, palpitations, chest discomfort, and, when MR is severe, symptoms of diminished cardiac reserve. Chest discomfort may be typical of angina pectoris but is more often atypical in that

Figure 46-22 Electron micrographs of mitral valve. *A,* Normal mitral valve: Elastic fiber is composed of amorphous component (A), associated with microfibrils (M) oriented in parallel. Collagen fibrils (C) are compactly arranged (Kajikawa stain; original magnification 22,000). *B,* Prolapsed mitral valve. Collagen fibrils show spiraling appearance in longitudinal section (arrow) and flower-like appearance (arrowhead) in transverse section (Kajikawa stain; original magnification 27,000). *(From Tamura K, Fukuda Y, Ishizaki M, et al: Abnormalities in elastic fibers and other connective-tissue components of floppy mitral valve. Am Heart J 129:1149, 1995.)*

it is prolonged, not clearly related to exertion, and punctuated by brief attacks or severe stabbing pain at the apex. The discomfort may be secondary to abnormal tension on papillary muscles. In patients with MVP and severe MR, the symptoms of the latter (fatigue, dyspnea, and exercise limitation, see p. 1658) are present. Patients with MVP and arrhythmias (to be discussed) may have symptoms related to the latter.

Physical Examination

The body weight is often low, and the habitus may be asthenic. Blood pressure is usually normal or low; orthostatic hypotension may be present. As already mentioned, patients with MVP have a higher than expected prevalence of "straight back syndrome," scoliosis, and pectus excavatum.[222] MR ranges from nonexistent to severe.

The auscultatory findings are best elicited with the diaphragm of the stethoscope. The

patient should be examined in the supine, left decubitus, and sitting positions. The physical findings unique to the MVP syndrome are detected by auscultation and can be corroborated by phonocardiography. The most important is a nonejection systolic click at least 0.14 second after S_1 (see Fig. 4-30) . [237A] This can be differentiated from a systolic ejection click by phonocardiography because it occurs *after* the beginning of the carotid pulse upstroke. Occasionally, multiple mid- and late systolic clicks are audible, most readily along the lower left sternal border. The clicks are believed to be produced by sudden tensing of the elongated chordae tendineae and of the prolapsing leaflets. They are often, although not invariably, followed by a mid- to late crescendo systolic murmur that continues to A_2 . This murmur is similar to that produced by papillary muscle dysfunction, which is readily understandable because both result from mid- to late systolic

Figure 46-23 *Left panel,* The dynamic spectrum and progression of mitral valve prolapse (MVP) are shown. A subtle gradation exists between the normal mitral valve and valves that produce mild MVP without mitral regurgitation (no MR). Progression from the level MVP-no MR to another level may or may not occur. Most of the MVP syndrome cases occupy the area above the dotted line, whereas progressive mitral valve dysfunction cases occupy the area below the dotted line. *Right panel,* The large circle represents the total number of patients with MVP. Patients with MVP may be symptomatic or asymptomatic. Symptoms may be directly related to mitral valve dysfunction (black circle) or to autonomic dysfunction (pink circle). Certain patients with symptoms directly related to mitral valve dysfunction may present with and continue to have symptoms secondary to autonomic dysfunction. *(From Boudoulas H, Wooley CF: Mitral Valve Prolapse and the Mitral Valve Prolapse Syndrome. Mount Kisco, NY, Futura Publishing Co, Inc, 1988.)*

Figure 46-24 Dynamic auscultation in MVP. Any maneuver that decreases left ventricular (LV) volume (e.g., decreased venous return, tachycardia, decreased outflow impedance, increased contractility) will worsen the mismatch in size between the enlarged mitral valve and LV chamber, resulting in prolapse earlier in systole and movement of the click (C) and murmur (M) toward the first heart sound (S_1). Conversely, maneuvers that increase LV volume (e.g., increased venous return, bradycardia, increased outflow impedence, decreased contractility) will delay the occurrence of prolapse, resulting in movement of the click and murmur toward the second heart sound. (S_2). Ao = aorta. *(From Prabhu SD, O'Rourke RA: Mitral valve prolapse. In Rahimtoola SH (ed): Valvular Heart Disease. Atlas of Heart Diseases. Vol. 11. Braunwald E, series ed. Philadelphia: Current Medicine, 1997, pp 10.1-10.18 Adapted from O'Rourke RA, Crawford MH: The systolic click-murmur syndrome: Clinical recognition and management. Curr Probl Cardiol 1:9, 1976.)*

MR. In general, the duration of the murmur is a function of the severity of the MR. When the murmur is confined to the latter portion of systole, MR usually is not severe. However, as MR becomes more severe, the murmur commences earlier and ultimately becomes holosystolic.

It is important to emphasize the variability of the physical findings in the MVP syndrome. Some patients exhibit both a midsystolic click and a mid- to late systolic murmur; others present with only one of these two findings; still others have only a click on one occasion and only a murmur on another, both on a third examination, and no abnormality at all on a fourth. Conditions other than MVP cause midsystolic clicks; these

include tricuspid valve prolapse, atrial septal aneurysms, and extracardiac causes.

DYNAMIC AUSCULTATION.

The auscultatory (and phonocardiographic) findings are exquisitely sensitive to physiological and pharmacological interventions, and recognition of the changes induced by these interventions is of great value in the diagnosis of the MVP syndrome (Fig. 46-24 ; see also Tables 4-4 and 46-4) . The mitral valve begins to prolapse when the reduction of left ventricular volume during systole reaches a critical point at which the valve leaflets no longer coapt; at that instant, the click occurs and the murmur commences. Any maneuver that decreases left ventricular volume, such as a reduction of impedance to left ventricular outflow, a reduction in venous return, tachycardia, or an augmentation of myocardial contractility, results in an earlier occurrence of prolapse during systole. As a consequence, the click and onset of the murmur move closer to S_1 . When prolapse is severe and/or left ventricular size is markedly reduced, prolapse may begin with the onset of systole. As a consequence, the click may not be audible, and the murmur may be holosystolic. On the other hand, when left ventricular volume is augmented by an

increase in the impedance to left ventricular emptying, an increase in venous return, a reduction of myocardial contractility, or bradycardia, both the click and the onset of the murmur will be delayed.

During the straining phase of the Valsalva maneuver, upon sudden standing, and early during the inhalation of amyl nitrite, cardiac size decreases, and both the click and the onset of the murmur occur earlier in systole. In contrast, a sudden change from the standing to the supine position, leg-raising, squatting, maximal isometric exercise, and, to a lesser extent, expiration will delay the click and the onset of the murmur. During the overshoot phase of the Valsalva maneuver (i.e., six to eight cycles following release) and with prolongation of the R-R interval, either following a premature contraction or in atrial fibrillation, the click and onset of the murmur are usually delayed, and the intensity of the murmur is reduced. Maneuvers that elevate arterial pressure, such as isometric exercise, increase the intensity of the click and murmur. In general, when the onset of the murmur is delayed, both its duration and intensity are diminished, reflecting a reduction in the severity of MR.

The response to several interventions may be helpful in differentiating hypertrophic obstructive cardiomyopathy (HOCM) from MVP. During the strain of the Valsalva maneuver, the murmur of HCM increases in intensity, whereas the murmur of MVP becomes longer but usually not louder. The murmur of HCM becomes louder after amyl nitrite inhalation, whereas that of MVP does not. Following a premature beat, the murmur of HCM increases in intensity and duration, whereas that due to MVP usually remains unchanged or decreases.

LABORATORY EXAMINATION

ELECTROCARDIOGRAPHY

The ECG is usually normal in asymptomatic patients with MVP. In a minority of asymptomatic patients and in many symptomatic patients, the ECG shows inverted or biphasic T waves and nonspecific ST segment changes in leads II III, and a_{Vf} and occasionally in the anterolateral leads as well.

ARRHYTHMIAS.

A spectrum of arrhythmias have been observed. These include atrial and ventricular premature contractions and supraventricular and ventricular tachyarrhythmias,[238] [239] [239A] as well as bradyarrhythmias due to sinus node dysfunction or varying degrees of atrioventricular block. The mechanism of the arrhythmias is not clear. Diastolic depolarization of muscle fibers in the anterior mitral leaflet in response to stretch has been demonstrated experimentally, and the abnormal stretch of the prolapsed leaflet may be of pathogenetic significance. Wit and associates have shown that mitral valve leaflets contain atrium-like muscle fibers in continuity with left atrial myocardium.[240] It is possible that mechanical stimulation of these fibers generates slow-response action potentials and sustained rhythmic action that penetrates the cardiac chambers.[240]

Paroxysmal supraventricular tachycardia is the most common sustained tachyarrhythmia in patients with MVP and may be related to what may be an increased incidence of left atrioventricular bypass tracts.[238] The incidence of MVP among patients with the Wolff-Parkinson-White syndrome is increased.[241] There is also an increased association between MVP and prolongation of the QT interval, and this association may play a role in the pathogenesis of serious ventricular arrhythmias.[238] Patients with MVP have an increased incidence of abnormal late potentials on signal-averaged ECGs, as well as reduced heart rate variability.[239]

MITRAL VALVE PROLAPSE AND SUDDEN DEATH.

The relation between the MVP syndrome and sudden death is not clear. However, the best evidence suggests that MVP increases the risk of sudden death slightly,[209] [242] [243] [243A] especially in patients with severe MR or severe valvular deformity. The immediate cause of the sudden, unexpected death is probably ventricular fibrillation.[244] Kligfield and Devereux have identified the following as potential risks for sudden death in patients with MVP: the presence of severe MR, complex ventricular arrhythmias, QT interval prolongation, and a history of syncope and palpitations.[238]

ECHOCARDIOGRAPHY (See also Chap. 7) .

Echocardiography plays a key role in the diagnosis of MVP and has been most useful in the delineation of this syndrome[244A] (see Figs. 7-57 and 7-58) . The most common

finding on M-mode echocardiography is abrupt posterior movement of the posterior leaflet or of both mitral leaflets in midsystole with the leaflet interface greater than 2 mm posterior to the C-D line. This movement occurs simultaneously with the systolic click. A second finding is pansystolic posterior prolapse of one or both leaflets, giving rise to a U- or hammock-shaped configuration 3 mm or more posterior to the C-D segment.

To establish the diagnosis, the two-dimensional echocardiogram must show that one or both mitral valve leaflets billow by at least 2 mm into the left atrium during systole in the long-axis view (Fig. 46-25) .[202] [245] [246] Thickening of the involved leaflet to greater than 5 mm supports the diagnosis. This finding is also helpful in identifying patients at significant risk for developing severe MR or infective endocarditis.[214] The mitral annular diameter is often abnormally increased.[245] [247] Transesophageal echocardiography provides additional details regarding the mitral valve apparatus, such as rupture of chordae tendineae. In MR secondary to MVP, the echocardiogram provides valuable information regarding left ventricular function.

The variability in physical findings in this syndrome, already commented upon, extends to the echocardiogram.[247] [248] Thus, some patients have a systolic click with or without a murmur and show no evidence of MVP on the echocardiogram. Conversely, the echocardiographic findings of MVP may be observed in patients without a click or murmur. Others have both the typical echocardiographic and auscultatory features. The echocardiographic findings of MVP have been reported to occur in a large number of first-degree relatives of patients with established MVP. Two-dimensional echocardiography has also revealed prolapse of the tricuspid and aortic valves in approximately 20 percent of patients with MVP.[249] Conversely, however, prolapse of the tricuspid and aortic

Figure 46-25 Diagram of parasternal view of two-dimensional echocardiography in normal subject and in patient with MVP. *A,* Normal parasternal long-axis view at end-diastole immediately preceding mitral valve closure. Labeled are the anterior leaflet (AL), posterior leaflet (PL), ventricular septum (VS), posterior wall (PW), aorta (AO), left atrium (LA), and left ventricle (LV). Systolic prolapse may be predominantly anterior leaflet (*B,* arrows), predominantly posterior (*C,* arrow), or both (*D,* arrows). The presence of leaflet thickening, leaflet redundancy, chordal elongation, and annular dilatation should also be assessed on the two-dimensional study. Color flow and pulsed-wave Doppler studies are used to determine the presence and extent of mitral regurgitation, an important supporting finding in borderline cases. *(From Prabhu SD, O'Rourke RA: Mitral valve prolapse. In Rahimtoola SH (ed): Valvular Heart Disease. Atlas of Heart Diseases. Vol. 11. Braunwald E, series ed. Philadelphia: Current Medicine, 1997, pp 10.1-10.18.)*

valves occurs *uncommonly* in patients without prolapse of the mitral valve.[249]

Doppler echocardiography frequently reveals mild MR that is not always associated with an audible murmur. Color flow Doppler echocardiography is useful in identifying the location and severity of the regurgitant jets. MR is moderate or severe in about 10

percent of patients with MVP, most commonly in men over the age of 50.[247]

STRESS SCINTIGRAPHY.

The differential diagnosis between two common conditions--MVP associated with atypical chest pain and ECG abnormalities and primary coronary artery disease associated with MVP--may be aided by exercise electrocardiography. However, myocardial perfusion scintigraphy using thallium-201 or sestamibi during pharmacological exercise stress (see Chap. 9) is more specific. When findings are normal, i.e., when there is no evidence of stress-induced regional myocardial ischemia, the diagnosis of MVP unrelated to ischemic heart disease is favored.[250]

ANGIOGRAPHY.

The configuration of the left ventriculogram during systole is helpful in confirming the diagnosis of MVP. The right anterior oblique projection is most useful for defining the posterior leaflet of the mitral valve, and the left anterior oblique projection is most useful for studying the anterior leaflet. The most helpful sign is extension of the mitral leaflet tissue inferiorly and posteriorly to the point of attachment of the mitral leaflets to the mitral annulus.[251] Angiography may also reveal scalloped edges of the leaflets, reflecting redundancy of tissue. Other abnormalities noted on angiography of some patients with MVP include dilatation, decreased systolic contraction, and calcification of the mitral annulus and poor contraction of the basal portion of the left ventricle.[252]

NATURAL HISTORY

The outlook for children with MVP is excellent; a large majority remain asymptomatic for many years without any change in clinical or laboratory findings[209] [234] [253] [253A] (see Fig. 46-23) . Zuppiroli and associates monitored 316 patients with MVP for an average of more than 8 years; 70 percent were women and 29 percent had familial MVP.[234] Serious complications (cardiac death, need for cardiac surgery, acute infective endocarditis, or cerebral embolic events) occurred at a rate of only 1 per 100 patient years.[234]

Progressive MR with gradual increase in left atrial and left ventricular size, atrial fibrillation, pulmonary hypertension, and the development of congestive heart failure is the most frequent serious complication,[234] [254] occurring in about 15 percent of patients over a 10- to 15-year period. The incidence of this complication is significantly greater in patients with both murmurs and clicks than in those with an isolated click. In many patients, rupture of chordae tendineae is responsible for the precipitation and/or intensification of the MR. Severe MR occurs more frequently in men older than 50 years of age with MVP and in patients with thickened (>5 mm diameter) mitral valve leaflets.[243] [254] [255] [256] Patients with the MVP syndrome are also at risk of developing infective endocarditis.[257] [257A] Although the incidence of infective endocarditis appears to be extremely low in patients with only a midsystolic click, it increases in patients with a systolic murmur. The incidence is higher in men than in women and in those more than 50 years of age. Infective endocarditis often aggravates the severity of MR and

therefore the need for surgical treatment.

Acute hemiplegia, transient ischemic attacks, cerebellar infarcts, amaurosis fugax, and retinal arteriolar occlusions have been reported to occur more frequently in patients with the MVP syndrome, suggesting that cerebral emboli are unusually common in this condition.[258] [259] [259A] It has been proposed that these neurological complications are associated with loss of endothelial continuity and tearing of the endocardium overlying the myxomatous valve, which initiates platelet aggregation and the formation of mural platelet-fibrin complexes.[258] Although it has been proposed that embolization secondary to MVP may be a significant cause for unexplained strokes in young people without cerebrovascular disease, a large case-controlled study showed no association between MVP and ischemic neurological events in persons under 45 years of age.[260]

MANAGEMENT (Table 46-6)

Patients with the physical findings of MVP (and those without such findings who have been given the diagnosis) should have two-dimensional and color flow Doppler echocardiography. This procedure should also be performed in first-degree relatives of patients with MVP.[51] The diagnosis of MVP requires definitive echocardiographic findings, and overdiagnosis and incorrect "labeling" have been a major problem with this condition. *Asymptomatic patients* (or those whose principal complaint is anxiety), with no arrhythmias evident on a routine extended ECG tracing and without evidence of MR, have an excellent prognosis. They should be reassured about the favorable prognosis and be encouraged to engage in normal life styles, but should have follow-up examinations every every 3 to 5 years. This should include a two-dimensional echocardiogram and a color flow Doppler study.

Patients with a long systolic murmur may show progression of MR and should be evaluated more frequently, at intervals of approximately 12 months. *Endocarditis prophylaxis* is advisable for patients with a typical click and systolic murmur and in those with only a click and characteristic echocardiographic features of MVP. Prophylaxis does *not* appear to be necessary for patients with a midsystolic

TABLE 46-6 -- MATCHING RISK AND MANAGEMENT IN PATIENTS WITH MITRAL VALVE PROLAPSE

RISK LEVEL	PATIENTS	MANAGEMENT
Lowest	Patients without mitral regurgitant murmurs or regurgitation revealed by Doppler echocardiography, especially women younger than age 45	Reassurance; prophylactic antibiotics not clearly necessary and if used should not include medication with risk of allergic reactions; reevaluation and echocardiography at moderate intervals (5 years)

Moderate	Patients with intermittent or persistent mitral murmurs and mild regurgitation revealed by Doppler echocardiography	Antibiotic prophylaxis with erythromycin or amoxicillin; treatment of even mild established hypertension; reevaluation and echocardiography more frequently (2 to 3 years)
High	Patients with moderate or severe mitral regurgitation	Antibiotic prophylaxis with amoxicillin (unless allergic); optimization of afterload (arterial pressure); reevaluation with Doppler echocardiography and other tests if needed annually; consider valve repair or replacement for exertional dyspnea or decline of left ventricular function into low-normal range

From Devereux RB: Recent developments in the diagnosis and management of mitral valve prolapse. Curr Opin Cardio 10:107, 1995. Modified from Devereux RB, Kligfield P: Mitral valve prolapse. In Rakel R: Current Therapy. Philadelphia, WB Saunders, 1992, pp 237, 241.

click without a systolic murmur or without typical echocardiographic findings (see also Chap. 47) .[261]

Patients with a history of palpitations, lightheadedness, dizziness, or syncope or those who have ventricular arrhythmias or QT prolongation on a routine ECG should undergo ambulatory (24-hour) ECG monitoring and/or exercise ECG to detect arrhythmias. Because of the risk, albeit very low, of sudden death,[238] electrophysiologic studies may be carried out to characterize arrhythmias if they exist. Beta-adrenergic blockers are useful in the treatment of palpitations secondary to frequent premature ventricular contractions and for self-terminating episodes of supraventricular tachycardia. These drugs may also be useful in the treatment of chest discomfort, both in patients with associated coronary artery disease and in those with normal coronary vessels in whom the symptoms may be due to regional ischemia secondary to MVP. Radiofrequency ablation of atrioventricular bypass tracts is useful for frequent or prolonged episodes of supraventricular tachycardia.

Aspirin should be given to patients with MVP who have had a documented focal neurological event and in whom no other cause, such as a left atrial thrombus or atrial fibrillation, is apparent. Treatment with an angiotensin-converting enzyme inhibitor has been reported to reduce the severity of MR in patients with MVP.[171]

Patients with MVP and severe MR should be treated similarly to other patients with severe MR (see p. 1661) and may require mitral valve surgery. Reconstructive surgery without valve replacement is usually possible (see Fig. 46-15) .[179A] [211] [261A] Therefore, the threshold for surgical treatment in these patients is lower than in patients with MR in

whom MVR may be necessary. Approximately 50 percent of all mitral valve reconstructions for MR are now carried out in patients with MVP. Among 252 such patients operated upon at the Brigham and Women's Hospital, resection of the most deformed leaflet segment and insertion of an annuloplasty ring to reduce the dilated annulus was the most commonly employed procedure. Rupture of the chordae tendineae to the anterior leaflet could sometimes be treated by chordal transfer from the posterior leaflet. In other patients, shortening of the chordae tendineae and/or papillary muscle was necessary. The operative mortality was 2 percent; structural valve degeneration occurred in 15 percent of patients at 5 years. Chordal replacement with polytetrafluoroethylene sutures has been reported to enhance mitral valve repair in patients with MVP.[210]

Coronary arteriography should be performed in patients with angina pectoris on effort and/or ischemic ECG changes or those with abnormalities on a stress myocardial perfusion scan. Treatment should take into account both the responsiveness of symptoms to medical management and the coronary anatomy.

Although this discussion has focused attention on complications of the MVP syndrome, it should not be forgotten that, on the whole, this is a benign condition and that the *vast majority* of patients with this syndrome remain asymptomatic for their entire lives and require, at most, observation every few years and reassurance.

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Aortic Stenosis

ETIOLOGY AND PATHOLOGY

Obstruction to left ventricular outflow is localized most commonly at the aortic valve and is discussed in this section. However, obstruction may also occur above the valve (supravalvular stenosis) or below the valve (discrete subvalvular aortic stenosis [see Chap. 43]), or it may be caused by hypertrophic obstructive cardiomyopathy (see Chap. 48) . Valvular aortic stenosis (AS) *without accompanying mitral valve disease* is more common in men than in women and very rarely occurs on a rheumatic basis. Instead, isolated AS is usually either congenital or degenerative in origin[262] [263] (Figs. 46-26 and 46-27) .

CONGENITAL AORTIC STENOSIS (See also Chaps. 43 and 44) .

Congenital malformations of the aortic valve may be unicuspid, bicuspid, or tricuspid, or there may be a dome-shaped diaphragm. *Unicuspid valves* produce severe obstruction in infancy and are the most frequent malformations found in fatal valvular AS in children under the age of 1 year. Congenitally *bicuspid valves* may be stenotic with commissural fusion at birth, but more often they are not responsible for serious narrowing of the aortic orifice during childhood. Their abnormal architecture induces turbulent flow, which traumatizes the leaflets and leads to fibrosis, increased rigidity, calcification of the leaflets, and narrowing of the aortic orifice in adulthood[264] (Fig. 46-28) . Infective endocarditis may develop on a congenitally bicuspid valve, which then becomes regurgitant. Rarely, a congenitally bicuspid valve is purely regurgitant in the absence of antecedent infection.

A third form of a congenitally malformed valve is *tricuspid,* with the cusps of unequal

size and some commissural fusion. Although many of these valves retain normal function throughout life, it has been postulated that the turbulent flow produced by the mild congenital architectural

Figure 46-26 Types of aortic valve stenosis. *A,* Normal aortic valve. *B,* Congenital aortic stenosis. *C,* Rheumatic aortic stenosis. *D,* Calcific aortic stenosis. *E,* Calcific senile aortic stenosis. *(From Brandenburg RO, et al: Valvular heart disease--When should the patient be referred? Pract Cardiol 5:50, 1979.)*

Figure 46-27 Causes of aortic stenosis, shown for two age groups. Among patients younger than 70 years (*top*), calcification of congenitally bicuspid valves accounted for half of the surgical cases. In contrast, in those 70 years of age or older (*bottom*), degenerative calcification accounted for almost half of the cases. *(From Passik CS, et al: Temporal changes in the causes of aortic stenosis: A surgical pathologic study of 646 cases. Mayo Clin Proc 62:119, 1987.)*

abnormality may lead to fibrosis and ultimately to calcification and stenosis. Tricuspid stenotic aortic valves in adults may be congenital, rheumatic, or degenerative in origin.

ACQUIRED AORTIC STENOSIS.

Rheumatic AS results from adhesions and fusions of the commissures and cusps and vascularization of the leaflets of the valve ring, leading to retraction and stiffening of the free borders of the cusps. Calcific nodules develop on both surfaces, and the orifice is reduced to a small round or triangular opening. As a consequence, the rheumatic valve is often regurgitant as well as stenotic.[262] The heart frequently exhibits other stigmata of rheumatic disease, especially mitral valve involvement. With the decline in rheumatic fever in industrialized nations, rheumatic AS is decreasing in frequency.

Age-related degenerative calcific (formerly termed senile) AS is now the most common cause of AS in adults and the most frequent reason for aortic valve replacement in patients with AS.[265] It appears to result from years of normal mechanical stress on a valve that sometimes exhibits inflammatory changes with infiltration of macrophages and T lymphocytes. The cusps are immobilized, and the stenosis is caused by deposits of calcium along the flexion lines at their bases. Immunohistochemical evidence of *Chlamydia pneumoniae* has been found in early lesions of age-related degenerative AS.[266] In a population-based echocardiographic study, 2 percent of persons 65 years of age or older had frank calcific AS, whereas 29 percent exhibited age-related aortic valve sclerosis without stenosis, defined by Otto and colleagues as irregular thickening of the aortic valve leaflets detected by echocardiography without significant obstruction and believed to represent a milder and/or earlier disease process.[265] This form of AS may be accompanied by calcifications of the mitral annulus and coronary arteries but rarely

by aortic regurgitation. Both diabetes mellitus and hypercholesterolemia are risk factors for the development of age-related AS or degenerative calcific AS.[267] [268] It has been suggested that the hypercholesterolemia accelerates age-related degenerative changes in the aortic root and valve.[269] In turn, it has been noted that age-related aortic valve sclerosis and calcific AS are associated with traditional risk factors for atherosclerosis such as cigarette smoking, a history of hypertension, and low high-density-lipoprotein cholesterol values.[270] Not surprisingly, age-related aortic valve sclerosis is associated with an increased risk of cardiovascular death and mycoardial infarction.[265] In *atherosclerotic* aortic valve stenosis, severe atherosclerosis involves the aorta and other major arteries; this form of AS occurs most frequently in patients with severe hypercholesterolemia and is observed in children with homozygous type II hyperlipoproteinemia.[271]

Calcific AS is observed in a number of other conditions, including Paget disease of bone[272] and end-stage renal disease.[273] *Rheumatoid involvement* of the valve is a rare cause of AS and results in nodular thickening of the valve leaflets and involvement of the proximal portion of the aorta. *Ochronosis* with alkaptonuria is another rare cause of AS.[274]

Roberts studied hearts with AS obtained at autopsy from patients between 15 and 65 years of age and found that almost 40 percent had tricuspid aortic valves.[275] Because thickening of the mitral valve and a history of acute rheumatic fever were present in 50 percent of these patients, it is likely that the AS was rheumatic in etiology; in the remainder, it was either congenital or degenerative in origin. In 90 percent of hearts examined at autopsy in patients with AS who were older than 65 years of age, the valves were tricuspid, with nodular calcific deposits on the aortic aspects of the cusps, but without commissural fusion,[275] indicative of age-related degenerative calcific AS.

Hemodynamically significant AS leads to severe concentric left ventricular hypertrophy,[276] with heart weights as great as 1000 gm. The interventricular septum often bulges into and encroaches on the right ventricular cavity. When left ventricular failure supervenes, the ventricle dilates, the left atrium enlarges, and changes secondary to backward failure occur in the pulmonary vascular bed, the right side of the heart, and the systemic venous bed.

PATHOPHYSIOLOGY (Fig. 46-29)

The left ventricle responds to *sudden* severe obstruction to outflow by dilatation and reduction of stroke volume.[277] However, in adults with AS, the obstruction usually develops and increases gradually over a prolonged period. In infants and children with congenital AS, the valve orifice shows little change as the child grows, thereby intensifying the relative obstruction quite gradually. Left ventricular function can be well maintained in experimentally produced, gradually developing subcoronary AS in animals. In the experimental model, as well as in children and adults

Figure 46-28 Calcific aortic stenosis. *A,* Congenitally bicuspid aortic valve, characterized by two equal cusps with basal mineralization. *B,* Congenitally bicuspid aortic valve having two unequal cusps, the larger with a central raphe (arrow). *C,* Otherwise anatomically normal tricuspid aortic valve in an elderly patient, characterized by isolated cusps with calcification localized to basilar aspect; cuspal free edges are not involved. *D* and *E,* Photomicrographs of calcific deposits in calcific aortic stenosis; deposits are rimmed by arrows (hematoxylin and eosin, original magnification ×15). *D,* Deposits with underlying cusp largely intact; transmural calcific deposits are shown in *E. (A and C from Schoen FJ, St. John Sutton M: Contemporary issues in the pathology of valvular heart disease. Hum Pathol 18:568, 1987.)*

with chronic, severe AS, left ventricular output is maintained by the presence of left ventricular hypertrophy, which may sustain a large pressure gradient across the aortic valve for many years without a reduction in cardiac output, left ventricular dilatation, or the development of symptoms. Critical obstruction to left ventricular outflow is usually characterized by (1) a peak systolic pressure gradient exceeding 50 mm Hg in the presence of a normal cardiac output or (2) an effective aortic orifice (calculated by the Gorlin formula [see Chap. 11]) less than about 0.8 cm^2 in an average-sized adult, i.e., 0.5 cm^2/m^2 of body surface area (less than approximately one-fourth of the normal aortic orifice of 3.0 to 4.0 cm^2). An aortic valve orifice of 1.0 to 1.5 cm^2 is considered moderate stenosis, and an orifice of 1.5 to 2.0 cm^2 is referred to as mild stenosis (see Fig. 11-13) .

As contraction of the left ventricle becomes progressively more isometric, the left ventricular pressure pulse exhibits a rounded, rather than flattened, summit. The elevated left ventricular end-diastolic pressure, which is characteristic of severe AS, often reflects diminished compliance of the hypertrophied left ventricular wall.[278] [279]

In patients with severe AS, large *a* waves usually appear in the left atrial pressure pulse because of the combination of enhanced contraction of a hypertrophied left atrium and diminished left ventricular compliance. Atrial contraction plays a particularly important role in filling of the left ventricle in AS. It raises left ventricular end-diastolic pressure

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Figure 46-29 Pathophysiology of aortic stenosis. Left ventricular (LV) outflow obstruction results in an increased LV systolic pressure, increased left ventricular ejection time (LVET), increased left ventricular diastolic pressure, and decreased aortic (Ao) pressure. Increased LV systolic pressure with LV volume overload increases LV mass, which may lead to LV dysfunction and failure. Increased LV systolic pressure, LV mass, and LVET increase myocardial oxygen (O_2) consumption. Increased LVET results in a decrease of diastolic time (myocardial perfusion time). Increased LV diastolic pressure and decreased Ao diastolic pressure decrease coronary perfusion pressure. Decreased diastolic time and coronary

perfusion pressure decrease myocardial O_2 supply. Increased myocardial O_2 consumption and decreased myocardial O_2 supply produce myocardial ischemia, which further deteriorates LV function (= increased, = decreased). *(From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB: Cardiovascular Disorders: Pathogenesis and Pathophysiology. St. Louis, CV Mosby Co, 1993, p 64.)*

without causing a concomitant elevation of mean left atrial pressure.[280] This "booster pump" function of the left atrium prevents the pulmonary venous and capillary pressures from rising to levels that would produce pulmonary congestion, while at the same time maintaining left ventricular end-diastolic pressure at the elevated level necessary for effective contraction of the hypertrophied left ventricle. Loss of appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation or atrioventricular dissociation, may result in rapid clinical deterioration in patients with severe AS.

Although the *cardiac output* at rest is within normal limits in the majority of patients with severe AS, it often fails to rise normally during exertion. Late in the course of the disease, the cardiac output, stroke volume, and therefore the left ventricular-aortic pressure gradient all decline, whereas the mean left atrial, pulmonary capillary, pulmonary arterial, right ventricular systolic and diastolic, and right atrial pressures rise, often sequentially. As a consequence of pulmonary hypertension and/or bulging of the hypertrophied septum into the right ventricular cavity, the *a* wave in the right atrial pressure pulse becomes prominent.

Left ventricular end-diastolic volume usually remains normal until late in the course of severe AS, but left ventricular mass increases in response to the chronic pressure overload, resulting in an increase in the mass/volume ratio. However, the increase in mass may not be as great as that seen with aortic regurgitation (AR) or combined AS and AR.

Gender differences in the response of the left ventricle to AS have been reported.[281] [282] [283] Women more frequently exhibit normal or even supernormal ventricular performance and a smaller, thicker-walled, concentrically hypertrophied left ventricle with diastolic dysfunction (to be discussed) and normal or even subnormal systolic wall stress. Men more frequently have eccentric left ventricular hypertrophy, excessive systolic wall stress, systolic dysfunction, and ventricular dilatation[284] [285] [286] (Fig. 46-30) .

MYOCARDIAL FUNCTION IN AORTIC STENOSIS

When the aorta is suddenly constricted in experimental animals, left ventricular pressure rises, wall stress increases significantly, and both the extent and the velocity of shortening decline. As pointed out in Chapter 16 , the development of ventricular hypertrophy is one of the principal mechanisms by which the heart adapts to such an increased hemodynamic burden. The increased systolic wall stress induced by AS leads to parallel replication of sarcomeres and concentric hypertrophy (see Fig. 16-4) . The increase in left ventricular wall thickness is often sufficient to counterbalance the increased pressure, so that peak systolic wall tension returns to normal or remains normal if the obstruction develops slowly.[287] An inverse correlation between wall stress

and ejection fraction has been described in patients with AS.[288] This suggests that the depressed ejection fraction and velocity of fiber shortening that occur in *some* patients are a consequence of inadequate wall thickening,[289] resulting in "afterload mismatch."[290] In others, the lower ejection fraction is secondary to a true depression of contractility; in this group, surgical treatment is less effective.[291] Thus, both increased afterload and altered contractility are operative to varying extents in depressing left ventricular performance.[281] [282] In order to evaluate myocardial function in patients with AS, the ejection

Figure 46-30 The difference in pressure-generating capabilities of the left ventricle in an 83-year-old woman and a 60-year-old man with a similar degree of aortic stenosis is shown. dP/dt = rate of pressure increase. *(Reproduced with permission from Carroll JD, Carroll EP, Felman T, et al: Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 86:1099, 1992. Copyright 1992 American Heart Association.)*

phase indices, such as ejection fraction and myocardial fiber shortening, should be related to the existing wall tension.

DIASTOLIC PROPERTIES (see also Chap. 15) .

Although ventricular hypertrophy is a key adaptive mechanism to the pressure load imposed by AS, it has an adverse pathophysiological consequence; i.e., it increases diastolic stiffness. As a result, greater intracavitary pressure is required for ventricular filling.[278] [279] [292] Some patients with AS manifest an increase in stiffness of the left ventricle (increased *chamber* stiffness) due simply to increased muscle mass with no alteration in the diastolic properties of each unit of myocardium (normal *muscle* stiffness); others exhibit increases in both chamber and muscle stiffness. This increased stiffness, however produced, contributes to the elevation of ventricular diastolic filling pressure at any level of ventricular diastolic volume[293] [294] and may be responsible for flash pulmonary edema in patients with AS. Diastolic dysfunction may revert toward normal as hypertrophy regresses following relief of AS.[279]

CARDIAC STRUCTURE.

An increase in the total collagen volume of the myocardium and in the orthogonal collagen fiber network in AS has been reported.[295] [296] This likely contributes to the altered diastolic properties just discussed. An inverse correlation between the left ventricular ejection fraction and myocardial fiber diameter has been reported.[297] Changes in the myocardial ultrastructure in patients with severe AS include unusually large nuclei, loss of myofibrils, accumulation of mitochondria, large cytoplasmic areas devoid of contractile material, and proliferation of fibroblasts and collagen fibers in the interstitial space. The depression of myocardial function that occurs late in the course of the disease may well be related to these morphological alterations. In adults with AS,

both myocardial cellular hypertrophy and relative and absolute increases in connective tissue occur.

ISCHEMIA.

In patients with AS, coronary blood flow at rest is elevated in absolute terms but is normal when corrections are made for myocardial mass.[298] There may be inadequate myocardial oxygenation in patients with severe AS, even in the absence of coronary artery disease. The hypertrophied left ventricular muscle mass, the increased systolic pressure, and the prolongation of ejection all elevate myocardial oxygen consumption. The abnormally heightened pressure compressing the coronary arteries may exceed the coronary perfusion pressure, and the shortening of diastole interferes with coronary blood flow,[299] [300] thus leading to an imbalance between myocardial oxygen supply and demand. Myocardial perfusion is also impaired by the relative decrease in myocardial capillary density as myocardial mass increases and by the elevation of left ventricular end-diastolic pressure, which lowers the aortic-left ventricular pressure gradient in diastole (i.e., the coronary perfusion pressure gradient). This underperfusion may be responsible for the development of subendocardial ischemia, especially during tachycardia. Marcus and associates have demonstrated a reduction in the velocity of coronary blood flow during reactive hyperemia in patients with severe AS,[301] and this may correlate with the angina pectoris commonly observed in these patients.

Myocardial ischemia in patients with severe AS and normal coronary arteries may be secondary to high systolic and diastolic stresses caused by inadequate ventricular hypertrophy and the reduced coronary flow reserve just described.[302] [303] Metabolic evidence of myocardial ischemia, i.e., lactate production, can be demonstrated when myocardial oxygen needs are stimulated by exercise or by isoproterenol in patients with AS, even in the absence of coronary artery narrowing.

CLINICAL MANIFESTATIONS

History

In the natural history of adults with AS, a long latent period exists during which there is gradually increasing obstruction and an increase in the pressure load on the myocardium while the patient remains asymptomatic.[304] The cardinal manifestations of acquired AS, which commence most commonly in the fifth or sixth decades of life, are angina pectoris, syncope, exertional dyspnea, and ultimately heart failure.[305]

Angina occurs in approximately two-thirds of patients with critical AS (about half of whom have associated significant coronary artery obstruction).[306] It usually resembles the angina observed in patients with coronary artery disease, in that it is commonly precipitated by exertion and relieved by rest. In patients without coronary artery disease, angina results from the combination of the increased oxygen needs of the hypertrophied myocardium and the reduction of oxygen delivery secondary to the excessive compression of coronary vessels[298] [301] [302] [303] (see Ischemia, just discussed). In patients with coronary artery disease, angina is caused by a combination of the

epicardial coronary artery obstruction and the earlier-described oxygen imbalance characteristic of AS. Rarely, angina results from calcium emboli to the coronary vascular bed.[307]

Syncope is most commonly due to the reduced cerebral perfusion that occurs during exertion when arterial pressure declines consequent to systemic vasodilation in the presence of a fixed cardiac output. Syncope has also been attributed to malfunction of the baroreceptor mechanism in severe AS[277] , as well as to a vasodepressor response to a greatly elevated left ventricular systolic pressure during exercise.[308] Premonitory symptoms of syncope are common. Exertional hypotension may also be manifested as "graying out" spells or dizziness on effort. Syncope at rest may be due to transient ventricular fibrillation,[309] from which the patient recovers spontaneously; to transient atrial fibrillation with loss of the atrial contribution to left ventricular filling, which causes a precipitous decline in cardiac output; or to transient atrioventricular block due to extension of the calcification of the valve into the conduction system. Exertional dyspnea with orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema reflect varying degrees of pulmonary venous hypertension. These are relatively late symptoms in patients with AS, and their presence for more than 5 years should suggest the possibility of associated mitral valvular disease.

Gastrointestinal bleeding, either idiopathic or due to angiodysplasia (most commonly of the right colon) or other vascular malformations, occurs more often in patients with calcific AS than in persons without this condition; it may cease after aortic valve replacement.[310] Infective endocarditis is a greater risk in younger patients with milder valvular deformity than in older patients with rocklike calcific aortic deformities. Cerebral emboli resulting in stroke or transient ischemic attacks may be due to microthrombi on thickened bicuspid valves.[311] Calcific AS may cause embolization of calcium to various organs, including the heart, kidneys, and brain. Abrupt loss of vision has been reported when calcific emboli occlude the central retinal artery.[307] [312]

Because cardiac output is usually well maintained for many years in patients with severe AS, marked fatigability, debilitation, peripheral cyanosis, and other clinical manifestations of a low cardiac output are usually not prominent until quite late in the course of the disease. Other late findings in patients with isolated AS include atrial fibrillation, pulmonary hypertension, and systemic venous hypertension. Although AS may be responsible for sudden death, this usually occurs in patients who had previously been symptomatic (see Chap. 26) .

In patients in whom the obstruction remains unrelieved, the prognosis is poor once these symptoms are manifested. Survival curves show that the interval from the onset of symptoms to the time of death is approximately 2 years in patients with heart failure, 3 years in those with syncope, and 5 years in those with angina (Fig. 46-31) .

Physical Examination (Table 46-7)

The arterial pulse characteristically rises slowly and is small and sustained (pulsus parvus et tardus) (see Fig. 4-8 *B*).[313] [314] In the late stage of AS, systolic and pulse pressures are both reduced. However, in patients with mild AS with associated AR and

in older patients with an inelastic arterial bed, both systolic and pulse pressures may be normal or even increased. A systolic pressure exceeding 200 mm Hg is rare in patients with critical AS. The anacrotic notch and coarse systolic vibrations are felt most readily in the carotid arterial pulse, producing the so-called carotid shudder. Simultaneous palpation of the apex and carotid arteries reveals a lag in the latter in patients with

Figure 46-31 Natural history of aortic stenosis without operative treatment. *(Reproduced with permission from Ross J Jr, Braunwald E: Aortic stenosis. Circulation 38[Suppl V]:61, 1968. Copyright 1968 American Heart Association.)*

severe AS.[315] Although left ventricular alternans occurs commonly in patients who have AS with left ventricular dysfunction,[316] obstruction of the aortic valve may prevent its recognition in the peripheral arterial pulse. The jugular venous pulse usually shows prominent *a* waves, reflecting reduced right ventricular compliance consequent to hypertrophy of the ventricular septum.[317] With pulmonary hypertension and secondary right ventricular failure and tricuspid regurgitation, *v* or *c-v* waves may become prominent.

The cardiac impulse is sustained and becomes displaced inferiorly and laterally with left ventricular failure. Presystolic distention of the left ventricle (i.e., a prominent precordial *a* wave) is often both visible and palpable. A hyperdynamic left ventricle suggests concomitant aortic and/or mitral regurgitation. A systolic thrill is usually best appreciated when the patient leans forward during full expiration. It is palpated most readily in the second left intercostal space on either side of the sternum or in the suprasternal notch and is frequently transmitted along the carotid arteries. A systolic thrill is quite specific for severe AS.

Rarely, right ventricular failure with systemic venous congestion, hepatomegaly, and edema precedes left ventricular failure. This is probably caused by the so-called Bernheim effect, which results when the hypertrophied ventricular septum bulges into and encroaches on the right ventricular cavity and leads to impairment of right ventricular filling. In such cases, the jugular venous pressure is elevated, and the *a* wave is prominent.

AUSCULTATION (See Table 46-7) .

S_1 is normal or soft and S_4 is prominent, presumably because atrial contraction is vigorous and the mitral valve is partially closed during presystole.[318] S_2 may be single because calcification and immobility of the aortic valve make A_2 inaudible, because P_2 is buried in the prolonged aortic ejection murmur, or because prolongation of left ventricular systole makes A_2 coincide with P_2 . Paradoxical splitting of S_2 , which

suggests associated left ventricular dysfunction, may also occur. In patients with left ventricular failure and secondary pulmonary hypertension, P_2 may become accentuated. When the aortic valve is rigid, which is the usual finding in adults with severe AS, A_2 may be inaudible, but when the valve is flexible, as may occur in patients with congenital AS, A_2 may be snapping and accentuated.

An aortic ejection sound occurs simultaneous with the halting upward movement of the aortic valve (see Fig. 4-15) . Like an audible A_2 , this sound is dependent on mobility of the valve cusps and disappears when they become severely calcified. Thus, it is common in children with congenital AS but is rare in adults with acquired calcific AS and rigid valves. The ejection sound occurs approximately 0.06 second after the onset of S_1 .

The *systolic murmur* of AS is usually late peaking and heard best at the base of the heart but is often well transmitted both along the carotid vessels and to the apex. Cessation of the murmur before A_2 is usually helpful in differentiating it from a pansystolic mitral murmur. However, the systolic murmur may be mistaken for a pansystolic murmur because it may end with S_2 , which represents pulmonic valve closure, whereas the pansystolic murmur is soft or even inaudible. In patients with calcified aortic valves, the systolic murmur is loudest at the base of the heart, but high-frequency components selectively radiate to the apex (the so-called Gallavardin phenomenon [see Fig. 4-24]), where it may actually be more prominent and where it may be mistaken for the murmur of MR. Frequently, there is a

TABLE 46-7 -- DIFFERENTIAL DIAGNOSIS OF AORTIC STENOSIS: PHYSICAL FINDINGS

TYPE OF STENOSIS	MAXIMUM MURMUR AND THRILL	AORTIC EJECTION SOUND	AORTIC COMPONENT OF SECOND SOUND	REGURGITANT DIASTOLIC MURMUR	ARTERIAL PULSE
Acquired nonrheumatic or rheumatic	Second right sternal border to neck; may be at apex in the aged	Uncommon	Decreased or absent	Common	Delayed upstroke; anacrotic notch; ± small amplitude
Hypertrophic subaortic	Fourth left sternal border to apex (± regurgitant systolic murmur at apex)	Rare	Normal or decreased	Very rare	Brisk upstroke, sometimes bisferiens

Congenital valvular	Second right sternal border to neck (along left sternal border in some infants)	Very common in children, disappearing with decrease in valve mobility with age	Normal or increased in children; decreased with decrease in valve mobility with age	Uncommon in children; not uncommon in adults	Delayed upstroke; anacrotic notch; ± small amplitude
Congenital subvalvular	Discrete: like valvular; tunnel: left sternal border	Rare	Not helpful (normal, increased, decreased, or absent)	Almost all	
Congenital supravalvular	First right sternal border to neck and sometimes to medial aspect of right arm; occasionally greater in neck than in chest	Rare	Normal or decreased	Uncommon	Rapid upstroke in right carotid, delayed in left carotid; right arm pulse pressure greater than left

From Levinson GE: Aortic stenosis. In Dalen JE, Alpert JS (eds): Valvular Heart Disease. 2nd ed. Boston, Little, Brown and Co, 1987, p 202.

"quiet area" between the base and apex where the murmur is diminished in intensity, supporting the erroneous impression that the apical and basal murmurs have different origins. In general, the more severe the stenosis, the longer the duration of the murmur and the more likely that it peaks later in systole.[320]

Patients with degenerative aortic sclerosis may have severe valvular calcification; however, obstruction may be mild or absent because the commissural fusion characteristic of congenital and rheumatic AS is not present.[92] The nonfused, calcified cusps vibrate freely, resulting in a softer and more musical murmur that is more prominent at the apex than the murmur of congenital or rheumatic AS. High-pitched decrescendo diastolic murmurs secondary to aortic regurgitation are common in many patients with dominant AS.

When the left ventricle fails and the stroke volume falls, the systolic murmur of AS becomes softer; rarely, it disappears altogether. The slow rise in the arterial pulse is more difficult to recognize. Stated simply, with left ventricular failure, the clinical picture changes from typical AS to that of severe left ventricular failure with a low cardiac output. Thus, occult AS may be a cause of intractable heart failure, and critical AS should be ruled out by echocardiography in patients with severe heart failure of unknown cause because operative treatment may be life-saving and may result in substantial clinical improvement.[321]

DYNAMIC AUSCULTATION (see Table 46-4) .

The intensity of the systolic murmur varies from beat to beat when the duration of diastolic filling varies, as in atrial fibrillation or following a premature contraction. This characteristic is helpful in differentiating AS from MR, in which the murmur is usually unaffected. The murmur of valvular AS is augmented by squatting, which increases stroke volume. It is reduced in intensity during the strain of the Valsalva maneuver and when standing, which reduce transvalvular flow.[322] Findings on physical examination including a delay in the carotid upstroke, a loud, long systolic murmur, and a single S_2 all correlate with severe stenosis.[323]

LABORATORY EXAMINATION

ELECTROCARDIOGRAPHY.

The principal ECG change is left ventricular hypertrophy (Fig. 5-19) , which is found in approximately 85 percent of patients with severe AS. The absence of left ventricular hypertrophy does not exclude the presence of critical AS, and the correlation between the absolute ECG voltages in precordial leads and the severity of obstruction is poor in adults but is quite good in children with congenital AS. T wave inversion and ST segment depression in leads with upright QRS complexes are common. ST segment depressions greater than 0.2 mV in patients with AS (left ventricular "strain") suggest that severe ventricular hypertrophy is present. Occasionally, a "pseudoinfarction" pattern is present, characterized by a loss of r waves in the right precordial leads. There is evidence of left atrial enlargement in more than 80 percent of patients with severe, isolated AS. The principal manifestation is prominent late negativity of the P wave in lead V_1 rather than an increased duration in lead II, suggesting hypertrophy rather than dilatation. Atrial fibrillation is an uncommon and late sign of pure AS, and its presence in a patient who does not appear to have end-stage aortic disease should suggest coexisting mitral valvular disease.

The extension of calcific infiltrates from the aortic valve into the conduction system may cause various forms and degrees of atrioventricular and intraventricular block in 5 percent of patients with calcific AS.[324] Such conduction defects are more common in patients who have associated mitral annular calcification.

RADIOLOGICAL FINDINGS.

(See Figs. 8-8 , 8-19 , and 8-20) . Routine radiological examination may be normal in patients with critical AS. The heart is usually of normal size or slightly enlarged, with a rounding of the left ventricular border and apex, unless regurgitation or left ventricular failure is present and causes substantial cardiomegaly. Poststenotic dilatation of the ascending aorta is a common finding. Calcification of the aortic valve is found in almost all adults with hemodynamically significant AS.[325] It is more readily detected on fluoroscopy or echocardiography than on roentgenography. The absence of calcium in the aortic valve region on careful fluoroscopic examination in a patient older than 35 years of age essentially rules out severe valvular AS. The converse is not true, however, and in patients over the age of 65 with degenerative AS, severe calcification of the aortic valve may occur with no or only mild obstruction. The left atrium may be slightly enlarged in patients with severe AS, and there may be radiological signs of pulmonary venous hypertension. However, when left atrial enlargement is marked, the presence of associated mitral valvular disease should be suspected.

ANGIOGRAPHY.

There is some hazard associated with the rapid injection of a large volume of contrast material into a high-pressure left ventricle, and therefore this procedure is usually not advisable in patients with AS and critical obstruction. Angiographic studies of the left ventricle and aortic valve in these patients are best performed by injecting contrast material into the pulmonary artery and filming in the 30-degree right anterior oblique and 60-degree left anterior oblique projections. These examinations often make it possible to ascertain the number of cusps of the stenotic valve and to demonstrate doming of a thickened valve and a systolic jet.

ECHOCARDIOGRAPHY (see also Chap. 7 and Figs. 7-60 to 7-63) .

The normal range of opening of the aortic valve is 1.6 to 2.6 cm. Two-dimensional transthoracic echocardiography is helpful in detecting valvular calcification, in outlining the valve leaflets, and sometimes in determining the severity of the stenosis by imaging the orifice.[326] The orifice may be more clearly defined by transesophageal echocardiography, which offers a precise short-axis view of the aortic valve.[327] Multiplanar transesophageal echocardiography is particularly useful.[328] Two-dimensional echocardiography is invaluable in detecting associated mitral valve disease and in assessing left ventricular systolic performance, diastolic function, dilatation, and hypertrophy. Doppler echocardiography allows calculation of the left ventricular-aortic pressure gradient[329] using a modified Bernoulli (continuity) equation (see Fig 7-25) . The gradients noninvasively determined by this method correlate well with those determined by left-heart catheterization.[329] [330] Color flow Doppler imaging is helpful in detecting and determining the severity of aortic regurgitation (which coexists in approximately 75 percent of patients with predominant AS) and in estimating pulmonary artery pressure.[331] Indeed, in a large majority of patients the echocardiographic examination provides the information obtained by cardiac catheterization (except for the status of the coronary arteries).[329] Echocardiography has become the most important

laboratory technique for evaluating and following patients with AS and selecting them for operation.

NATURAL HISTORY

In contrast to MS, which leads to symptoms almost immediately after its development, patients with severe AS may be asymptomatic for many years despite the presence of severe obstruction.[304] [306] The systolic pressure gradient may exceed 150 mm Hg, and the peak left ventricular systolic pressure may reach approximately 300 mm Hg with relatively little increase in overall heart size on radiological examination and with normal left ventricular end-diastolic and end-systolic volumes.

Patients with severe, chronic AS tend to be free of cardiovascular symptoms until relatively late in the course of the disease. Thus, there is a long latent period during which mortality and morbidity are very low.[51] In Rapaport's report, 40 percent of patients treated medically survived for 5 years and 20 percent for 10 years after diagnosis.[147] In another series of patients with hemodynamically significant valvular AS treated medically, the 5-year survival rate was 64 percent. However, obstruction is progressive and often insidious, with the aortic valve area decreasing by an average of 0.12 cm^2 /year in one study.[331] When symptoms develop, the valve area is, on average, 0.6 cm^2 .[332] Once patients with AS develop angina pectoris or syncope, the average survival is 1 to 3 years[333] [334] [335] (see Fig. 46-31) . In an analysis of elderly patients with severe AS and symptoms of heart failure who declined surgery, 50 percent had died by 18 months of follow-up; the ejection fraction correlated

inversely with survival.[336] Among symptomatic patients with severe AS, the outlook is poorest when the left ventricle has failed and the cardiac output and transvalvular gradient are both low.

Asymptomatic patients have an excellent prognosis.[92] [337] [338] Sudden death, like syncope, in patients with severe AS may be due to cerebral hypoperfusion followed by arrhythmia. Although severe AS is a potentially lethal disease, death (even when sudden) usually occurs in *symptomatic* patients. A number of authors who have followed asymptomatic patients with critical AS have found that sudden death is extremely rare in this group. Of 229 asymptomatic patients with critical AS, only 5 (2 percent) died suddenly (certainly not higher than the mortality from operation).[51] [337]

MANAGEMENT

Medical Treatment

Patients with known severe AS who are asymptomatic should be advised to report promptly the development of any symptoms possibly related to AS. Patients with critical

obstruction should be cautioned to avoid vigorous athletic and physical activity. However, such restrictions do not apply to patients with mild obstruction. The need for infective endocarditis prophylaxis should be explained (see Chap 47) . Because of the gradual increase in the severity of obstruction, noninvasive assessment of this finding by Doppler echocardiography should be carried out at intervals. Doppler-derived gradients have been shown to increase by 4 to 8 mm Hg per year.[92] In patients with mild obstruction, this measurement should be repeated every 2 years. In asymptomatic patients with severe obstruction, repeat echocardiography should be carried out every 6 to 12 months, with particular attention to detecting changes in left ventricular function. Exercise stress testing should be avoided in symptomatic patients, but may be carried out in asymptomatic patients to detect limited exercise capacity.

Symptomatic patients with severe AS are usually operative candidates, as medical therapy has little to offer. However, medical therapy may be necessary in patients who are considered to be inoperable (usually because of comorbid conditions that preclude surgery.) Digitalis glycosides are indicated if the ventricular volume is increased or the ejection fraction is reduced. Although diuretics are beneficial when there is abnormal accumulation of fluid, they must be used with caution because hypovolemia may reduce the elevated left ventricular end-diastolic pressure, lower cardiac output, and produce orthostatic hypotension. Betaadrenergic blockers can depress myocardial function and induce left ventricular failure and should be avoided in patients with AS.

Atrial flutter or fibrillation occurs in fewer than 10 percent of patients with severe AS, perhaps because of the late occurrence of left atrial enlargement in this condition. When such an arrhythmia is observed in a patient with AS, the possibility of associated mitral valvular disease should be considered. When atrial fibrillation occurs, the rapid ventricular rate may cause angina pectoris. The loss of the atrial contribution to ventricular filling and a sudden fall in cardiac output may cause serious hypotension. Therefore, atrial fibrillation should be treated promptly, usually with cardioversion, and a search for previously unrecognized mitral valvular disease should be undertaken. Adults with severe AS who are being considered for surgical therapy should undergo coronary arteriography. Left-heart catheterization is also indicated if there is a discrepancy between the clinical picture and the echocardiographic findings.[50]

Surgical Treatment

INDICATIONS FOR OPERATION.

Children.

The indications for surgery, as well as the techniques and results of operation, depend on the patient's age, the type of valvular deformity, and the function of the left ventricle. In children and adolescents with noncalcific congenital AS, who most commonly have bicuspid aortic valves, simple commissural incision under direct vision usually leads to substantial hemodynamic improvement with low risk (i.e., a mortality rate of less than 1 percent) (see Chap. 43) .[339] Therefore, this procedure (or now, more commonly, balloon aortic valvuloplasty) is indicated not only in symptomatic patients but also in asymptomatic children and adolescents with severe AS, which is often defined as a

calculated effective orifice less than 0.8 cm^2 or 0.5 cm^2/m^2 body surface area (BSA). Despite the salutary hemodynamic results following this procedure, the valve is not rendered entirely normal anatomically. The turbulent blood flow through the valve may subsequently lead to further deformation, calcification, the development of regurgitation, and restenosis after 10 to 20 years, probably requiring reoperation and valve replacement later.

Adults.

In most adults with calcific AS, satisfactory long-term valvular function cannot usually be restored even by careful sculpturing procedures under direct vision, and valve replacement is the surgical treatment of choice. Aortic valve replacement (AVR) (Fig. 46-32) should, in general, be performed in adults who have hemodynamic evidence of severe obstruction (aortic valve orifice <0.8 to 0.9 cm^2 or <0.5 to 0.6 cm^2/m^2 BSA) and whose symptoms are believed to result from AS. AVR should also be carried out in asymptomatic patients with *progressive* left ventricular dysfunction or a hypotensive response to exercise.[340] Although a prospective randomized controlled study has not been done, the long-term mortality in asymptomatic patients with critical AS and left ventricular dysfunction who undergo operation appears to be lower than that in medically treated patients who do not undergo operation.[51] As prosthetic valves and surgical skills continue to improve, it is likely that patients with severe AS will become candidates for operation at progressively earlier stages in the natural history of their disease.[340A] At the present time, however, I do *not* recommend prophylactic replacement of a critically narrow calcific aortic valve in *asymptomatic* adults unless they have progressive left ventricular dysfunction.

AVR is also indicated in patients with severe stenosis who are undergoing another cardiovascular operation (e.g., coronary artery bypass grafting or surgery on the aorta or another heart valve).[51] Surgical risk is higher in patients with impaired left ventricular function[340] (EF < 35 percent). However, since their prognosis is very poor without operation and some patients even in this group have clinical and functional recovery following AVR,[341] [341A] the procedure should generally be offered to these patients. Even octogenarians with left ventricular dysfunction can have improved survival after AVR.[342] [343] [343A] Exceptions are patients with advanced congestive heart failure or left ventricular dysfunction that can be related to previous myocardial infarction.

RESULTS.

Successful replacement of the aortic valve results in substantial clinical and hemodynamic improvement in patients with AS, aortic regurgitation, or combined lesions.[343] In patients without frank left ventricular failure, the operative risk ranges from 2 to 5 percent in most centers, and in patients under 70 years of age, the operative risk has been reported to be as low as 1 percent.[344] The Society of Thoracic Surgeons National Database Committee reported an overall operative mortality rate of 4.3 percent in 26, 317 patients undergoing isolated AVR, 8.0 percent in 22,713 patients undergoing AVR and coronary artery bypass

Figure 46-32 Interrupted suture technique for aortic valve replacement. *A,* The aortic valve is excised, leaving 1 or 2 mm of annular tissue as a sewing cuff. *B,* Pledgetted Tyeron mattress sutures (2-0) are placed with the pledget on the aortic side. Sutures are placed in the aortic ring and passed directly onto the prosthetic valve sewing ring held at a distance. *C,* After all sutures are placed, the valve is lowered in place and the sutures tied. The valve is then inspected for proper function and fit. *(From Albertucci M, Karp RB: Prosthetic valve replacement. In Al-Zaibag M, Duran CMG [eds]: Valvular Heart Disease. New York, Marcel Dekker, 1994, pp 601-634.)*

grafting, 7.4 percent in 938 patients undergoing AVR and repair of another valve, and 9.7 percent in 1723 patients undergoing AVR and aortic aneurysm repair[104] (see Table 46-2) .

Risk factors causing a higher mortality rate include a high NYHA class, impairment of left ventricular function, advanced age, and the presence of associated coronary artery disease. The 10-year actuarial survival rate of hospital survivors in surgically treated patients is approximately 85 percent.[345] [345A] Risk factors for late death include higher preoperative NYHA class, advanced age, concomitant untreated coronary artery disease, preoperative impaired left ventricular function, preoperative ventricular arrhythmias, and associated significant aortic regurgitation.

Symptoms of pulmonary congestion (exertional dyspnea) and of myocardial ischemia (angina pectoris) are relieved in almost every patient. Hemodynamic results of AVR are also impressive; elevated end-diastolic and end-systolic volumes show significant reduction. Impaired ventricular performance returns to normal more frequently in patients with AS than in those with aortic or mitral regurgitation. Diastolic function is improved as well.[278] [279] However, the finding that the strongest predictor of postoperative left ventricular dysfunction is preoperative dysfunction[346] [347] suggests that patients should, if possible, be operated on *before* left ventricular function becomes seriously impaired. The increased left ventricular mass is reduced toward (but not to) normal within 18 months after AVR in patients with AS.[348] [349] When patients were restudied 5 years postoperatively, left ventricular mass usually had returned to normal.[350] [350A] Myocyte hypertrophy regresses as well. Diastolic dysfunction returns to normal long after systolic dysfunction.[351]

When operation is carried out in patients with critical AS, frank left ventricular failure, a depressed ejection fraction, or a low cardiac output (and hence a reduced transaortic pressure gradient[351A] [351B]), the operative risk is higher, and the mortality rate ranges from 8 to 20 percent, depending on the skill of the surgical team and the severity of heart failure.[341A] Obviously, performing surgery before heart failure develops is desirable, but emergency operation, even in patients with heart failure, is sometimes life-saving. In view of the extremely poor prognosis of such patients who are treated medically, unless serious comorbid conditions exist that preclude surgery, there is usually little choice but to advise immediate mechanical relief of obstruction, i.e., balloon angioplasty (see below) or urgent AVR. Since many symptomatic patients with calcific

AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary functions. However, the results of AVR are often quite satisfactory in patients older than 70 or even 80 years of age.[352] Therefore, advanced age per se, while adding to the risk, should not be considered a contraindication to operation.

In patients with AS and obstructive coronary artery disease (a relatively common combination), AVR and myocardial revascularization should be performed together.[353] [353A] Although the risk of AVR is increased when accompanied by coronary artery bypass grafting (see Table 46-2) ,[104] the surgical risk increases even more when severe coronary artery disease is left untreated. The ability to avoid serious myocardial ischemia in the perioperative period is a major factor that has served to reduce operative mortality in these patients. Characteristics of patients that have been shown to increase the risk of AVR, as reported in different series, are shown in Table 46-8 .

There has been increasing interest in performing AVR through a very small incision, generally a transverse sternotomy, so-called "minimally invasive surgery." Although the advantages (shorter hospital stay, less tissue damage, better cosmetic results) are clear, the procedure is technically demanding and the mortality rate may actually be higher than when a standard approach is employed.[354] [354A]

BALLOON AORTIC VALVULOPLASTY (See alsoChap. 38)

Balloon aortic valvuloplasty (BAV) represents an increasingly attractive alternative to aortic valvotomy in children, adolescents, and young adults with congenital noncalcific AS (see Chap. 43) ,[355] [356] but its value is limited in adults with calcific AS. A series of balloon dilation catheters are advanced along a guidewire positioned at the left ventricular apex. Fracture of calcified nodules, separation of fused commissures, and stretching of the aortic valve ring are responsible for the relief of obstruction.[355] [357] [358] Although the response of adult patients with calcific AS varies considerably, BAV initially results in relief of obstruction in most patients[359] [360] [361] [362] (Fig. 46-33) . The valve area in these patients initially increased from 0.5 to 0.8 cm^2 , and the mean transvalvular gradient declined from approximately 55 to 29 mm Hg. Left ventricular ejection fraction tends to rise in patients with depressed left ventricular function who undergo BAV. In a report of a multicenter registry involving 674 seriously ill, elderly patients (average age 78

TABLE 46-8 -- PREDICTORS OF POOR OUTCOME AFTER AORTIC VALVE REPLACEMENT FOR AORTIC STENOSIS

Advanced age (>70 yr)
Female gender
Emergent surgery

Coronary artery disease
Previous coronary artery bypass grafting surgery
Hypertension
Left ventricular dysfunction (ejection fraction <45% or 50%)
Heart failure
Atrial fibrillation
Concurrent mitral valve replacement or repair
Renal failure
Adapted from Otto CM: Valvular Heart Disease. Philadelphia, WB Saunders, 1999, p 203.

years) treated at 24 centers, the procedural mortality rate was 3 percent, the 30-day mortality rate was 14 percent, and the one-year mortality rate was 45 percent. Better survival was seen in patients with higher preoperative pressure gradients, in those with better preserved left ventricular systolic function, and in women. In addition to the procedural mortality, another 6 percent of patients developed serious complications such as myocardial perforation, myocardial infarction, and severe aortic regurgitation.[363]

The major disadvantage of BAV in adults with critical calcified AS is restenosis due to scarring, which occurs in about 50 percent of patients within 6 months. Symptoms lessen in severity in the majority of patients but recur in approximately 30 percent by 6 months.

Although the overall intermediate-term results (6 to 12 months) of BAV have been disappointing, largely because of restenosis, the procedure does have a role in the management of severe calcific AS in patients who are not surgical candidates. Indications include: (1) patients with cardiogenic shock due to critical AS,[364] (2) patients with critical AS who require an urgent noncardiac operation, (3) patients with severe heart failure who are at extremely high operative risk as a "bridge" to AVR, (4) pregnant women with critical AS,[365] (5) patients with severe comorbid conditions that preclude surgery, and (6) patients with critical AS who refuse surgical treatment. However, in adults with calcified AS, BAV is *not* a substitute for surgery (as balloon mitral valvuloplasty may be in patients with MS [see p. 1651]).

Figure 46-33 Plots of changes in pressure gradient, valve area, cardiac index, and ejection fraction at baseline (Base) after balloon aortic valvuloplasty (BAV). *(Reproduced with permission from Berland J et al: Percutaneous balloon valvuloplasty in patients with severe aortic stenosis and low ejection fraction. Circulation 79:1189, 1989. Copyright 1989 American Heart Association.)*

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Aortic Regurgitation

ETIOLOGY AND PATHOLOGY

Aortic regurgitation (AR) may be caused by primary disease of the aortic valve leaflets and/or the wall of the aortic root (Fig. 46-34) . Among patients with *pure* AR who undergo valve replacement, the percentage with aortic root disease has been increasing steadily during the past few decades and now accounts for more than 50 percent of all such patients.[262]

Valvular Disease

Rheumatic fever is a common cause of primary disease of the aortic valve that leads to regurgitation[92] [366] (Fig. 46-35) . The cusps become infiltrated with fibrous tissues and retract, a process that prevents cusp apposition during diastole and usually leads to regurgitation into the left ventricle through a defect in the center of the valve.[5] The associated fusion of the commissures may restrict the opening of the valve, resulting in combined AS and AR; some associated mitral valve involvement is also common. Other primary valvular causes of AR include calcific AS in the elderly, in which some degree (usually mild) of AR is present in 75 percent of patients; *infective endocarditis* (see Chap. 47) , in which the infection may destroy or cause perforation of a leaflet, or the vegetations may interfere with proper coaptation of the cusps; and *trauma* that results in a tear of the ascending aorta, in which loss of commissural support can cause prolapse of an aortic cusp. Although the most common complication of a congenitally *bicuspid valve* in adults is stenosis, incomplete closure and/or prolapse of a bicuspid valve may also cause isolated regurgitation or a combination of stenosis and regurgitation.[367] [368] [369] Progressive AR may occur in patients with a large ventricular septal defect as well as in patients with membranous subaortic stenosis (see Chap. 43) and as a

complication of radiofrequency catheter ablation.[370] Progressive regurgitation may also occur in patients with myxomatous proliferation of the aortic valve.[371] An increasingly common cause of valvular AR is structural deterioration of a bioprosthetic valve (see p. 1701).

Less common causes of AR include various forms of congenital AR, such as unicommissural and quadricuspid valves, or rupture of a congenitally fenestrated valve,[372] particularly in the presence of hypertension.[373] Other less common

Figure 46-34 Diagram of various causes of pure aortic regurgitation. *(From Waller BF: Rheumatic and nonrheumatic conditions producing valvular heart disease. In Frankl WS, Brest AN [eds]: Cardiovascular Clinics. Valvular Heart Disease: Comprehensive Evaluation and Management. Philadelphia, FA Davis Co, 1986, pp 30-31.)*

causes of AR occur in association with systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis,[374] Jaccoud arthropathy, Takayasu disease, Whipple disease,[375] Crohn disease, [376] and, in the past, use of certain anorectic drugs. Isolated congenital AR is an uncommon lesion on necropsy studies, but, when present, is usually associated with a bicuspid valve.[377]

Aortic Root Disease (See also Chap. 40)

AR secondary to marked dilatation of the ascending aorta is now more common than primary valve disease in patients undergoing AVR for pure AR.[262] The conditions responsible for aortic root disease include age-related (degenerative) aortic dilatation, cystic medial necrosis of the aorta (either isolated or associated with classic Marfan syndrome), aortic dissection, osteogenesis imperfecta, syphilitic aortitis, ankylosing spondylitis, the Behcet syndrome, psoriatic arthritis, arthritis associated with ulcerative colitis, relapsing polychondritis, the Reiter syndrome, giant cell arteritis, and systemic hypertension,[378] [379] [380] [381] as well as the ingestion of some appetite suppressant drugs.[381A]

When the aortic annulus becomes greatly dilated, the aortic leaflets separate, and AR may ensue. Dissection of the diseased aortic wall may occur and aggravate the AR. Dilatation of the aortic root may also have secondary effects on the aortic valve because dilatation causes tension and bowing of the individual cusps, which may thicken, retract, and become too short to close the aortic orifice. This leads to intensification of the AR, further dilating the ascending aorta and thus leading to a vicious circle in which, as is the case for MR, "regurgitation begets regurgitation."

AR, regardless of its cause, produces dilatation and hypertrophy of the left ventricle, dilatation of the mitral valve ring, and sometimes hypertrophy and dilatation of the left

atrium. Endocardial pockets frequently develop in the left ventricular cavity at sites of impact of the regurgitant jet.

Figure 46-35 Chronic rheumatic aortic regurgitation with cuspal fibrosis, thickening, and retraction, with a jet lesion consisting of endocardial fibrosis (large arrow) and a "pocket" (small arrow) below the valve. Warty, small vegetations resulting from acute rheumatic fever are on the aortic valve edge, the aortic and mitral valve leaflets, and the chordae tendinae (open arrow). *(From Rozich JD, et al: Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation: Mechanisms for differences in postoperative ejection performance. Circulation 86:7718, 1992.)*

PATHOPHYSIOLOGY (Fig. 46-36)

In contrast to MR, in which a fraction of the left ventricular stroke volume is ejected into the low-pressure left atrium, in AR the entire left ventricular stroke volume is ejected

Figure 46-36 Pathophysiology of aortic regurgitation. Aortic regurgitation results in an increased left ventricular (LV) volume, increased stroke volume, increased aortic (Ao) systolic pressure, and decreased effective stroke volume. Increased LV volume results in an increased LV mass, which may lead to LV dysfunction and failure. Increased LV stroke volume increases systolic pressure and prolongation of left ventricular ejection time (LVET). Increased LV systolic pressure results in a decrease in diastolic time. Decreased diastolic time (myocardial perfusion time), diastolic aortic pressure, and effective stroke volume reduce myocardial O_2 supply. Increased myocardial O_2 consumption and decreased myocardial O_2 supply produce myocardial ischemia, which further deteriorates LV function (= increased, = decreased). *(From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB: Cardiovascular Disorders: Pathogenesis and Pathophysiology. St. Louis, CV Mosby Co, 1993, p 64.)*

Figure 46-37 Pressure curves obtained from a 63-year-old man with symptoms of left ventricular failure and a loud decrescendo diastolic murmur. The femoral arterial (FA) pressure tracing demonstrates a widened pulse pressure of 115 mm Hg and equalization with left ventricular (LV) pressure late in diastole. The LV pressure curve exhibits a steady pressure increase throughout diastole, culminating in a markedly elevated end-diastolic pressure of 45 mm Hg. These findings are indicative of severe aortic regurgitation.

into a high-pressure chamber, i.e., the aorta (although the low aortic diastolic pressure does facilitate ventricular emptying during early systole). In MR, especially acute MR, the reduction of wall tension (i.e., reduced afterload) allows more complete systolic emptying; in AR the increase in left ventricular end-diastolic volume (i.e., increased preload) provides hemodynamic compensation.[382] [383]

Figure 46-38 Left ventricular (LV) diastolic pressure-volume (P-V) curve relationships: effects of chronic valve regurgitation. When the AR is mild to moderate, the LV end-diastolic volume (LVEDV) is increased moderately, the LV diastolic P-V curve is moved to the right (curve B) of normal (curve A) and the LV end-diastolic pressure (LVEDP) is usually normal. In severe AR, the LV diastolic P-V curves are moved to the right (curves C and D). If the LV systolic pump function is normal, the LVEDV can be quite large without significant elevation of LVEDP (curve C). However, if the LVEDV increases further, the LVEDP will be increased. If LV systolic pump dysfunction supervenes, the LV diastolic P-V curve relationships are moved even further to the right (curve D) with quite marked LV dilatation and increases in LVEDP. *(From Rahimtoola SH: Aortic valve regurgitation. In Rahimtoola SH (ed): Valvular Heart Disease. Atlas of Heart Diseases. Vol. 11. Braunwald E, series ed. Philadelphia, Current Medicine, 1997, pp 7.1-7.26 Adapted from Rahimtoola SH: Management of heart failure in valve regurgitation. Clin Cardiol 15(Suppl I):322-327, 1992.)*

Severe AR may occur with a normal effective forward stroke volume and a normal ejection fraction (forward plus regurgitant stroke volume/end-diastolic volume), together with an elevated left ventricular end-diastolic volume, pressure, and stress[384] (Fig. 46-37) . In accord with Laplace's law (which indicates that wall tension is related to the product of the intraventricular pressure and radius divided by wall thickness), left ventricular dilatation also increases the left ventricular systolic tension required to develop any level of systolic pressure. The volume overload leads to eccentric hypertrophy, with replication of sarcomeres in series and elongation of myocytes and myocardial fibers. In compensated AR, there is sufficient wall thickening so that the ratio of ventricular wall thickness to cavity radius remains normal. This maintains or returns end-diastolic wall stress to normal levels.[385] AR contrasts with AS, in which there is pressure overload (concentric) hypertrophy with replication of sarcomeres largely in parallel and an increased ratio of wall thickness to radius. In AR, left ventricular mass is usually greatly increased, often to levels even higher than in isolated AS,[276] and sometimes exceeding 1000 g. As AR persists and increases in severity over time, wall thickening fails to keep pace with the hemodynamic load and end-systolic wall stress rises.[386] [387] At this point, the ejection fraction falls.

Patients with severe chronic AR have the largest end-diastolic volumes of those with any form of heart disease (resulting in so-called cor bovinum). However, end-diastolic pressure is not uniformly elevated (i.e., left ventricular compliance is often increased Fig. 46-38).[388]

In the more severe cases of AR, the regurgitant flow may exceed 20 liters/min, so that the total left ventricular output at rest approaches 25 liters/min, a level that can be achieved acutely only by a trained endurance runner during maximal exercise. Thus, the adaptive response to gradually increasing, chronic AR permits the ventricle to function as an effective high-compliance pump, handling a large stroke volume, often with little increase in filling pressure. During exercise, peripheral vascular resistance declines, and with an increase in heart rate, diastole shortens and the regurgitation per beat decreases,[389] [390] facilitating an increment in effective (forward) cardiac output without substantial increases in end-diastolic volume and pressure. The ejection fraction and related ejection phase indices are often within normal limits, both at rest and during

exercise, even though myocardial function, as reflected in the slope of the end-systolic pressure-volume relationship, is depressed.

LEFT VENTRICULAR FUNCTION.

As the left ventricle decompensates, interstitial fibrosis increases, compliance declines, and left ventricular end-diastolic pressure and volume rise (Fig. 46-39) . In advanced stages of decompensation, left atrial, pulmonary artery wedge, pulmonary arterial, right ventricular, and right atrial pressures rise and the effective (forward) cardiac output falls, at first during exercise[390] and then at rest. The normal decline in end-systolic volume or the rise in ejection fraction fails to occur during exercise. Symptoms of heart failure, particularly those secondary to pulmonary congestion, develop.

MYOCARDIAL ISCHEMIA.

When *acute* AR is induced experimentally, myocardial oxygen requirements rise substantially,[132] secondary to an increase in wall tension. In patients with chronic, severe AR, total myocardial oxygen requirements are also augmented by the increase in left ventricular mass. Because the major portion of coronary blood flow occurs during diastole, when arterial pressure is lower than normal

Figure 46-39 Hemodynamics of aortic regurgitation. *A,* Normal conditions. *B,* The hemodynamic changes that occur in severe acute aortic regurgitation. Although total stroke volume is increased, forward stroke volume is reduced. Left ventricular end-diastolic pressure rises dramatically. *C,* Hemodynamic changes occurring in chronic compensated aortic regurgitation are shown. Eccentric hypertrophy produces increased end-diastolic volume, which permits an increase in total as well as forward stroke volume. The volume overload is accommodated and left ventricular filling pressure is normalized. Ventricular emptying and end-systolic volume remain normal. *D,* In chronic decompensated aortic regurgitation, impaired left ventricular emptying produces an increase in end-systolic volume and a fall in ejection fraction, total stroke volume, and forward stroke volume. There is further cardiac dilatation and re-elevation of left ventricular filling pressure. *E,* Immediately following valve replacement, preload estimated by end-diastolic volume decreases, as does filling pressure. End-systolic volume also is decreased, but to a lesser extent. The result is an initial fall in ejection fraction. Despite these changes, elimination of regurgitation leads to an increase in forward stroke volume. AoP = aortic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; RF = regurgitant fraction. *(From Carabello BA: Aortic regurgitation: Hemodynamic determinants of prognosis. In Cohn LH and DiSesa VJ [eds]: Aortic Regurgitation: Medical and Surgical Management. New York, Marcel Dekker, Inc, 1986.)*

in AR, coronary perfusion pressure is reduced. Studies in experimentally induced AR have shown a reduction in coronary flow reserve with a change in forward coronary flow from diastole to systole.[391] The result--a combination of increased oxygen demand and reduced supply--sets the stage for the development of myocardial ischemia, especially during exercise.[392] Thus, patients with severe AR exhibit a reduction of coronary

reserve,[393] which may be responsible for myocardial ischemia, which in turn may play a role in the deterioration of left ventricular function.

Acute Aortic Regurgitation

Acute AR is caused most commonly by infective endocarditis, aortic dissection, or trauma. In contrast to the pathophysiological events in chronic AR just described, in which the left ventricle is able to adapt to the increased hemodynamic load, in acute AR the regurgitant volume fills a ventricle of normal size that cannot accommodate the combined large regurgitant volume and inflow from the left atrium.[394] Because the ability of total stroke volume to rise acutely is limited, forward stroke volume declines. The sudden increase in left ventricular filling causes the left ventricular diastolic pressure to rise rapidly above left atrial pressure during early diastole,[382] causing the mitral valve to close prematurely in diastole (Fig. 46-40) . [395] Premature closure of the mitral valve protects the pulmonary venous bed from backward transmission of the greatly elevated end-diastolic pressure unless it is accompanied by diastolic mitral regurgitation.[396] Premature closure of the mitral valve, together with tachycardia that also shortens diastole, reduces the time interval during which the mitral valve is open. Left ventricular and aortic *systolic* pressures exhibit little change. Because aortic diastolic pressure cannot decline below the elevated left ventricular end-diastolic pressure, the systemic arterial pulse pressure widens relatively little.

CLINICAL MANIFESTATIONS

History

CHRONIC AORTIC REGURGITATION.

In patients with chronic, severe AR, the left ventricle gradually enlarges while the patient remains asymptomatic or almost so.[397] Symptoms of reduced cardiac reserve or myocardial ischemia develop, most often in the fourth or fifth decade and usually only *after* considerable cardiomegaly and myocardial dysfunction have occurred. The principal complaints of exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea usually develop gradually. Angina pectoris is prominent late in the course; nocturnal angina may be troublesome and is often accompanied by diaphoresis that occurs when the heart rate slows and arterial diastolic pressure falls to extremely low levels. Patients with severe AR often complain of an uncomfortable awareness of the heartbeat, especially on lying down, and disagreeable thoracic pain due to pounding of the heart against the chest wall. Tachycardia, occurring with emotional stress or exertion, may cause troubling palpitations and head pounding. Premature ventricular contractions are particularly distressing because of the great heave of the volume-loaded left ventricle during the postpremature beat. These complaints may be present for many years before symptoms of overt left ventricular dysfunction develop.

ACUTE AORTIC REGURGITATION.

In light of the limited ability of the left ventricle to tolerate acute, severe AR, patients with

this valvular lesion often develop clinical manifestations of sudden cardiovascular collapse, including weakness, severe dyspnea, and hypotension secondary to the reduced stroke volume and elevated left atrial pressure.

Figure 46-40 Schematic representations contrasting the hemodynamic, echocardiographic (ECHO), and phonocardiographic (PCG) manifestations of acute severe (*A*) and chronic severe (*B*) aortic regurgitation. Ao = aorta; LV = left ventricle; LA = left atrium; EDP = end-diastolic pressure; f = flutter of anterior mitral valve leaflet; AML = anterior mitral valve leaflet; PML = posterior mitral valve leaflet; SM = systolic murmur; DM = diastolic murmur; C = closure point of mitral valve. *(From Morganroth J et al: Acute severe aortic regurgitation. Ann Intern Med 87:225, 1977.)*

Physical Examination (See also Chap. 4)

In patients with chronic, severe AR, the head frequently bobs with each heartbeat (*de Musset sign*), [398] and the pulses are of the "water-hammer" or collapsing type with abrupt distention and quick collapse (*Corrigan pulse*). The arterial pulse is often prominent and can be best appreciated by palpation of the radial artery with the patient's arm elevated. A *bisferiens pulse* may be present (see Fig. 4-8 *C*) and is more readily recognized in the brachial and femoral arteries than in the carotid arteries. A variety of auscultatory findings provide confirmation of a wide pulse pressure. *Traube sign* (also known as "pistol shot sounds"[399]) refers to booming systolic and diastolic sounds heard over the femoral artery, *Muller sign* consists of systolic pulsations of the uvula, and *Duroziez sign* consists of a systolic murmur heard over the femoral artery when it is compressed proximally and a diastolic murmur when it is compressed distally. Capillary pulsations, i.e., *Quincke sign,* can be detected by pressing a glass slide on the patient's lip or by transmitting a light through the patient's fingertips.

Systolic arterial pressure is elevated, and diastolic pressure is abnormally low. *Hill sign* refers to popliteal cuff systolic pressure exceeding brachial cuff pressure by more than 60 mm Hg. Korotkoff sounds often persist to zero even though intraarterial pressure rarely falls below 30 mm Hg. The point of change in Korotkoff sounds, i.e., the muffling of these sounds in phase IV, correlates with the diastolic pressure. As heart failure develops, peripheral vasoconstriction may occur and arterial diastolic pressure may rise. This finding should not be interpreted as the presence of mild AR.

The apical impulse is diffuse and hyperdynamic and is displaced laterally and inferiorly; there may be systolic retraction over the parasternal region. A rapid ventricular filling wave is often palpable at the apex (as is a *systolic* thrill), at the base of the heart or suprasternal notch, and over the carotid arteries, resulting from the augmented stroke volume. In many patients, a carotid shudder is palpable or may be recorded.[400]

CHRONIC AORTIC REGURGITATION.

The PR interval may be prolonged, causing a soft S_1 . A_2 may be normal or accentuated when AR is due to disease of the aortic root, but is soft or absent when the valve is causing AR. P_2 may be obscured by the early diastolic murmur. Thus, S_2 may be absent or single or exhibit narrow or paradoxical splitting. A systolic ejection sound, presumably related to abrupt distention of the aorta by the augmented stroke volume, is frequently audible. An S_3 gallop correlates with an increased left ventricular end-diastolic volume. Its development may be a sign of impaired left ventricular function, which is useful in identifying patients with severe regurgitation who are candidates for surgical treatment.

The aortic regurgitant murmur, the principal physical finding of AR,[401] is one of high frequency that begins immediately after A_2 . It may be distinguished from the murmur of pulmonic regurgitation by its earlier onset, i.e., immediately after A_2 rather than after P_2 , and usually by the presence of a widened pulse pressure. The murmur is heard best with the diaphragm of the stethoscope while the patient is sitting up and leaning forward, with the breath held in deep exhalation. In severe AR, the murmur reaches an early peak and then has a dominant decrescendo pattern throughout diastole.

The severity of the regurgitation correlates better with the *duration* than with the *intensity* of the murmur. In mild AR, the murmur may be limited to early diastole and is typically high pitched and blowing. In severe AR, the murmur is holodiastolic and may have a rough quality. When the murmur is musical ("cooing dove" murmur), it usually signifies eversion or perforation of an aortic cusp. In patients with severe AR and left ventricular decompensation, equilibration of aortic and left ventricular pressures in late diastole (see Fig. 46-40) abolishes this component of the regurgitant murmur. When regurgitation is caused by primary valvular disease, the diastolic murmur is heard best along the left sternal border in the 3rd and 4th intercostal spaces. However, when it is due mainly to dilatation of the ascending aorta, the murmur is often more readily audible along the right sternal border.

A mid- and late diastolic apical rumble, the *Austin Flint murmur,* is common in severe AR and may occur in the presence of a normal mitral valve. This murmur appears to be created by rapid antegrade flow across a mitral orifice that is narrowed by the rapidly rising left ventricular diastolic pressure caused by severe aortic reflux impinging on the anterior leaflet of the mitral valve.[402] The Austin Flint murmur may be difficult to differentiate from that due to MS, but the presence of an opening snap and a loud S_1 in MS and the absence of these findings in AR are helpful clues. As the left ventricular end-diastolic pressure rises, the Austin Flint murmur commences and terminates earlier, and in acute AR with premature diastolic closure of the mitral valve, the presystolic portion of the Austin Flint murmur is eliminated. A short midsystolic murmur, caused by the increased ejection rate and stroke volume, may be audible at the base of the heart and transmitted to the carotid vessels. It may be higher pitched and less rasping than the murmur of AS but is often accompanied by a systolic thrill.

DYNAMIC AUSCULTATION.

The diastolic murmur of AR may be accentuated when the patient sits up and leans forward or by interventions that raise the arterial pressure, such as squatting or isometric exercise. The intensity of the murmur is reduced by interventions that lower the systolic pressure, such as inhalation of amyl nitrite or the strain of the Valsalva maneuver. The Austin Flint murmur, like the murmur of AR, is augmented by isometric exercise and administration of vasopressors and is reduced by amyl nitrite inhalation.[403]

ACUTE AORTIC REGURGITATION.

Patients with acute, severe AR appear gravely ill, with tachycardia, severe peripheral vasoconstriction and cyanosis, and sometimes pulmonary congestion and edema.[394] [404] The peripheral signs of AR are often not impressive and certainly not as dramatic as in patients with chronic AR. Duroziez murmur, Traube sign over the peripheral arteries, and bisferiens pulses are usually *absent* in acute AR. The normal or only slightly widened pulse pressure may lead to serious underestimation of the severity of the valvular lesion. The left ventricular impulse is normal or nearly so, and the rocking motion of the chest characteristic of chronic AR is not apparent. S_1 may be soft or absent because of premature closure of the mitral valve,[405] and the sound of mitral valve closure in mid- or late diastole is occasionally audible. However, closure of the mitral valve may be incomplete, and diastolic mitral regurgitation may occur.[395] Evidence of pulmonary hypertension, with an accentuated P_2 , S_3 , and S_4 , is frequently present. The early diastolic murmur of acute AR is lower pitched and shorter than that of chronic AR, because as left ventricular diastolic pressure rises, the (reverse) pressure gradient between the aorta and the left ventricle is rapidly reduced. A systolic murmur is common, resulting in "to and fro" sounds. The Austin Flint murmur, if present, is brief and ceases when left ventricular pressure exceeds left atrial pressure in diastole.

LABORATORY EXAMINATION

ELECTROCARDIOGRAM.

Chronic, severe AR results in left axis deviation and a pattern of left ventricular diastolic volume overload, characterized by an increase in initial forces (prominent Q waves in leads I, aVL, and V_3 through V_6) and a relatively small *r* wave in lead V_1 (Fig. 46-41) . With the passage of time, these initial forces diminish, but the

Figure 46-41 Atrial fibrillation and left ventricular hypertrophy in a patient with chronic AR. The most prominent features are the gross increase in precordial voltage (RV_5 +SV_2 =70 mm) and the marked anterolateral ST/T wave changes (leads I, aVL, and V_4 through V_6). The patient had aortic regurgitation and normal coronary arteries and was not taking digitalis. (Normal standardization, i.e., 1 mV=10 mm.)

(From Hall RJ, Julian DG: Diseases of the Cardiac Valves. New York, Churchill Livingstone, 1989, p 39.)

total QRS amplitude increases (Fig. 5-20) . The T waves may be tall and upright in the left precordial leads early in the course, but, more commonly they are inverted, with ST segment depressions. A left ventricular "strain" pattern correlates with the presence of dilatation and hypertrophy.[92] [406] Left intraventricular conduction defects occur late in the course and are usually associated with left ventricular dysfunction. The ECG is not an accurate predictor of the severity of AR or cardiac weight. When AR is caused by an inflammatory process, prolongation of the PR interval may be present.[407]

In *acute* AR, the ECG may or may not show left ventricular hypertrophy, depending upon the severity and duration of the regurgitation. However, nonspecific ST segment and T wave changes are common.

RADIOLOGICAL FINDINGS (See Figs. 8-4 , 8-8 , and 8-24.)

Cardiac size is a function of the duration and severity of regurgitation and the state of left ventricular function. In acute AR, there may be minimal cardiac enlargement, but marked enlargement is a common finding in chronic AR. Typically, the left ventricle enlarges in an inferior and leftward direction, causing a significant increase in the long axis (see Fig. 8-24) but sometimes causing little or no increase in the transverse diameter of the heart. Calcification of the aortic valve is uncommon in patients with pure AR but is often present in patients with combined AS and AR. Distinct left atrial enlargement in the absence of heart failure suggests associated mitral valve disease. Dilatation of the ascending aorta is usually more marked than in AS and may involve the entire aortic arch, including the aortic knob. Severe aneurysmal dilatation of the aorta suggests that aortic root disease (e.g., the Marfan syndrome, cystic medial necrosis, or annuloaortic ectasia) is responsible for the AR. Linear calcifications in the wall of the ascending aorta are seen in syphilitic aortitis but are nonspecific and are observed in degenerative disease as well.

For angiographic assessment of AR, contrast material should be injected rapidly (i.e., 25 to 35 ml/sec) into the aortic root, and filming should be carried out in the right and left anterior oblique projections. Opacification may be improved by filming during a Valsalva maneuver. In acute AR, there is only a slight increase in ventricular end-diastolic volume, but with the passage of time both the end-diastolic volume and the thickness of the ventricular wall increase, usually in parallel.

ECHOCARDIOGRAPHY (See Figs. 7-64 to 7-67).

This technique is helpful in identifying the cause of AR. The echocardiogram may show thickening of the valve cusps, prolapse of the valve, a flail leaflet, vegetations, or dilatation of the aortic root.[379] Two-dimensional studies are useful for the measurement of left ventricular end-diastolic and end-systolic dimensions, volumes, shortening fraction, ejection fraction, and mass. These measurements, when made serially, are of great value in selecting the optimal time for surgical intervention (see p. 1688). Although transthoracic imaging is usually satisfactory, transesophageal echocardiography often

provides more detail.

In acute AR, the echocardiogram reveals a reduction in amplitude of the opening movement, premature closure and delayed opening of the mitral valve.[408] Left ventricular end-diastolic dimensions are not markedly increased, and fractional shortening is normal. This contrasts with the findings in chronic AR, in which end-diastolic dimensions and wall motion are increased. Occasionally, with equilibration of aortic and left ventricular pressures in diastole, premature opening of the aortic valve may be detected.[409]

High-frequency fluttering of the anterior leaflet of the mitral valve during diastole is an important echocardiographic finding in both acute and chronic AR; however, it does not develop when the mitral valve is rigid, as occurs with rheumatic involvement. This sign, which, unlike the Austin Flint murmur, occurs even in mild AR, results from the movement imparted to the anterior leaflet of the mitral valve by the jet of blood regurgitating from the aorta.

Doppler echocardiography and color flow Doppler imaging are the most sensitive and accurate noninvasive techniques in the assessment of AR.[410] [411] [412] [413] [413A] They readily detect mild degrees of AR that may be inaudible on physical examination. Both the aortic regurgitant orifice size and the aortic regurgitant flow can be estimated. Serial studies permit determination of the progression of regurgitation and its effect on the left ventricle.

RADIONUCLIDE IMAGING (See Chap. 9) .

Radionuclide angiography provides an accurate noninvasive assessment of the severity of AR by allowing determination of the regurgitant fraction and of the left ventricular/right ventricular stroke volume ratio.[414] This technique is nonspecific because the ratio is increased by the presence of associated MR and reduced by tricuspid or pulmonary regurgitation. However, in the absence of these complicating lesions, a left ventricular/right ventricular stroke volume ratio of 2.0

or more denotes severe AR. Radionuclide angiography is also of value in the assessment of left ventricular function in patients with AR.[415] Serial measurements are useful in the early detection of deterioration of left ventricular function.

MAGNETIC RESONANCE IMAGING (see Fig. 10-23) .

This technique provides accurate measurements of regurgitant volumes and of ventricular end-systolic and diastolic volumes and allows calculation of the regurgitant orifice and of ventricular mass.[416] Although expensive, nuclear magnetic resonance imaging is the most accurate noninvasive technique for assessing the patient with AR

(see Chap. 10) .

MANAGEMENT

The management of severe AR must take account of the natural history. Since this differs in patients with chronic and acute AR, the two disorders are presented separately.

NATURAL HISTORY OF CHRONIC AORTIC REGURGITATION.

Moderately severe or even severe chronic AR may be associated with a generally favorable prognosis for many years. Approximately 75 percent of patients survive for 5 years and 50 percent for 10 years after diagnosis.[147] However, as is the case for AS, once the patient becomes symptomatic, the downhill course becomes progressive. Congestive heart failure, punctuated by episodes of acute pulmonary edema, and sudden death may occur, usually in previously symptomatic patients who have considerable left ventricular dilatation. Without surgical treatment, death usually occurs within 4 years after the development of angina pectoris and within 2 years after the onset of heart failure. In a multivariate analysis of patients with severe or moderately severe AR diagnosed by Doppler echocardiography, Dujardin and colleagues found that the following were associated with a poor outcome: advanced age, progressive symptoms, atrial fibrillation, and end-systolic diameter >25 mm/m^2 BSA.[417] Gradual deterioration of left ventricular function may occur even during the asymptomatic period; it is therefore important to intervene surgically before these changes have become irreversible.[418] A review of multiple studies on the natural history of chronic AR has been described by Bonow and associates[51] (Table 46-9) .

ACUTE AORTIC REGURGITATION.

Since early death due to left ventricular failure is frequent in patients with *acute, severe* AR despite intensive medical management, prompt surgical intervention is indicated. Even a normal ventricle cannot sustain the burden of acute, severe volume overload; therefore, the risk of *acute* AR is much greater than that of chronic AR.[394] [404] While the patient is being prepared for surgery, treatment with an intravenous positive

TABLE 46-9 -- NATURAL HISTORY OF AORTIC REGURGITATION

Asymptomatic patients with normal LV systolic function:	
Progression to symptoms and or LV dysfunction	<6%/yr
Progression to asymptomatic LV dysfunction	<3.5%/yr
Sudden death	<0.2%/yr
Asymptomatic patients with LV systolic dysfunction:	

Progression to cardiac symptoms	>25%/yr
Symptomatic patients:	
Mortality rate	>10%/yr

LV=left ventricular.

From Bonow RO, Carabello B, de Leon AC Jr, et al: ACC/AHA Guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol 32:1486, 1998.

inotropic agent (dopamine or dobutamine) and/or a vasodilator (nitroprusside) may be necessary. The agent and dosage should be selected on the basis of arterial pressure (see Chap. 21) . Beta-blocking agents and intraaortic balloon counterpulsation are contraindicated. In hemodynamically stable patients with acute AR secondary to active infective endocarditis, operation may be deferred to allow 5 to 7 days of intensive antibiotic therapy. However, AVR should be undertaken at the earliest sign of hemodynamic instability or if echocardiographic evidence of diastolic closure of the mitral valve develops.[419]

Medical Treatment

Patients with mild or moderate AR who are asymptomatic with normal or only minimally increased cardiac size require no therapy but should be followed clinically and by echocardiography every 12 or 24 months. These patients should also receive antibiotic prophylaxis for infective endocarditis. Asymptomatic patients with chronic, severe AR and normal left ventricular function should be examined at intervals of approximately 6 months. In addition to clinical examination, serial echocardiographic assessments of left ventricular size and ejection fraction should be made. Left-heart catheterization and aortography are useful in patients whose noninvasive test results are inconclusive or discordant with clinical findings.[51] As is the case for patients with other valvular lesions, adult surgical candidates who may need coronary artery bypass grafting should undergo coronary arteriography.

Patients with limitations of cardiac reserve and/or left ventricular dysfunction secondary to AR should not engage in vigorous sports or heavy exertion. Systemic arterial diastolic hypertension, if present, should be treated because it increases the regurgitant flow; however, beta-blocking agents should be used with great caution. Atrial fibrillation and bradyarrhythmias are poorly tolerated and should be prevented if possible. If these arrhythmias occur, they must be treated promptly and vigorously. Even though nitroglycerin and other nitrates are not as helpful in relieving anginal pain in patients with AR as they are in patients with coronary artery disease or AS, they are worth a trial. Although patients with left ventricular failure secondary to AR require prompt surgical treatment, they respond, at least temporarily, to treatment with digitalis glycosides, salt restriction, and diuretics.

The response to vasodilator therapy is often impressive. Hemodynamic studies have shown beneficial effects of intravenous hydralazine,[420] sublingual nifedipine,[421]

felodipine,[421A] as well as oral prazosin. [422] Vasodilator therapy may be particularly helpful in stabilizing patients with acute lesions or those with decompensated chronic AR who are awaiting operation. However, because of the high incidence of side effects of hydralazine, attention has focused on calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors.[423] In a comparison of digoxin with nifedipine in asymptomatic patients with severe AR, nifedipine delayed the need for operation as the result of development of symptoms or of left ventricular dysfunction.[424] In children with severe AR, therapy with an ACE inhibitor for one year has been reported to reverse ventricular dilatation and left ventricular wall stress.[425]

Thus, vasodilator therapy is indicated for patients with chronic, severe AR under the following circumstances: (1) as short-term therapy to improve the hemodynamic profile in the presence of heart failure while preparing for AVR; (2) as chronic therapy for patients in whom AVR is not possible; (3) as therapy for asymptomatic patients; and (4) as therapy for patients with left ventricular dysfunction after AVR.[51]

Surgical Treatment

INDICATIONS FOR OPERATION.

Because of their excellent prognosis in the short and medium term, operative correction should be deferred in patients with chronic, severe AR who are asymptomatic, have good exercise tolerance, *and* have an ejection fraction greater than 50 percent *without* severe left ventricular dilatation (i.e., an enddiastolic diameter <70 mm and an end-systolic diameter <50 mm). Similarly, in the absence of obvious contraindications or serious comorbidity, surgical treatment is advisable for symptomatic patients with severe AR. Between these two ends of the clinical-hemodynamic spectrum are many patients in whom it may be quite difficult to balance the immediate risks of operation and the continuing risks of an implanted prosthetic valve on the one hand against the hazards of allowing a severe volume overload to damage the left ventricle on the other.[426] [427] [428]

Since severe symptoms (NYHA Class III or IV) and left ventricular dysfunction with an ejection fraction less than 40 percent are independent risk factors for poor postoperative survival, surgery should be carried out in NYHA Class II patients before severe left ventricular dysfunction has developed.[51] Even after successful correction of AR, patients with severe left ventricular dysfunction may have persistent cardiomegaly and depressed left ventricular function.[429] [430] [431] Such patients often exhibit histological changes in the left ventricle, including massive fiber hypertrophy and increased interstitial fibrous tissue. Therefore, it is highly desirable to operate on patients *before* irreversible left ventricular changes have occurred.

Because AR has complex effects on both preload and afterload, the selection of appropriate indices of ventricular contractility to identify patients for operation is

challenging. The relationship between end-systolic wall stress and ejection fraction or percent fractional shortening is a useful measurement.[136] However, in the absence of such measurements, *serial* changes in ventricular end-diastolic and end-systolic volumes or dimensions can be used to detect *relative* deterioration of ventricular function. Although left ventricular end-diastolic volume and the ejection phase indices such as ejection fraction and ventricular fraction shortening are strongly influenced by loading conditions, they are nonetheless useful empirical predictors of postoperative function.

Serial echocardiograms or radionuclide ventriculograms should be obtained to detect changes in left ventricular size and function in asymptomatic patients with severe AR. Both techniques allow repeated evaluation of ejection fraction and end-systolic volume (or dimensions) both at rest and during exercise. Impaired left ventricular function at *rest* is the basis for selecting patients for operation; normal left ventricular function at rest with failure of the ejection fraction to rise normally with *exercise* is not considered an indication for surgery *per se,* but is an early warning sign that portends impaired function at rest.[432]

Bonow and colleagues have reported that asymptomatic patients with severe AR but normal left ventricular function have an excellent prognosis and do not warrant prophylactic operation (see Table 46-9) .[427] Less than 4 percent of patients per year require operation because of the development of symptoms of left ventricular dysfunction. The end-systolic diameter determined by two-dimensional echocardiography is valuable in predicting outcome in asymptomatic patients. Patients with severe AR and an end-systolic diameter less than 40 mm almost invariably remain stable and can be followed without immediate surgery. However, patients with an end-systolic diameter greater than 55 mm (see Fig. 46-43) , an end-systolic volume greater than 55 ml/m^2 , an end-diastolic volume greater than 200 ml/m^2 , or an ejection fraction less than 50 percent have an increased risk of death secondary to left ventricular dysfunction if they are not operated upon. Furthermore, Bonow and coworkers found that patients with *prolonged* left ventricular dysfunction had poor postoperative survival.[430]

In *summary,* the following considerations apply to the selection of patients with chronic AR for surgical treatment. Operation should be *deferred* in asymptomatic patients with normal and stable left ventricular function and should be *recommended* in symptomatic patients. In asymptomatic patients with left ventricular dysfunction, a decision should be based not on a single abnormal measurement but rather on several observations of depressed performance and impaired exercise tolerance, carried out at intervals of 2 to 4 months. If evidence of left ventricular dysfunction is borderline or is not consistent, continued close follow-up is indicated. If abnormalities are progressive or consistent (i.e., the left ventricular ejection fraction declines to 50 to 55 percent, the left ventricular end-systolic diameter rises to >55 mm, or the left ventricular end-systolic volume increases to >55 ml/m^2 [the "55 rule"[124]]), operation should be strongly considered even in asymptomatic patients. The threshold for operation may be lower when the surgeon believes that AVR will not be necessary (to be discussed), but this prediction may be difficult. Symptomatic patients with severe AR who have normal, mildly depressed, or moderately depressed left ventricular function should be operated upon. Patients with severely impaired left ventricular function (ejection fraction < 25 percent)

are at high surgical risk and have a guarded prognosis even after successful

Figure 46-42 Repair of the aortic valve in patient with severe AR. Conduit tailoring in the supravalvular position. The conduit is cut to replace three (*left*), two (*middle*), or one (*right*) individual sinuses. The aortic aneurysm is replaced and the valve is spared. *(From David TE, Feindel CM, Bos J: Repair of the aortic valve in patients with aortic insufficiency and aortic root aneurysm. J Thorac Cardiovasc Surg 109:345, 1995.)*

Figure 46-43 Relation of preoperative ventricular function to postoperative survival. Data of Greves and colleagues (*left*) and those of Bonow and associates (*right*) show remarkable agreement: Both groups incorporated limits clearly in the abnormal range. Cunha and coworkers (*center*) selected a limit that was well within normal range. These and other published data indicate that preoperative ventricular function is an important determinant of postoperative survival. SEF = systolic ejection fraction; ESD = echocardiographically measured dimension at end-systole; angio = angiography; echo = echocardiography. *(From Errichetti A et al: Is valve replacement indicated in asymptomatic patients with aortic stenosis or aortic regurgitation? In Cheitlin M [ed]: Dilemmas in Clinical Cardiology. Philadelphia, FA Davis Co, 1990, p 204.)*

AVR. Their outlook is also poor when they receive medical therapy, and their management should be considered on an individual basis.

The indications for surgery in patients with severe AR secondary to aortic root disease are similar to those in patients with primary valvular disease. However, progressive expansion of the aortic root and/or a diameter greater than 50 mm by echocardiography with any degree of regurgitation is also an indication for surgery in patients with aortic root disease.

OPERATIVE PROCEDURES.

Because an increasing proportion of patients with severe, isolated AR coming to operation now have primary aortic root rather than primary valvular disease, an increasing number can be treated surgically by correcting the dilated aortic root.[433] One of two annuloplasty procedures may be employed--an encircling suture of the aorta or a subcommissural annuloplasty. Aneurysmal dilatation of the ascending aorta requires excision, replacement with a graft that includes a prosthetic valve, and reimplantation of the coronary arteries.[434]

AVR is required for a large majority of patients with severe AR due to primary valve disease (as opposed to aortic root disease) and for many patients with combined AS and AR. In some patients with aortic root disease, the native valve can be spared when the aortic root is replaced (Fig. 46-42) . Because the aortic annulus in patients with severe AR is usually not as narrow as it is in patients with AS, a larger prosthetic valve

can be inserted, and mild postoperative obstruction to left ventricular outflow is less of a problem than it is in some patients with AS (to be discussed). Occasionally, when a leaflet has been torn from its attachments to the aortic annulus by trauma, surgical replacement without repair may be possible. In patients with AR secondary to prolapse of an aortic leaflet, aortic cusp resuspension or cusp resection may be employed. When AR is caused by leaflet perforation resulting from healed infective endocarditis, a pericardial patch can be used for repair.[435] [436]

In general, the risks and results of AVR in patients with AR are similar to those in patients with AS (see p. 1679), with a large percentage of patients exhibiting striking improvement in symptoms. Reductions in heart size and in left ventricular diastolic volume and mass occur in the majority of patients. Exceptions are patients who are in Class NYHA III or IV heart failure and/or patients who have severe left ventricular dysfunction preoperatively.[433] As is true for patients with AS, the operative risk of AVR for patients with AR depends on the general condition of the patient, the state of left ventricular function, and the skill and experience of the surgical team.[437] The mortality rate ranges from 3 to 8 percent in most medical centers (see Table 46-2) . A late mortality of approximately 5 to 10 percent per year is observed in survivors who had marked cardiac enlargement and/or prolonged left ventricular dysfunction preoperatively (Fig. 46-43) . Follow-up studies have shown both early rapid and then slower long-term reductions of ventricular mass, ejection fraction, myocyte hypertrophy, and ventricular fibrous content following relief of AR.[296] [350] By extending the indications for operation to symptomatic patients with normal left ventricular function as well as to asymptomatic patients with left ventricular dysfunction, both early and late results are improving.[437] With the continued improvement of surgical techniques and results, it will likely become possible to extend the recommendation for operative treatment to asymptomatic patients with severe regurgitation and normal cardiac function. However, given the risks of operation and the long-term complications of presently available prosthetic valves, I believe that the time for such a policy has not yet arrived.

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Tricuspid, Pulmonic, and Multivalvular Disease

TRICUSPID STENOSIS

Etiology and Pathology

Tricuspid stenosis (TS) is almost always rheumatic in origin.[7] Other causes of obstruction to right atrial emptying are unusual and include congenital tricuspid atresia (see Chap. 43) ; right atrial tumors, which may produce a clinical picture suggesting rapidly progressive TS[438] (see Chap. 49) ; and the carcinoid syndrome (see Chap. 48) , which more frequently produces tricuspid regurgitation. Rarely, obstruction to right ventricular inflow can be due to endomyocardial fibrosis, tricuspid valve vegetations,[438A] a pacemaker lead,[438B] or extracardiac tumors.

The majority of patients with rheumatic tricuspid valve disease present with tricuspid regurgitation or a combination of stenosis and regurgitation. Isolated rheumatic TS is uncommon and *almost* never occurs as an isolated lesion but generally accompanies mitral valve disease.[51] [439] In many patients with TS, the aortic valve is also involved

(i.e., trivalvular stenosis is present). TS is found at autopsy in about 15 percent of patients with rheumatic heart disease but is of clinical significance in only about 5 percent.[92] Organic tricuspid valve disease is more common in India, Pakistan, and other developing nations near the equator than in North America or Western Europe; it has been reported to occur in the hearts of more than one-third of patients with

rheumatic heart disease studied at autopsy on the Indian subcontinent.[440]

The anatomical changes of rheumatic TS resemble those of MS, with fusion and shortening of the chordae tendineae and fusion of the leaflets at their edges, producing a diaphragm with a fixed central aperture. However, valvular calcification is rare. As is the case with MS, TS is more common in women. The right atrium is often greatly dilated in TS, and its walls are thickened. There may be evidence of severe passive congestion, with enlargement of the liver and spleen.

Pathophysiology

A diastolic pressure gradient between the right atrium and ventricle--the hemodynamic expression of TS--is augmented when the transvalvular blood flow increases during inspiration or exercise and is reduced when the blood flow declines during expiration. A relatively modest diastolic pressure gradient (i.e., a mean gradient of only 5 mm Hg) is usually sufficient to elevate mean right atrial pressure to levels that result in systemic venous congestion and, unless sodium intake has been restricted or diuretics have been given, is associated with jugular venous distention, ascites, and edema.

In patients with sinus rhythm, the right atrial *a* wave may be very tall and may even approach the level of the right ventricular systolic pressure. Resting cardiac output is usually markedly reduced and fails to rise during exercise. This accounts for the normal or only slightly elevated left atrial, pulmonary arterial, and right ventricular systolic pressures, despite the presence of accompanying mitral valvular disease.

A *mean* diastolic pressure gradient across the tricuspid valve as low as 2 mm Hg is sufficient to establish the diagnosis of TS. However, exercise, deep inspiration, and the rapid infusion of fluids or the administration of atropine may greatly enhance a borderline pressure gradient in a patient with TS. Therefore, when this diagnosis is suspected, right atrial and ventricular pressures should be recorded simultaneously, using two catheters or a single catheter with a double lumen, with one lumen opening on either side of the tricuspid valve. The effects of respiration on any pressure difference should be examined.

Clinical Manifestations (Table 46-10)

HISTORY.

The low cardiac output characteristic of TS causes fatigue, and patients often complain of discomfort due to hepatomegaly, swelling of the abdomen, and anasarca. The severity of these symptoms, which are secondary to an elevated systemic venous pressure, is out of proportion to the degree of dyspnea. Some patients complain of a fluttering discomfort in the neck, caused by giant *a* waves in the jugular venous pulse. Despite the coexistence of MS, the symptoms characteristic of this valvular lesion (i.e., severe dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) are usually mild or absent in the presence of severe TS because the latter prevents surges of blood into the pulmonary circulation behind the stenotic mitral valve. Indeed, the *absence* of

symptoms of pulmonary congestion in a patient with obvious MS should suggest the possibility of TS.

TABLE 46-10 -- CLINICAL AND LABORATORY FEATURES OF RHEUMATIC TRICUSPID STENOSIS

HISTORY
Long history
Progressive fatigue, edema, anorexia
Minimal orthopnea, paroxysmal nocturnal dyspnea
Rheumatic fever in two-thirds of patients
Female preponderance
Pulmonary edema and hemoptysis are rare
PHYSICAL FINDINGS
Signs of multivalvular involvement
Wasting
Peripheral cyanosis
Neck vein distention, with prominent *v* waves
Right ventricular lift
Associated murmurs of mitral and aortic valve disease
Holosystolic murmur maximal at lower left sternal border, accentuating with inspiration
Hepatic pulsation
Ascites, peripheral edema
LABORATORY FINDINGS
Normal sinus rhythm is frequently present with large *a* waves in the neck veins
Absent right ventricular lift
Auscultation reveals a diastolic rumble at lower left sternal border, increasing in intensity with inspiration
Electrocardiogram shows tall right atrial P waves and no right ventricular hypertrophy
Chest roentgenogram shows a dilated right atrium without an enlarged pulmonary artery segment
Modified from Ockene IS: Tricuspid valve disease. In Dalen JE, Alpert JS (eds): Valvular Heart Disease. 2nd ed. Boston, Little, Brown and Co, 1987, pp 356, 390.Ebstein's anomaly
/Normal Circumference Abnormal

PHYSICAL EXAMINATION.

Because of the high frequency with which MS occurs in patients with TS and the similarity in the physical findings between the two valvular lesions, the diagnosis of TS is commonly missed. The physical findings are mistakenly attributed to MS, which is more common and may be more obvious. Therefore, a high index of suspicion is required to detect the tricuspid valvular lesion. In the presence of sinus rhythm, the *a* wave in the jugular venous pulse is tall, and a presystolic hepatic pulsation is often palpable. The *y* descent is slow and barely appreciable. The lung fields are clear, and despite engorged neck veins and the presence of ascites and anasarca, the patient may be comfortable while lying flat. Thus, the diagnosis of TS may be suspected from inspection of the jugular venous pulse in a patient with MS but without clinical evidence of pulmonary hypertension. This suspicion is strengthened when a diastolic thrill is palpable at the lower left sternal border, particularly if the thrill appears or becomes more prominent during inspiration.

The auscultatory findings of the accompanying MS are usually prominent and often overshadow the more subtle signs of TS. A tricuspid opening snap (OS) may be audible but is often difficult to distinguish from a mitral OS. However, the tricuspid OS usually follows the mitral OS and is localized to the lower left sternal border, whereas the mitral OS is usually most prominent at the apex and radiates more widely. The diastolic murmur of TS is also commonly heard best along the lower left parasternal border in the 4th intercostal space and is usually softer, higher pitched, and shorter in duration than the murmur of MS. The presystolic component of the TS murmur has a scratchy quality and a crescendo-decrescendo configuration that diminishes before S_1 .[439] The diastolic murmur and OS of TS are both augmented by maneuvers that increase transtricuspid valve flow, including inspiration, the Mueller maneuver, assumption of the right lateral decubitus position, leg raising, inhalation of amyl nitrite, squatting, and isotonic exercise. They

are reduced during expiration or the strain of the Valsalva maneuver and return to control levels immediately (i.e., within two to three beats) after Valsalva release.

Laboratory Examination

ELECTROCARDIOGRAM.

In the absence of atrial fibrillation in a patient with valvular heart disease, TS is suggested by the presence of ECG evidence of right atrial enlargement (see Chap. 5) . The P wave amplitude in leads II and V_1 exceeds 0.25 mV. Because most patients with TS have mitral valvular disease, the EGG signs of biatrial enlargement are commonly found. The amplitude of the QRS complex in lead V_1 may be reduced by the dilated right

atrium.

RADIOLOGICAL FINDINGS.

The key radiological finding is marked cardiomegaly with conspicuous enlargement of the right atrium (i.e., prominence of the right heart border), which extends into a dilated superior vena cava and azygos vein, but without conspicuous dilatation of the pulmonary artery. The vascular changes in the lungs characteristic of mitral valvular disease may be masked, with little or no interstitial edema or vascular redistribution, but left atrial enlargement may be present.

Angiography carried out following injection of contrast material into the right atrium and filming in the 30-degree right anterior oblique projection characteristically shows thickening and decreased mobility of the leaflets, a diastolic jet through the constricted orifice, and thickening of the normal atrial wall.

ECHOCARDIOGRAM (See also Chap. 7) .

The echocardiographic changes of the tricuspid valve in TS resemble those observed in the mitral valve in MS (see pp. 1648 and 1695). Two-dimensional echocardiography characteristically shows diastolic doming of the leaflets (especially the anterior tricuspid valve leaflet), thickening and restricted motion of the other leaflets, reduced separation of the tips of the leaflets,[441] and a reduction in diameter of the tricuspid orifice (Fig. 46-44) . Transesophageal echocardiography allows added delineation of the details of valve structure.[442] Doppler echocardiography shows a prolonged slope of antegrade flow and compares well with cardiac catheterization in the quantification of TS and in the assessment of associated tricuspid regurgitation.[443] [443A]

Management

Although the fundamental approach to the management of severe TS is surgical treatment, intensive sodium restriction and diuretic therapy may diminish the symptoms secondary to the accumulation of excess salt and water. A preparatory period of diuresis may diminish hepatic congestion and thereby improve hepatic function sufficiently to diminish the risks of subsequent operation.

Most patients with TS have coexisting valvular disease that requires surgery. In patients with combined TS and MS, the former must *not* be corrected alone because pulmonary congestion or edema may ensue. Surgical treatment of TS should be carried out at the time of mitral valve repair or replacement in patients with TS in whom the mean diastolic pressure gradient exceeds 5 mm Hg and the tricuspid orifice is less than approximately 2.0 cm^2 . The final decision concerning surgical treatment is often made at the operating table.[444]

Because TS is almost always accompanied by some TR, simple finger fracture valvotomy may not result in significant hemodynamic improvement but may merely substitute severe regurgitation for stenosis. However, open valvotomy in which the

stenotic tricuspid valve is converted into a functionally bicuspid valve may result in substantial improvement. The commissures between the anterior and septal leaflets and between the posterior and septal leaflets are opened. It is not advisable to open the commissure between the anterior and posterior leaflets for fear of producing severe regurgitation. If open valvotomy does not restore reasonably normal valve function, the tricuspid valve may have to be replaced.[445] [446] [447] [447A] A large porcine bioprosthesis

Figure 46-44 Two-dimensional echocardiograms in the long-axis view in a patient with tricuspid stenosis. *Top,* Systolic frame. *Bottom,* Diastolic frame that shows doming of both leaflets of the tricuspid valve (TV) (arrows). RA = right atrium; RV = right ventricle. *(From Shimada R et al: Diagnosis of tricuspid stenosis by M-mode and two-dimensional echocardiography. Am J Cardiol 53:164, 1984.)*

(see p. 1704) is preferred to a mechanical prosthesis in the tricuspid position because of the high risk of thrombosis of the latter[447] and the longer durability of bioprostheses in the tricuspid than in the mitral or aortic positions.[448] [449] [450] [451] The feasibility of tricuspid balloon valvuloplasty has been demonstrated, and this procedure may be combined with mitral balloon valvuloplasty.[452]

TRICUSPID REGURGITATION

Etiology and Pathology (Table 46-11)

The most common cause of tricuspid regurgitation (TR) is not intrinsic involvement of the valve itself (i.e., primary TR) but rather *dilatation of the right ventricle* and of the tricuspid annulus causing secondary (functional) TR. This may be a complication of right ventricular failure of any cause. It is observed in patients with right ventricular hypertension secondary to any form of cardiac or pulmonary vascular disease, most commonly mitral valve disease.[452] [453] [454] [455] In general, a systolic right ventricular systolic pressure greater than 55 mm Hg will cause functional TR.[51] TR can also occur secondary to right ventricular infarction,[456] congenital heart disease (see Chap. 43) (e.g., pulmonic stenosis and pulmonary hypertension secondary to Eisenmenger syndrome), primary pulmonary hypertension, and, rarely, cor pulmonale. In infants, TR may complicate right ventricular failure secondary to neonatal pulmonary diseases and pulmonary hypertension with persistence of

TABLE 46-11 -- CAUSES AND MECHANISMS OF PURE TRICUSPID REGURGITATION

CAUSES
Anatomically ABNORMAL valve
Rheumatic

Nonrheumatic
Infective endocarditis
Ebstein anomaly
Floppy (prolapse)
Congenital (non-Ebstein)
Carcinoid
Papillary muscle dysfunction
Trauma
Connective tissue disorders (Marfan)
Rheumatoid arthritis
Radiation injury
Anatomically NORMAL valve (functional)
Elevated right ventricular systolic pressure (dilated annulus)

MECHANISMS

Condition	**Leaflet Area**	**Annular Circumference**	**Leaflet Insertion**
Floppy			Normal
Ebstein anomaly			Abnormal
Pulmonary/right ventricular systolic hypertension	Normal		Normal
Papillary muscle dysfunction	Normal	Normal	Normal
Carcinoid	/Normal	Normal	Normal
Rheumatic	/Normal	Normal	Normal
Infective endocarditis	/Normal	Normal	Normal

Modified from Waller BF: Rheumatic and nonrheumatic conditions producing valvular heart disease. In Frankl WS, Brest AN (eds): Cardiovascular Clinics. Valvular Heart Disease: Comprehensive Evaluation and Management. Philadelphia, FA Davis Co, 1989, pp 35, 95. Autologous MANUFACTURER Toronto Stentless (TSP) FIRST CLINICAL (thousands)

the fetal pulmonary circulation. [457] In all of these cases, TR reflects the presence of, and in turn aggravates, severe right ventricular failure. Functional TR may diminish or disappear as the right ventricle decreases in size with the treatment of heart failure. TR

can also occur as a consequence of dilatation of the annulus in the Marfan syndrome, in which right ventricular dilatation secondary to pulmonary hypertension is not present.

A variety of disease processes can affect the tricuspid valve apparatus *directly* and lead to regurgitation (primary TR).[457] Thus, organic TR may occur on a congenital basis, as part of *Ebstein anomaly,* in atrioventricular canal, and when the tricuspid valve is involved in the formation of an aneurysm of the ventricular septum,[458] or in corrected transposition of the great arteries,[459] or it may occur as an isolated congenital lesion.[457] Rheumatic fever may involve the tricuspid valve directly.[92] When this occurs, it usually causes scarring of the valve leaflets and/or chordae tendineae, leading to limited leaflet mobility and either isolated TR or a combination of TR and TS. Rheumatic involvement of the mitral, and often aortic, valves coexist.

TR or the combination of TR and TS is an important feature of the *carcinoid syndrome* (Fig. 46-45) , which leads to focal or diffuse deposits of fibrous tissue on the endocardium of the valvular cusps and cardiac chambers and on the intima of the great veins and coronary sinus[460] [461] [462] [463] (see Chap. 48) . The white, fibrous carcinoid plaques are most extensive on the right side of the heart, where they are usually deposited on the ventricular surfaces of the tricuspid valve and cause the cusps to adhere to the underlying right ventricular wall, thereby producing TR. Endomyocardial fibrosis with shortening of the tricuspid leaflets and chordae tendineae is an important cause of TR in tropical Africa (see Chap. 48) . TR may result from prolapse of the tricuspid valve caused by myxomatous changes in the valve and chordae tendineae; prolapse of the mitral valve is usually present in these patients as well.[464] [465] Prolapse of the tricuspid valve occurs in about 20 percent of all patients with mitral valve prolapse. Tricuspid valve prolapse may also be associated with atrial septal defect. Other causes of TR include penetrating and nonpenetrating trauma,[460] dilated cardiomyopathy, [467] infective endocarditis[468] (particularly staphylococcal endocarditis in narcotics addicts), and following surgical excision of the tricuspid valve in patients with infective endocarditis that is unresponsive to medical management.[469] Less common causes of TR[470] include cardiac tumors (particularly right atrial myxoma), transvenous pacemaker leads, repeated endomyocardial biopsy in a transplanted heart,[471] endomyocardial fibrosis, methysergide-induced valvular disease,[472] administration of fenfluramine-phentermine,[473] and systemic lupus erythematosus involving the tricuspid valve.[474]

Clinical Manifestations

HISTORY.

In the absence of pulmonary hypertension, TR is generally well tolerated. However, when pulmonary hypertension and TR coexist, cardiac output declines, and the manifestations of right-sided heart failure become intensified.[475] Thus, the symptoms of TR result from a reduced cardiac output and from ascites, painful congestive hepatomegaly, and massive edema. Occasionally, patients have throbbing pulsations in the neck, which intensify on effort and are due to jugular venous distention; and systolic pulsations of the eyeballs have also been described.[476] In the many patients with TR who have mitral valve disease, the symptoms of the latter usually predominate.

Symptoms of pulmonary congestion may abate as TR develops, but they are replaced by weakness, fatigue, and other manifestations of a depressed cardiac output.

PHYSICAL EXAMINATION.

Evidence of weight loss and cachexia, cyanosis, and jaundice are often present on inspection in patients with severe TR. Atrial fibrillation is common. There is jugular venous distention,[477] the normal

Figure 46-45 Septal tricuspid leaflet thickened by carcinoid plaques and fused to underlying ventricular septum.*(From Callahan JA et al: Echocardiographic features of carcinoid heart disease. Am J Cardiol 50:766, 1982.)*

x and *x*
descents disappear, and a prominent systolic wave, i.e., a *c-v* wave (or *s* wave), is apparent (see Fig. 4-5) . The descent of this wave, the *y* descent, is sharp and becomes the most prominent feature of the venous pulse (unless there is coexisting TS, in which case it is slowed). A venous systolic thrill and murmur in the neck may be present in patients with severe TR.[478] The right ventricular impulse is hyperdynamic and thrusting in quality. Systolic pulsations of an enlarged, tender liver are commonly present initially. However, in patients with chronic TR and congestive cirrhosis, the liver may become firm and nontender. Ascites and edema are frequent.

Auscultation.

This usually reveals an S_3 originating from the right ventricle, which is accentuated by inspiration. When TR is associated with and secondary to pulmonary hypertension, P_2 is accentuated as well. When TR occurs in the presence of pulmonary hypertension, the systolic murmur is usually high-pitched, pansystolic, and loudest in the 4th intercostal space in the parasternal region but occasionally is loudest in the subxiphoid area. When TR is mild, the murmur may be short. When TR occurs in the absence of pulmonary hypertension (e.g., in infective endocarditis or following trauma), the murmur is usually of low intensity and limited to the first half of systole. When the right ventricle is greatly dilated and occupies the anterior surface of the heart, the murmur may be prominent at the apex and difficult to distinguish from that produced by MR.

The response of the systolic murmur to respiration and other maneuvers is of considerable aid in establishing the diagnosis of TR (see Table 4-4) . The murmur is characteristically augmented during inspiration (Carvallo sign). However, when the failing ventricle can no longer increase its stroke volume in the recumbent or sitting positions, the inspiratory augmentation may be elicited by standing. The murmur also increases during the Mueller maneuver (forced inspiration against a closed glottis),

exercise, leg-raising, and hepatic compression. It demonstrates an immediate overshoot after release of the Valsalva strain but is reduced in intensity and duration in the standing position and during the strain of the Valsalva maneuver. Increased atrioventricular flow across the tricuspid orifice in diastole may cause a short early diastolic flow rumble in the left parasternal region following S_3 . Tricuspid valve prolapse, like mitral valve prolapse, causes nonejection systolic clicks and late systolic murmurs. However, in tricuspid valve prolapse, these findings are more prominent at the lower left sternal border. With inspiration, the clicks occur later, and the murmurs intensify and become shorter in duration.

Laboratory Examination

ELECTROCARDIOGRAM.

This is usually nonspecific and characteristic of the lesion causing TR. Incomplete right bundle branch block, Q waves in lead V_1 , and atrial fibrillation are commonly found.

RADIOLOGICAL FINDINGS.

In patients with functional TR, marked cardiomegaly is usually evident, and the right atrium is prominent. Evidence of elevated right atrial pressure may include distention of the azygos vein and the presence of a pleural effusion. Ascites with upward displacement of the diaphragm may be present. Systolic pulsations of the right atrium may be present on fluoroscopy.

ECHOCARDIOGRAM (See Figs. 7-68 and 7-69) .

The goal of echocardiography is to detect TR, estimate its severity, and assess pulmonary arterial pressure and right ventricular function.[443A] In patients with TR secondary to dilation of the tricuspid annulus, the right atrium, right ventricle, and tricuspid annulus are all usually greatly dilated on echocardiography.[479] [480] There is evidence of right ventricular diastolic overload with paradoxical motion of the ventricular septum similar to that observed in atrial septal defect. Exaggerated motion and delayed closure of the tricuspid valve are evident in patients with Ebstein anomaly. Prolapse of the tricuspid valve due to myxomatous degeneration may be evident on echocardiography.[465] [466] Echocardiographic indications of tricuspid valve abnormalities, especially TR by Doppler examination, can be detected in the majority of patients with carcinoid heart disease.[463] In patients with TR due to endocarditis, echocardiography may reveal vegetations on the valve or a flail valve. Transesophageal echocardiography enhances detection of TR.

Contrast Echocardiography.

This involves rapid injection of saline indocyanine green dye or sanicated human albumin (Albunex)[481] into an antecubital vein while a two-dimensional echocardiogram is recorded[482] (see Chap. 7) . The injection produces microcavities that are readily

visible on echocardiography and normally travel as a bolus through the circulation. In TR, these microcavities can be seen to travel back and forth across the tricuspid orifice and to pass into the inferior vena cava and hepatic veins during systole.

Pulsed Doppler Echocardiography.

This reveals systolic flow from the right ventricle to the right atrium and is a sensitive technique for detecting and quantifying[483] [484] TR. Reverse flow can also be recorded in the inferior vena cava and hepatic veins. The peak velocity of TR flow is useful in the noninvasive estimation of right ventricular (and pulmonary arterial) systolic pressure. Color flow Doppler imaging is a sensitive and specific method for assessing TR and is helpful in selecting patients for surgical treatment and in evaluating postoperative results.

HEMODYNAMIC FINDINGS.

The right atrial and right ventricular end-diastolic pressures are often elevated in TR, whether the condition is due to organic disease of the tricuspid valve or is secondary to right ventricular systolic overload. The right atrial pressure tracing usually reveals absence of the *x* descent and a prominent *v* or *c-v* wave ("ventricularization" of the atrial pressure). Absence of these findings essentially excludes moderate or severe TR.[485] As the severity of TR increases, the contour of the right atrial pressure pulse increasingly resembles that of the right ventricular pressure pulse (Fig. 46-46) . A rise or no change in right atrial pressure on deep inspiration, rather than the usual fall, is a characteristic finding. Determination of the pulmonary arterial (or right ventricular) systolic pressure may be helpful in deciding whether the TR is primary (i.e., due to disease of the valve or its supporting structures) or functional (i.e., secondary to right ventricular dilatation). A pulmonary arterial or right ventricular systolic pressure less than 40 mm Hg favors a primary cause, whereas a pressure greater than 55 mm Hg suggests that TR is secondary. Intermediate values are not helpful. Diagnosis and quantitative assessment of TR can be aided in many instances by right ventriculography.[486]

Management

TR in the absence of pulmonary hypertension usually is well tolerated and may not require surgical treatment. Indeed,

Figure 46-46 Appearance of right atrial (RA) pressure contour in patients with severe tricuspid regurgitation (TR), moderate TR, and no TR (normal). Note the regurgitant systolic ("s") wave that blends with the normal filling ("v") wave in severe TR. The resultant RA pressure waveform resembles a right ventricular (RV) pressure recording.*(From Grossman W [ed]: Cardiac Catheterization and Angiography. 5th ed. Philadelphia, Lea and Febiger, 1996.)*

both human patients and experimental animals with normal pulmonary arterial pressure may tolerate total excision of the tricuspid valve as long as right ventricular systolic pressure is normal. Dilatation of the right side of the heart usually occurs months or years after tricuspid valvectomy (usually carried out for acute infective endocarditis). *Surgical treatment* of acquired regurgitation secondary to annular dilatation was greatly improved when Carpentier introduced the concept of suturing the annulus to a prosthetic ring.[487] Annuloplasty without insertion of a prosthetic ring (the so-called DeVega annuloplasty) has also been found to be effective in patients with annular dilatation. This technique is now widely employed.[444] [475] [488] [489] [490]

At the time of mitral valve surgery in patients with TR secondary to pulmonary hypertension, the severity of the regurgitation should be assessed by palpation of the tricuspid valve. In addition, it should be determined whether the TR is secondary to pulmonary hypertension, in which case the valve is normal, or whether it is secondary to rheumatic fever. Patients with mild TR usually do not require surgical treatment[491] ; pulmonary vascular pressures decline following successful mitral valve surgery, and the mild TR tends to disappear. Excellent results have been reported in patients with moderate TR with the use of suture annuloplasty of the posterior (unsupported) portion of the annulus. Patients with severe TR and primary rheumatic tricuspid valve disease with commissural fusion require valvotomy and ring annuloplasty.[488] The latter is also employed for TR secondary to annular dilatation. A surgical mortality rate of 13.9 percent has been reported (see Table 46-2) .[104] If these procedures do not provide a good functional result at the operating table (as assessed by transesophageal echocardiography), valve replacement using a large porcine mitral heterograft may be required.

When organic disease of the tricuspid valve (Ebstein anomaly or carcinoid heart disease[449]) causes TR severe enough to require surgery, valve replacement is usually needed. The risk of thrombosis of mechanical prostheses is greater in the tricuspid than in the mitral or aortic positions, presumably because pressure and flow rates are lower in the right side of the heart. For this reason, the artificial valve of choice for the tricuspid position in adults is a large porcine heterograft.[450] [451] Anticoagulants are not required, and a graft durability of more than 10 years has been established.

In treating the difficult problem of tricuspid endocarditis in heroin addicts (see Chap. 47) , total excision of the tricuspid valve *without immediate replacement* can generally be tolerated by these patients, who usually do not have associated pulmonary hypertension. When antibiotic therapy is unsuccessful, valvular replacement frequently results in reinfection or continued infection. Therefore, diseased valvular tissue should be excised to eradicate the endocarditis, and antibiotic treatment can then be continued. Initially, most patients tolerate loss of the tricuspid valve without great difficulty. Later, right ventricular dysfunction usually occurs. A bioprosthetic valve may therefore be inserted 6 to 9 months after valve excision and control of the infection.

PULMONIC VALVE DISEASE

Etiology and Pathology

PULMONIC STENOSIS.

The *congenital* form is the most common cause of pulmonic stenosis (PS).[492] Manifestations in children are discussed in Chapter 43 and in adults in Chapter 44 . *Rheumatic* inflammation of the pulmonic valve is very uncommon, is usually associated with involvement of other valves, and rarely leads to serious deformity. However, in one study, a high incidence of significant pulmonic valve involvement secondary to rheumatic fever was reported in Mexico City, perhaps related to the pulmonary hypertension that occurs at high altitudes and the resultant greater stress on the pulmonic valve.[493] *Carcinoid* plaques, similar to those involving the tricuspid valve, are often present in the outflow tract of the right ventricle of patients with malignant carcinoid. The plaques result in constriction of the pulmonic valve ring, retraction and fusion of the valve cusps, and either PS or the combination of PS and pulmonic regurgitation (Fig. 46-47) . [494] [495] Obstruction in the region of the pulmonic valve may be extrinsic to the valve apparatus and may be produced by cardiac tumors or by aneurysm of the sinus of Valsalva.[496]

Management of congenital PS focuses on balloon dilation (see Chaps. 38 , 43 , and 44) .

PULMONIC REGURGITATION.

By far the most common cause of pulmonic regurgitation (PR) is dilatation of the valve ring secondary to pulmonary hypertension (of any etiology) or to dilatation of the pulmonary artery, either idiopathic[497] [498] or consequent to a connective tissue disorder such as the Marfan syndrome. The second most common cause of PR is infective endocarditis.[499] Less frequently, PR is iatrogenic and is induced at the time of surgical treatment of congenital PS or tetralogy of Fallot.[499A] PR may also result from various lesions that directly affect the pulmonic valve. These include congenital malformations, such as absent, malformed, fenestrated, or supernumerary leaflets. These anomalies may occur as isolated lesions[500] but more often are associated with other congenital anomalies,[501] particularly tetralogy of Fallot, ventricular septal defect, and pulmonic valvular stenosis. Less common causes include trauma, carcinoid syndrome,[494] rheumatic involvement, injury produced by a pulmonary artery flow-directed catheter,[502] syphilis, and chest trauma.[503]

Figure 46-47 Carcinoid heart disease; pulmonary valve viewed from above (*A*) and opened (*B*). The thickened and retracted cusps result in valvular incompetence. The constricted annulus results in valvular stenosis. Carcinoid plaques (arrows) extend onto the pulmonary trunk. *(From Callahan, JA et al:*

Echocardiographic features of carcinoid heart disease. Am J Cardiol 50:767, 1982.)

Clinical Manifestations

Like TR, isolated PR causes right ventricular volume overload and may be tolerated for many years without difficulty unless it complicates, or is complicated by, pulmonary hypertension. In this case, PR is usually accompanied by and aggravates right ventricular failure. Patients with PR caused by infective endocarditis who develop septic pulmonary emboli and pulmonary hypertension often exhibit severe right ventricular failure.[503] In most patients, the clinical manifestations of the primary disease are severe and usually overshadow the PR, which often results only in incidental auscultatory findings. *Physical examination* reveals a hyperdynamic right ventricle that produces palpable systolic pulsations in the left parasternal area and an enlarged pulmonary artery that often results in systolic pulsations in the 2nd left intercostal space. Sometimes systolic and diastolic thrills are felt in the same area. A tap reflecting pulmonic valve closure is usually easily palpable in the 2nd intercostal space in patients with pulmonary hypertension and secondary PR.

AUSCULTATION.

P_2 is not audible in patients with congenital absence of the pulmonic valve; however, this sound is accentuated in patients with PR secondary to pulmonary hypertension. There may be wide splitting of S_2 caused by prolongation of right ventricular ejection accompanying the augmented right ventricular stroke volume.[501] A nonvalvular systolic ejection click due to the sudden expansion of the pulmonary artery by the augmented right ventricular stroke volume frequently initiates a midsystolic ejection murmur, most prominent in the 2nd left intercostal space. An S_3 and S_4 originating from the right ventricle are often audible, most readily in the 4th intercostal space at the left parasternal area, and are augmented by inspiration.

In the absence of pulmonary hypertension, the diastolic murmur of PR is low pitched and usually heard best at the 3rd and 4th left intercostal spaces adjacent to the sternum (see Fig. 4-37) .[504] The murmur commences when pressures in the pulmonary artery and right ventricle diverge, approximately 0.04 second after P_2 . It is diamond-shaped in configuration and brief, reaching a peak intensity when the gradient between these pressures is maximal and ending with equilibration of the pressures. The murmur becomes louder during inspiration.

The Graham Steell Murmur.

When systolic pulmonary arterial pressure exceeds approximately 55 mm Hg, dilatation of the pulmonic annulus results in a high-velocity regurgitant jet that is responsible for the Graham Steell murmur of PR. (Doppler ultrasonography reveals pulmonary

regurgitation at much lower pulmonary arterial pressures.) The Graham Steell murmur is a high-pitched, blowing, decrescendo murmur beginning immediately after P_2 and is most prominent in the left parasternal region in the 2nd to 4th intercostal spaces. Thus, although it resembles the murmur of AR, it is usually accompanied by severe pulmonary hypertension, i.e., an accentuated P_2 or fused S_2 , an ejection sound, and a systolic murmur of TR, and not by a widened arterial pulse pressure. Sometimes a low-frequency presystolic murmur is present, i.e., a right-sided Austin Flint murmur originating from the mitral valve.[505]

The Graham Steell murmur of PR secondary to pulmonary hypertension usually increases in intensity with inspiration, exhibits little change after amyl nitrite inhalation or vasopressor administration, is diminished during the Valsalva strain, and returns to baseline intensity almost immediately after release of the Valsalva strain. This murmur resembles and may be confused with the diastolic blowing murmur of AR. However, indicator dilution studies[506] and aortography have established that a diastolic blowing murmur along the left sternal border in patients with rheumatic heart disease and pulmonary hypertension (even in the *absence* of peripheral signs of AR) is usually due to AR rather than PR.

Laboratory Examination

ELECTROCARDIOGRAM.

In the absence of pulmonary hypertension, PR often results in an ECG that reflects right ventricular diastolic overload, i.e., an rSr (or rsR) configuration in the right precordial leads. PR secondary to pulmonary hypertension is usually associated with ECG evidence of right ventricular hypertrophy.

RADIOLOGICAL FINDINGS.

Both the pulmonary artery and the right ventricle are usually enlarged, but these signs are nonspecific. Fluoroscopy may demonstrate pronounced pulsation of the main pulmonary artery. PR can be diagnosed by observing opacification of the right ventricle following injection of contrast material into the main pulmonary artery (Fig. 46-48) . The diagnosis is supported by noting

Figure 46-48 Pulmonic valvular regurgitation. Contrast material has been injected into the main pulmonary artery (PA) and regurgitates back into an enlarged right ventricle (RV).*(Reproduced with permission from Carlsson E et al: The radiological diagnosis of cardiac valvular insufficiency. Circulation 55:921, 1977. Copyright 1977, American Heart Association.)*

superimposition of the pulmonary arterial and right ventricular pressure curves during mid- and late diastole. Indicator dilution studies with injections into the pulmonary artery and sampling from the right ventricle,[507] as well as intracardiac phonocardiography, can also be helpful in establishing the diagnosis in mild cases.

ECHOCARDIOGRAM.

Two-dimensional echocardiography shows right ventricular dilatation and, in patients with pulmonary hypertension, right ventricular hypertrophy as well. Right ventricular function can be estimated. Abnormal motion of the septum characteristic of volume overload of the right ventricle in diastole and/or septal flutter[508] may be evident. The motion of the pulmonic valve may point to the cause of the PR. Absence of *a* waves and systolic notching of the posterior leaflet suggest pulmonary hypertension; large *a* waves indicate pulmonic stenosis. PR can be detected by contrast echocardiography. The pulsed Doppler technique is also extremely accurate in detecting PR and in helping to estimate its severity. Abnormal Doppler signals in the right ventricular outflow tract with velocity sustained throughout diastole are generally observed in patients in whom PR is caused by dilatation of the valve ring secondary to pulmonary hypertension. When the velocity falls during diastole, the pulmonary artery pressure is usually normal, and the regurgitation is caused by an abnormality of the valve itself.[509]

Management

PR alone is seldom severe enough to require specific treatment. Cardiac glycosides are useful in the management of right ventricular dilatation or failure. Treatment of the primary condition, such as infective endocarditis, or the lesion responsible for the pulmonary hypertension, such as surgery for mitral valvular disease, often ameliorates the PR. Surgical treatment directed specifically at the pulmonic valve (e.g., in patients in whom surgical correction of tetralogy of Fallot has caused severe PR[509A]) is required only occasionally because of intractable right heart failure. Under such circumstances, valve replacement may be carried out,[510] [510A] [510B] preferably with a porcine bioprosthesis or a pulmonary allograft.[499A]

MULTIVALVULAR DISEASE

Multivalvular involvement is caused most frequently by rheumatic fever, and various clinical and hemodynamic syndromes can be produced by different combinations of valvular abnormalities. The Marfan syndrome and other

connective tissue disorders may cause multivalve prolapse and dilatation, resulting in multivalvular regurgitation. Degenerative calcification of the aortic valve may be associated with degenerative mitral annular calcification and cause AS and MR. Different pathological conditions may affect two valves in the same patient, such as infective endocarditis on the aortic valve causing AR and ischemia causing MR. Development of PR and TR secondary to dilatation of the pulmonic valve ring and tricuspid annulus, as a consequence of pulmonary hypertension secondary to mitral and/or aortic valvular disease, was discussed previously, as was the combination of organic rheumatic tricuspid and mitral valvular disease.

In patients with multivalvular disease, the clinical manifestations depend on the relative severities of each of the lesions. When the valvular abnormalities are of approximately equal severity, clinical manifestations produced by the more proximal (upstream) of the two valvular lesions (i.e., the mitral valve in patients with combined mitral and aortic valvular disease and the tricuspid valve in patients with combined tricuspid and mitral valvular disease) are generally more prominent than those produced by the distal lesion. Thus, the proximal lesion tends to mask the distal lesion.

It is important to recognize multivalvular involvement preoperatively because failure to correct all significant valvular disease at the time of operation increases mortality considerably. In patients with multivalvular disease, the relative severity of each lesion may be difficult to estimate by clinical examination and noninvasive techniques because one lesion may mask the manifestations of the other. For this reason, patients suspected of having multivalvular involvement and who are being considered for surgical treatment should undergo right- and left-cardiac catheterization and angiography. These studies are in addition to careful clinical examination and a noninvasive workup, with emphasis on two-dimensional and Doppler echocardiography. If there is any question concerning the presence of significant AS in patients undergoing mitral valve surgery, the aortic valve should be inspected because overlooking this condition can lead to a high perioperative mortality. Similarly, it is useful to palpate the tricuspid valve at the time of mitral valve surgery.

MITRAL STENOSIS AND AORTIC REGURGITATION

Approximately two-thirds of patients with severe MS have an early blowing diastolic murmur along the left sternal border with a normal pulse pressure. In about 90 percent of these patients, the murmur is due to mild or moderate AR and is usually of little clinical importance. However, approximately 10 percent of patients with MS have severe rheumatic AR,[511] which can generally be recognized by the usual signs of AR (i.e., a widened pulse pressure, left ventricular dilatation and increased wall motion on echocardiography, and signs of left ventricular enlargement on radiological and ECG examinations).

In keeping with the general observation that a proximal lesion may mask a distal lesion, significant AR may be missed in patients with severe MS.[512] The widened pulse pressure, in particular, may be absent. On the other hand, MS may be missed or, conversely, may be falsely diagnosed on clinical examination of patients with obvious AR. An accentuated S_1 and an opening snap in a patient with AR should suggest the possibility of mitral valvular disease. However, an Austin Flint murmur is often inappropriately considered to be the diastolic rumbling murmur of MS. These two murmurs may be distinguished at the bedside by means of amyl nitrite inhalation, which diminishes the Austin Flint murmur but augments the murmur of MS; isometric handgrip and squatting augment both the diastolic murmur of AR and the Austin Flint murmur. Echocardiography, particularly pulsed Doppler echocardiography, is of decisive value in detecting MS and MR.

Since double-valve replacement is associated with increased short-term and long-term

risk,[114] [512A] balloon mitral valvotomy can be the first procedure. If this causes left ventricular dilatation, aortic valve replacement can follow. Alternatively, open mitral valvotomy and aortic valve replacement can be performed at the same time.[51]

MITRAL STENOSIS AND AORTIC STENOSIS

The left ventricle of a patient with these two lesions is usually small, stiff, and hypertrophied. When severe MS and AS coexist, the former masks many of the manifestations of the latter.[513] The cardiac output tends to be reduced more than in patients with isolated AS. The reduced cardiac output lowers both the transaortic valvular pressure gradient and the left ventricular systolic pressure, diminishes the incidence of angina pectoris, and retards the development of aortic valvular calcification and left ventricular hypertrophy.[514] On the other hand, clinical manifestations associated with MS, such as pulmonary congestion and hemoptysis, atrial fibrillation, and systemic embolization, occur more frequently in patients with coexisting MS and AS than in those with isolated AS.

On physical examination, an S_4 , (which is common in patients with pure AS) is usually not present. The midsystolic murmur characteristic of AS may be reduced in intensity and duration because the stroke volume is reduced by the MS. The ECG may fail to demonstrate left ventricular hypertrophy, but left atrial enlargement is common. The chest roentgenogram is usually typical of MS except that calcium may be present in the region of the aortic valve. The two-dimensional and Doppler echocardiograms are of the greatest value because stenosis of both valves may be evident. However, the low cardiac output characteristic of the combined lesions may reduce the transvalvular pressure gradients estimated by Doppler echocardiography.

It is vital to recognize the presence of hemodynamically significant aortic valvular disease (i.e., stenosis and/or regurgitation) preoperatively in patients who are to undergo mitral valvotomy. This procedure may be hazardous because it can impose a sudden hemodynamic load on the left ventricle that had previously been protected by the MS and may lead to acute pulmonary edema. Balloon mitral valvotomy and aortic valve replacement may be the treatment of choice.

AORTIC STENOSIS AND MITRAL REGURGITATION

This combination of lesions is usually caused by rheumatic heart disease, although AS may be congenital and MR may be due to mitral valve prolapse. The combination of severe AS and MR is a hazardous one, but fortunately it is relatively uncommon. Obstruction to left ventricular outflow augments the volume of MR flow,[123] whereas the presence of MR diminishes the ventricular preload necessary for maintenance of the left ventricular stroke volume in patients with AS. The result is a reduced forward cardiac output and marked left atrial and pulmonary venous hypertension. The development of atrial fibrillation (due to left atrial enlargement) has an adverse hemodynamic effect in the presence of AS. The physical findings may be confusing because it may be difficult to recognize two distinct systolic murmurs. On echocardiography and roentgenography, the left atrium and ventricle are usually larger than in isolated AS. In patients with

severe AS and MR, both valves must usually be treated surgically by aortic valve replacement and, if possible, by mitral valve repair.

AORTIC REGURGITATION AND MITRAL REGURGITATION

This relatively frequent combination of lesions[515] may be caused by rheumatic heart disease, by prolapse of both the aortic and the mitral valves due to myxomatous degeneration,[516] or by dilatation of both annuli in patients with connective tissue disorders. The left ventricle is usually greatly dilated. The clinical features of AR usually predominate, and it is sometimes difficult to determine whether the MR is due to organic involvement of this valve or to dilatation of the mitral valve ring secondary to left ventricular enlargement. When both valvular leaks are severe, this combination of lesions is poorly tolerated. The normal mitral valve ordinarily serves as a "backup" to the aortic valve, and premature (diastolic) closure of the mitral valve limits the volume of reflux that occurs in patients with acute AR.[382] With severe combined regurgitant lesions, regardless of the cause of the mitral lesion, blood may reflux from the aorta through both chambers of the left side of the heart into the pulmonary veins. Physical and laboratory examinations usually show evidence of both lesions. An S_3 and a brisk arterial pulse are frequently present. The relative severity of each lesion can be assessed best by Doppler echocardiography and contrast angiography. This combination of lesions leads to severe left ventricular dilatation.

MR that occurs in patients with AR secondary to left ventricular dilatation often regresses following aortic valve replacement alone. If severe, the MR may be corrected by annuloplasty at the time of aortic valve replacement. An intrinsically normal mitral valve that is regurgitant because of a dilated annulus should not be replaced.

Surgical Treatment of Multivalvular Disease

Combined aortic and mitral valve replacement is usually associated with a higher risk and poorer survival than is replacement of either of the valves alone.[517] [517A] The operative risk of double-valve replacement is about 70 percent higher than it is for single-valve replacement. The Society of Thoracic Surgeons National Database Committee reported an overall operative mortality rate of 9.6 percent for

multiple (usually double) valve replacement in 3840 patients, compared with 4.3 percent and 6.4 percent for isolated aortic valve replacement and mitral valve replacement, respectively[104] (see Table 46-2) . Kirklin and Barrat-Boyes reported a 5-year survival rate of 63 percent after double-valve replacement compared with 80 percent for single-valve replacement.[517] The long-term survival depends strongly on the preoperative functional status. Patients operated on for combined AR and MR have poorer outcomes than patients receiving double-valve replacement for any of the other combinations of lesions, presumably because both AR and MR may produce irreversible left ventricular damage. Mitral repair or balloon valvotomy in combination

with aortic valve replacement is preferable to double-valve replacement and should be carried out whenever possible. Risk factors that reduce long-term survival after double-valve replacement include advanced age, higher NYHA class, greater left ventricular enlargement, and accompanying ischemic heart disease requiring coronary artery bypass grafting.

Given the higher risks, a higher threshold is required for multivalvular versus single-valve surgery. Thus, patients are generally advised not to undergo multivalvular surgery until they reach late NYHA Class II or Class III. Despite a detailed noninvasive and invasive workup, the decision to treat more than one valve is often made by palpation or by direct inspection at the operating table.

THREE-VALVE DISEASE.

Hemodynamically significant disease involving the mitral, aortic, and tricuspid valves is uncommon. Patients with trivalvular disease may present in advanced heart failure with marked cardiomegaly, and surgical correction of all three valvular lesions is imperative. However, triple-valve replacement is a long and complex operation. Early in the experience with this procedure, the mortality rate was 20 percent for patients in NYHA Class III and 40 percent for patients in Class IV. More recently, the mortality rate has declined, but, nevertheless, triple-valve replacement should be avoided if possible. In many patients with trivalvular disease, it is possible to replace the aortic valve, repair the mitral valve, and perform a tricuspid annuloplasty or valvuloplasty.

Patients who survive triple-valve replacement surgery usually show substantial clinical improvement during the early postoperative period,[517B] [518] [518A] and postoperative catheterization studies show marked reductions in pulmonary arterial and capillary pressures. However, some patients die of arrhythmias or congestive heart failure in the late postoperative period despite three normally functioning prostheses.[519] The cause of cardiac failure in this situation is not known, but it may be related to intraoperative myocardial ischemia, microemboli from the multiple prostheses, or continued subclinical episodes of rheumatic myocarditis.

When multiple prosthetic valves must be inserted, it is logical to select either two bioprostheses or two mechanical prostheses for the left side of the heart. If the patient is to be exposed to the hazards of anticoagulants for one mechanical prosthesis, it seems unreasonable to add the potential risks of early failure of a bioprosthesis. However, if two mechanical prostheses are selected for the left side of the heart, the use of a bioprosthesis in the tricuspid position is suggested.

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Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Copyright © 2001 W. B. Saunders Company

Prosthetic Cardiac Valves

The first successful replacements of cardiac valves in the human were accomplished by Nina Braunwald and colleagues,[520] Harken and coworkers,[521] and Starr and Edwards [522] in 1960. Two major groups of artificial (prosthetic) valves are currently available in models designed for both the atrioventricular (mitral and tricuspid) and the aortic positions: mechanical prostheses and bioprostheses (tissue valves).[523]

MECHANICAL PROSTHESES

Mechanical prosthetic valves are classified into two major groups: caged-ball and tilting-disc valves. The *StarrEdwards* caged-ball valve, the oldest prosthetic valve in continuous use (Figs. 46-49 and 46-50) (Figure Not Available) , has the longest record of predictable performance of any artificial valve.[523] [524] [525] The poppet is made of silicone rubber, the cage of Stellite alloy, and the sewing ring of Teflon/polypropylene cloth. A disadvantage is its bulky cage design. Therefore, the Starr-Edwards valve is not suitable for the mitral position in patients with a small left ventricular cavity or for the aortic position in those with a small aortic annulus or a valve-aortic arch composite graft. In a small number of patients, this valve induces hemolysis, which may be greatly exaggerated and become clinically important if a perivalvular leak develops. When they are of small size, the Starr-Edwards valve may cause mild obstruction, and the incidence of thromboembolism is slightly higher than with the tilting-disc valve.[526]

Several types of disc valves are widely employed; these are less bulky, have a lower profile than the caged-ball valve, and are therefore superior hemodynamically. The *St. Jude* bileaflet valve (see Fig. 46-49 *D*), currently the most widely used prosthesis worldwide (Table 46-12) , is coated with pyrolytic carbon and has two semicircular discs that pivot between open and closed positions without the need for supporting struts. It

has favorable flow characteristics and causes a lower transvalvular pressure gradient at any outer diameter and cardiac output than the caged-ball or single-leaflet tilting valves.[527] The St. Jude valve appears to have particularly favorable hemodynamic characteristics in the smaller sizes; therefore, it is especially useful in children. Thrombogenicity in the mitral position *may* be less than that associated with other prosthetic valves. However, as with other mechanical prostheses, lifelong anticoagulation is needed.[528] A variation of the St. Jude valve, the *Carbomedics* prosthesis[529] (see Fig. 46-49 *E*), is also a bileaflet valve composed of pyrolytic carbon with a titanium housing that can be rotated so as to avoid interference with disc excursion by subvalvular tissue.

The *Omniscience* valve (see Fig. 46-49 *B*), the successor to the *Lillehei-Kaster* pivoting-disc valve, consists of a titanium valve housing with a polyester knit sewing ring in which a pyrolytic disc is suspended. In the open position, the disc swings to an angle of 80 degrees, providing a large central flow orifice.[530] A closely related valve is the *Medtronic-Hall* valve[531] (see Fig. 46-49 *C*), which has a Teflon sewing ring and titanium housing; its thin, carbon-coated pivoting disc has a central perforation that allows improved hemodynamics. Thrombogenicity appears to be quite low (less than one episode per 100 patient-years in the mitral position[532]), and mechanical performance is excellent over the long term. Both the bileaflet and the tilting-disc valves

Figure 46-49 *A,* The Starr-Edwards caged ball valve. *B,* The Omniscience valve. *C,* The Medtronic-Hall valve. *D,* The St. Jude bileaflet valve. *E,* The Carbomedics bileaflet valve.*(From Cohn, LH: Aortic valve prostheses. Cardiol Rev 2:219, 1995.)*

are associated with small (
5-10 ml/beat) obligatory (normal) regurgitation.[92] All have distinctive auscultatory features (Fig. 46-51) .

DURABILITY AND THROMBOGENICITY.

All mechanical prosthetic valves have an excellent record of durability, up to 40 years for the Starr-Edwards valve. In the mitral position, perivalvular regurgitation appears to occur more frequently with mechanical than with tissue valves.[533] However, patients with any *mechanical* prosthesis, regardless of design or site of placement, require long-term anticoagulation and aspirin administration because of the hazard of thromboembolism, which is greatest in the first postoperative year. Without anticoagulants and aspirin, the incidence of thromboembolism is three- to sixfold higher than when proper doses of these medications are administered. Very rarely, thrombosis of the mechanical valve occurs. This may be a fatal event, but when nonfatal, it interferes with prosthetic valve function.

Warfarin should begin about 2 days after operation, and the international normalized ratio (INR) should be in the range of 2.0 to 3.0 for patients with the bileaflet disc and the Medtronic-Hall valve in the aortic position. The INR should be between 2.5 and 3.5 for patients at higher risk for thrombosis (e.g., atrial fibrillation, previous thromboembolism) as well as for patients with other mechanical valves in the aortic position and for *all* valves in the mitral position (see also p. 1722 and Chap. 62) .[51] This relatively conservative approach reduces the risk of anticoagulant hemorrhage but does not appear to be associated with a greater frequency of thromboembolism than an INR of 3.0 to 4.0, which was used in the past.[534] [535] [536] Antiplatelet agents without anticoagulants do not provide adequate protection.

Figure 46-50 (Figure Not Available) Designs and flow patterns of major categories of prosthetic heart valves: caged-ball, caged-disc, tilting-disc, bileaflet tilting-disc, and bioprosthetic (tissue) valves. Whereas flow in mechanical valves must course along both sides of the occluder, bioprostheses have a central flow pattern.*(Reproduced by permission from Schoen FJ et al: Bioengineering aspects of heart valve replacement. Ann Biomed Eng 10:97, 1982. Copyright 1983, Pergamon Press Limited, 1983; and from Schoen FJ: Pathology of cardiac valve replacement. In Morse D, Steiner RM, Fernandez J [eds]: Guide to Prosthetic Cardiac Valves. New York, Springer-Verlag, 1985, p. 209. Copyright 1985 Springer-Verlag, Inc.)*

TABLE 46-12 -- FDA-APPROVED PROSTHETIC HEART VALVES

TYPE	MANUFACTURER	MODEL	YEAR OF FIRST CLINICAL USE	IMPLANTS* (thousands)
Mechanical				
Ball	Baxter-Edwards	Starr-Edwards	1965	200
Disc	Medtronic	Medtronic-Hall	1977	178
	Medical Inc.	Omniscience	1978	48
	Alliance	Monostrut	1982	94
Bileaflet	St. Jude	St. Jude	1977	580
	Baxter-Edwards	Duromedics	1982	20
	CarboMedics	CarboMedics	1986	110
Biological				
Porcine	Medtronic	Hancock Standard	1970	177
		Hancock MO	1978	32
	Baxter-Edwards	CE Standard	1971	400

		CE SupraAnnular	1982	45
	St. Jude	Toronto Stentless (TSP)	1991	5
	Medtronic	Free Style Stentless	1992	5
Pericardial	Baxter-Edwards	CE	1982	35
Homograft	Noncommercial		1962	12
	Cryolife		1984	14
Autologous	Noncommerical	Pulmonary autograft	1967	2

CE=Carpentier-Edwards; FDA=Food and Drug Administration; MO=modified orifice.

Adapted from Grunkemeier G, Starr A, Rahimtoola SH: Replacement of heart valves. In O'Rourke RA (ed): The Heart: Update I. New York, McGraw-Hill Publishing Co; 1996, pp 98-123. From Bonow RO, Carabello B, de Leon AC Jr, et al: ACC/AHA Guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol 32:1486, 1998.

*Approximate number of implants through part or all of 1994.

Discontinued in 1988.

Does not require FDA approval for clinical use.

However, the addition of aspirin, 80 to 150 mg daily, together with warfarin may reduce the risk of thromboembolism and should be given to all patients with prosthetic valves.

Prosthetic valve thrombosis should be suspected by the sudden appearance of dyspnea and muffled sounds or new murmurs on auscultation (see Fig. 46-51) . This serious complication is diagnosed by transesophageal two-dimensional and Doppler echocardiography. Treatment consists of infusion of a thrombolytic agent for 24 to 72 hours, heparin, and aspirin. Surgery is required for nonresponders and for patients with mobile thrombi.[537]

It must be recognized that (1) the administration of warfarin carries its own mortality and morbidity, i.e., serious hemorrhage, estimated at 0.2 and 2.2 episodes per 100 patient-years,

Figure 46-51 Auscultatory characteristics of various prosthetic valves in the aortic and mitral positions, with schematic diagrams of normal findings and descriptions of abnormal findings. OC = opening click; CC = closing click; SEM = systolic ejection murmur; DM = diastolic murmur; AC = aortic closure; MC =

mitral valve closure; MO = mitral opening.*(From Vongpatanasin W, Hillis LD, Lange RA: Prosthetic heart valves. N Engl J Med 335:407, 1996.)*

respectively; and (2) despite treatment with anticoagulants, the incidence of thromboembolic complications with the best mechanical prosthesis is still about 0.2 fatal complications and 1.0 to 2.0 nonfatal complications per 100 patient-years for aortic valves and 2.0 to 3.0 nonfatal complications for mitral valves.[538] Valve thrombosis, a particularly hazardous complication, occurs at an incidence of about 0.1 percent per year in the aortic position and 0.35 percent per year in the mitral position. Thrombosis of mechanical prostheses in the tricuspid position is quite high, and for this reason bioprostheses are preferred at this site. The incidence of embolization in patients who have experienced repeated emboli from a prosthetic valve despite anticoagulants may be reduced by replacement with a tissue valve.

Mechanical prostheses regularly cause mild hemolysis,[538] but this is not severe enough to be of clinical importance unless the patient develops periprosthetic regurgitation.

TISSUE VALVES

Tissue valves (bioprostheses) have been developed primarily to overcome the risk of thromboembolism that is inherent in all mechanical prosthetic valves and the attendant hazards and inconvenience of permanent anticoagulant therapy.[539A] The first tissue valves to be widely used were chemically sterilized aortic homografts (allografts) obtained from cadavers. However, these had a high incidence of breakdown within 3 years, and antibiotic-treated, cryopreserved, frozen, irradiated homografts were then developed. These homografts are more durable, but, although they have many desirable properties, their use has been restricted by the problems inherent in their procurement (to be discussed).

PORCINE HETEROGRAFTS.

Stented porcine aortic heterografts were developed for both the mitral and the aortic positions and have been in wide clinical use since 1965.[523] The semirigid stents facilitate implantation and maintain the three-dimensional relationship between the leaflets.[92] Three porcine heterografts are widely used today.[523] [540] [541] [542] [543] [543A] The *Hancock* valve (Fig. 46-52 *A*) is fixed and preserved in glutaraldehyde and is mounted on a Dacron cloth-covered flexible polypropylene strut. In the smaller aortic models, the right coronary cusp is replaced by a posterior cusp from another valve to reduce obstruction resulting from the septal shelf of the valve. The *Carpentier-Edwards* valve (Fig. 46-52 *B*) is pressure-fixed, preserved in glutaraldehyde, and mounted on a Teflon-covered Eljgiloy strut so as to minimize the septal shelf. The *Intact* valve is also glutaraldehyde-treated but at a fixation pressure of zero and with toluidine in an attempt to inhibit calcium deposition. The hemodynamic profiles of the porcine heterografts are

similar to those of comparably sized low-profile mechanical prostheses.[541] [544]

During the first 3 postoperative months, while the sewing ring becomes endothelialized, the thromboembolic rate is high enough that anticoagulation is extremely desirable. Thereafter, anticoagulants are not required for porcine valves in the aortic position, and the thromboembolic rate is approximately 1 to 2 episodes per 100 patient-years

Figure 46-52 *A,* Hancock porcine valve. *B,* Carpentier-Edwards porcine valve. *C,* Carpentier pericardial valve. *D,* Cryopreserved homograft valve. *E,* Incisions for placement of pulmonary autograft valve into the aortic position.*(From Oury JH: Pulmonary autograft--past, present and future. J Heart Valve Dis 2:366, 1993.)*

without these drugs.[545] [546] When these valves have been placed in the mitral position in patients who are in sinus rhythm, who do not have heart failure or thrombus in the left atrium or the left atrial appendage, and who do not have a history of embolism preoperatively, anticoagulants are not needed after the first 3 postoperative months, and the thromboembolic rate is also approximately 1 to 2 episodes per 100 patient-years. This rate is comparable to that observed in patients with the St. Jude or other mechanical valves who are receiving anticoagulants and are therefore subject to the risks of hemorrhage. It is unlikely that any mitral valve replacement can be associated with a thromboembolic rate much below 0.5 episode per 100 patient-years because some of the emboli in patients with longstanding mitral disease are derived from the left atrium rather than from the valve itself.[546] In patients undergoing mitral valve replacement (MVR) with a bioprosthesis who have experienced a previous embolism, in whom thrombus is found in the left atrium at operation, or who remain in atrial fibrillation postoperatively (approximately one-third of all patients receiving MVR), the hazard of thromboembolism and the need for anticoagulants persist. This negates the principal advantage of the tissue valves, and mechanical prostheses would appear to be preferable to bioprostheses in these patients.

The major problem with porcine bioprostheses is their limited durability (Fig. 46-53) . Cuspal tears, degeneration, fibrin deposition, disruption of the fibrocollagenous structure, perforation, fibrosis, and calcification sufficiently severe to require reoperation begin to appear in some patients in the fourth or fifth postoperative year, and by 10 years the rate of primary tissue failure averages 30 percent. It then accelerates, and by 15 years postoperatively the actuarial *freedom* from bioprosthetic primary tissue failure has ranged from 30 to 60 percent in several series. Structural valve deterioration is more frequent in patients with bioprostheses in the mitral than in the aortic position, presumably because of the higher closing pressure. With the passage of time, even more of these valves will likely fail, and essentially all valves implanted into patients less than 60 years of age may have to be replaced ultimately.[547] Fortunately, however, these valves usually do not fail suddenly (as is often the case for structural failure or thrombosis of mechanical prostheses). Re-replacement of a bioprosthetic valve should

be carried out when significant and/or progressive structural deterioration is evident but before operation becomes an emergency. The second operation, when carried out on an elective basis, may be associated with a surgical mortality rate of 10 to 15 percent.

Color Doppler echocardiography with two-dimensional imaging is extremely helpful in the early detection of bioprosthetic valve malfunction. Transesophageal echocardiography is more sensitive than transthoracic imaging in detecting bioprosthetic valve deterioration. Even patients without new murmurs or other physical findings of valve dysfunction should have routine echocardiographic studies to look for early bioprosthetic valve dysfunction every year for 5 to 6 years after valve replacement and every 6 months after that.

The time after implantation at which tissue valves fail varies inversely with age[543A] (Fig. 46-54) . Valve failure is prohibitively rapid in children and in adults under 35 to 40 years of age. Therefore, bioprostheses are *not* advisable in these age groups. On the other hand, degeneration is rare when these valves are implanted into patients over 70 years of age.[547] Bioprostheses also have extremely limited durability in patients with chronic renal failure and hypercalcemia related to secondary hyperparathyroidism.

Figure 46-53 Unified model for bioprosthetic heart valve failure relating isolated tissue processes of mineralization and collagen degeneration to gross clinical failures. Such failures have calcification with cuspal stiffening (1), cuspal defects without calcific deposits (2), or cuspal tears associated with mineralization (1 and 2). These processes may occur independently or they may be synergistic. Specifically, implant and host factors interact to induce the collagen-oriented and cell-oriented calcific deposits noted ultrastructurally. The deposits predominate in the central portions of valve cusps, particularly at flexion points such as the commissures (Pathway 1). Stress causes shear between and fracture of collagen fibers, which may create gross cuspal defects (Pathway 2). Although dynamic mechanical activity is not a prerequisite for calcification, stress may promote (i.e., accelerate) this process by means of unknown mechanisms. *(Amended from Schoen FJ, Levy RJ: Bioprosthetic heart valve failure: Pathology and pathogenesis. Cardiol Clin 2:717, 1984.)*

Figure 46-54 Estimates of freedom from structural valve deterioration (SVD) for patients undergoing porcine aortic valve replacement (AVR) are stratified according to age.*(From Fann JI, Miller DC, Moore KA, et al: Twenty-year clinical experience with porcine bioprostheses. Ann Thorac Surg 62:1301, 1996. Reprinted with permission from the Society of Thoracic Surgeons.)*

Prosthetic valve endocarditis is a serious, often grave illness (see Chap. 47) .

STENTLESS PORCINE XENOGRAFTS.

Since the stent adds to the obstruction and thereby increases stress on the leaflets, stentless valves have been developed for the aortic position[548] and are now being used

increasingly, especially in patients with small aortic roots.[549] These include the Toronto SPV stentless valve (St. Jude Medical valve),[550] the Edwards stentless valve,[551] and the Medtronic freestyle valve.[548] It is hoped that the slightly improved hemodynamics provided by the stentless valves will translate into better long-term durability than that of valves mounted on stents.

HOMOGRAFT (ALLOGRAFT) AORTIC VALVES.

These are harvested from cadavers, often along with kidneys, usually within 24 hours of donor death. They are sterilized with antibiotics and cryopreserved for long periods at -196°C (see Fig. 46-52 *D*). They are inserted directly, usually in the aortic position, *without* being placed into a prosthetic stent. Their hemodynamics are superior to those of stented porcine valves. Like porcine xenografts, their thrombogenicity is low, but cryopreserved valves appear to have a similar rate of structural deterioration.[552] [552A] Perhaps this rate is reduced with the use of freshly harvested valves and approximate matching of donor's and patient's ages. Homograft aortic valves are indicated for patients with native or prosthetic valve endocarditis, but they are difficult to use when the aortic root and ascending aorta are greatly enlarged. Availability is often limited.[553]

PULMONARY AUTOGRAFTS.

In this operation, the Ross procedure, the patient's own pulmonary valve and adjacent main pulmonary artery are removed and used to replace the diseased aortic valve and often the neighboring aorta, with reimplantation of the coronary arteries into the graft[554] (see Fig. 46-52 *E*). A human pulmonary or aortic homograft is then inserted into the pulmonary position. The autograft is nonthrombogenic.[555] In children and adolescents, there is evidence that the autograft grows along with the patient. The risk of endocarditis is very low, anticoagulants are not required, and, perhaps most important, the long-term durability appears to be excellent.[556] Although the pulmonary autograft is the replacement valve of choice in children, adolescents, and younger adults who have a long (>20-year) life expectancy, its use has been limited because the operation is technically much more complex than a simple aortic valve replacement. The procedure should be carried out only by experienced surgeons.

PERICARDIAL AUTOGRAFTS.

The patient's own pericardium is inserted into a frame on the operating table (the Carpentier-Edwards Perimount pericardial bioprosthesis) and is inserted into either the aortic or the mitral position. Long-term durability appears to be excellent; in 267 patients undergoing isolated aortic valve replacement, the 14-year actuarial freedom of need for re-replacement because of structural valve dysfunction was 85 percent (94 percent in patients > 65 years of age).[557] Good results have also been reported for this valve in the mitral position, in which the results are also exceptional in older patients. However, there is a greater risk for the development of stenosis in the mitral position.[558]

HEMODYNAMICS OF VALVE REPLACEMENTS

The most commonly used prosthetic valves, i.e., mechanical prostheses and stented porcine xenografts, have an effective in vitro orifice size that is *smaller* than the normal valve at the same site. (Unstented, i.e., free, homografts and pulmonary autografts do not have this problem.) After implantation, tissue ingrowth and endothelialization reduce the size of the effective orifice even more. Therefore, the prosthetic valves that are currently available must be considered to be mildly stenotic. However, postoperative hemodynamic measurements of the mechanical prostheses show reasonably good function, with effective mitral valve orifice areas averaging 1.7 to 2.0 cm^2 and mitral valve gradients of 4 to 8 mm Hg at rest. The cloth-covered StarrEdwards valve appears to be intrinsically slightly more stenotic than the Medtronic-Hall or Omniscience tilting-disc valves. The bileaflet St. Jude and Carbomedics valves, in turn, may be slightly superior to the Medtronic-Hall or Omniscience valve. In hemodynamic studies, the stented porcine mitral valves behave in a manner similar to mechanical prosthetic valves of the same diameter. *Serious* hemodynamic obstruction of an artificial valve in the mitral position is quite uncommon, unless the valve (most commonly the Starr-Edwards valve) is placed into a small left ventricular cavity or into an unusually small mitral annulus or the prosthesis chosen is of inappropriate size.

The problem of prosthetic valve stenosis may be more serious in patients who undergo aortic valve replacement for AS. The annulus into which the prosthesis is inserted in these patients is usually smaller than it is in patients with AR, and the surgeon may be forced to select an artificial valve of relatively small size. As a consequence, aortic valve replacement, may not abolish obstruction in patients with AS but may merely convert severe to mild or moderate obstruction. When the smaller models of the stented porcine xenograft or mechanical prosthesis are placed into the aortic position, effective orifice areas of about 1.1 to 1.3 cm^2 are common. In such patients, peak transvalvular gradients as high as 40 mm Hg during exercise have been recorded. The poor late results observed in a minority of patients undergoing replacement of stenotic aortic valves may possibly be related to the moderate stenosis of the prosthesis. In patients with AS who do not exhibit clinical improvement postoperatively, it is important to evaluate the function of both the prosthetic valve and the left ventricle. Rarely, reoperation to correct a malfunctioning prosthesis may be necessary.

SELECTION OF AN ARTIFICIAL VALVE (Table 46-13)

Most comparisons of mechanical and bioprosthetic valves indicate similar overall results in terms of early and late mortality, prosthetic valve endocarditis and other complications, and the need for reoperation, at least for the first 5 years postoperatively. As indicated, there appear to be no significant differences insofar as hemodynamics are concerned, except that patients with an unusually small left ventricular cavity or mitral or aortic annulus may have better results with the low-profile (tilting-disc) St. Jude or Carbomedics prosthesis or a tissue valve.[559] Patients with a small aortic annulus may

be better candidates for unstented homografts, heterografts, or pulmonary autografts.

The major task in selecting an artificial valve is to weigh the advantage of durability and the disadvantages of the risks of thromboembolism and anticoagulant treatment inherent in mechanical prostheses on the one hand with the advantage of low thrombogenicity and the disadvantage of abbreviated durability of bioprostheses on the other. Hammermeister and associates[560] have compared the outcome in 575 men who were randomized to replacement of the mitral or the aortic valve with either mechanical or a bioprosthetic valve. There was no difference in survival or in the probability of developing a valve-related complication, including endocarditis, valve thrombosis, and systemic embolism, in patients receiving either a mechanical or a bioprosthetic valve. The rate of structurally related valve failure requiring reoperation (which is associated with about twice the mortality of the initial procedure) was much higher in patients receiving tissue as opposed to mechanical valves. As anticipated, anticoagulant-related bleeding was higher in patients receiving mechanical valves. Patients with mechanical valves also had a higher incidence of perivalvular regurgitation in the mitral position. In the Edinburgh randomized trial, which also compared a mechanical with a porcine xenograft valve,[561] actuarial survival rates tended to be better and the freedom from all valve-related adverse events was significantly better with mechanical valves. Retrospective cohort analyses are in agreement with the results of these trials.[562] [563] [564] Therefore, mechanical prostheses, usually of the bileaflet variety, are the valves of choice in the majority of patients under 65 years of age.

However, the following groups of patients should receive bioprostheses: (1) patients with coexisting disease who are prone to hemorrhage and who therefore tolerate anticoagulants poorly, such as those with bleeding disorders, intestinal polyposis, and angiodysplasia; (2) patients who are

TABLE 46-13 -- VALVE SELECTION FOR AN INDIVIDUAL PATIENT

RELATIVE INDICATIONS FOR A MECHANICAL VALVE
Long expected lifetime (age<40 years)
Previous dysfunctional tissue valve
Anticoagulation required anyway
Double valve replacement
Composite graft (aortic root+valve) needed
Renal failure, dialysis
RELATIVE INDICATIONS FOR A BIOPROSTHESIS
Short expected lifetime (age 65 years)
Unreliable anticoagulant risk
Previous thrombosed valve
Anticoagulant intolerance

Pregnancy anticipated

From Grunkemeier GL, Rahimtoola SH, Starr A: Prosthetic heart valves. In Rahimtoola SH (ed): Valvular Heart Disease. Atlas of Heart Diseases. Vol 11. Braunwald E, series ed. Philadelphia, Current Medicine, 1977, pp 13.1-13.27.

likely to be noncompliant with permanent anticoagulant treatment, who are unwilling to take anticoagulants on a regular basis, or who live in developing nations and cannot be monitored; (3) patients over the age of 65 years in whom bioprosthetic valves deteriorate very slowly, who are unlikely to outlive their bioprostheses, and who because of their age may also be at greater risk of hemorrhage while taking anticoagulants; (4) patients with a small aortic annulus in whom an unstented (free) bioprosthetic graft may provide superior hemodynamics; and (5) younger patients (< 40 years of age), especially women wishing to bear children, who require aortic valve replacement and in whom a pulmonary autograft may be preferable. However, the technical difficulties associated with the last procedure must be taken into account.

Special Situations

PREGNANCY (see also Chap. 65) .

Women with artificial valves can tolerate the hemodynamic burden of pregnancy well, but the hypercoagulable state of pregnancy increases the risk of thromboembolism in pregnant patients with mechanical prostheses. Anticoagulation must not be interrupted, although an increased risk of fatal fetal hemorrhage occurs in women in whom anticoagulants are continued. There is also a risk of fetal malformation caused by the probable teratogenic effect of warfarin. Although these problems represent rationales for the use of tissue valves in all women of childbearing age,[565] [566] their limited durability in young adults makes their use unacceptable. Therefore, unless a pulmonary autograft can be employed (for patients who require aortic valve replacement), every effort should be made to defer valve replacement until after childbirth. In pregnant women with critical MS or AS, balloon valvuloplasty should be considered, and, if at all possible, mitral valve repair instead of replacement should be undertaken for patients with MR. Women of childbearing potential who have a mechanical prosthesis should be counseled against pregnancy. When a woman who already has a mechanical prosthetic valve becomes pregnant, the risk to the fetus if the mother receives oral anticoagulants appears to be lower than the risk to the mother if anticoagulants are discontinued. Therefore, coumarin derivatives should be continued and the INR maintained between 2.0 and 3.0 until 2 weeks before expected delivery, at which time the patient should be switched to intravenous heparin.[564] Heparin should be discontinued at the onset of labor but may be restarted, along with coumarin, several hours after delivery. Alternatively, warfarin may be briefly interrpted at the 38th week of gestation and planned cesarean section carried out.[567]

NONCARDIAC SURGERY.

When noncardiac surgery is required in patients with prosthetic valves who are receiving anticoagulants, the risk is minimal when the anticoagulant is stopped 1 to 3

days preoperatively and for a similar period postoperatively. It may be desirable, however, to protect the patient with low-molecular-weight dextran during the perioperative period and to resume anticoagulation rapidly with intravenous heparin.

PATIENTS DESTINED TO RECEIVE ANTICOAGULANTS.

Patients with earlier implantation of a mechanical prosthesis, chronic atrial fibrillation with an enlarged left atrium, a history of thromboembolism, or a thrombus in the left atrium at operation and who therefore are destined to receive anticoagulants should receive a mechanical valve prosthesis because the potential advantage of a tissue valve is negated.

CHILDREN AND PATIENTS RECEIVING CHRONIC HEMODIALYSIS.

The high incidence of bioprosthetic valve failure in children and adolescents[568] [569] and in patients on chronic hemodialysis virtually prohibits their use in these

groups. In young adults between the ages of 25 and 35 years, the failure of bioprosthetic valves is somewhat higher than it is in older adults; this serves as a relative, but not an absolute, contraindication to their use in this age group.

In children, a mechanical prosthesis (generally the St. Jude valve) with its favorable hemodynamics is preferred despite the disadvantages inherent in the need for anticoagulants in this age group.[570] Similarly, mechanical valve prostheses should be used in patients with chronic renal failure and/or hypercalcemia. Alternatively, if an experienced surgical team is available and the patient requires an aortic valve replacement, a pulmonary autograft may be employed.

TRICUSPID POSITION.

The risk of thrombosis for all valves is highest in the tricuspid position because of the lower pressures and velocity of blood flow. This complication appears to be highest for tilting-disc valves, intermediate for caged-ball valves, and lowest for bioprostheses, which are the valves of choice as tricuspid replacements. Fortunately, bioprostheses exhibit a much slower rate of mechanical deterioration in the tricuspid position than in the mitral or aortic positions.

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GUIDELINES MANAGEMENT OF VALVULAR HEART DISEASE

Thomas H. Lee

Guidelines for management of patients with valvular heart disease were published by an American College of Cardiology/American Heart Association (ACC/AHA) committee in 1998.[1] As is the case for other ACC/AHA guidelines, the indications for various tests and procedures are divided into classes:

Class I:
: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II:
: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa:
: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb:
: Usefulness/efficacy is less well established by evidence/opinion.

Class III:
: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Some material from these guidelines is presented elsewhere in this book. Guidelines for prevention and treatment of infective endocarditis are summarized in Chapter 47 and its guidelines. Guidelines for management of anticoagulation in pregnancy are included in the appendix to Chapter 65 . Recommendations for prevention of recurrence of

rheumatic fever are included in the appendix to Chapter 66 .

The guidelines emphasize that the decision to use echocardiography to evaluate patients with cardiac murmurs should be influenced by the patient's symptomatic status and the physical examination. Additional reassurance that a murmur is clinically insignificant may be drawn from other clinical tests, such as the electrocardiogram and chest roentgenogram, if these tests are normal. Echocardiography is considered inappropriate (Class III) for evaluation of murmurs that experienced observers consider innocent or functional. In contrast, echocardiography is considered appropriate even in asymptomatic patients with murmurs suggesting significant valvular disease or in patients with other signs or symptoms of cardiovascular disease (Table 46-G-1) .

Mitral Stenosis

Transthoracic echocardiography is endorsed in the ACC/AHA guidelines as a valuable test for diagnosis and follow-up of patients with mitral stenosis. The ACC/AHA guidelines do not endorse routine use of transesophageal echocardiography for evaluation of mitral valve morphology, but do note a potential role (Class IIa) for detection of left atrial thrombus in patients being considered for percutaneous balloon mitral valvotomy or cardioversion.

Anticoagulation is endorsed for patients with mitral stenosis who have a history of atrial fibrillation or a prior embolic event. The ACC/AHA panel is not strongly supportive of anticoagulation on the basis of a left atrial dimension >55 mm in patients in sinus rhythm. Surgical therapy with valvotomy, valve repair, or valve replacement is indicated for patients with moderate or severe mitral stenosis (valve 1.5 cm^2) and NYHA functional class III or IV, with the choice of the procedure dictated by the anatomical findings. Balloon valvotomy is also endorsed for patients who are NYHA functional class II. For patients with mild or no symptoms of mitral stenosis, balloon valvotomy is considered appropriate (Class IIa) in the presence of pulmonary hypertension and in the absence of left atrial thrombus or moderate to severe mitral regurgitation.

Mitral Regurgitation

Echocardiography is considered appropriate for the diagnosis of acute or chronic mitral regurgitation, as well as in annual or semiannual surveillance of left ventricular function in patients with severe mitral regurgitation, even if the patients are asymptomatic. Serial use of chest roentgenograms and electrocardiograms is considered to be of less value. In asymptomatic patients with mild mitral regurgitation and no evidence of left ventricular enlargement or dysfunction, the guidelines recommend yearly evaluations to detect worsening symptomatic status, but do not support annual echocardiography. Transesophageal echocardiography is considered most appropriate for intraoperative guidance and when transthoracic studies are inadequate.

Cardiac catheterization is usually performed before surgery in patients with mitral

regurgitation. Coronary angiography is not considered routinely necessary in the ACC/AHA guidelines for patients younger than age 35 years who have no clinical suspicion of coronary artery disease. Left ventriculography and hemodynamic assessment are appropriate when noninvasive studies do not provide definitive information about the severity of mitral regurgitation or left ventricular dysfunction or the need for surgery.

Surgery is considered appropriate for patients with acute symptomatic mitral regurgitation and for those with chronic severe mitral regurgitation and symptoms of congestive heart failure, even if they have normal left ventricular function. Even if patients are asymptomatic, surgery is appropriate when they have mild or more severe left ventricular dysfunction (i.e., ejection fraction 50 to 60 percent and end-systolic dimension 50 to 55 mm).

Mitral Valve Prolapse

Recommendations on use of echocardiography for patients with mitral valve prolapse were adopted from the recommendations of an earlier ACC/AHA task force on echocardiography.[2] These guidelines emphasize that the diagnosis of mitral valve prolapse should be made by physical examination and that echocardiography is primarily appropriate for evaluation of mitral regurgitation and ventricular compensation. Echocardiography is also appropriate for *excluding* the diagnosis of mitral valve prolapse in patients who have been given the diagnosis inappropriately. Serial use of echocardiography in stable patients with mild or no regurgitation is discouraged.

Antibiotic prophylaxis is considered appropriate for patients with the characteristic click-murmur complex or with echocardiographic evidence of mitral value prolapse with regurgitation. (Additional information on the use of antibiotic prophylaxis is included in the guidelines to Chapter 47.) Daily aspirin therapy is recommended for patients who have had cerebral transient ischemic attacks and for patients younger than age 65 years who have atrial fibrillation without other complicating factors. Warfarin therapy is recommended for poststroke patients and for older patients with atrial fibrillation.

Aortic Stenosis

Doppler echocardiography is considered a highly appropriate test for diagnosis and assessment of aortic stenosis and for evaluation of left

TABLE 46--G-1 -- MANAGEMENT OF VALVULAR HEART DISEASE IN ADULTS

Indication	Class I	Class IIa	Class IIb	

Echocardiography in asymptomatic patients with cardiac murmurs	1. Diastolic or continuous murmurs 2. Holosystolic or late systolic murmurs 3. Grade 3 or greater midsystolic murmurs	1. Murmurs associated with abnormal physical findings on cardiac palpation or auscultation 2. Murmurs associated with an abnormal ECG or chest roentgenogram	--
Echocardiography in symptomatic patients with cardiac murmurs	1. Symptoms or signs of congestive heart failure, myocardial ischemia or syncope 2. Symptoms or signs consistent with infective endocarditis or thromboembolism	Symptoms or signs likely due to noncardiac disease with cardiac disease not excluded by standard cardiovascular evaluation	--

Transesophageal echocardiography in patients with MS	--	1. Assess for presence or absence of left atrial thrombus in patients being considered for percutaneous balloon mitral valvotomy or cardioversion 2. Evaluate mitral valve morphology and hemodynamics when transthoracic echocardiographic data are suboptimal	--
Anticoagulation in patients with MS	1. Patients with paroxysmal or chronic atrial fibrillation 2. Patients with a prior embolic event	--	1. Patients with severe MS and left atrial dimension 55 mm by echocardiography

Cardiac catheterization in patients with MS	Perform percutaneous balloon mitral valvotomy in properly selected patients	1. Assess severity of MR in patients being considered for percutaneous balloon mitral valvotomy when clinical and echocardiographic data are discordant 2. Assess pulmonary artery, left atrial, and LV diastolic pressures when symptoms and/or estimated pulmonary arterial pressure is discordant with the severity of MS by 2-D and Doppler echocardiography 3. Assess hemodynamic response of pulmonary atrial and left atrial pressure to stress when clinical symptoms and resting hemodynamics are discordant.	--

Percutaneous balloon mitral valvotomy	1. Symptomatic patients (NYHA functional Class II, III, or IV), moderate or severe MS (mitral valve area 1.5 cm^2), and valve morphology favorable for percutaneous balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR	1. Asymptomatic patients with moderate or severe MS (mitral valve area 1.5 cm^2) and valve morphology favorable for percutaneous balloon valvotomy who have pulmonary hypertension (pulmonary arterial systolic pressure >50 mm Hg at rest or 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR 2. Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area 1.5 cm^2), and a nonpliable calcified valve who are at high risk for surgery in the absence of left atrial thrombus or moderate to severe MR	1. Asymptomatic patients with moderate to severe MS (mitral valve area 1.5 cm^2) and valve morphology favorable for percutaneous balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR 2. Patients in NYHA function Class III-IV, moderate or severe MS (mitral valve area cm^2), and a nonpliable calcified valve who are low-risk candidates for surgery

Mitral valve repair for MS	Patients with NYHA functional Class III-IV symptoms, moderate or severe MS (mitral valve area 1.5 cm^2), and valve morphology favorable for repair if percutaneous balloon mitral valvotomy is not available	--	Patients with NYHA functional Class I symptoms, moderate or severe MS (mitral valve area 1.5 cm^2), and valve morphology favorable for repair who have had recurrent embolic events on adequate anticoagulation
Mitral valve replacement for MS	Patients with moderate or severe MS (mitral valve area 1.5 cm^2), and NYHA functional Class III-IV symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair	1. Patients with severe MS (mitral valve area 1.0 cm^2) and severe pulmonary hypertension (pulmonary arterial systolic pressure >60 to 80 mm Hg) with NYHA functional Class I-II symptoms who are not considered candidates for percutaneous balloon valvotomy or mitral valve repair	--

Coronary angiography in patients with MR	1. When mitral valve surgery is contemplated in patients with angina or previous myocardial infarction 2. When mitral valve surgery is contemplated in patients with one or more risk factors of CAD 3. When eschemia is suspected as an etiologic factor in MR	--	To confirm noninvasive tests in patients not suspected of having CAD
Left ventriculography and hemodynamic measures in patients with MR	1. When noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery 2. When there is a discrepancy between clinical and noninvasive findings regarding severity of MR	--	--

Mitral valve surgery in patients with nonischemic severe MR	1. Patients with acute symptomatic MR in whom repair is likely 2. Patients with NYHA functional Class II, III, or IV symptoms with normal LV function, defined as ejection fraction >60% and end-systolic dimension <45 mm 3. Symptomatic or asymptomatic patients with mild LV dysfunction, ejection fraction 50% to 60%, and end-systolic dimension 45 to 50 mm 4. Symptomatic or asymptomatic patients with moderate LV dysfunction, ejection fraction 30%, to 50%, and/or end-systolic dimension 50 to 55 mm	1. Asymptomatic patients with preserved LV function and atrial fibrillation 2. Asymptomatic patients with preserved LV function and pulmonary hypertension (pulmonary arterial systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise) 3. Asymptomatic patients with ejection fraction 50% to 60% and end-systolic dimension <45 mm, and asymptomatic patients with ejection fraction >60% and end-systolic dimension 45 to 55 mm 4. Patients with severe LV dysfunction (ejection fraction <30% and/or end-systolic dimension >55 mm) in whom chordal preservation is highly unlikely	1. Asymptomatic patients with chronic MR with preserved LV function in whom mitral valve repair is highly likely 2. Patients with MVP and preserved LV function who have recurrent ventricular arrhythmias despite medical therapy

Antibiotic endocarditis prophylaxis for patients with MVP undergoing procedures associated with bacteremia	1. Patients with characteristic systolic click-murmur complex 2. Patients with isolated systolic click and echocardiographic evidence of MVP and MR	Patients with isolated systolic clock, echocardiographic evidence of high-risk MVP	--
Aspirin and oral anticoagulants in patients with MVP	1. Aspirin therapy for transient ischemic attacks 2. Warfarin therapy for patients aged 65 years in atrial fibrillation with hypertension, MR, or history of heart failure 3. Aspirin therapy for patients aged <65 years in atrial fibrillation with no history or MR, hypertension, or heart failure 4. Warfarin therapy for poststroke patients	1. Warfarin therapy for patients with transient ischemic attacks despite aspirin therapy 2. Aspirin therapy for poststroke patients with contraindications to anticoagulants	1. Aspirin therapy for patients in sinus rhythm with echocardiographic evidence of high-risk MVP

Cardiac catheterization in patients with aortic stenosis	1. Coronary angiography before aortic valve replacement in patients at risk for CAD 2. Assessment of severity of aortic stenosis in symptomatic patients when aortic valve replacement is planned, when noninvasive tests are inconclusive, or when there is a discrepancy with clinical findings regarding severity of aortic stenosis or need for surgery	--	Assessment of severity of aortic stenosis before aortic valve replacement when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed

Aortic valve replacement in patients with aortic stenosis	1. Symptomatic patients with severe aortic stenosis 2. Patients with severe aortic stenosis undergoing coronary artery bypass surgery 3. Patients with severe aortic stenosis undergoing surgery on the aorta or other heart valves	1. Patients with moderate aortic stenosis undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves 2. Asymptomatic patients with severe aortic stenosis and: a. LV systolic dysfunction, or b. Abnormal response to exercise (e.g., hypotension)	1. Asymptomatic patients with severe aortic stenosis and: a. Ventricular tachycardia, or b. Marked or excessive LV hypertrophy, or c. Valve area $<0.6\ cm^2$
Aortic balloon valvotomy in adults with aortic stenosis	--	A "bridge" to surgery in hemodynamically unstable patients who are at high risk for AVR	1. Palliation in patients with serious comorbid conditions 2. Patients who require urgent noncardiac surgery

Vasodilator therapy for patients with chronic aortic regurgitation	1. Chronic therapy in patients with severe regurgitation who have symptoms and/or LV dysfunction, when surgery is not recommended because of additional cardiac or noncardiac factors 2. Long-term therapy in asymptomatic patients with severe regurgitation who have LV dilatation but normal systolic function 3. Long-term therapy in asymptomatic patients with hypertension and any degree of regurgitation 4. Long-term ACE inhibitor therapy in patients with persistent LV systolic dysfunction after AVR 5. Short-term therapy to improve hemodynamic profile of patients with severe heart failure symptoms and severe LV	--	--

	profile of patients with severe heart failure symptoms and severe LV dysfunction before AVR		
Cardiac catheterization in patients with chronic AR	1. Coronary angiography before AVR in patients at risk for CAD 2. Assessing severity of regurgitation when noninvasive tests are inconclusive or discordant with clinical findings regarding severity of regurgitation or need for surgery 3. Assessing LV function noninvasive tests are inconclusive or discordant with clinical findings regarding LV dysfunction and need for surgery in patients with severe AR	--	Assessing LV function and severity of regurgitation before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed

Aortic valve replacement in patients with chronic severe AR	1. Patients with NYHA function Class III or IV symptoms and preserved LV systolic function, defined as normal ejection fraction at rest (ejection fraction 50%) 2. Patients with NYHA function Class II symptoms and preserved LV systolic function (ejection fraction 50% at rest) but with progressive LV dilatation or declining ejection fraction at rest on serial studies or declining effort tolerance on exercise testing 3. Patients with Canadian Heart Association functional Class II or greater angina with or without CAD 4. Asymptomatic or symptomatic patients with mild to moderate LV dysfunction at rest (ejection fraction 25% to 49%) 5. Patients undergoing	1. Patients with NYHA functional Class II symptoms and preserved LV systolic function (ejection fraction 50% at rest) with stable LV size and systolic function on serial studies and stable exercise tolerance 2. Asymptomatic patients with normal LV systolic function (ejection fraction >50%) but with severe LV dilatation (diastolic dimension >75 mm or end-systolic dimension >55 mm; consider lower threshold values for patients of small stature	1. Patients with severe LV dysfunction (ejection fraction <25%) 2. Asymptomatic patients with normal systolic function at rest (ejection fraction >50%) and progressive LV dilatation when the degree of dilatation is moderately severe (end-diastolic dimension 70 to 75 mm, end-systolic dimension 50 to 55 mm) 3. Asymptomatic patients with normal systolic function at rest (ejection fraction >50%) but with decline in ejection fraction during exercise radionuclide angiography

	dysfunction at rest (ejection fraction 25% to 49%) 5. Patients undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves		
Recommendations for surgery for patients with TR	Annuloplasty for severe TR and pulmonary hypertension in patients with mitral valve disease requiring mitral valve surgery	1. Valve replacement for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair 2. Valve replacement or annuloplasty for severe TR with mean pulmonary arterial pressure <60 mm Hg when symptomatic	Annuloplasty for mild TR in patients with pulmonary hypertension secondary to mitral valve disease requiring mitral valve surgery

Follow-up strategy in patients with prosthetic heart valves	1. History, physical exam, ECG, chest roentgenogram, echocardiogram, CBC, serum chemistries, and INR (if indicated) at first postoperative outpatient evaluation (this evaluation should be performed 3 to 4 weeks after hospital discharge) 2. Radionuclide angiography or magnetic resonance imaging to evaluate LV function if echocardiography is unsatisfactory 3. Routine follow-up visits at yearly intervals with earlier reevaluations for change in clinical status		Routine serial echocardiograms at time of annual follow-up visit in absence of change in clinical status

Valve replacement with a mechanical prosthesis	Patients with expected long life spans Patients with a mechanical prosthetic valve already in place in a different position that the valve to be replaced	1. Patients in renal failure, on hemodialysis, or with hypercalcemia (Class II rather than IIa) 2. Patients requiring warfarin therapy because of risk factors for thromboembolism 3. Patients 65 years for AVR and 70 years for MVR	Valve re-replacement for thrombosed biological valve
Valve replacement with a bioprosthesis	1. Patients who cannot or will not take warfarin therapy 2. Patients >65 years needing AVR who do not have risk factors for thromboembolism	1. Patients considered to have possible compliance problems with warfarin therapy 2. Patients >70 years needing MVR who do not have risk factors for thromboembolism	1. Valve re-replacement for thrombosed mechanical valve 2. Patients <65 years

AR = atrial regurgitation; AVR = aortic valve replacement; CAD = coronary artery disease; CBC = com
blood count; 2-D = two-dimensional; ECG = electrocardiogram; INR = international normalized ratio; L
ventricle; MR = mitral regurgitation; MS = mitral stenosis; MVP = mitral valve prolapse; MVR = mitral v
replacement; NYHA = New York Heart Association; TR = tricuspid regurgitation.

*In centers with expertise in cardiac magnetic resonance imaging, cardiac MRI may be used in place of radionuclide angiography for these indications.

ventricular function in patients with this condition. The ACC/AHA guidelines note that yearly echocardiograms may be helpful for management of asymptomatic patients with severe aortic stenosis, but recommend an interval of 2 years for echocardiography in asymptomatic patients with moderate aortic stenosis and 5 years for asymptomatic patients with mild stenosis.

The guidelines indicate that exercise testing of asymptomatic patients can be performed safely and can provide useful information; however, the need for supervision by an experienced physician with close monitoring of blood pressure and electrocardiographic findings is emphasized. Recommendations from the Task Force on Acquired Valvular Heart Disease of the 26th Bethesda Conference address the issue of participation in competitive athletics.[3] These guidelines recommend that patients with severe aortic stenosis be advised to limit such activity to relatively low levels.

Coronary angiography is considered appropriate in the ACC/AHA guidelines for patients with possible coronary artery disease and may be needed to assess the severity of stenosis in symptomatic patients when other data are inconclusive. The guidelines discourage catheterization solely for the purpose of confirming information available from noninvasive tests.

Aortic valve replacement is indicated for virtually all symptomatic patients with severe aortic stenosis, and the ACC/AHA guidelines are generally supportive (Class IIa) of this procedure for asymptomatic patients with severe aortic stenosis, and left ventricular systolic dysfunction or exertional hypotension (see Table 46-G-1) . However, valve replacement for asymptomatic patients is otherwise discouraged. Aortic balloon valvotomy is given qualified support only as a "bridge" to surgery in hemodynamically unstable patients who cannot undergo immediate aortic valve replacement.

Aortic Regurgitation

Doppler echocardiography is a highly appropriate test for diagnosis and serial assessment of patients with aortic regurgitation. For new patients in whom the chronic nature of the lesion is uncertain, the guidelines support repeating the physical examination and echocardiogram 2 to 3 months after the initial evaluation to ensure that rapid progression is not underway. Asymptomatic patients with mild aortic regurgitation, normal left ventricular function, and little or no left ventricular dilatation can be seen on an annual basis, and echocardiography can be performed every 2 to 3 years in the absence of changes in symptoms. However, the guidelines support echocardiography every 6 to 12 months for patients with severe aortic regurgitation and significant left ventricular dilatation, such as an end-diastolic dimension greater than 60 mm. For patients with even more advanced left ventricular dilatation, echocardiography as often as every 4 to 6 months is endorsed.

Exercise testing is considered appropriate for assessment of functional capacity in patients in whom the history is not definitive, but the impact of this test on management is not otherwise strongly supported by the ACC/AHA guidelines. Radionuclide angiography is endorsed as an alternative to echocardiography for assessment of left ventricular volume and function. However, the ACC/AHA guidelines emphasize that there is no need for serial testing using both techniques.

The ACC/AHA guidelines consider vasodilator therapy appropriate for patients with aortic regurgitation who have hypertension or left ventricular dysfunction, even if the

patients are asymptomatic. However, the guidelines do not endorse vasodilator therapy for normotensive patients with normal left ventricular function and mild aortic regurgitation. The guidelines emphasize that vasodilator therapy is *not* an alternative to surgery for patients who are appropriate candidates for valve replacement.

Cardiac catheterization is not routinely needed to confirm the diagnosis or assess the severity of aortic regurgitation when echocardiographic studies are adequate. The most common appropriate indication for cardiac catheterization is the performance of coronary angiography before surgery. Aortic valve replacement is considered clearly appropriate in patients with severe (NYHA functional Class III or IV) symptoms, progressive left ventricular dilatation, mild-to-moderate left ventricular dysfunction, or declining exercise tolerance. The guidelines are not supportive of surgery solely because of a decline in ejection fraction during exercise.

Other Valvular Diseases

Tricuspid valve annuloplasty is an appropriate procedure for patients with severe tricuspid regurgitation and pulmonary hypertension who are undergoing surgery for mitral valve disease, but is inappropriate for patients whose pulmonary arterial systolic pressure does not exceed 60 mm Hg or more.

Valvular Disease in Young Adults

For adolescents and young adults with aortic stenosis, ACC/AHA guidelines reflect a lower threshold for exercise testing and cardiac catheterization to assess the risk of participation in athletics (Table 46-G-2) (Table Not Available) . In this population, balloon valvotomy is an effective and appropriate option. Since this procedure has little morbidity and mortality, the indications for intervention are more liberal in younger patients than in older adults. The indications for management of chronic aortic regurgitation and mitral valvular disease are similar to those for older adult patients (see Table 46-G-1) . Pulmonic valvotomy is considered an appropriate intervention for patients who have symptomatic pulmonic stenosis and for asymptomatic patients with a peak valve gradient greater than 50 mm.

TABLE 46--G-2 -- GUIDELINES FOR MANAGEMENT OF VALVULAR HEART DISEASE IN ADOLESCENTS AND YOUNG ADULTS

(Not Available)

TABLE 46--G-3 -- AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR APPROPRIATE (CLASS I) ANTITHROMBOTIC THERAPY IN PATIENTS WITH PROSTHETIC HEART VALVES

Indication	Medication	Target	Class
1. First 3 months after valve replacement	Warfarin	INR 2.5 to 3.5	I
2. 3 months after valve replacement:			
a. Mechanical valve:	Warfarin	INR 2.0 to 3.0	I
(1). AVR and no risk factors *	Warfarin	INR 2.5 to 3.5	I
Bileaflet valve or Medtronic-Hall valve	Warfarin	INR 2.5 to 3.5	I
(2). Other disc valves or Starr-Edwards valve	Warfarin	INR 2.5 to 3.5	I
(3). AVR plus risk factors*	Aspirin	80 to 100	I
(4). MVR	Warfarin	mg/day	I
b. Bioprosthesis:	Aspirin	INR 2.0 to 3.0	I
(1). AVR and no risk factors*	Warfarin	80 to 100	I
(2). AVR and risk factors*		mg/day	
(3). MVR and no risk factors*		INR 2.5 to 3.5	
(4). MVR and risk factors*			

AVR = aortic valve replacement; INR = international normalized ratio; MVR = mitral valve replacement.

*Risk factors: Atrial fibrillation, left ventricular dysfunction, previous thromboembolism, hypercoagulable conditions.

Patients with Prosthetic Heart Valves

The ACC/AHA guidelines recommend that INR be maintained between 2.0 and 3.0 for patients with bileaflet mechanical valves and Medtronic-Hall valves and between 2.5 and 3.5 for other disc valves and Starr-Edwards valves (Table 46-G-3) . Aspirin therapy is considered appropriate for patients with aortic or mitral valve bioprostheses and no risk factors for thromboembolism.

The guidelines indicate that hospital admission to administer heparin before noncardiac surgery or dental care is usually unnecessary. They recommend that heparin be reserved for patients who have had a recent thrombosis or embolism, those with demonstrated thrombotic problems when previously off therapy, those with a

Bjork-Shiley valve, and those with three or more risk factors for thromboembolism.

After prosthetic valve implantation, asymptomatic patients need be seen only at 1-year intervals (see Table 46-G-1) . Routine serial echocardiograms are not strongly endorsed (Class IIb).

The ACC/AHA guidelines offer general recommendations to guide the selection of bioprosthetic versus mechanical valves. Bioprostheses are considered *inappropriate* for patients in renal failure, on hemodialysis, or with hypercalcemia, or for adolescent patients who are still growing.

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Chapter 47 - Infective Endocarditis

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DEFINITION

Infective endocarditis (IE) is a microbial infection of the endothelial surface of the heart. The characteristic lesion, the vegetation, is a variably sized amorphous mass of platelets and fibrin in which abundant microorganisms and scant inflammatory cells are enmeshed. Heart valves are most commonly involved; however, infection may occur at the site of a septal defect or on chordae tendineae or mural endocardium. Infection of arteriovenous shunts, arterioarterial shunts (patent ductus arteriosus), or coarctation of the aorta, although actually an endarteritis, is clinically and pathologically similar to IE. Many species of bacteria and fungi, mycobacteria, rickettsiae, chlamydiae, and mycoplasmas cause IE; nevertheless, streptococci, staphylococci, enterococci, and fastidious gram-negative coccobacilli cause the majority of cases of IE.

The terms *acute* and *subacute* are often used to describe IE. Acute IE presents with marked toxicity and progresses over days to several weeks to valvular destruction and metastatic infection. In contrast, subacute IE evolves over weeks to months with only modest toxicity and rarely causes metastatic infection. Acute IE is caused typically, although not exclusively, by *Staphylococcus aureus,* whereas the subacute syndrome is

more likely caused by viridans streptococci, enterococci, coagulase-negative staphylococci, or gram-negative coccobacilli.

EPIDEMIOLOGY

The incidence of IE remained relatively stable from 1950 through 1987 at about 4.2 per 100,000 patient-years. During the early 1980s, the yearly incidence of IE per 100,000 population was 2.0 in the United Kingdom and Wales and 1.9 in the Netherlands.[1] A higher incidence was noted from 1984 through 1990; 5.9 and 11.6 episodes per 100,000 population were reported from Sweden and Metropolitan Philadelphia, respectively.[2] [3] Injection drug abuse accounted for approximately half of the cases in Philadelphia. Endocarditis usually occurred more frequently in men; gender-derived ratios range from 1.6 to 2.5. The age-specific incidence of endocarditis increased progressively after 30 years of age and exceeded 15 to 30 cases per 100,000 person-years in the sixth through eighth decades of life.[2] From 55 to 75 percent of patients with native valve endocarditis (NVE) have predisposing conditions: rheumatic heart disease, congenital heart disease, mitral valve prolapse, degenerative heart disease, asymmetrical septal hypertrophy, or intravenous drug abuse.[24] [5] From 7 to 25 percent of cases involve prosthetic valves.[2] [3] Predisposing conditions cannot be identified in 25 to 45 percent of patients. The nature of predisposing conditions and, in part, the microbiology of IE correlate with the age of patients (Table 47-1) .

CHANGE IN PATIENTS WITH IE.

Changes in the epidemiology of IE appear incontestable despite the hazard of referral bias in available data. As a consequence of changes in both the frequency of predisposing conditions encountered in patients with IE as well as the increasing age of the population at risk for IE, the median age of patients has gradually increased from 30 to 40 years of age in the preantibiotic and early antibiotic eras to 47 to 69 years in recent decades.[2] [4] [5] Rheumatic fever with subsequent rheumatic heart disease in children and young adults has been markedly reduced in developed countries. Acquired valvular disease emerges as a risk for IE as patients enjoy greater longevity. Additionally, during their later years, many of these patients require valve replacement, which places them at greater risk for endocarditis. The increasing life span of the general population results in the emergence of degenerative heart disease as a major substrate for IE. Finally, nosocomial endocarditis presents with increased frequency among the elderly, who experience high rates of hospitalization for underlying illnesses.[6] In recent decades, only the increasing role of intravenous (IV) drug abuse as predisposition for IE and the high IE risk in children and young adults surviving after correction of complex congenital heart disease favor the occurrence of infection in younger patients.[2] [7]

CHANGES IN THE MICROBIOLOGY OF IE.

Coagulase-negative staphylococci, previously a minor cause of NVE, are an important cause of prosthetic valve endocarditis (PVE) and nosocomial IE.[8] *S. aureus* is the predominant cause of IE among IV drug abusers, particularly of infection involving the tricuspid valve. In addition, *Pseudomonas aeruginosa,* other gram-negative bacilli, and

Candida species, unusual causes of NVE in other settings, are important causes of IE in drug abusers. Even in series not biased by inclusion of large numbers of cases

TABLE 47-1 -- PREDISPOSING CONDITIONS AND MICROBIOLOGY OF NATIVE VALVE ENDOCARDITIS

	CHILDREN (%)		ADULTS (%)	
	Neonates	**2 mo-15 yr**	**15-60 yr**	**>60 yr**
Predisposing Conditions				
RHD		2-10	25-30	8
CHD	28	75-90*	10-20	2
MVP		5-15	10-30	10
DHD			Rare	30
Parenteral drug abuse			15-35	10
Other			10-15	10
None	72	2-5	25-45	25-40
Microbiology				
Streptococci	15-20	40-50	45-65	30-45
Enterococci		4	5-8	15
S. aureus	40-50	25	30-40	25-30
Coagulase-negative staphylococci	10	5	3-5	5-8
GNB	10	5	4-8	5
Fungi	10	1	1	Rare
Polymicrobial	4		1	Rare
Other			1	2
Culture negative	4	0-15	3-10	5

RHD=rheumatic heart disease; CHD=congenital heart disease; MVP=mitral valve prolapse; DHD=degenerative heart disease; GNB=gram-negative bacteria, frequently *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis.*

*50% of cases follow surgery and may involve implanted devices and foreign material.

Often tricuspid valve IE.

associated with drug abuse, *S. aureus* causes an increasing proportion of cases and rivals viridans streptococci.[2] [9] IE caused by enterococci, which are associated with genitourinary tract manipulations, and by *Streptococcus bovis,* which is associated with gastrointestinal malignancy and colonic polyps, occurs more frequently in the elderly, the population likely to experience these precipitating conditions.

PATIENT GROUPS

CHILDREN.

The incidence of IE among hospitalized children ranges from 1 in 4500 to 1 in 1280.[10] In the Netherlands, IE was noted in 1.7 and 1.2 per 100,000 male and female children younger than 10 years, respectively.[1] IE has been noted in neonates with increasing frequency. Among neonates, IE typically involves the tricuspid valve of structurally normal hearts and is associated with very high mortality rates. It is likely that many of these episodes arise as a consequence of infected IV and right-heart catheters as well as cardiac surgery.[10] [11]

The vast majority of children with IE occurring after the neonatal period have identifiable structural cardiac abnormalities (see Table 47-1) . In some series, rheumatic heart disease was an infrequent predisposition for IE (
4 percent).[11] [12] Congenital heart abnormalities, particularly those involving the aortic valve; ventricular septal defects; tetralogy of Fallot; and other complex structural anomalies associated with cyanosis are found in 75 to 90 percent of cases. Of children with IE on congenital defects, 50 percent develop infection after cardiac surgery; in these children, infection frequently involves prosthetic valves, valved conduits, or synthetic patches.[7] [11] [12] Secundum atrial septal defects are not associated with an increased risk for IE nor is patent ductus arteriosus or pulmonic stenosis after repair.[7] Since 1990, mitral valve prolapse has been recognized to predispose to IE in children; it, generally in association with a regurgitant murmur, was the predisposing cardiac abnormality in 15 percent and 5 percent of cases in two series.[12]

Endocarditis among neonates is caused primarily by *S. aureus,* coagulase-negative staphylococci, and group B streptococci.[10] Occasionally, infection is caused by gram-negative bacilli and *Candida* species.[10] [11] Among older children, streptococci, the predominant cause, account for at least 40 percent of cases, and *S. aureus* occurring as a nosocomial or community-acquired acute infection is the second most common cause of IE.[10] [11] [12] *Streptococcus pneumoniae,* a common cause of bacteremia in children, is nevertheless an uncommon cause of IE. *S. aureus* and *S. pneumoniae* may involve normal or abnormal valves, present as acute fulminant IE, cause rapid valve destruction and heart failure, and often result in death.[10]

The clinical features and echocardiographic findings of IE in children are similar to those noted among adults with NVE or PVE, respectively.[10] In contrast, IE among neonates is

more cryptic; the clinical picture is dominated by bacteremia, and classical signs of IE are rare.[10]

ADULTS.

Mitral valve prolapse (MVP) has emerged as a prominent predisposing structural cardiac abnormality and in adults accounts for 7 to 30 percent of NVE in cases not related to drug abuse or nosocomial infection.[1] [4] [5] The frequency of MVP in IE is not entirely a direct reflection of risk but rather arises because of the high frequency of the lesion in the general population, 2 to 4 percent of healthy persons and 20 percent among young women.

The relative risk of endocarditis among patients with MVP ranges from 3.5 to 8.2. This increased risk of endocarditis is largely confined to patients with both prolapse and a mitral regurgitation murmur. Risk is also increased among men and patients older than 45 years. Valve redundancy and thickened leaflets (>5 mm) by echocardiography also identify a population at increased risk for IE (see Chap. 46) . Among patients with MVP and a systolic murmur, the incidence of IE is 52 per 100,000 person-years, compared with a rate of 4.6 per 100,000 person-years among those with prolapse and no murmur or among the general population. The microbiology of IE engrafted on MVP is similar to that of NVE that is not associated with drug abuse. Similarly, the mortality rate of 14 percent approximates that of NVE in general.

Rheumatic heart disease was the predisposing cardiac lesion for IE in 20 to 25 percent of cases in the 1970s and 1980s.[13] In reports from hospitals in North America and Europe in the 1980s, rheumatic heart disease predisposed to IE in only 7 and 18 percent of cases.[2] [4] [5] [9] In patients with rheumatic heart disease, endocarditis occurs most frequently on the mitral valve, a site at which women are more commonly infected. The aortic valve is the next most common site for IE; infection in this setting occurs more commonly in men.

Congenital heart disease is the substrate for IE in 10 to 20 percent of younger adults and 8 percent of older adults. Among adults, the common predisposing lesions are patent ductus arteriosus, ventricular septal defect, and bicuspid aortic valve, the latter particularly found among older men (>60 years).[2] [9]

In settings where NVE among adults is not skewed dramatically by infection occurring among IV drug abusers and nosocomial disease, the microbiology is notably similar to that shown in Table 47-1 .[2] [9] *Coxiella burnetii,* an uncommon cause of IE in the United States, caused 3 percent of all cases in the United Kingdom from 1976 to 1985 and is a prominent cause of IE in France.[14] *Bartonella* species have emerged as a significant cause of IE, accounting for 3 percent of cases in one report.[15]

INTRAVENOUS DRUG ABUSERS.

The risk for IE among IV drug abusers, 2 to 5 percent per patient-year, is estimated to be severalfold greater than that of patients with rheumatic heart disease or prosthetic

valves.[16] In one study, IE was diagnosed in 74 (6.4 percent) of 1150 IV drug abusers who were hospitalized during 12 months. In metropolitan Philadelphia, 5.3 of a total of 11.6 cases of IE per 100,000 population was attributed to injection drug abuse.[3] From 65 to 80 percent of cases of IE in this population occurs in men, and the average age of patients ranges from 27 to 37 years.[17] [18] [19] [20]

Endocarditis occurring in IV drug abusers has a unique propensity to infect right heart valves.[16] [17] [20] On postmortem examination of 80 addicts with active or healed IE involving 103 valves, evidence of infection was seen on the tricuspid valve in 44 percent, the mitral valve in 43 percent, the aortic valve in 40 percent, and the pulmonic valve in 3 percent. Because mortality rates are higher in patients with left-sided versus right-sided IE, this distribution is undoubtedly skewed. In clinical series, distribution of valve involvement is tricuspid in 46 to 78 percent, mitral in 32 to 24 percent, and aortic in 8 to 19 percent (as many as 16 percent of patients have infection at multiple sites).[18] In IV drug abusers, the valves were normal before infection in 75 to 93 percent of patients.[16] [17] [18] The remaining patients have preexisting aortic or mitral valve abnormalities, resulting primarily from rheumatic heart disease, congenital heart disease, or prior episodes of IE. IV drug abuse is a risk factor for recurrent NVE.

The microbiology of IE occurring in IV drug abusers is unique in several respects (Table 47-2) . In contrast to NVE among adults in general, *S. aureus* causes more than 50 percent of these infections overall and 60 to 70 percent of those involving the tricuspid valve. The well-established predilection for *S. aureus* to infect normal as well as abnormal left heart valves is noted in addicts. Although the phenomenon of *S. aureus* infection of normal tricuspid valves is not unique to addicts, the high frequency is characteristic.[16] [21] Streptococcal and enterococcal infection of previously abnormal mitral or aortic valves in addicts is comparable to that noted generally in NVE. In contrast, infection of right and left heart valves by *P. aeruginosa* and other gram-negative bacilli and left heart valves by fungi occurs with increased frequency among drug abusers. In addition, unusual organisms, some of which are likely related to injection of contaminated materials, cause endocarditis in these patients, e.g., *Corynebacterium* species, *Lactobacillus, Bacillus cereus,* and nonpathogenic *Neisseria* species. Polymicrobial endocarditis occurs with increased frequency in IV drug abusers.

The clinical manifestations of IE in IV drug abusers depend on the valve(s) involved and, to a lesser degree, on the infecting organism. Tricuspid valve endocarditis, particularly when caused by *S. aureus,* presents with pleuritic

TABLE 47-2 -- MICROBIOLOGY OF ENDOCARDITIS ASSOCIATED WITH INTRAVENOUS DRUG ABUSE

	NUMBER OF CASES (%) Endocarditis In Drug Addicts*		
	Right-Sided	***Left-Sided***	***Total***
	N=346	***N=204***	***N=675***
Streptococci§	17 (5)	31 (15)	80 (12)
Enterococci	7 (2)	49 (24)	59 (9)
Staphylococcus aureus	267 (77)	47 (23)	396 (57)
Gram-negative bacilli¶	17 (5)	26 (13)	45 (7)
Fungi (predominantly *Candida* species)	--	25 (12)	26 (4)
Polymicrobial/miscellaneous	28 (8)	20 (10)	49 (7)
Culture negative	10 (3)	6 (3)	20 (3)

*Ten patients with right- and left-sided IE are counted twice.

Data from references 16, 17, 136.

Data from references 9, 16-18, 136.
§Includes viridans streptococci, *Streptococcus bovis,* other nongroup A groupable streptococci, *Abiotrophia* species (nutritionally variant streptococci).
¶*P. aeruginosa, S. marcescens,* and Enterobacteriaceae.

chest pain, shortness of breath, cough, and hemoptysis. In 65 to 75 percent of patients, chest roentgenograms reveal abnormalities due to septic pulmonary emboli. Murmurs of tricuspid regurgitation are noted in less than half of these patients. Infection of the aortic or mitral valve in addicts clinically resembles IE seen in other patients. That caused by *S. aureus* generally presents as acute endocarditis with marked systemic toxicity. Symptoms and signs of left heart failure, neurologic injury, systemic emboli, metastatic infections, and the classical peripheral stigmata of IE are strongly associated with left-sided endocarditis.[16] [18]

Infection with human immunodeficiency virus (HIV) has been noted in 27 to 73 percent of IV drug abusers with IE[18] [19] [20] (see Chap. 68) . Among drug abusers with IE, HIV serostatus does not significantly modify the clinical presentation, microbiology, complications, and overall survival. However, among HIV-infected drug abusers with IE, the risk of death is increased among those with a CD4 count less than 200/mm^3 .[19] [20]

PROSTHETIC VALVE ENDOCARDITIS.

Epidemiologic studies suggest that prosthetic valve endocarditis (PVE) comprises 10 to 30 percent of all cases of IE in developed countries.[19] In metropolitan Philadelphia, 0.94 cases of IE per 100,000 population involved prosthetic valves.[3] The cumulative incidence of PVE estimated actuarially has ranged from 1.4 to 3.1 percent at 12 months

and 3.2 to 5.7 percent at 5 years.[22] [23] [24] [25] [26] The risk of PVE over time, however, is not uniform. The risk is greatest during the initial 6 months after valve surgery (particularly during the initial 5 to 6 weeks) and thereafter declines to a lower but persistent risk (0.2 to 0.35 percent per year).[22] [23] [24] [25] [26] [27]

PVE has been called "early" when symptoms begin within 60 days of valve surgery and "late" with onset thereafter. These terms were established to distinguish early PVE that arose as a complication of valve surgery from late infection that was more likely community acquired. In fact, many cases with onset between 60 days and 1 year after surgery are likely to be nosocomial and, despite their delayed presentation, derive from events during the surgical admission.[28] Studies to identify risk factors for PVE have not resulted in a coherent picture. Data suggest that, during the initial months after valve implantation, mechanical prostheses are at greater risk of infection than bioprosthetic valves but that after 12 months the risk of infection of bioprostheses exceeds that of mechanical valves.[23] [24] [25] [26] [27] Patients with antecedent NVE, particularly if the disease is active, are at increased risk for PVE.[23] [24] [25] [26] [27]

Microbiology.

The microbiology of PVE is relatively predictable and reflects in part the presumed nosocomial or community acquisition of infection (Table 47-3) . Coagulase-negative staphylococci, which when speciated are primarily *Staphylococcus epidermidis,* are the predominant causes of PVE diagnosed within 60 days after surgery. *S. aureus,* gram-negative bacilli, diphtheroids (particularly *Corynebacterium jeikeium*), and fungi (particularly *Candida* species) are also common causes of PVE during this period.

Occasional cases of nosocomial PVE caused by *Legionella* species, atypical mycobacteria, mycoplasma, and fungi other than *Candida* have been reported. The spectrum and frequency of microorganisms causing PVE that occurs between 2 and 12 months after cardiac surgery and within the initial 60 postoperative days are similar. More than 80 percent of the coagulase-negative staphylococci from either of these periods are resistant to methicillin and all other beta-lactam antibiotics. In contrast, 30 percent or fewer of the coagulase-negative staphylococci causing PVE with onset more than 1 year after valve surgery are methicillin resistant.[25] [28] PVE with onset 1 year or more postoperatively presumably results from transient bacteremia arising from dental, gastrointestinal, and genitourinary manipulations; breaks in the skin barrier; and intercurrent infections.[27] [28] Consequently, the microbiology of these cases resembles that in community-acquired NVE in nonaddicts: streptococci, *S. aureus,* enterococci, and fastidious gram-negative coccobacilli (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella,* and *Kingella*-the so-called HACEK group). Coagulase-negative staphylococci cause about 10 percent of these cases of PVE.

Pathology.

The intracardiac pathology of PVE differs notably from the largely leaflet-confined pathology of NVE. Infection on mechanical prostheses commonly extends beyond the valve ring into the annulus and periannular tissue as well as the mitral-aortic

intravalvular fibrosa, resulting in ring abscesses, septal abscesses, fistulous tracts, and dehiscence of the prosthesis with hemodynamically significant paravalvular regurgitation (Fig. 47-1) . In autopsy experience with 74 patients, which is clearly biased toward the

TABLE 47-3 -- MICROBIOLOGY OF PROSTHETIC VALVE ENDOCARDITIS 1975-1994

	NUMBER OF CASES (%)*		
	Time Of Onset After Valve Surgery		
	<2 mo N=144	***2-12 mo N=31***	***>12 mo N=194***
Streptococci	2 (1)	3 (9)	61 (31)
Pneumococci	--	--	--
Enterococci	12 (8)	4 (12)	22 (11)
Staphylococcus aureus	32 (22)	4 (12)	34 (18)
Coagulase-negative staphylococci	47 (33)	11 (32)	22 (11)
Fastidious gram-negative coccobacilli (HACEK group)	--	--	11 (6)
Gram-negative bacilli	19 (13)	1 (3)	11 (6)
Fungi, *Candida* species	12 (8)	4 (12)	3 (1)
Polymicrobial/miscellaneous	4 (3)	2 (6)	9 (5)
Diphtheroids	9 (6)	--	5 (3)
Culture negative	7 (5)	2 (6)	16 (8)

Adapted from Karchmer AW: Infections of prosthetic valves and intravascular devices. In Mandell GL, Bennett JE, Dolin R (eds): Principles and Practice of Infectious Diseases. 5th ed. New York, Churchill Livingstone, 2000.

*Data from references 9 and 133.

Includes viridans streptococci, *Streptococcus bovis,* other nongroup A groupable streptococci, *Abiotrophia* species (nutritionally variant streptococci).

Includes *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae.*

Figure 47-1 *S. epidermidis* infection of a bioprosthetic aortic valve 3 months after surgery. Contrast material injected supravalvularly fills a paravalvular abscess and regurgitates into the left ventricle.

most severe pathology, annular invasion was noted in 85 percent, myocardial abscess in 32 percent, and valve obstruction by vegetation overgrowth, a phenomenon of PVE at the mitral site, in 19 percent.[28] Erosion through the aortic annulus to cause pericarditis occurred in 5 percent[28] (Fig. 47-2) . In clinical series encompassing 85 patients, the rate of annulus invasion was 42 percent, myocardial abscess 14 percent, valve obstruction 4 percent, and pericarditis 2 percent.[28] Bioprosthetic valve IE may result in invasive disease, comparable to that noted when PVE involves mechanical valves, as well as leaflet destruction (see Fig. 47-1) . Among 85 patients with bioprosthetic PVE, 29 (59 percent) of 49 with infection within a year after surgery had invasive disease, in contrast to only 9 (25 percent) of 36 patients with infection occurring more than 1 year postoperatively.[28] In surgically treated bioprosthetic IE, invasion was confirmed in 15 of 19 cases (79 percent), with onset in the initial 12 months after surgery but in only 22 of 71 bioprostheses (31 percent) when infection began more than 12 months after surgery.[29] Fernicola and Roberts, at surgery or autopsy, noted annular invasion in 4 of 5 bioprosthetic infections with onset within 60 days of surgery and in 17 of 32 infected bioprostheses with presentation occurring more than 60 days after surgery.[30] Aortic site and clinical onset within a year of valve surgery were significantly correlated with an increased risk of invasive infection.

Signs and symptoms in patients developing PVE within 60 days of cardiac surgery may be obscured by surgery or other postoperative complications. Peripheral signs of endocarditis (5 to 14 percent) and central nervous system emboli (10 percent) occur less frequently in these patients than in those with PVE occurring later after surgery. Among patients with later-onset PVE, congestive heart failure occurs in 40 percent, cerebrovascular complications in 26 to 28 percent, and peripheral signs in 15 to 28 percent.[28] [31] [32]

NOSOCOMIAL ENDOCARDITIS.

Hospital-acquired endocarditis unrelated to concurrent cardiac surgery comprises 5 to 29 percent of all cases of IE in various series.[4] [5] [6] [33] Nosocomial IE has involved abnomal native cardiac valves, normal valves including the tricuspid, and prosthetic valves and occurs with similar frequency among patients with NVE and PVE (unrelated to valve surgery).[1] [4] Infected intravascular devices and catheters give rise to 45 to 65 percent of the bacteremia that results in nosocomial IE.[6] [33] Other sources of bacteremia include genitourinary and gastrointestinal tract instrumentation or surgery. Right-sided endocarditis was found in 5 and 7 percent of patients with central venous catheters extending into or near the right atrium and those with flow-directed pulmonary artery catheters, respectively. The onset of nosocomial IE is usually acute, and although a changing murmur may be heard, other classical signs of endocarditis are infrequent.[33] Mortality rates among these patients, many of whom are elderly and have serious underlying diseases, are high (40 to 56 percent).[6] [33]

Microbiology.

Gram-positive cocci are the predominant cause of nosocomial IE. Among 45 episodes from two series, *S. aureus* caused 44 percent, coagulase-negative staphylococci 22 percent, enterococci 18 percent, and streptococci and *Candida* species and gram-negative bacilli each 4 percent. One patient (2 percent) had negative cultures.[6] In a meta-analysis, the mean rate of endocarditis or other deep-seated *S. aureus* infections after catheter-related bacteremia was 6.1 percent (95 percent confidence interval 2.0 to 10.2 percent).[34] When patients with *S. aureus* catheter-related bacteremia were studied with transesophageal echocardiography (TEE), 16 of 69 (23 percent) were found to have IE.[35] Accordingly, patients with catheter-related *S. aureus* bacteremia should be studied by transthoracic echocardiography (TTE) and, if IE is not diagnosed, should be evaluated by TEE.

Catheter-associated *S. aureus* bacteremia occurs with sufficient frequency to be the predominant predisposing factor for nosocomial IE.[6] [34] [35] [36] IE complicates 0.85 to 3.1 percent of cases of nosocomial enterococcal bacteremia; although the risk of nosocomial enterococcal IE is increased in patients with abnormal valves, it remains small, relative to that for nosocomial *S. aureus* bacteremia.[6] Among 115 patients who had prosthetic valves and who experienced a nosocomial bacteremia that was not indicative of PVE, 18 (15.6 percent) subsequently developed PVE that was the apparent consequence of the bacteremia. *S. aureus* and *S. epidermidis* were the most common organisms in these cases of PVE, although gram-negative bacilli and fungi also caused episodes of PVE.[37] Bacteremia persisting for days before treatment or for 72 hours or more after removal of an infected catheter and initiation of treatment, especially in patients with abnormal heart valves or prosthetic valves, suggests the diagnosis of IE.[6] [33] [36]

Figure 47-2 *A,* A large vegetation caused by *Candida albicans* partially occludes the orifice of a bioprosthetic valve removed from the mitral position.*(From Karchmer AW: Infections of prosthetic heart valves. In Korzeniowski OM [ed]: Cardiovascular Infection, vol. x, Atlas of Infectious Diseases. Philadelphia, Current Medicine; with permission.) B,* A Starr-Edwards prosthesis removed from the aortic position, where this large vegetation due to *Aspergillus* infection partially obstructed the outflow tract but also allowed regurgitation by preventing valve closure.

Etiological Microorganisms

VIRIDANS STREPTOCOCCI.

These streptococci, which cause 30 to 65 percent of NVE cases unrelated to drug abuse, are normal inhabitants of the oropharynx, characteristically produce alpha-hemolysis when grown on sheep blood agar, and are usually nontypable using

Lancefield's system. Using earlier taxonomy, the species causing streptococcal NVE were distributed as follows: *Streptococcus mitior* (31 percent of cases), *Streptococcus sanguis* (24 percent), *S. bovis* (27 percent), *Streptococcus mutans* (7 percent), *Streptococcus milleri* (4 percent). *Streptococcus faecalis* (now *Enterococcus faecalis*) (7 percent), and *Streptococcus salivarius* and other species (2 percent). Another study, adjusted for the new taxonomy, has reported a similar distribution of streptococci causing IE.[38] Nutritional variant organisms that require media supplemented with either pyridoxal hydrochloride or L-cysteine for growth and were previously speciated as *Streptococcus adjacens* or *Streptococcus defectivus,* cause 5 percent of streptococcal NVE. These organisms have been reclassified into a new genus, *Abiotrophia.*[39]

The viridans streptococci, other than the nutritionally variant organisms, had been in general highly susceptible to penicillin (minimum inhibitory concentration [MIC] 0.1 mug/ml for 83 percent) and are killed in an enhanced manner (synergistically) by penicillin plus gentamicin.[39] Viridans streptococci isolated from blood, although not specifically from patients with IE, have demonstrated increased resistance to penicillin (penicillin MIC > 0.12 mug/mL).[40] This finding raises the concern that strains causing IE may also be less susceptible to penicillin than in the past. *Abiotrophia* species, previously called *S. adjacens* and *S. defectivus,* appear more resistant to penicillin (MIC > 0.12 mug/ml in more than 30 percent of strains).[39] Although penicillin-aminoglycoside synergy was not demonstrated in vitro with *S. adjacens* and *S. defectivus,* in therapy of experimental endocarditis caused by these organisms, penicillin-aminoglycoside combinations were more effective than penicillin alone; also, therapy with vancomycin alone was comparable to that with the penicillin-aminoglycoside combination.[39]

STREPTOCOCCUS BOVIS AND OTHER STREPTOCOCCI.

S. bovis, part of the gastrointestinal tract normal flora, causes 27 percent of the episodes of streptococcal NVE. Although superficially resembling the enterococci, this species can be easily distinguished by its biochemical characteristics. The distinction is important because *S. bovis* is highly penicillin susceptible, in contrast to the relative penicillin resistance of enterococci. *S. bovis* NVE is frequently associated with coexistent colonic polyps or malignancy.[41]

Group A streptococci, which can infect normal valves, cause rare episodes of endocarditis. Among IV drug abusers, group A streptococci have caused tricuspid valve IE similar to that noted with *S. aureus.* Group B organisms, *Streptococcus agalactiae,* are part of the normal flora of the mouth, genital tract, and gastrointestinal tract. Group B streptococci infect normal and abnormal valves and cause a morbid NVE syndrome with a high incidence of systemic emboli and septic musculoskeletal complications (arthritis, diskitis, osteomyelitis).[42] The organisms' failure to produce fibrinolysin may result in large vegetations and a high rate of systemic emboli. Endocarditis caused by this organism may be associated with villous adenomas and colonic neoplasms. Group G streptococci also produce a destructive, highly morbid left-sided NVE. The *S. milleri* group, now divided into three species--*Streptococcus intermedius, Streptococcus constellatus,* and *Streptococcus anginosus*--are highly pyogenic organisms that cause destructive infections similar to those caused by *S. aureus* and accounted for 2 to 5

percent of streptococcal NVE cases.[38]

STREPTOCOCCUS PNEUMONIAE.

Although pneumococcal bacteremia occurs frequently, *S. pneumoniae* accounts for only 1 to 3 percent of NVE cases. When causing IE, *S. pneumoniae* frequently involves a previously normal aortic valve and progresses rapidly with valve destruction, myocardial abscess formation, and acute congestive heart failure (CHF).[43] The mortality rate among medically treated patients exceeded 60 percent but was 32 percent among those undergoing medical-surgical therapy.[43] Alcoholism is a risk factor for pneumococcal IE, and concurrent pneumonia or meningitis is common. Pneumococci that are resistant to penicillin and ceftriaxone are increasingly common causes of infection, particularly in children. These strains remain susceptible to vancomycin. In the future, these penicillin-resistant strains are likely to cause sporadic cases of IE; therefore, vancomycin might be included in the therapy of suspected pneumococcal IE until definitive susceptibility results for the isolate become available.[44]

ENTEROCOCCI.

E. faecalis and *Enterococcus faecium* cause 85 percent and 10 percent of cases of enterococcal IE, respectively. Enterococci are part of the normal gastrointestinal flora and cause genitourinary tract infection. Enterococci account for 5 to 15 percent of cases of NVE and a similar percentage of PVE cases (see Tables 47-2 and 47-3) .[9] [28] [45] Cases occur in young women as a consequence of genitourinary tract manipulation or infection and in older predominantly male patients, who have the urinary tract as a likely portal of entry. Enterococci infect either normal or previously abnormal valves and present as either acute or subacute IE.[45]

Enterococci are overtly resistant to cephalosporins, semisynthetic penicillinase-resistant penicillins (oxacillin and nafcillin), and therapeutic concentrations of aminoglycosides. Most enterococci are inhibited by modest concentrations of the cell wall-active antibiotics--penicillin, ampicillin, vancomycin, and teicoplanin (not licensed in the United States). Bactericidal antienterococcal activity can be achieved by combining an inhibitory cell wall-active agent and an appropriate aminoglycoside. This bactericidal activity called *synergy,* is essential for optimal treatment of enterococcal IE.[45] Strains of enterococci that are highly resistant to penicillin and ampicillin, resistant to vancomycin, and highly resistant to all aminoglycosides have been identified as causes of nosocomial infections.[45] [46]

STAPHYLOCOCCI.

The coagulase-positive staphylococci are a single species, *S. aureus.* Of the 13 species of coagulase-negative staphylococci that colonize humans, one, *S. epidermidis,* has emerged as an important pathogen in the setting of implanted devices and hospitalized patients. Coagulase-negative staphylococci on the surface of foreign devices have altered phenotypes, including increased resistance to the bactericidal effects of many

antibiotics.[47] [48]

Antibiotic Resistance.

In excess of 90 percent of *S. aureus* cases, whether acquired in the hospital or community, produce beta-lactamase and thus are resistant to penicillin, ampicillin, and the ureidopenicillins. These organisms are, however, susceptible to the penicillinase-resistant beta-lactam antibiotics (oxacillin, nafcillin, cefazolin, and other first-generation cephalosporins). Methicillin-resistant strains of *S. aureus* are increasingly prevalent in nosocomial settings and among selected, nonhospitalized populations (IV drug abusers, nursing home residents) and must be considered when selecting initial empirical therapy for IE in patients from these groups.[17] [49] Coagulase-negative staphylococci frequently produce beta-lactamase; furthermore, strains causing community-acquired infections are frequently methicillin susceptible, whereas those causing nosocomial infections, including IE, are commonly methicillin resistant.[50] Coagulase-negative staphylococci may not always phenotypically express methicillin resistance (a property called *heteroresistance*). Consequently, special testing may be required to detect this resistance.[49] [50] Staphylococci, including most strains that are resistant to methicillin, remain susceptible to vancomycin and telcoplanin.[49]

Clinical Features.

S. aureus is a major cause of IE in all population groups (see Tables 47-1 and 47-2) . *S. aureus* IE is characterized by a highly toxic febrile illness, frequent focal metastatic infection, and a 30 to 50 percent rate of central nervous system complications.[49] A cerebrospinal fluid polymorphonuclear pleocytosis, with or without *S. aureus* cultured from the cerebrospinal fluid, is common.[49] Heart murmurs are heard in 30 to 45 percent of patients on initial evaluation and are ultimately heard in 75 to 85 percent as a consequence of intracardiac damage. The mortality rate in nonaddicts with left-sided *S. aureus* endocarditis ranges from 16 to 46 percent overall and increases in those over 50 years of age, in those with significant underlying diseases, and when IE is complicated by a major neurologic event valve dysfunction or CHF.[49] [51] [52] Among addicts, left-sided *S. aureus* IE resembles that in nonaddicts. In contrast, in patients with IE limited to the tricuspid valve, complications are rare and mortality rates are only 2 to 4 percent.[18] Tricuspid staphylococcal IE occasionally results in overwhelming septic pulmonary emboli, pyopneumothorax, and severe respiratory insufficiency.

Coagulase-Negative Staphylococci.

These are a major cause of PVE, particularly during the initial year after valve surgery, an important cause of nosocomial IE, and the cause of 3 to 8 percent of NVE cases, usually in the setting of prior valve abnormalities (see Tables 47-1 and 47-2 .[49] [50] The vast majority of coagulase-negative staphylococci causing PVE, when speciated, are *S. epidermidis.*[49] In contrast, when infection involves native valves, only 50 percent of isolates are *S. epidermidis.* [49] [50] *Staphylococcus lugdunensis,* a coagulase-negative species, has caused highly destructive, often fatal NVE and PVE.[53] *S. lugdunensis* IE is usually community acquired, and the organism is often susceptible to many

antistaphylococcal antibiotics, including penicillin.[53]

GRAM-NEGATIVE BACTERIA.

Organisms of the so-called HACEK group, which are part of the upper respiratory tract and oropharyngeal flora, infect abnormal cardiac valves, causing subacute NVE, and cause PVE that occurs a year or more after valve surgery.[54] in NVE, the HACEK organisms have been associated with large vegetations and a high incidence of systemic emboli.[54] These organisms are fastidious and slow growing; when they are suspected, blood cultures should be incubated for 3 weeks. *Haemophilus* species, primarily *H. aphrophilus* followed by *H. parainfluenzae* and *H. Influenzae,* account for 0.5 to 1.0 percent of all IE.

P. aeruginosa is the gram-negative bacillus that most commonly causes endocarditis. The proclivity of *P. aeruginosa,* as opposed to Enterobacteriaceae, to cause IE correlates with its resistance to the bactericidal activity of human sera and its adherence to cardiac valves and platelet-fibrin thrombi. Pseudomonal IE involves normal and abnormal valves on both sides of the heart and often causes valve destruction and heart failure.[54]

The Enterobacteriaceae, despite causing frequent episodes of bacteremia, are implicated in only sporadic cases of IE.

Neisseria gonorrhoeae, a common cause of IE during the preantibiotic era, rarely causes endocarditis today.[55] [56] Gonococci, similar to pneumococci, infect the aortic valve of young patients, resulting in valve destruction abscess formation, and a probable need for valve replacement.[53] [54] [55] [56] Penicillinase production and intrinsic resistance

to penicillin are common among gonococci; however, all strains remain susceptible to ceftriaxone.

OTHER ORGANISMS.

Corynebacterium species, often called diphtheroids, although often contaminants in blood cultures, cannot be ignored when isolated from multiple blood cultures. Prolonged incubation of blood cultures is often required to isolate these slow-growing, fastidious organisms from patients with IE. They are an important cause of PVE occurring during the initial year after valve surgery and a surprisingly common cause of endocarditis involving abnormal valves.[28] [56] [57] *Listeria monocytogenes,* a small gram-positive rod, causes occasional cases of IE involving abnormal left heart valves and prosthetic devices.[56] *Bartonella quintana, Bartonella elizabethae,* and *Bartonella henselae* have caused IE and can be isolated from blood cultures by prolonged incubation (2 weeks) followed by blind subculturing to fresh chocolate agar or sheep blood agar, which is in

turn incubated for 2 to 3 weeks in 5 to 8 percent carbon dioxide.[58] [59] In the absence of special efforts in culturing, or serologic testing, many cases would have been "culture negative."[15] [58] [59] *Tropheryma whippelii,* the cause of Whipple's disease, has caused a cryptic afebrile form of IE with associated arthralgias but without diarrhea. The diagnosis has been established by examination of valve tissue by polymerase chain reaction and by microscopic identification of the organism in periodic acid-Schiff (PAS) or silver-stained vegetations.[60]

The rickettsia *C. burnetii* infects humans after inhalation of desiccated materials from infected animals or contact with infected parturient animals. At variable intervals after acute infection by *C. burnetii* (Q fever), persons with abnormal mitral or aortic valves who have not been able to eradicate the organism develop subacute IE with typical manifestations and often with valve dysfunction causing heart failure.[14] The diagnosis is typically based on high IgG and IgA antibody titers to phase I *C. burnetii* antigens. The organism can be demonstrated in excised cardiac valves by immunohistological or Gimenez staining.[14] *Chlamydia psittaci,* the agent of psittacosis, has caused occasional episodes of subacute IE and has resulted in hemodynamically significant valve damage.

FUNGI.

Candida albicans, nonalbicans *Candida* species, *Torulopsis glabrata,* and *Aspergillus* species are the most common of the many fungal organisms identified as causing IE. Fungal endocarditis arises in specific settings. Valve replacement cardiac surgery and IV drug abuse are major predispositions. The most frequent fungi causing PVE are *C. albicans, Aspergillus* species, and nonalbicans *Candida* species, whereas addiction-associated fungal IE is most commonly caused by non*albicans Candida* species, particularly *C. parapsilosis.*[61] [62] [63] [64] Fungal IE resulting from prolonged IV antimicrobial therapy and parenteral alimentation is caused predominantly by *C. albicans* and *T. glabrata.* Patients who are severely immunodepressed occasionally experience IE caused by *Candida* species, *Aspergillus* species, or opportunistic mycelia fungi. Blood cultures frequently are positive when *Candida* species or *T. glabrata* causes IE but rarely yield organisms when IE is caused by mycelial organisms. Bulky vegetations, which embolize frequently, are common in fungal IE. Removal and careful microbiological evaluation of an embolic vegetation may provide an etiological diagnosis in fungal IE.[61] [62]

PATHOGENESIS

The interactions between the human host and selected microorganisms that culminate in IE involve the vascular endothelium, hemostatic mechanisms, the host immune system, gross anatomic abnormalities in the heart, surface properties of microorganisms, and peripheral events that initiate bacteremia. Each component of these interactions is in itself complex, influenced by many factors and not fully elucidated. The rarity of endocarditis and endarteritis in the presence of frequent transient asymptomatic and symptomatic bacteremia indicates that the intact endothelium is resistant to infection. Endothelial damage results in platelet-fibrin deposition, which in turn is more receptive to colonization by bacteria than is the intact endothelium. It is hypothesized that platelet-fibrin deposition occurs spontaneously in

persons vulnerable to endocarditis and that these deposits, called nonbacterial thrombotic endocarditis (NBTE), are the sites at which microorganisms adhere during bacteremia to initiate IE.[65] The relative uniformity of organisms causing IE, as contrasted with the variety of organisms causing overt and asymptomatic bacteremia, and the infectiousness of specific organisms in animal models of endocarditis indicate that certain microorganisms are advantaged in their ability to colonize and infect NBTE. The events after colonization that lead to IE entail survival and multiplication of microorganisms and the accrual of vegetation, as well as complex host-pathogen interactions.[66]

DEVELOPMENT OF NONBACTERIAL THROMBOTIC ENDOCARDITIS.

Two major mechanisms appear pivotal in the formation of NBTE: endothelial injury and a hypercoagulable state. NBTE has been found in 1.3 percent of patients at autopsy and is more common with increasing age. These lesions have also been noted frequently in patients with malignancy, disseminated intravascular coagulation, uremia, burns, systemic lupus erythematosus, valvular heart disease, and intracardiac catheters.[66] The platelet-thrombin deposits are found at the valve closure-contact line on the atrial surfaces of the mitral and tricuspid valves and on the ventricular surfaces of the aortic and pulmonic valves, the sites of infected vegetations in patients with IE.

Three hemodynamic circumstances may injure the endothelium, initiating NBTE: (1) a high-velocity jet impacting endothelium, (2) flow from a high- to a low-pressure chamber, and (3) flow across a narrow orifice at high velocity. Flow through a narrowed orifice, as a consequence of Venturi's effect, deposits bacteria maximally at the low-pressure sink immediately beyond an orifice or at the site where a jet stream impacts a surface. These are the same sites where NBTE forms as a result of hemodynamic circumstances. The superimposition of NBTE formation and preferential deposition of bacteria help to explain the distribution of infected vegetations. [67]

CONVERSION OF NBTE TO IE.

Bacteremia is the initiating event that ultimately converts NBTE to IE. The frequency and magnitude of bacteremia associated with daily activities and health care procedures appear related to specific mucosal surfaces and skin, the density of colonizing bacteria, the disease state of the surface, and the extent of the local trauma. Bacteremia rates are highest for events that traumatize the oral mucosa, particularly the gingiva, and progressively decrease with procedures involving the genitourinary tract and the gastrointestinal tract.[68] A diseased mucosal surface--particularly one that is infected--is associated with an increased risk of bacteremia.

Although IE develops when circulating microorganisms are deposited at a site of NBTE, the coincidence of bacteremia and NBTE does not uniformly result in IE. To cause IE, the organism must be able to persist and propagate on the endothelium. This requires resistance to host defenses. The complement-mediated bactericidal activity of serum limits the ability of susceptible aerobic gram-negative bacilli to cause IE. Only strains resistant to the bactericidal activity of serum, e.g., selected *E. coli, P. aeruginosa,* and *Serratia marcescens,* cause IE with significant frequency or are virulent in the rabbit

model of endocarditis.[66] The precise role of granulocytes in eradicating early colonizing organisms is not clear. Platelet-released microbicidal material has been shown to eliminate recently adherent, susceptible viridans streptococci from valves in experimental endocarditis, and the resistance of *S. aureus* to these peptides correlates with ability of strains to cause endocarditis in animal models as well as IE and intravascular infection in patients.[68] [69] [70] [71]

The adherence of microorganisms to the NBTE is a pivotal early event in the development of IE. Those organisms that most frequently cause endocarditis adhere more vigorously in vitro to cardiac valves than do organisms that rarely cause IE. Many mechanisms promote this adherence, including the surface carbohydrates of bacteria. Bacteremic steptococci that produce extracellular dextran cause endocarditis more frequently than do strains that do not produce dextran. Dextran on the surface of streptococci can be shown to mediate adherence to platelet fibrin lattices and injured valves. Dextran production, however, is not universal among the major microbial causes of IE; thus, other mechanisms of adherence are likely.

Fibronectin has been identified as an important factor in this process. Fibronectin has been identified in lesions on heart valves and is produced by endothelial cells, platelets, and fibroblasts in response to vascular injury; a soluble form binds to exposed subendothelial collagen. Receptors for fibronectin are present on the surface of *S. aureus;* viridans streptococci; groups A, C, and G streptococci; enterococci;

S. pneumoniae; and *C. albicans.* Fibronectin has numerous binding domains and thus can bind simultaneously to fibrin, collagen, cells, and microorganisms and can serve to facilitate adherence of bacteria to the valve at the site of injury or NBTE. Clumping factor (or fibrinogen-binding surface protein) of *S. aureus* also mediates the binding of these organisms to platelet fibrin thrombin and to aortic valves in models of endocarditis.[72] The glycocalyx or slime on the surface of *S. epidermidis* does not appear to function as an adhesin but may render organisms more virulent by virtue of enhancing their ability to avoid eradication by host defenses.[73]

The mechanism by which virulent organisms colonize and infect intact valvular endothelium is less clearly understood. Endothelial cells in monolayers in vitro can phagocytize *S. aureus* and *Candida.* Multiplication of the organism intracellularly results in cell death, which in turn disrupts the endothelial surface and initiates formation of platelet-fibrin deposits. Alternatively, fibronectin may facilitate the adherence of *S. aureus* to intact endothelium.

After adherence to the NBTE or endothelium, persistence and multiplication result in a complex dynamic process during which the infected vegetation increases in size by platelet-fibrin aggregation, microorganisms are shed into the blood, and vegetation fragments embolize. Staphylococci and streptococci promote platelet aggregation and growth of the vegetation. Surface antigens that promote platelet adhesion (class I

antigen) and aggregation (class II antigen that functionally mimics a platelet interactive domain of collagen) are expressed by *S. aureus.* Strains of *S. sanguis* with the aggregation antigen cause more severe endocarditis in the rabbit model than do antigen-negative strains.[74] Fibrin deposition is enhanced by tissue factor (a tissue thromboplastin that binds to factor VII) elaborated by endothelial cells, fibroblasts, or monocytes interacting with bacteria.[75] The persistence of this cycle results in the clinical syndrome of IE.

PATHOPHYSIOLOGY

Aside from the constitutional symptoms of infection, which are likely mediated by cytokines, the clinical manifestations of IE result from (1) the local destructive effects of intracardiac infection; (2) the embolization of bland or septic fragments of vegetations to distant sites, resulting in infarction or infection; (3) the hematogenous seeding of remote sites during continuous bacteremia; and (4) an antibody response to the infecting organism with subsequent tissue injury due to deposition of preformed immune complexes or antibody-complement interaction with antigens deposited in tissues.

The intracardiac consequences of IE range from trivial, characterized by an infected vegetation with no attendant tissue damage, to catastrophic, when infection is locally destructive or extends beyond the valve leaflet. Distortion or perforation of valve leaflets, rupture of chordae tendineae, and perforations or fistulas between major vessels and cardiac chambers or between chambers themselves as a consequence of burrowing infection may result in CHF that is progressive (Fig. 47-3) .[76] [77] Infection, particularly that involving the aortic valve or prosthetic valves, may extend into paravalvular tissue and result in abscesses and persistent fever due to antibiotic-unresponsive infection, disruption of the conduction system with electrocardiographic conduction abnormalities and clinically relevant arrhythmias, or purulent pericarditis.[78] Large vegetations, particularly at the mitral valve, can result in functional valvular stenosis and hemodynamic deterioration.[28] [79] In general, intracardiac complications involving the aortic valve evolve more rapidly than those associated with the mitral valve; nevertheless, the progression is highly variable and unpredictable in individual patients.

Embolization of fragments from vegetations is clinically evident in 11 to 43 percent of patients.[9] [67] [80] [81] However, pathologic evidence of emboli at autopsy is found more frequently (45 to 65 percent). Emboli from left-sided IE produce symptoms by infection or infarction at the site of lodgment. Although not demonstrated in all studies, pooled data suggest that larger vegetations (>10 mm) are associated with a higher frequency of emboli, as are hypermobile vegetations and those attached to the mitral valve, particularly the anterior leaflet.[82] [83] Pulmonary emboli, which are often

Figure 47-3 A normal valve with a large, bulky vegetation caused by *Staphylococcus aureus* infection. Clot is present centrally in the vegetation, obscuring a valve fenestration.

septic, occur in 66 to 75 percent of IV drug abusers with tricuspid valve IE (Fig. 47-4) .[16] [18]

The persistent bacteremia of IE, with or without septic emboli, may result in metastatic infection. These infections may present as local signs and symptoms or as persistent fever during therapy.[78] [84] IE caused by virulent organisms, particularly *S. aureus* or beta-hemolytic streptococci, is complicated more frequently by metastatic infection than is that due to avirulent bacteria, e.g., viridans streptococci. Virtually any organ or tissue may be hematogenously infected. Metastatic abscesses are often small and miliary. Metastatic infection assumes particular importance when the required therapy is more than the antibiotics indicated for IE or when these infections constitute a focus that engenders relapse.[84]

The humoral and cell-mediated arms of the immune system are stimulated in patients with IE. Antibodies to the infecting organism in the three major classes--IgM, IgG, and IgA--with functional capacity including opsonization, agglutination, and complement fixation have been noted. Additionally, hypergammaglobulinemia and cryoglobulinemia have been noted. Cellular responses are suggested by activated circulating macrophages and splenomegaly.

Circulating immune complexes in high titer have been detected in most patients with bacteremic IE and PVE. The frequency and titer of the circulating immune complexes are highest in IE of long duration, in the presence of extravalvular manifestation, and in right-sided IE. Although circulating immune complex titers fall with effective antibiotic therapy, titers are not widely used to monitor therapy. Immune complexes are clinically relevant when, with complement, they deposit

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Figure 47-4 Infiltrates in the right and left midlung fields caused by septic pulmonary emboli arising from *Staphylococcus aureus* tricuspid valve infective endocarditis in an intravenous drug abuser.

subepithelially along the glomerular basement membrane to cause diffuse or focal glomerulonephritis.[67] Histological examination of affected glomeruli stained with fluorescent-labeled antibody to human globulin reveals a "lumpy-bumpy" pattern. The immunoglobulin eluted from the glomerular lesions reacts with bacterial antigens. Rheumatological manifestations of IE and some peripheral manifestations of IE, such as Osler's nodes, have been attributed to local deposition of immune complexes.[67] Osler's nodes, however, have also been associated with septic embolization in *S. aureus* IE.

Rheumatoid factor (an IgM antibody directed against IgG) is present in half of the patients with IE of greater than 6 weeks' duration.[67] The titer of rheumatoid factor decreases slowly with effective antimicrobial therapy.

CLINICAL FEATURES

The interval between the presumed initiating bacteremia and the onset of symptoms of IE is estimated to be less than 2 weeks in more than 80 percent of patients with NVE. Interestingly, in some patients with intraoperative or perioperative infection of prosthetic valves, the incubation period may be prolonged (2 to 5 or more months).[28]

Fever is the most common symptom and sign in patients with IE (Table 47-4) . Fever may be absent or minimal in the elderly or in those with CHF, severe debility, or chronic renal failure and occasionally in patients with NVE caused by coagulase-negative staphylococci.[50] [85]

Heart murmurs are noted in 80 to 85 percent of patients with NVE and are emblematic of the lesion predisposing to IE. Murmurs are commonly not audible in patients with tricuspid valve IE. Similarly, in acute NVE due to *S. aureus,* murmurs are heard in only 30 to 45 percent of patients on initial evaluation but are ultimately noted in 75 to 85 percent. The new or changing murmurs (alterations unrelated to heart rate or cardiac output but rather regurgitant murmurs indicative of valve dysfunction) are relatively infrequent

TABLE 47-4 -- CLINICAL FEATURES OF INFECTIVE ENDOCARDITIS

SYMPTOMS	PERCENT	SIGNS	PERCENT
Fever	80-85	Fever	80-90
Chills	42-75	Murmur	80-85
Sweats	25	Changing/new murmur	10-40
Anorexia	25-55		
Weight loss	25-35	Neurological abnormalities	30-40
Malaise	25-40		
Dyspnea	20-40	Embolic event	20-40
Cough	25	Splenomegaly	15-50
Stroke	13-20	Clubbing	10-20
Headache	15-40	Peripheral manifestation	
Nausea/vomiting	15-20		
Myalgia/arthralgia	15-30	Osler's nodes	7-10
Chest pain*	8-35	Splinter hemorrhage	5-15
Abdominal pain	5-15		
Back pain	7-10	Petechiae	10-40
Confusion	10-20	Janeway's lesion	6-10
		Retinal lesion/Roth's spots	4-10

Central nervous system.
*More common in intravenous drug abusers.

in subacute NVE and are more prevalent in acute IE and PVE.[28] [86] They frequently are important harbingers of CHF.

Enlargement of the spleen is noted in 15 to 50 percent of patients and is more common in subacute IE of long duration.

The classical peripheral manifestations of IE are encountered less frequently today and are absent in IE restricted to the tricuspid valve.[4] [16] *Petechiae* (Fig. 47-5) , the most common of these manifestations, are found on the palpebral conjunctiva, the buccal and palatal mucosa, and the extremities. They are not specific for endocarditis even on the conjunctiva. *Splinter or subungual hemorrhages* (Fig. 47-6) are dark red, linear, or occasionally flame-shaped streaks in the nail bed of the fingers or toes. Distal lesions are likely due to trauma, whereas the more proximal ones are more likely related to IE. *Osler's nodes* are small, tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persist for hours to several days. These too are not pathognomonic for

Figure 47-5 Conjunctival petechiae in a patient with infective endocarditis. *(From Kaye D: Infective Endocarditis. Baltimore, University Park Press, 1976.)*

Figure 47-6 Subungual hemorrhages (splinter hemorrhages) and digital petechiae in a patient with infective endocarditis.*(From Korzeniowski OM, Kaye D: Infective endocarditis. In Braunwald E [ed]: Heart Disease. 4th ed. Philadelphia, WB Saunders, 1992.)*

IE. [86] Janeway's lesions are small erythematous or hemorrhagic macular nontender lesions on the palms and soles and are the consequence of septic embolic events. Roth's spots (Fig. 47-7) , oval retinal hemorrhages with pale centers, are infrequent findings in patients with IE. They have been noted in patients with collagen vascular disease and hematologic disorders, including severe anemia.

Musculoskeletal symptoms, unrelated to focal infection, are relatively common in patients with IE. These include arthralgias and myalgias, occasional true arthritis with nondiagnostic but inflammatory synovial fluid findings, and prominent back pain without evidence of vertebral body, disc space, or sacroiliac joint infection.[86] In patients with arthritis or back pain, focal infection must be precluded because additional therapy may

be required.

Systemic emboli are among the most common clinical sequelae of IE, occurring in up to 40 percent of patients, and are frequent subclinical events found only at autopsy.[9] [67] [80] [81] Emboli often antedate diagnosis. Although embolic events may occur during or after antimicrobial therapy, the incidence decreases promptly during administration of effective

Figure 47-7 Roth spot (retinal hemorrhage with a clear center) in a patient with infective endocarditis.*(From Korzeniowski OM, Kaye D: Infective endocarditis. In Braunwald E [ed]: Heart Disease. 4th ed. Philadelphia, WB Saunders, 1992.)*

antibiotic therapy.[85] [87] Embolic splenic infarction may cause left upper quadrant abdominal pain and left shoulder pain. Renal emboli may occur asymptomatically or with flank pain and may cause gross or microscopic hematuria. Embolic stroke syndromes, predominantly involving the middle cerebral artery territory, occur in 15 to 20 percent of patients with NVE and PVE.[28] [88] Coronary artery emboli are common findings at autopsy but rarely result in transmural infarction. Emboli to the extremities may produce pain and overt ischemia, and those to mesenteric arteries may cause abdominal pain, ileus, and guaiac-positive stools.

Neurological symptoms and signs occur in 30 to 40 percent of patients with IE, are more frequent when IE is caused by *S. aureus,* and are associated with increased mortality rates.[80] [86] [89] [90] Embolic stroke is the most common and clinically important of the neurological manifestations. Intracranial hemorrhage occurs in 5 percent of patients with IE. Bleeding results from rupture of a mycotic aneurysm, rupture of an artery due to septic arteritis at the site of embolic occlusion, or hemorrhage into an infarct.[91] Mycotic aneurysms, with or without rupture, occur in 2 to 10 percent of patients with IE; approximately half of these involve intracranial arteries (Fig. 47-8) . Cerebritis with microabscesses complicates IE caused by invasive pathogens such as *S. aureus,* but large brain abscesses are rare.[88] Purulent meningitis complicates some episodes of IE caused by *S. aureus* or *S. pneumoniae,* but more typically the cerebrospinal fluid has an aseptic profile.[43] [89] Other neurological manifestations include severe headache (a potential clue to a mycotic aneurysm), seizure, and encephalopathy.

CHF complicating IE is primarily the result of valve destruction or distortion or rupture of chordae tendineae. Intracardiac fistulas, myocarditis, or coronary artery embolization may occasionally contribute to the genesis of CHF, as obviously can underlying cardiac disease. In the absence of surgery to correct valvular dysfunction, CHF, particularly that due to aortic insufficiency, is associated with very high mortality rates.[76]

Renal insufficiency as a result of immune complex-mediated glomerulonephritis occurs in less than 15 percent of patients with IE. Azotemia as a result of this process may develop or progress during initial therapy; it usually improves

Figure 47-8 An irregular mycotic aneurysm of the middle cerebral artery lies laterally on the cerebral cortex. A second aneurysm is projected just lateral to the anterior cerebral artery.

with continued administration of effective antibiotic therapy.[86] Focal glomerulonephritis and embolic renal infarcts cause hematuria but rarely result in azotemia. Renal dysfunction in patients with IE is most commonly a manifestation of impaired hemodynamics or toxicities associated with antimicrobial therapy (interstitial nephritis or aminoglycoside-induced injury).

DIAGNOSIS

The symptoms and signs of endocarditis are often constitutional and, when localized, often result from a complication of IE rather than reflect the intracardiac infection itself (see Table 47-4) . Consequently, if physicians are to avoid overlooking the diagnosis of IE, a high index of suspicion must be maintained. The diagnosis must be investigated when patients with fever present with one or more of the cardinal elements of IE: a predisposing cardiac lesion or behavior pattern, bacteremia, embolic phenomenon, and evidence of an active endocardial process. Because patients with prosthetic heart valves are always at risk for PVE, the presence of fever or new prosthesis dysfunction at any time warrants considering this diagnosis. In patients at risk for endocarditis, concurrent illnesses or iatrogenic events may create clusters of symptoms and signs that superficially mimic IE and require careful consideration to arrive at a correct diagnosis. Even when the illness seems typical of endocarditis, the definitive diagnosis requires positive blood cultures or positive cultures (or histology or polymerase chain reaction recovery of a microorganism's DNA) from the vegetation or embolus. There are many culture-negative mimics of IE: atrial myxoma, acute rheumatic fever, systemic lupus erythematosus or other collagen-vascular disease, marantic endocarditis, the antiphospholipid syndrome, carcinoid syndrome, renal cell carcinoma with increased cardiac output, and thrombotic thrombocytopenic purpura.

When used judiciously over the entire evaluation sequence, i.e., not limited to initial findings, published criteria provide a sensitive and specific approach to the diagnosis of IE (Table 47-5) .[92] [94] Erroneous rejection of the diagnosis of endocarditis is unlikely. When using these diagnostic criteria to guide therapy, patients who are categorized with possible endocarditis should be treated as if they have IE. This management philosophy, however, may lead to the treatment of individuals as possible IE patients who are not likely to have the infection.[96] Requiring at least one major criterion or three minor criteria to designate possible endocarditis may reduce this potential for overdiagnosis.[94]

To use bacteremia due to coagulase-negative staphylococci or diphtheroids (organisms that may cause IE but more often contaminate blood cultures) to support the diagnosis of endocarditis, blood cultures must be persistently positive or the organisms recovered

in several sporadically positive cultures must be proved to represent a single clone.[92]

Inclusion of echocardiographic evidence of endocardial infection in these criteria recognizes the high sensitivity of two-dimensional echocardiography with color Doppler, especially if multiplanar TEE and TTE are combined, and the relative infrequency of false-positive studies when experienced operators use specific definitions for vegetations.[94] [97] [98] Although the sensitivity of TEE to detect vegetations in patients with suspected infective endocarditis is 82 to 94 percent (or higher if a follow-up study is performed), a negative study result does not preclude the diagnosis or the need for therapy if the clinical suspicion is high.[98] The likelihood of a false-negative result can be reduced to 5 to 10 percent if TEE is repeated, especially if the study is biplanar or multiplanar.[94] [98] Thus, these studies help to preclude the diagnosis when the clinical suspicion is

TABLE 47-5 -- DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Definitive Infective Endocarditis
Pathological criteria
Microorganisms: demonstrated by culture or histology in a vegetation, *or* in a vegetation that has embolized, *or* in an intracardiac abscess, *or*
Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
Clinical criteria, using specific definitions listed below
Two major criteria, *or*
One major and three minor criteria, *or*
Five minor criteria
Possible Infective Endocarditis
Findings consistent with infective endocarditis that fall short of definite endocarditis but are not rejected
Rejected
Firm alternative diagnosis for manifestations of endocarditis, *or*
Sustained resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*
No pathological evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less
Criteria for Diagnosis of Infective Endocarditis
Major Criteria
Positive blood culture
Typical microorganism for infective endocarditis from two separate blood cultures
Viridans streptococci, *Streptococcus bovis,* HACEK group *or*

Community-acquired *Staphylococcus aureus* or enterococci in the absence of a primary focus, *or*

Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

Blood cultures drawn more than 12 hr apart, *or*

All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart

Evidence of endocardial involvement

Positive echocardiogram

Oscillating intracardiac mass, on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomical explanation, *or*

Abscess, *or*

New partial dehiscence of prosthetic valve, *or*

New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

Predisposition: predisposing heart condition *or* intravenous drug use

Fever
38.0°C (100.4°F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions

Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

Microbiological evidence: positive blood culture but not meeting major criterion as noted previously* *or* serologic evidence of active infection with organism consistent with infective endocarditis

Echocardiogram: consistent with infective endocarditis but not meeting major criterion

Adapted from Durack DT, Lukes AS, Bright DK: New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Am J Med 96:200, 1994.

*Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

low. [94] [98] Nevertheless, when the clinical suspicion is high, even these highly sensitive tests cannot preclude the diagnosis. These guidelines are vulnerable to misidentifying

as culture-negative IE the vegetations that complicate marasmus, malignancy, cryptic collagen-vascular disease, or the antiphospholipid antibody syndrome.

A microbial cause of IE is established by recovering the infecting agent from the blood or by identifying it in surgically removed vegetations or embolic material. In detecting the bacteremia of IE there is no advantage to obtaining blood cultures in relationship to fever nor from arterial blood (as opposed to venous blood). In patients who have not received prior antibiotics and who will ultimately have blood culture-positive IE, it is likely that 95 to 100 percent of all cultures obtained will be positive and that one of the first two cultures will be positive in at least 98 percent of patients. Prior antibiotic therapy is a major cause of blood culture-negative IE, particularly when the causative microorganism is highly antibiotic susceptible. At least 35 percent of cases of culture-negative IE can be attributed to prior antimicrobial therapy.[99] After subtherapeutic antibiotic exposure, the time required for reversion to positive cultures is directly related to the duration of antimicrobial therapy and the susceptibility of the causative agent; days to a week or more may be required.

OBTAINING BLOOD CULTURES.

Three separate sets of blood cultures, each from a separate venipuncture, obtained over 24 hours, are recommended to evaluate patients with suspected endocarditis.[94] Each set should include two flasks, one containing an aerobic medium and the other containing thioglycollate broth (anaerobic medium) into which at least 10 ml of blood should be placed. For optimal processing, the laboratory should be advised that endocarditis is a possible diagnosis and which, if any, unusual bacteria are suspected (*Legionella* species, *Bartonella* species, HACEK organisms). If a clinically stable patient has received an antimicrobial agent during the past several weeks, it is prudent to delay therapy so that repeat cultures can be obtained on successive days. If fungal endocarditis is suspected, blood cultures should be obtained using the lysis-centrifugation method. The laboratory should be asked to save the organism causing endocarditis until successful therapy has been completed. Serologic tests are occasionally used to make the presumptive etiological diagnosis of endocarditis caused by *Brucella* species, *Legionella* species, *Bartonella* species, *C. burnetii,* or *Chlamydia* species. By special techniques, including polymerase chain reaction, these agents and others that are difficult to recover in blood culture can be identified in or recovered from blood or vegetations.[14] [58] [59] [60] [94] [100] [101]

Laboratory Tests

Many other tests are inevitably performed in the evaluation of patients with suspected IE.[102] Hematological parameters are commonly abnormal. Anemia, with normochromic normocytic red blood cell indices, a low serum iron level, and low serum iron-binding capacity, is found in 70 to 90 percent of patients. Anemia worsens with increased duration of illness and thus in acute IE may be absent. In subacute IE, the white blood cell count is usually normal; in contrast, a leukocytosis with increased segmented granulocytes is common in acute IE. Thrombocytopenia occurs only rarely.

The *erythrocyte sedimentation rate* (ESR) is elevated (average approximately 55 mm/hr)

in almost all patients with IE; the exceptions are those with CHF, renal failure, or disseminated intravascular coagulation. Other tests often indicate immune stimulation or inflammation (see Pathophysiology): circulating immune complexes, rheumatoid factor, quantitative immune globulin determinations, cryoglobulins, and C-reactive protein. Although the results of these tests parallel disease activity, the tests are costly and not efficient ways to diagnose IE or monitor response to therapy. Measurement of circulating immune complexes and complement may be useful in evaluating for azotemia due to diffuse immune complex glomerulonephritis.[102]

The *urinalysis* result is often abnormal, even when renal function remains normal. Proteinuria and microscopic hematuria are noted in 50 percent of patients. Urinalysis has a standard role in the evaluation of azotemia.

Serological tests are used to evaluate blood culture-negative IE (see Diagnosis). The presence or absence of antibodies to ribitol teichoic acids from staphylococci does not distinguish uncomplicated *S. aureus* bacteremia from that associated with IE or other deep-seated infection.

Echocardiography (See also Chap. 7)

Evaluation of patients with clinically suspected IE by this technique frequently allows morphological confirmation of infection and increasingly aids in decisions about management.[97] [98] Echocardiography should not be used as a screening test for IE in unselected patients with positive blood cultures or in patients with fevers of unknown origin when the clinical probability is low.[94] [95] Nevertheless, echocardiographic evaluation should be performed in all patients with clinically suspected IE, including those with negative blood cultures.[94] Although many patients with NVE involving the aortic or mitral valve can be imaged adequately by TEE using biplane or multiplane technology with incorporated color flow and continuous as well as pulsed Doppler is the state of the art.[94] [99] [103] TEE allows visualization of smaller vegetations and provides improved resolution compared with TTE. Not only is TEE the preferred approach in patients with clinically suspected IE in whom TTE is suboptimal, it is also the procedure of choice for imaging the pulmonic valve, patients with PVE (especially at the mitral site), and patients who are at high risk for intracardiac complications or those with signs of persistent or invasive infection despite adequate antimicrobial therapy.[94] [97] [103] [104] [105]

A decision analysis evaluation of echocardiography for diagnosis of IE involving native valves suggests that, assuming the diagnostic enhancement of TEE over TTE is 15 percent, the most cost-effective strategy (yielding optional quality adjusted life years) is 1) if prior probability of IE is less than 2 percent, treat for bacteremia without echocardiography; 2) if prior probability is 2 to 4 percent, use TTE; 3) if prior probability is 5 to 45 percent, use TEE in lieu of TTE, which would be followed by TEE if negative. If the prior probability of IE is greater than 45 percent, therapy without echocardiography is cost effective, although studies may still be desirable to evaluate for complications and other risks.[105A]

The sensitivity of TTE for the detection of vegetations in NVE is less than 65 percent,

although its specificity is excellent. In contrast, in proven NVE, the sensitivity for vegetation detection of TEE was 100 and 90 percent, and in clinically suspected NVE, it ranged from 82 to 94 percent (see Diagnosis).[98] In patients with PVE, TTE is limited by the shadowing effect of mitral valve prostheses. The sensitivity of TEE for detecting vegetations in PVE involving mechanical or bioprosthetic devices ranged from 82 to 96 percent, whereas that of TTE was from 36 to 16 percent.[104] [105] [106]

Despite the sensitivity of TEE in detecting vegetations in patients with proven IE, echocardiography does not itself provide a definite diagnosis. Vegetations and valve dysfunction may be demonstrated, but determination of causality requires clinical or direct anatomical and microbiological confirmation. Infectious vegetations cannot be distinguished from marantic lesions, nor can vegetations be distinguished from thrombus or pannus on prostheses. Furthermore, it is usually not possible to distinguish active from healed vegetations in NVE.[97] [107] Thickened valves, ruptured chordae or valves, valve calcification, and nodules may be mistaken for vegetations, indicating the specificity limitations of echocardiography.[97]

Valve dysfunction due to tissue disruption or large obstructing vegetations can be visualized and quantitated by echocardiogram with Doppler.[82] [97] Some degree of regurgitation by Doppler is almost universal early in the course of NVE and PVE and does not necessarily predict subsequent hemodynamic deterioration.[97] Extension of infection beyond the valve leaflet into surrounding tissue is an ominous step in the progression of IE. It can result in abscesses in various areas of the annulus or adjacent structures, mycotic aneurysms of the sinus of Valsalva or mitral valve, intracardiac fistulas, and purulent pericarditis. Myocardial abscesses are more readily detected by TEE than TTE in patients with NVE or PVE.[104] [105] [106] The sensitivity and specificity for abscess detection were 28 percent and 98 percent for TTE, compared with 87 percent and 95 percent for TEE. Other studies have reported similar findings, especially in recognizing subaortic invasive disease.[108]

The natural history of vegetations during therapy is variable. On repeat echocardiogram 3 weeks to 3 months after initiation of ultimately effective antimicrobial therapy, 29 percent of 41 initial vegetations were no longer detectable. Of the 29 vegetations that remained detectable, 58 percent were unchanged, 24 percent were smaller, and 17 percent were larger. Mobility and extent (valves involved) of vegetations were unchanged in 86 and 65 percent, respectively. The evolution of these vegetations was not related to the duration of therapy or initial vegetation size, nor did it predict late complications of IE.[107] [108] In another study among patients, not all of whom were responding to therapy, persistence or increase in vegetation size during therapy was associated with an increased rate of complications. Accordingly, changes in vegetations must be interpreted in a clinical context and do not in themselves reflect the efficacy of therapy.

Stratification of patients into groups that are at high and low risk for CHF, systemic embolization, need for surgical intervention, and death based on the presence or

absence of vegetations remains controversial.[82] [94] [97] The heterogeneous nature of the patients examined, the technologies used, and the lack of correlation with other features of IE, as well as the increasing ability to visualize vegetations in most patients with IE using TEE, undermine this debate. Although not demonstrated in all individual studies, pooled data from two-dimensional echocardiographic studies suggest that patients with larger vegetations (>10 mm in diameter) are at increased risk for embolic complications (20 percent versus 40 percent).[82] [97] This increased risk appears to be associated with large vegetations involving the mitral valve, particularly the anterior leaflet, and with the mobility of vegetations.[94] [97] The correlation of aortic or mitral valve vegetation size, extent, mobility, and site with CHF, need for surgical intervention, and mortality (other than that associated with embolic events) has not been fully established.[94] [97]

Among patients with right-sided IE, visualization of vegetations by TTE has been correlated with prolonged fever during therapy and increased right ventricular end-diastolic dimensions. These findings were not related to vegetation size, nor did the presence of vegetations or their size predict the failure of medical therapy and a need for surgical intervention.

MAGNETIC RESONANCE IMAGING.

This technique has identified paravalvular extension of infection, aortic root aneurysms, and fistulas; however, its utility relative to echocardiography has not been established.

SCINTIGRAPHY.

Efforts to identify vegetations and intracardiac abscess in patients with IE and in animal models have used scintigraphy with gallium-67 citrate, indium-111-labeled granulocytes, and indium-111-labeled platelets. These efforts have not been sufficiently sensitive or anatomically localizing to be useful clinically.[109]

TREATMENT

Two major objectives must be achieved to treat IE effectively. The infecting microorganism in the vegetation must be eradicated. Failure to accomplish this results in relapse of infection. Also, invasive, destructive intracardiac and focal extracardiac complications of infection must be resolved if morbidity and mortality are to be minimized. The second objective often exceeds the capacity of effective antimicrobial therapy and requires cardiac or other surgical intervention.

Bacteria in vegetations multiply to population densities approaching 10^{9} to 10^{10} organisms per gram of tissue, become metabolically dormant, and are difficult to eradicate. Clinical experience and animal model experiments suggest that optimal therapy should use bactericidal antibiotics or antibiotic combinations rather than bacteriostatic agents. Additionally, antibiotics reach the central areas of avascular vegetations by passive diffusion. To reach effective antibiotic concentrations in vegetations, high serum concentrations must be achieved, and penetration by some agents is limited even then. Parenteral antimicrobial therapy is used whenever feasible

in order to achieve suitable serum antibiotic concentrations and to avoid the potentially erratic absorption of orally administered therapy. Treatment is continued for prolonged periods to ensure eradication of dormant microorganisms.

In selecting antimicrobial therapy for patients with IE, one must consider the ability of potential agents to kill the causative organism as well as the MIC and minimum bactericidal concentration (MBC) of these antibiotics for the organism. The MIC is the lowest concentration that inhibits growth, and the MBC is the lowest concentration that decreases a standard inoculum of organisms 99.9 percent during 24 hours. For the vast majority of streptococci and staphylococci, the MIC and MBC of penicillins, cephalosporins, or vancomycin are the same or differ by only a factor of two to four. Organisms for which the MBC for these antibiotics is 10-fold or greater than the MIC are occasionally encountered. This phenomenon has been termed *tolerance.*[110] Most of the tolerant strains are simply killed more slowly than nontolerant strains, and with prolonged incubation (48 hours) their MICs and MBCs are similar. Enterococci exhibit what superficially appears to be tolerance when tested against penicillins and vancomycin; however, these organisms are, in fact, not killed by these agents but are merely inhibited, even after longer incubation times. Enterococci can be killed by the combined activity of selected penicillins or vancomycin and an aminoglycoside. This enhanced antibiotic activity of the combination against enterococci, if of sufficient magnitude, is called *synergy* or a *synergistic bactericidal* effect.[45] [110] A similar effect can be seen with these combinations against streptococci and staphylococci; this effect overcomes tolerance.[110]

A synergistic bactericidal effect is required for optimal therapy of enterococcal endocarditis and has been used to achieve more effective therapy or effective short-course therapy of IE caused by other organisms. Tolerance in streptococci or staphylococci has been associated with reduced eradication of organisms from vegetations in animal model experiments.[111] [112] However, this finding in organisms causing endocarditis has not been correlated with decreased cure rates or delayed responses to treatment with penicillins, cephalosporins, or vancomycin. Accordingly, the presence of tolerance in streptococci or staphylococci has not required combination therapy, and, in fact, regimens are designed using the MICs of these organisms.[113]

The regimens recommended for the treatment of IE caused by specific organisms are designed to provide high concentrations of antibiotics in serum, also deep in vegetations. Concentrations that exceed the organism's MIC throughout most, if not all, of the interval between doses are recommended. Although antibiotic concentrations in vegetations of patients with IE have been measured infrequently, the success of the recommended regimens suggests that this goal has been achieved. Accordingly, for optimal therapy, it is important that the recommended regimens be followed carefully.

Antimicrobial Therapy for Specific Organisms

The antimicrobial therapy for endocarditis should not only eradicate the causative agent but should do so while causing little or no toxicity. Therapy for a given patient requires

modification to accommodate end-organ dysfunction, existing allergies, and other anticipated toxicities. With the exception of staphylococcal endocarditis, the antimicrobial regimens recommended for the treatment of NVE and PVE are similar, although more prolonged treatment is often advised for PVE.[28] [113]

PENICILLIN-SUSCEPTIBLE VIRIDANS STREPTOCOCCI OR *STREPTOCOCCUS BOVIS.*

Four regimens provide highly effective, comparable therapy for patients with endocarditis caused by penicillin-susceptible

TABLE 47-6 -- TREATMENT FOR NATIVE VALVE ENDOCARDITIS DUE TO PENICILLIN-SUSCEPTIBLE VIRIDANS STREPTOCOCCI AND *STREPTOCOCCUS BOVIS* (MINIMUM INHIBITORY CONCENTRATION 0.1 mug/ml)*

ANTIBIOTIC	DOSAGE AND ROUTE	DURATION (WK)
Aqueous penicillin G	12-18 million units/24 hr IV either continuously or every 4 hr in six equally divided doses	4
Ceftriaxone	2 gm once daily IV or IM	4
Aqueous penicillin G	12-18 million units/24 hr IV either continuously or every 4 hr in six equally divided doses	2
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	2
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*For nutritionally variant streptococci (*Streptococcus adjacens, Streptococcus defectivus*), see Table 47-8 .

Dosages given are for patients with normal renal function. Vancomycin and gentamicin doses must be reduced for treatment of patients with renal dysfunction. Vancomycin and gentamicin doses are calculated using ideal body weight (men=50 kg+2.3 kg per inch over 5 feet; women=45.5 kg+2.3 kg per inch over 5 feet).

TABLE 47-7 -- TREATMENT FOR NATIVE VALVE ENDOCARDITIS DUE TO STRAINS OF VIRIDANS STREPTOCOCCI AND *STREPTOCOCCUS BOVIS* RELATIVELY RESISTANT TO PENICILLIN G (MINIMUM INHIBITORY CONCENTRATION >0.1 mug/ml AND <0.5 mug/ml)

ANTIBIOTIC	DOSAGE AND ROUTE*	DURATION (WK)
Aqueous penicillin G	18 million units/24 hr IV either continuously or every 4 hr in 6 equally divided doses	4
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	2
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*Dosages are for patients with normal renal function. See Table 47-6 , footnote.

streptococci and *S. bovis* (Table 47-6) . The 4-week regimens yield bacteriologic cure rates of 98 percent among patients who complete therapy. Treatment with the synergistic combination of penicillin plus gentamicin for 2 weeks is as effective in selected cases as treatment with the 4-week regimens. The combination regimen is recommended for patients who have uncomplicated native valve endocarditis and who are not at increased risk for aminoglycoside toxicity. Patients with endocarditis caused by nutritionally variant streptococci, endocarditis involving a prosthetic valve, or endocarditis complicated by a mycotic aneurysm, myocardial abscess, perivalvular infection, or an extracardiac focus of infection should not be treated with this short-course regimen. From 2 to 8 percent of viridans streptococci and *S. bovis* causing endocarditis are highly resistant to streptomycin (MIC >2000 mug/ml) and are not killed synergistically by penicillin plus streptomycin. These highly streptomycin-resistant strains are, however, killed synergistically by penicillin plus gentamicin. Consequently, unless a causative streptococcus can be evaluated to preclude high-level resistance to streptomycin, gentamicin is recommended for use in the short-course combination regimen.[114] Ceftriaxone 2 gm once daily plus either gentamicin (3 mg/kg) or netilmicin (4 mg/kg) given as a single daily dose for 14 days has effectively treated endocarditis caused by penicillin-susceptible streptococci.[115] [116] Nevertheless, experience with single daily doses of aminoglycosides in the treatment of IE is limited, and these regimens are not currently recommended. The *Abiotrophia* species, previously called nutritionally variant streptococci, *S. adjacens* and *S. defectivus,* are generally more resistant to penicillin than are other viridans streptococci.[39] Patients with endocarditis caused by these organisms are treated with regimens recommended for enterococcal endocarditis (see Table 47-8) ; however, outcome remains unsatisfactory.

For the treatment of streptococcal endocarditis in patients with a history of immediate allergic reactions (urticarial or anaphylactic reactions) to a penicillin or cephalosporin antibiotic, vancomycin is recommended (see Table 47-6) . Patients with other forms of penicillin allergy (delayed maculopapular skin rash) may be treated cautiously with the ceftriaxone regimen (see Table 47-6) or with cefazolin, 2 gm IV every 8 hours for 4 weeks.

For patients with PVE caused by penicillin-susceptible streptococci, treatment with 6 weeks of penicillin is recommended, with gentamicin given during the initial 2 weeks.[28]

RELATIVELY PENICILLIN-RESISTANT STREPTOCOCCI.

Four weeks of high-dose parenteral penicillin plus an aminoglycoside (primarily gentamicin for the reasons noted previously) during the initial 2 weeks is recommended for treatment of patients with endocarditis caused by streptococci with MICs for penicillin between 0.2 and 0.5 mug/ml (Table 47-7) . Patients who cannot tolerate penicillin because of immediate hypersensitivity reactions can be treated with vancomycin alone. For those with nonimmediate penicillin hypersensitivity, effective treatment can be accomplished with either vancomycin alone or by adding gentamicin to the initial 2 weeks of the ceftriaxone regimen (see Table 47-6) . Patients with endocarditis caused by streptococci that are highly resistant to penicillin (MIC > 0.5 mug/ml) should be treated with one of the regimens recommended for enterococcal endocarditis (see Table 47-8) .

STREPTOCOCCUS PYOGENES, STREPTOCOCCUS PNEUMONIAE, AND GROUPS B, C, AND G STREPTOCOCCI.

Endocarditis caused by these streptococci has been either refractory to antibiotic therapy or associated with extensive valvular damage. Penicillin G in a dose of 3 million units IV every 4 hours for 4 weeks is recommended for the treatment of group A streptococcal and pneumococcal endocarditis. Pneumococci that are relatively resistant (MIC>0.1

mug/ml to 1.0 mug/ml) and highly resistant (MIC>1.0 mug/ml) to penicillin are widely distributed and likely to cause sporadic cases of endocarditis. Treatment with ceftriaxone plus vancomycin may be preferable until the penicillin susceptibility of the infecting strain is confirmed.[44] IE caused by group G, C, or B streptococci is more difficult to treat than that caused by penicillin-susceptible viridans streptococci. Consequently, the addition of gentamicin to the first 2 weeks of a 4-week regimen using high doses of penicillin is often advocated[42] (see Table 47-7) . Early cardiac surgery to correct intracardiac complications is needed in almost half of these cases; prompt intervention may improve outcome.[42]

BACTEREMIA.

Sustained bacteremia is typical of IE. In evaluating positive blood cultures, sustained bacteremia (persisting over >1 hour) should be distinguished from transient bacteremia. When several blood cultures obtained over 24 hours or more are positive, the diagnosis of IE must be considered. The identity of the organism is also helpful in determining the intensity with which the diagnosis is entertained. Organisms can be divided into those that commonly cause IE, those that rarely cause IE, and the intermediate-behaving organisms, e.g., enterococci and *S. aureus,* which, when in the blood, may or may not indicate IE. Finally, the presence or absence of alternative sources for the bacteremia aids in the assessment of bacteremia. These considerations are embodied in the diagnostic criteria for IE (see Table 47-5) .[90] [92]

Among patients with *S. aureus* bacteremia, the risk of IE has been greatest in those with community-acquired infection, those who lack a peripheral site of infection, those who are IV drug abusers, those who have evidence of valvular disease, and those who are diabetic with chronic cutaneous infections. Screening of patients with community-acquired *S. aureus* bacteremia using TTE demonstrated 20 percent of the patients to have either occult IE or valve lesions predisposing to IE.[93] Early studies have suggested that *S. aureus* catheter-associated bacteremia leads to IE in only 6.1 percent of patients.[34] IE was noted in 23 percent of 69 patients with catheter-associated *S. aureus* bacteremia. [35] In an additional study, 50 percent of patients with *S. aureus* IE had an intravascular catheter or a hemodialysis graft as the presumed source of infection.[52] In both of these studies, TTE was not sufficiently sensitive, and TEE was frequently required to diagnose IE. Thus, it is prudent to use TTE to evaluate patients with catheter-associated *S. aureus,* who appear to be at moderate clinical risk of having IE and to use TEE if that is negative or not diagnostic.[51] [94] [95] Patients with *S. aureus* bacteremia who have known underlying valvular heart disease, have a new significant heart murmur, or have persistent fever or bacteremia for 3 days or more after removal of the presumed primary focus of infection (intravascular catheter or drainage of an abscess) and initiation of therapy are at high risk for IE and require full echocardiographic evaluation.[36] [93]

ENTEROCOCCI.

Optimal therapy for enterococcal endocarditis requires synergistic bactericidal interaction of an antimicrobial targeted against the bacterial cell wall (penicillin, ampicillin, or vancomycin) and an aminoglycoside that is able to exert a lethal effect (primarily streptomycin or gentamicin). High-level resistance, defined as the inability of high concentrations of streptomycin (2000 mug/ml) or gentamicin (500 to 2000 mug/ml) to inhibit the growth of an enterococcus, is predictive of the agent's inability to exert this lethal effect and participate in the bactericidal synergistic interaction in vitro and in vivo.[45] [46] The standard regimens recommended for the treatment of enterococcal endocarditis (Table 47-8) are designed to achieve bactericidal synergy. Synergistic combination therapy has resulted in cure rates of approximately 85 percent, compared with 40 percent with single-agent, nonbactericidal treatment.[45]

TABLE 47-8 -- STANDARD THERAPY FOR ENDOCARDITIS DUE TO ENTEROCOCCI*

ANTIBIOTIC	DOSAGE AND ROUTE	DURATION (WK)
Aqueous penicillin G	18-30 million units/24 hr IV given continuously or every 4 hr in six equally divided doses	4-6
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	4-6
Ampicillin	12 gm/24 hr IV given continuously or every 4 hr in six equally divided doses	4-6
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	4-6
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses not to exceed 2 gm/24 hr unless serum levels are monitored	4-6
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	4-6

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*All enterococci causing endocarditis must be tested for antimicrobial susceptibility in order to select optimal therapy. These regimens are for treatment of endocarditis caused by enterococci that are susceptible to vancomycin or ampicillin and not highly resistant to gentamicin. These may also be used for treatment of endocarditis caused by penicillin-resistant (MIC>0.5) viridans streptococci and nutritionally variant streptococci (*S. defectivus, S. adjacens*), or enterococcal PVE.

Dosages are for patients with normal renal function. See Table 47-6 , footnote.

Cephalosporins are not alternatives to penicillin/ampicillin in penicillin-allergic patients.

Some authorities prefer gentamicin doses of 1.5 mg/kg every 8 hours; however, because this dose may be associated with an increased frequency of nephrotoxicity, others advocate doses of 1 mg/kg every 8 hours. Peak serum gentamicin concentrations of approximately 5 mug/ml and 3.5 mug/ml are sought with these doses, respectively. In the absence of high-level resistance to streptomycin in a causative strain, streptomycin, 7.5 mg/kg intramuscularly (IM) or IV, every 12 hours, to achieve a peak serum concentration of approximately 20 mug/ml, can be substituted for gentamicin in the standard regimens. For patients allergic to penicillin, the vancomycin-aminoglycoside regimen (Table 47-8) is recommended; alternatively, patients can be desensitized to penicillin. Desensitization may be desirable when

preexisting renal dysfunction favors avoiding the potentially more nephrotoxic vancomycin-aminoglycoside combination. Cephalosporins are not effective in the treatment of enterococcal endocarditis. Therapy is administered for 4 to 6 weeks, with the longer course used to treat patients with IE that was symptomatic for more than 3 months, with complicated disease, and with enterococcal PVE. During treatment, careful clinical follow-up of patients and aminoglycoside levels is required to prevent nephrotoxicity and ototoxicity.

Previously, 40 percent of enterococci demonstrated high-level resistance to streptomycin, and none was highly resistant to gentamicin. Furthermore, penicillin, ampicillin, and vancomycin inhibited all enterococci at concentrations achieved in the serum with standard IV doses. Accordingly, one of the standard regimens could be selected for treatment with confidence that bactericidal synergy would be achieved. Antimicrobial resistance among enterococci is now complex and cannot be predicted without in vitro testing. High-level resistance to gentamicin has been noted in 25 percent of *E. faecalis* and 50 percent of *E. faecium* infections, and resistance to penicillin, ampicillin, and vancomycin has become commonplace, especially in *E. faecium* infections. Resistance to these antibiotics is most common among enterococci isolated from hospitalized or previously hospitalized persons.

Nevertheless, all enterococci causing endocarditis must be evaluated carefully in order to select effective therapy (Table 47-9) . The strain causing endocarditis must be tested for high-level resistance to both streptomycin and gentamicin, as well as to determine its susceptibility to penicillin, ampicillin, and vancomycin. If the strain is either resistant to achievable serum concentrations of the cell wall-active agent or highly resistant to the aminoglycosides, synergy and optimal therapy cannot be obtain with a standard regimen that includes the inactive antimicrobial. Furthermore, high-level resistance to gentamicin predicts resistance to all other aminoglycosides except

TABLE 47-9 -- STRATEGY FOR SELECTING THERAPY FOR ENTEROCOCCAL ENDOCARDITIS CAUSED BY STRAINS RESISTANT TO COMPONENTS OF THE STANDARD REGIMEN 1

I. Ideal therapy includes a cell wall-active agent plus an effective aminoglycoside to achieve bactericidal synergy
II. Cell wall-active antimicrobial
A. Determine MIC for ampicillin and vancomycin; test for beta-lactamase production (nitrocefin test)
B. If ampicillin and vancomycin susceptible, use ampicillin
C. If ampicillin resistant (MIC 16 mug/ml) and vancomycin susceptible, use vancomycin
D. If beta-lactamase produced, use vancomycin or consider ampicillin-sulbactam

E. If ampicillin resistant and vancomycin resistant (MIC 16 mug/ml), consider teicoplanin*

F. If ampicillin resistant and highly resistant to vancomycin and teicoplanin (MIC 256 mug/ml), see IV C, D

III. Aminoglycoside to be used with cell wall-active antimicrobial

A. If no high level resistance to streptomycin (MIC<2000 mug/ml) or gentamicin (MIC<500-2000 mug/ml), use gentamicin or streptomycin

B. If high-level resistance to gentamicin (MIC>500-2000 mug/ml), test streptomycin. If no high-level resistance to streptomycin, use streptomycin

C. If high-level resistance to gentamicin and streptomycin, omit aminoglycoside therapy; use prolonged therapy (8-12 wk) with cell wall-active antimicrobial if the organism is susceptible (see II A-E) or alternative therapy (see IV C,D)

IV. Alternative regimens and approaches

A. Single drug therapy (see III C) and surgical intervention

B. Consider ampicillin, vancomycin (or teicoplanin), and gentamicin (or streptomycin) based on absence of high-level resistance

C. Consider quinupristin/dalfopristin therapy for infective endocarditis due to susceptible *Enterococcus faecium* and surgical intervention

D. Consider suppressive therapy with chloramphenicol or tetracycline and surgical intervention

E. Treatment with fluoroquinolones, rifampin, or trimethoprim-sulfamethoxazole of questionable efficacy

MIC=minimum inhibitory concentration.

*Not approved by the Food and Drug Administration for use in the United States; may be available by compassionate-use protocol.

streptomycin. These susceptibility data allow selection of a bactericidal synergistic regimen, if one is possible, or alternative treatment (see Table 47-9) . [46]

STAPHYLOCOCCI.

More than 90 percent of coagulase-positive and coagulase-negative staphylococci are penicillin resistant. Methicillin resistance is common among coagulase-negative staphylococci and is a less frequent but important characteristic among *S. aureus.* Methicillin-resistant strains are resistant to all beta-lactam antibiotics but usually remain susceptible to vancomycin. Although staphylococci are killed by cell wall-active antibiotics, the bactericidal effects of these agents can be enhanced by aminoglycosides. Combinations of semisynthetic penicillinase-resistant penicillins or vancomycin with rifampin do not result in predictable bactericidal synergism; nevertheless, rifampin has unique activity against staphylococcal infections that involve

foreign material.[28] [117] Staphylococcal infections involving prosthetic heart valves are treated differently from native valve endocarditis caused by the same species (Table 47-10) .[28] [50] [113]

STAPHYLOCOCCAL NATIVE VALVE ENDOCARDITIS.

The semisynthetic penicillinase-resistant penicillins are the cornerstones of the treatment of endocarditis caused by methicillin-susceptible staphylococci. When patients have a penicillin allergy that does not induce urticaria or anaphylaxis, a first-generation cephalosporin can be used. The synergistic interaction of beta-lactam antibiotics with an aminoglycoside has not increased the cure rates for staphylococcal endocarditis; however, treatment with these combinations has modestly accelerated the eradication of staphylococci in vegetations and from the blood. To achieve this potential benefit, gentamicin may be added to beta-lactam antibiotic therapy for *S. aureus* during the initial 3 to 5 days of treatment.[113] More prolonged administration of gentamicin has been associated with nephrotoxicity and should be avoided. The role for combination therapy is less well defined in NVE caused by coagulase-negative staphylococci; pooled data suggest improved cure rates with combination therapy.[50] In IV drug addicts, Methicillin-susceptible *S. aureus* endocarditis that is apparently uncomplicated and limited to the right heart valves has been effectively treated with 2 weeks of semisynthetic penicillinase-resistant penicillin (but not vancomycin) plus an aminoglycoside (doses as noted in Table 47-10) .[118] However, some patients with right-sided *S. aureus* endocarditis remain febrile and toxic for a significant portion or the entire 2 weeks of combination

TABLE 47-10 -- TREATMENT FOR STAPHYLOCOCCAL ENDOCARDITIS IN THE ABSENCE OF PROSTHETIC MATERIAL

ANTIBIOTIC	DOSAGE AND ROUTE*	DURATION (WK)
Methicillin-Susceptible Staphylococci		
Nafcillin or oxacillin	2 gm IV every 4 hr	4-6
With optional addition of gentamicin	1 mg/kg IM or IV every 8 hr	3-5 days
Cefazolin (or other first-generation cephalosporins in equivalent dosages)	2 gm IV every 8 hr	4-6
With optional addition of gentamicin	1 mg/kg IM or IV every 8 hr	3-5 days
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4-6
Methicillin-Resistant Staphylococci		

Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4-6

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*Dosages are for patients with normal renal function; see Table 47-6 footnote.

For treatment of endocarditis due to penicillin-susceptible staphylococci (minimum inhibitory concentration
0.1 mug/ml), aqueous penicillin G (18-24 million units/24 hr) can be used for 4-6 wk instead of nafcillin or oxacillin.

Cefazolin, other first-generation cephalosporins, or vancomycin may be used in selected penicillin-allergic patients.

therapy. Hence, clinical judgment must be exercised when this abbreviated regimen is used. Therapy should be extended in those patients who remain febrile after 1 week of treatment or who develop signs suggesting left-sided infection.

Endocarditis caused by methicillin-resistant staphylococci requires treatment with vancomycin (see Table 47-10) . Trimethoprim-sulfamethoxazole treatment of right-sided endocarditis caused by *S. aureus* susceptible to this antimicrobial has been only moderately successful.[119] Truly suitable alternatives to vancomycin are not available. Teicoplanin, a glycopeptide antibiotic similar to vancomycin but not available in the United States, has been considered a possible alternative; however, some strains of *S. aureus* have become resistant to teicoplanin.[120] If the methicillin-resistant strain is susceptible to gentamicin, the aminoglycoside can be used in combination with vancomycin to enhance activity against these organisms. However, the frequency of renal toxicity may also be increased by this combination. The addition of rifampin to vancomycin for treatment of methicillin-resistant *S. aureus* NVE has not been beneficial. Right-sided endocarditis caused by methicillin-resistant *S. aureus* is not treated with a 2-week regimen.

STAPHYLOCOCCAL PROSTHETIC VALVE ENDOCARDITIS.

Staphylococcal infections of prosthetic heart valves should be treated with two or preferably three antibiotics in combination. Rifampin provides unique antistaphylococcal activity when infection involves foreign bodies.[117] However, rifampin-resistant staphylococci rapidly emerge when rifampin is used alone or in combination with vancomycin to treat staphylococcal PVE.[28] Consequently, staphylococcal PVE is

treated with two antimicrobials plus rifampin.[28] I prefer to delay rifampin therapy briefly until treatment with two effective antistaphylococcal agents is begun.

For PVE caused by methicillin-resistant staphylococci, treatment is initiated with vancomycin plus gentamicin, with rifampin added if the organism is susceptible to gentamicin. If the organism is resistant to gentamicin, an alternative aminoglycoside to which the organism is susceptible should be sought. Alternatively, for treatment of PVE caused by an organism resistant to all aminoglycosides, a quinolone to which it is susceptible may be used in lieu of an aminoglycoside.[28] For treatment of PVE caused by methicillin-susceptible staphylococci, a semisynthetic penicillinase-resistant penicillin should be substituted for vancomycin in the combination regimen (Table 47-11) .

Patients with a nonimmediate penicillin allergy can be treated with a first-generation cephalosporin in lieu of the semisynthetic penicillin. PVE caused by coagulase-negative staphylococci that occurs within the initial year after valve placement is often complicated by perivalvular extension of infection, and valve replacement surgery is often required to eradicate infection and maintain suitable valve function.[28] Patients with *S. aureus* PVE have frequent intracardiac complications and exceptionally high mortality rates. Cure of *S. aureus* PVE is significantly more likely if early surgical intervention is combined with appropriate combination antimicrobial therapy.[121] [122]

***HAEMOPHILUS PARAINFLUENZAE, HAEMOPHILUS APHROPHILUS, ACTINOBACILLUS ACTINOMYCETEMCOMITANS, CARDIOBACTERIUM HOMINIS, EIKENELLA CORRODENS, AND KINGELLA KINGAE* (HACEK ORGANISMS).**

Endocarditis caused by the HACEK group has in the past been treated with ampicillin administered alone or in combination with gentamicin. Occasional HACEK organisms that are ampicillin resistant by virtue of beta-lactamase production have been isolated. Given the marked susceptibility of both beta-lactamase-producing and non-beta-lactamase-producing HACEK strains to third-generation cephalosporins, ceftriaxone or a comparable third-generation cephalosporin is recommended for treatment of NVE or PVE caused by these organisms (Table 47-12) .[113] For endocarditis caused by strains that do not produce beta-lactamase, ampicillin combined with gentamicin can be used in lieu of ceftriaxone (see Table 47-12) .

OTHER PATHOGENS.

Antimicrobial therapy for patients with IE caused by unusual organisms is based on limited clinical experience

TABLE 47-11 -- TREATMENT OF STAPHYLOCOCCAL ENDOCARDITIS IN THE PRESENCE OF A PROSTHETIC VALVE OR OTHER PROSTHETIC MATERIAL

ANTIBIOTIC	DOSAGE AND ROUTE*	DURATION (WK)
Regimen for Methicillin-Resistant Staphylococci		

Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	6
plus		
Rifampin *and* gentamicin	300 mg PO every 8 hr	6
	1.0 mg/kg IM or IV every 8 hr	2
Regimen for Methicillin-Susceptible Staphylococci		
Nafcillin or oxacillin	2 gm IV every 4 hr	6
plus		
Rifampin *and* gentamicin	300 mg PO every 8 hr	6
	1.0 mg/kg IM or IV every 8 hr	2
Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.		

*Dosages are for patients with normal renal function. See Table 47-6 , footnote.

Use during initial 2 wk of treatment. If strain is gentamicin resistant, see text for alternatives.

and data from animal models and in vitro studies. Therapeutic regimens for most of these infections are beyond the scope of this chapter: in fact, physicians are urged to review the published experience with a specific causative agent as well as to seek assistance from experienced infectious disease consultants when treating these infections. Among the more common of the unusual agents causing endocarditis are *P. aeruginosa, Candida* species, and *Corynebacterium* species. The preferred treatment for endocarditis caused by *P. aeruginosa* is an antipseudomonal penicillin (ticarcillin or piperacillin) plus high doses of tobramycin (8 mg/kg/d IM or IV in divided doses every 8 hours to achieve peak serum concentrations of 15 mug/ml). Endocarditis caused by *P. aeruginosa* is often both destructive and poorly responsive to antibiotic therapy. As a result, many patients with *P. aeruginosa* endocarditis require cardiac surgery.

Amphotericin at full doses, often combined with 5-fluorocytosine, is recommended for treatment of *Candida* endocarditis. Several patients with *Candida* NVE and PVE without intracardiac complications are reported to have been cured by prolonged treatment with fluconazole.[123] [124] Nevertheless, surgical intervention shortly after beginning amphotericin treatment remains the standard treatment for *Candida* endocarditis.[125] [126] Prolonged or indefinite finuconazole administration has been advocated for patients

treated either medically or surgically [124] [125] [126]

TABLE 47-12 -- TREATMENT FOR ENDOCARDITIS DUE TO HACEK MICROORGANISMS*

ANTIBIOTIC	DOSAGE AND ROUTE	DURATION (WK)
Ceftriaxone	2 gm once daily IV or IM	4
Ampicillin	12 gm/24 hr IV given continuously or every 4 hr in six equally divided doses	4
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	4

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*HACEK microorganisms are *Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

Dosages are for those with normal renal function. See Table 47-6 , footnote.

Cefotaxime or ceftizoxime in comparable doses may be substituted for ceftriaxone.

The antimicrobial susceptibility of corynebacteria causing endocarditis must be carefully evaluated. Many remain susceptible to penicilin, vancomycin, and aminoglycosides. Strains susceptible to aminoglycosides are killed synergistically by penicillin in combination with an aminoglycoside. *C. jelkeium,* although often resistant to penicillin and aminoglycosides, is killed by vancomycin. NVE or PVE caused by *Corynebacterium* species can be treated with the combination of penicillin plus an aminoglycoside or vancomycin, contingent on the susceptibilities of the causative strain.[55]

The Enterobacteriaceae (*E. coli* and *Klebsiella, Enterobacter, Serratia,* and *Proteus* species) are highly susceptible to third-generation cephaloporins, imipenem, and aztreonam. One of these antimicrobial agents in high doses is combined with an aminoglycoside to treat IE caused by Enterobacteriaceae.

Coxiella burnetii IE is difficult to eradicate. Prolonged therapy (at least 4 years) using doxycycline (100 mg twice daily) or another tetracycline combined with a quinolone has been advocated. Treatment with doxycycline combined with hydroxychloroquine for 18 to 48 months (mean 31 months, median 26 months) may be as effective as longer

courses of doxycycline plus a quinolone.[127] Surgery is important in effective treatment.

CULTURE-NEGATIVE ENDOCARDITIS.

Special studies to diagnose IE caused by fastidious bacteria and other organisms must be performed (see Diagnosis). Thereafter, unless clinical or epidemiologic clues suggest an etiological diagnosis, the recommended treatment for culture-negative NVE is ampicillin plus gentamicin (see standard regimen for enterococcal endocarditis, Table 47-8) ; because in the absence of confounding antibiotic therapy enterococci and staphyclococci are unlikely causes of culture-negative NVE, ceftriaxone could be used in this regimen instead of ampicillin. For patients with culture-negative PVE, vancomycin is added to this regimen.[28] [128] Mortality rates are lower for patients who have culture-negative endocarditis and who received antibiotics before obtaining blood cultures and those who become afebrile during the initial week of antimicrobial treatment.[96] [128] Marantic endocarditis should be carefully considered when treating patients for culture-negative IE. Surgical intervention should be considered for those who do not fully respond to empirical antimicrobial therapy. If surgical intervention is undertaken, a detailed microbiological and pathological examination of excised material must be performed to establish an etiologic diagnosis.

TIMING THE INITIATION OF ANTIMICROBIAL THERAPY.

Current cost-containment pressures frequently result in initiation of antimicrobial therapy for suspected endocarditis immediately after blood cultures have been obtained. This practice is appropriate in the treatment of patients with acute IE that is highly destructive and rapidly progressive and of patients presenting with hemodynamic decompensation requiring urgent or emergent surgical intervention. Immediate therapy may have a favorable impact on outcome in these patients. In contrast, precipitous initiation of therapy in hemodynamically stable patients with suspected subacute endocarditis does not prevent early complications and may, by compromising subsequent blood cultures, obscure the etiological diagnosis of endocarditis. In these latter patients, it is prudent to delay antibiotic therapy briefly pending the results of the initial blood cultures. If these cultures are not positive promptly, this delay provides an important opportunity to obtain additional blood cultures without the confounding effect of empirical treatment. This opportunity is particularly important when patients have received antibiotics recently.

MONITORING THERAPY FOR ENDOCARDITIS.

Patients must be carefully monitored during therapy and for several months thereafter. Failure of antimicrobial therapy, myocardial or metastatic abscess, emboli, hypersensitivity to antimicrobial agents, and other complications of therapy (catheter-related infection, thrombophlebitis) or intercurrent illness may be manifested by persistent or recurrent fever. Adverse reactions occur in 33 percent of patients treated for IE with beta-lactam antimicrobials, especially penicillin and ampicillin. The reactions include fever, rash, and neutropenia; they are increasingly frequent after 15 days of therapy.[129] Clinical events may indicate a need for potentially life-saving

revision of antimicrobial therapy or adjunctive surgical therapy.

The serum bactericidal titer (SBT), the highest dilution of the patient's serum during therapy that in vitro kills 99.9 percent of a standard inoculum of the patient's infecting organism, has been used to assess the adequacy of antimicrobial therapy. The SBT has correlated poorly with outcome of therapy because it has been performed in a nonstandardized manner and because of the marked impact of complications on outcome. Peak and trough titers of at least 1:64 or 1:32 and 1:32, respectively, obtained with a standardized SBT method, correlate with bacteriological cure. When using regimens considered optimal on the basis of clinical experience, monitoring therapy with this test is not recommended.[113] The SBT may be useful when treating patients with endocarditis caused by organisms for which optimal therapy is not established or when using unconventional antimicrobial regimens.

The serum concentration of vancomycin or aminoglycosides should be measured periodically. This allows dose adjustment to ensure optimal therapy and avoid adverse events. Additionally, renal function should be monitored in patients receiving these two antimicrobials, and the complete blood count should be checked at least weekly in patients receiving high-dose beta-lactam antibiotics or vancomycin.

Repeat blood cultures should be obtained during the initial days of therapy or if fever persists to determine if the bacteremia has been controlled. In patients with recrudescent fever after treatment, prompt cultures are essential to assess possible relapse of endocarditis.

OUTPATIENT ANTIMICROBIAL THERAPY.

Technical advances allowing safe administration of complex antimicrobial regimens, combined with well-developed home care systems that provide supplies and monitor outpatient treatment, make it feasible to treat patients with endocarditis on an outpatient basis. Doing so can significantly reduce the cost of therapy. However, only those patients who have responded to initial therapy and are free of fever, who are not experiencing threatening complications, who will be compliant with therapy, and who have a home situation that is physically suitable should be considered for outpatient treatment. Furthermore, patients being treated at home must be apprised of the potential complications of endocarditis, instructed to seek advice promptly when encountering unexpected or untoward clinical events, and have assiduous clinical and laboratory monitoring. Finally, outpatient therapy must not result in compromises of antimicrobial therapy leading to suboptimal treatment.

Surgical Treatment of Intracardiac Complications

Cardiac surgical intervention has an increasingly important role in the treatment of intracardiac complications of endocarditis. Retrospective data suggest that mortality is unacceptably high when these complications are treated with antibiotics alone, whereas mortality is reduced when treatment combines antibiotics and surgical intervention.[76] [130] [131] Accordingly, these complications have become indications for cardiac surgery

(Table 47-13) .

VALVULAR DYSFUNCTION.

Medical therapy of NVE that is complicated by moderate to severe (New York Heart Association Class III and IV) CHF due to new or worsening valvular dysfunction results in mortality rates of 50 to 90 percent. Survival rates for a similar group of patients treated with antibiotics and cardiac surgery are 60 to 80 percent.[76] [130] [131] Although survival rates among surgically treated patients with PVE complicated by valvular dysfunction and CHF are 45 to 85 percent, few PVE patients with these complications are alive at 6 months when treated with antibiotics alone.[28] [29] Worsening aortic valve incompetence is associated with more severe and more rapidly progressive CHF than is mitral valve incompetence. Hence, patients with aortic valve endocarditis not only account for

TABLE 47-13 -- CARDIAC SURGERY IN PATIENTS WITH INFECTIVE ENDOCARDITIS

Indications
Moderate to severe congestive heart failure due to valve dysfunction
Unstable prosthesis
Uncontrolled infection despite optimal antimicrobial therapy
Unavailable effective antimicrobial therapy: endocarditis due to fungi, *Brucellae, Pseudomonas aeruginosa* (aortic or mitral valves)
Staphylococcus aureus PVE with an intracardiac complication
Relapse of PVE after optimal therapy
Relative Indications*
Perivalvular extension of infection, intracardiac fistula
Poorly responsive *S. aureus* NVE (aortic or mitral valves)
Relapse of NVE after optimal antimicrobial therapy
Culture-negative NVE or PVE with persistent fever (10 d)
Large (>10 mm diameter) hypermobile vegetation (with or without prior arterial embolus)
Endocarditis due to highly antibiotic-resistant enterococci
PVE=prosthetic valve endocarditis; NVE=native valve endocarditis.

*Surgery commonly required for optimal outcome.

the majority of surgically treated patients but also require surgery on a more urgent basis when heart failure supervenes. Severe mitral valve insufficiency, nevertheless, results in inexorable heart failure and ultimately requires surgical intervention. Doppler echocardiography and color flow mapping indicating significant valvular regurgitation during the initial week of endocarditis treatment do not reliably predict those patients who will require valve replacement during active endocarditis. Alternatively, despite the absence of significant valvular regurgitation on early echocardiography, marked CHF may still develop. Decisions about surgical intervention should not be made solely on the basis of echocardiographic findings but rather by integrating clinical data during careful serial monitoring. On occasion, very large vegetations on the mitral valve, particularly a mitral valve prosthesis, result in significant obstruction and require surgery.[28]

UNSTABLE PROSTHESES.

Dehiscence of an infected prosthetic valve is a manifestation of perivalvular infection and often results in hemodynamically significant valvular dysfunction. Surgical intervention is recommended for PVE patients with these complications.[28] [130] The risk of invasive infection is increased among patients with onset of PVE within the year after valve implantation and those with infection of an aortic valve prosthesis. Endocarditis in these patients is often caused by invasive antimicrobial-resistant organisms; consequently, the benefit of combined medical-surgical therapy is enhanced further. Patients who appear clinically stable but who have overtly unstable and hypermobile prostheses, a finding indicative of dehiscence in excess of 40 percent of the circumference, are likely to experience progressive valve instability and warrant surgical treatment. Occasional patients with PVE caused by noninvasive, highly antibiotic-susceptible organisms, e.g., streptococci, despite a favorable clinical course during antibiotic therapy, late in treatment experience minor valve dehiscence without prosthesis instability or hemodynamic deterioration. Surgical treatment of these patients can be deferred unless clear indications arise.

UNCONTROLLED INFECTION OR UNAVAILABLE EFFECTIVE ANTIMICROBIAL THERAPY.

Surgical intervention has improved the outcome of several forms of endocarditis when maximal antibiotic therapy fails to eradicate infection or, in some instances, even to suppress bacteremia. Amphotericin B is inadequate therapy for fungal endocarditis, including that caused by *Candida* species, and surgical intervention is recommended shortly after initiation of full doses of antifungal therapy. Endocarditis caused by some gram-negative bacilli, e.g., *P. aeruginosa, Achromobacter xylosoxidans,* may not be eradicated by maximum tolerable antibiotic therapy and may require surgical excision of the infected tissue to achieve cure. Similarly, standard therapy of endocarditis caused by *Brucella* species includes surgery because medical therapy is rarely successful.[94] Surgical intervention is recommended when patients with enterococcal endocarditis caused by a strain resistant to synergistic bactericidal therapy do not respond to initial therapy or relapse. Perivalvular invasive infection is in some instances a form of

ineradicable infection. Relapse of PVE after optimal antimicrobial therapy reflects invasive disease or the difficulty in eradicating infection involving foreign devices. Patients with relapse of PVE are treated surgically.[28] In contrast, patients with NVE that relapses, unless it is associated with a highly resistant microorganism or demonstrable perivalvular infection, often are treated again with an intensified, prolonged course of antimicrobial therapy.[132]

S. AUREUS PROSTHETIC VALVE ENDOCARDITIS.

Among 129 patients who had *S. aureus* PVE and who were culled from large retrospective general series of PVE, the crude mortality rate for those treated with antibiotics alone and with antibiotics plus surgery was 73 and 25 percent, respectively.[51] [122] [133] [134] The overall mortality rate in 33 cases of *S. aureus* PVE treated at a single institution was 42 percent.[122] In these latter cases, when a multivariate model was used for analysis to adjust for confounding variables, the presence of intracardiac complications was associated with a 13.7-fold increased risk of death, and surgical intervention during active disease was accompanied by a 20-fold reduction in mortality. These data suggest that surgical treatment can improve outcome. Although the occurrence of central nervous system emboli is often considered to limit the opportunity for surgical intervention, in fact, appropriately timed surgery remains the preferred treatment. Thus, surgical intervention is recommended for *S. aureus* PVE with intracardiac complication and may benefit even those patients with uncomplicated *S. aureus* PVE.[122] [133]

PERIVALVULAR INVASIVE INFECTION.

NVE at the aortic site and PVE are most commonly associated with perivalvular invasion with abscess or intracardiac fistula formation.[28] Invasive infection occurs in 10 to 14 percent of patients with NVE and 45 to 60 percent of those with PVE.[28] Persistent, otherwise unexplained fever despite appropriate antimicrobial therapy or pericarditis in patients with aortic valve endocarditis suggests infection extending beyond the valve leaflet.[78] New-onset and persistent electrocardiographic conduction abnormalities, although not a sensitive indicator of perivalvular infection (28 percent), are relatively specific (85 to 90 percent).[135] TEE is superior to TTE for detecting invasive infection in patients with NVE and PVE. Doppler and color flow Doppler or contrast two-dimensional echocardiography optimally define fistulas. Patients who have IE and in whom an abscess is suspected but not detected by an initial and repeat TEE should undergo magnetic resonance imaging, including magnetic resonance angiography. Cardiac catheterization adds little to these imaging studies and is not recommended unless coronary angiography is needed.

In patients with endocarditis complicated by perivalvular extension of infection, cardiac surgery should be considered to debride invasive infection, ablate abscesses, and reconstruct anatomical damage. Surgery is warranted in patients with invasive disease that significantly disrupts cardiac structures, that is associated with CHF, that results in instability of a prosthetic valve, or that renders infection uncontrolled (persistent fever). However, it is likely that increasingly sensitive imaging techniques will elucidate invasive

infections that do not require immediate surgery. Sporadic case reports of medically treated invasive infection suggest that these infections will be small, structurally nonsignificant abscesses in which the cavity is open to the circulatory stream.

LEFT-SIDED *S. AUREUS* ENDOCARDITIS.

Because this infection is difficult to control, highly destructive, and associated with high mortality, some investigators have suggested that these patients should be considered for surgical treatment when the response to antimicrobial therapy is not prompt and complete. Additionally, patients with *S. aureus* NVE (aortic or mitral valve) and vegetations that are visible by TTE are at increased risk for arterial emboli and death and should be considered for surgery.[52] In contrast, IV drug abusers with *S. aureus* endocarditis limited to the tricuspid or pulmonary valves often experience prolonged fever during antimicrobial therapy; nevertheless, the vast majority of these patients respond to antimicrobial therapy and do not require surgery.[136]

UNRESPONSIVE CULTURE-NEGATIVE ENDOCARDITIS.

Patients who have culture-negative endocarditis and who experience unexplained persistent fever during empirical antimicrobial therapy, particularly those with PVE, should be considered for surgical intervention. If endocarditis is not marantic, persistent fever in these patients is likely to represent either unrecognized perivalvular infection or ineffective antimicrobial therapy.

LARGE VEGETATIONS (>10 mm) AND THE PREVENTION OF SYSTEMIC EMBOLI.

Systemic embolization was increased in patients with vegetations greater than 10 mm versus those with smaller or no detectable vegetations, 33 percent versus 19 percent.[82] Larger mitral valve vegetations (>10 mm), particularly those on the anterior mitral valve leaflet, are uniquely associated with systemic emboli. Although a relationship may exist between vegetation characteristics--including size, mobility, and extent (number of leaflets involved)--and embolic complications, the implications for surgical intervention are not clear. Yet to be performed are multivariate analyses examining the relationship between outcome or the need for surgical intervention and variables including not only vegetation characteristics but also valve dysfunction, perivalvular invasion by infection, organism, and infection site. Nevertheless, some researchers have concluded that vegetation characteristics alone might warrant surgery to prevent arterial emboli. This recommendation can be questioned, as can the recommendation for valve surgery after two major arterial emboli.[94]

In deciding to intervene in the therapy of IE with cardiac surgery to prevent arterial emboli, many factors must be considered carefully. The rate of systemic or cerebral emboli in patients with NVE and PVE decreases during the course of effective antibiotic

therapy.[87] [137] Additionally, it is not clear that surgical intervention reduces the frequency of systemic emboli.[76] [130] Finally, the risks of morbidity and mortality caused by cerebral and coronary emboli, the major events to be prevented, must be compared with the immediate and long-term risks of valve replacement surgery. The latter include perioperative mortality, recrudescent endocarditis on the prosthesis, thromboembolic complications, early and late valve dysfunction requiring repeat valve replacement, the hazards of warfarin anticoagulation (including its contraindication during pregnancy), and the risk and morbidity of late-onset PVE.[128] Vegetation size alone is rarely an indication for surgery. The clinical findings and echocardiographic evidence for other intracardiac complications must be weighed against the immediate and remote hazards of cardiac surgery, including the possibility of valve preservation by vegetectomy and valve repair, when recommending therapy.[82] [94] Thus, the risk for systemic embolization as related to vegetation size or prior systemic embolus is not an independent indication for surgical intervention but is only one of many factors to be considered when planning treatment.[87] [94] [137]

TECHNIQUES FOR REPAIR OF INTRACARDIAC DEFECTS.

New surgical techniques to address severe tissue destruction in NVE and PVE have been developed. Although these are beyond the scope of this discussion, examples include valve composite graft replacement of the aortic root, use of sewing skirts attached to the prostheses, and homograft replacement of the aortic valve and root with coronary artery reimplantation.[138] [139] Furthermore, repair of the mitral valve in patients with acute or healed endocarditis avoids the need for insertion of prosthetic materials and the associated hazards.[140] Although tricuspid valvulectomy without valve replacement has been advocated for treatment of uncontrolled tricuspid valve infection in IV drug abusers at high risk of recidivism and recurrent endocarditis, the likelihood of refractory right-heart failure with time after valvulectomy makes tricuspid valve repair preferable. Cardiac transplantation has been used to salvage an occasional patient with refractory endocarditis.

TIMING OF SURGICAL INTERVENTION.

When endocarditis is complicated by valvular regurgitation and significant impairment of cardiac function, surgical intervention before the development of severe intractable hemodynamic dysfunction is recommended, regardless of the duration of antimicrobial therapy.[130] [141] Postoperative mortality correlates with the severity of preoperative hemodynamic dysfunction; consequently, this approach is justified.[94] In patients who have valvular dysfunction and in whom infection is controlled and cardiac function is compensated, surgery may be delayed until antimicrobial therapy has been completed. However, if infection is not controlled, surgery should be performed promptly. Similarly, if a patient who requires valve replacement in the near future has a large vegetation, indicating a high risk for systemic embolization, early cardiac surgery is appropriate.

To avoid worsening of neurological status or death in patients who have sustained recent neurological injury, the timing of surgical intervention may require modification. Among patients who have had a nonhemorrhagic embolic stroke, exacerbation of cerebral dysfunction occurs during cardiac surgery in 44 percent of cases when the

interval between the stroke and surgery is 7 days or less, in 17 percent when the interval is 8 to 14 days, and in 10 percent or less when more than 2 weeks has elapsed. After hemorrhagic intracerebral events, the risk for neurological worsening or death with cardiac surgery persists at 20 percent even after 1 month.[142]

Thus, when the response of IE to antimicrobial therapy and hemodynamic status permit, delaying cardiac surgery for 2 to 3 weeks after a significant embolic infarct and at least a month after intracerebral hemorrhage (with prior repair of a mycotic aneurysm) has been recommended.[142] [143] In another study of patients with nonhemorrhagic focal cerebral lesions or encephalopathy, those undergoing cardiac surgery without delay experienced no greater mortality or neurological deterioration than did those treated medically. This study suggests that the improved outcomes reported with delayed surgery may simply reflect selection of hardier patients and that more prompt cardiac surgery in patients with nonhemorrhagic cerebral complications, if required, is reasonable and potentially beneficial.[144] Contrast-enhanced cerebral tomography is recommended as the initial study of choice to detect intracerebral hemorrhage with subsequent magnetic resonance angiography or standard cerebral angiography to further evaluate hemorrhagic lesions for a leaking mycotic aneurysm.[143] [145] It is prudent to evaluate the cerebral vasculaturs in patients who have sustained an embolic infarct or who have persistent headaches before cardiac surgery. If a mycotic aneurysm is found, the timing of cardiac surgery should be reconsidered and prostheses that require postoperative anticoagulant therapy should be avoided.[94]

DURATION OF ANTIMICROBIAL THERAPY AFTER SURGICAL INTERVENTION.

Inflammatory changes and bacteria are commonly found in vegetations removed from patients who have received most or all of the standard antibiotic therapy recommended for endocarditis caused by the specific microorganism. If valve cultures are negative, this does not indicate that antimicrobial therapy has failed or that a full course of antibiotic therapy is needed postoperatively. The duration of antimicrobial therapy after surgery depends on the length of preoperative therapy, the antibiotic susceptibility of the causative organism, the presence of paravalvular

invasive infection, and the culture status of the vegetation. In general, for endocarditis caused by relatively antibiotic-resistant organisms with negative cultures of operative specimens, preoperative plus postoperative therapy should at least equal a full course of recommended therapy; for those patients with positive intraoperative cultures, a full course of therapy should be given postoperatively. Patients with PVE should receive a full course of antimicrobial therapy postoperatively when organisms are seen in resected material.[28]

Treatment of Extracardiac Complications

SPLENIC ABSCESS.

Three to 5 percent of patients with IE develop a splenic abscess.[80] Although splenic defects can be identified by ultrasonography and computed tomography, these tests usually cannot discriminate between abscess and infarct. Persistent fever and progressive enlargement of the lesion during antimicrobial therapy suggest that it is an abscess; this can be confirmed by percutaneous needle aspiration. Successful therapy of splenic abscesses generally requires drainage, which can often be accomplished by percutaneous placement of a catheter.[84] In patients with endocarditis complicated by numerous splenic abscesses or in whom percutaneous drainage is unsuccessful, splenectomy is required.[84] [94] Splenic abscesses should be effectively treated before valve replacement surgery. If they are not effectively treated before cardiac surgery, splenectomy should be performed as soon thereafter as surgical risks permit.[94]

MYCOTIC ANEURYSMS AND SEPTIC ARTERITIS.

From 2 to 10 percent of patients with endocarditis have mycotic aneurysms; in 1 to 5 percent, the aneurysms involve cerebral vessels.[88] Cerebral mycotic aneurysms occur at the branch points in cerebral vessels, are generally located distally over the cerebral cortex, and are found most commonly in branches of the middle cerebral artery. The aneurysms arise either from occlusion of vessels by septic emboli with secondary arteritis and vessel wall destruction or from bacteremic seeding of the vessel wall through the vasa vasorum. *S. aureus* is commonly implicated in the former and viridans streptococci in the latter.[91] Many patients with mycotic aneurysms or septic arteritis present with devastating intracranial hemorrhage. Focal deficits from embolic events, persistent focal headache, or sterile meningeal irritation (cerebrospinal fluid pleacytosis) may be premonitory symptoms. Cerebral angiography is required to evaluate patients with subarachnoid hemorrhage, and this or magnetic resonance angiography has been recommended for patients experiencing premonitory symptoms, especially if cardiac surgery or anticoagulant therapy is planned.[88] [94] Mycotic aneurysms may resolve during antimicrobial therapy[94] ; however, when anatomically feasible, aneurysms that have ruptured should be repaired surgically. Aneurysms that have not leaked should be monitored angiographically during antimicrobial therapy. Surgery should be considered for a single lesion that enlarges during or after antimicrobial therapy. Anticoagulant therapy should be avoided in patients with a persisting mycotic aneurysm. Although persistent stable aneurysms may rupture after completion of standard antimicrobial therapy, there is no accurate estimation of risk for late rupture, and recommendations for surgical intervention are arbitrary. Nevertheless, prevailing opinion favors, whenever possible without serious neurological injury, the resection of single aneurysms that persist after therapy. The potential existence of occult aneurysms in patients without neurological symptoms or in those who have had a nondiagnostic angiographic evaluation is not considered a contraindication to anticoagulant therapy after completion of antimicrobial therapy.

Extracranial mycotic aneurysms should be managed as outlined for cerebral aneurysms. Those that leak, are expanding during therapy, or persist after therapy should be repaired. Particular attention should be given to aneurysms that involve

intraabdominal arteries, rupture of which could result in life-threatening hemorrhage.[94]

ANTICOAGULANT THERAPY.

Patients with PVE involving devices that would usually warrant maintenance anticoagulation are continued on anticoagulant therapy.[28] Prothrombin times should be maintained at 1.5 times the control (INR = 3.0). Anticoagulation is not initiated as prophylaxis against thromboembolism in patients with PVE involving devices that do not usually require this therapy. Among patients with NVE, no evidence shows that anticoagulant therapy prevents embolization, and in some instances it may contribute to intracranial hemorrhage, particularly in the presence of a recent cerebral infarct or a mycotic aneurysm.[88] Anticoagulant therapy in patients with NVE is limited to those patients for whom there is a clear indication for this therapy and for whom there is not a known increased risk for intracranial hemorrhage. If central nervous system complications occur in patients who have IE and who are receiving anticoagulant therapy, anticoagulation should be reversed immediately.[28]

Response to Therapy and Outcome

Within a week after initiation of effective antimicrobial therapy, almost 75 percent of patients with IE, including those with PVE, are afebrile and 90 percent have defervesced by the end of the second week of treatment.[47] [137] [28] [76] [146] The duration of fever during therapy is longer in patients with IE due to *S. aureus, P. aeruginosa,* and culture-negative IE as well as IE characterized by microvascular phenomena and major embolic complications.[76] [146] Persistence or recurrence of fever more than 7 to 10 days after initiation of antibiotic therapy identified patients with increased mortality rates and with complications of infection or therapy.[28] [78] [146] Those patients with prolonged or recurrent fever should be evaluated for intracardiac complications, focal extracardiac septic complications, intercurrent nosocomial infections, recurrent pulmonary emboli (patients with right-sided IE), drug-associated fever, additional underlying illnesses, and, if appropriate, in-hospital substance abuse.

Blood cultures should be repeated in search of persistent bacteremia or the presence of additional pathogens, e.g., previously unrecognized polymicrobial IE. The antimicrobial susceptibility of the causative organism should be reevaluated, as should the adequacy of antibiotic therapy. Drug reactions have accounted for fever in 17 to 28 percent of these patients.[78] [124] Drug fever attributed to the antimicrobial therapy itself may warrant revision of treatment if a suitable alternative is available. In the absence of effective alternative therapy, treatment can be continued despite drug fever if the antimicrobial is not causing significant end-organ toxicity. In 33 to 45 percent of patients, persistent fever was associated with significant intracardiac complications, many of which required surgical intervention.[76]

Many clinical and laboratory features of IE are slow to resolve despite effective antimicrobial therapy. Systemic emboli occur during the early weeks of treatment, although with decreasing frequency.[87] The increased ESR and anemia may not correct until after therapy has been completed.

Mortality rates for large series of NVE treated between 1975 and 1993 range from 16 to 27 percent.[1] [4] [5] [9] [134] Death due to IE has been associated with increased age (>65 to 70 years old), underlying diseases, infection involving the aortic valve, development of CHF, renal failure, and central nervous system complications.[1] [5] The treatment of heart failure due to valve dysfunction by early surgical intervention has decreased the mortality associated with CHF, but subsequently, neurological events and septic complications, e.g., uncontrolled infection and myocardial abscess, have accounted for a larger proportion of deaths and have been associated with high mortality rates.[80]

Mortality rates among patients with IE caused by viridans streptococci and *S. bovis* have ranged from 4 to 16 percent.[1] [4] [9] Higher mortality rates are reported with left-sided NVE caused by other organisms: enterococci, 15 to 25 percent[1] [4] [9] ; *S. aureus,* 25 to 47 percent[1] [4] [9] [50] [73] ; nonviridans streptococci (groups B, C, and G), 13 to 50 percent[42] [147] ; *C. burnetti,* 5 to 37 percent[31] [114] [124] ; *P. aeruginosa,* Enterobacteriaceae, and fungi, greater than 50 percent.[54] [61]

In a retrospective study of patients with NVE with either Class III or IV heart failure (New York Heart Association) or invasive uncontrolled infection, only 9 percent of patients treated surgically died, compared with 51 percent of those treated with antibiotics alone.[76] Mortality rates among patients who have NVE, particularly involving the aortic valve, and who were treated surgically have ranged from 5 to 26 percent, with rates toward the high end of this range reported more frequently.[148] [149] [150] Severity of heart failure, abscess, *S. aureus* infection, and decreased renal function (possibly related to heart failure) have been associated with

increased postoperative mortality.[150] Nevertheless, survival rates of 85 percent can be achieved when patients with paravalvular abscesses undergo meticulous debridement and reconstructive cardiac surgery.[151]

Outcome for patients with PVE, as contrasted with NVE, has been less desirable. Before 1980, mortality rates among patients with onset less than 60 days after surgery and later-onset PVE averaged 70 and 45 percent, respectively. With the recognition that PVE was frequently complicated by invasive infection and that patients would benefit from surgical intervention, mortality rates have decreased to 33 to 45 percent, with lower rates in later-onset cases.[28] [151] Long-term survival was adversely affected by the presence of moderate or severe heart failure at discharge. Survival rates after aggressive surgery for PVE ranged from 75 to 85 percent and were not related to time of onset after cardiac surgery.[29] [139]

Among patients with NVE (nonaddicts) discharged after medical or medical-surgical therapy, long-term survival was 88 percent at 5 years and 81 percent at 10 years.[134] Among patients treated surgically for NVE, survival at 5 years ranged from 70 to 80 percent.[138] [149] Among patients with PVE treated surgically, survival rates at 4 to 6 years

range from 50 to 82 percent.[29] [139]

RELAPSE AND RECURRENCE.

Relapse of IE usually occurs within 2 months of discontinuing antibiotic treatment. Of patients who have NVE caused by penicillin-susceptible viridans streptococci and who receive a recommended course of therapy, less than 2 percent suffer relapse. From 8 to 20 percent of patients with enterococcal IE experience relapse after standard therapy.[132] Patients with IE caused by *S. aureus,* Enterobacteriaceae, or fungi are more likely to experience overt failure of therapy rather than relapse; nevertheless, 4 percent of patients with *S. aureus* IE suffer relapse.[132] Relapse of fungal endocarditis at long intervals after treatment has been reported. Relapse occurs in 10 percent of patients with PVE overall and in 6 to 15 percent of those treated surgically. [131]

Among nonaddicts with an initial episode of NVE or PVE, 4.5 to 7 percent experience one or more additional episodes.[132] [134] Among these patients, recurrent IE shares the clinical, microbiological, and response to therapy noted in primary episodes of IE. IV drug abuse is now the most common predisposition for recurrent IE (43 percent of patients).

PREVENTION

During bacteremia provoked by daily activities, infections, or health care procedures, bacteria adhere to and colonize the platelet fibrin aggregates, NBTE, that have formed on the valve endothelium as a consequence of preexisting congenital or acquired cardiac disease. If the adherence and the subsequent multiplication of bacteria at this site exceed the capacity of host defenses for bacterial eradication, IE results. Although many bacteria enter the bloodstream, those uniquely suited to adhere to NBTE cause the majority of cases of endocarditis. These organisms and the cardiac abnormalities vulnerable to IE are evident from reported cases. Events that predispose to bacteremia by organisms causing endocarditis have been identified. By identifying the patients at risk, the causative bacteria, and the events that induce bacteremia, strategies for prevention of some episodes of IE have been formulated and are routinely recommended even in the absence of supporting clinical trials.[152] [153] [154]

Viridans streptococci, the most common cause of NVE and late-onset PVE, are the primary target for prophylaxis used in conjunction with procedures involving the oral cavity, respiratory tract, or esophagus. Procedures involving the genitourinary and gastrointestinal tracts commonly precede the development of enterococcal endocarditis. Accordingly, the prophylaxis for endocarditis used in conjunction with procedures involving these mucosal surfaces is targeted against enterococci. When incision and drainage of infected skin or soft tissue infections are undertaken, prophylaxis is focused on *S. aureus.*

Procedures for which IE prophylaxis is recommended or not recommended have been identified by the American Heart Association and others (Table 47-14) . [152] [153] [154] [155] Although prophylaxis is advised for all at-risk patients who undergo dental procedures

that cause gingival bleeding, extractions

TABLE 47-14 -- PROCEDURES FOR WHICH PROPHYLAXIS AGAINST ENDOCARDITIS IS CONSIDERED

PROPHYLAXIS RECOMMENDED	PROPHYLAXIS NOT RECOMMENDED
Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning and scaling	Dental procedures not likely to cause bleeding, such as adjustment of orthodontic appliances and simple fillings above the gum line
Tonsillectomy or adenoidectomy	
Surgery involving gastrointestinal or upper respiratory mucosa	Intraoral injection or local anesthetic (nonintraligamentary)
Bronchoscopy with rigid bronchoscope	Shedding of primary teeth
Sclerotherapy for esophageal varices	Tympanostomy tube insertion
Esophageal dilation	Endotracheal tube insertion
Endoscopic retrograde cholangiography with biliary obstruction	Bronchoscopy with flexible bronchoscope, with or without biopsy
Gallbladder surgery	
Cytoscopy, urethral dilation	Transesophageal echocardiography
Urethral catheterization if urinary infection is present	Cardiac catheterization, coronary angioplasty
Urinary tract surgery, including prostate surgery	Pacemaker implantation
Incision and drainage of infected tissue*	Gastrointestinal endoscopy, with or without biopsy
	Gastrointestinal endoscopy, with or without biopsy
	Incision or biopsy of scrubbed skin
	Cesarean section
	Vaginal hysterectomy
	Circumcision

	In the absence of infection: urethral catheterization, dilatation and curettage, uncomplicated vaginal delivery, therapeutic abortion, insertion or removal of intrauterine device, sterilization procedures, laparoscopy

Adapted from Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations of the American Heart Association from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. JAMA 277:1794, 1997; and from Durack DT: Prevention of endocarditis. N Engl J Med 332:38, 1995.

In patients at highest risk, physicians may elect to use prophylaxis for these procedures.
*Antibiotic prophylaxis should be directed against the most likely endocarditis-associated pathogen(s), often staphylococci.

TABLE 47-15 -- RELATIVE RISK OF INFECTIVE ENDOCARDITIS ASSOCIATED WITH PREEXISTING CARDIAC DISORDERS

RELATIVELY HIGH RISK	INTERMEDIATE RISK	VERY LOW OR NEGLIGIBLE RISK*
Prosthetic heart valves	Mitral valve prolapse with regurgitation (murmur) or thickened valve leaflets	Mitral valve prolapse without regurgitation (murmur) or thickened valve leaflets
Previous infective endocarditis*		
Cyanotic congenital heart disease*	Pure mitral stenosis	
Patent ductus arteriosus	Tricuspid valve disease	Trivial valvular regurgitation on echocardiography without structural abnormality
Aortic regurgitation	Pulmonary stenosis	
Aortic stenosis	Asymmetrical septal hypertrophy	

Mitral regurgitation	Bicuspid aortic valve or calcific aortic sclerosis with minimal hemodynamic abnormality	Isolated atrial septal defect (secundum)
Mitral stenosis and regurgitation		Arteriosclerotic plaques
Ventricular septal defect		Coronary artery disease
Coarctation of the aorta	Degenerative valvular disease in elderly patients	Cardiac pacemaker, implanted defibrillators
Surgically repaired intracardiac lesion with residual hemodynamic abnormality or prosthetic device	Surgically repaired intracardiac lesions with minimal or no hemodynamic abnormality, less than 6 mo after operation	Surgically repaired intracardiac lesions, with minimal or no hemodynamic abnormality, more than 6 mo after operation (atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis)
Surgically constructed systemic-pulmonary shunts*		
		Prior coronary bypass graft surgery
		Prior Kawasaki's disease or rheumatic fever without valvular dysfunction
Adapted from Durack DT: Prevention of infective endocarditis. N Engl J Med 332:38, 1995; and Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations of the American Heart Association from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. JAMA 277:1794, 1997. Copyright 1997 American Medical Association.		

*Prophylaxis against endocarditis not recommended.

Lesions considered at highest risk for endocarditis.

are the most strongly associated with subsequent IE.[154] Because endocarditis has been reported only rarely in association with other gastrointestinal endoscopic procedures with or without biopsy, prophylaxis is not routinely recommended in this situation. Prophylaxis is not recommended with routine cardiac catheterization or TEE.[152] [155]

Based on the frequency of a lesion among patients with endocarditis compared with the general population, lesions have been assigned to high, intermediate, low, and

negligible risk categories (Table 47-15) . [7] [13] [155] [156] [157] [157A] Rheumatic heart disease currently is a less common predisposition for IE in most of the developed countries; however, the attack rate of IE among persons with rheumatic valvular disease approaches that with prosthetic valves and suggests that these lesions entail a high risk also.[158]

The risk of IE for patients with mitral valve prolapse and the resulting role of prophylaxis among these patients have been controversial. Mitral valve prolapse has been identified frequently among patients with IE. However, the risk of endocarditis among patients with mitral valve prolapse and a murmur of mitral regurgitation is still relatively low. It is 5- to 10-fold higher than that in the general population but 100-fold less than that among patients with rheumatic valvular heart disease.[158] As a result, mitral valve prolapse with a murmur of mitral regurgitation or mitral valve thickening and prolapse defines a patient with an intermediate risk for IE and one for whom prophylaxis against endocarditis is recommended.

GENERAL METHODS.

The incidence of IE can be significantly reduced by total surgical correction of some congenital lesions that otherwise predispose patients to IE, e.g., patent ductus arteriosus, ventricular septal defect, and pulmonary stenosis.[7] [157] The incidence of IE remains high among patients who have undergone surgical correction of other major congenital defects, especially those involving a stenotic aortic valve.[7] Patients with persisting as well as many corrected congenital lesions and those with acquired valvular heart disease who remain at risk for IE should be given written material about their predisposing lesion, their risk for endocarditis, and the recommended antibiotic prophylaxis.

Maintenance of attentive oral hygiene which decreases the frequency of bacteremia that accompanies daily activities (chewing, brushing teeth), may be a more important preventive than procedure-focused chemoprophylaxis.[156] Oral hygiene should be addressed before prosthetic valves are placed electively.

Among patients at risk for IE, some activities or procedures likely to induce bacteremia should be avoided. Oral irrigating devices, which may produce bacteremia even in patients with normal gingiva, are not recommended. Similarly, the use of central intravascular catheters and urinary catheters should be minimized. Infections associated with bacteremia must be treated promptly and if possible eradicated before the involved tissues are incised or manipulated.[153]

CHEMOPROPHYLAXIS.

The widely promulgated recommendations of antimicrobial prophylaxis for endocarditis are based on circumstantial evidence supplemented by studies of prophylaxis using animal models. Studies suggest that prophylactic antibiotics prevent endocarditis by inhibiting growth of the bacteria adherent to NBTE sufficiently to allow their subsequent complete elimination by host defenses.[155] [159] Experimental studies that mimic

single-dose amoxicillin prophylaxis in humans suggest adequate margins of efficacy are present after a single prophylactic dose. Nevertheless, because a more sustained inhibitory effect can be achieved through a postprocedure dose of antibiotics this is recommended for patients in the high-risk group.[152] [160]

Clinical studies supporting the efficacy of antibiotic prophylaxis for endocarditis are limited. A retrospective study of patients who had prosthetic valves and who underwent dental and surgical procedures suggested that antibiotic prophylaxis prevented PVE.[161] However, a large case-control study failed to identify dental procedures as a risk for IE among persons with valvular abnormalities and questioned the benefit of antibiotic prophylaxis for these procedures.[162] Additionally, failures of antibiotic prophylaxis unrelated to resistant bacteria have been noted.[155]

Risk-benefit and cost-benefit analyses have raised significant questions about antibiotic prophylaxis for patients with mitral valve prolapse. Unless both the cost and risks of prophylaxis are very low, the cost per case of IE prevented is high and mortality or morbidity may not be reduced. From a population perspective, prophylaxis in low-

TABLE 47-16 -- REGIMENS FOR PROPHYLAXIS AGAINST ENDOCARDITIS: USE WITH GENITOURINARY AND GASTROINTESTINAL (EXCEPT ESOPHAGEAL) PROCEDURES

SETTING	ANTIBIOTIC	REGIMEN*
High-risk patients	Ampicillin plus gentamicin	Ampicillin 2.0 gm IV/IM plus gentamicin 1.5 mg/kg within 30 min of procedure, repeat ampicillin 1.0 gm IV/IM or give amoxicillin 1.0 gm PO 6 hr later
High-risk, penicillin-allergic patients	Vancomycin plus gentamicin	Vancomycin 1.0 gm IV over 1-2 hr plus gentamicin 1.5 mg/kg IM/IV infused or injected 30 min before procedure. No second dose recommended
Moderate-risk patients	Amoxicillin or ampicillin	Amoxicillin 2.0 gm PO 1 hr before procedure or ampicillin 2.0 gm IM/IV 30 min before procedure
Moderate-risk, penicillin-allergic patients	Vancomycin	Vancomycin 1.0 gm IV infused over 1-2 hr and completed within 30 min of procedure

Adapted from Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations by the American Heart Association from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. JAMA 277:1794-1801, 1997.

*Dosing for children: ampicillin 50 mg/kg IV/IM, vancomycin 20 mg/kg IV, gentamicin 1.5 mg/kg IV/IM

(children's doses should not exceed adult doses).

to intermediate-risk settings may not be cost or risk beneficial, and prophylaxis might be reserved for patients who have high-risk cardiac lesions and who are undergoing high-risk procedures.[162]

Even if antibiotic prophylaxis is effective as well as safe and inexpensive, only a small percentage of the cases are preventable. For example, only 55 to 75 percent of patients with NVE have preexisting endocarditis-prone valvular disease, and many are not aware of the lesion before the onset of NVE.[4] [5] [155] [156] Additionally, among patients with IE, only a small fraction (5 percent) had both a known valve lesion and a procedure within 30 days of onset of IE that would have warranted prophylaxis.[156] Nevertheless, the morbidity and mortality associated with IE are used to justify prophylaxis (Table 47-16; see Table 43-4) in patients who have high- and intermediate-risk cardiac lesions (see Table 47-15) and who are to undergo bacteremia-inducing procedures (see Table 47-14) . Penicillin-resistant flora may emerge among patients who are receiving continuous penicillin for prevention of rheumatic fever or repetitive courses of antibiotics for serial dental procedures. Consequently, a nonpenicillin prophylaxis regimen is preferred for these patients. Initiation of prophylaxis several days before a procedure encourages the emergence of antibiotic-resistant organisms at the mucosal site and is not recommended.

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GUIDELINES
PREVENTION, EVALUATION, AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

THOMAS H. LEE

Guidelines for antibiotic prophylaxis were issued by the American Heart Association (AHA) in 1997.[1] These guidelines represented a major departure from prior recommendations by emphasizing that most cases are not attributable to an invasive procedure. According to these guidelines, patients with preexisting cardiac disease should be divided into high-, moderate-, and negligible-risk categories on the basis of their potential outcomes if endocarditis were to develop (see Table 47-15) . For dental work, for example, antibiotic prophylaxis is recommended only for patients who have high- and moderate-risk cardiac conditions and who are undergoing high-risk procedures (Table 47-G-1) . For nondental procedures, endocarditis prophylaxis is recommended only for high-risk patients undergoing high-risk procedures (see Table 47-15) ; this strategy is considered optional for medium-risk patients. Antibiotic regimens are described in Table 47-16 .

The 1998 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for patients with valvular heart disease[2] endorse the earlier guidelines from the AHA, with a few caveats (Table 47-G-2) . The ACC/AHA guidelines recommend antibiotic prophylaxis for patients with hypertrophic cardiomyopathy only when latent or resting obstruction is a factor. In addition, the ACC/AHA committee expressed concern that an increased risk for endocarditis may exist for some patients with mitral valve prolapse without regurgitation; hence, this group was not willing to state that antibiotic prophylaxis was inappropriate for such patients. Instead, the ACC/AHA guidelines indicate that this issue must be addressed by using clinical judgment in individual cases.

Finally, the ACC/AHA guidelines specified that antibiotic prophylaxis was not necessary for patients with physiological mitral regurgitation in the absence of a murmur.

INDICATIONS FOR ECHOCARDIOGRAPHY

Echocardiography is strongly supported in virtually all patients with suspected or known infective endocarditis, but the 1997 ACC/AHA guidelines on echocardiography[3] do *not* recommend transesophageal echocardiography (TEE) as the initial test of choice in the diagnosis of native valve endocarditis (see Table 47-G-2) . Instead, the guidelines urge use of TEE when specific questions are not adequately addressed by the initial transthoracic echocardiography (TTE) evaluation, such as when the TTE study is of poor quality, when the TTE is nondiagnostic despite a high clinical suspicion of endocarditis, when a prosthetic valve is involved, when there is a high suspicion such as in

TABLE 47--G-1 -- DENTAL PROCEDURES AND ENDOCARDITIS PROPHYLAXIS[1]

Endocarditis Prophylaxis Recommended for Patients with High- and Moderate-Risk Cardiac Conditions (see Table 47-1)
Dental extractions
Periodontal procedures including surgery, scaling and root planing, probing, and recall maintenance
Dental implant placement and reimplantation of avulsed teeth
Endodontic (root canal) instrumentation or surgery only beyond the apex
Subgingival placement of antibiotic fibers or strips
Initial placement of orthodontic bands but not brackets
Intraligamentary local anesthetic injections
Prophylactic cleaning of teeth or implants where bleeding is anticipated
Endocarditis Prophylaxis Not Recommended
Restorative dentistry* (operative and prosthodontic) with or without retraction cord
Local anesthetic injections (nonintraligamentary)
Intracanal endodontic treatment; post placement and buildup
Placement of rubber dams
Postoperative suture removal
Placement of removable prosthodontic or orthodontic appliances
Taking of oral impressions
Fluoride treatments
Taking of oral radiographs

Orthodontic appliance adjustment
Shedding of primary teeth
From Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations by the American Heart Association. Circulation 96:358-366, 1997.

*This includes restoration of decayed teeth (filling cavities) and replacement of missing teeth.

Clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.

TABLE 47--G-2 -- ACC/AHA GUIDELINES FOR PREVENTION, EVALUATION, AND TREATMENT OF ENDOCARDITIS[2] [3]

Indication	Class I*	Class IIa	Class IIb	Class III§
Antibiotic endocarditis prophylaxis for patients with mitral valve prolapse undergoing procedures associated with bacteremia	1. Patients with characteristic systolic click-murmur complex 2. Patients with isolated systolic click and echocardiographic evidence of MVP and MR	1. Patients with isolated systolic click, echocardiographic evidence of high-risk MVP		1. Patients with isolated systolic click and equivocal or no evidence of MVP

Echocardiography in infective endocarditis: Native valves (from 3)	1. Detection and characterization of valvular lesions, their hemodynamic severity, and/or ventricular compensation¶ 2. Detection of vegetations and characterization of lesions in patients with congenital heart disease in whom infective endocarditis is suspected 3. Detection of associated abnormalities (e.g., abscesses, shunts)¶ 4. Reevaluation studies in complex endocarditis (e.g., virulent organism, severe hemodynamic lesion, aortic valve involvement, persistent fever or bacteremia, clinical change, or symptomatic deterioration) 5. Evaluation of patients with high clinical suspicion of culture-negative endocarditis¶	1. Evaluation of bacteremia without a known source¶ 2. Risk stratification in established endocarditis¶	1. Routing reevaluation in uncomplicated endocarditis during antibiotic therapy	1. Evaluation of fever and nonpathological murmur without evidence of bacteremia

Echocardiography in infective endocarditis: Prosthetic valves (from 3)	1. Detection and characterization of valvular lesions, their hemodynamic severity, and/or ventricular compensation¶ 2. Detection of associated abnormalities (e.g., abscesses, shunts)¶ 3. Reevaluation in complex endocarditis (e.g., virulent organism, severe hemodynamic lesion, aortic valve involvement, persistent fever or bacteremia, clinical change, or symptomatic deterioration) 4. Evaluation of suspected endocarditis and negative cultures¶ 5. Evaluation of bacteremia without a known source¶	1. Evaluation of persistent fever without evidence of bacteremia or new murmur¶	1. Routine reevaluation in uncomplicated endocarditis during antibiotic therapy¶	1. Evaluation of transient fever without evidence of bacteremia or new murmur

Surgery for native valve endocarditis (criteria also apply to repaired mitral and aortic allograft or autograft valves)	1. Acute AF or MR with heart failure 2. Acute AF with tachycardia and early closure of the mitral valve 3. Fungal endocarditis 4. Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm 5. Evidence of valve dysfunction and persistent infection after a prolonged period (7 to 10 days) of appropriate antibiotic therapy, as indicated by presence of fever, leukocytosis, and bacteremia, provided there are no noncardiac causes of infection	1. Recurrent emboli after appropriate antibiotic therapy 2. Infection with gram-negative organisms or organisms with a poor response to antibiotics in patients with evidence of valve dysfunction	1. Mobile vegetations >10 mm	1. Early infections of the mitral valve that can likely be repaired 2. Persistent pyrexia and leukocytosis with negative blood cultures

Surgery for prosthetic valve endocarditis (criteria exclude repaired mitral and aortic allograft or autograft valves)	1. Early prosthetic valve endocarditis (first 2 months or less after surgery) 2. Heart failure with prosthetic valve dysfunction 3. Fungal endocarditis 4. Staphylococcal endocarditis not responding to antibiotic therapy 5. Evidence of paravalvular leak, annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new-onset conduction disturbances 6. Infection with gram-negative organisms or organisms with a poor response to antibiotics	1. Persistent bacteremia after a prolonged course (7 to 10 days) of appropriate antibiotic therapy without noncardiac causes of bacteremia 2. Recurrent peripheral embolus despite therapy	1. Vegetation of any size on or near the prosthesis

AF=atrial fibrillation; MR=mitral regurgitation; MVP=mitral valve prolapse.

*Procedure or treatment is beneficial, useful, and effective.

Weight of evidence in favor of usefulness/efficacy.

Usefulness/efficacy less well established.
§Procedure or treatment not considered useful or effective.
¶Transesophageal echocardiography may provide incremental value in addition to information obtained by transthoracic imaging.

a patient with staphylococcus bacteremia, or in an elderly patient with valvular abnormalities that make diagnosis difficult.

Diagnosis of prosthetic valve endocarditis with TTE is more difficult than diagnosis of

endocarditis of native valves. Thus, the ACC/AHA guidelines suggest a lower threshold for performance of TEE in patients with prosthetic valves and suspected endocarditis (see Table 47-G-2) .

SURGERY FOR ACTIVE ENDOCARDITIS

The ACC/AHA guidelines for valvular heart disease support performance of surgery for patients with life-threatening congestive heart failure or cardiogenic shock due to active endocarditis. Indications for surgery for patients with stable endocarditis are considered less clear (see Table 47-G-2) .

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Chapter 48 - The Cardiomyopathies and Myocarditides

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The cardiomyopathies constitute a group of diseases in which the dominant feature is direct involvement of the heart muscle itself. They are distinctive because they are *not* the result of pericardial, hypertensive, congenital, valvular, or ischemic diseases. Although the diagnosis of cardiomyopathy requires the exclusion of these etiological factors, the features of cardiomyopathy are often sufficiently distinctive--both clinically and hemodynamically--to allow a definitive diagnosis to be made.[1] With increasing awareness of this condition, along with improvements in diagnostic techniques, cardiomyopathy is being recognized as a significant cause of morbidity and mortality.[2] Whether the result of improved recognition or of other factors, the incidence and prevalence of cardiomyopathy appear to be increasing.[2] Although coronary artery disease is the most common cause of congestive heart failure (accounting for about two thirds of all cases), we avoid using the term *cardiomyopathy* in this setting, because the primary problem is in the coronary arteries and not the heart muscle itself.

TABLE 48-1 -- CLASSIFICATION OF THE CARDIOMYOPATHIES

DISORDER	DESCRIPTION

Dilated cardiomyopathy	Dilatation and impaired contraction of the left or both ventricles. Caused by familial/genetic, viral and/or immune, alcoholic/toxic, or unknown factors, or is associated with recognized cardiovascular disease.
Hypertrophic cardiomyopathy	Left and/or right ventricular hypertrophy, often asymmetrical, which usually involves the interventricular septum. Mutations in sarcoplasmic proteins cause the disease in many patients.
Restrictive cardiomyopathy	Restricted filling and reduced diastolic size of either or both ventricles with normal or near-normal systolic function. Is idiopathic or associated with other disease (e.g., amyloidosis, endomyocardial disease).
Arrhythmogenic right ventricular cardiomyopathy	Progressive fibrofatty replacement of the right, and to some degree left, ventricular myocardium. Familial disease is common.
Unclassified cardiomyopathy	Diseases that do not fit readily into any category. Examples include systolic dysfunction with minimal dilatation, mitochondrial disease, and fibroelastosis.
Specific Cardiomyopathies	
Ischemic cardiomyopathy	Presents as dilated cardiomyopathy with depressed ventricular function not explained by the extent of coronary artery obstructions or ischemic damage.
Valvular cardiomyopathy	Presents as ventricular dysfunction that is out of proportion to the abnormal loading conditions produced by the valvular stenosis and/or regurgitation.
Hypertensive cardiomyopathy	Presents with left ventricular hypertrophy with features of cardiac failure due to systolic or diastolic dysfunction.
Inflammatory cardiomyopathy	Cardiac dysfunction as a consequence of myocarditis.
Metabolic cardiomyopathy	Includes a wide variety of causes, including endocrine abnormalities, glycogen storage disease, deficiencies (such as hypokalemia), and nutritional disorders.
General systemic disease	Includes connective tissue disorders and infiltrative diseases such as sarcoidosis and leukemia.
Muscular dystrophies	Includes Duchenne, Becker-type, and myotonic dystrophies.
Neuromuscular disorders	Includes Friedreich ataxia, Noonan syndrome, and lentiginosis.
Sensitivity and toxic reactions	Includes reactions to alcohol, catecholamines, anthracyclines, irradiation, and others.
Peripartal cardiomyopathy	First becomes manifest in the peripartum period, but it is likely a heterogeneous group.

Derived from Richardson P, McKenna W, Bristow M, et al: Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. Circulation 93:841, 1996. Copyright 1996, American Heart Association.

Figure 48-1 Diagram comparing three morphologic types of cardiomyopathies of unknown cause. Ao = aorta; LA = left atrium; LV = left ventricle. *(From Waller BF: Pathology of the cardiomyopathies. J Am Soc Echocardiogr 1:4, 1988.)*

Figure 48-2 Gross pathology of dilated cardiomyopathy. Prominent ventricular dilatation is apparent in this heart, which has been opened so that the interior of the left ventricle can be seen. Wall thickness is normal, but the shape of the heart has become more globular. (From Kasper EK, Hruban RH, Baughman KL: Idiopathic dilated cardiomyopathy. \i\In\r\ Abelmann WH, Braunwald E ;obeds.;cb: Atlas of Heart Diseases. Vol 2. Cardiomyopathies, Myocarditis, and Pericardial Disease. Philadelphia, Current Medicine, 1995, pp 3.1-3.18.)

A variety of schemes have been proposed for classifying the cardiomyopathies. The most widely recognized classification is that promulgated jointly by the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) (Table 48-1) .[3] In the WHO/ISFC classification, the cardiomyopathies are classified based on their predominant pathophysiological features; other diseases that affect the myocardium that are associated with a specific cardiac disorder or are part of a generalized systemic disorder are termed *specific cardiomyopathies* (in the previous WHO/ISFC classification, they were termed *specific heart muscle diseases*).[3]

Three basic types of functional impairment have been described (Fig. 48-1; Table 48-2) : (1) *dilated* (DCM, formerly called congestive), the most common form, accounting for 60 percent of all cardiomyopathies[4] and characterized by ventricular dilatation, contractile dysfunction, and often symptoms of congestive heart failure (Fig. 48-2) ; (2) *hypertrophic* (HCM), recognized by inappropriate left ventricular hypertrophy, often with asymmetrical involvement of the interventricular septum, with preserved or enhanced contractile function until late in the course; and (3) *restrictive* (RCM), the least common form in western countries, marked by impaired diastolic filling and in some cases with endocardial scarring of the ventricle. Two other forms of cardiomyopathy are recognized: *arrhythmogenic right ventricular cardiomyopathy* and *unclassified;* the latter includes fibroelastosis, systolic dysfunction with minimal dilatation, and mitochondrial involvement.[3] The distinction

TABLE 48-2 -- FUNCTIONAL CLASSIFICATION OF THE CARDIOMYOPATHIES

	DILATED	RESTRICTIVE	HYPERTROPHIC

Symptoms	Congestive heart failure, particularly left sided	Dyspnea, fatigue	Dyspnea, angina pectoris
	Fatigue and weakness	Right-sided congestive heart failure	Fatigue, syncope, palpitations
	Systemic or pulmonary emboli	Signs and symptoms of systemic disease: amyloidosis, iron storage disease, etc.	
Physical Examination	Moderate to severe cardiomegaly: S_3 and S_4	Mild to moderate cardiomegaly: S_3 or S_4	Mild cardiomegaly
			Apical systolic thrill and heave; brisk carotid upstroke
	Atrioventricular valve regurgitation, especially mitral	Atrioventricular valve regurgitation; inspiratory increase in venous pressure (Kussmaul sign)	S_4 common Systolic murmur that increases with Valsalva maneuver
Chest Roentgenogram	Moderate to marked cardiac enlargement, especially left ventricular	Mild cardiac enlargement	Mild to moderate cardiac enlargement
	Pulmonary venous hypertension	Pulmonary venous hypertension	Left atrial enlargement
Electrocardiogram	Sinus tachycardia	Low voltage	Left ventricular hypertrophy
	Atrial and ventricular arrhythmias	Intraventricular conduction defects	ST segment and T wave abnormalities
	ST segment and T wave abnormalities	Atrioventricular conduction defects	Abnormal Q waves
	Intraventricular conduction defects		Atrial and ventricular arrhythmias
Echocardiogram	Left ventricular dilatation and dysfunction	Increased left ventricular wall thickness and mass	Asymmetrical septal hypertrophy (ASH)

	Abnormal diastolic mitral valve motion secondary to abnormal compliance and filling pressures	Small or normal-sized left ventricular cavity	Narrow left ventricular outflow tract
		Normal systolic function	Systolic anterior motion (SAM) of the mitral valve
		Pericardial effusion	Small or normal-sized left ventricle
Radionuclide Studies	Left ventricular dilatation and dysfunction (RVG)	Infiltration of myocardium (^{201} Tl)	Small or normal-sized left ventricle (RVG)
		Small or normal-sized left ventricle (RVG)	Vigorous systolic function (RVG)
		Normal systolic function (RVG)	Asymmetrical septal hypertrophy (RVG or ^{201} Tl)
Cardiac Catheterization	Left ventricular enlargement and dysfunction	Diminished left ventricular compliance	Diminished left ventricular compliance
	Mitral and/or tricuspid regurgitation	"Square root sign" in ventricular pressure recordings	Mitral regurgitation
			Vigorous systolic function
	Elevated left- and often right-sided filling pressures	Preserved systolic function	Dynamic left ventricular outflow gradient
		Elevated left- and right-sided filling pressures	
	Diminished cardiac output		

RVG=Radionuclide ventriculogram; ^{201} Tl=thallium-201.

TABLE 48-3 -- CLINICAL INDICATIONS FOR ENDOMYOCARDIAL BIOPSY

DEFINITE
Monitoring of cardiac allograft rejection
Monitoring of anthracycline cardiotoxicity
POSSIBLE
Detection and monitoring of myocarditis
Diagnosis of secondary cardiomyopathies
Differentiation between restrictive and constrictive heart disease
UNCERTAIN
Unexplained, life-threatening ventricular tachyarrhythmias
Acquired immunodeficiency syndrome
Formulation of prognosis in idiopathic dilated cardiomyopathy
From Mason JW, O'Connell JB: Clinical merit of endomyocardial biopsy. Circulation 79:971, 1989. Copyright 1989, American Heart Association.

between the three major functional categories is not absolute, and often there is overlap; in particular, patients with HCM also have increased wall stiffness (as a consequence of the myocardial hypertrophy) and thus present some of the features of an RCM.[3] Late in their course, ventricular dilation and systolic heart failure, bearing some resemblance to DCM, may occur.

Examples of *specific cardiomyopathies* include ischemic cardiomyopathy, valvular cardiomyopathy, hypertensive cardiomyopathy, and inflammatory cardiomyopathy (myocarditis with cardiac dysfunction) (see Table 48-1). [3] Most forms of specific cardiomyopathy are characterized by the DCM pattern. The term *ischemic cardiomyopathy* (see Chap. 37) has been used to describe the condition in which coronary artery disease causes multiple infarctions, diffuse fibrosis, and/or severe ischemia that leads to left ventricular dilatation with congestive heart failure; it may or may not be associated with angina pectoris.[5]

Endomyocardial Biopsy

Evaluation of some patients suspected of suffering from a cardiomyopathy has been facilitated by the use of endomyocardial biopsy.[6] Using a flexible bioptome, the clinician may obtain tissue samples from the right ventricle (and left ventricle when required) through a transvenous (or transarterial) approach with ease and safety (see Chap. 11). The availability of disposable transfemoral bioptomes has further facilitated endomyocardial biopsy. Two-dimensional echocardiography may help guide the placement of the bioptome and reduce or eliminate radiation exposure.[7] Endomyocardial biopsy results in a small tissue sample (average size 1 to 2 mm), and multiple samples (usually four or more) are required because pronounced topographical variations may be found within the myocardium. Which patients should be subjected to

biopsy remains controversial, but there is general agreement that biopsy may be of benefit in certain specific situations (Table 48-3) . [6] There is little debate as to its clinical utility in detecting infiltrative disorders of the myocardium and in monitoring for anthracycline cardiotoxicity and cardiac transplant rejection.

Although on occasion endomyocardial biopsy may identify a specific etiological agent in an individual patient with cardiac disease of uncertain cause (Table 48-4) , the clinical utility of routine biopsy in cardiomyopathy is limited (particularly because no definitive pattern has been found in DCM) (Fig. 48-3) .[8] [9] It has been estimated that a specific etiological diagnosis is obtained by biopsy in fewer than 10 percent of patients with cardiomyopathy and a treatable disease is found in only about 2 percent.[6]

DALLAS CRITERIA.

Interpretation of biopsy specimens had been plagued by a high degree of interobserver variability; the adoption of a generally accepted set of histological definitions, the *Dallas criteria,* has improved agreement.[10] It is hoped that newer immunohistochemical and molecular biological techniques (such as the polymerase chain reaction or in situ hybridization techniques to detect viral infection of the heart) may expand further the diagnostic utility of endomyocardial biopsy.[10] [11] [12]

TABLE 48-4 -- SPECIFIC DIAGNOSES THAT CAN BE CONFIRMED BY MYOCARDIAL BIOPSY

Cardiac allograft rejection	Fabry disease of the heart	Henoch-Schonlein purpura
Myocarditis	Carcinoid disease	Rheumatic carditis
Giant cell myocarditis	Irradiation injury	Chagasic cardiomyopathy
Doxorubicin cardiotoxicity	Glycogen storage disease	Chloroquine cardiomyopathy
Cardiac amyloidosis	Cardiac tumors of cardiac origin	Lyme carditis
Cardiac sarcoidosis	Cardiac tumors of noncardiac origin	Carnitine deficiency cardiomyopathy
Cardiac hemochromatosis	Kearns-Sayre syndrome	Right ventricular lipomatosis
Endocardial fibrosis	Cytomegalovirus infection	Hypereosinophilic syndrome
Endocardial fibroelastosis	Toxoplasmosis	

From Mason JW, O'Connell JB: Clinical merit of endomyocardial biopsy. Circulation 79:971, 1989. Copyright 1989, American Heart Association.

Figure 48-3 Histological specimens obtained by right ventricular endomyocardial biopsy. *A,* Idiopathic dilated cardiomyopathy with varying degrees of interstitial fibrosis and myocyte hypertrophy (trichrome stain, 210×). *B,* Myocarditis with dense focal area of mononuclear cell infiltrate adjacent to necrotic and degenerating myocytes, with irregular myocytic hypertrophy and dense interstitial fibrosis (hematoxylin-eosin, 210×). *(From Dec GW, Fuster V: Idiopathic dilated cardiomyopathy. N Engl J Med 331:1564, 1994. Copyright 1994, Massachusetts Medical Society.)*

Dilated Cardiomyopathy

IDIOPATHIC DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is a syndrome characterized by cardiac enlargement and impaired systolic function of one or both ventricles (see Fig. 48-2). Although it was formerly called congestive cardiomyopathy, the term *dilated cardiomyopathy* is now preferred because the earliest abnormality usually is ventricular enlargement and systolic contractile dysfunction, with the signs and symptoms of congestive heart failure often (but not invariably) developing later. In an occasional patient, the predominant finding is that of contractile dysfunction with only a mildly dilated left ventricle. In the WHO/ISFC classification scheme, this variant of DCM is placed in the unclassified cardiomyopathy group. Conversely, apparently normal elite athletes may demonstrate considerable ventricular enlargement with *normal* systolic performance. It is presumed that this is a physiological adaptation to intense athletic training and does not appear to represent a disease state, although the long-term consequences are not fully known.[13]

The incidence of DCM is reported to be 5 to 8 cases per 100,000 population per year and appears to be increasing, although the true figure likely is higher as a consequence of underreporting of mild or asymptomatic cases.[14] It occurs almost three times more frequently in blacks and males as in whites and females, and this difference does not appear to be related solely to differing degrees of hypertension, cigarette smoking, or alcohol use.[2] [15] [16] Survival in blacks and males appears to be worse than in whites and females.[17]

Although the cause is not definable in many cases, more than 75 specific diseases of heart muscle can produce the clinical manifestations of DCM. It is likely that this condition represents a final common pathway that is the end result of myocardial damage produced by a variety of cytotoxic, metabolic, immunological, familial, and infectious mechanisms. Alcohol, for example, may lead to severe cardiac dysfunction and may produce clinical, hemodynamic, and pathological findings identical to those present in idiopathic DCM (see p. 1758).

NATURAL HISTORY.

The natural history of DCM is not well established. Many patients have minimal or no symptoms, and the progression of the disease in these patients is unclear, although there is some evidence that the long-term prognosis is not good.[18] Nevertheless, in symptomatic patients the course usually is one of progressive deterioration, with one quarter of newly diagnosed patients referred to major medical centers dying within a year and half dying within 5 years, although a minority improve, with a reduction in cardiac size and longer survival.[14] Recent data suggest that in patients with mild dilatation not referred to a medical center the prognosis may be more favorable, no doubt reflecting at least in part earlier diagnosis and perhaps more effective treatment options now available in the community.[1] [19] [20] About a fourth of patients with recent-onset DCM improve spontaneously, even some sick enough initially to be considered for cardiac transplantation.[21] In some patients clinical and functional improvement may occur years after initial presentation.

PROGNOSIS.

A variety of clinical predictors of patients at enhanced risk of dying of DCM have been identified, including the presence of a protodiastolic (S_3) gallop, ventricular arrhythmias, advanced age, and specific endomyocardial biopsy features.[22] However, the predictive reliability of any single feature is not high,[23] and it may be difficult to predict with any accuracy the clinical course and outcome in an individual patient.[14] [20] Nevertheless, greater ventricular enlargement and worse dysfunction tend to correlate with poorer prognosis,[16] [22] [24] particularly if the right ventricle is dilated and dysfunctional as well.[25]

Cardiopulmonary exercise testing also can provide prognostic information (see Chap. 6). Marked limitation of exercise capacity manifested by reduced maximal systemic oxygen uptake (especially when below 10 to 12 ml/kg/min) is a reliable predictor of mortality and is used widely as an indicator for consideration of cardiac transplantation.[14] [16] It has been suggested that specific endomyocardial biopsy morphological findings (such as loss of intracellular myofilaments) may offer some predictive information regarding prognosis.[14] [26]

Pathology

MACROSCOPIC EXAMINATION.

This reveals enlargement and dilatation of all four cardiac chambers; the ventricles are more dilated than the atria (see Fig. 48-2). Although the thickness of the ventricular wall is increased in some cases, the degree of hypertrophy often is less than might be expected given the severe dilatation present.[14] The development of left ventricular hypertrophy appears to have a protective or beneficial role in DCM, presumably because it reduces systolic wall stress and thus protects against further cavity dilatation. The cardiac valves are intrinsically normal, and intracavitary thrombi, particularly in the

ventricular apex, are common.[14] The coronary arteries usually are normal. The right ventricle is preferentially involved in some cases of DCM, sometimes on a familial basis.

HISTOLOGICAL EXAMINATION.

Microscopic study reveals extensive areas of interstitial and perivascular fibrosis, particularly involving the left ventricular subendocardium (see Fig. 48-3). Small areas of necrosis and cellular infiltrate are seen on occasion, but these typically are not prominent features. There is marked variation in myocyte size; some myocardial cells are hypertrophied, and others are atrophied. No viruses or other etiological agents have been identified with any regularity in tissue from patients with DCM. Particularly disappointing has been the failure to identify any immunological, histochemical, morphological, ultrastructural, or microbiological marker that might be used to establish the diagnosis of idiopathic DCM or to clarify its cause.

Etiology

About a fourth of the cases of congestive heart failure in the United States are due to idiopathic DCM[27] ; most of the remainder are caused by the sequelae of coronary artery or hypertensive heart disease. It is likely that idiopathic DCM represents a common expression of myocardial damage that has been produced by a variety of as yet unestablished myocardial insults. Although the cause(s) remain unclear, interest has centered on three possible basic mechanisms of damage: (1) familial and genetic factors; (2) viral myocarditis and other cytotoxic insults; and (3) immunological abnormalities (Figs. 48-4 and 48-5) .[14] [28]

Familial linkage of DCM occurs more commonly than often is appreciated. In 20 percent or more of patients, a first-degree relative also shows evidence of DCM, suggesting that familial transmission is relatively frequent.[20] [29] [30] [31] [32] [33] [299A] Some asymptomatic relatives of patients with DCM have subclinical left ventricular enlargement and/or dysfunction that may progress to overt symptomatic DMC.[29] Most familial cases demonstrate autosomal dominant transmission; six chromosomal loci have been identified, and more are likely to be found.[34] However, the disease is genetically quite heterogeneous[32] and autosomal recessive [35] and X-linked inheritance[36] have been found. One form of familial X-linked DCM is due to a deletion in the promoter region and the first exon of the gene that codes for the protein dystrophin, a component of the cytoskeleton of myocytes.[37] [38] This has fueled speculation that a resulting deficiency of cardiac dystrophin is the cause of the associated DCM (see also Chap. 21). Mutations involving mitochondrial DNA have been reported as well. [39] [40] [41]

Whether any of the patients without apparent familial linkage has a genetic predisposition to DCM remains un

Figure 48-4 Diagram showing the cardiac myocyte and the molecules that have been implicated in dilated cardiomyopathy. The actin cytoskeleton is linked to the extracellular matrix by dystrophin and the dystrophin-associated glycoprotein complex. Linkage of the actin cytoskeleton to the contractile

apparatus is hypothesized to occur through the muscle LIM (Lin-11, Isl-1, Mec-3) protein (MLP). A nuclear transcription factor, cyclic AMP response-element binding protein (CREB), is shown binding to a cyclic AMP response element in the myocyte DNA. Mutations in dystrophin and other members of the dystrophin-associated glycoprotein complex, as well as in MLP and CREB, have all been shown to result in dilated cardiomyopathy in mice or humans. (From Leiden JD: The genetics of dilated cardiomyopathy: Emerging clues to the puzzle. N Engl J Med 337:1080, 1997. Copyright 1997, Massachusetts Medical Society.)

Figure 48-5 Hypotheses to explain the pathogenesis of dilated cardiomyopathy. MHC=myosin heavy chain. *(From Mestroni L, Krajinovic M, Severini GM, et al: Familial dilated cardiomyopathy. Br Heart J 72:S35, 1994.)*

known. There is great interest in using molecular genetic techniques to identify markers of disease susceptibility in asymptomatic carriers at risk for the eventual development of overt clinical DCM.[36] [42] An example of such a marker may be the angiotensin-converting enzyme DD genotype that is found with increased frequency in DCM patients.[43] One intriguing familial metabolic deficiency is that of carnitine, with improvement occurring in the myopathy with carnitine repletion.[44]

SEQUELA OF VIRAL MYOCARDITIS.

Wide speculation exists that an episode of subclinical viral myocarditis initiates an autoimmune reaction that culminates in the development of full-blown DCM.[27] [45] Although this hypothesis is inviting, it remains largely unsupported[46] ; it has been estimated that only about 15 percent of patients with myocarditis progress to DCM. In some patients who exhibit the clinical features of DCM, endomyocardial biopsy reveals evidence of an inflammatory myocarditis (see Fig. 48-3 *B*). The reported frequency of evidence of an inflammatory infiltrate in DCM varies widely and undoubtedly depends largely on patient selection and the criteria used for diagnosis; using rigorous criteria, only about 10 percent (or less) of patients with DCM have biopsy evidence of myocarditis.[6] Other evidence favoring the concept that DCM is a postviral disorder includes the presence of high antibody viral titers, viral-specific RNA sequences, and apparent viral particles in patients with "idiopathic" DCM.[47] On the other hand, the more rigorous technique of polymerase chain reaction generally has not confirmed the presence of viral remnants in the myocardium of most cardiomyopathy patients,[48] although data are conflicting.[49] [50]

AUTOIMMUNITY.

Abnormalities of both humoral and cellular immunity have been found in patients with DCM,[28] [51] [52] although the findings have not been completely reproducible. There is speculation that antibodies might be the *result* of myocardial damage, rather than the cause.[53] There appears to be an association with specific HLA Class II antigens (particularly DR4), suggesting that abnormalities of immunoregulation may play a role in DCM.[31] [54] Circulating antimyocardial antibodies to a variety of antigens (including the myosin heavy chain, the beta adrenoreceptor, the muscarinic receptor, laminin, and mitochondrial proteins) have been identified.[28] [55] [56] [57] Additional evidence for the

significance of circulating antimyocardial antibodies comes from the demonstration of short-term clinical improvement in the manifestations of heart failure in a small number of patients treated with immunoadsorption and elimination of anti-beta$_1$ -adrenergic receptor antibodies. [58] [58A] [58B] Abnormalities of various T cells, including cytotoxic T cells, suppressor T lymphocytes, and natural killer cells, have been found in some studies.[14] [59] These immunological abnormalities may be the consequence of prior viral myocarditis.[59] It has been postulated that viral components may be incorporated into the cardiac sarcolemma, only to serve as an antigenic source that directs the immune response to attack the myocardium. Nevertheless, the precise

role of either humoral or cellular immunomodulation in the pathogenesis of DCM remains unestablished.[14]

PROINFLAMMATORY CYTOKINES.

A variety of proinflammatory cytokines such as tumor necrosis factor-alpha (and the related tumor necrosis factor-alpha converting enzyme) are expressed in DCM and may play a role in producing contractile dysfunction; whether viral infection, autoimmune abnormalities, or other factors induce their expression is unknown.[60] [61] Similarly, the vasoconstrictor peptide endothelin is increased in decompensated DCM and has been implicated as a cause of the heightened vascular tone that accompanies congestive heart failure.[62]

OTHER POTENTIAL CAUSES.

A variety of other possible causes have been proposed, although none is accepted as *the* cause of DCM. Thus, endocrine abnormalities as well as the effects of chemicals or toxins have been suggested as possible etiological factors. It has been suggested that microvascular hyperreactivity (spasm) may lead to myocellular necrosis and scarring, with resultant heart failure, although this remains speculative.[5] Apoptosis, or programmed cell death, has been demonstrated in the hearts of patients with DCM and arrhythmogenic right ventricular cardiomyopathy, although there is some controversy regarding the veracity of these findings in DCM.[63] Even if true, the significance of this finding, and whether it is a primary or secondary event in the development of cardiomyopathy, remains unclear. From a clinical standpoint, the more important causes of nonidiopathic DCM include alcohol and cocaine abuse, human immunodeficiency virus (HIV) infection[64] (see Chap. 68), metabolic abnormalities, and the cardiotoxicity of anticancer drugs (especially doxorubicin).

ABNORMALITIES OF THE SYMPATHETIC NERVOUS SYSTEM.

Several abnormalities of the sympathetic nervous system have been demonstrated in DCM, but they appear to be the result rather than the cause of the disease.[14] [65] A

reduction in density of membrane-associated beta adrenoreceptors[66] is believed to be a consequence of the development of anti-beta-adrenoreceptor autoantibodies. An alteration in the signal transmission pathway by which the beta adrenoreceptors stimulate the contractile apparatus (the G-protein system) has been found as well. Inhibition of this system is enhanced in DCM patients, perhaps accounting for their depressed contractile function. An increase of the subunits of the inhibitory guanine nucleotide-binding protein (G_i) has been reported to occur in the membranes of myocytes from failing hearts.[67] This increase in G_i is associated with a striking reduction of basal adenylate cyclase activity and of the positive inotropic effects of isoproterenol and the phosphodiesterase inhibitor milrinone. These findings suggest that the increase of G_i might contribute to the reduced effects of endogenous catecholamines in DCM.

The precise cause of contractile dysfunction at the cellular level in patients with DCM remains speculative. Although there are demonstrable abnormalities of cellular metabolism and calcium handling by cardiomyopathic tissue,[5] [68] [69] [70] the significance of these findings is not yet clear.[62]

Clinical Manifestations

HISTORY.

Symptoms usually develop gradually in patients with DCM. Some patients are asymptomatic and yet have left ventricular dilatation for months or even years. This dilatation may be recognized clinically only later when symptoms develop or when routine chest roentgenography demonstrates cardiomegaly. A relatively small number of patients develop symptoms of heart failure for the first time after recovery from what appears to be a systemic viral infection. In still others, severe heart failure develops acutely during an episode of myocarditis; although some recovery occurs, chronic manifestations of diminished cardiac reserve persist and heart failure reappears months or years later. It is important to question the patient and family carefully about alcohol consumption, because excessive alcohol consumption is a major cause of DCM, and its cessation may result in substantial clinical improvement.[14] Although patients of any age may be affected, the disease is most common in middle age and is more frequent in men than in women.

The most striking symptoms of DCM are those of left ventricular failure. Fatigue and weakness due to diminished cardiac output are common. Right-sided heart failure is a late and ominous sign and is associated with a particularly poor prognosis. Chest pain occurs in about one third of patients and may suggest concomitant ischemic heart disease.[1] [14] The demonstrated reduction in the vasodilator reserve of the coronary microvasculature in DCM suggests that subendocardial ischemia may play a role in the genesis of chest pain that occurs despite angiographically normal coronary arteries.[71] Chest pain secondary to pulmonary embolism and abdominal pain secondary to congestive hepatomegaly are frequent in the late stages of illness.

PHYSICAL EXAMINATION (See also Chaps. 4 and 17).

Examination usually reveals variable degrees of cardiac enlargement and findings of

congestive heart failure. The systolic blood pressure is usually normal or low, and the pulse pressure is narrow, reflecting a diminished stroke volume. *Pulsus alternans* (see Fig. 17-5) is common when severe left ventricular failure is present. Cheyne-Stokes breathing may be present and is associated with a poor prognosis.[72] The jugular veins are distended when right-sided heart failure appears, but on initial presentation most patients do not have evidence of this.[14] Prominent *a* and *v* waves may be visible. Grossly pulsatile jugular veins with prominent regurgitant waves indicate the presence of tricuspid valvular regurgitation; this is usually a late and often ominous finding. The liver may be engorged and pulsatile. Peripheral edema and ascites are present when right-sided heart failure is advanced.

The precordium usually reveals left and, occasionally, right ventricular impulses, but the heaves are not sustained as they are in patients with ventricular hypertrophy. The apical impulse is usually displaced laterally, reflecting left ventricular dilatation. A presystolic *a* wave may be palpable on occasion and is generated in a similar manner as a presystolic (S_4) gallop heard on auscultation. The second heart sound (S_2) is usually normally split, although paradoxical splitting may be detected in the presence of left bundle branch block, an electrocardiographic (ECG) finding that is not unusual in DCM. If pulmonary hypertension is present, the pulmonary component of S_2 may be accentuated and the splitting may be narrow. Presystolic gallop sounds (S_4) are almost universally present and often precede the development of overt congestive heart failure.[14] Ventricular gallops (S_3) are the rule once cardiac decompensation occurs, and a summation gallop is heard when there is concomitant tachycardia.

Systolic murmurs are common and are usually due to mitral or, less commonly, tricuspid valvular regurgitation.[14] Mitral regurgitation results from enlargement and abnormal motion of the mitral annulus; ventricular dilatation with resultant distortion of the geometry of the subvalvular apparatus ("papillary muscle dysfunction") plays a lesser role. Gallop sounds and regurgitant murmurs can often be elicited or intensified by isometric handgrip exercise with its attendant enhancement of systemic vascular resistance and impedance to left ventricular outflow. Systemic emboli resulting from dislodgement of intracardiac thrombi from the left atrium and ventricle and pulmonary emboli that originate in the venous system of the legs are common late complications.

NONINVASIVE LABORATORY EXAMINATIONS.

To identify potentially reversible causes of DCM, several basic screening biochemical tests are indicated, including determination of levels of serum phosphorus (hypophosphatemia), serum calcium (hypocalcemia), and serum creatinine and urea nitrogen (uremia), thyroid function studies (hypothyroidism and hyperthyroidism), and iron studies (hemochromatosis). It is prudent to test for HIV as well, because this infection is an important and often unrecognized cause of congestive heart failure[64] (see Chap. 68). The chest roentgenogram usually reveals generalized cardiomegaly and pulmonary vascular redistribution; interstitial and alveolar edema are less common on initial presentation.[14] Pleural effusions may be present, and the azygos vein and superior vena cava may be dilated when right-sided heart failure supervenes.

Electrocardiography.

The ECG often shows sinus tachycardia when heart failure is present. The entire spectrum of atrial and ventricular tachyarrhythmias may be

seen. Poor R wave progression and intraventricular conduction abnormalities, especially left bundle branch block, are common.[14] Anterior Q waves may be present when there is extensive left ventricular fibrosis, even without a discrete myocardial scar or evidence of coronary artery disease.[14] ST segment and T wave abnormalities are common, as are P wave changes, especially left atrial abnormality. Ambulatory monitoring demonstrates the ubiquity of ventricular arrhythmias, with about half of monitored patients with DCM exhibiting nonsustained ventricular tachycardia.[14] There is no consensus that complex or frequent ventricular arrhythmias predict sudden (presumably arrhythmic) death, although they do appear to predict *total* mortality. [73] Perhaps ventricular arrhythmias as detected on ambulatory monitoring are a marker for the extent of myocardial damage in DCM and therefore are associated with sudden death without necessarily being its cause. In occasional cases, particularly in children, recurrent and/or incessant supraventricular or ventricular tachyarrhythmias may actually be the cause (rather than the result) of ventricular dysfunction.[74] [75] In those cases, restoration of sinus rhythm or slowing of the heart rate may reverse the cardiomyopathy.[76] [77]

Echocardiography.

Two-dimensional and Doppler forms of echocardiography are useful in assessing the degree of impairment of left ventricular function and for excluding concomitant valvular or pericardial disease (see Fig. 7-99).[20] In addition to examining all four cardiac valves for evidence of structural or functional abnormalities, echocardiography allows evaluation of the size of the ventricular cavity and thickness of the ventricular walls. A pericardial effusion may be demonstrated on occasion. Doppler studies are useful in delineating the severity of mitral (and tricuspid) regurgitation. Patients with a pattern of left ventricular filling on Doppler studies that simulates that seen with RCM appear to have more advanced disease.[78] Combining echocardiography with dobutamine infusion may identify patients with left ventricular dysfunction due to coronary artery disease by demonstrating provocable differences in regional wall motion and thus distinguish them from patients with idiopathic DCM.[79] It has been suggested that thallium-201 imaging may be helpful in distinguishing left ventricular enlargement caused by DCM from that caused by coronary artery disease,[80] although there is not complete agreement on this point.[14] [81] Scanning with gallium or antimyosin antibody (see Chap. 9) may help to identify patients more likely to have evidence of myocarditis on biopsy, although whether this finding is useful clinically is not yet established.[14] [82]

Radionuclide Ventriculography.

Like echocardiography, radionuclide ventriculography reveals increased end-diastolic and end-systolic left ventricular volumes, reduced ejection fraction in one or both ventricles, and wall motion abnormalities (see Chap. 9); it is used most commonly when echocardiography is technically suboptimal.[14] Like echocardiography, it may demonstrate segmental wall motion abnormalities in DCM even in the absence of coronary artery disease, the disease process that most commonly produces regional dysfunction. In most patients it is not necessary to carry out serial studies or batteries of noninvasive tests to follow patients with DCM and evaluate their response to treatment; adjustments in pharmacological therapies usually are made based on routine bedside clinical features and symptomatic response.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY.

Only certain patients with DCM require cardiac catheterization (particularly those with chest pain and a suspicion of ischemic disease or patients thought to have a treatable systemic disease such as sarcoidosis or hemochromatosis, where myocardial biopsy is an important part of the catheterization procedure).[14] When cardiac catheterization is carried out, the left ventricular end-diastolic, left atrial, and pulmonary artery wedge pressures usually are elevated. Modest degrees of pulmonary arterial hypertension are common. Advanced cases may demonstrate right ventricular dilatation and failure as well, with resultant elevation of the right ventricular end-diastolic, right atrial, and central venous pressures.

Left ventriculography demonstrates enlargement of this chamber, typically with diffuse reduction in wall motion. Segmental wall motion abnormalities are not uncommon and may simulate the angiographic findings in ischemic heart disease. However, prominent localized wall motion disturbances are more characteristic of ischemic heart disease, whereas diffuse global dysfunction is more typical of DCM. The ejection fraction is reduced and the end-systolic volume is increased as a result of the impairment of left ventricular contractility. Sometimes left ventricular thrombi may be visualized within the left ventricle as intracavitary filling defects. Mild mitral regurgitation is often present. On occasion, it may be difficult to distinguish left ventricular dilatation secondary to severe mitral regurgitation due to intrinsic mitral valve disease from DCM with secondary mitral regurgitation.

Coronary arteriography usually reveals normal vessels, although coronary vasodilatory capacity may be impaired[83] [84] ; in some cases this may relate to marked elevation of the left ventricular filling pressures.[85] This examination may be of particular value in excluding coronary artery disease in patients with abnormal Q waves on the ECG or regional left ventricular wall motion abnormalities on noninvasive evaluation (although noninvasive testing, including electron-beam computed tomography [CT], may be sufficiently reliable to exclude important coronary artery disease without resorting to arteriography).[86] Coronary arteriography, when necessary, thus helps to distinguish between myocardial infarction as a result of obstructive coronary artery disease and extensive localized myocardial fibrosis secondary to severe DCM in the absence of

coronary artery obstruction.

Management

Because the cause of idiopathic DCM, by definition, is unknown, specific therapy is not possible.[27] Treatment, therefore, is for heart failure, as discussed in Chapters 18 and 21 .

Many of the therapeutic approaches are directed at modifying the results of the long-term activation of two interrelated neurohormonal/autocrine-paracrine systems, the adrenergic and renin-angiotensin systems.[87] Physical, dietary, and pharmacological interventions may help to control symptoms; regular physical exercise (as tolerated) increases exercise capacity by improving endothelial dysfunction and augmenting blood flow in skeletal muscles.[88] Only cardiac transplantation (see Chap. 20) and specific pharmacological therapy (the vasodilators enalapril or hydralazine plus nitrates, the beta-adrenoceptor blocker carvedilol, and the aldosterone receptor blocker spironolactone) have been shown to prolong life.[14] [27] [89] [90] [91]

BETA-ADRENERGIC RECEPTOR BLOCKADE.

Because of evidence that activation of the adrenergic system may have deleterious cardiac effects (rather than being an important compensatory mechanism as traditionally thought), beta-adrenoceptor blockade has been suggested as treatment for DCM (see Chaps. 18 and 21).[78] [92] Results to date generally have been favorable, with evidence of improved symptoms, exercise capacity, and left ventricular function and a suggestion that survival has been improved.[14] [93] [94] [95] [96] [97] [97A] Beta-adrenoceptor blockade has been surprisingly well tolerated, with infrequent aggravation of heart failure (which, on occasion, may be profound). The mechanism of beneficial action of beta-adrenoceptor blockers is unknown but may relate to (1) negative chronotropic effect with reduced myocardial oxygen demand, (2) reduced myocardial damage due to catecholamines, (3) improved diastolic relaxation (both early active and late passive properties), (4) inhibition of sympathetically mediated vasoconstriction, (5) increase ("upregulation") in myocardial beta-adrenoceptor density, (6) improved calcium handling at slower heart rates, (7) modulation of postreceptor inhibitory G proteins, and/or (7) a direct effect on myocyte and interstitial growth, with attendant inhibition of the remodeling process (remodeling refers to the change in ventricular shape, size, and geometry that occurs after myocyte dysfunction).[90] [92] [98] [99] [100] Modulation of the remodeling process has also

been implicated in the successful use of growth hormone in a small number of patients with DCM.[101]

Beta-adrenergic blocker therapy is now accepted as part of the four-drug approach (along with digoxin, vasodilators and diuretics) advocated for all suitable patients with

symptomatic congestive heart failure (see Chap. 21). Patients with advanced heart failure or in a decompensated state should not ordinarily be given a beta-adrenergic blocker for fear of worsening the failure.[102] Recent data indicate that carvedilol (a beta-adrenoceptor blocker with alpha-adrenoceptor blocking and antioxidant effects) substantially reduces mortality in DCM.[90] It remains unestablished whether carvedilol has additional clinical benefits beyond those found with the other beta-adrenergic blockers, although some patients appear to respond more favorably.[103] [104]

CALCIUM ANTAGONISTS.

Because of the possible link between DCM, microvascular circulatory abnormalities, and abnormal myocardial calcium handling, there has been interest in the use of calcium antagonists. These agents have generally been well tolerated when used in DCM patients, although myocardial depression is an important potential side effect of the calcium antagonists as a group. Unfortunately, combining a calcium antagonist with traditional standard therapy (digoxin, diuretics, and vasodilator) does not appear to have substantial clinical benefit, nor does it reduce further the mortality in DCM.[105] At present, the routine use of calcium antagonists in DCM is considered nonstandard and not first-line therapy.[106]

ANTIARRHYTHMICS.

Although there is no definitive evidence that antiarrhythmic agents prolong life or prevent sudden death in DCM,[14] [73] [107] it may be appropriate to use them in the treatment of symptomatic arrhythmias. Because of the adverse effects of most available agents, many of which depress myocardial contractility and have a proarrhythmic effect (see Chap. 23), treatment should be individualized, with both efficacy and toxicity carefully monitored. Unfortunately, electrophysiological testing is of limited utility in DCM because it is positive in a minority of patients at risk,[14] [108] the lack of inducibility of ventricular tachyarrhythmias does not identify a low-risk group, and pharmacological suppression of provoked arrhythmias does not necessarily predict freedom from recurrences.[109] The recording of late potentials by the signal-averaged ECG has appeared to be of benefit in assessing the risk of death in some studies, although this has not been a universal finding and awaits further confirmation.[110] [111] The implantable cardioverter-defibrillator (ICD) (see Chap. 24) should be considered in appropriate candidates with symptomatic ventricular tachyarrhythmias.[112] [113] Even patients with unexplained syncope and no demonstrated tachyarrhythmia (even during electrophysiological testing) may profit from the insertion of an ICD.

ANTICOAGULANTS.

There is a lack of agreement as to the appropriateness and usefulness of chronic anticoagulant therapy in DCM to protect against pulmonary and especially systemic emboli.[114] [115] Even in the absence of controlled clinical trials demonstrating their efficacy,[116] we believe that the available observational data support the use of anticoagulants in good-risk patients with DCM and heart failure.[114] [117] There is general agreement that anticoagulants should be used in the presence of atrial fibrillation, if the patient has previously had a stroke, and when there is visible thrombus on

echocardiography. Oral warfarin is used to achieve a prolongation of the prothrombin time of 2.0 to 3.0 international normalized ratio.

IMMUNOSUPPRESSIVES.

In those patients with chronic heart failure secondary to DCM and lymphocytic infiltrate on myocardial biopsy, treatment with corticosteroids and immunosuppressive agents had been advocated in the past. Unfortunately, such therapy does not appear to have a clinically important effect on symptoms, exercise performance, or ejection fraction (in more than just the short term) and may be associated with significant complications.[118] Routine clinical use of immunosuppressive therapy thus cannot be recommended at present.

DUAL CHAMBER PACING.

This has been used in some patients with DCM and intact atrioventricular conduction in an attempt to change the sequence of ventricular depolarization, reduce functional mitral regurgitation, and thus improve clinical status; some symptomatic and hemodynamic improvement has been reported, especially in patients with intraventricular conduction delay or those with disturbed timing of atrioventricular mechanical activation.[119] [120] In a small number of patients followed short term, biventricular or left ventricular pacing appeared to be preferable to traditional right ventricular pacing.[120A] However, the data to date are largely anecdotal and equivocal, and demonstration of long-term benefit is lacking.[109] [121]

SURGICAL TREATMENT.

Mitral annuloplasty or replacement of regurgitant valves has been attempted in some patients with DCM and prominent atrioventricular valvular regurgitation. The results of operation are usually less than satisfactory because of the degree of preexisting cardiac dysfunction and damage, although some patients have shown some degree of symptomatic improvement, at least over the intermediate term.[122] In appropriately selected patients, cardiac transplantation (see Chap. 20) may be an attractive alternative to medical therapy, with a 5-year survival rate of about 75 percent. Surgical translocation of the latissimus dorsi muscle to wrap around the heart and augment cardiac performance (dynamic cardiomyoplasty) appears to have benefited some patients who are not otherwise suitable candidates for cardiac transplantation.[53] [123] Excision of part of the left ventricle (partial ventriculotomy) has been proposed as an additional surgical alternative to cardiac transplantation[124] ; the lack of a randomized control trial demonstrating efficacy has limited the widespread adoption of the procedure.

ALCOHOLIC CARDIOMYOPATHY

Chronic excessive consumption of alcohol may be associated with congestive heart failure, hypertension, cerebrovascular accidents, arrhythmias, and sudden death; it is the major cause of secondary, nonischemic DCM in the western world and accounts for

upward of one third of all cases of DCM.[125] It is estimated that two thirds of the adult population use alcohol to some extent, and more than 10 percent are heavy users.[126] Therefore, it is not surprising that alcoholic cardiomyopathy is a major problem. Ceasing alcohol consumption early in the course of alcoholic cardiomyopathy may halt the progression of or even reverse left ventricular contractile dysfunction, unlike nonalcoholic cardiomyopathy, which often is marked by progressive clinical deterioration.[9] [127]

The consumption of alcohol may result in myocardial damage by three basic mechanisms: (1) a presumed direct toxic effect of alcohol or its metabolites; (2) nutritional effects, most commonly in association with thiamine deficiency that leads to beriberi heart disease (see Chap. 17); and (3) rarely, toxic effects due to additives in the alcoholic beverage (cobalt) (see p. 1759).[9] [128] There had been speculation that alcohol caused myocardial damage only through dietary deficiencies, but it is now clear that alcoholic cardiomyopathy occurs in the absence of nutritional deficiencies.[125] [126] [129]

Typical Oriental beriberi (see Chap. 17) may coexist with alcoholic cardiomyopathy, although it is no longer noted with any frequency.[130] The distinguishing features of each include peripheral vasodilatation and high-output heart failure, often right sided, in the former and reduced contractility with typically left-sided low-output failure in the latter.[125] [130]

Alcohol results in acute as well as chronic depression of myocardial contractility and may produce reversible cardiac dysfunction even when ingested by normal nonalcoholic individuals. What is responsible for the transition from the reversible acute effects to permanent myocardial damage remains unclear.[126]

The precise mechanisms of cardiac depression produced by alcohol are undetermined, but a direct toxic effect on striated muscle is likely (particularly because alcoholics often demonstrate concomitant skeletal myopathy and cardiomyopathy).[125] [126] In acute studies, alcohol and its metabolite acetaldehyde have been shown to interfere with a number of membrane and cellular functions that involve the transport and binding of calcium, mitochondrial respiration, myocardial lipid metabolism, myocardial protein synthesis, and signal transduction.[126] Studies in isolated ferret papillary muscles have shown that ethanol in concentrations similar to those occurring in intoxicated humans depresses myocardial contractility by interfering with excitation-contraction coupling through inhibition of the interaction between calcium and the myofilaments.[126] There are data supporting the role of free radical damage and defects in protein synthesis in the genesis of alcohol-induced myocardial damage.[126] The role that other associated electrolyte imbalances (hypokalemia, hypophosphatemia, hypomagnesemia) may play in alcohol-mediated damage has not been settled.

PATHOLOGY.

The gross and microscopic pathological findings are nonspecific and similar to those observed in idiopathic DCM, with interstitial fibrosis, myocytolysis, evidence of small vessel coronary artery disease, and myocyte hypertrophy.[125] [131] Electron microscopy

shows enlarged and disorganized mitochondria, with large glycogen-containing vacuoles.[126]

Clinical Manifestations

Alcoholic cardiomyopathy most commonly occurs in men 30 to 55 years of age who have been heavy consumers of whisky, wine, or beer, usually for more than 10 years. Female alcoholics who develop cardiomyopathy appear to have a lower cumulative lifetime dose of alcohol than men.[127] Although alcoholic cardiomyopathy may be observed

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in the homeless, malnourished, "skid row" alcoholic man, many patients are well-nourished individuals of middle and even upper socioeconomic status without liver disease or peripheral neuropathy. Accordingly, unless a high index of suspicion is maintained, it may be easy to miss a history of alcohol abuse.[132] Persistent questioning of the patient and particularly the relatives of patients with unexplained cardiomegaly or cardiomyopathy is often required to elicit a history of alcoholism.

It is frequently possible to demonstrate mild depression of cardiac function in chronic alcoholics even before cardiac dysfunction becomes clinically manifest. Abnormalities of both systolic function (reduced ejection fraction) and diastolic function (increased myocardial wall stiffness) have been demonstrated in alcoholic patients without cardiac symptoms by a variety of invasive and noninvasive techniques.[132A] Although overt alcoholic liver disease and cardiac involvement usually do not occur together, even cirrhotic patients without signs or symptoms of heart disease have demonstrable evidence of asymptomatic myocardial disease.

The development of symptoms may be insidious, although some patients have acute and florid left-sided congestive heart failure. A paroxysm of atrial fibrillation is a relatively frequent initial presenting finding. More advanced cases demonstrate findings of biventricular failure, with left ventricular dysfunction usually dominating. Dyspnea, orthopnea, and paroxysmal nocturnal dyspnea frequently are observed. Palpitations may be present and usually are due to supraventricular tachyarrhythmias. Syncope may be seen as well and may be the result of supraventricular, or more likely ventricular, tachyarrhythmias. Angina pectoris does not occur unless there is concomitant coronary artery disease or aortic stenosis, although atypical chest pain may be seen.

PHYSICAL EXAMINATION.

The cardiac findings resemble those seen in idiopathic DCM (see p. 1756). Examination usually reveals a narrow pulse pressure, often with an elevated diastolic pressure secondary to excessive peripheral vasoconstriction. There is cardiomegaly, and protodiastolic (S_3) and presystolic (S_4) gallop sounds are common. An apical

systolic murmur of mitral regurgitation often is found. The severity of right-sided heart failure varies, but jugular venous distention and peripheral edema are common. A concomitant skeletal muscle myopathy involving the shoulder and pelvic girdle is a frequent finding, and the degree of muscle weakness and histological abnormality in the skeletal muscles parallels that in the heart.[125]

LABORATORY EXAMINATION.

The chest roentgenogram in advanced cases demonstrates considerable cardiac enlargement, pulmonary congestion, and pulmonary venous hypertension (see Chap. 8). Pleural effusions often are seen. ECG abnormalities are common and frequently are the only indication of alcoholic heart disease during the preclinical phase. Alcoholic patients without other evidence of heart disease often are seen after developing palpitations, chest discomfort, or syncope, typically after a binge of alcohol consumption on a weekend, particularly during the year-end holiday season. This is dubbed the "holiday heart syndrome." The most common arrhythmia observed is atrial fibrillation, followed by atrial flutter and frequent ventricular premature contractions. Alcohol consumption may predispose to atrial flutter or fibrillation, even in nonalcoholics. Hypokalemia may play a role in the genesis of some of these arrhythmias. Supraventricular arrhythmias are also frequently observed in patients with overt alcoholic cardiomyopathy. Sudden unexpected death is not uncommon in young adult alcoholics, and it is likely that ventricular fibrillation is responsible.

Atrioventricular conduction disturbances (most commonly first-degree heart block), bundle branch block, left ventricular hypertrophy, poor R wave progression across the precordium, and repolarization abnormalities are common ECG findings. Prolongation of the QT interval is noted frequently. ST segment and T wave changes are often restored to normal within several days after cessation of alcohol consumption.

The hemodynamic findings observed at cardiac catheterization and the assessment of left ventricular function by noninvasive methods (echocardiography and isotope angiography) resemble those found in idiopathic DCM.

MANAGEMENT.

The natural history of alcoholic cardiomyopathy depends on the drinking habits of the patient. Total abstinence in the early stages of the disease may lead to resolution of the manifestations of congestive heart failure and a return of heart size toward normal, although patients with severe heart failure may show no improvement in function or prognosis.[9] [133] Continued alcohol consumption leads to further myocardial damage and fibrosis, with the development of refractory congestive heart failure. Death may be due to arrhythmia, heart block, or systemic or pulmonary embolism, in addition to myocardial failure.

The key to the long-term treatment of alcoholic cardiomyopathy is immediate and total abstinence as early in the course of the disease as possible. This may be quite effective in improving the signs and symptoms of congestive heart failure.[133] The reversibility of

alcoholic myocardial depression is supported by the demonstration of a reduction of myocardial uptake of labeled monoclonal antimyosin antibodies (a marker of myocyte damage) in alcoholics who stop drinking.[82] The prognosis in patients who continue to drink is poor, particularly if they have been symptomatic for a long time. Prolonged bed rest is thought to result in functional improvement, although its major benefit may simply be the decreased alcohol consumption.

The management of acute episodes of congestive heart failure is similar to that of idiopathic DCM (see p. 1757). For patients with severe congestive heart failure, it is prudent to administer thiamine on the chance that beriberi may be contributing to the heart failure.[130] Whether to use chronic anticoagulation (as is often considered in idiopathic DCM) is a difficult question; we usually do not prescribe warfarin unless there are unequivocal and pressing indications because of the risk of bleeding due to noncompliance, trauma, and over-anticoagulation due to hepatic dysfunction.

COBALT CARDIOMYOPATHY

A previously unrecognized syndrome of severe congestive heart failure appeared in the mid 1960s, first in Canada and subsequently in the United States and Europe.[129] The disease was found in people who drank a particular brand of beer to which cobalt sulfate had been added as a foam stabilizer. Since cobalt was removed from the process, no more cases of the disease have been reported. On very rare occasions occupational exposure to cobalt may result in myocardial damage and attendant congestive heart failure.[129] [134]

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (See also Chap. 25)

This unique cardiomyopathy (which is also called arrhythmogenic right ventricular dysplasia [ARVD]) is marked by myocardial cell loss with partial or total replacement of right ventricular muscle by adipose and fibrous tissue; apoptosis appears to be a principal cause of the cell death (Fig. 48-6) .[135] [136] ARVD is associated with reentrant ventricular tachyarrhythmias of right ventricular origin (producing a left bundle branch block configuration of the QRS complex) and the risk of sudden death.[137] [138] In about one third of the cases there is autosomal dominant inheritance of the disease, and several distinct genetic mutations have been reported.[137] [139] One variant, found on the Greek island

Figure 48-6 Top left, Postmortem pathological section of heart (four-chamber) in a patient with right ventricular cardiomyopathy (arrhythmogenic right ventricular dysplasia) and biventricular involvement. Severe widespread fatty infiltration of right ventricular (RV) wall is present; an apical aneurysm is present at the left ventricular level (arrow). \i\Top right,\r\ Histological section at level of RV inflow (hematoxylin-eosin, ;ts 2.5). Severe transmural fibrofatty infiltration of RV wall is present, compatible with

RV dysplasia. \i\Bottom,\r\ Histological section at the level of the left ventricle (outflow) (hematoxylin-eosin, ;ts2.5) shows focal severe [chfibrofatty infiltration with myo[chcellular atrophy, compatible with left ventricular involvement. (From Pinamonti B, Pagnan L, Bussani R, et al: Right ventricular dysplasia with biventricular involvement. Circulation 98:1943\en\1945, 1998. Copyright 1998, American Heart Association.)

of Naxos, is inherited as a recessive trait but with a high degree of penetrance.[138]

ARVD appears to be distinct from *Uhl disease,* which is marked by extreme thinning of the ventricular wall.[138] [140] The diagnosis is based on a constellation of clinical, ECG, histological, and echocardiographic findings.[137] Typical clinical features include male predominance, normal physical examination, inverted T waves in the right precordial ECG leads, symptoms of palpitations and syncope, and a risk of sudden death.[137] [141] [142] In some patients with ventricular arrhythmias of no evident cause, clinically subtle right ventricular dysplasia may be etiological.[143]

Noninvasive and invasive evaluation demonstrate a dilated, poorly contractile right ventricle, usually with a normal left ventricle, although some degree of left ventricular dysfunction has been seen.[138] [141] [144] Magnetic resonance imaging (MRI) shows promise for identifying patients with this condition.[145] Antiarrhythmic therapy, especially with beta-adrenoceptor blockers, sotalol, or amiodarone, often is effective in controlling the arrhythmias.[140] The arrhythmias may be related to abnormalities of regional right ventricular sympathetic innervation, or impaired presynaptic catecholamine reuptake, as has been demonstrated by noninvasive scintigraphy.[146] Cryo- or catheter-based radiofrequency ablation of the presumed arrhythmogenic focus has been successful in resolving the ventricular arrhythmia in some patients unresponsive to or intolerant of antiarrhythmic drug therapy.[147] [148] Insertion of an ICD or cardiac transplantation is reserved for recalcitrant cases.[140]

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Hypertrophic Cardiomyopathy

Although first described over a century ago, the unique features of HCM were not studied systematically until the late 1950s.[148] [149] [150] [151] [152] [153] [154] The characteristic finding was inappropriate myocardial hypertrophy that occurred in the absence of an obvious cause for the hypertrophy (e.g., aortic stenosis or systemic hypertension), often predominantly involving the interventricular septum of a nondilated left ventricle that showed hyperdynamic systolic function (Fig. 48-7; see also Fig. 48-13 (Figure Not Available)).[152] [153] A distinctive clinical feature was soon recognized in some patients with HCM--a dynamic pressure gradient in the subaortic area that divided the left ventricle into a high-pressure apical region and a lower-pressure subaortic region (Fig. 48-8) . Although subsequent studies have shown that only a minority of patients (perhaps a fourth)[155] demonstrate this outflow gradient, its unique features attracted much attention and led to a myriad of terms (more than 75) used to describe the disease (among the more popular terms were *idiopathic hypertrophic subaortic stenosis* [*IHSS*] and *muscular subaortic stenosis*).[156] The term *hypertrophic cardiomyopathy* (HCM) is now preferred because most patients do not have an outflow gradient or "stenosis" of the left ventricular outflow tract.[153] Because hypertrophy typically occurs in the absence of a pressure gradient, the characteristic distinguishing feature of HCM is myocardial hypertrophy that is out of proportion to the hemodynamic load.

Figure 48-7 *A,* Pathological findings in a patient with hypertrophic cardiomyopathy who had a left ventricular outflow tract gradient during life. The heart is opened in the longitudinal plane. This patient had mitral regurgitation that was due partially to abnormal insertion of an anomalous papillary muscle (arrow) onto the ventricular surface of the anterior mitral leaflet. *(Modified from Wigle ED, Sasson Z, Henderson MA, et al: Hypertrophic cardiomyopathy: The importance of the site and the extent of hypertrophy. A review. Prog Cardiovasc Dis 28:1, 1985.) B,* Histological specimen of a patient with hypertrophic cardiomyopathy showing myofibrillar disarray. In the central area the myofibrils cross each other in a

disorganized manner, but in adjacent areas on each side the appearance is more normal, with parallel arrays of myofibrils. (PTHA stain, 240×.) *(From Davies MJ, McKenna WJ: Hypertrophic cardiomyopathy: An introduction to pathology and pathogenesis. Br Heart J 72:S2, 1994.) C,* Diagrammatic representation showing usual location of myocyte disarray in interventricular septum in hypertrophic cardiomyopathy. This explains why disarray is usually deep or absent in septectomy specimen, and why endomyocardial biopsy (3-mm maximum dimension) is also unlikely to sample a zone of disarray. RV=right ventricle, LV=left ventricle. *(From Tazelaar HD, Billingham ME: The surgical pathology of hypertrophic cardiomyopathy. Arch Pathol Lab Med 111:257, 1987.)*

Figure 48-8 Left-sided heart pressures in various conditions. In each horizontal panel there is an idealized depiction of the pressure tracing that would be obtained as a catheter is withdrawn from the left ventricular body through the left ventricular outflow tract into the proximal aortic root. On the far right is a superimposition of the pressures in the left ventricular body and in the aorta. The vertical lines bound the regional catheter position within the heart during withdrawal. All forms of discrete stenosis (supravalvular, valvular, and subvalvular) have delayed aortic upstroke rates downstream from the stenosis. Only in hypertrophic cardiomyopathy is the aortic upstroke rate rapid and parallel to the left ventricular pressure. L.V. = left ventricular; Out = outflow tract. *(From Criley JM, Siegel RJ: Subaortic stenosis revisited: The importance of the dynamic pressure gradient. Medicine 72:412, 1993.)*

The physiological characteristics of HCM differ substantially from those of DCM (Table 48-5) . The most characteristic pathophysiological abnormality in HCM is *diastolic* rather than systolic dysfunction (see Chap. 15) . Thus, HCM is characterized by abnormal stiffness of the left ventricle with resultant impaired ventricular filling. This abnormality in diastolic relaxation produces increased left ventricular end-diastolic pressure with resulting pulmonary congestion and dyspnea, the most common symptoms in HCM, despite typically hyperdynamic left ventricular systolic function. The overall prevalence of HCM is low, although probably higher than thought previously; it is found in about 0.2 percent (1 in 500) of the general population and in 0.5 percent of unselected patients referred for an echocardiographic examination.[152] It may be the most common genetically transmitted cardiac disorder.[153]

Pathology

MACROSCOPIC EXAMINATION.

This typically discloses a marked increase in myocardial mass, and the ventricular cavities are small (see Fig. 48-7 *A*).[157] [158] The left ventricle is usually more involved in the hypertrophic process than is the right. The atria are dilated and often hypertrophied, reflecting the high resistance to filling of the ventricles caused by diastolic dysfunction and the effects of atrioventricular valve regurgitation. The pattern and extent of left ventricular hypertrophy in HCM vary greatly from patient to patient, and a characteristic feature is heterogeneity in the amount of hypertrophy evident in different regions of the left ventricle.[153] [157] [158] A feature found in most patients with HCM is disproportionate involvement of the interventricular septum and anterolateral wall compared with the posterior segment of the free wall of the left ventricle.[153] [157] When hypertrophy is

largely localized to the anterior septum, the process has been called asymmetrical septal hypertrophy (ASH). A wide variety of other patterns of hypertrophy may be seen, and about 30 percent of patients show only localized and relatively mild hypertrophy in a single region of the ventricle.[153] The differentiation of the "physiological" hypertrophy that occurs in some highly trained male athletes from that seen in HCM may be difficult; athletes may demonstrate left ventricular wall thicknesses up to 16 mm in the absence of HCM (normal <12 mm).[159] Additional features that may permit differentiation of the two are the abnormal response of Doppler ultrasound-derived indices of diastolic function in response to isometric handgrip and the identification of HCM in a relative.[153] [160] Some patients with HCM have substantial hypertrophy in unusual locations, such as the posterior portion of the septum, the posterobasal free wall, and the midventricular level.[157]

The degree of hypertrophy is dynamic in most patients; although prominent hypertrophy may be found in infants, the typical patient develops hypertrophy during adolescence.[153] Development of the morphological features of HCM is unusual after the age of about 18 years,[153] although when it occurs it is seen especially with a mutation of cardiac myosin-binding protein C (where hypertrophy may occur at any time during adult life).[161] [162] There usually is an inverse relationship between the extent of hypertrophy

TABLE 48-5 -- DIFFERENCES IN SYSTOLIC AND DIASTOLIC FUNCTION IN DILATED (CONGESTIVE) AND HYPERTROPHIC CARDIOMYOPATHY

	DILATED CARDIO-MYOPATHY	**HYPERTROPHIC CARDIOMYOPATHY**
Left ventricular volume		
End-diastolic	Increased	Normal
End-systolic	Markedly increased	Decreased
Left ventricular mass	Increased	Markedly increased
Mass/volume ratio	Decreased	Increased
Systolic function		
Ejection fraction	Decreased	Normal or increased
Myocardial shortening	Decreased	Increased
Wall stress	Increased	Decreased
Diastolic function		
Chamber stiffness	Decreased	Increased
Myocardial stiffness	Increased	Increased

From Chatterjee K: Pathophysiology of cardiomyopathy. In Giles TD, Sander GE (eds): Cardiomyopathy. Middleton, MA, PSG Publishing Co, 1988, p 65.

in HCM and age. Whether this is due to premature death of younger patients with greater hypertrophy or progressive reduction in the extent of hypertrophy is unknown.[153] [157]

Other morphological abnormalities include enlargement and elongation of the mitral valve leaflets and anomalous papillary muscle insertion directly into the anterior mitral valve leaflet.[153]

APICAL HCM.

A variant with predominant involvement of the apex is common in Japan and is estimated to represent a fourth of Japanese HCM patients.[163] In other parts of the world, apical HCM is much less common. Typical features include a characteristic spadelike configuration of the left ventricle during angiographic study (although some patients with this variant do not demonstrate this abnormality),[164] giant negative T waves in the precordial ECG leads, the absence of an intraventricular pressure gradient, mild symptoms, and a generally benign course (Fig. 48-9) .[157] [165]

HCM may on occasion present in the elderly and often demonstrates unique features, including an especially small left ventricular cavity but with relatively mild hypertrophy.[166] Other findings include marked anterior displacement of the mitral valve, extensive submitral (annular) calcification in some patients, a left ventricular outflow gradient, and the late appearance of severe and progressive symptoms.[167]

Gross cardiac morphological features similar to those in HCM may be seen in infants of diabetic mothers and in patients with hyperparathyroidism, neurofibromatosis, generalized lipodystrophy, lentiginosis, pheochromocytoma, Friedreich ataxia, and Noonan syndrome.[168] Rarely, the findings may be simulated by amyloid, glycogen storage disease, or tumor involvement of the septum.[169]

HISTOLOGY.

Microscopic findings in HCM are distinctive,

Figure 48-10 Cartoon showing components of the sarcomere and mutations in hypertrophic cardiomyopathy. Cardiac contraction occurs when calcium binds the troponin complex (subunits C, I, and T) and alpha-tropomyosin. Actin stimulates ATPase activity in the globular myosin head and results in the production of force along actin filaments. Cardiac myosin-binding protein C binds myosin and modulates contraction. In hypertrophic cardiomyopathy, mutations may impair these and other protein interactions, result in ineffectual contraction, and produce hypertrophy. Percentages represent the estimated frequency with which a mutation causes hypertrophic cardiomyopathy. (From Spirito P, Seidman C,

McKenna WJ, et al: The management of hypertrophic cardiomyopathy. N Engl J Med 336:775, 1997. Copyright 1997, Massachusetts Medical Society.)

with myocardial hypertrophy and gross disorganization of the muscle bundles resulting in a characteristic whorled pattern; abnormalities are found in the cell-to-cell arrangement (disarray) (see Fig. 48-7 *B*) and disorganization of the myofibrillar architecture within a given cell.[157] Fibrosis is usually prominent and may be extensive enough to produce grossly visible scars. Foci of disorganized cells are often interspersed between areas of hypertrophied but otherwise normal-appearing muscle cells. Interstitial (matrix) connective tissue elements are increased.[157] Disarray in HCM patients is found in grossly hypertrophied myocardial segments as well as relatively normal segments.[170] Although abnormally arranged cardiac muscle cells initially were considered specific for HCM, it is now recognized that they may be found in a variety of acquired and congenital heart conditions. [157] What is unique about the disarray in HCM is its ubiquity and frequency. Almost all HCM patients have some degree of disarray, and most have involvement of 5 percent or more of the myocardium; in general, a fourth or more of the myocardium demonstrates disarray.[153] In contrast, disarray in non-HCM patients (when it occurs) usually involves only about 1 percent of the myocardium.[157]

Abnormal intramural coronary arteries, with a reduction in the size of the lumen and thickening of the vessel wall, are common in HCM, occurring in more than 80 percent of patients.[155] [157] The prominence of abnormal intramural coronary arteries in areas of extensive myocardial fibrosis is consistent with the hypothesis that these abnormalities may

Figure 48-9 Findings in apical hypertrophic cardiomyopathy. *Top left,* Electrocardiogram showing prominent T wave inversion (arrows). *Bottom left,* Thallium-201 scan demonstrating increased apical myocardial uptake (arrow). *Right,* Two-dimensional echocardiogram (apical view) showing apical hypertrophy and "ace-of-spades" configuration. LA = left atrium; LV = left ventricle. *(From Reddy V, Korcarz C, Weinert L, et al: Apical hypertrophic cardiomyopathy. Circulation 98:2354, 1998. Copyright 1998, American Heart Association.)*

be responsible for the development of myocardial ischemia.[153]

Etiology

GENETICS OF HYPERTROPHIC CARDIOMYOPATHY (see also Chap. 56).

Familial HCM occurs as an autosomal dominant mendelian-inherited disease at least 50 percent of the time.[166] [171] [172] It is thought that some if not all of the sporadic forms of the disease are due to spontaneous mutations.[171] [173] At least eight different genes, all encoding sarcomeric polypeptides, are associated with HCM (Fig. 48-10) . Over 125 different mutations have been discovered thus far. It is clear that not all of the genetic

defects have been identified yet.[172] Most of the mutations are of the missense type. Familial HCM thus is a genetically heterogeneous disease (i.e., it can be caused by genetic defects at more than one locus).[174] However, the genetic heterogeneity does *not* appear to explain the clinical variability.

The genetic basis of HCM was first reported in 1989 by Seidman and her collaborators, who reported the existence of a disease gene located on chromosome 14q11-12.[175] Subsequently they found this to be the gene encoding for beta cardiac myosin heavy chain (MHC). Sequencing of this gene in one family with HCM revealed that the abnormality was caused by a gene duplication in which the alpha and beta MHC genes were fused and present in an extra copy. In the second family, there was a point mutation in the beta MHC sequence that altered the myosin's arginine to glutamine. Both of these mutations affect the polypeptides crucial to the structure of myofibrils and might be responsible for the myocyte and myofibrillar disarray characteristic of familial HCM. Other disease loci that have been identified include chromosome 1g3 (encoding troponin T); chromosome 19p13 (encoding troponin I); chromosome 15q2 (encoding alpha-tropomyosin); chromosome 11p11 (encoding myosin-binding protein C); chromosomes 3p21 and 12q23 (encoding essential and regulatory myosin light chains); and chromosome 15q11-14 (encoding actin).[166] [172] [176] [176A] There is an (as yet) unidentified mutation on chromosome 7q3 that has been found in a large Irish family with HCM and the Wolff-Parkinson-White syndrome.[177]

It is estimated that about 30 percent of familial HCM is due to mutations of the cardiac MHC gene, 15 percent is caused by mutations of the cardiac troponin T gene, less than 3 percent is due to mutations of the tropomyosin gene, and the remainder is due to mutations of other genes.[178] It now appears that HCM is genetically transmitted in most patients as an autosomal dominant trait with disease loci on one of at least eight different chromosomes (chromosomes 1, 3, 7, 11, 12, 14, 15, and 19).[166] The cause of HCM in the remainder of patients is unknown. Morphological evidence of the disease is found in about one fourth of the first-degree relatives of a patient with HCM; in many of the relatives the disease is milder than in the propositus, the degree of hypertrophy is less and is more localized, and outflow gradients usually are lacking. Symptoms often are absent or minimal, and the disease is detected only by echocardiography.

Thus, there is wide variation in the phenotypical expression of a specific mutation of a given gene, with variability in clinical symptoms and the degree as well as time course of appearance of hypertrophy.[179] [180] [181] Of particular interest are mutations of the troponin T gene that typically result in only modest (or no) hypertrophy but indicate a poor prognosis and a high risk of sudden death (although at least one mutation has a favorable prognosis).[166] [178] [182] Conversely, certain genes and mutations are associated with more favorable prognoses (Fig. 48-11) (Figure Not Available) .[183] [184] In some patients with an abnormal gene and no echocardiographic evidence of HCM, the ECG is abnormal. Therefore, otherwise unexplained abnormalities

Figure 48-11 (Figure Not Available) Kaplan-Meier product-limit curves for survival of individuals with hypertrophic cardiomyopathy and three gene mutations. Survival was good in patients with Phe110Ile mutation in the troponin T gene and similar to that for benign Phe513Cys beta-cardiac myosin heavy chain gene mutation. A significant difference (p = 0.0002) in the life expectancy was observed in individuals with Phe110Ile versus malignant Arg719Trp mutation in the beta-cardiac myosin heavy chain

gene. *(From Anan R, Shono H, Kisanuki A: Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. Circulation 98:391, 1998. Copyright 1998, American Heart Association.)*

of the ECG in first-degree relatives of patients with HCM may be indicative of a carrier or preclinical state. Unfortunately, genetic testing is not yet easily available for routine clinical use and remains largely a research tool.

Pathophysiology

SYSTOLE.

Since the initial descriptions of HCM, the feature that has attracted the greatest attention is the dynamic pressure gradient across the left ventricular outflow tract (Figs. 48-8 and 48-12 (Figure Not Available)). Although this pressure gradient was initially attributed to a muscular sphincter action in the subaortic region or was believed by some to be an artifact,[156] it is now considered to be related to further narrowing of an already small outflow tract (narrowed by the prominent septal hypertrophy and possibly abnormal location of the mitral valve) by systolic anterior motion of often elongated mitral valve leaflets against the hypertrophied septum.[154] [157]

There continues to be considerable controversy about the cause and significance of the outflow gradient.[156] [185] Central to the disagreement is whether there is true obstruction to left ventricular ejection or whether the pressure gradient is simply the consequence of vigorous ventricular

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Figure 48-12 (Figure Not Available) Hypertrophic cardiomyopathy with intracardiac pressure and phonocardiographic (phono) recordings from aorta (AO), left ventricle (LV), left ventricular outflow tract (LVOT), and left atrium (LA). Note the marked accentuation of the murmur and gradient (shaded) (in the third cycle) after a premature ventricular contraction with failure of the aortic pulse pressure to rise in the post premature ventricular contraction beat (Brockenbrough-Braunwald sign). ECG = electrocardiogram; SSC = systolic anterior motion of the mitral valve septal contact. *(From Murgo JP: Systolic ejection murmurs in the era of modern cardiology: What do we really know? J Am Coll Cardiol 32:1596, 1998.)*

emptying. Most now favor the view that a true mechanical impediment to left ventricular ejection occurs when outflow gradients are present and is the result of distal portions of the mitral valve apparatus moving anteriorly across the outflow tract and contacting the ventricular septum in mid systole.[153] It is likely that the mitral valve is displaced anteriorly because of Venturi effects and as a result of the increased ejection velocities produced by the abnormal left ventricular outflow tract orientation and geometry.[185]

DIASTOLE.

Most patients with HCM demonstrate abnormalities of diastolic function (see Chap. 15) at rest or with stress, whether or not a pressure gradient is present and whether or not

they are symptomatic.[160] [186] These abnormalities of global diastolic filling are largely independent of the extent and distribution of myocardial hypertrophy; patients with mild and apparently localized hypertrophy may demonstrate prominent diastolic dysfunction, suggesting that the myopathic process occurs in ventricular regions that are not macroscopically hypertrophied.[163] Others have found that diastolic filling varies in different regions of the left ventricle and is influenced by the thickness of the septum.[187] Diastolic dysfunction in turn leads to increased filling pressure despite a normal or small left ventricular cavity and appears to result from abnormalities of left ventricular relaxation and distensibility. Early diastolic filling is impaired when relaxation is prolonged, perhaps related to abnormal calcium kinetics, subendocardial ischemia, or the abnormal loading conditions found in HCM.[188] Late diastolic filling is altered when left ventricular distensibility is impaired; as a consequence, filling pressures rise. HCM may cause abnormal distensibility of the ventricle because of fibrosis or cellular disorganization.[189]

MYOCARDIAL ISCHEMIA.

Myocardial ischemia is common and multifactorial in HCM (Table 48-6) .[190] Major

TABLE 48-6 -- PROPOSED CAUSES OF ISCHEMIA IN HYPERTROPHIC CARDIOMYOPATHY DESPITE NORMAL EPICARDIAL CORONARY ARTERIES

Increased muscle mass
Inadequate capillary density
Elevated diastolic filling pressures
Abnormal intramural coronary arteries
Impaired vasodilatory reserve
Systolic compression of arteries
Enhanced myocardial oxygen demand (increased wall stress)

causes include impaired vasodilator reserve (perhaps related to the thickened and narrowed small intramural coronary arteries found in HCM)[191] ; increased oxygen demand, especially in patients with outflow gradients; and elevated filling pressures with resultant subendocardial ischemia.[157] [190] [192] [193] [194] In children, compression of intramyocardial segments of the left anterior descending coronary artery (so-called myocardial bridge) may predispose to myocardial ischemia and sudden death.[195]

Clinical Manifestations

SYMPTOMS.

The majority of patients with HCM are asymptomatic or only mildly symptomatic[152] and often are identified during screening of relatives of a patient with HCM. Unfortunately, the first clinical manifestation of the disease in such individuals may be sudden death. The disease is identified most often in adults in their 30s and 40s; it occurs more often

than is commonly suspected in elderly patients. The condition has been observed at necropsy in stillborns and both clinically and pathologically in octogenarians. The importance of recognizing this disorder in children at the earliest possible time is highlighted by the higher mortality rate in younger patients; death is often sudden and unexpected. When HCM is first diagnosed in older patients, several features are distinctive and are in contrast to findings in younger patients: generally mild degrees of left ventricular hypertrophy; frequent demonstration of outflow gradients; and appearance of marked symptoms late in life (typically after age 55).[167] A particularly high index of suspicion of this condition must be maintained to make the clinical diagnosis in the elderly because their symptoms may easily be confused with those due to coronary artery or aortic valve disease. Because syncope and sudden death have been associated with competitive sports and severe exertion in patients with HCM, it is important to diagnose this condition so that these activities may be proscribed. The disease is slightly more common in men, although women may be more likely to be severely disabled and may initially present at a younger age than men.[196]

The clinical picture varies considerably, ranging from the asymptomatic relative of a patient with recognized HCM who has a slightly abnormal echocardiogram but no other overt manifestation of the disease to the patient with incapacitating symptoms. A general relationship exists between

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the extent of hypertrophy and the severity of symptoms, but the relationship is not absolute, and some patients have severe symptoms with only mild and apparently localized hypertrophy, and vice versa.[157] A complex interaction occurs between left ventricular hypertrophy, the left ventricular pressure gradient, diastolic dysfunction, and myocardial ischemia, which accounts for the great variability in symptoms from patient to patient.

The most common symptom is *dyspnea,* occurring in up to 90 percent of symptomatic patients, which is largely a consequence of the elevated left ventricular diastolic (and therefore left atrial and pulmonary venous) pressure, which results principally from impaired ventricular filling owing to diastolic dysfunction.[157] Angina pectoris (found in about three fourths of symptomatic patients), fatigue, presyncope, and syncope are also common. Palpitations, paroxysmal nocturnal dyspnea, overt congestive heart failure, and dizziness are found less frequently, although severe congestive heart failure culminating in death may be seen. Exertion tends to exacerbate many of the symptoms.[197] A variety of mechanisms may contribute to the production of angina pectoris (see Table 48-6). It is at least in part the result of an imbalance between oxygen supply and demand as a consequence of the greatly increased myocardial mass. Abnormalities of the small coronary arteries may contribute to myocardial ischemia, particularly during exertion, and perhaps 20 percent of older patients with HCM may have concurrent atheromatous obstructive coronary artery disease. Transmural infarction may occur in the absence of narrowing of the extramural coronary arteries.[157] Impaired diastolic relaxation may produce subendocardial ischemia as a result of prolonged maintenance of wall tension with a concomitant slower-than-normal

decrease in the impedance to coronary blood flow. Syncope may result from inadequate cardiac output with exertion or from cardiac arrhythmias. It occurs most commonly in young patients with small left ventricular chamber size and evidence of ventricular tachycardia on ambulatory monitoring.[198] Near-syncopal ("graying out") spells that occur in the erect posture and that can be relieved by immediately lying down are common. However, in contrast to valvular aortic stenosis, syncope or near-syncope may not be an ominous finding in adult patients with HCM; some patients have a history of such episodes dating back many years without clinical deterioration.[152] In children and adolescents, however, presyncope and syncope identify patients at increased risk of sudden death (see Natural History).

PHYSICAL EXAMINATION.

This may be normal in asymptomatic patients without gradients, particularly those with the apical variant of HCM, save for a left ventricular lift and a loud S_4 , but findings are usually prominent in patients with a left ventricular outflow tract pressure gradient. The apical precordial impulse is often displaced laterally and is usually abnormally forceful and diffuse.[196] Because of decreased left ventricular compliance, a prominent presystolic epical impulse that results from forceful atrial systole often is present. This may result in a double apical impulse as a result of the prominent *a* wave.[154] A more characteristic but less frequently recognized abnormality is a triple apical beat, the third impulse consisting of a late systolic bulge that occurs when the heart is almost empty and is performing near-isometric contraction.[196] The jugular venous pulse may demonstrate a prominent *a* wave, reflecting diminished right ventricular compliance secondary to massive hypertrophy of the ventricular septum.[159] The carotid pulse typically rises briskly and then declines in midsystole as the gradient develops, followed by a secondary rise.[196] This may be appreciated on physical examination but can be demonstrated more clearly by means of indirect carotid pulse tracings.

Auscultation.

The S_1 is normal and is often preceded by an S_4 that corresponds to the apical presystolic impulse.[196] The S_2 usually is normally split. In some patients, however, it is narrowly split and in others, particularly those with severe outflow gradients, paradoxical splitting may be noted.[154] An S_3 may be present but does not have the same ominous significance as in patients with valvular aortic stenosis. Systolic ejection sounds relating to rapid acceleration of blood flow may be found on occasion. The auscultatory hallmark of HCM associated with an outflow gradient is a systolic murmur that typically is harsh and crescendo-decrescendo in configuration (Fig. 4-46) ; it usually commences well after S_1 and is best heard between the apex and the left sternal border.[196] It often radiates well to the lower sternal border, the axillae, and base of the heart but not into the neck vessels. In patients with large gradients, the murmur usually reflects both left ventricular outflow tract turbulence and concomitant mitral regurgitation.[154] Accordingly, the murmur is often more holosystolic and blowing at the apex and in the axillae (due to mitral regurgitation) and midsystolic and harsher along the lower sternal border (due to turbulent flow across the narrowed outflow tract).[196]

The systolic murmur is labile in intensity and duration, and a variety of maneuvers may be used to augment or suppress it (Table 48-7) . [154] A diastolic rumbling murmur, reflecting increased transmitral flow, may occur in patients with marked mitral regurgitation. The murmur of aortic regurgitation is observed in about 10 percent of patients, although mild aortic regurgitation can be demonstrated by Doppler echocardiography in one third.[199] It may develop after operation to correct the outflow gradient or following infective endocarditis.

Differentiation from Valvular Aortic Stenosis.

It is important to emphasize the features of physical examination that permit differentiation of HCM from fixed orifice obstruction, most commonly due to valvular aortic stenosis (see Chap. 46). The character of the carotid pulse and features of the murmur are most useful in this regard. Because there is obstruction to left ventricular emptying from the

TABLE 48-7 -- EFFECTS OF INTERVENTIONS ON OUTFLOW GRADIENT AND SYSTOLIC MURMUR IN HYPERTROPHIC CARDIOMYOPATHY

	CONTRACTILITY	PRELOAD	AFTER-LOAD
Increase in Gradient and Murmur			
Valsalva maneuver (during strain)	--		
Standing	--		--
Postextrasystole			--
Isoproterenol			
Digitalis			--
Amyl nitrite	-- then	then	
Nitroglycerin	--		
Exercise			
Tachycardia			--
Hypovolemia			

Decrease in Gradient and Murmur			
Mueller maneuver	--		
Valsalva overshoot	--		
Squatting	--		
Alpha-adrenoceptor stimulation (phenylephrine)	--	--	
Beta-adrenoceptor blockade			--
General anesthesia		--	--
Isometric handgrip	--	--	

=increase;
=decrease; --=no major change.

beginning of systole with fixed valvular stenosis, the carotid upstroke is slowed and of low amplitude (pulsus parvus et tardus).[200] With HCM, initial ejection of blood from the left ventricle is actually enhanced, and therefore the arterial upstroke is brisk. The murmur of HCM, as opposed to that of aortic stenosis, can be reliably identified by its increase with the Valsalva maneuver and during standing from a squatting position, and its decrease during squatting from a standing position, passive leg elevation, and hand grip (see Table 48-7).[196] Other features that may be helpful but are of considerably less significance are the location of the murmur (it radiates along the carotid arteries in valvular aortic stenosis but not in HCM) and the location of the systolic thrill when present (most prominent in the second right intercostal space in valvular aortic stenosis and in the fourth interspace along the left sternal border in HCM).

ELECTROCARDIOGRAM.

This is usually abnormal in HCM[201] and invariably so in symptomatic patients with left ventricular outflow tract gradients.[157] Entirely normal ECGs are seen in only 15 to 25 percent of patients and usually are found in the presence of only localized left ventricular hypertrophy.[202] The most common abnormalities are ST segment and T wave abnormalities, followed by evidence of left ventricular hypertrophy, with QRS complexes that are tallest in the midprecordial leads.[157] Progressive ECG evidence of hypertrophy may develop over time. Giant negative T waves in the midprecordial leads

of Japanese patients are characteristic of HCM involving the apex[203] (see p. 1762), but such a pattern in whites may be found with HCM involving segments other than the apex. Prominent Q waves are relatively common, occurring in 20 to 50 percent of patients. The Q wave abnormalities often involve the inferior (II, III, aV_F) and/or precordial (V_2 -V_6) leads. The cause of the Q waves remains unestablished; although they do not correlate simply with the degree of septal hypertrophy,[157] they may relate to the balance of electrical forces emanating from the left versus the right ventricle.[154] A variety of other ECG abnormalities may occur, including abnormal electrical axis (usually left-axis deviation) and P wave abnormalities (usually left atrial abnormality). Accessory atrioventricular pathways have been found in HCM, although they are uncommon.[204] Clinically significant abnormalities of atrioventricular conduction are uncommon but may cause syncope.[205]

ARRHYTHMIAS.

Although hemodynamic or ischemic mechanisms may play roles in the death of patients with HCM (particularly the young),[206] many deaths, particularly those that are known to have been sudden, likely are due to an arrhythmia.[207] [208] Because of the systolic and diastolic abnormalities in this disorder, rhythm disturbances are less well tolerated.

Ventricular arrhythmias are common in patients with HCM, occurring in more than three fourths of patients undergoing continuous ambulatory ECG monitoring. Runs of nonsustained ventricular tachycardia are found in about one fourth of patients with HCM, although sustained monomorphic tachycardia is uncommon.[207] In some it is a harbinger of subsequent sudden death; however, its overall predictive value in identifying patients at high risk for sudden death is limited. Treadmill testing may expose arrhythmias that are not present at rest, although continuous ambulatory monitoring is superior in detecting repetitive ventricular tachyarrhythmias.

Supraventricular tachycardia may be found in one fourth to one half of patients.[207] Atrial fibrillation occurs in about 10 percent of patients (often those with no gradient and mild hypertrophy), and the resultant loss of the atrial contribution to the filling of a hypertrophied, stiff ventricle may result in clinical deterioration.[157] [209] Treatment is often effective in controlling symptoms and restoring sinus rhythm; if this is done, long-term survival usually is not jeopardized.[210] The signal-averaged ECG has not proved to be helpful in identifying patients at increased risk of sustained or lethal ventricular arrhythmia, although additional studies are necessary.[211] Reduced heart rate variability on ambulatory monitor recordings, a predictor of increased sudden death risk after myocardial infarction, appears to be less useful in risk stratification in HCM patients.[212]

ELECTROPHYSIOLOGICAL TESTING.

The role of electrophysiological studies in identifying HCM patients at increased risk of sudden death is controversial; despite earlier enthusiasm, it is now generally believed that it is of limited predictive value.[152] [157] These studies may identify a variety of abnormalities in HCM patients; they induce polymorphic ventricular tachycardia in many patients with HCM, but such a response is generally believed to be nonspecific and

does not identify high-risk patients.[152] Unfortunately, unlike its utility in ischemic heart disease, the predictive value of the more typical inducible sustained ventricular arrhythmias during electrophysiological testing is low in HCM. Aggressive stimulation protocols are required to induce a sustained arrhythmia in high-risk HCM patients, often resulting in arrhythmias in low-risk patients as well.[208] Tilt-table testing has not been particularly useful in identifying the cause of syncope in HCM; neurally mediated syncope is uncommon in this setting and true positive tests are uncommon, but false-positive tests are frequent and significantly limit the usefulness of the test.[213]

CHEST ROENTGENOGRAM.

The findings on radiographic examination are variable; the cardiac silhouette may range from normal to markedly increased, and in most cases of apparent "cardiomegaly" the enlarged cardiac silhouette is the result of left ventricular hypertrophy and/or left atrial enlargement.[157] Left atrial enlargement is observed frequently, especially when significant mitral regurgitation is present.[154] Aortic root enlargement and valvular calcification are not seen unless associated diseases are present, although calcification of the mitral annulus is common in HCM.

ECHOCARDIOGRAPHY.

Because echocardiography combines the attributes of high resolution and no known risk, it has been widely used in the evaluation of HCM. It is useful in the study of patients with suspected HCM and also in the screening of relatives of HCM patients. The echocardiogram is of value in identifying and quantifying morphological features (i.e., distribution of septal hypertrophy), functional aspects (e.g., hypercontractile left ventricle), and (when combined with Doppler recordings) hemodynamic findings (e.g., magnitude of outflow gradient). (See Figs. 7-99 , 7-100 , and 7-101 .)

Left Ventricular Hypertrophy.

The cardinal echocardiographic feature of HCM is left ventricular hypertrophy. Although the characteristic feature is hypertrophy of the septum and anterolateral free wall, the echocardiogram is useful in identifying involvement of other left ventricular locations, including portions of the free wall and the apex.[157] [170] [214] Considerable variability exists in the degree and pattern of hypertrophy; in most patients, there is variation in the extent of hypertrophy from one left ventricular region to another.[157] Maximal hypertrophy of the septum often occurs midway between the base and apex of the left ventricle. The finding of a thickened septum that is at least 1.3 to 1.5 times the thickness of the posterior wall when measured in diastole just before atrial systole has been the time-honored criterion for the diagnosis of ASH. The septum not only is relatively thicker than the posterior wall but is typically at least 15 mm in thickness (normal 11 mm). Although the average wall thickness detected on echocardiography is about 20 mm (i.e., almost twice normal), there is great variation, ranging from very mild hypertrophy (13 to 15 mm) to massive hypertrophy (50 mm).[159]

An unusual echocardiographic pattern consisting of a ground-glass appearance has

been noted in portions of the hypertrophied myocardium in some patients with HCM. Even when abnormalities are not apparent on visual inspection, quantitative texture analysis often identifies them in both nonhypertrophied (but presumably abnormal) and hypertrophied regions of the ventricle and can be used to distinguish HCM patients from those with secondary hypertrophy.[215] It has been speculated that this pattern may be related to the abnormal cellular architecture and myocardial fibrosis that has been noted in pathological studies.[216]

Outflow Tract Obstruction.

A second echocardiographic feature often found in HCM in addition to left ventricular hypertrophy is narrowing of the left ventricular outflow tract, which is formed by the interventricular septum anteriorly and the anterior leaflet of the mitral valve posteriorly. The mitral valve leaflets are abnormally large and elongated and are associated with abnormal left ventricular outflow tract geometry that culminates in the production of a pressure gradient.[214] [217] [218] This abnormal geometry is causally related to the mitral regurgitation that accompanies an outflow gradient; the degree of mitral regurgitation correlates with the extent of anterior and posterior leaflet malcoaptation.[219] When HCM is associated with a pressure gradient, there is abnormal systolic anterior motion of the anterior leaflet, and occasionally the posterior leaflet of the mitral valve.[214] A close relationship exists between the degree of systolic anterior motion and the magnitude of the outflow gradient. Prolonged interventricular septal contact of the mitral apparatus is limited to HCM with resting pressure gradients, and a close temporal relationship exists between the onset of the pressure gradient and the onset of septal apposition of the mitral apparatus.

MECHANISMS OF SYSTOLIC ANTERIOR MOTION.

Three explanations have been offered for systolic anterior motion: (1) the mitral valve is *pulled* against the septum by contraction of abnormally oriented papillary muscles and elongated leaflets[220] ; (2) the mitral valve is *pushed* against the septum (perhaps by the left ventricular posterior wall) because of its abnormal position in the outflow tract; and (3) the mitral valve is drawn toward the septum because of the lower pressure that occurs as blood is ejected at a high velocity through a narrowed outflow tract (Venturi effect).[221] In a minority of cases (less than 15 percent), one or both papillary muscles insert anomalously directly into the anterior mitral leaflet, causing a long area of midventricular narrowing that results in an intraventricular pressure gradient.

Systolic anterior motion of the mitral valve and dynamic left ventricular gradients are not pathognomonic of HCM but may be found in a variety of other conditions, including hypercontractile states, left ventricular hypertrophy, transposition of the great arteries, and infiltration of the septum. Even mild degrees of left ventricular hypertrophy may be associated with systolic anterior motion and outflow gradients, particularly under conditions of enhanced sympathetic tone. In many cases in conditions other than HCM,

systolic anterior motion is due to buckling of the chordae tendineae rather than to movement of the anterior mitral valve leaflet as occurs in HCM (although the chordae tendineae and papillary muscles may contribute to systolic anterior motion in HCM).

Other Echocardiographic Findings.

The following may be present: (1) a small left ventricular cavity; (2) reduced septal motion and thickening during systole, particularly of the upper septum (presumably because of the disarray of the myofibrillar architecture and abnormal contractile function)[222] ; (3) normal or increased motion of the posterior wall; (4) a reduced rate of closure of the mitral valve in mid diastole secondary to a decrease in left ventricular compliance or abnormal transmittal diastolic flow; (5) mitral valve prolapse; and (6) partial systolic closure or, more commonly, coarse systolic fluttering of the aortic valve related to turbulent blood flow in the outflow tract. MRI studies have shown that regional left ventricular function and the degree of local hypertrophy are inversely related and the hypertrophied septum typically is hypokinetic.[222] [223] The echocardiographic findings that accompany a left ventricular outflow tract gradient (systolic anterior motion and aortic valve partial closure) may be quite labile, and provocative measures such as the Valsalva maneuver, pharmacologically induced vasodilatation with amyl nitrite, stimulation of contractility with isoproterenol, or an induced premature ventricular contraction may be required to precipitate the findings.[150] [224]

Abnormalities of diastolic function (see Chap. 15) may be demonstrated by echocardiography and Doppler recordings in about 80 percent of patients with HCM, independent of the presence or absence of a systolic pressure gradient.[157] Because the septum typically is hypokinetic, the rate of left ventricular filling is determined primarily by the rate of free wall thinning. Little relationship exists between the extent of hypertrophy and the severity of abnormalities of diastolic function. Doppler ultrasonography has confirmed the virtual ubiquity of mitral regurgitation when an outflow pressure gradient is present[157] and has accurately measured the magnitude of the outflow tract gradient.[155] Doppler color flow imaging reveals mitral regurgitation, most prominent in late systole, accompanying the appearance of turbulent flow in the left ventricular outflow tract. Recordings from the left ventricular outflow tract support the concept that true obstruction to flow occurs and accounts for the pressure gradient.[155]

RADIONUCLIDE SCANNING.

Thallium-201 myocardial imaging, particularly when tomographic imaging (single-photon emission computed tomography [SPECT]) is performed (see Chap. 9), permits direct determination of the relative thicknesses of the septum and free wall and may be of particular value when technical constraints limit the reliability of echocardiographic evaluation in a given patient with presumed HCM. Reversible thallium defects, presumably indicative of ischemia, are common findings in HCM in the absence of obstructive coronary artery disease.[225] They are common in adult patients with HCM and in those young patients with a history of sudden death or syncope, suggesting that myocardial ischemia is an important factor and probably a mechanism of demise in younger patients.[226] Fixed defects, probably indicative of myocardial scarring, occur primarily in patients with impaired systolic function. Gated radionuclide ventriculography

with blood pool labeling permits the evaluation of not only the size but also the motion of the septum and left ventricle. As with the echocardiogram, abnormal diastolic filling of the ventricle has been observed in patients with HCM (both with and without gradients) by computer analysis of the blood pool scan.[227] Because of the ease and availability of transthoracic and transesophageal echocardiography, this technique is not widely used in the evaluation of HCM.

Hemodynamics and Angiography

CARDIAC CATHETERIZATION.

Heart catheterization is not required for the diagnosis of HCM, because noninvasive evaluation almost always suffices; it is reserved for situations where concomitant coronary artery disease is a consideration, or when invasive modalities of therapy (e.g., pacemaker, surgery) are being considered.[154] It discloses diminished diastolic left ventricular compliance and in some patients a systolic pressure gradient within the body of the left ventricle (see Fig. 48-8) , which is separated from a subaortic chamber by the thickened septum and the anterior leaflet of the mitral valve that abuts the septum (see Fig. 48-12 (Figure Not Available)).[155] The pressure gradient may be quite labile and may vary between 0 and 175 mm Hg in the same patient under different conditions (see later). The arterial pressure tracing may demonstrate a "spike and dome" configuration similar to the carotid pulse recording.[155] As a consequence of diminished left ventricular compliance, the mean and particularly the *a* wave in the left atrial pressure pulse and the left ventricular end-diastolic pressures are usually elevated. Artifactual outflow gradients may occur if the left ventricular catheter becomes entrapped in the trabeculae of a markedly hypertrophied left ventricle.[156] Proper technique and choice of catheters with side holes should clarify the mechanism of such gradients. Cardiac output may be depressed in patients with long-standing severe gradients, but in the majority of patients it is normal; occasionally it is elevated.

Hemodynamic abnormalities in HCM are not limited to the left side of the heart. Approximately one fourth of patients demonstrate pulmonary hypertension, which is usually mild but in some cases may be moderate to severe. This is due (at least in part) to elevated mean left atrial pressures as a consequence of diminished left ventricular compliance. A pressure gradient in the right ventricular outflow tract occurs in approximately 15 percent of patients who have obstruction to left ventricular outflow[196] [228] and

appears to result from markedly hypertrophied right ventricular tissue.[229] Right atrial and right ventricular end-diastolic pressures may be slightly elevated.

LABILITY OF GRADIENT.

A feature characteristic of HCM is the variability and lability of the left ventricular outflow

gradient (see Table 48-7).[149] [150] [230] A given patient may demonstrate a large outflow gradient on one occasion but have none at another time. In some patients without a resting gradient, it may be temporarily provoked. Three basic mechanisms are involved in the production of dynamic gradients, all of which act by reducing ventricular volume and presumably accentuate the apposition of the anterior mitral leaflet against the septum[150] : (1) increased contractility, (2) decreased preload, and (3) decreased afterload. In a minority of patients with HCM, the gradient is midventricular and may be intensified by increased contractility, which exerts a direct muscular sphincter action.[154] [155] The stimuli that provoke or intensify left ventricular outflow tract gradients in HCM generally improve myocardial performance in normal subjects and in patients with most other forms of heart disease. Conversely, reductions in contractility or increases in preload or afterload, which increase left ventricular dimensions, reduce or abolish the left ventricular outflow gradient.

Alterations in the magnitude of the gradient are reflected by changes in the findings on physical examination, noninvasive tests, and left-sided heart catheterization. *This dynamic characteristic of HCM distinguishes it from the discrete forms of obstruction to ventricular outflow.* An increase in the gradient usually results in a louder murmur, a longer ejection period with a more characteristic spike and dome configuration in the carotid pulse, and more flagrant echocardiographic evidence of systolic anterior motion of the anterior mitral leaflet. In some patients, the intensity of the murmur may *not* track with the gradient, perhaps because in many cases the murmur reflects mitral regurgitation (at least in part).[154]

A number of bedside procedures may be useful in the evaluation of suspected HCM.[154] Perhaps the most helpful is sudden standing from a squatting position. Squatting results in an increase in venous return and an increase in aortic pressure, which increases ventricular volume, diminishing the gradient and decreasing the intensity of the murmur. Sudden standing has the opposite effects and results in accentuation of the gradient and the murmur.

VALSALVA MANEUVER.

This is another useful bedside technique for eliciting or exacerbating the gradient. After a transient increase in arterial pressure that usually lasts for four or five cardiac cycles after the onset of the strain and coincident with an increase in heart rate, the arterial systolic and pulse pressures and ventricular volume decline and the gradient (and murmur) increases. After release of the strain, a compensatory overshoot of arterial pressure and venous return with cardiac slowing occur, all of which increase ventricular volume and reduce the magnitude of the gradient and the murmur. Occasional patients may show paradoxical attenuation of the systolic murmur despite an increase in the pressure gradient, presumably related to a critical reduction in stroke volume. Inhalation of amyl nitrite also intensifies the murmur and the abnormality of the arterial pulse. The murmur of HCM is attenuated by passive leg elevation, hand grip, and sudden squatting from a standing position.

Postextrasystolic Changes.

One of the most potent stimuli for enhancing the gradient is *postextrasystolic potentiation* (see Chap. 14), which may occur after a spontaneous premature contraction or be induced by mechanical stimulation with a catheter.[231] The resultant increase in contractility in the beat after the extrasystole is so marked that it outweighs the otherwise salutary effect of increased ventricular filling caused by the compensatory pause and produces an increase in the gradient and often of the murmur as well. A characteristic change often occurs in the directly recorded arterial pressure tracing, which, in addition to displaying a more marked spike and dome configuration, exhibits a pulse pressure that fails to increase as expected or actually decreases (the so-called Brockenbrough-Braunwald phenomenon) (see Fig. 48-12 (Figure Not Available)). This is one of the more reliable signs of dynamic obstruction of the left ventricular outflow tract. In some patients, the postextrasystolic murmur is attenuated despite an increase in the outflow gradient, apparently because in this setting the murmur (a hybrid of outflow tract turbulence and mitral regurgitation) is mirroring to a greater degree changes in the severity of mitral regurgitation rather than changes in the outflow tract gradient.

POSITIVE INOTROPIC AGENTS.

Digitalis glycosides and the beta-adrenoceptor agonist isoproterenol augment the gradient because they increase myocardial contractility, whereas nitroglycerin and amyl nitrite exaggerate the gradient by decreasing arterial pressure and ventricular volume. The ingestion of alcoholic beverages may exacerbate the outflow pressure gradient by producing systemic vasodilatation.[232] Hypovolemia (as a result of hemorrhage or overly aggressive diuresis) may also provoke overt obstruction to left ventricular outflow. The intensity of the murmur and the left ventricular outflow gradient may be decreased by beta-adrenoceptor blockade, although the effect of the latter is often not dramatic and is of greatest hemodynamic benefit in protecting against the *increase* in the gradient that may be provoked by exercise. In most patients the severity of mitral regurgitation and the intensity of the apical blowing regurgitant murmur vary with the degree of obstruction of left ventricular outflow.

ANGIOGRAPHY.

Left ventriculography shows a hypertrophied ventricle; when an outflow gradient is present, the anterior leaflet of the mitral valve moves anteriorly during systole and encroaches on the outflow tract. Associated with this motion of the leaflet is mitral regurgitation, which is a constant finding in patients with gradients. The left ventricular cavity is often small, and systolic ejection is typically vigorous, resulting in virtual obliteration of the cavity at end systole (Fig. 48-13) (Figure Not Available) , although the apparent hypercontractile state may relate more to reduced afterload (low end-systolic wall stress) than to enhanced inotropy. The papillary muscles are often prominent and may fill the left ventricular cavity in late systole. In patients with apical involvement, the extensive hypertrophy may convey a spadelike configuration to the left ventricular angiogram.[165]

It may be helpful to supplement angiographic evaluation of the left ventricle with

simultaneous right ventriculography in a cranially angulated left anterior oblique projection to obtain optimal visualization of the size, shape, and configuration of the interventricular septum. The left septal surface either is flat or bulges into the left ventricular cavity at its mid or lower portion, in contrast to the normal findings of the septum curving toward the right ventricle.

In patients older than 45 years of age, obstructive coronary artery disease may be present, although the symptoms of ischemic pain are indistinguishable from those of patients with normal coronary angiograms and HCM. The left anterior descending and septal perforator coronary arteries may demonstrate phasic narrowing and associated abnormalities of flow during systole.[233]

Natural History

The clinical course in HCM is varied; in many patients symptoms are absent or mild, remain stable, and in some instances improve over a period of 5 to 10 years. The annual mortality is about 3 percent in adults seen in large referral centers[234] but probably is closer to 1 percent when all patients with HCM are included.[235] [236] [237] The risk of sudden death is higher in children, perhaps as high as 6 percent per year.[171] Clinical deterioration (aside from sudden death) usually is slow. Although symptoms are unrelated to the severity or even the presence of a gradient,[157] the percentage of severely symptomatic patients does increase with age. The onset of atrial fibrillation may lead to an increase in symptoms, although counterintuitively often it appears to be well tolerated.[210] Conversion to sinus rhythm by pharmacological or electrical cardioversion should be

Figure 48-13 (Figure Not Available) *A,* Left ventriculogram in the right anterior oblique view showing the typical appearance of hypertrophic cardiomyopathy with a very small end systolic cavity, hypertrophied papillary muscles, and associated severe mitral regurgitation. *B,* Postmortem transverse section through the heart at the level of the ventricles in a case of sudden death in hypertrophic cardiomyopathy. There is marked left ventricular hypertrophy particularly affecting the interventricular septum (approximately 4.5 cm) with associated fibrosis and virtual obliteration of the left and right ventricular cavities. *(From Davies MK: Images in cardiology. Hypertrophic cardiomyopathy. Br Heart J 74:527, 1995.)*

attempted, although maintenance of sinus rhythm may be difficult.[157] Patients who develop atrial fibrillation ordinarily are started on long-term therapy with oral anticoagulants.

Progression of HCM to left ventricular dilatation and dysfunction without a gradient (i.e., DCM) occurs in 10 to 15 percent of patients.[157] [238] It appears to result, at least in part, from wall thinning and scar formation as a consequence of myocardial ischemia caused by small vessel coronary artery disease and abnormal coronary vasodilator reserve (Fig. 48-14) (Figure Not Available) .[157] It is more likely to occur in patients with marked septal hypertrophy and generally is associated with a poor prognosis. The extent of left ventricular hypertrophy in adults usually remains stable over time, although a majority of

children demonstrate increasing degrees of hypertrophy (often considerable) and many adults demonstrate a very gradual degree of regression of hypertrophy over time (Fig. 48-15) (Figure Not Available) .[239] In some children, the findings of HCM may develop despite a previous normal echocardiogram; this is not common in adults, but it may be seen in particular with the cardiac myosin-binding protein C mutation.[161] [166] Its occurrence emphasizes that a single normal echocardiogram does *not* exclude HCM in a child or adolescent; cellular disarray and the attendant risk of sudden death may be present even in the absence of left ventricular hypertrophy. A marker for the later appearance of clinical HCM may be an initially abnormal ECG demonstrating increased QRS voltage.

SUDDEN DEATH.

Death is most often sudden in HCM and may occur in previously asymptomatic patients, in individuals who were unaware they had the disease, and in patients with an otherwise stable course (Fig. 48-16) (Figure Not Available) . There is great difficulty in identifying those patients at particular risk of sudden death[240] [240A] ; nevertheless, the features that most reliably identify high-risk patients include young age (< 30 years) at diagnosis, a family history of HCM with sudden death (so-called malignant family history), an abnormal blood pressure response to exercise (presumably related to subendocardial ischemia[241]), and genetic abnormalities associated with increased prevalence of sudden death.[152] [234] [242] [242A] The presence or severity of an outflow tract gradient, the degree of functional limitation, and symptoms in general do not correlate with the risk of death.[208] [234] A history of syncope is ominous in children but less so in adults. In the latter, nonsustained ventricular tachycardia (NSVT) on 48-hour electrocardiographic monitoring has some predictive value for subsequent sudden

Figure 48-14 (Figure Not Available) Hypothetical model for the pathogenesis of the end-stage phase of hypertrophic cardiomyopathy. Asterisk designates the following possibilities: (1) enhanced myocardial oxygen requirements and reduced myocardial capillary density relative to marked left ventricular (LV) hypertrophy (LVH) and (2) increased diastolic wall tension and coronary vascular resistance resulting from abnormal LV relaxation and impaired filling. CHF = congestive heart failure. *(From Maron BJ, Spirito P: Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 81:1339-1344, 1998.)*

Figure 48-15 (Figure Not Available) Patterns of left ventricular (LV) remodeling in the natural history of hypertrophic cardiomyopathy (HC). LVH = left ventricular hypertrophy. *(Reprinted from Maron BJ, Spirito P: Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 81:1339-1344, 1998.)*

death, although most patients (more than 75 percent) with NSVT do *not* die suddenly.[243] The absence of NSVT is a stronger predictor of a good prognosis than is the presence of NSVT of a bad one.[207] It is presumed, but not established, that sudden death is due to a ventricular arrhythmia, although atrial arrhythmias may play a role in sensitizing the heart so that ventricular arrhythmias appear subsequently.[242]

Despite the difficulty in identifying patients at high risk of sudden death, the *absence* of a variety of characteristics (including the absence of severe symptoms, malignant family history, NSVT, marked hypertrophy, marked left atrial dilatation, and abnormal blood pressure response to exercise) identifies a low-risk group who require little in the way of routine therapy.[152] [244] Although avoidance of intense physical exertion is probably appropriate, participation in recreational sports activities is not believed to be contraindicated.[152]

Children.

The mechanism of death may be different in children with HCM, because spontaneous ventricular arrhythmias and inducibility on electrophysiological testing are much less common. It is thought that ischemia may play a prominent role in these patients.[226] [245] [246] Hemodynamic mechanisms may also be involved, because younger patients are more likely to demonstrate abnormal changes in peripheral vascular resistance in response to exercise.[247] Sudden death often occurs during exercise but also demonstrates a circadian distribution, with clustering of deaths in the morning and early evening.[248]

Competitive Sports.

Guidelines for participation in competitive sports have been developed; strenuous exertion should probably be proscribed in all patients with HCM whether or not symptoms are prominent, especially if high-risk clinical characteristics are present. Unsuspected HCM is the most common abnormality found at autopsy in young competitive athletes who die suddenly. Cardiovascular screening before participation in competitive sports appears to reduce the frequency of unexpected sudden death from HCM,[142] although whether large-scale screening of athletes is administratively feasible or cost effective is another matter.[249]

Why some athletes with HCM die suddenly and others are able to continue to compete without limitation or death is not known.[250] It has been speculated that the extent and severity of myocardial disarray may play an important role in determining prognosis, although this is not a finding that is ordinarily or easily obtainable in a living patient! Patients with marked hypertrophy are at increased risk.[251] Sudden death is unlikely, however, in asymptomatic or mildly symptomatic patients with mild hypertrophy.[252] Bradyarrhythmias and disease of the atrioventricular conduction system may also play a role in sudden death.

Management

Management of patients with HCM is directed toward alleviation of symptoms, prevention of complications, and reduction in the risk of death (Fig. 48-17) . Whether asymptomatic patients should receive drug therapy is not established because no adequate controlled studies are available.[152] [157] Digitalis glycosides should generally be avoided unless atrial fibrillation or systolic dysfunction develops. Diuretics were

previously thought to be contraindicated

Figure 48-16 (Figure Not Available) Assessment of risk of sudden cardiac death (SD) in overall hypertrophic cardiomyopathy (HCM) population. Treatment for prevention of sudden death is limited to the small subset perceived to be at the highest risk. Asterisk indicates asymptomatic individuals with mild left ventricular hypertrophy (LVH) and without ventricular tachycardia (VT) on Holter monitoring, hypotensive blood pressure response to exercise, and family history of premature HCM-related death. ICD = internal cardioverter-defibrillator; NSVT = nonsustained VT. *(From Maron BJ: Hypertrophic cardiomyopathy. Lancet 350:127-133. © by The Lancet Ltd. 1997.)*

Figure 48-17 The principal clinical presentations of hypertrophic cardiomyopathy and corresponding treatment strategies. The size of the arrows indicates the approximate proportion of patients with hypertrophic cardiomyopathy in each subgroup. The dashed arrow indicates the present uncertainties regarding the size of this subgroup, and the question mark indicates the uncertainties regarding the therapeutic efficacy of pacing. *(Modified from Spirito P, Seidman C, McKenna W, et al: The management of hypertrophic cardiomyopathy. N Engl J Med 336:775, 1997. Copyright 1997, Massachusetts Medical Society.)*

to avoid precipitating or worsening the outflow gradient. More recent experience indicates that cautious use of diuretics often helps reduce symptoms of pulmonary congestion, particularly when they are combined with beta-adrenergic blockers or calcium antagonists.[154] [253] Beta-adrenergic agonists may improve diastolic filling but should not be used because they may produce ischemia and usually worsen the outflow gradient. The vast majority of patients with HCM require only medical management; invasive interventions are needed in only 5 to 10 percent of patients, and then only in those patients with outflow gradients who remain severely symptomatic despite optimal medical therapy.[152]

BETA-ADRENOCEPTOR BLOCKERS.

These drugs are the mainstay of medical therapy of HCM. With their use, angina, dyspnea, and presyncope may all be improved. In patients with resting or provocable gradients beta-adrenoceptor blockade may prevent the increase in outflow obstruction that accompanies exertion, although resting gradients are largely unchanged.[152] The drugs reduce the determinants of myocardial oxygen consumption and thus angina pectoris and perhaps exert an antiarrhythmic action as well. Angina pectoris generally responds more favorably to treatment with a beta-adrenoceptor blocker than does dyspnea. It has been suggested that beta-adrenoceptor blockade may prevent sudden death, and accordingly some use prophylactic beta-adrenoceptor blockade therapy in asymptomatic patients. However, its efficacy for this purpose has not been established.[155] [171] Beta-adrenoceptor blockade also blunts the heart's chronotropic response, thus limiting the demand for increased myocardial oxygen delivery. Beta-adrenoceptor blockade previously was thought to have a beneficial effect on diastolic ventricular filling, but it now appears that any benefit is simply the consequence

of a slower heart rate.[155] The overall clinical response to beta-adrenoceptor blockade is variable, and only about one third to two thirds of patients experience symptomatic improvement.[155] One small blinded trial of beta-adrenoceptor blocker therapy found that nadolol improved symptoms more than placebo or a calcium antagonist but did not improve exercise capacity.[254] If beta-adrenoceptor blockers are discontinued, they probably should be withdrawn slowly to avoid rebound adrenergic hypersensitivity.

CALCIUM ANTAGONISTS.

These are an alternative to beta-adrenoceptor blockade in the management of HCM; most of the experience has been with verapamil, with more limited use of nifedipine, diltiazem, and amlodipine.[155] [157] No clear consensus exists as to whether therapy should be initiated first with a beta-adrenoceptor blocker or a calcium antagonist, although verapamil often is effective in improving symptoms in patients who have failed beta-adrenoceptor blockade.[157] Exercise performance in particular may be improved when patients are changed from a beta-adrenoceptor blocker to verapamil. Both the hypercontractile systolic function and the abnormalities of diastolic filling may be related to abnormal calcium kinetics, and drugs that block the inward transport of calcium across the myocardial cell membrane may be able to rectify both abnormalities.

Verapamil has been the most widely used calcium antagonist in this condition.[157] Its use was suggested, at least in part, by the observation that it produces a protective and beneficial effect in the hereditary cardiomyopathy of the Syrian hamster, a condition marked by intracellular calcium overload in which propranolol is ineffective.[255] Although the vasodilator effects of verapamil should not be helpful in HCM, it appears that by depressing myocardial contractility, verapamil can decrease the left ventricular outflow gradient when given intravenously or orally. Perhaps more important from a symptomatic point of view, verapamil improves diastolic filling in HCM, at least in part by reducing asynchronous regional diastolic performance.[155] [157] It also improves regional myocardial blood flow

in some patients, which may contribute to the improvement in diastolic behavior.[256] Verapamil appears to improve diastolic filling by improving relaxation rather than by changing left ventricular diastolic stiffness; at any given diastolic volume, filling pressure is reduced. Although variable clinical responses have been reported with verapamil, about two thirds or more of patients show increased exercise capacity and an improved symptomatic status. Sustained symptomatic improvement has been noted with the long-term administration of verapamil in ambulatory patients, although important adverse effects, including sudden death, have been observed in a small fraction of patients so treated.[152] Complications with verapamil include suppression of sinus node automaticity and inhibition of atrioventricular conduction, vasodilatation, and negative inotropic effects. These side effects may culminate in hypotension, pulmonary edema, and death; antiarrhythmic agents, especially quinidine, may exacerbate the deleterious hemodynamic effects of verapamil. Because of these adverse effects, it has been suggested that verapamil should not be used, or should be used only with extreme

caution, in patients with high left ventricular filling pressure or symptoms of paroxysmal nocturnal dyspnea or orthopnea.[152] Unfortunately, these are usually the patients in greatest need of therapy.

Nifedipine has also been used in HCM, and it may have theoretical advantages over verapamil because it causes less depression of atrioventricular conduction. This may be counteracted by its more potent vasodilator action. Its effect on diastolic function have been inconsistent.[155] Nifedipine may alleviate the chest pain in HCM patients. Combined administration of nifedipine and propranolol may be of benefit in some patients, particularly those with outflow gradients. However, it should be recognized that the potent vasodilator effects of nifedipine may lead to systemic hypotension and an increase in the outflow gradient,[152] and in high doses it may depress left ventricular function. *Diltiazem* has also shown beneficial effects in HCM, producing improved diastolic function, although like verapamil and nifedipine it has caused an increase in the outflow gradient and a worrisome elevation of pulmonary capillary pressure.[155] [257]

The combination of a beta-adrenoceptor blocker and a calcium antagonist may be effective in patients responding inadequately to monotherapy, although there are only anecdotal reports of the superiority of combination therapy.[152] [258]

OTHER DRUGS.

Disopyramide, an antiarrhythmic drug that alters calcium kinetics, has produced symptomatic improvement and abolition of the pressure gradient in patients with HCM, presumably as a consequence of depression of left ventricular systolic performance as well as a peripheral vasoconstrictor effect.[259] It does not appear to have significant effects on diastolic function,[259] although this issue has not been entirely resolved.[260] Long-term experience with disopyramide is limited, particularly in asymptomatic patients and those without outflow gradients, although the initial benefits appear to decrease with time.[152]

Beta-adrenoceptor blockers, calcium antagonists, and the conventional antiarrhythmic agents do not appear to suppress serious ventricular arrhythmias or reduce the frequency of supraventricular arrhythmias. However, amiodarone is effective in the treatment of both supraventricular and ventricular tachyarrhythmias in HCM.[243] Although there is some belief that amiodarone improves prognosis in HCM, only limited and inconclusive data are available.[152] [153] [261] Amiodarone may also improve symptoms and exercise capacity, although its putative beneficial effects on diastolic ventricular function are controversial. [155] Experience with sotalol, although limited, has been generally favorable; in addition to its antiarrhythmic effects on supraventricular and ventricular arrhythmias, its beta-adrenoceptor blocking effects are beneficial.[262] We do not favor empirical use of amiodarone (or other antiarrhythmic agents for that matter) in unselected HCM patients, and we worry about possible proarrhythmic effects and potential toxicity, including sudden death.[213] [214] [236]

Strenuous exercise should be avoided because of the risk of sudden death; almost half of deaths in HCM occur during or just after strenuous physical activity.[263] Even though many individuals with subclinical HCM exercise vigorously, the threat of sudden death is

sufficiently real that competitive sports are proscribed in patients with marked hypertrophy or other factors believed to be associated with increased risk (see Figs. 48-16 (Figure Not Available) and 48-17). Atrial fibrillation should usually be pharmacologically or electrically converted because of the hemodynamic consequences of the loss of the atrial contribution to ventricular filling in this disorder. Anticoagulants should be given to patients with chronic atrial fibrillation when no contraindication exists. Infective endocarditis may occur in about 5 percent of patients but appears to be limited to those with an outflow gradient; accordingly, appropriate antibiotic prophylaxis is indicated in this group.[157] [264] The infection usually occurs on the aortic valve or mitral apparatus, on the endocardium, or at the site of the contact lesion on the septum; thus, chronic endocardial trauma may provide a nidus for subsequent infection.

DEVICES AND SEPTAL ABLATION.

Insertion of a dual-chamber DDD pacemaker may be useful in some patients with an outflow gradient and severe symptoms, especially the elderly,[265] [266] [267] [268] but it is likely that no more than 10 percent of HCM patients are candidates. Symptoms generally are improved, and the gradient is reduced by an average of about 25 percent, although better symptomatic and hemodynamic results appear to follow surgery (Fig. 48-18) .[157] Benefits have been described even after termination of pacing, suggesting a modification of myocardial properties. [265] The long-term utility of pacing, however, is not known at present, and a substantial placebo effect has been demonstrated.[267] [269] [270] [271] [271A] The benefit of its use in patients without a resting outflow gradient is even more equivocal; it usually improves symptoms and exercise capacity, but there is no improvement or even worsening of various hemodynamic variables and pharmacological therapy usually needs to be reinstituted.[272] Therefore, its use in this setting generally is not recommended at present.

In high-risk patients (especially the minority of HCM patients with sustained monomorphic ventricular tachycardia) or those with aborted sudden death, an ICD should be inserted,[242] [273] although an ICD may be less beneficial in HCM than in other conditions with aborted sudden death.[274]

A number of patients with severe obstruction have derived benefit at least over the short-term from intentional infarction of a portion of the interventricular septum by the infusion of alcohol into a selectively catheterized septal artery, with reduction of the outflow gradient and improvement in symptoms (Fig. 48-19) .[275] [276]

SURGICAL TREATMENT.

A number of surgical procedures aimed at reducing the outflow gradient have been developed. They are most commonly used in the markedly symptomatic patient with a gradient at rest above 50 mm Hg who has not responded well to medical management.[157] [277] [278]

Myectomy.

The most widely used operation for HCM consists of excising a portion of the hypertrophied septum using a transaortic approach (the operation has been called the Morrow procedure, named after the cardiac surgeon who developed the technique).[279] Left transventricular as well as combined transaortic and left ventricular approaches have also been used successfully. Operative management is facilitated by intraoperative echocardiography, and operative mortality is now less than 5 percent[280] ; large centers have reported mortalities of 3 percent or less.[157] [228]

Figure 48-18 Change in Doppler ultrasound-derived resting left ventricular outflow tract (LVOT) gradient from baseline (pre) to follow-up assessment (post) in patients with hypertrophic cardiomyopathy undergoing surgery or pacemaker insertion. Both groups (surgical myectomy, *left;* dual-chamber pacing, *right*) show significant reductions in resting gradient ($p < 0.05$). *(From Ommen SR, Nishimura RA, Squires RW, et al: Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 34:191, 1999.)*

[281] [282] Operation often relieves the obstruction (Figs. 48-18 and 48-20) as well as the mitral regurgitation. [281] The reduction in the left ventricular systolic pressure produced by the operation leads to reduced evidence of postoperative myocardial ischemia on thallium stress testing.[283] Patients older than the age of 65 as well as younger than the age of 10 years have undergone successful operations; the operative risk is higher in older patients.[282] [284]

Surgery results in long-term improvement in symptoms and exercise capacity in most patients.[281] [282] [285] [286] Occasional patients experience myocardial damage and fibrosis as a consequence of the procedure.[283] Significant aortic regurgitation

Figure 48-19 Coronary angiograms in a patient with hypertrophic cardiomyopathy undergoing percutaneous septal ablation. *A,* Identification of target vessel in right anterior oblique view (arrows). *B,* Balloon inflation in proximal part of target vessel. *C,* Injection of contrast dye to define perfusion area and to exclude reflux into other vessels. *D,* Final visualization of vessel stump after completed percutaneous occlusion of vessel. *(From Faber L, Seggewiss H, Gleichmann U: Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: Results with respect to intraprocedural myocardial contrast echocardiography. Circulation 98:2415, 1999. Copyright 1999, American Heart Association.)*

Figure 48-20 Three-dimensional transesophageal echocardiographic images before (*left*) and after (*right*) surgical myectomy of the left ventricular outflow tract (LVOT) in a patient with hypertrophic cardiomyopathy. The maximal width and depth of the myectomy trough are marked by large arrows. Small arrows indicate limits of myectomy trough. LA = left atrium. *(From Franke A, Schondube FA, Kuhl HP, et al: Quantitative assessment of the operative results after extended myectomy and surgical reconstruction of the subvalvular mitral apparatus in hypertrophic obstructive cardiomyopathy using dynamic three-dimensional transesophageal echocardiography. J Am Coll Cardiol 31:1641, 1998.)*

is an uncommon complication of the transaortic valve approach, occurring in less than 4 percent of patients.[287] Myotomy-myectomy may be combined with other necessary operative procedures (particularly coronary artery bypass grafting), although the surgical risk is increased.[280] There has been recent enthusiasm for combining septal myotomy-myectomy with plication of the anterior leaflet of the mitral valve and reconstruction of the submitral valvular apparatus.[288]

Mitral Valve Replacement.

Although this procedure or mitral valve repair is performed in fewer centers than myotomy-myectomy, the long-term results also have been favorable, with symptomatic benefit and an improvement in hemodynamics.[289] The rationale for this operation is that it abolishes obstruction by preventing systolic anterior motion of the mitral valve. It appears to be of particular value in patients with less than severe (<18 mm) hypertrophy of the upper septum or other atypical septal morphology, in those with previous myotomy-myectomy with persistent severe symptoms and obstruction, and in patients with intrinsic mitral valve disease. In appropriate candidates not responding to maximal standard medical and surgical therapy, cardiac transplantation may be considered; this usually is required only for patients who have entered the dilated phase of HCM and have intractable symptoms of congestive heart failure.[290]

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Restrictive and Infiltrative Cardiomyopathies

Of the three major functional categories of the cardiomyopathies (dilated, hypertrophic, and restrictive), restrictive cardiomyopathy (RCM) is the least common form in Western countries, although nonidiopathic forms of RCM such as endomyocardial disease (Table 48-8) are common in specific geographical regions of the world.[291] [292] The hallmark of the RCMs is abnormal diastolic function; the ventricular walls are excessively rigid and impede ventricular filling. Systolic function, on the other hand, often is unimpaired, even in many cases with extensive infiltration of the myocardium.[291] [293] [294] Thus, RCM bears some functional resemblance to constrictive pericarditis, which is also characterized by normal or nearly normal systolic function but abnormal ventricular filling (see Chap. 50).[291] Differentiation of the two conditions is mandatory because of the potential for successful surgical treatment of constriction.[292] [295]

A variety of specific pathological processes may result in restrictive cardiomyopathy, although the cause often remains unknown. Myocardial fibrosis (Fig. 48-21) , infiltration, or endomyocardial scarring is usually responsible for the abnormal diastolic behavior; in the idiopathic variety there often is histological evidence of myocyte hypertrophy.[291] [296] Myocardial involvement with amyloid is a common cause of RCM, although it can be caused by a variety of other conditions (see Table 48-8).[291] [292]

Some patients may manifest the clinical features of an RCM and yet exhibit the pathological findings of left ventricular hypertrophy and fibrosis[294] ; certainly ventricular hypertrophy, especially HCM, can cause diminished ventricular compliance, but not RCM per se. RCM on occasion is inherited; in such cases there may be an associated skeletal muscle disease.[291]

HEMODYNAMICS.

The clinical and hemodynamic features of restrictive heart disease simulate those of chronic constrictive pericarditis; endomyocardial biopsy, CT and radionuclide angiography may be particularly useful in differentiating the two diseases by demonstrating myocardial scarring or infiltration (biopsy) or thickening of the pericardium (CT and MRI).[292] [297] With the use of these modalities, exploratory thoracotomy should rarely be required; nevertheless, if the differentiation between constriction and restrictive cardiomyopathy cannot be established with certainty, surgical exploration is in order.[291] The characteristic hemodynamic feature in both conditions is a deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole

Figure 48-21 Endomyocardial biopsy specimens from patients with idiopathic restrictive cardiomyopathy. \i\A,\r\ This histologic specimen (hematoxylin-eosin, ;ts250) shows myocytes with slight hypertrophy but is otherwise normal. \i\B,\r\ Another specimen (hematoxylin-eosin, ;ts40), from another patient, shows marked interstitial fibrosis, which may also occur in idiopathic restrictive cardiomyopathy. (From Kushwaha SS, Fallon JT, Fuster V: Restrictive Cardiomyopathy. N Engl J Med 336:267, 1997. Copyright 1997, Massachusetts Medical Society.)

TABLE 48-8 -- CLASSIFICATION OF TYPES OF RESTRICTIVE CARDIOMYOPATHY ACCORDING TO CAUSE

Myocardial
Noninfiltrative
Idiopathic cardiomyopathy*
Familial cardiomyopathy
Hypertrophic cardiomyopathy
Scleroderma
Pseudoxanthoma elasticum
Diabetic cardiomyopathy
Infiltrative
Amyloidosis*
Sarcoidosis*
Gaucher disease
Hurler disease

Fatty infiltration
Storage Diseases
Hemochromatosis
Fabry disease
Glycogen storage disease
Endomyocardial
Endomyocardial fibrosis*
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic cancers
Radiation*
Toxic effects of anthracycline*
Drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)
From Kushwaha S, Fallon JT, Fuster V: Restrictive cardiomyopathy. N Engl J Med 336:267, 1997. Copyright 1997, Massachusetts Medical Society.

*This condition is more likely than the others to be encountered in clinical practice.

(although this finding is absent in some patients with RCM).[291] This dip and plateau has been termed the *square root sign* (see Chap. 50) and is manifested in the atrial pressure tracing as a prominent *y* descent followed by a rapid rise and plateau. The *x* descent may also be rapid, and the combination results in the characteristic M or W waveform in the atrial pressure tracing.[291] The *a* wave is prominent and often is of the same amplitude as the *v* wave. Both systemic and pulmonary venous pressures are elevated, although patients with restrictive heart disease typically have left ventricular filling pressures that exceed right ventricular filling pressure by more than 5 mm Hg; this difference is accentuated by exercise, fluid challenge, and Valsalva maneuver (although not all patients demonstrate this finding).[291] [298]

In this respect they differ from patients with constrictive pericarditis, in whom diastolic pressures are similar in both ventricles, usually differing by no more than 5 mm Hg. The pulmonary artery systolic pressure is often greater than 50 mm Hg in patients with RCM but is lower in constrictive pericarditis.[291] Furthermore, the plateau of the right ventricular diastolic pressure is usually at least one third of the peak right ventricular systolic pressure in patients with constrictive pericarditis, whereas it is frequently lower in RCM.[291]

CLINICAL MANIFESTATIONS.

Exercise intolerance is frequent because of the inability of patients with RCM to increase their cardiac output by tachycardia without further compromising ventricular filling. Weakness and dyspnea are often prominent. Exertional chest pain may be prominent in some patients but is usually absent. Particularly in advanced cases, the central venous pressure is elevated, with attendant peripheral edema, enlarged liver, ascites, and anasarca. *Physical examination* may reveal jugular venous distention and an S_3 , S_4 , or both. An inspiratory increase in venous pressure may be seen. However, in contrast to constrictive pericarditis, the apex impulse is usually palpable in RCM.[291]

LABORATORY STUDIES.

Various ancillary laboratory findings in addition to endomyocardial biopsy, CT and MRI[297] (see Chap. 10) may be useful in distinguishing between constrictive and restrictive disease. Although pericardial calcification is neither absolutely sensitive nor specific for constrictive pericarditis (see Chap. 50), its presence in a patient in whom the differential diagnosis rests between RCM and constrictive pericarditis lends strong support to the latter diagnosis. The echocardiogram may demonstrate thickening of the left ventricular wall and an increase of left ventricular mass in patients with infiltrative disease causing RCM. The pattern of filling of the left ventricle differs in the two conditions, as can be demonstrated by transthoracic and transesophageal Doppler ultrasonography.[291] [295] [299] In patients with RCM, there is increased early left ventricular filling velocity, decreased atrial filling velocity, and decreased isovolumetric relaxation time.[291]

The prognosis in RCM is variable; usually it is one of relentless symptomatic progression and high mortality.[295] [299A] No specific therapy (other than symptomatic) is available (excepting the cardiomyopathy due to iron overload which is improved by removal of the iron and amyloidosis, in which some patients appear to benefit from alkylating-based chemotherapy).[295]

AMYLOIDOSIS

ETIOLOGY AND TYPES.

Amyloidosis is a disease complex that results from deposition of unique twisted beta-pleated sheet fibrils formed from various proteins by several different pathogenic mechanisms.[300] Amyloid may be found in almost any organ, but clinically evident disease does not appear unless infiltration is extensive. Several classification systems have been used to characterize the different clinical presentations of amyloidosis. The condition with the traditional designation of primary amyloidosis is now known to be caused by the production of an amyloid protein composed of portions of immunoglobulin light chain (designated *AL*) by a monoclonal population of plasma cells, often as a consequence of multiple myeloma. Secondary amyloidosis is due to the production of a nonimmunoglobulin protein termed *AA.*[300]

Familial Amyloidosis.

This condition, inherited as an autosomal dominant trait, results from the production of a variant prealbumin protein termed *transthyretin;* more than 50 different point mutations have been described so far.[301] [302] It generally occurs in one of three clinical presentations: progressive neuropathy, cardiomyopathy, or nephropathy. Senile systemic amyloidosis is due to the production of either an atrial natriuretic-like protein or transthyretin[300] and is becoming increasingly common as the average age of the population increases. It is four times as common in blacks as in whites.[303] Scattered deposits of amyloid localized to the aorta or atria are virtually ubiquitous in individuals older than the age of 80.[292] [300] Small deposits of amyloid may often be found in the pulmonary vessels or the vessels of other organs as well.

Cardiac Amyloidosis

Involvement of the heart is a common finding and is the most frequent cause of death in amyloidosis associated with an immunocyte dyscrasia.[304] Clinically apparent heart disease is present in one third of patients, although the heart is virtually always involved when studied pathologically. In secondary amyloidosis, on the other hand, clinically significant cardiac involvement is uncommon; the myocardial deposits are typically small and perivascular and usually do not result in significant myocardial dysfunction.[300] Familial amyloidosis is associated with overt cardiac involvement in about one fourth of the afflicted patients, usually late in the course of the disease.[305] The clinical course is usually dominated by neurological or renal dysfunction, although death is due to heart failure or

arrhythmia about half the time.[305] Cardiac involvement in senile amyloidosis varies from small atrial deposits that do not result in functional impairment to extensive ventricular involvement with resultant cardiac failure.[302]

Cardiac amyloidosis occurs more commonly in men than in women, and it is rare before the age of 30 years. Even in the familial form, the onset of clinical cardiac disease usually does not occur before the age of 35 years and generally occurs much later in life.[305]

PATHOLOGY.

The pathological findings often include mild atrial enlargement, usually without significant ventricular dilatation. The walls of both ventricles are typically firm, rubbery, noncompliant, and thickened. Amyloid is present between the myocardial fibers, often with extensive deposition in the papillary muscles. Endocardial involvement of the atria and ventricles is frequent. Amyloidosis often results in focal thickening of or deposits on

the cardiac valves, but these abnormalities do not appear to interfere with valvular function other than to produce murmurs. The intramural coronary arteries and veins frequently contain amyloid deposits in the media and adventitia, occasionally compromising the lumina of the vessels.[293] [301]

CLINICAL MANIFESTATIONS.

Involvement of the cardiovascular system by amyloidosis occurs in four general forms:

1. The most common presentation of cardiac amyloidosis is that of RCM.[291] Right-sided findings dominate the clinical presentation; peripheral edema is a prominent finding, whereas paroxysmal nocturnal dyspnea and orthopnea are absent.[292] Amyloid infiltration of the myocardium results in increased stiffness of the myocardium, producing the characteristic diastolic dip and plateau (square root sign) in the ventricular pressure pulse that may simulate constrictive pericarditis. In contrast to the accelerated early left ventricular diastolic filling found in constrictive pericarditis, cardiac amyloidosis is marked by an impaired rate of early diastolic filling.
2. A second common presentation is congestive heart failure due to systolic dysfunction.[302] Hemodynamic evidence of restriction of ventricular filling may not be prominent in these patients. In some patients amyloid deposition in the atria may be responsible for loss of atrial transport function despite the maintenance of electrical "sinus" rhythm, with the production of congestive heart failure.[306] The course of this form of the disease is often one of relentless progression, usually poorly responsive to treatment. Angina pectoris occurs on occasion despite angiographically normal coronary arteries.[293]
3. Orthostatic hypotension occurs in about 10 percent of cases. Although most likely due to amyloid infiltration of the autonomic nervous system or of blood vessels, amyloid deposition in the heart and adrenals may contribute to the pathogenesis of this variant. Hypovolemia as a result of the nephrotic syndrome secondary to renal amyloidosis may aggravate the postural hypotension.[305]
4. An abnormality of cardiac impulse formation and conduction is the fourth and least common mode of presentation and may result in arrhythmias and conduction disturbances. Sudden death, presumably arrhythmic in origin, is relatively common and may be preceded by episodes of syncope.[305] [307]

PHYSICAL EXAMINATION.

This often reveals congestive heart failure, especially right sided[292] ; a systolic murmur due to atrioventricular valvular regurgitation may be present. Jugular venous distention, a protodiastolic gallop, hepatomegaly, peripheral edema, and a narrow pulse pressure are found in patients presenting with RCM. An S_4 is uncommon, presumably due to amyloid infiltration of the atrium with attendant reduced systolic function of the atrial myocardium.[306] Patients typically are normotensive or hypotensive; even previously hypertensive individuals usually have a fall in blood pressure as the disease progresses.

NONINVASIVE TESTING.

The chest roentgenogram usually shows cardiomegaly in patients with systolic dysfunction, although heart size may be normal in patients with the restrictive form.[92] Pulmonary congestion may be prominent in patients with congestive heart failure. The ECG is often abnormal; the most characteristic feature (but often absent) is diffusely diminished voltage.[292] Myocardial infarction is often simulated because of small or absent R waves in right precordial leads or, less frequently, by Q waves in the inferior leads.[300] Arrhythmias, particularly atrial fibrillation, are common, although they rarely are the presenting feature of cardiac amyloidosis. Complex ventricular arrhythmias are found frequently in patients with cardiac amyloidosis and may be a harbinger of sudden death.[301] Various forms of atrioventricular conduction defects are often seen and may be associated with increased mortality, although significant infra-Hisian block may only be apparent on electrophysiological testing.[305] [308] Abnormalities of atrioventricular conduction appear to be particularly common in familial amyloidosis with polyneuropathy.[305] Sinus node involvement is common, and the clinical and ECG features of the sick sinus syndrome may be present (see Chap. 25).

Echocardiography (see Fig. 7-103).

In advanced cases this most commonly reveals increased thickness of the walls of the ventricles, small ventricular chambers, dilated atria, and thickening of the interatrial septum (Fig. 48-22) ,[309] although the findings are more prominent in the familial than in the primary (AL) form.[293] Left ventricular dysfunction may be seen, especially in advanced cases, but systolic function often is surprisingly normal.[293] Early preclinical unsuspected cardiac involvement may be detectable only by echocardiography or Doppler ultrasonography.[291] Although the cardiac valves may be thickened, they usually move normally.[302] A pericardial effusion is common but rarely results in tamponade. The appearance of the thickened cardiac walls is often distinctive on two-dimensional echocardiography, demonstrating a granular sparkling texture, presumably due to the amyloid deposit.[309] In some cases the pattern of increased wall thickness is nonuniform and may resemble HCM. Echocardiographic demonstration of thick left ventricular walls with concomitant low voltage on the ECG appears to distinguish cardiac amyloidosis from pericardial disease or left ventricular hypertrophy, and this distinctive voltage/mass ratio is characteristic of myocardial infiltration by amyloid.[309] Doppler ultrasonography and radionuclide ventriculography routinely demonstrate abnormalities of diastolic function, and, by estimating the degree of cardiac involvement by amyloid, provide prognostic information.[310] MRI may be of some help by using tissue characterization signatures to identify myocardial infiltration.[311]

Nuclear Imaging.

Scintigraphy with technetium-99m pyrophosphate is often strongly positive with prominent amyloid involvement, although in some patients it is falsely negative.[309] [312] Positive scans tend to correlate with extensive cardiac involvement. Scanning with indium-labeled antimyosin antibody may also detect cardiac amyloid involvement.[313] Scanning with specialized agents has shown sympathetic denervation in patients with

cardiac amyloidosis.[312]

DIAGNOSIS.

Whereas two or three decades ago the clinical diagnosis of systemic amyloidosis was made correctly ante mortem in about one fourth of cases, with more recent clinical awareness of the disease and the utilization of *biopsy techniques* the diagnosis is now made before death in the majority of patients. An abdominal fat aspirate has been the single most useful diagnostic procedure, combining the attributes of ease of performance, sensitivity, and safety.[292] Biopsy of rectum, gingiva, bone marrow, liver, kidney, and various other tissues has also been used. Endomyocardial biopsy of the right or left ventricles may be

Figure 48-22 Serial echocardiographic findings in a patient developing cardiac amyloidosis. *Top,* Serial two-dimensional echocardiographic findings. Note the thickening of all myocardial walls and valves. *Bottom,* Serial M-mode echocardiography shows gradual increase of interventricular septal, left ventricular posterior wall, and right ventricular wall thickness. The date of the study is shown at the bottom (year.month.day). *(From Youn H, Chae JS, Lee KY, et al: Images in cardiovascular medicine: Amyloidosis with cardiac involvement. Circulation 97:2093, 1998. Copyright 1998, American Heart Association.)*

Figure 48-23 Endomyocardial biopsy specimens from patients with cardiac amyloidosis. \i\A,\r\ This histologic section (hematoxylin and eosin, ;ts250) shows interstitial deposition of amyloid fibrils in a specimen from the right ventricle. \i\B,\r\ Immunofluorescent stain (;ts400) shows lambda light chains. (From Kushwaha SS, Fallon JT, Fuster V: Restrictive cardiomyopathy. N Engl J Med 336:267, 1997. Copyright 1997, Massachusetts Medical Society.

helpful in establishing the diagnosis of cardiac amyloidosis (Fig. 48-23) if the abdominal fat aspirate is negative.[292] Immunohistochemical staining of tissue samples is important to distinguish systemic senile, familial, and primary forms of amyloidosis in otherwise equivocal presentations, because prognosis and management differ in the various forms.[302] [314]

MANAGEMENT.

The treatment of cardiac amyloidosis is generally unsatisfactory, although there has been some improvement in survival and functional state with the use of alkylating agents in primary (AL) amyloidosis.[302] [315] [316] Digitalis glycosides should be used with caution because patients with cardiac amyloidosis appear to be particularly sensitive to digitalis preparations, and the use of ordinary doses may lead to serious arrhythmias; this may relate to selective binding of digoxin to amyloid fibrils in the myocardium.[292]

Similarly, nifedipine binds to amyloid fibrils; its use and that of the other calcium antagonists may lead to exacerbation of congestive heart failure symptoms due to an enhanced negative inotropic effect.[292] [317] Insertion of a permanent pacemaker may be beneficial in the short term in patients with symptomatic conducting system disease.[318] Careful use of low doses of diuretics and vasodilators may afford some symptomatic benefit, but there is a risk of hypotension and hypoperfusion with use of these agents.[291] In patients with atrial standstill due to amyloid infiltration, anticoagulation may be appropriate even in the absence of atrial arrhythmias, because there is some risk of thrombus formation, presumably as a consequence of stasis in the atrium.[306]

Autologous stem cell transplantation is being used with increasing frequency in primary (AL) amyloidosis, but the long-term benefit, especially in patients with cardiac involvement, is not known.[319] A small number of patients have undergone cardiac transplantation, with poor long-term results (39 percent survival at 4 years in one study) due to progressive amyloidosis in other organs or recurrence in the transplanted heart, although a few carefully selected patients have shown long-term survival and functional improvement.[291] [320] An heroic alternative approach for the familial form of cardiac amyloidosis is simultaneous heart and liver transplantation because the circulating transthyretin in these patients is produced in the liver and can be corrected with liver transplantation.[301] [302] No therapy is effective for the senile form, but survival is about 10 times longer than in the primary form (60 vs. 6 months).[314]

INHERITED INFILTRATIVE DISORDERS CAUSING RESTRICTIVE CARDIOMYOPATHY

The intramyocardial accumulation or infiltration of an abnormal metabolic product typically produces a restrictive picture with impaired diastolic ventricular filling. Systolic impairment may be seen as well but is not invariably found. A variety of infiltrative diseases, often inherited, may result in this hemodynamic picture, including the glycogenoses, the mucopolysaccharidoses, Fabry disease, and Gaucher disease.

FABRY DISEASE

Fabry disease (angiokeratoma corporis diffusum universale) is an X-linked recessive disorder of glycosphingolipid metabolism due to a deficiency of the lysosomal enzyme alpha-galactosidase A that is caused by one of more than four dozen mutations.[321] Some mutations result in no detectable alpha-galactosidase A activity and widespread manifestations throughout the body, whereas others produce

some degree of enzyme activity with attendant atypical variants of Fabry disease with involvement limited solely to the myocardium.[322] The disease is characterized by an intracellular accumulation of a neutral glycolipid, with prominent involvement of the skin and kidneys as well as the myocardium in the classic form. *Histological examination* often reveals widespread involvement of the myocardium, vascular endothelium,

conducting tissues, and valves, particularly the mitral valve. The major clinical manifestations of the disease result from the accumulation of the glycolipid substrate in endothelial cells, with eventual occlusion of small arterioles. The accumulation of the glycolipid occurs in the lysosomes of the cardiac tissues and is responsible for the multiple cardiovascular manifestations of Fabry disease (Fig. 48-24) .

CARDIAC FINDINGS.

These typically include angina and myocardial infarction caused by accumulation of lipid moieties in coronary endothelial cells, but coronary arteries are usually angiographically normal. There is increased left ventricular wall thickness simulating HCM, left ventricular dysfunction and failure due to lipid accumulation in myocytes, and mitral regurgitation (due to deposition in valvular fibroblasts).[323] Symptomatic cardiovascular involvement occurs eventually in most affected males, whereas female carriers usually are asymptomatic or only minimally symptomatic. Systemic hypertension, mitral valve prolapse, and congestive heart failure are common clinical manifestations. ECG abnormalities may include a short PR interval, atrioventricular block, and ST segment and T wave abnormalities.[323] The echocardiogram usually reveals increased left ventricular wall thickness as a result of glycolipid deposition, which may simulate HCM.[323] Differentiation from other hypertrophic or restrictive processes (such as cardiac amyloidosis) may not be possible on echocardiographic grounds but may be possible with MRI (Fig. 48-25) . Endomyocardial biopsy may be of considerable value in making a definitive diagnosis, as is low plasma alpha-galactosidase A activity.

GAUCHER DISEASE

Gaucher disease is an uncommon inherited disorder of glycosyl ceramide metabolism. It is secondary to a deficiency of the enzyme beta-glucosidase and results in accumulation of cerebrosides in the spleen, liver, bone marrow, lymph nodes, brain, and myocardium. Diffuse interstitial infiltration of the left ventricle by cells laden with cerebroside produces reduced left ventricular compliance and cardiac output. Clinical evidence of cardiac involvement is uncommon, but when present it is characterized by left ventricular dysfunction, hemorrhagic pericardial effusion, increased left ventricular wall mass, and thickening of the left-sided valves.[324] Liver transplantation may produce a reduction in tissue infiltration by cerebrosides.[325]

HEMOCHROMATOSIS (See also Chap. 69)

Hemochromatosis is characterized by excessive deposition of iron in a variety of parenchymal tissues (heart, liver, gonads, and pancreas). It may occur (1) as a familial (autosomal recessive) or idiopathic disorder; (2) in association with a defect in hemoglobin synthesis resulting in ineffective erythropoiesis; (3) in chronic liver disease; and (4) with excessive oral or parenteral intake of iron (or blood transfusions) over many years.[326] [327] Although patients who have iron deposits in the myocardium almost always have deposits in other organs (e.g., liver, spleen, pancreas, bone marrow), the severity of myocardial involvement varies widely and only roughly parallels that in other

organs.

Figure 48-24 Electron microscopy of cardiac tissue in Fabry disease, showing complex concentric lamellar bodies (arrow) (original magnification 2000×). *(From Cantor WJ, Butany J, Iwanochko M, Liu P: Restrictive cardiomyopathy secondary to Fabry's disease. Circulation 98:1457, 1998. Copyright 1998, American Heart Association.)*

Figure 48-25 Cardiac MRI (T1-weighted spin echo) in Fabry disease, showing marked ventricular thickening (arrow). Coronal view. *(From Cantor WJ, Butany J, Iwanochko M, Liu P: Restrictive cardiomyopathy secondary to Fabry's disease. Circulation 98:1457, 1998. Copyright 1998, American Heart Association.)*

Cardiac involvement leads to a mixed DCM/RCM with both systolic and diastolic dysfunction, often with associated arrhythmias.[326] [328] [329] [330] Myocardial damage is thought to be due to direct tissue toxicity of the free iron moiety rather than simply to tissue infiltration.[326] Although cirrhosis and hepatocellular carcinoma are the most common causes of death, cardiac mortality is an important additional concern (especially in the group of patients--usually men--who present at a young age).[327]

PATHOLOGICAL FINDINGS.

These consist of a dilated heart with thickened ventricular walls. Myocardial iron deposits are found within the sarcoplasmic reticulum and are most common in the subepicardial region, followed by the subendocardial region, and are least common in the midmyocardial wall.[326] They are more extensive in ventricular than in atrial myocardium. Involvement of the cardiac conducting system is common. Myocardial degeneration and fibrosis may also occur.

The severity of myocardial dysfunction is proportional to the quantity of iron present in the myocardium.[331] Extensive deposits of cardiac iron (particularly those grossly visible at postmortem examination) are invariably associated with cardiac dysfunction.

CLINICAL MANIFESTATIONS.

These vary widely, depending on the extent of myocardial involvement. Some patients remain asymptomatic despite echocardiographic evidence of myocardial involvement, which is expressed initially as increased left ventricular wall thickness and later as chamber enlargement and contractile dysfunction.[331] In such cases, a variety of noninvasive techniques (CT and especially MRI) may demonstrate early subclinical myocardial involvement in which treatment is most effective (Fig. 48-26) .[226] [332] Symptomatic cardiac involvement is usually associated with ECG abnormalities, including ST segment and T wave abnormalities, as well as supraventricular arrhythmias[331] ; these ECG changes correlate with the degree of iron deposit in the

heart.

Cardiac involvement usually is evident from the clinical and echocardiographic features; endomyocardial biopsy may be useful to confirm (but not exclude) the diagnosis.[327] The diagnosis is aided by finding an elevated plasma iron level, a normal or low total iron-binding capacity, and markedly elevated values for serum ferritin, urinary iron, liver iron, and especially saturation of transferrin.[327] Repeated phlebotomies or the use of the chelating agent desferrioxamine may be clinically beneficial.[326] [333]

GLYCOGEN STORAGE DISEASES

Adult patients may demonstrate cardiac involvement in these diseases; in type III (glycogen debranching enzyme deficiency), cardiac involvement is found only in patients with deficient enzyme in muscle tissue.[334] Cardiac involvement is marked most commonly by apparent left ventricular hypertrophy on the ECG and echocardiogram. [169] [334] [335]

Figure 48-26 Standard-plane CT of chest without contrast medium enhancement at level of seventh thoracic vertebra in a patient with cardiac hemochromatosis. Gated scanning was not used, and scanning speed was one scan per 4 seconds. Right ventricle (*top*), left ventricle (*bottom*), and left atrium were scanned at this level. Left ventricular wall and part of right ventricular wall could be identified as a high-density area as a result of iron deposition in the myocardium. *(From Niwano S, Yokoyama J, Niwano H, et al: Images in cardiovascular medicine: Iron deposition in myocardium documented on standard computed tomography in cardiac hemochromatosis. Circulation 97:2371, 1998. Copyright 1998, American Heart Association.)*

Sarcoidosis

Sarcoidosis is a granulomatous disorder of unknown cause, characterized by multisystem involvement. Infiltration of the lungs, reticuloendothelial system, and skin usually dominates the clinical picture, but virtually any tissue may be affected. The most important manifestation results from pulmonary involvement. This often leads to diffuse fibrosis that may result in fatal right-sided heart failure. Primary cardiac involvement is not often recognized clinically, although it may be demonstrated at autopsy in 20 to 30 percent of cases, most of which demonstrate generalized sarcoidosis.[336]

Clinical manifestations of sarcoid heart disease are present in less than 5 percent of patients, although myocardial involvement may result in heart block, congestive heart failure, ventricular arrhythmias, and sudden death.[337] [338] Myocardial sarcoidosis may have restrictive as well as congestive features because cardiac infiltration by sarcoid granulomas results not only in increased stiffness of the ventricular wall but in diminished systolic contractile function as well. Myocardial sarcoidosis typically affects young or middle-aged adults of either gender; there usually is evidence of generalized

sarcoidosis.[336]

PATHOLOGY.

The typical pathological feature of sarcoidosis is the presence of noncaseating granulomas, which occur in many organs. They infiltrate the myocardium and may eventually form fibrotic scars.[336] The granulomas may involve any region of the heart, although the left ventricular free wall and the interventricular septum are the most common sites, and extensive granulomas and scar tissue in the cephalad portion of the interventricular septum are constant findings in patients with abnormalities of the conduction system.[339] Cardiac infiltration may range from a few scattered lesions to extensive involvement. Because of the variable cardiac involvement, myocardial biopsy may be positive in only about half of the patients, and therefore a negative biopsy by no means excludes the diagnosis.[336] Transmural involvement is common, and large portions of the ventricular wall may be replaced by scar tissue, which may lead to aneurysm formation. Although involvement of small coronary artery branches may be found in sarcoidosis, the larger conductance vessels are uninvolved.[336]

CLINICAL MANIFESTATIONS.

Sudden death is the most feared and unfortunately one of the more common manifestations of cardiac sarcoidosis.[336] [340] Conduction disturbances and congestive heart failure are common manifestations of symptomatic involvement in nonfatal cases, but many patients are asymptomatic despite extensive cardiac involvement.[337] Syncope is common and may reflect paroxysmal arrhythmias or conduction disturbances.[336] Atrial and ventricular arrhythmias, especially ventricular tachycardia, are observed frequently.[336] Although cor pulmonale as a consequence of pulmonary sarcoidosis accounts for some of the symptoms of heart failure, many symptoms are caused by direct myocardial involvement by granulomas and scar tissue, and patients show the clinical features of RCM and/or DCM[336] Symptoms of myocardial sarcoid may be present for variable lengths of time; however, the disease may progress rapidly to death, and in some patients the interval from the onset of cardiac symptoms to death is measured in months. In others, survival may be considerably longer.[336]

Cardiac dysfunction is often severe and progressive. Occasionally, patients with extensive involvement develop overt left ventricular aneurysms. Pericardial effusions are not uncommon.[341]

The physical examination may reveal findings of extracardiac sarcoid or may be totally normal. A systolic murmur reflecting mitral regurgitation is common. This appears to be more the result of left ventricular dilatation than of direct sarcoid involvement of the papillary muscles.

The ECG frequently is abnormal and most commonly demonstrates T wave abnormalities. Sarcoidosis appears to have an affinity for involvement of the atrioventricular junction and bundle of His, and thus varying degrees of intraventricular or atrioventricular block are common.[336] [340] With extensive myocardial involvement,

pathological Q waves may appear and simulate myocardial infarction (Fig. 48-27) . Characteristic echocardiographic features include left ventricular dilatation and dysfunction, often with regional wall motion abnormalities suggestive of ischemic heart disease[336] ; wall thinning and increased echogenicity

Figure 48-27 Electrocardiogram in patient with cardiac sarcoidosis shows abnormal Q wave in leads II, III, and aVF and ST segment elevation in V_5 and V_6 . *(From Shindo T, Kurihara H, Ohishi N, et al: Images in cardiovascular medicine: Cardiac sarcoidosis. Circulation 97: 1306, 1998. Copyright 1998, American Heart Association.)*

are sometimes observed (Fig. 48-28) . A small to moderate-sized pericardial effusion is seen in about 20 percent.[341]

DIAGNOSIS.

In many cases the diagnosis may be suspected in patients with bilateral hilar lymphadenopathy on chest roentgenogram in whom there is clinical or ECG evidence of myocardial disease. Endomyocardial biopsy may be useful in establishing the diagnosis, although the nonuniform involvement of the heart by sarcoidosis means that a negative biopsy does not exclude the diagnosis. The echocardiogram demonstrates diffuse and often regional left ventricular wall motion abnormalities in patients with clinical cardiac involvement (see Fig. 48-28). Myocardial imaging with thallium-201 or technetium-99m sestimibi may be helpful in demonstrating segmental perfusion defects that result from sarcoid infiltration of the myocardium.[337] [342] [343] Imaging may also indicate the presence of right ventricular hypertrophy in patients with right ventricular overload due to pulmonary fibrosis and pulmonary hypertension. Uptake of technetium pyrophosphate, gallium, and labeled antimyosin antibody may aid in the diagnosis, as may MRI.[336] [343] [344] [345] [346] [347]

MANAGEMENT.

The treatment of myocardial sarcoidosis is difficult.[340] Arrhythmias are often refractory to antiarrhythmic drugs. Permanent pacing may be helpful in patients with involvement of the atrioventricular conduction system. Although the matter is not settled, corticosteroids may be of some benefit in treating the conduction disturbances, arrhythmias, and myocardial dysfunction of sarcoidosis.[336] [348]

Figure 48-28 Echocardiographic findings in cardiac sarcoidosis. *Top,* Parasternal long-axial echocardiographic view. Arrows show wall thinning and increased echogenicity of inferior wall. *Bottom,* Parasternal short-axial view showing end-diastolic (*lower left*) and end-systolic (*lower right*) phases.

These is impaired systolic shortening. Arrows show increased echogenicity. *(From Shindo T, Kurihara H, Ohishi N, et al: Images in cardiovascular medicine. Cardiac sarcoidosis. Circulation 97:1306, 1998. Copyright 1998, American Heart Association.)*

It has been suggested that further benefit may be derived from the addition of hydroxychloroquine, methotrexate, or cyclophosphamide.[340] Because the risk of sudden death appears to be greatest in patients with extensive myocardial involvement, it may be reasonable to attempt to halt the progression of the disease with corticosteroids before irreversible fibrosis occurs. Insertion of an ICD may be considered in appropriate patients at high risk of sudden death.[349] Heart or heart-lung transplantation has been used in selected patients with intractable heart failure, although recurrent sarcoid involvement of the transplanted heart can occur.[291]

ENDOMYOCARDIAL DISEASE

DEFINITION AND PATHOGENESIS.

Endomyocardial disease (EMD) is a common form of restrictive cardiomyopathy that typically is found in a geographical distribution near the equator.[350] It is most frequent in equatorial Africa and is encountered with less frequency in South America, Asia, and nontropical countries, including the United States.[351] It is marked by intense endocardial fibrotic thickening of the apex and subvalvular regions of one or both ventricles that results in obstruction to inflow of blood into the respective ventricle, thus producing restrictive physiology. For many years it had been thought that there are two variants of the disease, one occurring principally in tropical countries (termed *endomyocardial fibrosis* [EMF] or Davies disease) and the other in temperate countries (Loffler's endocarditis parietalis fibroplastica or hypereosinophilic syndrome).[292] However, despite the pathological similarities,[352] there are important contrasts in clinical presentation that challenge the concept of a single disease process.[353] In addition to the geographical differences, the temperate form of the disease is a more aggressive and rapidly progressive disorder, affecting principally males, and is associated with hypereosinophilia, thromboembolic phenomena, and generalized arteritis. EMF, conversely, shows no gender predilection, occurs in younger patients, and is not associated with an intense eosinophilia.[292]

DIFFERENCES BETWEEN LOFFLER ENDOCARDITIS AND EMF.

Part of the thesis that Loffler endocarditis and EMF are different phases of a single disease is based on a theory of pathogenesis involving the toxic effect of eosinophils on the heart.[354] Under this formulation, an initial hypereosinophilia of whatever cause results in damage to the myocardium that produces the first phase of EMD: a necrotic phase, marked by an intense myocarditis, rich in eosinophils, and with an associated arteritis (i.e., Loffler endocarditis).[354] This initial phase occurs within the first few months of illness. It may be followed by a thrombotic stage, occurring about a year after initial presentation, during which the myocarditis has receded, nonspecific thickening of the myocardium is beginning, and there is a variable degree of superimposed thrombus formation.[354] The putative last stage is one of fibrosis, presenting all of the features of EMF. The three stages--necrotic, thrombotic, and fibrotic--have been defined on the

basis of postmortem material, and it is not suggested by proponents of the unified pathogenesis hypothesis that each patient with advanced disease (manifested by EMF) has necessarily passed through the earlier phases.

ROLE OF EOSINOPHILS.

The possible role of eosinophils in the production of the cardiac abnormalities has intrigued investigators for years.[354] [355] Eosinophils may damage tissues by direct invasion or by the release of toxic substances. The presence of degranulated eosinophils in the peripheral blood of patients with Loffler endocarditis suggests that the protein constituents of the eosinophil's granule may be cardiotoxic, first producing the necrotic phase of EMD, followed by the thrombotic and fibrotic phases after the disappearance of the initial eosinophilia.[353]

There is now, however, increasing speculation that this continuum occurs only in the temperate countries, and the endemic EMF found in tropical countries is a distinct and separate disease, because a link with eosinophilia has been difficult to document, despite the frequency of parasitic diseases.[292] [356] [357] [358] Other etiological factors have been implicated (Fig 48-29) ; the fibrosis of tropical EMF has been linked to the higher levels of cerium and lower concentrations of magnesium that apparently are found in endemic areas.[356] [359] [360]

Because the clinical manifestations of EMD demonstrate geographical and clinical differences, Loffler endocarditis and EMF are discussed separately, even though they could be part of the same disease continuum.

Loffler Endocarditis: The Hypereosinophilic Syndrome

Marked eosinophilia of any cause may be associated with endomyocardial disease. The typical patient who presents

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Figure 48-29 The pathogenesis of Loffler syndrome. Tissue damage is caused by major basic and cationic proteins derived from cytotoxic eosinophils. These cytotoxic proteins may stay in the myocardium for a prolonged period and produce continuous tissue damage. In the fibrotic phase, various types of heart diseases, such as endomyocardial fibrosis, dilated cardiomyopathy, atrioventricular block, or valvular regurgitation can be seen according to the site of the most dominant involvement. *(From Hirota Y: Restrictive cardiomyopathy, cardiac amyloidosis, and hypereosinophilic heart disease. In Abelmann WH, Braunwald E [eds]: Atlas of Heart Diseases. Vol 2. Cardiomyopathies, Myocarditis, and Pericardial Disease. Philadelphia, Current Medicine, 1995.)*

with Loffler endocarditis is a man in his fourth decade who lives in a temperate climate and has the hypereosinophilic syndrome (i.e., persistent eosinophilia with 1500 eosinophils/mm^3 for at least 6 months or until death, with evidence of organ

involvement).[292] [354] [361] Cardiac involvement in the hypereosinophilic syndrome is the rule, occurring in more than three fourths of patients.[362] Hypereosinophilia and cardiac involvement are also seen in the Churg-Strauss syndrome, which is differentiated by asthma or allergic rhinitis and a necrotizing vasculitis.[292] The cause of the eosinophilia in most patients with Loffler endocarditis is unknown, although in some it may be the result of leukemia, or it may be reactive (i.e., secondary to various parasitic, allergic, granulomatous, hypersensitivity, or neoplastic disorders).[355]

PATHOLOGY.

In the hypereosinophilic syndrome, a variety of organs are usually involved besides the heart, including the lungs, bone marrow, and brain.[354] Cardiac involvement is often biventricular, with mural endocardial thickening of the inflow portions and apex of the ventricles.[292] Histological findings include variable degrees of (1) an acute inflammatory eosinophilic myocarditis involving the myocardium and endocardium; (2) thrombosis, fibrinoid change, and inflammatory reaction involving small intramural coronary vessels; (3) mural thrombosis, often containing eosinophils; and (4) fibrotic thickening of up to several millimeters.[292] [354]

CLINICAL MANIFESTATIONS.

The principal clinical features include weight loss, fever, cough, rash, and congestive heart failure. Although early cardiac involvement may be asymptomatic, overt cardiac dysfunction occurs in more than half of the patients and may be right and/or left sided.[362] Cardiomegaly, often without overt symptoms of congestive heart failure, may be present, and the murmur of mitral regurgitation is common.[354] Systemic embolism is frequent and may lead to neurological and renal dysfunction. Death is usually due to congestive heart failure, often with associated renal, hepatic, or respiratory dysfunction.[292]

LABORATORY EXAMINATION.

The chest roentgenogram may reveal cardiomegaly and pulmonary congestion or, less commonly, pulmonary infiltrates. The ECG most commonly shows nonspecific ST segment and T wave abnormalities.[292] Arrhythmias, especially atrial fibrillation, and conduction defects, particularly right bundle branch block, may also be present.

The echocardiogram commonly demonstrates localized thickening of the posterobasal left ventricular wall, with absent or markedly limited motion of the posterior leaflet of the mitral valve.[292] There may be obliteration of the apex by thrombus. Enlargement of the atria may be seen, along with Doppler ultrasound evidence of atrioventricular regurgitation. Systolic function often is well preserved, in keeping with the restrictive picture seen in this condition.

The hemodynamic consequences of the dense endocardial scarring seen in Loffler endocarditis are those of an RCM, with abnormal diastolic filling due to increased stiffness of the ventricles and a reduction in the size of the ventricular cavity by

organized thrombus.[354] Atrioventricular valvular regurgitation may occur because of involvement of the supporting apparatus of the mitral or tricuspid valves.[362] *Cardiac catheterization* reveals markedly elevated ventricular filling pressures, and there may be evidence of tricuspid or mitral regurgitation. A characteristic feature on angiocardiography is largely preserved systolic function with obliteration of the apex of the ventricles.[354] The diagnosis is often confirmed by percutaneous endomyocardial biopsy, but the biopsy is not invariably positive.

MANAGEMENT.

Medical therapy during the course of early Loffler endocarditis and surgical therapy during the later phases of fibrosis may have a positive effect on symptoms and survival. Corticosteroids appear to have a beneficial effect on acute myocarditis[363] and together with cytotoxic drugs (hydroxyurea in particular) may improve survival substantially.[291] [354] A limited number of patients not responding to standard therapy have responded to treatment with interferon.[355] [361] Routine cardiac therapy with digitalis, diuretics, afterload reduction, and anticoagulation as indicated are adjuncts in the management of these patients.[354] Surgical therapy (see p. 1782) appears to offer significant palliation of symptoms once the fibrotic stage has been reached.[292] [354]

Endomyocardial Fibrosis

Endomyocardial fibrosis occurs most commonly in tropical and subtropical Africa, particularly Uganda and Nigeria. It is characterized by fibrous endocardial lesions of the inflow of the right or left ventricle or both and often involves the atrioventricular valves, resulting in regurgitation.[356] It is a relatively frequent cause of heart failure and death in equatorial Africa, accounting for 10 to 20 percent of deaths due to heart disease.[353]

Although most prominent in Africa, it is also found in tropical and subtropical regions in the rest of the world, typically within 15 degrees of the equator,[350] including India,[360] Brazil, Colombia, and Sri Lanka.[353] EMF is most common in specific ethnic groups, notably the Rwanda tribe in Uganda, and in people of low socioeconomic status.[364] The disease is equally frequent in both genders, and, although most common in children and young adults, its reported age

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range is 4 to 70 years.[351] It is most common in blacks, but cases have been reported occasionally in whites in temperate climates, rarely in the absence of prior residence in tropical areas.

PATHOLOGY.

A pericardial effusion, which may be quite large, may be present. The heart is normal in size or slightly enlarged, but massive cardiomegaly does not occur. The right atrium is

often dilated, and in patients with severe right ventricular involvement there may be massive enlargement of this chamber. Indentation of the right border of the heart above the apex as a result of apical scarring may occur.

Combined right and left ventricular disease occurs in about half the cases, with pure left ventricular involvement occurring in 40 percent and pure right ventricular involvement in the remaining 10 percent of patients who are examined post mortem.[352] When affected, the right ventricle exhibits extensive dense fibrous thickening of the inflow tract and apex, with involvement of the papillary muscles and chordae tendineae. Involvement of the right ventricle may lead to obliteration of the apex, with a mass of thrombus and fibrous tissue filling the cavity.[352] The tricuspid valve is often distorted by the fibrous process involving the supporting structures. Right atrial thrombi occur commonly. Left ventricular involvement is similar, with fibrosis extending from the apex up the inflow portion of the left ventricle to the posterior mitral valve leaflet. The anterior leaflet of the mitral valve and the outflow portion of the left ventricle are usually spared. Thrombi often overlie the endocardial lesions, and widely distributed endocardial calcific deposits may occur.[353] The epicardial coronary arteries are free of obstructive lesions.

HISTOLOGIC FINDINGS.

Microscopically, the involved endocardium demonstrates a thick layer of collagen tissue on top of a layer of loosely arranged connective tissue.[351] Septa composed of fibrous and granulation tissue extend for variable distances into the myocardium.[353] Interstitial edema is often present, but there is no prominent cellular infiltration. Small patches of fibroelastosis may occur in both ventricular outflow tracts beneath the semilunar valves but are thought to be a secondary phenomenon due to local trauma rather than a result of the basic pathological process. The intramural coronary arteries may show medial degeneration and fibrosis and fibrin deposits.[353]

CLINICAL MANIFESTATIONS.

Because EMF may involve both ventricles or either ventricle selectively, symptoms vary. Left-sided involvement results in symptoms of pulmonary congestion, whereas predominant right-sided disease may present features of an RCM and therefore simulate constrictive pericarditis. There is often regurgitation of one or both atrioventricular valves. The onset of the disease is usually insidious, but it is sometimes ushered in by an acute febrile illness. Rarely, the disease appears to stabilize; although survival for up to 12 years has been observed, EMF is usually relentlessly progressive.[292] Death is due to progressive myocardial failure, often associated with pulmonary congestion, infection, or infarction, or sudden, unexpected cardiovascular collapse, presumably arrhythmic in origin. Survival appears to be unrelated to the site of predominant involvement (right or left ventricle), although patients presenting in advanced right-sided failure have a worse prognosis than other patients.[292]

RIGHT VENTRICULAR EMF.

Pure or predominant right ventricular involvement is characterized by fibrous obliteration

of the right ventricular apex that diminishes the capacity of this chamber.[352] The fibrosis often extends to the supporting apparatus of the tricuspid valve,[365] resulting in tricuspid regurgitation. Clinical manifestations in patients with right-sided involvement include an elevated jugular venous pressure, a prominent *v* wave, and a rapid *y* descent. A protodiastolic gallop sound may be heard along the lower sternal border, reflecting right ventricular dysfunction.[352] The liver is usually large and pulsatile, and ascites, splenomegaly, and peripheral edema are common. Pulmonary congestion is not present in the absence of left-sided involvement, and the pulmonary artery and pulmonary capillary wedge pressures are normal. A pericardial effusion, which is sometimes quite large, may be present. The right atrium is often enlarged, sometimes massively so.

Laboratory Findings.

The ECG is usually abnormal, with diminished QRS voltage (probably resulting from the presence of a pericardial effusion), ST segment and T wave abnormalities, and findings suggestive of right-sided enlargement, especially a qR pattern in lead V_1 .[351] The chest roentgenogram demonstrates cardiac enlargement, usually with gross prominence of the right atrium and a pericardial effusion. Calcification in the walls of the right or, less commonly, the left ventricle may be seen.[353] Echocardiography may demonstrate right ventricular thickening, obliteration of the apex, dilated atrium, strong echoes emanating from the endocardial surface, and abnormal septal motion in patients with tricuspid regurgitation.[352] [357] [366] At angiography the right ventricular apex is characteristically not visualized because of obliteration by the fibrous endocardium, but tricuspid regurgitation, right atrial enlargement, and filling defects in the right atrium due to intraatrial thrombi are sometimes seen.[351] Early angiographic changes that may be present before advanced disease develops include a change in the endocardial appearance, small apical filling defects, and mild tricuspid regurgitation.

LEFT VENTRICULAR EMF.

With predominant *left-sided* involvement, the endomyocardial fibrosis invades the apex of the ventricle and usually the chordae tendineae or the posterior mitral valve leaflet as well, leading to mitral regurgitation.[367] The murmur may be confined to late systole, as is characteristic of the papillary muscle dysfunction type of murmur, or it may be pansystolic. Findings of pulmonary hypertension may be prominent. A protodiastolic gallop is commonly heard.

Laboratory Findings.

The ECG usually shows T wave abnormalities. QRS voltage may be diminished in the presence of a pericardial effusion, although left ventricular hypertrophy may be present.[292] There may be findings of left atrial abnormality. As with right-sided involvement, atrial fibrillation often is present. Echocardiographic features include thickening and reduced motion of the posterobasal wall and posterior mitral leaflet, increased echoreflectivity of the endocardium, preserved systolic wall motion in the presence of apical obliteration, dilated atrium, and Doppler ultrasound evidence of mitral regurgitation.[292] Cardiac catheterization often reveals pulmonary hypertension, with

elevated left ventricular filling pressures and a reduced cardiac index.[367] The left ventriculogram usually shows mitral regurgitation, and a filling defect due to an intracavitary thrombus within the ventricle may be seen on occasion. Coronary arteriography does not reveal obstructive disease.

BIVENTRICULAR EMF.

This form of EMF occurs more frequently than either isolated right- or left-sided disease.[351] If there is more than minimal right ventricular involvement, severe pulmonary hypertension does not occur and the right-sided findings dominate the clinical presentation. Typical patients with biventricular involvement may have the features of right ventricular EMF, with only a mitral regurgitant murmur to suggest left ventricular involvement. Systemic embolization may occur in up to 15 percent of patients; infective endocarditis is even less frequent and is found in less than 2 percent.

DIAGNOSIS.

This is based on the presence in an individual of the typical clinical and laboratory features, particularly angiography, from the appropriate geographical area. Eosinophilia is usually not a prominent feature and when present may reflect associated parasitic infestation. Endomyocardial biopsy may occasionally be helpful in establishing the diagnosis. However, this risks dislodging a mural thrombus, with resultant embolization. Left-sided biopsy is *not* recommended. In addition, because the disease is often focal, the biopsy may miss the pathological process, particularly if a right ventricular biopsy is performed in a patient with isolated left-sided disease.

MANAGEMENT.

The medical treatment of EMF is often difficult and not particularly effective. In patients with advanced disease, the outlook is poor, with a 35 to 50 percent 2-year mortality. Substantially better survival may be seen in less symptomatic patients who have milder forms of the disease. Digitalis glycosides may be helpful in controlling the ventricular rate in patients with atrial fibrillation,[292] but the response of congestive symptoms is disappointing, and the development of atrial fibrillation is a poor prognostic sign.[368] Diuretics are not particularly helpful in the treatment of ascites.[292] Once endomyocardial disease has reached the fibrotic stage, surgery offers the possibility of symptomatic improvement and is the treatment of choice.[369] Operative excision of the fibrotic endocardium and replacement of the mitral and/or tricuspid valves have led to substantial symptomatic improvement, especially with predominant left-sided involvement.[291] [370] Mitral valve repair, rather than replacement, can be accomplished in some patients.[371] Postoperative catheterization has provided objective evidence of hemodynamic improvement with a reduction in ventricular filling pressures, an increase in cardiac output, and normalization of the angiographic appearance. Operative mortality has been high, running between 15 and 25 percent in the larger series,[291] [292] [369] although it appears to be lower if valve replacement can be avoided.[371] Long-term results suggest that surgery is at best palliative, with recurrent fibrosis, continued functional limitation, and cumulative mortality limiting the overall success of an operative

approach.[369]

Endocardial Fibroelastosis (See Chap. 45)

Carcinoid Heart Disease (See also Chap. 46)

ETIOLOGY.

The carcinoid syndrome is caused by a metastasizing carcinoid tumor and is characterized by cutaneous flushing, diarrhea, bronchoconstriction, and endocardial plaques composed of a unique type of fibrous tissue. The vasomotor, bronchoconstrictor, and cardiac manifestations are undoubtedly related to circulating humoral substances secreted by the tumor,[372] although the precise substance(s) responsible remains to be elucidated.[373] Virtually all patients develop diarrhea and flushing, and cardiac abnormalities are found on echocardiography in more than half; clinically apparent and severe right-sided disease is seen in a fourth of patients.[372] [374]

Sixty to 90 percent of tumors arise in the small bowel and appendix, and the rest originate in other areas of the

gastrointestinal tract and bronchus.[372] Carcinoid tumors of the ileum are the most likely to metastasize, with involvement of the regional lymph nodes and liver. Usually only carcinoid tumors that invade the liver result in carcinoid heart disease.[372] The cardiac lesions may be related to large circulating quantities of serotonin, bradykinin, or other substances secreted by the tumor, which usually are inactivated by the liver, lungs, and brain.[375] Hepatic metastases apparently allow large quantities of tumor products to reach the heart.[374] The preferential right-sided involvement presumably is related to inactivation of the offending humoral substance(s) by the lungs. In 5 to 10 percent of cases, significant left-sided valvular disease develops,[376] related in most to passage of blood directly from the right to the left side of the heart through a patent foramen ovale, or less commonly by tumor involvement of the lungs.[372]

PATHOLOGY.

The characteristic pathological findings are fibrous plaques that involve the "downstream" aspect of the tricuspid and pulmonic valves, the endocardium of the cardiac chambers, and the intima of the venae cavae, pulmonary artery, and coronary sinus (see Figs. 46-45 and 46-47). The fibrous tissue in the plaques results in structural and functional distortion of the valves, leading to both stenosis and regurgitation. [372] Histologically, the plaques consist of deposits of fibrous tissue located superficially on the endocardium, often with extension into the underlying layers. Identical morphological features have been found in some patients treated with the anorectic drugs fenfluramine and dexfenfluramine.[374] Ultrastructural and immunohistochemical studies have

demonstrated that the plaques are composed of smooth muscle cells embedded in a stroma rich in acid mucopolysaccharides and collagen. Metastatic involvement of the myocardium itself is rare.[372]

CLINICAL MANIFESTATIONS.

Physical examination usually reveals a systolic murmur along the left sternal border, produced by tricuspid regurgitation; in some cases, there may be a concomitant murmur of pulmonic stenosis and/or regurgitation.[372]

The chest roentgenogram is normal in half of the patients, but it may reveal enlargement of the heart and pleural effusions or nodules; the pulmonary artery trunk is typically of normal size, without evidence of poststenotic dilatation as occurs in congenital pulmonic stenosis. No specific ECG pattern is diagnostic of carcinoid heart disease.[372] Right atrial enlargement may be seen on occasion, but ECG evidence of right ventricular hypertrophy usually is lacking. Nonspecific ST segment and T wave abnormalities and sinus tachycardia are the most common findings, although severely symptomatic patients usually have low QRS voltage.[377] Echocardiography may reveal tricuspid and/or pulmonary valve thickening, along with right atrial and right ventricular dilatation; small pericardial effusions are present in a minority.[372]

The hemodynamic findings most commonly encountered are those of tricuspid regurgitation and occasionally pulmonic stenosis. A rare patient with the carcinoid syndrome demonstrates a hyperkinetic state (which may lead to high-output heart failure) but without the typical cardiac lesions; in one patient this was caused by profound vasodilatation by substance P.[378]

MANAGEMENT.

In patients with mild congestive heart failure therapy includes digitalis and diuretics. Symptomatic improvement and improved survival have been noted with the use of somatostatin analogs.[374] [375] Balloon valvuloplasty of the right-sided valves has produced symptomatic improvement in some patients with stenotic tricuspid or pulmonary valves,[379] although others have developed recurrent symptoms despite "successful" valvuloplasty.[380] Surgical replacement of the tricuspid valve and pulmonic valvotomy or valvectomy may result in symptomatic improvement in severely symptomatic patients with serious valvular dysfunction, although the operative mortality is high (35 percent in one series).[377] Surgery may improve the functional status and survival of patients with carcinoid heart disease, but patients older than the age of 60 years have a very high surgical mortality (reportedly over 50 percent).[376] The long-term mortality remains high regardless of treatment modality, with half the patients dead within 1 to 2 years.[372] [377]

Obesity and Heart Disease (See Chap. 64)

Diabetic Cardiomyopathy (See Chap. 63)

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Myocarditis

Myocarditis is considered to be present when the heart is involved in an inflammatory process, often caused by an infectious agent. The inflammation may involve the myocytes, interstitium, vascular elements, and/or pericardium; involvement of the latter structure is discussed in Chapter 50 .

Etiology

Myocarditis has been described during and after a wide variety of viral, rickettsial, bacterial, protozoal, and metazoal diseases; indeed, virtually any infectious agent may produce cardiac inflammation (Table 48-9) (Table Not Available) . Infectious agents cause myocardial damage by three basic mechanisms: (1) invasion of the myocardium, (2) production of a myocardial toxin (e.g., diphtheria), and (3) immunologically mediated myocardial damage.[381] The principal mechanism of cardiac involvement in viral myocarditis is believed to be a cell-mediated immunological reaction to new cell surface changes or a new antigen related to the virus, and not merely the result of cell damage caused by viral replication. [382] [383] Additional evidence for an immune-mediated mechanism is the demonstration of a marked increase in major histocompatibility complex antigen expression in the biopsy specimens from patients with myocarditis.[384] Antibodies against intracellular components may also play a role.[385] Such cross-reactivity of antibodies to both virus and myocardial proteins (termed *molecular mimicry*) may play a role in producing immune-mediated myocardial damage.[386] Patients with ongoing myocarditis (unlike those with resolved myocarditis) have myocytes that express intercellular adhesion molecule-1 (ICAM-1), and it is speculated that the persistent expression of ICAM-1 may play a role in continued myocardial inflammation. Thus, the ultimate impact of the immune response associated with viral infection is a result of the balance between its protective and deleterious effects.[386]

Although the term is often mistakenly used to indicate myocardial inflammation solely due to an infective agent, myocarditis may also be caused by allergic reactions and pharmacological agents, as well as occurring during the course of some systemic diseases such as vasculitis.

Myocarditis may be an acute or a chronic process and may occur during the peripartum period (see Chap. 65).[387] In North America, viruses (especially enteroviruses) are believed to be the most common agents producing myocarditis,[388] whereas in South America, Chagas disease (produced by *Trypanosoma cruzi*) is far more common. The identification

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TABLE 48-9 -- INFECTIOUS CAUSES OF MYOCARDITIS

(Not Available)

From Pisani B, Taylor D, Mason J: Inflammatory myocardial disease and cardiomyopathies. Am J Med 102:459, 1997.

of the specific etiological agent responsible for infective myocarditis usually rests on the associated extracardiac findings because the cardiovascular signs and symptoms are often nonspecific. The histological findings vary, depending on the stage of the disease, the mechanism of myocardial damage, and the specific etiological agent. Myocardial involvement may be focal or diffuse; it appears that myocarditis may begin as a focal process but then spread to involve the myocardium diffusely over a period of several weeks.[389] The clinical consequences depend to a large extent on the size and distribution of the myocarditic lesions. However, a single small lesion may have profound consequences if it is located within the cardiac conducting system. The histological findings are usually nonspecific (except for some parasitic and granulomatous forms of myocarditis), and with certain exceptions (see p. 1753) myocardial biopsy seldom elucidates the specific etiological agent.

Clinical Manifestations

The clinical expression of myocarditis ranges from the asymptomatic state associated with limited and focal inflammation to fulminant fatal congestive heart failure due to diffuse myocarditis.[27] In some patients, otherwise unexplained ventricular arrhythmias may be due to silent myocarditis.[390] An initial episode of viral myocarditis, perhaps unrecognized and forgotten, may be the initial event that eventually culminates in an "idiopathic" DCM.[10] In experimental animals, the structural and functional myocardial alterations that follow viral myocarditis may persist well beyond the stage of viral replication and myocardial inflammatory response, and the late changes resemble those of DCM.

The outcome after viral myocarditis is quite variable,[27] [390A] perhaps related to differing

genetic susceptibility of individual patients. In most patients, the event is entirely self-limited and often unrecognized.[388] [391] More overt myocarditis may result in acute congestive heart failure.[338] In others, unrecognized myocarditis may be the cause of arrhythmias in what appears to be a structurally normal heart.[392] Some patients with chest pain and angiographically normal coronary arteries may have had subclinical myocarditis at some point in the past. Most intriguing is the possibility that viral myocarditis may culminate in DCM, presumably as a consequence of viral-mediated immunological cardiac damage.[391]

Although transient ECG abnormalities suggesting myocardial involvement are noted in many patients with infectious disease, most patients do not have other clinical manifestations of myocarditis. It is postulated that these ECG changes reflect subclinical myocardial involvement. That unrecognized myocardial involvement occurs with systemic infections is supported by histological evidence of unsuspected myocarditis found during routine postmortem examinations; this occurs about 1 percent of the time.[338] Some degree of myocardial involvement, often subepicardial in location, also frequently occurs in patients with acute pericarditis.

Because myocardial involvement is subclinical in most acute infectious diseases, the majority of patients have no

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specific complaints referable to the cardiovascular system; the presence of myocarditis is often inferred from ST segment and T wave abnormalities on the ECG. From a clinical viewpoint, myocardial involvement is associated with nonspecific symptoms including fatigue, dyspnea, palpitations, and precordial discomfort.[338] Chest pain usually reflects associated pericarditis, but precordial discomfort suggestive of myocardial ischemia is occasionally observed. In some cases, the clinical presentation (with chest pain, ECG abnormalities, increased muscle enzyme levels in the blood, and regional wall motion abnormalities) may simulate an acute myocardial infarction.[393] [394]

PHYSICAL EXAMINATION.

Tachycardia is usual and may be out of proportion to the temperature elevation. The S_1 is often muffled, and a protodiastolic gallop may be present. A transient apical systolic murmur may appear,[338] but diastolic murmurs are rare. Clinical evidence of congestive heart failure occurs only in the more severe cases. The heart is usually normal in size in the clinically silent cases, but it may be dilated in patients with congestive heart failure. Pulmonary and systemic emboli may occur.

LABORATORY FINDINGS.

ECG abnormalities are usually transient and occur far more frequently than does clinical myocardial involvement. The most common changes are abnormalities of the ST

segment and T wave, but atrial and, in particular, ventricular arrhythmias, artrioventricular and intraventricular conduction defects, and, rarely, Q waves may be seen.[395] Complete artrioventricular block is usually transient and resolves without sequelae, but it is occasionally a cause of sudden death in patients with myocarditis. Intraventricular conduction abnormalities are associated with more severe myocardial damage and a worse prognosis.[396] On radiological examination, heart size may range from normal to markedly enlarged, and pulmonary congestion may be present in patients with fulminant disease. Blood levels of myocardial enzymes (serum transaminases, creatine kinase) may be normal or elevated, reflecting the absence or presence of variable degrees of clinically detectable myocardial necrosis; cardiac troponin levels are more sensitive to myocardial damage and may be detected when other enzymes are not elevated.[397] Echocardiography demonstrates some degree of left ventricular dysfunction (surprisingly often regional in nature) in many patients with clinical myocarditis, although wall motion may be normal. Other findings may include increased wall thickness, left ventricular thrombi, and abnormal diastolic filling despite normal systolic function.[398] Radionuclide scanning after the administration of gallium-67, indium-111 antimyosin antibody, or technetium-99m pyrophosphate may identify inflammatory and necrotic changes characteristic of myocarditis, as may MRI (Fig. 48-30) . [338] [399]

DIAGNOSIS.

This is often predicated on the identification of the associated systemic illness and its characteristic features.[10] The diagnosis of viral myocarditis is supported by the identification of the virus in stool, throat washings, blood, myocardium, or pericardial fluid or by a distinct (usually fourfold) increase in virus-neutralizing antibody, complement-fixation, or hemagglutination inhibition titers, but cultures usually are negative and serological tests nondiagnostic.[338] [400] Even in fatal cases, isolation of virus from the myocardium at necropsy is unusual.[401] Endomyocardial biopsy frequently is used to confirm the diagnosis of myocarditis.[10] A borderline or negative biopsy does not exclude the diagnosis, and, if clinically indicated, a repeat biopsy may be appropriate and diagnostic.[338] Molecular biological techniques such as the polymerase chain reaction (using tissue obtained by endomyocardial biopsy or samples obtained from other sites) offer promise as a way of rapidly and confidently diagnosing acute myocarditis.[11] [402] Coronary arteriography is not usually required nor is its use routinely recommended. It may, in fact, provide confusing information; some patients with myocarditis are discovered

Figure 48-30 *A,* Precontrast T1-weighted transaxial (*upper*) and coronal (*lower*) magnetic resonance (MR) images through the left ventricle in case with myocarditis. *B,* Postcontrast MR images at the same levels after contrast injection. Note enhancement of the myocardial signal in the septum and apical region (arrows). *(From Matsouka H, Hamada M, Honda T, et al: Evaluation of acute myocarditis and pericarditis by Gd-DTPA enhanced magnetic resonance imaging. E Heart J 15:283, 1994.)*

to have coincidental coronary artery disease that is not playing a significant role in their illness.[403]

PATHOLOGY.

Patients with myocarditis demonstrate a wide spectrum of gross and histological changes, reflecting the range of disease seen clinically. Grossly, the hearts in acute cases are flabby, with focal hemorrhages; in chronic cases, the hearts are enlarged and hypertrophied. The histological hallmark of myocarditis is an inflammatory myocardial infiltrate, with associated evidence of myocyte damage.[338] The inflammatory infiltrate may be composed of a variety of cell types, including polymorphonuclear cells, lymphocytes, macrophages, plasma cells, eosinophils, and/or giant cells. In bacterial myocarditis, polymorphonuclear cells predominate; in viral infections, lymphocytes predominate; and in hypersensitivity myocarditis, eosinophils are seen in abundance. In some cases, morphological changes are absent and evidence of inflammation is provided by immunohistologic techniques.[12] Routine histological examination of the heart rarely provides a specific diagnosis, although in some instances electron microscopic and immunofluorescent techniques may allow elucidation of a specific cause.

Management

Therapy is often supportive and is usually directed at the more prominent systemic manifestations of the disease.[27] The demonstration of a particular predilection for involvement of the artrioventricular conducting system in some forms of myocarditis suggests that patients with suspected myocarditis should be observed closely for any evidence of conduction abnormality. Bed rest (or at least restricted activity) is advisable because exercise in experimental animals with myocarditis is deleterious.[338] Because myocarditis often occurs in young adults, it is important to limit their athletic activities; it is recommended that athletes abstain from sports for a 6-month convalescent period, and until heart size and function have returned to normal. Congestive heart failure responds to routine management, including digitalization and diuresis,[338] although patients

with myocarditis appear to be particularly sensitive to digitalis and toxicity should be watched for. Significant symptomatic arrhythmias should be treated with antiarrhythmic agents, although beta-adrenoceptor blockers are probably best avoided in view of their negative inotropic action (it should be noted that there have been too few reports of their use in humans to make a firm recommendation).[338] [404] Participation in athletic and sporting activities should be proscribed until arrhythmias have resolved.

The use of corticosteroids is controversial.[27] [381] [405] Although these agents were previously thought to be proscribed in acute viral myocarditis (because increased tissue necrosis and viral replication have been demonstrated after their use in experimental myocarditis), their use in a small number of patients has not been associated with similar dire short-term consequences.[391] A randomized trial of immunosuppression in

myocarditis found no improvement in left ventricular ejection fraction or survival, however, and they are generally believed to be of limited value.[118] [406] Nonsteroidal antiinflammatory agents--indomethacin, salicylates, and ibuprofen, along with cyclosporine--are contraindicated during the acute phase of viral myocarditis (the first 2 weeks) because they increase myocardial damage in animal models.[381] [400] On the other hand, nonsteroidal antiinflammatory agents appear to be safe in the late phase of myocarditis. High-dose intravenous gamma globulin appears to be associated with more rapid resolution of left ventricular dysfunction and perhaps improved survival, at least in children (and in a small number of adults who have been so treated).[407] [408] In experimental models of myocarditis, the converting enzyme inhibitor captopril has beneficial effects in the acute phase of myocarditis; human data are not yet available.[338] [409]

It is hoped that effective antiviral agents, immunosuppressive agents, or immunomodulating agents for treating viral myocarditis will become available for clinical use.[118] [410] [411] Antibiotics may be employed with benefit in infections caused by atypical pneumonia and psittacosis.

VIRAL MYOCARDITIS

Approximately two dozen viruses may be associated with clinical evidence of myocarditis (see Table 48-9 (Table Not Available)). [338] The myocarditis characteristically develops after a latent period of several weeks after the initial systemic infection, suggesting involvement of an immunological mechanism.[412] In animals, a variety of factors appears to enhance susceptibility to myocardial damage, including radiation, malnutrition, corticosteroids, exercise, and previous myocardial injury. Viral myocarditis may be particularly virulent in infants[388] and in pregnant women.

HUMAN IMMUNODEFICIENCY VIRUS (See Chap. 68)

COXSACKIEVIRUS.

Both coxsackieviruses A and B may produce myocarditis, although infection with coxsackievirus B is more common; this agent is the most frequent cause of viral myocarditis, causing more than half the cases.[413] The myocardium appears to be particularly susceptible to the effects of this virus because of the apparent affinity of myocardial membrane receptors for the viral particles. Necropsy often demonstrates a pericardial effusion, pericarditis, cardiac enlargement, and a predominantly mononuclear inflammatory infiltrate, with necrosis of the atrial and ventricular myocardium. In some cases, focal myocardial necrosis simulating myocardial infarction is seen, despite normal coronary arteries.[414]

Although most infections are benign, self-limited, and subclinical, coxsackieviral myocarditis appears to be particularly virulent in the neonate and child (see Chap. 45).[415] In most infections in adults, the other clinical manifestations of viral involvement, such as pleurodynia, myalgia, upper respiratory tract symptoms, and arthralgias, predominate. Severe cases in the adult are characterized by myopericardial involvement with pleuritic or pericarditic chest pain, palpitations, and fever. Many

patients with overt myocardial involvement develop congestive heart failure with cardiomegaly and pulmonary edema.[415]

The *electrocardiogram* is virtually always abnormal, with ST segment and T wave abnormalities and arrhythmias, often ventricular in origin; artrioventricular conduction disturbances are common. *Echocardiography* may reveal diffuse and regional left ventricular wall motion abnormalities that usually improve or disappear over time.

Most patients recover completely within weeks,[415] although the ECG and ventricular function may require months to return to normal. Rarely, coxsackieviral myocarditis is fatal in adults. Some patients become symptomatic after resolution of the infection, and they may present years later with DCM.[416]

Treatment.

This is symptomatic; despite occasional postmortem evidence of intracardiac thrombi, anticoagulation should probably be avoided because of the risk of a hemorrhagic pericardial effusion. Bed rest is indicated during the acute course of myocarditis, but no convincing evidence exists that a period of prolonged rest after apparent resolution of the acute process is useful. Heart failure and cardiac arrhythmias are treated in the usual fashion.

CYTOMEGALOVIRUS.

Unrecognized infection with cytomegalovirus (CMV) is extremely common in childhood, and the majority of the adult population have antibodies to CMV.[417] Primary infection after the age of 35 years is uncommon, and generalized infection usually occurs only in immunosuppressed patients with neoplastic disease, after transplantation, and with HIV infection.[418] The cardiovascular manifestations in adults are generally limited to asymptomatic and transient ECG abnormalities. Symptomatic cardiac involvement is rare, although a hemorrhagic pericardial effusion or myocarditis with left ventricular dysfunction and attendant congestive heart failure may occur.[419] The diagnosis of CMV myocarditis may be suggested by the presence of viral inclusions in myocardial biopsy specimens and confirmed by the detection of viral DNA in the myocardium.[418] Although fatalities are unusual, when they do occur, histological examination of the heart may reveal focal lymphocytic infiltration and fibrosis.

DENGUE.

Although previous dengue epidemics often were associated with symptomatic cardiac involvement, more recent outbreaks have been associated with fewer apparent cardiac complications.[420] [421] The major clinical feature is hypotension due to a capillary leak syndrome. Nonspecific ECG repolarization abnormalities are common but typically benign and transient.[421] Transient ventricular arrhythmias may be seen on occasion.

VIRAL HEPATITIS.

Clinical cardiac involvement in hepatitis is rare; an occasional patient may develop fulminant myocarditis with congestive heart failure, hypotension, and death.[422] There are contested data implicating hepatitis C viral infection as an etiological factor in at least some cases of DCM.[423] [424] [425] The characteristic pathological changes are minute foci of necrosis of isolated muscle bundles, often surrounded by lymphocytes and a diffuse serous inflammation.[422] The ventricles may be dilated, with petechial hemorrhages. Hemorrhage into the myocardium may be a conspicuous finding.[422] Myocardial damage may be produced indirectly through an immune-mediated mechanism or directly by viral invasion of the heart.[422]

Symptomatic myocarditis is generally observed in the first to third week of illness. Patients may have dyspnea, palpitations, and anginal chest pain; fatalities have been reported.[422] ECG changes, including bradycardia, ventricular premature beats, and ST segment and T wave abnormalities, may be seen during the course of hepatitis.[422] These abnormalities are usually transient and asymptomatic, although congestive heart failure, cardiomegaly, and sudden death have been reported.[422]

INFECTIOUS MONONUCLEOSIS.

Cardiac involvement in infectious mononucleosis is extremely rare, although nonspecific ST segment and T wave abnormalities may be seen. In rare cases, pericarditis and myocarditis (even simulating a myocardial infarction) may be present.[426]

INFLUENZA.

Although clinically apparent myocarditis is rare in influenza, the presence of preexisting cardiovascular disease greatly increases the risk of morbidity and mortality.[427] During epidemics, 5 to 10 percent of infected patients may experience cardiac symptoms.[10] Postmortem findings in fatal cases include biventricular dilatation, with evidence of a mononuclear infiltrate, especially in perivascular areas.[427]

Cardiac involvement typically occurs within 1 to 2 weeks of the onset of the illness and may be severe, sometimes contributing to mortality. The clinical manifestations include dyspnea, palpitations, anginal chest pain, arrhythmia, and heart failure; there may be concomitant involvement of the pericardium.[428] Sinus tachycardia or, less commonly, sinus bradycardia may be seen. The ECG may show transient ST segment and T wave abnormalities, conduction defects, and even complete atrioventricular block; death may be associated with massive hemorrhagic pulmonary edema due to viral or bacterial involvement of the lungs.

LASSA FEVER.

Lassa fever, a major cause of death in West Africa that is caused by an arenavirus,

often is associated with ECG abnormalities[429] that may represent subclinical myocardial involvement. More than half the patients demonstrate nonspecific repolarization changes and low voltage.[429] Pericardial involvement may occur. Pathological findings include myocardial congestion, edema, and a mononuclear cellular infiltrate. In most cases, however, the putative cardiac involvement does not appear to play a major clinical role.[429]

MUMPS.

Myocardial involvement during the course of mumps is rarely recognized.[430] The hearts of only a few patients with mumps have undergone postmortem examination, and they have been found to be both dilated and hypertrophied. Histologically, there is diffuse

interstitial fibrosis, with infiltration of mononuclear cells and areas of focal necrosis.[430] [430A] There is speculation that prior mumps myocarditis may be involved in the development of endocardial fibroelastosis.[431] Cardiac involvement is usually unrecognized clinically, and the diagnosis of myocarditis is based on nonspecific ECG changes.[430] Transient ST segment and T wave abnormalities are most common, but extrasystoles and atrioventricular conduction block may occur.[430] Tachycardia, a transient apical systolic murmur, and protodiastolic gallop may be present.

POLIOMYELITIS.

Myocarditis occurs in about 5 to 10 percent of epidemic poliomyelitis and is a frequent finding in fatal cases, occurring in half or more of all patients dying with this disease; death may be sudden.[12] Although myocardial involvement is usually focal and minimal in extent, some patients with bulbar disease succumb early in the course of the illness, often with cardiovascular collapse.[432] These patients all have viral infection of the medulla and severe systemic vasoconstriction that leads to pulmonary edema. Myocarditis appears to contribute to the heart failure.[432] The ECG is frequently abnormal, with ST segment and T wave abnormalities, prolongation of the PR and QT intervals, extrasystoles, tachycardia, and atrial fibrillation. Treatment is symptomatic, with aggressive support of pulmonary function; tracheostomy and prolonged mechanical ventilatory support may be required. Fortunately, this disease has been largely eliminated by immunization.

RESPIRATORY SYNCYTIAL VIRUS.

Although respiratory syncytial virus is an important cause of respiratory disease, particularly in children, it rarely results in cardiac involvement.[433] Congestive heart failure, pericardial effusion, arrhythmias, cardiogenic shock, and complete heart block have been seen on occasion.[433] [434]

RUBELLA AND RUBEOLA.

Congenital cardiovascular lesions may develop in the offspring when rubella is contracted by the mother during the first trimester of pregnancy, with persistent ductus arteriosus and pulmonary artery maldevelopment as prominent anomalies. Rare cases of postgestational myocarditis occur, with attendant conduction defects and heart failure.[435]

Overt myocarditis is rare in rubeola, although transient ECG abnormalities, including prolongation of the PR interval, ST segment and T wave changes, atrioventricular conduction abnormalities, and ventricular tachycardia, have been reported.[436] Congestive heart failure occurs on rare occasions, and its appearance is a poor prognostic sign, often indicating a fatal outcome. Histological examination of the heart in fatal cases has revealed evidence of myocarditis characterized predominantly by a perivascular lymphocytic infiltrate.[436]

VARICELLA.

Clinical myocarditis is a rare finding in varicella, although unsuspected myocarditis is common in fatal varicella. Occasionally, a patient may develop overt clinical evidence of myocarditis with congestive heart failure.[437] Histological findings include rare but characteristic intranuclear inclusion bodies within the myocardial cells, along with interstitial edema, cellular infiltrates, and myonecrosis.[437] The ECG may show conduction abnormalities, including complete heart block; sudden death occurs rarely.

VARIOLA AND VACCINIA.

Cardiac involvement after smallpox is rare, although several cases of myocarditis associated with acute cardiac failure and death have been reported. Myocarditis with pericardial effusion and congestive heart failure has also been observed as a complication of smallpox vaccination; an immunological mechanism has been suggested, and dramatic responses to corticosteroids have been reported.[438] The histological changes include a mixed mononuclear infiltrate, with interstitial edema and occasional degenerating or necrotic muscle bundles.

RICKETTSIAL MYOCARDITIS

The rickettsial diseases are frequently associated with evidence of myocardial involvement, but usually it is subclinical. Transient ST segment and T wave alterations are commonly observed. The circulatory collapse that may accompany these diseases is largely a manifestation of abnormalities of the peripheral vascular bed, but a myocardial component may also be present. The basic histopathological process is a vasculitis, with a periarterial interstitial infiltrate.

Q FEVER.

Endocarditis is the most common cardiac manifestation of infection with *Rickettsia burnetii* (Q fever).[439] Myocarditis is not a prominent feature,[439A] although dyspnea and chest pain, perhaps reflecting associated pericarditis, occur frequently. The ECG may demonstrate transient ST segment and T wave changes as well as paroxysmal ventricular arrhythmias. Abnormalities of the immune system have been implicated in the pathogenesis of the disease.

ROCKY MOUNTAIN SPOTTED FEVER.

Clinical evidence of myocarditis is more common than often appreciated in Rocky Mountain spotted fever (caused by *R. rickettsii*), and the heart is often involved in the multisystem damage that occurs as the result of a widespread vasculitis.[440] Unsuspected left ventricular dysfunction is common, and echocardiographic evidence of dysfunction may persist in some patients.

SCRUB TYPHUS.

Myocarditis is common during the course of scrub typhus (tsutsugamushi disease, caused by *R. tsutsugamushi*), especially in fatal cases.[441] The histological findings are those of a focal panvasculitis involving the small blood vessels. Myocardial necrosis is unusual, but hemorrhage into the heart and subepicardial petechiae may occur.[441] Clinical evidence of myocardial involvement typically is not severe and is usually not associated with residual cardiac damage. The ECG may show nonspecific ST segment and T wave abnormalities, as well as first-degree atrioventricular block.[441] A protodiastolic gallop and apical systolic murmur suggestive of mitral regurgitation are occasionally found.

BACTERIAL MYOCARDITIS

BRUCELLOSIS.

Cardiac involvement in the course of brucellosis is uncommon, usually consisting of endocarditis. Myocardial involvement, when it occurs, is manifested by T wave abnormalities and prolongation of atrioventricular conduction. An occasional patient develops fulminant myocarditis, with a lymphocytic and polymorphonuclear infiltrate.[442]

CLOSTRIDIAL INFECTION.

Cardiac involvement is common in patients with clostridial infections with multiple organ involvement. The myocardial damage results from the toxin elaborated by the bacteria, but the precise actions of the toxin remain to be elucidated.[443] The pathological findings are distinctive, with gas bubbles present in the myocardium. Areas of degenerated muscle fibers are apparent, but an inflammatory infiltrate is usually absent.[443]

Clostridium perfringens may cause myocardial abscess formation, with myocardial perforation and resultant purulent pericarditis.

DIPHTHERIA.

Myocardial involvement is one of the more serious complications of diphtheria and occurs in up to one fourth of cases.[443A] Indeed, myocardial involvement is the most common cause of death in this infection, and half of the fatal cases demonstrate cardiac involvement.[444] Cardiac damage is due to the liberation by the diphtheria bacillus of a toxin that inhibits protein synthesis by interfering with the transfer of amino acids from soluble RNA to polypeptide chains under construction. The toxin appears to have a particular affinity for the cardiac conducting system.

Pathological Findings.

These include a flabby and dilated heart with a myocardium that has a "streaky" appearance. Microscopic examination reveals characteristic fatty infiltration of the myocytes,[444] often with an interstitial inflammatory infiltrate, myocytolysis, and hyaline necrosis of muscle fibers. With time, fibrosis and hypertrophy of the remaining myocardial cells develop. The conduction system is often involved.

Clinical Manifestations.

Signs of cardiac dysfunction typically appear at the end of the first week of the illness. Cardiomegaly and severe congestive heart failure are often present. A protodiastolic gallop and pulmonary congestion may be prominent features. Elevation of the serum transaminase levels may be seen; a high level is associated with a poor prognosis. Sudden circulatory failure and death may occur. Many patients develop ST segment and T wave abnormalities, but atrial and ventricular arrhythmias and conduction defects may also occur.[444] Persistently abnormal ECGs are common after diphtheritic myocarditis, as are cardiomegaly and symptoms of reduced cardiac reserve. Some patients recover fully.

Because of the serious effects of the toxin on the myocardium, antitoxin should be administered as rapidly as possible.[444] Antibiotic therapy is of less urgency. Overt congestive heart failure may be resistant to therapy with cardiac glycosides. The development of complete atrioventricular block is an ominous complication, and mortality is high despite insertion of a transvenous pacemaker.

LEGIONNAIRES DISEASE.

Although pneumonia, rhabdomyolysis, renal failure, and hepatic as well as central nervous system involvement are common with *Legionella pneumophila,* overt cardiac involvement is not.[445] Occasional ECG changes may be noted, consisting primarily of ST segment and T wave abnormalities; ventricular arrhythmias may be seen. Rarely, pericardial effusion, myocarditis with evidence of myocardial necrosis, or congestive

heart failure may be seen.[445]

MENINGOCOCCAL INFECTION.

Myocardial involvement is common during the course of fatal meningococcal infections but is less commonly recognized in the usual case. Pathological findings include hemorrhagic myocardial lesions, occasionally associated with intracellular organisms. An interstitial myocarditis composed of lymphocytes, plasma cells, and polymorphonuclear leukocytes may be observed, occasionally with myonecrosis.

Meningococcal myocarditis may result in congestive heart failure as well as in pericardial effusion with tamponade. Death may occur suddenly and be associated with involvement of the atrioventricular node.[446]

MYCOPLASMA PNEUMONIAE INFECTION.

ECG abnormalities are common during the course of atypical pneumonia, although clinically apparent myocarditis is not. When carditis occurs, it may be serious, and, rarely, fatal.[447] Nonspecific ST segment and T wave abnormalities are the most common manifestations of cardiac involvement; a rare patient may develop complete heart block. The ECG findings usually resolve within 1 to 2 weeks. A cell-mediated autoimmune myocarditis has been postulated as the cause of the changes. Pericarditis may be

Figure 48-31 Findings in cardiac tuberculosis. \i\A,\r\ Chest radiograph reveals right-sided pleural effusion, cardiomegaly, and borderline perihilar edema. \i\B,\r\ CT of chest confirmed right-sided pleural effusion and also reveals pericardial effusion and pericardial thickening. \i\C,\r\ Cross section of heart shows thickened pericardium. \i\D,\r\ Close examination of apical myocardium (arrow) reveals myocardial tubercles. \i\E,\r\ Histology shows the presence of granulomas (arrowhead) with giant cells. (From Dhar SC, Hayes S, Cercek B, et al: Images in cardiovascular medicine: Cardiac tuberculosis. Circulation 98:730, 1998. Copyright 1998, American Heart Association.)

a prominent finding, and congestive heart failure is occasionally seen. A protodiastolic gallop and pericardial friction rub may be noted in occasional cases. Complete recovery is the rule in most patients, although occasional patients may have persistent sequelae, including arrhythmias.

PSITTACOSIS.

Myocarditis complicating psittacosis is a relatively common occurrence and is characterized by congestive heart failure and acute pericarditis.[448] Pathological changes include fibrinous pericarditis as well as endocarditis and myocarditis. Fever,

chest pain, ECG changes, cardiomegaly, systemic emboli, tachycardia, and hypotension may occur. Although most patients recover completely, fatalities have been reported. The systemic infection may be treated effectively with tetracycline, but the effect of the antibiotic on the myocardium is unknown.

SALMONELLOSIS.

Symptomatic myocardial involvement during *Salmonella* infections is rare, although ECG abnormalities are often seen, suggesting subclinical myocarditis.[449] [450] Other cardiovascular complications include infected mural thrombi, occasionally resulting in pulmonary and systemic emboli, and mycotic aneurysms. Myocardial abscesses may rupture, producing fatal cardiac tamponade. Myocarditis with congestive heart failure occurs most commonly in children who are severely ill with salmonellosis, and it is associated with a high mortality. When myocarditis occurs, it often develops rapidly, with evidence of biventricular failure, tachycardia, a protodiastolic gallop, an apical systolic murmur of mitral regurgitation, and peripheral edema.

ECG abnormalities include ST segment and T wave changes, prolonged PR or QT intervals, and low QRS voltage.[450]

STREPTOCOCCAL INFECTION.

The most commonly detected cardiac finding after beta-hemolytic streptococcal infection is acute rheumatic fever, which is discussed in detail in Chapter 66 .

Involvement of the heart by the streptococcus may produce a myocarditis that is distinct from acute rheumatic carditis.[451] It is characterized by an interstitial infiltrate composed of mononuclear cells with occasional polymorphonuclear leukocytes; the infiltrate may be focal or diffuse and may be localized to the subendocardial or perivascular region. There may be small areas of myocardial necrosis. ECG abnormalities, including prolongation of the PR and QT intervals, occur frequently. Although these abnormalities are rarely associated with other clinical manifestations of myocardial involvement, sudden death, conduction disturbances, and arrhythmias may occur.

TUBERCULOSIS.

Involvement of the myocardium by *Mycobacterium tuberculosis* (not as a complication of tuberculous pericarditis) is rare, particularly since the introduction of drugs effective against tuberculosis (Fig. 48-31) .[452] Most cases of myocardial tuberculosis are clinically silent and are diagnosed only at autopsy. Tuberculous involvement of the myocardium occurs by means of hematogenous or lymphatic spread or directly from contiguous structures; it may lead to arrhythmias, including atrial fibrillation and ventricular tachycardia, complete atrioventricular block, congestive heart failure, left ventricular aneurysms, and sudden death.[452] [453]

WHIPPLE DISEASE

Although overt involvement is rare, intestinal lipodystrophy, or Whipple disease, is not uncommonly associated with cardiac involvement, and periodic acid-Schiff (PAS)-positive macrophages may be found in the myocardium, pericardium, and heart valves of patients with this disorder.[454] [455] Coronary artery lesions, with smooth muscle necrosis, panarteritis, and medial scarring, may be seen. Electron microscopy has demonstrated rod-shaped structures in the myocardium similar to those found in the small intestine, and these represent the causative agent of the disease, *Tropheryma whippelii,* an agent related to the actinomycetes.[454] There may be an associated inflammatory infiltrate and foci of fibrosis. The valvular fibrosis may be severe enough to result in aortic regurgitation and mitral stenosis. Although usually asymptomatic, nonspecific ECG changes are most common; systolic murmurs, pericarditis, complete heart block, and even overt congestive heart failure may occur.[454] The cardiac manifestations of Whipple disease may be overshadowed by the prominent gastrointestinal symptoms that often are present. Antibiotic therapy appears to be effective in treating the basic disease; however, relapses can occur, often more than 2 years after initial diagnosis.

SPIROCHETAL INFECTIONS

LEPTOSPIROSIS (WEIL DISEASE).

Most patients with leptospiral infections have mild or subclinical disease and little evidence of heart involvement. Cardiac involvement in severe or fatal leptospirosis is common, however, with 50 to 100 percent of fatal cases demonstrating evidence of myocarditis.[456] Many patients with clinical systemic disease demonstrate atrial fibrillation, first-degree heart block, and transient ST segment and T wave abnormalities, presumably reflecting myocarditis, although significant left ventricular dysfunction is uncommon.[457] Bradycardia despite fever, ventricular premature depolarizations, congestive heart failure, and pericarditis may be seen as well. The pathological findings in the occasional fatal case include petechiae or large loci of hemorrhage (often located in the epicardium), an interstitial myocardial infiltrate (often subendocardial in location), aortitis, and coronary arteritis.

LYME CARDITIS.

Lyme disease is caused by a tickborne spirochete (*Borrelia burgdorferi*).[458] It usually begins during the summer months with a characteristic rash (erythema chronicum migrans), followed in weeks to months by neurological, joint, or cardiac involvement; some clinical manifestations may persist for years.[458]

About 10 percent of patients with Lyme disease develop evidence of transient cardiac involvement, the most common manifestation being variable degrees of atrioventricular block[459] [460] [461] at the level of the atrioventricular node. Syncope due to complete heart block is frequent with cardiac involvement because often there is an associated depression of ventricular escape rhythms. Ventricular tachycardia occurs uncommonly.[459] Diffuse ST segment and T wave abnormalities and transient, usually

asymptomatic, left ventricular dysfunction may be found in some patients, although cardiomegaly or symptoms of congestive heart failure are rare.[460] [462] A positive gallium or indium antimyosin antibody scan may point to suspected cardiac involvement in this disease.[463] The demonstration of spirochetes in myocardial biopsies of some patients with Lyme carditis suggests that the cardiac manifestations are due to a direct toxic effect, although there is speculation that immune-mediated mechanisms may be involved as well.

The value of specific therapy in Lyme carditis remains uncertain, and even without therapy the disease usually is self-limited with complete recovery the rule.[457] Nevertheless, it is thought that treating the early manifestations of the disease may prevent development of late complications.[458] Patients with second-degree or complete heart block should be hospitalized and undergo continuous ECG monitoring. Temporary transvenous pacing may be required for up to a week or longer in patients with high-grade block. Although the efficacy of antibiotics is not established, they are utilized routinely in Lyme carditis. Intravenous antibiotics (ceftriaxone, 2 gm, or penicillin G, 20 million units daily for 14 days) are suggested, although oral antibiotics (doxycycline, 100 mg twice daily, or amoxicillin, 500 mg three times daily for 14 to 21 days) may be used when there is only mild cardiac involvement (first-degree atrioventricular block of less than 40 milliseconds duration).[464] Whether antiinflammatory agents (salicylates, corticosteroids) can ameliorate heart block is not clear.

RELAPSING FEVER.

Many infections are currently observed in Ethiopia. During pandemics, mortality may be particularly high, reaching 70 percent, although sporadic cases are often more benign. Cardiac involvement is said to be a common complication and is often implicated as a cause of death, although one report involving 63 children did not find evidence of cardiac involvement.[465] Atrioventricular conduction

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defects occur frequently and may be responsible for sudden death, although tachyarrhythmias have also been implicated. Numerous petechiae are observed with a diffuse histiocytic interstitial infiltrate, particularly around small arterioles in the left ventricle.

SYPHILIS.

Aortitis is the most common manifestation of luetic involvement of the cardiovascular system (see Chap. 40). Aortic regurgitation and coronary ostial narrowing are associated findings. Syphilitic involvement of the myocardium itself in the form of gumma formation is uncommon and usually unsuspected clinically. Involvement of the base of the interventricular septum may result in damage to the conduction system and atrioventicular block. In one case a ruptured left ventricular aneurysm was found as a

result of syphilitic endarteritis.[466]

FUNGAL INFECTIONS OF THE HEART

Cardiac fungal infections occur most frequently in patients with malignant disease and/or those receiving chemotherapy, corticosteroids, radiation, or immunosuppressive therapy. Cardiac surgery, intravenous drug abuse, and infection with HIV are also predisposing factors for fungal cardiac involvement.

ACTINOMYCOSIS.

Myocarditis is a rare complication of actinomycotic infection, occurring in less than 2 percent of patients; more commonly, it produces pericardial or endocardial disease.[467] However, cardiac involvement is quite serious when it does occur. Involvement of the heart most commonly is the result of direct extension of disease within the thorax. Initially the pericardium is invaded, with eventual obliteration of the pericardial space. The myocardium may be involved by extension of the pericardial process. Myocardial seeding is less common. The myocardial lesion is a suppurative, necrotizing abscess containing the organism, surrounded by granulation tissue. Both right- and left-sided failure are common manifestations.[467] A pericardial rub may be heard, sometimes associated with clinical evidence of a pericardial effusion or constriction.

ASPERGILLOSIS.

Myocardial involvement is not uncommon in generalized aspergillosis, and when it occurs it is usually fatal.[468] It is being encountered increasingly in the immunocompromised patient.[469] On pathological examination, myocardial necrosis and infarction caused by thrombosis of vessels that contain fungal mycelia are commonly seen, along with myocardial abscesses and pericardial involvement. The ECG may be normal in the face of significant myocardial damage, but T wave changes may be present. The diagnosis of *Aspergillus* infection is often difficult.[469] Identification of *Aspergillus* through open-lung biopsy, aspiration lung biopsy, transtracheal aspiration, or bronchial brush technique may be successful. Treatment is difficult and usually unsuccessful.

BLASTOMYCOSIS.

Involvement of the heart by the fungus is quite uncommon, even in the immunocompromised heart. When involvement occurs, it is most often by direct extension from the pericardium.

CANDIDIASIS.

Disseminated candidal infections are common opportunistic infections, particularly in the compromised host. Endocarditis is the most frequent manifestation of cardiac involvement (see Chap. 47), occurring most commonly in cardiac surgical patients or

drug addicts, although multiple abscesses of the myocardium may occur as associated or independent findings. Complete heart block may be caused by microabscesses of the conduction system.

COCCIDIOIDOMYCOSIS.

Involvement of the heart is rare in patients with generalized coccidioidomycosis. The hearts may be grossly normal, although epicardial lesions with resultant pericarditis are common, and progression to constrictive pericarditis may occur (see Chap. 50). A nonspecific, focal interstitial, and perivascular cellular infiltrate with associated muscle fiber degeneration and interstitial edema is commonly found, although granulomas containing fungi are also seen sometimes.

CRYPTOCOCCOSIS.

Cryptococcal infection of the myocardium occurs most commonly in immunocompromised patients with disseminated malignancy or HIV infection. Pathological examination may show cardiac dilatation, with epithelial granulomas, giant cells, and an inflammatory infiltrate.[470] When congestive heart failure occurs, pulmonary congestion and muffled heart sounds may be found on physical examination, and cardiomegaly on the chest roentgenogram. The ECG may show first-degree atrioventricular block and T wave inversions; ventricular arrhythmias have been observed.

HISTOPLASMOSIS.

Cardiac involvement in histoplasmosis is rare and usually is related to mediastinal fibrosis, the most serious complication of histoplasmosis.[471] Pericarditis with effusion may occur (see Chap. 50), and superior vena caval obstruction has been observed.[471] Myocardial involvement is uncommon, although atrial arrhythmias and T wave abnormalities have been reported.

MUCORMYCOSIS.

Cardiac involvement in the setting of disseminated mucormycosis occurs in about 20 percent of patients and is characterized by fungal invasion of the coronary arteries with resultant areas of myocardial infarction. Valvular and pericardial involvement may be seen as well. Clinical manifestations are nonspecific, and cardiac involvement often is not suspected but may include congestive heart failure, arrhythmias, conduction defects, and endocarditis.[472]

PROTOZOAL MYOCARDITIS

Trypanosomiasis (Chagas Disease)

Chagas disease is caused by the protozoan *Trypanosoma cruzi.* The major

cardiovascular manifestation is an extensive myocarditis that typically becomes evident years after the initial infection. The disease is prevalent in Central and South America, particularly in Brazil, Argentina, and Chile, where it is a major public health problem (Fig. 48-32) . Upward of 20 million people are thought to be infected with the parasite, and an estimated 100 million are at risk of infection.[473] In rare cases, the disease may be found in nonendemic areas as a consequence of transfusion with contaminated blood products; somewhat more common is emigration of patients with the disease to nonendemic areas.[474]

The natural history of Chagas disease is characterized by three phases: acute, latent, and chronic. During the *acute phase,* the disease is transmitted to humans (usually below the age of 20 years) through the bite of a reduviid bug (subfamily Triatominae), which harbors the parasite in its gastrointestinal tract.[473] [475] This insect acquires the disease from feeding on infected animals, including the armadillo, raccoon, opossum, and skunk as well as domestic dogs and cats. The reduviid bug, popularly known in Argentina as *vinchuca,* meaning "to let oneself drop," lives in the walls and roofs of houses and, during nocturnal feedings, drops from the ceiling onto the sleeping person below. The bug then often bites the person around the eyes, and infection of the human host occurs when the trypanosomes in the animal's feces gain entry through abraded skin or through the conjunctivae.[473] Occasionally, this results in unilateral periorbital edema and swelling of the eyelid, termed the

Figure 48-32 Distribution of Chagas disease in the Americas. *(From Acquatella H: Chagas' disease. In Abelmann WH, Braunwald E [eds]: Atlas of Heart Diseases. Vol 2. Cardiomyopathies, Myocarditis, and Pericardial Disease. Philadelphia, Current Medicine, 1995, pp 8.1-8.18.)*

Romana sign, whereas entry through the skin may result in a lesion called a *chagoma.* [473] [475] Transmission may occur through blood transfusions; unfortunately, adequate screening to preclude transfusion-related disease is not possible in many areas due to financial and logistic constraints.[473]

ACUTE TRYPANOSOMIASIS.

After inoculation, the protozoa multiply and then migrate widely throughout the body. In less than 10 percent of cases an acute illness occurs; the latter is fatal in about 10 percent of patients.[474] [475] Pathological examination during the acute phase often reveals parasites in the cardiac fibers with a marked cellular infiltrate, particularly around cardiac cells that have ruptured and released the parasites.[475] Involvement may extend into the endocardium, resulting in thrombus formation, and into the epicardium, resulting in pericardial effusion. The pathogenesis of the myocardial lesions of acute Chagas disease appears to relate in large part to immune lysis by antibody and cell-mediated immunity directed against antigens released from *T. cruzi*-infected cells, which become

adsorbed onto the surface of infected and noninfected host cells.[473]

Clinical Manifestations.

These include fever, muscle pains, sweating, hepatosplenomegaly, myocarditis with congestive heart failure, pericardial effusion, and, occasionally, meningoencephalitis.[473] [475] Most patients recover, and their symptoms resolve over several months. Young children most commonly develop clinical acute disease and generally are more seriously ill than adults.

LATENT AND CHRONIC TRYPANOSOMIASIS.

The disease then enters a *latent phase* without clinical symptoms; however, there is evidence of early and progressive subclinical cardiomyopathy. ECG changes often appear at this stage and are a marker for the eventual clinical heart disease and increased mortality to become evident later. At an average of 20 years after the initial (and usually unrecognized) infestation, approximately 30 percent of infected individuals develop findings of *chronic Chagas disease,* the manifestations of which cover a wide spectrum from asymptomatic but seropositive patients through those with ECG abnormalities to those with advanced disease characterized by cardiomegaly, congestive heart failure, arrhythmias, thromboembolic phenomena, atypical chest pain, right bundle branch block, and sudden death.[474] In the advanced stage, cardiac dilatation typically involves all the cardiac chambers, although right-sided enlargement may predominate.[474]

The central paradox in the pathogenesis of this disorder is the poor correlation between the level of parasitemia and the severity of disease.[476] It is not unusual to be unable to detect parasites in patients dying of Chagas disease,[477] although evidence of prior infection may be detected more frequently by the much more sensitive polymerase chain reaction technique.[478] *T. cruzi* antigen is frequently found in biopsy specimens of the heart in chronic Chagas heart disease.[479] [480] An autoimmune etiological mechanism has been proposed, and this may explain the lack of correlation of parasitemia with disease severity.[476] [479] [480] Based on animal models, it appears that self-reactive cytotoxic T lymphocytes develop after the initial infection and produce various cytokines.[476] This results in the lysis of normal host cells, perhaps related to cross-reacting antigens of *T. cruzi* and striated muscle.[474] [481] A variety of antibodies against myocyte sarcoplasmic reticulum, laminin, and other constituents have also been implicated in the pathogenesis of Chagas myocarditis.[479] It is thought that the acute phase results in the release from parasite-modified host cells of self-components that are immunogenic.[474] Another hypothesis suggests that cardiac parasympathetic denervation leads to eventual chronic Chagas disease.[474] [477]

Pathology.

Nerves and autonomic ganglia are frequently abnormal, and megaesophagus and megacolon may occur; less commonly, there is dilatation of the stomach, duodenum, ureter, and bronchi. Different strains of *T. cruzi* may account for the geographical

differences in the expression of Chagas disease; megaesophagus and megacolon are common in Brazil but quite uncommon in Central America and Mexico, and megaesophagus is unusual in Venezuela.[473] Lesions of the cardiac nerves are routinely found in patients with chronic Chagas disease, with evidence of cardiac parasympathetic denervation.[473] Pathological cardiac findings include cardiac enlargement, with dilatation and hypertrophy of all cardiac chambers. In more than half the patients, the left (and occasionally right) ventricular apex is thin and bulging, resembling an aneurysm.[477] Thrombus formation is frequent and may fill much of the apex; the right atrium also frequently contains thrombus. It has been suggested that these characteristic apical aneurysms (Fig. 48-33) may be the result of intravascular platelet aggregation leading to focal myocardial necrosis.[479]

The microscopic findings are principally those of extensive fibrosis, particularly of the left ventricle.[474] [482] A chronic cellular infiltrate composed of lymphocytes, plasma cells, and macrophages often is present.[473] Increases in arteriole and capillary diameters have been reported.[482] Preferential involvement of the right bundle branch and the anterior fascicle of the left bundle branch by inflammatory and fibrotic changes explains the frequent occurrence of right bundle branch and left anterior fascicular block.[473] The basement membranes of capillaries, vascular smooth muscle cells, and myocytes are thickened.[479] It is unusual to be able to find parasites in the myofibers of autopsied patients.[477]

Clinical Manifestations.

These include anginal chest pain, symptomatic conducting system disease, and sudden death; chronic progressive heart failure, often predominantly right sided, is the rule in advanced cases.[474] Thus, although pulmonary congestion is occasionally noted, the usual findings include fatigue due to diminished cardiac output, peripheral edema, ascites, and hepatic congestion. Tricuspid regurgitation is often present, particularly in patients with severe right-sided heart failure, although mitral regurgitation is frequently present as well. The S_2 is widely split, often with an accentuated pulmonic component, reflecting the combined effects of right bundle branch block and pulmonary hypertension. Autonomic dysfunction is common, with marked abnormalities in the expected reflex changes in heart rate produced by various maneuvers. Deaths result most commonly from pump failure or occur suddenly. Apical aneurysms and left ventricular dilation place patients at high risk for the latter.[483]

Laboratory Findings.

The chest roentgenogram often demonstrates severe cardiomegaly, with or without pulmonary venous hypertension. The serum aldolase is usually elevated.[484] ECG abnormalities are the rule late in the course of the disease, particularly in patients who are seroreactive to *T. cruzi* antigen. Right bundle branch block, left anterior hemiblock, atrial fibrillation, and ventricular premature depolarizations are the most common findings in patients with chronic Chagas disease.[473] [485] ST segment and T wave abnormalities also are common, as are Q waves; P wave abnormalities and atrioventricular block are seen less frequently.[473] Early in the disease, the ECG may be normal or nearly so. Administration of the antiarrhythmic agent ajmaline may precipitate

the appearance of ECG abnormalities and thus identify patients with as yet clinically silent cardiac involvement.[473] Furthermore, electrophysiological testing of asymptomatic patients, even those with normal ECGs, may demonstrate abnormalities of the conducting system in many.

Ventricular arrhythmias are a prominent feature of chronic Chagas disease.[473] [479] [480] Frequent ventricular premature depolarizations, often with multiple morphologies, are seen frequently, and bouts of ventricular tachycardia may occur. Ventricular arrhythmias are particularly common during and after exercise,[473] occurring in the majority

Figure 48-33 Left ventriculogram in the right anterior oblique view of a 55-year-old woman with chronic Chagas disease. Multiple left ventricular aneurysms are noted in anterobasal, anterior, and inferior aspects of left ventricle (circled, right). *(From Venegoni P, Bhatia HS: Chagas' disease and ventricular arrhythmias. Circulation 96:1363, 1997. Copyright 1997, American Heart Association.)*

of patients subjected to stress ECG testing (including some without any clinical evidence of cardiac involvement). Ventricular tachycardia induced by electrophysiological testing is most common in patients with evidence of conduction abnormalities on the ECG, low ejection fraction, and apical left ventricular aneurysm and may predict sudden death.[486] [487] Syncope and sudden death due to ventricular fibrillation are constant threats and may develop even before cardiomegaly or heart failure.[473] [488] [489] Sinus bradycardia may also be seen, even in patients with severe heart failure when a tachycardia would be expected, presumably related to cardiac autonomic dysfunction.[473] Atrial arrhythmias, including atrial fibrillation (often with a slow ventricular response), also may occur.[473] Thromboembolic phenomena are a frequent complication, occurring in more than 50 percent of the patients.[490]

The echocardiographic findings in advanced cases are those of a dilated cardiomyopathy with increased end-diastolic and end-systolic volumes and reduced ejection fraction, often with enlargement of the left atrium and right ventricle.[473] Diastolic filling of the left ventricle is frequently abnormal, even in those without other clinical or echocardiographic evidence of cardiac involvement. In the majority of advanced cases, the echocardiographic appearance is distinctive, with left ventricular posterior wall hypokinesis and relatively preserved interventricular septal motion; an apical aneurysm is often seen on two-dimensional echocardiography. Ten to 15 percent of asymptomatic patients demonstrate apical dyskinesis.

Radionuclide ventriculography may, like echocardiography, demonstrate right or left ventricular wall motion abnormalities in the absence of an overall depression of global ventricular function. Perfusion scanning with thallium-201 may show fixed defects (corresponding to areas of fibrosis) as well as evidence of reversible ischemia.[491] MRI can identify morphological and functional aspects of cardiac involvement; with the use of gadolinium as a contrast medium, it can identify patients with more active myocardial

disease.[492]

Left ventricular cineangiography in advanced cases shows a dilated, hypokinetic left ventricle with one large or several apical aneurysms (see Fig. 48-33) containing intracavitary thrombus, often with evidence of mitral regurgitation.[473] Coronary angiography is usually normal, although abnormalities of the coronary microcirculation have been suggested as a cause of the clinical manifestations of Chagas disease.

The complement-fixation test (Machado-Guerreiro test) is useful in diagnosis; it has high sensitivity and specificity for the identification of chronic Chagas disease.[473] Also used in diagnosis are the indirect immunofluorescent antibody, the enzyme-linked immunosorbent assay, and the hemagglutination tests.[473] In endemic areas, perhaps the most widely used test is the detection of parasites in the blood of patients with chronic Chagas disease (which occurs in upward of 50 percent of cases) by means of xenodiagnosis.[493] The patient is bitten by reduviid bugs bred in the laboratory; the subsequent identification of parasites in the intestine of the insect is proof of infection in the human host.

MANAGEMENT.

The treatment of Chagas disease remains difficult; although slowly progressive at first, once cardiac decompensation develops there is usually a rapid and inexorable progression to death, which is usually due to arrhythmia, although congestive failure and systemic thromboembolism account for additional mortality.[474] Patients at greatest risk of mortality are those with left ventricular enlargement and especially those with impaired left ventricular function.[485] [488] Major efforts are aimed at interrupting transmission of the parasite to humans; such vector control methods have been generally successful.[473] They may prevent not only the initial infection but also reinfection that may play a role in determining the severity of the resulting cardiomyopathy.

Amiodarone appears to be effective in controlling the ventricular arrhythmias frequently seen in Chagas disease, although whether this translates into improved survival remains to be established.[494] ICDs are useful, and the indications are similar to those in patients with life-threatening arrhythmias associated with other causes (see Chap. 23).[495] Anticoagulation may be of some benefit in preventing recurrent thromboembolic episodes.[490] Although antiparasitic agents such as nifurtimox, benzimidazole, and itraconazole are effective in reducing parasitemia and are useful in acute

disease, no evidence indicates that they are efficacious in curing the late phases of the disease.[473] [496] A promising avenue of approach appears to be immunoprophylaxis, although a clinically useful vaccine is not yet available. Insertion of an ICD and the latissimus dorsi muscle wrap around the heart (dynamic cardiomyoplasty) have been used sparingly but are not practical options for the vast majority of patients. Similarly,

heart transplantation have been performed in a few patients, but the results so far appear to be inferior to those found in other conditions, and episodes of parasitemia and recurrent Chagas disease may be a problem.[497] [498]

AFRICAN TRYPANOSOMIASIS.

African sleeping sickness, caused by *Trypanosoma gambiense* or *T. rhodesiense,* may be associated with myocardial abnormalities, although they are usually of less functional significance than in Chagas disease. *T. rhodesiense,* in particular, may lead to cardiac failure,[499] although the central nervous system findings (excessive somnolence) usually dominate the clinical picture.

Pathological examination often reveals pericardial fluid. The heart is not as greatly dilated and hypertrophied as it is in Chagas disease and may appear to be grossly normal. There is often epicardial thickening with a cellular exudate composed of lymphocytes, plasma cells, and histiocytes. The myocardium typically displays a diffuse interstitial infiltrate, often with zones of patchy fibrosis and interstitial edema.

Nonspecific ECG changes, commonly ST segment and T wave abnormalities and prolongation of the QT interval, are observed in at least half of the patients.[499] Unlike Chagas disease, arrhythmias and conduction disturbances are usually not prominent features, and the arterial pressure is usually normal. Some patients have asymptomatic cardiomegaly, although both pulmonary congestion and peripheral edema have been reported.

TOXOPLASMOSIS.

Toxoplasma infections are caused by an obligate intracellular parasite (*T. gondii*); both congenital and acquired forms may occur. Symptomatic acquired toxoplasmic infections involving the heart are uncommon. They occur most commonly in immunosuppressed patients with malignant diseases and occasionally in patients with the acquired immunodeficiency syndrome and after cardiac or bone marrow transplantation.[500] An inflammatory infiltrate, often with eosinophils and variable degrees of edema and degeneration of the muscle bundles, and pericardial effusion are often present.

Most adult cases are asymptomatic, but *Toxoplasma* infections may produce a severe, fatal disease with multisystemic involvement. Toxoplasmic myocarditis, often with pericarditis, may occur as an isolated disease process or as part of a multisystemic disseminated disease. Manifestations may include arrhythmias (atrial and ventricular), sudden death, atrioventricular block, pericarditis, and heart failure.[501] Large pericardial effusions may be seen on occasion. Diagnosis may be aided by endomyocardial biopsy.[502]

Treatment is with a combination of pyrimethamine and triple sulfonamides, but the response to therapy is variable; treatment appears to have no effect on the cyst form.[500]

MALARIA.

Although myocardial changes may be demonstrated during the course of malaria, particularly with *Plasmodium falciparum,* clinical findings to indicate cardiac involvement are rare.[503] [504] The heart generally demonstrates few gross abnormalities. The principal findings are histological. The capillaries are often filled and even distended with an accumulation of parasites, sometimes totally occluding the lumen of the vessels. Thrombosis of the capillaries and ischemic myocardial changes may be seen.[504] Focal myocardial damage may be present, along with an interstitial infiltrate composed of lymphocytes, plasma cells, and macrophages. In rare cases, cardiac failure may contribute to or even cause death.[504] ST segment and T wave changes on the ECG may be the only clinical indications of myocardial involvement.[503]

METAZOAL MYOCARDIAL DISEASE

ECHINOCOCCUS (HYDATID CYST).

Echinococcus is endemic in many sheep-raising areas of the world, particularly Argentina, Uruguay, New Zealand, Greece, North Africa, and Iceland, but cardiac involvement in hydatid disease is uncommon, occurring in less than 2 percent of cases.[505] The usual host of *Echinococcus granulosus* is the dog, but humans may serve as intermediate hosts (rather than the sheep, the usual intermediate host) if they accidentally ingest ova from contaminated dog feces.

When cardiac involvement is present, the cysts usually are intramyocardial in the interventricular septum or left ventricular free wall (Fig. 48-34) ; involvement of the right ventricle or atrium may occur.[505] Involvement of the tricuspid valve may be seen on occasion; in most cases, a single cardiac cyst is present.

A myocardial cyst may degenerate and calcify, develop daughter cysts, or rupture. Rupture of the cyst is the most dreaded complication; rupture into the pericardium may result in acute pericarditis, which may progress to chronic constrictive pericarditis.[505] Rupture into the cardiac chambers may result in systemic or pulmonary emboli.[506] Rapidly progressive pulmonary hypertension may occur with rupture of right-sided cysts, with subsequent embolization of hundreds of scolices into the pulmonary circulation. The liberation of hydatid fluid into the circulation may produce profound, fatal circulatory collapse due to an anaphylactic reaction to the protein constituents of the fluid.[505]

Symptoms depend on the location, size, and integrity of the cyst; patients may be asymptomatic or in profound circulatory collapse. It is estimated that only about 10 percent of patients with cardiac hydatid cysts have clinical manifestations.[505] The ECG may reflect the location of the cyst; T wave changes and loss of QRS voltage may occur with left ventricular involvement, whereas atrioventricular conduction defects or right bundle branch block may be seen with involvement of the interventricular septum. Chest pain is usually due to rupture of the cyst into the pericardial space with resultant

pericarditis. Large cystic masses may sometimes produce right-sided obstruction.[505]

Diagnosis.

Recognition of an echinococcal cyst of the heart is a relatively simple matter if there is evidence of cysts in other organs, particularly the liver and lung. However, a cardiac cyst may be an isolated, solitary finding. The chest roentgenogram frequently shows an abnormal cardiac silhouette or a calcified lobular mass adjacent to the left ventricle.[505] Although CT and MRI may aid in the detection and localization of heart cysts, two-dimensional echocardiography is thought to be the best choice (see Fig. 48-34).[505] Eosinophilia, present in some patients, is a useful adjunctive finding. The Casoni skin test is not very helpful because both false-positive and false-negative results occur. Serological tests, including hemagglutination and complement fixation, may be more useful, but their predictive accuracy is limited.[505]

Management.

Until recently, treatment for hydatid disease was limited to surgical excision.[507] Experience suggests that the benzimidazole derivatives mebendazole and albendazole may be somewhat useful in the medical management of this disease.[505] [508] Despite the availability of drug therapy, adjuctive surgical excision is generally recommended, even for asymptomatic patients, because of the significant risk of rupture of the cyst and its attendant serious and sometimes fatal consequences.[505] The surgical results have been generally favorable.

VISCERAL LARVA MIGRANS.

People are occasional accidental hosts of the roundworm infestations of dogs due to *Toxocara canis,* but cardiac involvement is rare. Most cases occur in children 1 to 3 years of age.[509] Myocarditis may occur in association with invasion of the myocardium by larvae. The myocardial lesions include granulomas or extensive inflammatory infiltrates (often with eosinophils) with foci of muscle necrosis. Congestive heart failure and death may occur, although asymptomatic cardiac involvement may be seen as well.

SCHISTOSOMIASIS AND RELATED DISEASE.

Direct cardiac involvement

Figure 48-34 Involvement of interventricular septum by a hydatid cyst. *Left,* Transthoracic two-dimensional echocardiogram of parasternal long-axis view showing a 3-cm diameter hydatid cyst (hc) in the upper ventricular septum. *Right,* Transesophageal echocardiography showing a hydatid cyst (hc) having a rounded and well-contrasted capsule. la = left atrium; lv = left ventricle; rv = right ventricle; ao = aorta. *(From Aupetit J, Ritz B, Ferrini M, et al: Images in cardiovascular medicine: Hydatid cyst of the interventricular septum. Circulation 95:2325, 1997. Copyright 1997, American Heart Association.)*

in schistosomiasis, heterophyiasis, and cysticercosis is distinctly unusual. The principal cardiovascular manifestation of schistosomiasis is right-sided heart overload as a consequence of embolization of the ova to the pulmonary vasculature, with attendant pulmonary hypertension.

TRICHINOSIS.

Infestation with *Trichinella spiralis* is a common human finding. Mild myocarditis has been said to be a frequent finding, but recent data suggest that clinically detectable cardiac involvement occurs in a minority of patients.[510] Symptomatic involvement is uncommon and may be responsible for the majority of fatalities.[511] Less frequently, death is due to pulmonary embolism secondary to venous thrombosis or to neurologic complications.

Although the parasite may invade the heart, it does not usually encyst there, and it is rare to find larvae or larval fragments in the myocardium. Nonetheless, pathological findings at autopsy may be impressive. The heart may be dilated and flabby, and a pericardial effusion may be present.[510] A prominent focal infiltrate composed of lymphocytes and eosinophils is commonly found, with occasional microthrombi in the intramural arterioles. Areas of muscle degeneration and necrosis are present.

Clinical Manifestations.

Myocarditis usually is mild and goes unnoticed, but in occasional cases it is manifested by congestive heart failure and chest pain, usually appearing around the third week of the disease, when the general constitutional symptoms are abating. Physical examination may be normal, or there may be gross cardiomegaly with severe congestive heart failure. Sudden death may occur, usually in the fourth to eighth week of the illness.

ECG abnormalities may be detected in about 10 percent of patients with trichinosis and parallel the time course of clinical cardiac involvement, initially appearing in the second or third week and usually resolving by the seventh week of the illness. The most common ECG abnormalities are repolarization abnormalities and ventricular premature complexes.[510] The ECG changes usually resolve completely.

The diagnosis is usually based on the demonstration of a positive indirect immunofluorescent antibody test in a patient with the clinical features of trichinosis. Eosinophilia, when present, is a supportive finding. The skin test is usually but not invariably positive. Treatment is with anthelmintics and corticosteroids; dramatic improvement in cardiac function has been reported after their use.

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Toxic, Chemical, Immune, and Physical Damage to the Heart

A wide variety of substances other than infectious agents may act on the heart and damage the myocardium. In some cases, the damage is acute, transient, and associated with evidence of an inflammatory myocardial infiltrate with myocyte necrosis (e.g., with the arsenicals and lithium); in other cases, a hypersensitivity reaction occurs, without prominent evidence of necrosis (e.g., with sulfonamides). Other agents that damage the myocardium may lead to chronic changes with resulting histological evidence of fibrosis and a clinical picture of a DCM. Furthermore, many offending stimuli may be associated with both acute and chronic phases (e.g., alcohol, doxorubicin). The extent of myocardial damage often is related to the dose and rate of exposure to the toxin.

Numerous chemicals and drugs (both industrial and therapeutic) may lead to cardiac damage and dysfunction. Several physical agents (e.g., radiation and excessive heat) may also result in myocardial damage. Furthermore, myocardial involvement may be evident in a variety of systemic disease, which are described in Part V of this book.

Cocaine

The illicit use of this drug has increased dramatically. It may be associated with a variety of cardiovascular complications, including myocardial ischemia and infarction (unassociated with obstructive coronary artery disease in about one third of cases), accelerated atherosclerosis, arrhythmias and sudden death, electrophysiological effects, coronary vasoconstriction, myocarditis, DCM, rupture of the aorta, cerebrovascular events, increased platelet aggregation, arterial thrombosis, and an apparent predisposition to the development of endocarditis.[512] [513] [514] [515] [516] The actual frequency of these complications is in some dispute[517] ; the number of adverse events

reported in the literature is far less than the casual impression of medical caregivers in inner-city hospitals would suggest. In one study of cocaine abusers who presented to the hospital with chest pain, the frequency of documented myocardial infarction was low.[518] The effects of cocaine on the myocardium itself include transient depression of ventricular function whether the drug is taken acutely or chronically,[519] [520] scattered areas of myocardial necrosis and myocarditis unrelated to coronary artery disease (which in some cases include contraction band necrosis), and fibrosis.[521] In a some cases there has been evidence of dilated cardiomyopathy.[522] Even asymptomatic cocaine abusers may have myocardial depression, albeit clinically silent.[520]

The cardiovascular effects of cocaine likely are related to its principal pharmacological effects: blocking the reuptake of catecholamines in the presynaptic neurons; blocking sodium channels, leading to local anesthetic, membrane-stabilizing effects; and reducing spontaneous sympathetic activity as a result of effects on the brain stem.[521] It has been speculated that the myocardial damage seen with cocaine relates to excess catecholamines damaging myocytes because their reuptake is blocked; this may lead to calcium overload of the cells, or perhaps to local vasoconstriction with subsequent ischemic damage. Coronary vasoconstriction is mediated by action on alpha-adrenergic receptors and is intensified by cigarette smoking and by beta-adrenergic blockade.[523] The increase in myocardial oxygen needs resulting from tachycardia and hypertension, combined with coronary vasoconstriction, can cause myocardial ischemia and is likely responsible for the observation of more than 20-fold increase in the risk of myocardial infarction in the hour after cocaine use.[519] The monocellular infiltrate (myocarditis) that has been found may merely be a reaction to the associated myocyte death, or it could be a hypersensitivity reaction to the cocaine, a metabolite,[524] or a contaminant.

The Coronary Artery Risk Development in Young Adults (CARDIA) study reported that cocaine use was related to being male, single, unemployed, and black, and to higher levels of other substance use.[525] Patients presenting to the emergency department with chest pain are infrequently asked about cocaine use.[524] Although acute myocardial infarction is a real risk in cocaine users, it may be caused by skeletal muscle injury, with elevation of circulating creatine kinase or CK-MB. Therefore, cardiac-specific troponin T or I is especially useful for detecting myocardial necrosis in these patients.[526] Similarly, myocardial perfusion imaging with technetium-99m sestamibi has been found to be useful in excluding infarction in patients with cocaine-associated chest pain.[527]

Treatment of cocaine-induced myocardial ischemia consists of nitrates, alpha-adrenoceptor blockers, calcium antagonists, and thrombolytic therapy (for acute myocardial infarctions). Beta-adrenoceptor blockers probably should be avoided unless hypertension or tachycardia are present, because they have been shown to further reduce coronary blood flow and increase coronary vascular resistance during cocaine use and may predispose to cocaine-mediated cardiac conduction defects.[513] [514] [521] The ACC/AHA Guidelines for the management of unstable angina listed recommend "... immediate arteriography, if possible, in patients whose

ST segments remain elevated after nitroglycerin and calcium channel blocker. Thrombolysis if thrombus is detected." Additional recommendations include thrombolytic therapy if ST segments remain elevated despite nitroglycerine and calcium blockers and coronary arteriography is not possible, as well as coronary arteriography, if available, for patients with new ST depression or T-wave changes, who are unresponsive to nitroglycerin and calcium antagonists.[528]

DAUNORUBICIN AND DOXORUBICIN(See Chap. 69)

INTERFERON-ALPHA(see Chap. 69).

Interferon-alpha is a leukocyte-derived protein used therapeutically to treat malignancies and HIV infections. Cardiotoxicity, usually consisting of hypotension, tachycardia, and transient arrhythmias, occurs in a minority of patients (perhaps up to 10 percent).[522] Several patients have developed congestive heart failure and the clinical picture of a DCM during interferon-alfa therapy; in at least some patients, the cardiomyopathy resolves rapidly with discontinuation of the drug.[522] [529]

INTERLEUKIN-2 (see Chap. 69).

The lymphokine interleukin-2, an antineoplastic agent, has significant cardiovascular toxicity, the most prominent of which is a diffuse capillary leak syndrome with hypotension and tachycardia, although reversible left ventricular dysfunction is seen as well.[529] In about 5 percent of patients, additional cardiotoxicity is seen, consisting of myocardial ischemia, infarction, injury, arrhythmias, and eosinophilic myocarditis.[530]

TRICYCLIC ANTIDEPRESSANTS (see Chap. 70).

Although sinus tachycardia, postural hypotension, disturbances in rhythm, abnormalities of atrioventricular conduction, and even sudden death may be seen with the tricyclic antidepressants, particularly when taken as an overdose, important depression of left ventricular function usually does not occur, even in patients with preexisting heart disease.[529] There has been concern when using tricyclic antidepressants in patients with prior myocardial infarction and/or preexisting ventricular arrhythmias, because these agents have a Class I antiarrhythmic effect, prolong the QT interval, and might be proarrhythmic in these settings. The selective serotonin reuptake inhibitors are remarkably free of cardiovascular toxicity and do not appear to depress ventricular function.[529] They may produce side effects by interacting with the metabolism of drugs mediated through the cytochrome-P450 enzyme system.[530]

PHENOTHIAZINES (see Chap. 70).

The phenothiazines may be associated with a variety of cardiac disturbances, including ECG changes, atrial and ventricular arrhythmias, and sudden death.[531] [532] Postural hypotension may also be seen. The cardiac effects are largely dose dependent. ECG abnormalities may be observed with as little as 200 mg of thioridazine per day and consist of lengthening of the QT interval and T wave changes. Prolongation of the QT

interval may set the stage for the emergence of ventricular arrhythmias, particularly torsades de pointes.[530] [531] Higher doses may lead to frank T wave inversion and increased amplitude of the U wave. Changes in the P wave, QRS complex, and ST segment are usually absent. The ECG abnormalities and arrhythmias resolve with discontinuation of the drug, usually within 48 hours. An occasional patient may require temporary ventricular pacing.

Pathological changes in the hearts of patients who have received phenothiazines and who have died suddenly include the deposition of acid mucopolysaccharide between muscle bundles in periarteriolar regions as well as the conduction system, with myofibrillar degeneration, and endothelial proliferation in the smaller blood vessels, although a direct causal relationship between drug administration and cardiomyopathic changes is only inferential. A variety of explanations have been invoked for the apparent cardiac damage, including direct toxic effects of the phenothiazines on the myocardium, stimulation of higher autonomic centers, and changes in circulating or myocardial levels of catecholamines.

EMETINE.

Cardiovascular changes are said to be common with the chronic use of emetine, a drug often employed in the treatment of amebiasis and schistosomiasis as well as the active ingredient in ipecac syrup (used for childhood poisoning).[533] Myocardial lesions may be observed in some patients at autopsy, and similar cardiac damage is noted in experimental animals given emetine. The myocardial lesions consist of myofibrillar degeneration and necrosis, with an interstitial infiltrate of mononuclear cells and histiocytes.

The ECG, which may be abnormal in 50 percent of treated patients, most commonly shows reduced T wave amplitude or inversion. Prolongation of the QT interval and ST segment shifts may also be seen, although abnormalities of the P wave, PR segment, and QRS complex are infrequent. The ECG changes usually resolve within weeks or months after cessation of treatment. Sinus tachycardia and hypotension may also be seen, as well as transient or permanent left ventricular dysfunction.[534] Only rare fatalities have been reported. Dehydroemetine results in ECG abnormalities similar to those of emetine, but they are less prominent and of shorter duration.

METHYSERGIDE.

The widespread fibrotic reactions seen with this drug can also involve the heart. Up to 1 percent of patients treated long term may develop typically left-sided valvular lesions, resulting in stenosis and regurgitation.[535]

CHLOROQUINE.

This drug has been widely used in the prophylaxis and treatment of a variety of parasitic and other diseases, including collagen and dermatological disorders. ECG changes may be seen with its use, along with conduction disturbances and features of a restrictive

cardiomyopathy.[536] In toxic doses, chloroquine may result in depressed cardiac output, bradycardia, arrhythmias, heart block, and death.

ANTIMONY COMPOUNDS.

Various antimony compounds, such as stibophen and tartar emetic, have been widely used in the treatment of schistosomiasis; less toxic agents are now becoming available. The antimony compounds are associated with ECG changes in almost all patients. Typical ECG changes include prolongation of the QT interval with flattening or inversion of T waves. ST segment shifts and P wave changes may be seen, although the QRS complex usually demonstrates no abnormality. The majority of patients do not demonstrate cardiac findings, although chest pain, bradycardia, hypotension, ventricular arrhythmias (including paroxysmal ventricular tachycardia and torsades de pointes), congestive heart failure, and sudden death may occur.[537] [538]

LITHIUM (see Chap. 70).

Lithium carbonate, used in the treatment of bipolar disorders, is associated with T wave changes in one fourth or more of patients who receive the drug.[539] Clinical evidence of myocardial involvement is usually lacking, although intoxication with lithium may be associated on rare occasions with ventricular arrhythmias, symptomatic sinus node abnormalities, atrioventricular conduction disturbances, congestive heart failure, and in rare cases, death.[539] [540] In fatal lithium toxicity, the heart is said to be dilated, with evidence of myofibrillar degeneration associated with a lymphocytic interstitial infiltrate.

HYDROCARBONS.

The fluorinated hydrocarbons, commonly used as aerosol propellants, appear to be cardiac toxins, contrary to their reputation of being inert.[541] In animal models, and occasional humans, the aerosol propellants may cause ventricular tachyarrhythmias, depress myocardial contractility, and lower systemic vascular resistance and arterial pressure.[542] These cardiovascular effects may be involved in the sudden deaths seen in individuals who abuse aerosols for their psychotropic effect.[542]

CATECHOLAMINES.

A severe reversible DCM has been observed in conjunction with pheochromocytoma, and the myocardial damage has been attributed to high levels of circulating catecholamines (see Chap. 64).[543] [544] Similar changes have been demonstrated in experimental animals treated with prolonged infusions of l-norepinephrine.[544] Catecholamines also may produce acute myocarditis, with focal myocardial necrosis, inflammation, epicardial hemorrhages, tachycardia, and arrhythmias.[545] Similar findings have been described with excessive use of beta-adrenoceptor agonist inhalants and methylxanthines in the treatment of decompensated pulmonary disease.[546] The cardiomyopathy associated with pheochromocytoma is one of the conditions that should be considered when heart failure suddenly appears without other obvious

explanation.[544]

A variety of mechanisms of myocardial damage have been suggested. A direct toxic effect may be involved, or the damage may be secondary to relative tissue hypoxia because of heightened metabolic demands. Alternatively, the damage may result from changes in autonomic tone, enhanced lipid mobility, calcium overload, damaging effects of catecholamine oxidation products (free radicals), or increased sarcolemmal permeability.[545] Catecholamine-induced vasospasm also may play a role.[544]

LEAD.

The prominent features in lead poisoning generally center on the gastrointestinal and central nervous systems. However, myocardial involvement may contribute to or be the principal cause of death in some cases.[547] ECG changes, atrioventricular conduction defects, and overt congestive heart failure may occur. The ECG and myocardial changes appear to be reversible with chelation therapy.

CARBON MONOXIDE.

Both acute and chronic carbon monoxide toxicity can occur. While central nervous system findings usually dominate the clinical presentation, significant and occasionally fatal cardiac abnormalities have been reported, although some have found no precipitation of arrhythmias following exposure.[548] [549] Because carbon monoxide has a higher affinity for hemoglobin than does oxygen, reduced amounts of oxygen are delivered to the tissues. Thus, the cardiac toxicity may be partially caused by myocardial hypoxia, but a direct toxic effect of the gas on myocardial mitochondria may play an even more important role.[550] The histological features include focal areas of necrosis, most marked in the subendocardium. Focal perivascular infiltrates and punctate hemorrhages are also seen.[550]

Cardiac involvement may appear promptly after exposure, or it may be delayed for up to several days. Palpitations, sinus tachycardia, and various arrhythmias, including ventricular extrasystoles and atrial fibrillation, are common.[551] Bradycardia and atrioventricular block may occur in more severe cases.[551] In patients with ischemic heart disease, angina pectoris and myocardial infarction may be precipitated. ECG ST segment and T wave abnormalities are quite common. Transient right and/or left ventricular wall motion abnormalities may be present.[550] Administration of 100 percent oxygen, bed rest, and surveillance for serious rhythm or conduction abnormalities usually permit rapid recovery.

HYPOCALCEMIA.

In rare patients with chronic hypocalcemia (often

due to hypoparathyroidism), congestive heart failure may occur (see Chap. 16) and resolve only when the serum calcium level is raised.[552] Rapid transfusion of citrated blood can produce hypocalcemia and reversible myocardial depression, as can ambulatory peritoneal dialysis in patients with chronic renal failure.[553]

HYPOPHOSPHATEMIA.

A form of reversible left ventricular dysfunction may be seen with severe hypophosphatemia. Restoration of the serum phosphate level to normal results in hemodynamic recovery.

HYPOMAGNESEMIA.

Focal cardiac necrosis is found in experimental magnesium deficiency and may account for the supraventricular and ventricular arrhythmias and ECG changes that are seen clinically. In addition to arrhythmias, coronary spasm and acute myocardial infarction may be seen.[554] A rare case of fatal cardiomyopathy has been reported.[554] [555]

CARNITINE DEFICIENCY.

Carnitine, an essential cofactor for the oxidation of fatty acids, produces an HCM or DCM in children who have long-standing carnitine deficiency.[556] Carnitine supplementation can lead to symptomatic and functional improvement; determination of carnitine levels therefore is important in children with unexplained cardiomyopathy. Myocardial carnitine levels may be reduced in the hearts of patients with DCM,[557] but the significance of this observation is not known at present.

SELENIUM DEFICIENCY.

Dietary deficiency of the trace element selenium appears to be one of the principal factors responsible for a form of DCM endemic to certain rural areas in China, although the etiological role played by selenium has been questioned.[558] Termed *Keshan disease,* it affects mainly children and young women and apparently is prevented by the prophylactic administration of sodium selenite tablets. A similar cardiomyopathy may be found in westerners subjected to prolonged parenteral hyperalimentation; supplementation with oral selenium may reverse the cardiomyopathy.[559]

SCORPION STING.

The venom of the scorpion is mainly neurotoxic, but cardiac findings may be prominent and even fatal, particularly in children.[560] ECG changes and myocardial damage with elevated serum cardiac enzyme levels are common findings. Hearts are normal on gross examination, with prominent microscopic changes usually but not invariably

present, particularly in the subendocardial region and papillary muscles. Degeneration and necrosis of muscle fibers are noted, with interstitial edema and a mononuclear infiltrate. The histological features of scorpion sting suggest high levels of circulating catecholamines and are similar to those seen with experimental catecholamine infusion and in pheochromocytoma.[561]

The ECG often initially shows tall, peaked T waves that progress to inversions and ST segment shifts. Q waves may appear, and the QT interval is usually prolonged. Atrial, junctional, and ventricular arrhythmias may occur. Tachycardia, hypertension, anxiety, diaphoresis, and pulmonary edema--findings resembling those of a massive catecholamine effect--are striking in many patients.[561] A smaller number of patients are seen in shock with peripheral vascular collapse. Most deaths are due to pulmonary edema, presumably the result of left ventricular dysfunction.[560] Occasionally, sudden and unexpected deaths occur in a smaller percentage of patients, presumably as a consequence of arrhythmias. Adrenergic blocking agents and the use of specific antivenom appear to be useful in the management of the cardiovascular manifestation of scorpion stings, although a wide variety of agents has been tried.[561]

WASP STINGS.

Stings by the vespine wasps may lead to anaphylaxis, with hypotension, circulatory collapse, and cyanosis. Occasional patients may have chest pain and clinical findings compatible with acute myocardial infarction.[562] The mechanism of myocardial damage is unclear; perhaps it merely reflects necrosis from profound hypotension, although a direct toxic effect on the myocardium or an indirect effect on the coronary arteries may be involved.[563]

SNAKE BITE.

Cardiac complications are not prominent features of snake bites, and the clinical picture is usually dominated by the neurological, hematological, and vascular damage produced by the snakebite toxin.[564] Myocardial involvement is seen on occasion and may rarely contribute to morbidity and mortality. T wave abnormalities are the most common manifestation of myocardial involvement, although ST segment depression, QRS prolongation, and atrioventricular conduction defects may also be seen.[564] [565] The ECG changes are usually transient, but when persistent they are attributed to direct myocardial damage due to the toxin. Death may occur from circulatory collapse, myocardial depression, or myocardial infarction due to hypotension and coronary artery thrombosis. Coronary artery vasospasm may also be involved.

ARSENIC.

Myocardial involvement may be seen in both acute and chronic arsenical poisoning, usually from pesticides; the heart may be dilated, with accumulation of pericardial fluid.[566] Multiple local and confluent areas of subepicardial and subendocardial hemorrhage are characteristic findings. The myocardium is usually abnormal, with

evidence of a perivascular mononuclear infiltrate.[566]

Clinically unrecognized interstitial myocarditis is manifested by T wave inversions and ST segment depression, along with prolongation of the QT interval.[566] The ECG changes usually revert to normal within 2 to 4 weeks. The ECG abnormalities appear to resolve more rapidly when BAL (British antilewisite, dimercaprol) is used in therapy.

CYCLOPHOSPHAMIDE (see Chap. 69).

High doses of cyclophosphamide have been associated with ECG changes, congestive heart failure, and death from hemorrhagic myocarditis.[529] In the majority of treated patients, a reversible decrease of QRS voltage and systolic function is seen, often asymptomatic, although more than 20 percent may succumb as a consequence of myopericarditis. The myocardial damage appears to result from direct endothelial damage and resultant fibrin microthrombi in the capillaries.

5-FLUOROURACIL (see Chap. 69).

This antineoplastic agent has been associated with cardiotoxicity manifested by chest pain, ECG changes, and arrhythmia.[529] Coronary spasm has been implicated but not proven as the mechanism. There is speculation that 5-fluorouracil may also depress left ventricular dysfunction, but this has not been established with certainty.[529]

HYPERSENSITIVITY

Hypersensitivity to a variety of agents may result in allergic reactions that involve the myocardium. A variety of drugs (most commonly the sulfonamides, hydrochlorothiazide, the penicillins, and methyldopa) or other sensitizers may lead to an allergic myocarditis (Table 48-10) , characterized by peripheral eosinophilia and a perivascular infiltration of the myocardium by eosinophils, lymphocytes, and histiocytes; necrosis is seen on occasion.[338] Hypersensitivity myocarditis is rarely recognized clinically and is often first discovered at postmortem examination, although it is occasionally diagnosed on endomyocardial biopsy. Most patients who have hypersensitivity myocarditis are not critically ill, but nevertheless may die suddenly, presumably as a consequence of an arrhythmia. An occasional patient has intense eosinophilic infiltration of the myocardium of no obvious cause, with prominent necrosis evident and findings of hemodynamic collapse; some of these patients may have undiagnosed hypersensitivity myocarditis.[567] [568] Because of the potential for significant deleterious effects, a high index of suspicion for this condition should be maintained. Therapy includes discontinuation of the offending agent and corticosteroids and/or immunosuppression therapy in severe cases.

METHYLDOPA.

Although hepatitis is the most frequently encountered serious adverse reaction to methyldopa, sudden and unexpected death has been reported in a number of patients found at necropsy to have had an unsuspected myocarditis.[568] [569] The histological findings have the characteristics of an allergic myocarditis, showing an interstitial

inflammatory infiltrate with abundant eosinophils, vasculitis, and focal myocardial necrosis.[568] ECG changes include sinus bradycardia, sinus pauses, and first- and second-degree AV block.

PENICILLIN.

Allergic reactions to penicillin are fairly common, but myocardial involvement is rare.[570] Histological findings consist of a perivascular and interstitial infiltrate composed of eosinophils and

TABLE 48-10 -- PRINCIPAL DRUGS CAPABLE OF CAUSING HYPERSENSITIVITY MYOCARDITIS

Antibiotics	**AntlInfiammatory**
Amphotericin B	Indomethacin
Ampicillin	Oxyphenbutazone
Chloramphenicol	Phenylbutazone
Penicillin	
Tetracycline	**Diuretics**
Streptomycin	Acetazolamide
	Chlorthalidone
Sulfonamides	Hydrochlorothiazide
Sulfadiazine	Spironolactone
Sulfisoxazole	
	Others
Anticonvulsants	Amitriptyline
Phenindione	Methyldopa
Phenytoin	Sulfonylureas
Carbamazepine	Tetanus toxoid
Antituberculous	
Isoniazid	
Para-aminosalicylic acid	

From Kounis NG, Zavras GM, Soufras GD, Kitrou MP: Hypersensitivity myocarditis. Ann Allergy 62:71, 1989.

mononuclear cells.[568] Both myocardial infarction and pericarditis may occur and

account for some of the ECG changes.[570] Transient ECG changes may be the only manifestation of cardiac involvement, with sinus tachycardia, ST segment elevation, and T wave inversion.

SULFONAMIDES.

Sulfonamides may result in myocardial damage owing to a hypersensitivity vasculitis as well as a myocarditis.[570] In fatal cases eosinophilic myocarditis, sometimes with granulomas, can be demonstrated.[568] Although usually clinically silent, myocardial involvement may produce severe and even fatal congestive heart failure. ECG changes are usually absent, but nonspecific ST segment and T wave abnormalities may be seen.

TETRACYCLINE.

Allergic reactions to antibiotics of the tetracycline class include fever, tachycardia, and first-degree atrioventricular block. Postmortem findings include cardiac dilatation, fibrinoid muscle cell degeneration, and a diffuse interstitial and perivascular infiltrate.[568]

GIANT CELL MYOCARDITIS

Giant cell myocarditis is a rare disease of unknown cause characterized by the presence of multinucleated giant cells in the myocardium. (It is included here because of the possibility that it may be of immune or autoimmune origin.) Also called granulomatous myocarditis, this condition is typically a rapidly fatal disease, often of young to middle-aged adults.[571] Pathological findings are usually impressive. The ventricles are dilated, and mural thrombi may be present. A serpiginous area of myocardial necrosis may be seen involving the right as well as the left ventricle. Multinucleated giant cells are found, particularly at the margins of the areas of myocardial necrosis; a lymphocyte infiltrate is present,[572] with helper or suppressor T cells (Fig. 48-35) .[573] [574] [575]

Figure 48-35 Endomyocardial biopsy findings in giant-cell myocarditis. \i\Left,\r\ Active giant-cell myocarditis. Initial pretreatment biopsy showed several giant cells and a mixed lymphocyte-eosinophilic infiltrate (hematoxylin-eosin; original magnification, ;ts250). \i\Right,\r\ Healing giant-cell myocarditis. Biopsy after therapy showed interstitial fibrosis with residual mononuclear cells but no giant cells or myocyte necrosis (hematoxylin-eosin; original magnification, ;ts250). (From Levy NT, Olson LJ, Weyand C, et al: Histologic and cytokine response to immunosuppression in giant-cell myocarditis. Ann Intern Med 128:648, 1998.)

ETIOLOGY.

Giant cell myocarditis occurs on occasion in association with systemic diseases such as sarcoidosis, systemic lupus erythematosus, drug hypersensitivity, infections (especially syphilis and tuberculosis), thyrotoxicosis and malignant thymoma, but the cause of the disease remains obscure.[338] [576] In many ways the clinical features suggest a viral myocarditis except for the rapid and virulent course. Myocardial infection with

coxsackievirus B2 has been reported,[574] and an autoimmune reaction to altered cardiac tissue has been suggested based on the histological findings and the association of giant cell myocarditis with other autoimmune disorders, although there is little direct evidence supporting this view.[571]

CLINICAL MANIFESTATIONS AND TREATMENT.

Both sexes are equally affected; the onset typically is rapid, with dyspnea, chest pain, orthopnea, and hypotension. Fever is usually present, with ECG evidence of widespread myocardial involvement. Refractory ventricular arrhythmias, although present in a minority of patients, suggest the diagnosis when present.[571] Overt congestive heart failure and sudden death occur frequently.[571] [572] [573] [574] [575] [576] [577] Medical therapy often is unsuccessful, although corticosteroids and immunosuppressive agents appear to have benefited some patients. Because the prognosis in general is poor, an initial attempt at empirical immunosuppressive therapy is warranted.[578] [579] Occasional patients have had long-term survival after medical therapy,[579A] but cardiac transplantation is considered to be the treatment of choice for most patients; there is a risk of fatal recurrent giant cell myocarditis in the transplanted heart.[580]

PHYSICAL AGENTS

RADIATION (see Chap. 69).

The use of radiation therapy may result in a variety of cardiac complications, which are usually chronic and which include pericarditis with effusion, tamponade, or constriction; coronary artery fibrosis and myocardial infarction; valvular abnormalities; myocardial fibrosis; and conduction disturbances.[581] Although the heart has been regarded as one of the organs more resistant to the effects of radiation, the clinical significance of radiation-induced heart disease is greater than usually thought.[581] Although radiation probably results in some degree of tissue damage in all patients, clinically significant cardiac involvement occurs in the minority of patients, usually long after the radiation treatment has ended.[582] Radiation-induced cardiac damage is related to the dose of radiation, the mass of heart irradiated, and the dose schedule of the radiation.

The late cardiac damage that may follow irradiation appears to result from a long-lasting injury of the capillary endothelial cells, which leads to cell death, capillary rupture, and microthrombi.[581] [583] Because of this damage to the microvasculature, ischemia results and is followed by myocardial fibrosis. In addition to microvascular damage, the major epicardial coronary arteries may become narrowed, especially at the ostia.[582]

Only an occasional patient manifests acute clinical cardiac abnormality with radiation therapy; typically this consists of acute pericarditis. A mild, transient, asymptomatic depression of left ventricular function may be seen early after radiation therapy. The more common clinical expressions of radiation heart disease occur months or years after the exposure. The pericardium is the most common site of clinical involvement, with findings of chronic pericardial effusion or pericardial constriction (see Chap. 50).[581] Myocardial damage occurs less frequently and is characterized by myocardial

fibrosis with or without endocardial fibrosis or fibroelastosis. Left and/or right ventricular dysfunction at rest or with exercise appears to be a common, albeit usually asymptomatic, finding 5 to 20 years after radiation therapy, especially in those in whom the now-outmoded technique of a single anteroposterior port was used.[581] Occasional patients may develop usually asymptomatic left-sided (and rarely right-sided) valvular regurgitation (or on occasion stenosis) that rarely requires valve replacement[582] ; often there is a latent period of a decade or more between the radiation exposure and the development of valvular deformity.[583] ECG abnormalities, heart block, and a variety of arrhythmias may be seen months or years after therapeutic radiation, although usually they are of limited clinical significance.[583] [584]

HEAT STROKE

This condition results from failure of the thermoregulatory center following exposure to high ambient temperature. It is manifested principally by hyperpyrexia, renal insufficiency, disseminated intravascular coagulation, and central nervous system dysfunction.[585] However, cardiovascular abnormalities (usually ECG) appear to be common; pulmonary edema, and transient right and/or left ventricular dysfunction may occur, along with hypotension and circulatory collapse. Pathological changes include dilatation of the right side of the heart, particularly the right atrium. Hemorrhages of the subendocardium and the subepicardium are frequently seen at necropsy and often involve the interventricular septum and posterior wall of the left ventricle. Histological findings include degeneration and necrosis of muscle fibers as well as interstitial edema. Factors that have been implicated as possible causes of myocardial damage include direct thermal injury, myocardial hypoxia resulting from circulatory collapse, decreased coronary blood flow, and metabolic abnormalities resulting from widespread injury to other organs.

Sinus tachycardia is invariably present,[585] whereas atrial and ventricular arrhythmias usually are absent. Transient prolongation of the QT interval may be seen, along with ST segment and T wave abnormalities. It may take up to several months for these repolarization abnormalities to resolve. Serum enzyme levels may be elevated and may reflect myocardial damage, at least in part, although comcomitant rhabdomyolysis often is present.

HYPOTHERMIA

Low temperature may also result in myocardial damage. Cardiac dilatation may occur with epicardial petechiae and subendocardial hemorrhages.

Microinfarcts are found in the ventricular myocardium, presumably related to abnormalities in the microcirculation. The lesions are not due to the low temperature per se but appear to be the result of the circulatory collapse, hemoconcentration, capillary slugging, and depressed cellular metabolism that accompany hypothermia. Clinical

manifestations of hypothermia include sinus bradycardia, conduction disturbances, atrial (and occasionally ventricular) fibrillation, hypotension, a fall in cardiac output, reversible myocardial depression, and a characteristic deflection of the terminal portion of the QRS pattern (Osborn wave).[586] Treatment includes core warming (often utilizing extracorporeal blood warming), cardiopulmonary resuscitation, and management of pulmonary, hematological, and renal complications.[586] [587] [588]

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Chapter 49 - Primary Tumors of the Heart

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With an incidence of 0.002 to 0.3 percent in autopsy series,[1] [2] [3] [4] [5] [6] [7] primary tumors of the heart* are far less common than metastatic tumors to the heart.[8] Benign primary cardiac tumors occur more frequently than malignant ones. The most common cardiac tumor is the myxoma. In a large single-institution series of primary cardiac tumors, comprising 124 cases diagnosed at surgery and autopsy over 40 years (at the University of Minnesota), 42 percent were cardiac myxomas and 16 percent were malignant tumors (sarcomas) (Fig. 49-1) .[9] The proportion of myxomas in comparison with other tumors was increased (to 77 percent) when consideration was limited to surgically excised lesions.[9] [10] Before the advent of modern cardiopulmonary bypass surgical techniques, the correct antemortem diagnosis of an intracardiac tumor was largely academic, because effective therapy was not possible. However, now that many cardiac tumors are curable by operation, it is critically important to establish this diagnosis whenever possible. During the past decade, major advances in noninvasive cardiovascular diagnostic techniques--especially echocardiography (see Chap. 7) , computed tomography (CT), and magnetic resonance imaging (MRI) (see Chap. 10) --have greatly facilitated this task, and it is now possible safely and readily to screen patients suspected of having a cardiac tumor, in many cases arriving at a definitive

diagnosis preoperatively. Nevertheless, a high index of suspicion remains the most important element in diagnosing a cardiac tumor.

CLINICAL PRESENTATION

SYSTEMIC FINDINGS.

The cardiac tumor myxoma causes various nonspecific clinical signs and symptoms that often masquerade as many other more common cardiovascular and systemic diseases (Tables 49-1 and 49-2) . Cardiac myxoma can produce a broad array of systemic (i.e., noncardiac) findings including fever, cachexia, malaise, arthralgias, Raynaud's phenomenon, rash, clubbing, and episodic bizarre behavior,[11] [12] as well as systemic and pulmonary emboli. [12A] Various laboratory findings have been reported, including hypergammaglobulinemia, elevated erythrocyte sedimentation rate, thrombocytosis, thrombocytopenia, polycythemia, leukocytosis, and anemia. Systemic signs and symptoms frequently resolve when the tumor is removed.

Role of Interleukin-6.

The association of constitutional symptoms with cardiac myxoma is likely to be due to the tumor's constitutive synthesis and secretion of interleukin-6 (IL-6),[13] [14] [15] [16] [17] [18] [19] [20] [20A] an inflammatory cytokine thought to be a major inducer of the acute phase response, which is associated with fever, leukocytosis, and activation of the complement and clotting cascades.[14] In vitro, IL-6 induces the synthesis of C-reactive protein, serum amyloid A, alpha$_2$ -macroglobulin, and fibrinogen by human hepatocytes.[14] High levels of myxoma production of IL-6 may be accompanied by elevated serum concentration in patients who have cardiac myxoma and symptoms characteristic of autoimmune diseases.[18] In some cases, serum IL-6 levels become undetectable and the immunological features resolve on removal of the tumor.[19] Increased titers of antibodies to myocardium[20] and neutrophils[21] have also been found in patients with myxoma and were shown to decline after removal of the tumor. A case of multiple myeloma has been attributed to continuous immunological stimulation by a left atrial myxoma.[22] Because the cardiac findings are nonspecific and may be subtle or absent, it is not unusual for these systemic findings to lead to a diagnosis of collagen-vascular disease, infection, or noncardiac malignant disease.[23] [24] [25] Rarely, myxomas may be superinfected by bacteria or fungi.[26] [27] [28]

EMBOLIC PHENOMENA.

Embolization of tumor fragments or of thrombi from the surface of a tumor is a frequent and often dramatic clinical occurrence.[29] [30] [31] [32] [33] Although myxomas are the source of most tumor emboli because of the combination of their friable consistency and intracavitary location (Fig. 49-2) , other types of cardiac tumors occasionally may embolize.

The distribution of tumor emboli depends on the location of the tumor and the presence or absence of intracardiac shunts. Left-sided tumors embolize to the systemic

circulation, resulting in infarction and hemorrhage of viscera, including the heart,[29] as well as peripheral limb ischemia and vascular aneurysms. The diagnosis of an intracardiac tumor may be made after histological examination of systemic embolic material,[34] [35] and therefore it is of critical importance to make every effort to recover and examine embolic material. In some cases, particularly when petechiae are present, biopsy of skin or muscle[33] can demonstrate intravascular tumor emboli.

Multiple systemic emboli may mimic systemic vasculitis[33] or infective endocarditis, especially when associated with other manifestations of a systemic illness such as fever,

*Tumors arising elsewhere in the body and metastasizing to the pericardium and heart are discussed in Chap. 50 (Pericardial Disease) and Chap. 69 (Hematologic-Oncologic Disorders and Heart Disease).

Figure 49-1 Relative incidence of cardiac tumors. *A,* Incidences of both surgical and autopsy cases are considered. *B,* Relative incidences of only surgical series are considered. When only surgical series are considered, the proportion of myxomas increases. (Adapted from Molina JE, Edwards JE, Ward HB: Primary cardiac tumors: Experience at the University of Minnesota. Thorac Cardiovasc Surg 38:183, 1990.)

weight loss, arthralgias, elevated erythrocyte sedimentation rate, and elevated serum gamma globulins. The finding at angiography of numerous vascular aneurysms secondary to tumor emboli in the cerebral, renal, femoral, and coronary arteries is not infrequent[36] and may lead to the mistaken diagnosis of polyarteritis nodosa.[23] The neurological consequences of embolization include transient ischemic attacks, seizures, syncope, and cerebral, cerebellar, brain stem, spinal cord, or retinal infarction.[37] The neurological event may occasionally be the first or only clinical manifestation of a cardiac tumor. An embolic stroke in a young person without evidence of cerebrovascular disease, particularly in the presence of sinus rhythm, should raise the suspicion of intracardiac myxoma, as well as infective endocarditis and prolapse of the mitral valve.

TABLE 49-1 -- SYMPTOMS AND SIGNS OF CARDIAC MYXOMA

SYMPTOMS	INCIDENCE (%)
Dyspnea on exertion	>75
Paroxysmal dyspnea	~25
Fever	~50
Weight loss	~25
Severe dizziness/syncope	~20
Sudden death	~15
Hemoptysis	~15

SIGNS	INCIDENCE (%)
Mitral diastolic murmur	~75
Mitral systolic murmur	~50
Pulmonary hypertension	~70
Right heart failure	~70
Pulmonary emboli	~25
Anemia	>33
Elevated ESR	>33
Third heart sound (tumor plop)	>33
Atrial fibrillation	~15
Elevated globulins	~10
Clubbing	~5
Raynaud's phenomenon	<5

ESR=erythrocyte sedimentation rate.
From Fisher J: Cardiac myxoma. Cardiovasc Rev Rep 9:1195, 1983.

Right-sided cardiac tumors and left-sided cardiac tumors proximal to left-to-right intracardiac shunts may result in pulmonary emboli.[12A] [30] [31] Indeed, serious pulmonary hypertension and secondary cor pulmonale due to chronic recurrent pulmonary emboli from a right atrial myxoma

TABLE 49-2 -- CONDITIONS OFTEN CONFUSED WITH ATRIAL MYXOMA

Left Atrium
Rheumatic mitral valve disease (MS, MR)
Pulmonary hypertension (primary, or secondary to mitral valve disease or LV failure)
Intrinsic lung disease
Cerebrovascular disease (CVA, TIA)
Endocarditis
Rheumatic fever
Myocarditis
Vasculitis (polyarteritis, lupus erythematosus)
Right Atrium

Rheumatic tricuspid valve disease (TS, TR)
Ebstein's anomaly
Atrial septal defect
Pulmonary hypertension
Pulmonary emboli
Constrictive pericarditis
Pleuropericarditis (rub)
Carcinoid heart disease
Cardiomyopathy

Right Ventricle

Pulmonic stenosis
Infundibular stenosis
Pulmonary emboli
Pulmonary hypertension

Left Ventricle

Aortic stenosis
Subaortic stenosis
Cerebrovascular disease
Mural thrombus

MS=mitral stenosis; MR=mitral regurgitation; LV=left ventricular; CVA=cerebrovascular accident; TIA=transient ischemic attack; TS=tricuspid stenosis; TR=tricuspid regurgitation.
From Fisher J: Cardiac myxoma. Cardiovasc Rev Rep 9:1195, 1983.

Figure 49-2 Photographs of the two most frequent gross appearances of cardiac myxomas. *A,* Polypoid, smooth, round, hemorrhagic left atrial myxoma, noted at autopsy. The tumor mass nearly fills the left atrium and extends into the mitral valve orifice. *B,* irregular gelatinous, friable myxoma mass, surgically removed. The resection margin that surrounds the proximal portion of the stalk is indicated by an arrow. (*A* from Cotran RS, Kumar V, Robbins SL: Robbins' Pathologic Basis of Disease. 5th ed. Philadelphia, WB Saunders, 1994. *B* from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.)

have been noted. [38] Clinically, the findings may be indistinguishable from pulmonary emboli secondary to venous thromboembolism (see Chap. 52) . Although the findings on chest roentgenogram are nonspecific, perfusion lung scanning in such patients may yield results atypical of pulmonary embolism in two respects: (1) The tumor-produced perfusion defects may remain static for long periods, as opposed to typical pulmonary embolic disease in which the defects usually resolve over the course of a few weeks; and (2) flow to one lung may be completely absent while perfusion of the opposite lung is completely normal, a pattern unusual with typical pulmonary emboli.

Cardiac Manifestations

The specific signs and symptoms produced by tumors are more closely related to their precise anatomical location than to their histological types.[39] Thus, it is useful to consider the constellation of findings typical of each location. The presentation of *pericardial tumors* is considered in Chapter 50 and is not discussed here except to point out that primary tumors of the myocardium and endocardium may extend into the pericardial space and produce many of the clinical manifestations of pericardial tumors, including hemorrhagic pericardial effusion and compression of the heart by the effusion or the tumor itself.

MYOCARDIAL TUMORS.

When clinically apparent, myocardial tumors most commonly result in disturbances of conduction or rhythm,[40] [41] [42] [43] the precise nature of which is determined by the location of the tumor. Thus, tumors in the area of the atrioventricular (AV) node, typically angiomas and mesotheliomas, may produce AV conduction disturbances, including complete heart block, and asystole and can lead to sudden death (see Chap. 26) .[40] [41] [42] [43] A wide variety of arrhythmias may be produced, including atrial fibrillation or flutter, paroxysmal atrial tachycardia with or without block, nodal rhythm, premature ventricular beats, ventricular tachycardia, and ventricular fibrillation (see Chap. 25) .[39] [43] Intramural tumors can also produce symptoms by virtue of their size and location. Impairment of ventricular performance may simulate congestive, restrictive, or hypertrophic cardiomyopathy (see Chap. 48) . Tumor infiltration of the myocardial wall occasionally causes myocardial rupture.[44]

LEFT ATRIAL TUMORS.

Mobile, pedunculated, left atrial tumors may prolapse to various degrees into the mitral valve orifice, resulting in obstruction to AV blood flow and, frequently, mitral regurgitation. The resultant signs and symptoms often mimic those of mitral valve disease[1] [5] [44] (see Table 49-2) , especially mitral stenosis (see Chap. 46) ,[45] and include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, cough, hemoptysis, chest pain, peripheral edema, and fatigue. However, weight loss, pallor, syncope, and sudden death--manifestations that are uncommon with mitral valve disease--also occur. It is not unusual for the symptoms to be sudden in onset, intermittent, and related to the patient's body position.[5] [39] Although the majority of symptoms produced by left atrial tumors are nonspecific, the occurrence of paroxysmal symptoms that arise characteristically in a particular body position and are out of proportion to the clinical findings should raise suspicion of a left atrial tumor. The most common primary cardiac tumor presenting in the left atrium is the benign myxoma, which, in the large majority of cases, is solitary.

Physical Examination.

The physical examination may disclose signs of pulmonary congestion; an S_4 ; a loud S_1

, which is often widely split; a holosystolic murmur that is loudest at the apex and resembles mitral regurgitation; and a diastolic murmur resulting from obstruction to flow through the mitral orifice produced by the tumor. The loud S_1 that occurs in patients with left atrial myxoma may be

due to the late onset of mitral valve closure resulting from prolapse of the tumor through the mitral valve orifice.[46] Consequently, the left ventricular-left atrial pressure crossover occurs at a higher pressure, as in patients with mitral stenosis or a short PR interval. It has been suggested that the finding of a loud S_1 in the absence of a short PR interval or a mitral diastolic murmur should raise the suspicion of a left atrial tumor.[46] In many cases, an early diastolic sound, termed a *tumor plop,* can be identified. It is thought to be produced as the tumor strikes the endocardial wall or as its excursion is abruptly halted. Although in most cases the tumor plop occurs later than the opening snap of the mitral valve and earlier than the S_3 , it is not surprising that this sound is frequently confused with the opening snap or the S_3 .

RIGHT ATRIAL TUMORS.

Right atrial tumors frequently produce symptoms of right heart failure, including fatigue, peripheral edema, ascites, hepatomegaly, and prominent *a* waves in the jugular vein pulse.[39] [47] [48] [49] [50] The average time interval from the symptomatic presentation to the correct diagnosis of right atrial tumor may be years. The development of right-sided heart failure can be rapidly progressive and is often associated with new systolic or diastolic murmurs or both. The murmurs are generally the result of tumor obstruction to tricuspid valve flow or of tricuspid regurgitation caused by tumor interference with valve closure or valve destruction caused directly or indirectly by the tumor.[51] It is not surprising that right atrial tumors have been misdiagnosed as Ebstein's anomaly of the tricuspid valve, constrictive pericarditis, tricuspid stenosis, carcinoid syndrome, superior vena caval syndrome, and cardiomyopathy (see Table 49-2) . Pulmonary embolism and pulmonary hypertension occur and may simulate classic thromboembolic disease.[48] Right atrial hypertension may cause right-to-left shunting through a patent foramen ovale, with systemic hypoxia, cyanosis, clubbing, and polycythemia.[50] Whereas myxomas occur much more commonly in the left atrium than in the right atrium, sarcomas occur more commonly in the right atrium.

Physical Examination.

The physical examination can reveal peripheral edema, evidence of superior vena cava obstruction, hepatomegaly, and ascites. An early diastolic rumbling murmur, alone or in combination with a holosystolic murmur secondary to tricuspid regurgitation, may demonstrate respiratory or positional variation. Because of the rarity of *isolated* rheumatic tricuspid valvular disease, the lack of other valvular findings should raise the question of a right atrial tumor. A protodiastolic tumor plop has been described and is

thought to be similar in etiology to that produced by left atrial tumors.[52] The jugular venous pressure may be elevated, and a prominent *a* wave and steep *y* descent may be present.

RIGHT VENTRICULAR TUMORS.

Right ventricular tumors often present with right-sided heart failure as a result of obstruction to right ventricular filling or outflow. Clinical manifestations include peripheral edema, hepatomegaly, ascites, shortness of breath, syncope, and sudden death.

A systolic ejection murmur at the left sternal border is usually found on physical examination. A presystolic murmur and a diastolic rumble[39] have been noted and are thought to be due to obstruction of the tricuspid valve. An S_3 may be audible, and a low-pitched diastolic sound that coincides with the maximal anterior excursion of the tumor has been ascribed either to tumor or to late closure of the pulmonary valve.[53] P_2 is often delayed, and its intensity can be normal, decreased, or increased. Tumor emboli to the pulmonary arteries may result in pulmonary hypertension, and the presence of tumor in the pulmonic valve orifice may lead to pulmonary regurgitation. The jugular veins are frequently distended, with a prominent *a* wave, and may demonstrate Kussmaul's sign (see Chap. 4) .

The cardiac findings often lead to a diagnosis of pulmonic stenosis, restrictive cardiomyopathy, or tricuspid regurgitation. Whereas pulmonic stenosis is often asymptomatic and slowly progressive, the symptoms of right ventricular tumors are often rapidly progressive, and there is no poststenotic dilatation or systolic ejection click.

LEFT VENTRICULAR TUMORS.

When left ventricular tumors are predominantly intramural in location, they are often asymptomatic, they can present as conduction disturbances or arrhythmias, or they can interfere with ventricular function. However, when the tumor also has a significant intracavitary component, left ventricular outflow can be obstructed, resulting in syncope and findings consistent with left ventricular failure. Atypical chest pain has also been reported and, in some cases, can reflect obstruction of a coronary artery either directly by tumor involvement or as a result of a tumor embolus to the coronary artery.

Physical Examination.

The physical examination reveals a systolic murmur, and both the murmur and the blood pressure may vary with position. Left ventricular tumors may simulate the findings of aortic stenosis, subaortic stenosis, hypertrophic cardiomyopathy, endocardial fibroelastosis, and coronary artery disease.

Benign Versus Malignant Tumors

The types of benign and malignant mesenchymal tumors that can develop in the heart

are typical of those occurring in any mass of striated muscle and connective tissue. Although the exact incidence of each specific tumor type cannot be stated, about 75 percent of all cardiac tumors are benign histologically and the remainder are malignant.[1] The majority of benign cardiac tumors are myxomas, followed in frequency by a wide variety of other tumors (Table 49-3) . Almost all malignant cardiac tumors are sarcomas, and of these the angiosarcoma and rhabdomyosarcoma are the most common forms (Table 49-4) .

Although it is often difficult or impossible to differentiate benign from malignant tumors histologically before operation, certain findings may be helpful. Characteristics suggestive of malignancy include the presence of distant

TABLE 49-3 -- RELATIVE INCIDENCE OF BENIGN TUMORS OF THE HEART

BENIGN TUMOR	% OF GROUP		
	Adults	**Children**	**Infants**
Myxoma	46	15	0
Lipoma	21	0	0
Papillary fibroelastoma	16	0	0
Rhabdomyoma	2	46	65
Fibroma	3	15	12
Hemangioma	5	5	4
Teratoma	1	13	18
Mesothelioma of the atrioventricular node	3	4	2
Granular cell tumor	1	0	0
Neurofibroma	1	1	0
Lymphangioma	1	0	0
Hamartoma	0	1	0

Data representing the extensive investigations of the Armed Forces Institute of Pathology as well as the cumulative experience of other researchers. A total of 265, 82, and 49 benign tumors were found in adults (age >16 yr), children (age 1-16 yr), and infants (age <1 yr), respectively. Myxomas were the most common reported benign tumors in adults, whereas rhabdomyomas were the most common benign tumors in both children and infants; benign teratomas also occurred frequently in children and infants.
From Allard MF, Taylor GP, Wilson JE, McManus BM: Primary cardiac tumors. In Goldhaber S, Braunwald E (eds): Atlas of Heart Diseases. Philadelphia, Current Medicine, 1995, pp 15.1-15.22.

Extraskeletal osteosarcoma Adults Children Infants

TABLE 49-4 -- RELATIVE INCIDENCE OF BENIGN TUMORS OF THE HEART

TUMOR TYPE	% OF GROUP		
	Adults	Children	Infants
Angiosarcoma	33	0	0
Rhabdomyosarcoma	21	33	66
Mesothelioma	16	0	0
Fibrosarcoma	11	11	33
Malignant lymphoma	6	0	0
Extraskeletal osteosarcoma	4	0	0
Thymoma	3	0	0
Neurogenic sarcoma	3	11	0
Leiomyosarcoma	1	0	0
Liposarcoma	1	0	0
Synovial sarcoma	1	0	0
Malignant teratoma	0	44	0

A total of 117, 9, and 3 malignant tumors were found in adults (age >16 yr), children (age 1-16 yr), and infants (age <1 yr), respectively. Angiosarcomas were the most commonly reported malignant tumors in adults, but rhabdomyosarcomas and mesotheliomas were also relatively common. Malignant teratomas were the most common tumors in children. Rhabdomyosarcomas were the most frequently reported malignant tumors in infants, with fibrosarcomas the second most common.
From Allard MF, Taylor GP, Wilson JE, McManus BM: Primary cardiac tumors. In Goldhaber S, Braunwald E (eds): Atlas of Heart Diseases. Philadelphia, Current Medicine, 1995, pp 15.1-15.22.

Distributions of myxomas (%) 56 (39-82) SYNDROME

metastases, local mediastinal invasion, evidence of rapid growth in tumor size, hemorrhagic pericardial effusion, precordial pain, location of the tumor on the right side of the heart or on the atrial free wall, evidence of combined intramural and intracavitary location, and extension into the pulmonary veins. Benign tumors are more likely to occur on the left side of the interatrial septum and to grow slowly. Although benign tumors do not metastasize, distant tumor emboli can mimic peripheral or pulmonary metastases.[54] The preoperative differentiation between benign and malignant tumors can occasionally be made by examination of peripheral tumor emboli recovered by arteriotomy or by biopsy of skin or muscle.[5] [32] [34] [35]

SPECIFIC CARDIAC TUMORS

Benign Tumors

Myxomas

As already pointed out, myxomas are the most common type of primary cardiac tumor, comprising 30 to 50 percent of the total in most pathological series (or higher, when surgically excised tumors are considered).[1] [2] [3] [4] [5] [8] The mean age of patients with sporadic myxoma is 56 years, and 70 percent are females. However, myxomas have been described in patients ranging in age from 3 to 83 years and are now not infrequently diagnosed in elderly patients, in whom the symptoms and signs of cardiac tumor may have been attributed to other causes for a substantial time. Approximately 86 percent of myxomas occur in the left atrium, and more than 90 percent are solitary[5] [8] (see Fig. 49-2) . In the left atrium, the usual site of attachment is in the area of the fossa ovalis. Myxomas also may occur in the right atrium and, less often, in the right or left ventricle. Several tumors may occur in the same chamber or in a combination of chambers. Although myxomas may occasionally be found on the posterior left atrial wall, tumors presenting in this location should raise the suspicion of malignancy. Myxomas of the mitral and tricuspid valves have been reported.[49] [54]

The clinical signs and symptoms produced by cardiac myxomas include nonspecific manifestations as already discussed, embolization, and mechanical interference with cardiac function (see Table 49-1) . Not surprisingly, the symptoms produced by cardiac myxomas may simulate a wide variety of other cardiac and noncardiac conditions (see Table 49-2) .

FAMILIAL MYXOMAS.

Familial cardiac myxomas constitute approximately 10 percent or less of all myxomas and appear to have an autosomal dominant transmission.[1] [55] [56] [57] Some patients with cardiac myxoma have a syndrome, frequently called "syndrome myxoma" or "Carney's syndrome," that also consists of (1) myxomas in other locations (breast or skin), (2) spotty pigmentation (lentigines, pigmented nevi, or both) (Fig. 49-3), and (3) endocrine overactivity (pituitary adenoma, primary pigmented nodular adrenocortical disease, or testicular tumors involving the endocrine components).[58] [59] [60] [60A] [60B] Patients with Carney's syndrome tend to be younger (mean age, 20's), are more likely to have myxomas in locations other than the left atrium, sometimes have bilateral tumors, and are more likely to develop recurrences (Table 49-5) .

Although the cause of the syndrome myxoma is unknown, it has been proposed to result from a widespread abnormality resulting in excessive proliferation of certain mesenchymal cells, and excessive glycosaminoglycans production by them, possibly analogous to the neural masses in von Recklinghausen's neurofibromatosis.[61] Patients may have two or more components of this complex, and the first component generally is diagnosed at a relatively young age (mean age, 18 years). Some patients have been

said to have the NAME syndrome (*n*evi, *a*trial myxoma, *m*yxoid neurofibroma, *e*phelides) [57] [62] or the LAMB syndrome (*l*entigines, *a*trial *m*yxoma, and *b*lue nevi).[63]

Figure 49-3 Four patients with extensive facial freckling, a finding associated with syndrome myxoma. Patients with this syndrome tend to be younger than patients with sporadic myxoma and have a substantially higher incidence of ventricular, multiple, biatrial, recurrent, and familial myxomas of the heart. In addition, these patients, in contrast to patients with sporadic myxoma, may have noncardiac myxomas and endocrine neoplasms. (From Vidaillet HJ Jr, Seward JB, Fyke FE, et al: "Syndrome myxoma": A subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms. Br Heart J 57:247, 1987.)

TABLE 49-5 -- COMPARISON OF THE CLINICAL FEATURES OF SPORADIC MYXOMA AND SYNDROME MYXOMA

FEATURE	SPORADIC	SYNDROME
Age (yr) (range)	56 (39-82)	25 (10-56)
Female/male ratio	2.7:1	1.8:1
Patients (no.)	70	44
Cardiac myxomas (no.)	72	103
Distributions of myxomas (%)		
Atrial/ventricular	100/0	87/13
Single/multiple	99/1	50/50
Biatrial	0	23
Recurrent	0	18
Familial	0	27
Freckling (%)	0	68
Noncardiac tumors (%)	0	57
Endocrine neoplasm (%)	0	30

From Vidaillet HJ Jr, Seward JB, Fyke FE: "Syndrome myxoma": A subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasma. Br Heart J 57:247, 1987.

Because cardiac myxomas can be familial, routine echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young or has many tumors. In one study, screening of families of six patients with familial myxoma yielded four close relatives with cardiac myxoma.[64] Moreover, in patients who have a familial

history or other components of the previously described syndrome and who are undergoing resection, a careful search should be made preoperatively for several cardiac myxomas. Postoperatively, these patients should be observed closely for the development of other tumors; this occurs in 12 to 22 percent of such patients.[65] The pathological features of familial myxomas do not differ from those occurring sporadically (discussed later).[66]

PATHOLOGY.

Most cardiac myxomas are received by the pathologist as surgically excised specimens that have been removed because of clinical symptoms. Rarely, cardiac myxomas are encountered incidentally at autopsy. The pathological characteristics of myxomas are well described and are independent of location.[1] [54] [67] [68] [69]

Gross Pathology.

Myxomas are gelatinous (often termed myxoid), smooth, and round, with a glistening surface, or they may be variably friable and either irregular or polypoid (see Fig. 49-3). They are either sessile or pedunculated with a distinct stalk, which may be narrow or broad. In approximately 90 percent of cases arising in the atria, the base of attachment is the atrial septum, usually in the region of the limbus of the fossa ovalis. In approximately 10 percent of cases, the point of origin is the posterior or anterior atrial wall or atrial appendage; valvular myxomas are rare. Cardiac myxomas can be multicentric. Areas of hemorrhage are frequent. The tumors average 4 to 8 cm in diameter but range from less than 1 cm to 15 cm or greater.

Histology.

The diagnosis of myxoma is made by the observation of characteristic patterns of cells (often called "lipidic" cells) embedded in a myxoid stroma rich in glycosaminoglycans (Fig. 49-4) .[67] [68] [69] Myxoma cells have a round, elongated, or polyhedral shape; scant pink cytoplasm; and an ovoid nucleus with an open chromatin pattern. They are occasionally multinuclear. Although they may be present individually, myxoma cells are typically present as cords, rings, or florets, sometimes as many layers surrounding vascular structures. Diagnosis of myxoma requires the presence of characteristic isolated or clustered collections of myxoma cells. Hemorrhages; macrophages; often containing iron pigment; lymphocytes; and plasma cells are variably present. Calcification is present in approximately 10 to 20 percent of cardiac myxomas. Extramedullary hematopoiesis, which comprises glandular structures lined by mucin-filled goblet cells,[70] and cellular atypia may be present in a minority of cases; these features may simulate malignancy. Because emboli from myxomas usually derive from the most superficial portions, they may have less definitive histological features than the intracardiac lesion from which they originated.

Ultrastructural and Immunohistochemical Findings.

Myxoma cells have abundant fine cytoplasmic filaments similar to those of smooth

muscle cells.[69] The cells most resemble embryonic mesenchymal cells with multipotential capabilities for cellular differentiation, including vasoformative activity and expression of vascular endothelial growth factor,[69A] and are especially similar to embryonic endocardial cushion tissue.[71] *Immunohistochemical studies* demonstrate variable positivity for the endothelial cell markers factor VIII-related antigen and *Ulex europaeus.* More consistent positivity is obtained when myxomas are stained for *vimentin,* indicative of the mesenchymal derivation of the cells, as well as some neuroendocrine markers and smooth muscle cell antigens. Analysis by immunohistochemistry has not been useful for either diagnostic purposes or elucidation of histogenesis.

Embolization.

Although myxomas or other benign cardiac tumors can cause death due to coronary or cerebral embolization,[72] metastatic tumor implantation with wasting is rare. Occasional reports suggest that myxomas may have a malignant counterpart, with local invasion of the interatrial septum, recurrence, or metastasis.[72A] However, some cases of purported malignancy probably represent malignant tumors of other types with extensive areas of myxoid degeneration or of multicentricity that was not appreciated; others may represent inadequate excision or embolization of benign lesions.

Many of the morphological features of organizing mural thrombi resemble those of myxoma, including abundant loose amorphous extracellular matrix, connective tissue cells, and small vascular channels. It is difficult to distinguish between some myxomas and mural thrombi in various stages of organization; indeed, cellular intracardiac thrombi and peripheral thromboemboli occasionally receive an erroneous diagnosis of myxoma. The resemblance to organizing/organized thrombi has been put forth as evidence that myxomas have a thrombotic origin,[73] but most investigators currently find this notion untenable.[67] [71]

Histogenesis.

The histogenesis of cardiac myxomas is uncertain, but the weight of evidence favors benign neoplasia, with the tumor probably originating from subendocardial nests of primitive mesenchymal cells that may differentiate into several cell types, including endothelial and lipidic cells. Cytogenetic analyses demonstrating clonal chromosomal abnormalities provide the best support for this concept. Sporadic and familial atrial myxomas have been shown to have heterogeneous clonal telomeric rearrangements and other chromosome abnormalities primarily involving chromosomes 2, 12, and 17; a telomeric association between chromosomes 13 and 15, a rearrangement in 1q32, and loss of the Y chromosome have also been reported.[74] [75] [76] [77] [78] [79] [80] Linkage analysis of 11 kindreds affected by Carney's syndrome yielded a chromosomal locus for this disorder mapping to the short arm of chromosome 2 within a 6.4-cM interval (2p16).[74] A gene defect on chromosome 17q (17q2) was associated with Carney's complex in four unrelated families.[76] A most convincing case of clonal structural aberrations was reported by Dijkhuizen and colleagues[80] who found that a cardiac myxoma from a 48-year-old man had normal chromosome number but a complex clonal rearrangement, which included a breakpoint at 12p12, the location of the *Ki-ras*

oncogene. The researchers speculated that *Ki-ras* might have a role in the origin of cardiac myxoma. Although myocardial hypertrophy and failure as well as endocrine abnormalities such as pituitary and thyroid tumors have been associated with alterations in the heterotrimeric

Figure 49-4 Characteristic histological features of myxoma. *A,* Low-power view demonstrating individual tumor cells, clusters, and islands scattered throughout the characteristic pale-staining granular extracellular matrix. Hemorrhage is present at upper left. Scattered inflammatory cells are also present. *B,* Medium-power view, demonstrating groups of polygonal myxoma cells. *C,* High-magnification view, showing individual variably rounded to elongated myxoma cells, some arranged in cords (arrows). *A,* 50×; *B,* 175×; *C,* 400×; all stained with hematoxylin and eosin.

guanosine triphosphate-binding proteins, activating Gsalpha mutations have not been found in either atrial myxomas or other tumors from patients with Carney's complex.[81] The presence of aneuploidy in some cardiac myxomas provides additional support for the concept of a neoplastic origin.[82]

Before the discussion of nonmyxomatous cardiac tumors is continued later, it should be noted that peculiar microscopic-sized cellular cardiac lesions have been noted incidentally as part of endomyocardial biopsy or surgically removed tissue specimens or at cardiac surgery; these lesions are free floating or loosely attached to a valvular or endocardial mass.[83] [84] Not neoplastic, they have been termed mesothelial monocytic incidental cardiac excrescences (MICE). Histologically, such lesions are composed largely of clusters and ribbons of mesothelial cells and entrapped erythrocytes and leukocytes embedded within a fibrin mesh. Previously considered to be a reactive mesothelial and/or monocytic (histiocytic) hyperplasia, they are now considered to be common artifacts--formed by compaction of mesothelial strips (likely from the pericardium) or other tissue debris and fibrin that are transported via catheters or around an operative site on a cardiotomy suction tip.[85] Such tissue fragments are of importance only in that they should not be confused with metastatic carcinoma.

PAPILLARY TUMORS OF HEART VALVES (PAPILLARY FIBROELASTOMA).

The most common tumors of the cardiac valves, papillary fibroelastomas of the cardiac valves and adjacent endocardium, are not uncommonly found postmortem and may be identified during life by two-dimensional echocardiography.[86] [87] Although many are clinically insignificant, they have the potential to embolize to vital structures [88, 89] or to cause valvular dysfunction, and those on the aortic valve can partially obstruct a coronary arterial orifice.[90] These lesions have a characteristic frondlike appearance resembling a sea anemone. They may be single or numerous; up to 3 or 4 cm in diameter; and occur on any valve or on papillary muscle, chordae tendineae, or endocardium, usually attached by a short pedicle (Fig. 49-5) . Most often, the ventricular surface of semilunar valves and the atrial surface of AV valves are affected. The

tricuspid valve is most commonly involved in children, and the mitral and aortic valves in adults. Histologically, the tumor is covered by endothelium that surrounds a core of loose connective tissue rich in glycosaminoglycans, collagen, and elastic fibers and containing smooth muscle cells (often as a fine meshwork surrounding a central collagen or dense elastic fiber core).

Pathogenesis.

The pathogenesis of these lesions is uncertain, but it appears that they may originate secondary to endocardial trauma and/or the organization of mural thrombi.[73] Papillary tumors are generally distinguished from Lambi's excrescences, which are acellular deposits of thrombus and connective tissue covered by a single layer of endothelium and are found on heart valves at the site of endothellal damage in many adults, particularly along the closure margins of the aortic valve cusps. In contrast, papillary fibroelastomas are unusually found at valvular contact areas.

RHABDOMYOMAS.

These are the most common cardiac tumors of infants and children; approximately three-fourths occur in patients younger than 1 year.[91] [92] They occur with equal frequency in the left and right ventricular and septal myocardium; nearly all are multiple. Approximately one-third also involve either one or both atria. In approximately half of affected patients, at least one of the tumors is intracavitary and obstructive. Nonspecific clinical manifestations, including cardiomegaly; right or left ventricular failure or both; and an S_3 , S_4 , and systolic or diastolic murmurs, may mimic mitral stenosis, mitral atresia, aortic stenosis, subaortic stenosis, or infundibular pulmonic stenosis.

Association with Tuberous Sclerosis.

Rhabdomyomas are strongly associated with tuberous sclerosis, a familial syndrome characterized by hamartomas in several organs, epilepsy, mental deficiency, and adenoma sebaceum.[93] [94] [95] One study indicated that at least 80 percent

Figure 49-5 Papillary fibroelastoma. *A,* Gross photograph demonstrating resemblance of this lesion to a sea anemone, with myriad papillary fronds, arising from the chordae tendineae near the mitral leaflet. In this case, many lesions were present, all associated with the mitral valve apparatus. *B,* Histological appearance of papillary fibroelastoma, demonstrating the numerous papillary fronds consisting of a collagen core surrounded by elastic fibers and loose connective tissue, all covered by endocardial endothelium. 100×; stained with elastica van Gieson stain (elastin black).

of patients with cardiac rhabdomyomas have tuberous sclerosis, and 60 percent of patients less than 18 years old with tuberous sclerosis have cardiac rhabdomyomas.[95]

Conversely, approximately 50 percent or more of patients having tuberous sclerosis but no signs or symptoms of cardiac disease have been shown to have echocardiographic findings that are consistent with one or more rhabdomyomas. Rhabdomyomas causing significant intracavity obstruction may result in death within the first 24 hours of life, whereas patients with less severe involvement may either remain asymptomatic or have difficulty during infancy or early childhood.

Pathology.

Rhabdomyomas are yellow-gray and range from 1 mm to several centimeters in diameter. They are circumscribed but not encapsulated; microscopically, they are easily distinguished from the surrounding myocardium as clusters of abnormal cells. The microscopic hallmark, termed the *spider cell,* is a large (up to 80-mum diameter) cell containing a central cytoplasmic mass that is suspended by fine fibrillar processes radiating to the periphery, thus giving the appearance of a spider hanging in a net. Such cells are sufficiently characteristic that the tumor may be diagnosed by fine-needle aspiration.[96] The cytoplasm is rich in glycogen and stains positively with periodic acid-Schiff reagent. Electron microscopy demonstrates myofibrils, cytoplasmic and mitochondrial glycogen, and apparent intercellular junctions similar to intercalated discs. Immunohistochemistry reveals diffuse positivity for myoglobin, actin, desmin, and vimentin and the absence of neuroendocrine markers, similar to the staining pattern of the adjacent cardiac muscle. Evidence suggests that rhabdomyomas are actually myocardial hamartomas or malformations rather than true neoplasms. In support of this concept is their multiple occurrence and preponderance in children, especially in those with tuberous scierosis.

FIBROMAS.

Fibromas are benign connective tissue tumors that occur predominantly in children and constitute the second most common type of primary cardiac tumor occurring in the pediatric age group.[97] The majority occur before the age of 10 years, and about 40 percent are diagnosed in infants younger than 1 year. Males and females appear to be equally affected. Derived from fibroblasts and considered low-grade connective tissue tumors, cardiac fibromas resemble and have the same biological behavior as soft tissue fibromatoses at other sites.

Pathology.

Almost all cardiac fibromas occur within the ventricular myocardium, most frequently within the anterior free wall of the left ventricle or the interventricular septum and much less often in the posterior left ventricular wall or right ventricle. They typically are gray, firm, circumscribed, and not encapsulated and range in size from 3 to 10 cm. Grossly, they exhibit a whoried appearance on cut sections. Microscopically, cardiac fibromas consist of elongated fibroblasts admixed with fibrous tissue consisting mostly of collagen. Their cellularity is variable, and mitotic figures are rarely, if ever, seen. Fibrous tissue is intermingled with adjacent myocardial fibers at the margins of the lesion. Calcification and islands of bone formation may be seen microscopically and occasionally radiographically. The *Gorlin syndrome,* the main features of which are

multiple nevoid basal cell carcinomas, cysts of the jaw, and skeletal abnormalities, may be associated in some cases with cardiac tumors, either fibromas or fibrous histiocytomas.[98]

Clinical Manifestations.

Although fibromas may be incidental findings at postmortem examination, approximately 70 percent at some time cause mechanical interference with intracardiac flow, ventricular contraction abnormalities, or conduction disturbances. Clinical manifestations are protean and include murmurs, atypical chest pain, congestive heart failure and signs of subaortic stenosis, valvular or infundibular pulmonic stenosis with right ventricular hypertrophy, tricuspid stenosis, conduction disturbances, ventricular tachycardia, and sudden death. As in the case of rhabdomyomas, the increased use of echocardiography has rarely resulted in the detection of cardiac fibromas in patients without cardiac signs or symptoms. Surgical excision of cardiac fibromas may be possible.[99] [100]

LIPOMAS AND LIPOMATOUS HYPERTROPHY OF THE ATRIAL SEPTUM.

Lipomas occur at all ages and with equal frequency in both sexes. Most range in diameter from 1 to 15 cm, although some have been reported to weigh more than 2 kg. Most tumors are sessile or polypoid and occur in the subendocardium or subpericardium, although about one-fourth are completely intramuscular. Subendocardial tumors with intracavity extension produce symptoms that are characteristic of their location, whereas subepicardial tumors may cause compression of the heart and pericardial effusion. The most common chambers affected are the left ventricle, right atrium, and interatrial septum. Intramural tumors may be asymptomatic or result in arrhythmias, AV or intraventricular conduction disturbances, or mechanical interference. Many tumors are clinically silent, however, and are found only at autopsy or become apparent on a routine chest roentgenogram.

Microscopically, the lesions are usually well encapsulated and composed of typical mature fat cells; they occasionally contain fibrous connective tissue (fibrolipoma), muscular tissue (myolipoma), or vacuolated brown (fetal) fat, resembling a hibernoma.

Whereas lipomas are true neoplasms, a condition termed *lipomatous hypertrophy of the interatrial septum* represents the occurrence

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of a nonencapsulated hyperplastic accumulation of mature and fetal adipose tissue within the interatrial septum. These lesions range from 1 to 7 cm in dimension, most often protrude into the right atrium, and are more common in obese, elderly, or female patients.[101] Various atrial arrhythmias have been attributed to these lesions, but a cause-and-effect relationship has been difficult to establish.[101] Because this lesion may occasionally be detected by cineangiography, echocardiography, CT, or other diagnostic techniques, the major clinical dilemma is the differential diagnosis and

treatment of an intraatrial filling defect.

ANGIOMAS.

Composed of benign proliferations of endothelial cells, hemangiomas and lymphangiomas are extremely rare.[102] Anatomically, they may occur in any part of the heart, but usually they are intramural, often in the interventricular septum or AV node, where they may cause complete heart block and sudden death. Cardiac tamponade due to hemopericardium may be the presenting clinical syndrome. More commonly found in the right heart chambers, hemangiomas are red, hemorrhagic, generally sessile or polypoid subendocardial nodules, ranging from 2 to 4 cm in diameter. Histologically, the tumors consist of endothelium-lined spaces that may contain blood, lymph, or thrombi; they are classified according to the predominant type of proliferating vascular channel. Dilated, often thrombosed, subendocardial blood vessels (varices) are frequently mistaken for hemangiomas; they are usually found incidentally.

TERATOMAS.

These tumors, which contain elements of all three germ cell layers, occur within the heart less frequently than in the anterior mediastinum.[103] Teratomas are generally observed in children, and when located within the heart, they occur predominantly within the right atrium, right ventricle, or the interatrial or interventricular septum.

CYSTIC TUMOR ("MESOTHELIOMA") OF THE ATRIOVENTRICULAR NODE.

Of controversial histogenesis, these small tumors (usually <15 mm in largest dimension) frequently cause death by complete heart block, ventricular fibrillation,[41] or cardiac tamponade.[104] They occur in patients of virtually any age as poorly circumscribed, often multicystic nodules in the atrial septum, immediately cephalad to the commissure of the septal and anterior leaflets of the tricuspid valve, in the region of the AV node. These lesions are characterized by tubules and cysts lined by flat or cuboidal cells that are devoid of mitotic activity but may have secretory function. Although they are often considered to be derived from mesothelial rests, similar to the adenomatoid tumors of the ovary and testis that they resemble histologically, studies have suggested an endodermal rather than mesothelial origin.[105] [106]

ENDOCRINE TUMORS OF THE HEART.

Approximately 2 percent of *paragangliomas* are intrathoracic, and of these, most are located in the posterior mediastinum. However, these tumors can also occur in close association with the left atrial or left ventricular epicardium, where they are thought to have arisen from sympathetic fibers to the heart or from ectopic chromaffin cells. More rarely still, paragangliomas may arise within the interatrial septum. Tumors in any of these locations may secrete catecholamines and therefore can be associated with signs and symptoms characteristic of pheochromocytoma.[107]

Rarely, benign *thyroid tumors* arise within the heart, presumably from ectopic rests of

thyroid tissue.[107A] These tumors most often arise from the interventricular septum and present, not infrequently, as obstruction to right ventricular outflow.

Malignant Cardiac Tumors

About one-fourth of all cardiac tumors exhibit malignant histological characteristics and invasive or metastatic behavior. Nearly all of these are sarcomas, thus making these tumors second only to myxomas in overall frequency. Sarcomas may occur at any age but are most common between the third and fifth decades; they are distinctly unusual in infants and children and show no sex preference. In decreasing order of frequency, the sites involved are the right atrium, left atrium, right ventricle, left ventricle, and interventricular septum.

Sarcomas derive from mesenchyme and therefore may display a wide variety of morphological types, including angiosarcoma, rhabdomyosarcoma, fibrosarcoma, osteosarcoma, and others.[108] [109] [110]

From a clinical viewpoint, sarcomas characteristically display a rapid downhill course. Death most often occurs from a few weeks to 2 years after the onset of symptoms. These tumors proliferate rapidly and generally cause death through widespread infiltration of the myocardium, obstruction of flow within the heart, or distant metastases. About 75 percent of all patients with cardiac sarcomas have pathological evidence of distant metastases at the time of death.[111] [112] The most frequent sites are the lungs, thoracic lymph nodes, mediastinum, and vertebral column; the liver, kidneys, adrenals, pancreas, bone, spleen, and bowel are less often involved.

The cardiac findings are determined primarily by the location of the tumor and by the extent of intracavitary obstruction. Typical presentations include progressive, unexplained congestive heart failure, particularly of the right side; precordial pain; pericardial effusion; tamponade; arrhythmias; conduction disturbances; obstruction of the venae cavae; and sudden death. Tumors limited to the myocardium without intracavitary extension may produce no cardiac symptoms or may cause arrhythmias and conduction disturbances. Because of the rapid growth potential of sarcomas, they commonly extend into the cardiac chambers, the pericardial space, or both. In about 20 percent of cases, the tumor is sessile or polypoid. When there is extension into the pericardial space, hemorrhagic pericardial effusion is common and tamponade may occur. Because the right side of the heart is most commonly affected, sarcomas frequently cause signs of right-sided heart failure as a result of obstruction of the right atrium, right ventricle, or tricuspid or pulmonic valves. In addition, obstruction of the superior vena cava may result in swelling of the face and upper extremities, whereas obstruction of the inferior vena cava may result in visceral congestion.

ANGIOSARCOMAS.

Included within this category are angiosarcomas and Kaposi's sarcomas.[113] [114] [114A] [114B] All 40 patients in one series were adults. In distinction to most other cardiac sarcomas, in which the sex distribution is equal, there appears to be a 2:1 male-to-female ratio among patients with angiosarcomas. These tumors have a striking predilection for the

right atrium (Fig. 49-6) and may be infiltrative or polypoid in nature. Microscopically, angiosarcomas are characterized by ill-defined but variable anastomotic vascular channels lined with atypical, often heaped-up, endothelial cells. By electron microscopy, immature endothelial cells, primitive pericytes, and undifferentiated mesenchymal cells may be identified.[115]

RHABDOMYOSARCOMAS.

These tumors of striated muscle often diffusely infiltrate the myocardium but may also, on occasion, form a

Figure 49-6 Massive pericardial angiosarcoma, with deep myocardial invasion at several sites (arrowheads), particularly at the right atrium (arrow). (From Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.)

polypoid extension into the cardiac chambers and therefore have been clinically mistaken for myxoma.[116] Rhabdomyoblasts (cross-striations by light microscopy; thick and thin filaments and Z-band material by electron microscopy) are the histological hallmark of this tumor, and 20 to 30 percent of the tumors have cross-striations.

FIBROSARCOMAS AND MALIGNANT FIBROUS HISTIOCYTOMAS.

Fibrosarcomas of the heart have a whitish, soft "fish flesh" consistency characteristic of these tumor types elsewhere in the body.[117] Fibroblastic in differentiation, they are composed of spindle-shaped cells with elongated blunt-ended nuclei and frequent mitoses. They may contain areas of hemorrhage and necrosis and extensively infiltrate the heart, often involving more than one cardiac chamber. A thrombus may form in an obstructed pulmonary vein, in the vena cava, or over the mural surface of the tumor.

LYMPHOMAS.

Although cardiac involvement of a systemic lymphoma has been reported in 25 to 36 percent of cases, primary lymphoma involving only the heart or pericardium is much less common.[116] [118] Myocardial infiltration by lymphoma may be nodular or diffuse, and the clinical syndrome of hypertrophic cardiomyopathy has been mimicked. Some of these tumors are predominantly intracavitary.

PULMONARY ARTERY SARCOMAS.

Sarcomas of the pulmonary artery trunk, main branches, or pulmonic valves may present as tumor emboli to the lungs or as right ventricular outflow obstruction.[119]

These tumors usually present after the fourth decade, show a 2:1 female predominance, and may originate from undifferentiated tissue of the bulbis cordis. Typical symptoms include dyspnea, chest pain, cough, and hemoptysis and may be associated with radiographic findings of a pulmonary hilar mass or cardiomegaly. Right ventricular injection of contrast material helps to delineate the tumor. Although most reported cases were previously diagnosed at autopsy, it is likely that early diagnosis, surgical resection, and possibly chemotherapy may have an impact on survival of future patients with this tumor.[120]

DIAGNOSTIC TECHNIQUES

Although certain clinical manifestations can be suggestive of a cardiac tumor, no clinical finding or set of findings is pathognomonic. Furthermore, the majority of cardiac tumors produce signs and symptoms typical of the common forms of heart disease. The development of modern diagnostic methods has had a major impact on the diagnosis and hence the natural history of cardiac tumors. It is not unusual for cardiac tumors to be diagnosed and cured in patients who are totally asymptomatic or without signs of cardiovascular disease.[121] Although cardiac catheterization made possible the definitive preoperative diagnosis of cardiac tumors, it was not until the advent of echocardiography that it was feasible to evaluate all patients suspected of having this diagnosis. Both M-mode and two-dimensional echocardiography are effective screening techniques. However, two-dimensional echocardiography, and particularly transesophageal imaging (Fig. 49-7), is more sensitive and provides considerably more information about the site of tumor attachment, pattern of tumor movement, and size. In many centers, the information provided by two-dimensional echocardiography (see Chap. 7) , CT, or MRI (see Chap. 10) (Fig. 49-8) is considered sufficient to proceed directly to surgery without cardiac catheterization and angiography. However, catheterization and angiography should not be omitted in the absence of a technically adequate two-dimensional echocardiographic study, CT, or MRI that has visualized all four cardiac chambers.

It is imperative that noninvasive evaluation, preferably by two-dimensional echocardiography (or CT or MRI), be performed before cardiac catheterization whenever the diagnosis of cardiac tumor is considered. When left atrial myxoma is suspected, it is safest to visualize the left atrium by injecting the contrast agent into the pulmonary artery and film during the levophase. It is particularly important to avoid the transseptal approach, because this risks dislodgement of fragments of tumor that may be attached in the region of the fossa ovalis. Furthermore, because cardiac tumors may be numerous and present in more than one chamber, all four chambers should be visualized noninvasively before cardiac catheterization whenever possible.

Clinical and Noninvasive Methods

CLINICAL EXAMINATION.

When valvular or myocardial disease is suspected on clinical grounds, certain atypical findings can raise the suspicion of cardiac tumor. The intensity of the systolic or diastolic murmur caused by a left atrial myxoma is often exquisitely sensitive to positional

change, a finding atypical of valvular heart disease. S_1 may be delayed as a consequence of an elevated left atrial pressure, as in mitral stenosis. It is often intense and widely split, and an early systolic sound may occur, representing tumor movement toward the atrium during systole. In addition, a tumor plop may be present about 100 msec after S_2 ; it appears to result from the sudden tension of the tumor stalk as it prolapses into the left ventricle during diastole or from the tumor striking the myocardium. The tumor plop *precedes* the end of the rapid filling wave of the apexcardiogram and can thereby be differentiated from an S_3 ; as noted, it usually occurs later than an opening snap. Systolic time intervals are usually consistent with a reduced stroke

Figure 49-7 Transthoracic two-dimensional echocardiogram *(A)* and transesophageal two-dimensional echocardiogram *(B)* showing a left atrial (LA) mass prolapsing into and obstructing the mitral valve orifice. Note the superior resolution of the transesophageal echocardiogram. Although not visible here, the myxoma was attached to the midportion of the atrial septum. (From Allard MF, Taylor GP, Wilson JE, McManus BM: Primary cardiac tumors. *In* Goldhaber SZ, Braunwald E [eds]: Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 15.1-15.22.)

Figure 49-8 Magnetic resonance images illustrating a large tumor in the right ventricular apex, impinging on the apical septum. In the coronal view *(A),* the prominent mass indents the septum. In the axial views, the tumor shows areas of tissue inhomogeneity *(B)* and indents the ventricular septum *(C).* (From Allard MF, Taylor GP, Wilson JE, McManus BM: Primary cardiac tumors. *In* Goldhaber SZ, Braunwald E [eds]: Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 15.1-15.22.)

volume. Apexcardiography often shows a deep notch on the upstroke, which occurs at the time of extrusion of the tumor through the mitral valve in early systole.

Right atrial tumors may also result in a widely split S_1 and an early systolic sound. The S_2 may be paradoxically split as a result of early pulmonic valve closure. A tumor plop and systolic and diastolic murmurs, which are increased by inspiration, may also occur with right atrial tumors. The jugular venous pulse tracing may reflect obstruction of the tricuspid orifice, demonstrating an accentuated *a* wave, attenuation of the *x* descent, or an early, broad *v* wave.

RADIOLOGICAL EXAMINATION

Cardiac tumors may display several findings on plain chest roentgenograms. These include alterations in cardiac contour, changes in overall cardiac size, specific chamber enlargement, alterations in pulmonary vascularity, and intracardiac calcification (see

Chap. 8) . The cardiac contour may be normal, may display generalized or specific chamber enlargement that mimics virtually any type of valvular heart disease, or may demonstrate a bizarre appearance. Pericardial effusions are rather common and generally indicate invasion of the pericardial space by a malignant tumor. Mediastinal widening, due to hilar and paramediastinal adenopathy, may indicate spread of a malignant cardiac tumor. A bumpy, irregular, or fuzzy cardiac border may be seen when the pericardium is involved. Cardiac enlargement may reflect rapid tumor growth, particularly in the case of sarcomas, whereas specific chamber enlargement is frequently due to intracavitary obstruction, particularly by pedunculated tumors such as myxomas. Thus, left atrial myxoma may produce the radiological pattern characteristic of mitral stenosis. A large tumor mass occasionally displaces the heart and may simulate enlargement of a specific chamber.

Calcification visible by roentgenographic methods may occur with several types of cardiac tumor, including rhabdomyomas, fibromas, hamartomas, teratomas, myxomas, and angiomas. Visualization of intracardiac calcium in an infant or a child is unusual and should immediately raise the question of an intracardiac tumor. Cardiac fluoroscopy and laminography may be helpful in differentiating calcification of cardiac tumor from that of other structures, such as cardiac valves, coronary arteries, pericardium, and mural thrombus. Calcified atrial polypoid tumors may occasionally be seen to prolapse into the ventricle during diastole. Fluoroscopy is also useful in differentiating cardiac tumor from ventricular aneurysm, both of which may result in a localized protrusion on plain chest roentgenograms. However, on fluoroscopic examination, cardiac tumors do not display the paradoxical motion during ventricular contraction that is characteristic of ventricular aneurysm.

ECHOCARDIOGRAPHY.

Two-dimensional echocardiography provides substantial advantages over conventional M-mode echocardiography for the diagnosis and preoperative evaluation of intracardiac tumors.[5] In the majority of cases of cardiac tumors, the information provided by two-dimensional echocardiography provides adequate information about tumor size, attachment, and mobility to allow operative resection without preoperative angiography. This technique is sensitive for detection of small tumors and is especially useful for detection of left ventricular tumors and tumors that do not prolapse through the mitral or tricuspid valve orifices (see Figs. 49-7 and 7-115) .

Left atrial myxomas have been classified by their echocardiographic appearance as follows: Class I tumors are small and prolapse through the mitral valve; class II tumors are small and nonprolapsing; class III tumors are large and prolapse; and class IV tumors are large and nonprolapsing.[122]

The increased sensitivity of two-dimensional echocardiography makes possible the diagnosis of cardiac tumors in neonates and in utero.[123] The improved diagnostic power

and widespread use of two-dimensional echocardiography have resulted in an increase in the detection of primary cardiac tumors,[121] in many cases before the onset of clinical signs or symptoms.

Two-dimensional echocardiography may facilitate the differentiation between left atrial thrombus and myxoma, because the former typically produces a layered appearance and is generally situated in the posterior portion of the atrium whereas the latter is often mottled in appearance and rarely occurs in the posterior portion of the atrium. In some atrial myxomas, areas of echolucency may be seen within the tumor mass, corresponding to areas of hemorrhage within the tumor. Because these areas of echolucency are not found in thrombotic or infective lesions, this finding may be of value in the differential diagnosis of an intraatrial mass. Continuous-mode Doppler ultrasonography may be useful for evaluating the hemodynamic consequences of valvular obstruction or incompetence caused by cardiac tumors.[124]

Transesophageal Echocardiography.

This approach provides an unimpeded view of both atria and the atrial septum and appears to be superior to transthoracic echocardiography in many patients.[125] The potential advantages of transesophageal echocardiography include improved resolution of the tumor and its attachment (see Figs. 49-7 and 7-115), the ability to detect some masses not visualized by transthoracic echocardiography, and improved visualization of right atrial tumors. In 17 patients suspected of having a cardiac tumor, transthoracic echocardiography yielded four false positives and two false negatives, whereas transesophageal echocardiography resulted in only one false positive and no false negatives.[126] In the same series, transesophageal echocardiography proved to be superior for visualizing anatomical details such as tumor contour, cysts, and calcification and identified a stalk in 10 of 11 tumors subsequently shown to have a stalk at surgery, whereas transthoracic echocardiography identified a stalk in only 5 of the 11 tumors. Transesophageal echocardiography has been used to guide percutaneous biopsy of a right atrial myxoma.[127] Although transesophageal echocardiography does not appear warranted on a routine basis, it should be considered when the transthoracic study is suboptimal or confusing.

RADIONUCLIDE IMAGING.

Gated blood pool scanning has been used to identify atrial, ventricular, and intramural tumors.[128] Radionuclide ventriculography generally has a lower rate of resolution than does echocardiography or contrast injection angiography and therefore may be less sensitive for detecting small filling defects. In some cases in which the cardiac tumor was not evident by routine static or dynamic radionuclide imaging, it has been possible to delineate the tumor and its movement during a cardiac cycle by use of a computer-generated composite functional image.[128]

COMPUTED TOMOGRAPHY.

CT of the heart has been used to demonstrate cardiac tumors (see Fig. 10-47) .[129]

Although more experience will be necessary to establish its role, certain advantages are apparent. These include a high degree of tissue discrimination, which may allow definition of the degree of intramural tumor extension; evaluation of the extracardiac structures; and the ability to construct images in any plane. Resolution appears to be improved substantially by gating the computed tomographic acquisition to the cardiac cycle. CT currently appears to be most useful in the evaluation of suspected tumors of the heart to determine the degree of myocardial invasion and the involvement of pericardial and extracardiac structures. Ultrafast CT, a technique that uses electron beam technology, has a short scanning acquisition time that eliminates the motion artifacts occurring with conventional CT and appears to be useful for assessment of intracardiac masses.[129]

MAGNETIC RESONANCE IMAGING.

MRI may be of considerable value in detecting and delineating cardiac tumors and in some cases may depict the size, shape, and surface characteristics of the tumor more clearly than two-dimensional echocardiography.[130] The larger field of view with MRI (see Figs. 49-8, 10-20, and 10-21) provides better definition of tumor prolapse, secondary valve obstruction, and cardiac chamber size than does two-dimensional echocardiography. Contrast enhancement with gadolinium-diethylenetriaminepentaacetic acid and multislice imaging in the transaxial, sagittal, and long axes can provide precise three-dimensional information. MRI can also provide information about tissue composition that can help to differentiate tumors from thrombi.[131]

Angiography

Cardiac catheterization and selective angiocardiography are not necessary in all cases of cardiac tumors, because as already discussed, in many cases adequate preoperative information may be obtained by echocardiography, CT, or MRI. In several circumstances, however, the risk and expense of cardiac catheterization are outweighed by the supplemental information it may provide. These situations include cases in which (1) noninvasive evaluation has not been adequate in fully defining tumor location or attachment; (2) all four cardiac chambers have not been adequately visualized noninvasively; (3) a malignant cardiac tumor is considered likely; or (4) other cardiac lesions may coexist with a cardiac tumor and possibly dictate a different surgical approach. For instance, when a malignant cardiac tumor is suspected, cardiac angiography may provide valuable information about the degree of myocardial, vascular, and/or pericardial invasion. Likewise, in certain cases, such as the presence of pulmonary hypertension or the coexistence of significant valvular or coronary artery lesions, cardiac catheterization and angiography may provide information that significantly affects the surgical approach.[132]

The major angiographic findings in patients with cardiac tumors include (1) compression or displacement of cardiac chambers or large vessels, (2) deformity of cardiac chambers, (3) intracavitary filling defects, (4) marked variations in myocardial thickness, (5) pericardial effusion, and (6) local alterations in wall motion. Displacement of the cardiac chambers or the great vessels without deformation of the internal contour may

be observed in both benign and malignant tumors, whereas deformation of a cardiac chamber usually indicates an infiltrating malignant lesion. The most frequent angiographic findings are intracavitary filling defects, which may be either fixed or mobile. Fixed defects may be lobulated or appear as a coarse nodularity of the myocardium that is often difficult to distinguish from a mural thrombus. Such defects may reflect endocardial tumors with broad attachments or intramural tumors with intracavitary extension. Mobile intracavitary defects are usually pedunculated tumors, typically myxomas, although the stalk may be difficult to visualize. Such tumors may prolapse into the AV valve orifice during diastole or, in the case of ventricular tumors, into the left ventricular outflow tract during systole. An atrial ball thrombus may mimic a pedunculated tumor but is more likely to be associated with clot in the atrial appendage.

A localized increase in myocardial wall thickness, especially when accompanied by a pericardial effusion, suggests an infiltrating malignant tumor. It is often difficult to differentiate myocardial thickening from pericardial effusion, but this may be aided by observation of the thickness of the right atrial wall. Because the right atrial wall is seldom infiltrated by tumor, the finding of right atrial thickening to greater than 5 mm suggests a pericardial effusion.[132] In myocardial infiltration, localized areas of disordered wall motion may also be noted by cineangiography. Coronary arteriography may in some cases allow visualization of the vascular supply of the tumor, thus demarcating the extent of tumor invasion, the source of its blood supply, and its relation to the coronary arteries.[133] [134] However, the vascular pattern of cardiac tumors has not proved to be a useful sign of malignancy.

False-negative angiographic results generally occur when the diagnosis is not suspected before catheterization. False-positive results

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are most often due to thrombus but may also be produced by many entities, such as streaming of nonopaque venous blood, a hematoma in the atrial septum, an aneurysm of the muscular or membranous ventricular septum, Bernheim's syndrome, congenital septal dysplasia, and hydatid cysts of the interventricular septum.

The major risk of angiography is peripheral embolization due to dislodgement of a fragment of tumor or of an associated thrombus. Therefore, thorough evaluation of all cardiac chambers by noninvasive methods before catheterization is recommended for patients suspected of having cardiac tumors so that contrast material can be injected into the chamber proximal (upstream) to the location of the tumor. The transseptal approach to the left atrium is particularly hazardous because of the frequent occurrence of left atrial myxomas in the region of the fossa ovalis.[135]

TREATMENT AND PROGNOSIS

Benign Tumors

Operative excision is the treatment of choice for most benign cardiac tumors and in many cases results in a complete cure.[5] [136] [137] [138] Although many tumors are histologically benign, all cardiac tumors are potentially lethal as a result of intracavitary or valvular obstruction, peripheral embolization, and disturbances of rhythm or conduction. Unfortunately, it is not unusual for patients to die or experience a major complication while awaiting operation; therefore, it is mandatory to carry out the operation promptly after the diagnosis has been established.

Although some epicardial tumors may be removed without the aid of extracorporeal circulation, most intramural and intracavitary tumors must be excised under direct vision, requiring use of a heart-lung machine. Closed approaches are not now recommended because of the increased risk of dislodging tumor fragments. In addition, excision cannot be as complete, and adequate inspection of the other cardiac chambers for additional tumors is not possible.

Dislodgement of tumor fragments constitutes a major risk of operation and can result in peripheral emboli or dispersion of micrometastases, which may seed peripherally. To reduce this risk, manipulation of the heart before cardiopulmonary bypass should be minimized. Some surgeons recommend that venous cannulation for cardiopulmonary bypass be performed via the femoral or azygos vein rather than through the right atrium to avoid dislodging an unsuspected right atrial tumor. In addition, the tumor should be removed en bloc when possible and the chamber then irrigated well with saline.

ATRIAL MYXOMAS.

Numerous reports document complete cure of left and right atrial myxomas with follow-up periods of 10 to 15 years.[139] [140] In about 1 to 5 percent of cases, a recurrence or second cardiac myxoma has been reported after resection of the initial myxoma.[72A] [141] [142] Possible causes of the second tumor include incomplete excision of the original tumor with regrowth; growth from a second "pretumorous" focus, i.e., metasynchronous; or intracardiac implantation from the original tumor. Because of the first two possibilities, some surgeons have advocated excision of the entire region of the fossa ovalis and repair of the resultant atrial septal defect to remove presumably high concentrations of pretumorous cells thought to be located in that region. In one case, the large size of a myxoma, together with its location on the posterior left atrial wall, necessitated complete removal of the heart, which was followed by autotransplantation, i.e., reimplantation of the patient's excised heart.[143] Laser photocoagulation of a 1-cm area around the stalk attachment site has also been suggested as a way of eradicating pretumorous cells without the need for creating an atrial septal defect.[144] Other surgeons have reported equally successful long-term recurrence-free periods with simple excision of the tumor and a small rim at the base. It now appears that in approximately 7 percent of patients with (1) a familial history of cardiac myxoma, (2) features of the complex of lentigines and other abnormalities, or (3) synchronous tumor appearance (i.e., numerous tumors at the time of presentation), the incidence of a second tumor occurring at some time in the future is in the range of 12 to 22 percent, as compared with approximately 1 percent for patients with sporadic atrial myxoma.[142] It is believed that tumor recurrence in these cases is from a second pretumorous focus of cells. In these high-risk patients, a careful

search for additional tumors preoperatively and more extensive resection of the underlying endocardium, atrial septum, or both is recommended. Careful echocardiographic follow-up for detection of metasynchronous tumors is recommended[142] for all patients after resection of a myxoma.

OTHER BENIGN TUMORS.

Successful excision has also been reported for ventricular myxomas, as well as most other types of benign cardiac tumor, including rhabdomyoma, hamartoma, fibroma, lipoma, hemangioma, and papillary fibroelastoma.[145] [146] [147] The major surgical considerations in excision of ventricular tumors include preservation of adequate ventricular myocardium, maintenance of proper AV valve function, and preservation of as much of the conduction system as possible. Often, however, papillary muscles, chordae tendineae, or the AV conduction system must be sacrificed during the resection of a tumor, thereby necessitating replacement of the AV valve, implantation of a pacemaker, or both.

Malignant Tumors

Operation is not an effective treatment for the great majority of primary malignant tumors of the heart because of the large mass of cardiac tissue involved or the presence of metastases. The major role for surgery in such cases is to establish a diagnosis in order to preclude the possibility of a curable benign tumor. Nevertheless, in some cases, palliation of hemodynamics and/or constitutional symptoms and extension of life can be achieved by aggressive therapy. Survival for 1 to 3 years has been reported after partial resection, chemotherapy, radiation therapy, orthotopic cardiac transplantation, or various combinations of these modalities.[148] [149] [150] [151] [152] In some instances, localized recurrences have been eliminated by repeated operations. Some success in palliation of symptoms has been reported after the combination of chemotherapy and radiation therapy[153] and after radiation therapy alone.[152] Lymphosarcoma of the heart frequently responds to chemotherapy, radiation therapy, or both.[154] [155] Unfortunately, many other reports indicate a failure to alter the course of cardiac sarcomas despite various combinations of surgery, chemotherapy, and radiation therapy.

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Chapter 50 - Pericardial Diseases

DAVID H. SPODICK

PERICARDIAL ANATOMY AND PHYSIOLOGY

Anatomy

Pericardial anatomy is specialized to serve its complex active and passive normal functions (Fig. 50-1) . [1] [2] There are two pericardial layers with nerves, lymphatics, and blood vessels. The *serosa* is a sac lined by a monolayer of mesothelial cells attached by loose connective tissue to the heart surfaces and the inner aspect of the fibrosa, lying on the

Figure 50-1 The opened normal pericardium and heart in situ. The epicardial mesothelium is transparent; the parietal pericardium--mesothelium and fibrosa--is translucent. A curved probe is in the pericardial transverse sinus. (From Spodick DH: Acute Pericarditis. New York, Grune & Stratton, 1959; author's copyright.)

heart like a collapsed rubber glove with finger-like projections over the juxtacardiac

great vessels. It contains 15 to 35 ml of serous pericardial fluid, an ultrafiltrate of blood plasma. Externally, it is clasped by the fibrosa and continues upward an average of 6 cm above the aortic root over the aortic arch, where it blends with the deep cervical fascia, and over the venae cavae and pulmonary veins. *Ligaments* attach it to the sternum and the vertebral bodies loosely and to the central tendon of the diaphragm firmly. The serosa directly covering the heart surfaces is the *visceral pericardium* ("the epicardium"; see Fig. 50-1) . The fibrosa with the reflections of the serosal sac internally attached to it is the *parietal pericardium* ("the pericardium"). Parietal pericardial thickness varies from 0.8 to 2.5 mm (up to 3.5 mm on magnetic resonance imaging [MRI] and computed tomography [CT]).

PERICARDIAL SINUSES AND RECESSES.

The pericardial "cavity" is a nonuniform, mainly potential, space. During life most of the normal fluid is undetectable except in the major sinuses and the atrioventricular (AV) grooves and numerous recesses. In front of the atria and superior venae cavae and behind the proximal ascending aorta and pulmonary artery is a short pericardial passage, the *transverse sinus*, where the serosa encloses the terminal portions of the venae cavae and pulmonary veins, with separate recesses surrounding one third to two thirds of the proximal pulmonary artery. With the pulmonary veins it forms an inverted "U", framing a posterior projection, the *oblique sinus.* CT and MRI disclose numerous smaller recesses not detectable in the open pericardium at surgery and post mortem. The pericardial sinuses and recesses increase the pericardial capacity to accommodate increased fluid (or other contents), contributing to the *pericardial reserve volume.*

THE MESOTHELIUM.

Serosal mesothelial cells interdigitate and overlap, maintaining mechanical stability and permitting changes in surface configuration. Projecting *microvilli* presumably reduce friction and facilitate exchange of fluid and ions. *Cytoskeletal filaments* include keratins for structural support and actin. A basal lamina underlies the mesothelium and covers the subepicardial coronary vessels.

THE FIBROSA.

The fibrosa, which is composed mainly of *fibrocollagenous tissue,* is wavy in youth, arranged in fascicular bundles and thicker over thinner parts of the heart. The left atrium is tightly clasped by a dense fibrosal mesh. The fibrosa also contains *elastic fibers.*

NERVES, ARTERIES, LYMPHATICS, AND LYMPH NODES.

The *phrenic nerves* course upward over the anterior parietal pericardium and supply most of it. (They and their nutrient *pericardiacophrenic artery* must be protected during cardiac and pericardial surgery.) The esophageal plexus supplies vagal fibers. Parietal pericardial lymphatics drain to corresponding anterior and posterior mediastinal nodes while the superficial plexus of the cardiac lymphatics drains the visceral pericardium to

the tracheal and bronchial mediastinal nodes.

The internal mammary arteries and small aortic twigs contribute the arterial supply.

SUBEPICARDIAL FAT AND CONNECTIVE TISSUE.

Between the heart and the epicardial mesothelium is variable connective tissue and a fat layer that increases with increasing body weight and is disproportionately increased in coronary disease. The fat contains a prostaglandin-like angiogenic factor and important parasympathetic ganglia in a *sinoatrial fat pad.*

Physiology of the Normal Pericardium

PHYSICAL EFFECTS.

Purely mechanical pericardial effects belong mainly to the parietal pericardium and are minimal in euvolemic individuals with normal hearts.[3] [4] [4A] The normal parietal pericardium contributes to resting cavitary diastolic pressures and retracts when incised, indicating it is under stress--indeed it exerts a contact stress. Moreover, by exerting stress[5] (magnified by any increase in pericardial fluid pressure) the normal pericardium restricts overall heart filling with a much greater effect on thinner parts like the right ventricle and atrium that probably depend on pericardial constraint for much of their normal pressures and dimensions (after pericardiectomy right ventricular [RV] size increases). The pericardium also limits acute cavitary dilation.

Hypervolemia exaggerates all such effects: when cardiac volume is acutely increased, much of the increased ventricular diastolic pressure is borne by the pericardium, ensuring only minimal change in ventricular diastolic transmural

TABLE 50-1 -- ACUTE EFFECTS OF PERICARDIECTOMY/PERICARDIOTOMY

GENERAL EFFECTS
Macrophysiological effects are due to absent/reduced constraint of the heart.
Ventricular interaction:
Pericardium closed: right ventricle dominates
Pericardium open: left ventricle dominates
Experimental results depend on protocol:
Intact conscious closed-chest subjects vs. open-chest anesthetized subjects
Intact vs. blocked autonomic innervation

LA=left atrial; LV=left ventricular; RA=right atrial

SPECIFIC EFFECTS
Decreased
Interactions: ventricular; atrioventricular
Pulmonary volume overload in response to intravascular volume loading:
Excess intravascular volume redistributed from pulmonary to systemic circulation
RA mean pressure Systemic vascular resistance during maximal exercise
LA=left atrial; LV=left ventricular; RA=right atrial
Increased
Cardiac index and stroke work index due to improved LV systolic performance (Frank-Starling response to increased preload) LV end-diastolic diameter LV end-diastolic volume LV stroke volume LV transmural pressure Early LV filling velocity Early LV filling fraction LA booster pump function LA reservoir function Diastolic discharge frequency of LV mechanoreceptors
Increased Exercise Responses
Maximal O_2 consumption
Maximal cardiac output Maximal stroke volume LA pressure LA stroke volume LV end-diastolic pressure
LA=left atrial; LV=left ventricular; RA=right atrial
Tallest precordial Often conspicuous Never conspicuous

Figure 50-2 Schema of stress-strain and pressure-volume curves of the normal pericardium. After the relatively small *pericardial resolve volume* is exhausted by filling of the pericardial sinus and recesses, the curve at first rises gently, with continued filling at some point more acutely; the time scale and exact proportions are variable depending on the *rate of filling* of the intact pericardial sac. (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

pressures while increasing pericardial constraint. With *euvolemia* the parietal pericardium appears to have minimal direct influence and virtually no effect during *hypovolemia*, probably because decreased preload and reduced heart size free the

heart from pericardial constraint. Comparably, nitroglycerin, erect posture, and lower body negative pressure reduce cardiac volume acutely and hence pericardial effects on the myocardium. In contrast, both chronic pericardial effusion and chronic cardiomegaly lead to progressive stretch (time-dependent *stress relaxation* and *creep*) with subsequent hypertrophy of the parietal pericardium increasing its compliance and decreasing its constraining effect on the heart.

Pericardial constraint accounts for most of the resting diastolic right atrial (RA) and RV cavity pressures and contributes substantially to those on the left. Pericardiotomy augments RV filling and stroke volume with improved systolic function by the Frank-Starling relation. The numerous effects of pericardiectomy or pericardiotomy are summarized in Table 50-1 .

The parietal pericardium is stiffer than cardiac muscle. Its stiffness is related to regional fiber orientations: more parallel fibers yield more pericardial stiffness.[2] Its mechanical functions mainly relate to (1) its contribution to apparent cardiac stiffness, (2) the effects of a chamber filled with fluid at subatmospheric pressure surrounding the heart, and (3) circulatory "feedback" regulation by pericardial neuroreceptors and mechanoreceptors. On stretching, the parietal pericardium initially "gives," due to extension of its elastic fibers and straightening of its wavy collagen. Thereafter, rapidly increasing resistance to increasing stretch produces characteristic "J"-shaped stress-strain and pressure-volume curves (Fig. 50-2) : an initial slow rise in pressure as volume increases--and of strain as stress increases--followed by an angle and a sharp rise. With intact pericardia, ventricular pressure-volume curves are exactly parallel. Acutely increased pericardial fluid or intracardiac volume couple the pericardium to the heart more closely, exaggerating this effect. Removal or opening of the parietal pericardium makes ventricular pressure-volume curves significantly more gentle so that ventricular pressure begins its sharp rise later at a higher cardiac volume and thereafter increases more gradually.

PRESSURE-VOLUME RELATIONSHIPS.

Normal intrapericardial pressure (-5 to +5 mm Hg) is nearly always negative and approximates and varies with pleural pressure during respiration. With early increase in pericardial fluid pressure, changes tend to be small, owing

---

to the *pericardial reserve volume*--the volume by which the unstressed pericardium exceeds the cardiac volume. Large increases in right-sided heart pressures, as by volume loading, raise pericardial pressure, but the *myocardial transmural pressure* increase is small and well below the change in pericardial pressure.

THE PERICARDIAL HYDROSTATIC SYSTEM.

Normally, pericardial fluid distributes hydrostatic inertial and gravitational (e.g., postural)

forces over the cardiac surfaces. This favors approximation of end-diastolic transmural pressure throughout the ventricles and consequently uniform stretch of muscle fibers, tending to balance preload and so permit the Frank-Starling mechanism to operate uniformly. (Note that pericardial contact pressure measured by flat balloons[5] rather than catheters may better represent baseline pericardial constraint of the heart.)

VENTRICULAR INTERDEPENDENCE AND PERICARDIAL CONSTRAINT OF THE HEART.

Expressed as ventricular interaction, ventricular interdependence represents the effects of pressure and volume changes in one ventricle on the activities of the other, including filling, contraction, and relaxation. Pericardial contributions to ventricular interaction help to explain reduced ventricular compliance when there is increased pressure in the other ventricle. Although the normal right ventricle is much more compliant than the left, the pericardium constrains both similarly and tends to equalize their compliances (nonpericardial interaction also occurs by means of the circumferential and especially the septal myocardial muscles). *Moreover, either ventricle generates greater isovolumic pressure from any diastolic volume when the pericardium is intact than when it is open or removed.* Diastolic cardiac chamber interactions are greatly magnified by the pericardium, which minimally affects systolic interaction. For example, acutely increased RV size (e.g., cardiocirculatory volume overload or RV infarction) raises intrapericardial pressure significantly, imposing a steeper pressure-volume curve (increased stiffness) on both pericardially constrained ventricles.[6] Interaction operates continuously, although minimally, during normal breathing. Inspiration increases RV filling, which slightly reduces left ventricular (LV) filling, and consequently output, and decreases arterial pressure. Respiratory effects are exaggerated by even small increases in pericardial fluid and markedly in cardiac tamponade; this produces pulsus paradoxus.

TRANSMURAL PRESSURES.

Transmural pressures describe the force (related to pressure) balance across a cavity wall. The transmural pressure of the pericardium itself (pericardial pressure minus pleural pressure) approximates zero, although it is usually slightly negative and varies with pleural pressure. *Myocardial transmural pressure* (intracavitary pressure minus intrapericardial pressure) normally is less than 3 mm Hg and depends on pericardial pressure. Transmural pressure at end diastole is a measure of preload (the actual chamber-distending pressure); transmural pressure is thus a true "filling pressure." Therefore, the closed pericardial chamber, normally at slightly subatmospheric pressure, ensures that myocardial transmural pressure stays low relative to even large increases of cavitary diastolic pressures. Myocardial performance is largely determined by end-diastolic fiber length set by end-diastolic chamber volume, which is determined by end-diastolic transmural pressure due to pericardial constraint.

NORMAL RESPIRATORY EFFECTS: RIGHT HEART/LEFT HEART RECIPROCATION (Fig. 50-3) .

Intrapericardial pressure approximates pleural pressure and varies with its respiratory changes: about -3 mm Hg at end expiration to -6 mm Hg at end inspiration. The normal inspiratory fall in pleural pressure reduces pericardial, RA, RV, wedge, and systemic arterial pressures slightly. However, inspiratory pericardial pressure decreases more

than atrial pressures so that RA and other central transmural (distending) pressures increase, augmenting systemic venous return and right-sided heart filling and, therefore, RV preload and output (pulmonary artery flow velocity increases). Simultaneously, inspiratory aortic flow decreases as aortic transmural pressure increases (which increases impedance to ejection). Moreover, as the increased RV output crosses the lung any inspiratory "pooling" would reduce the gradient for left atrial (LA) filling. The corresponding slight inspiratory decrease in LV transmural pressure and the increased LV afterload (impedance to ejection) reduce LV stroke output. These are directionally identical, with far greater changes in the same measurements during pulsus paradoxus.

PASSIVE PERICARDIAL FUNCTIONS.

Membranous functions of the pericardium result from its physical presence. It appears to buttress thinner parts of the myocardium, particularly the RA and RV, and to block inflammation from contiguous structures. It reduces friction due to heart movement by means of the pericardial fluid and surfactant phospholipids. *Ligamentous functions* slightly limit cardiac displacement through attachments to adjacent structures.

MICROPHYSIOLOGY OF THE NORMAL PERICARDIUM[2]

Cardiocirculatory feedback regulation by pericardial servomechanisms include (1) *neuroreceptors* in epicardium and fibrosa that detect lung inflation and can alter blood pressure and heart rate through the vagus nerves; (2) *sympathetic efferents* doing the opposite; (3) *mechanoreceptors* sensitive to ventricular stretch, determined by ventricular volume and transmural pressure (myocardial dysfunction is sensed by mechanoreceptors monitoring beat-to-beat changes in cardiac volume, and other mechanoreceptors signal myocardial tension reflexly to match contraction strength with peripheral resistance); and (4) *chemoreceptors* sensitive to substances in the pericardial fluid, which respond to digitalis glycosides and perhaps contribute to their bradycardic effect.

NORMAL PERICARDIAL FLUID.[3]

Serous pericardial fluid (normally 15 to 35 ml) is mainly an ultrafiltrate of plasma including some overflow of myocardial interstitial fluid and lymph. Protein concentration is lower than in plasma but with relatively high albumin. Electrolyte concentrations yield an osmolarity less than plasma, consistent with such an ultrafiltrate.

MESOTHELIAL METABOLIC ACTIVITY.[1] [2] [3]

The mesothelium has cyclooxygenase, prostacyclin synthetase, and lipoxygenase activities; prostaglandin E_1 , eicosanoids, and large amounts of prostacyclin (PGI_2) are continually released into the pericardial cavity in response to hypoxia, pericardial stretch, and increased myocardial work and loading conditions. These prostanoids can alter pericardial sympathetic neurotransmission, myocardial work, loading conditions, and myocardial contractility and modulate the caliber and tone of the coronary vessels

with multiple effects on cardiac electrophysiology, possibly including reduction of reperfusion-induced arrhythmias. *Prostacyclin also inhibits*

Figure 50-3 Inspiratory effects on heart and pericardium (reversed in expiration). Inspiration, by means of diaphragm descent, reduces pleural cavity pressure while increasing abdominal pressure. Venous return to the right side of the heart is sharply increased, with filling at the expense of the left side of the heart (atrial and ventricular septa move to the left). This is accentuated by the fall in aortic transmural pressure, which increases impedance to ejection by the left ventricle. This is the normal response pattern; during compressive pericardial disorders (tamponade, constriction) its degree is increased (pulsus paradoxus). See text. LA=*left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle; SVC and IVC=superior and inferior venae cavae.*

platelet aggregation and thrombosis in the major coronary vessels as well as clotting during intrapericardial bleeding, whereas fibrinolytic activity by the mesothelium opposes both intrapericardial clotting and adhesion formation. Small amounts of complement (C3, C4, CH_{50}), other immune factors, myocardial cellular enzymes, and related compounds are continually released into the pericardial fluid.[3] During transmural cardiac injury and necrosis, pericardial fluid "washes" the cardiac surfaces, diluting substrates leaked into it that might adversely affect the superficial myocardial sympathetic nerves. A cell-to-cell interaction between pericardial mesothelium and ventricular myocytes in tissue culture may modulate myocyte structure, function, and gene expression, whereas fibroblast growth factor 2 (FGF_2) in pericardial fluid is a major determinant of myocyte growth and functionally significant angiogenesis. Other growth factors modulate activation of macrophages and coronary endothelial cells so that pericardial fluid analyses may give prognostic information with respect to neoangiogenesis and plaque stability. The effects on the heart, its nerves, and the coronary arteries of intrapericardially injected substances permit the pericardial sac to be used for local delivery of therapeutic agents and gene products. This has been accomplished by catheter through the RA appendage and with an instrument specifically designed for access to the normal pericardium (i.e., the perDUCER). [7] [8]

AUSCULTATORY PHENOMENA (See Chap. 4)

There are five categories of auscultatory phenomena in pericardial disorders: (1) pericardial rubs, (2) abnormal heart sounds, (3) clicks, (4) murmurs, and (5) the effect of pneumohydropericardium.[9] [10]

PERICARDIAL RUB.

The pericardial friction sound (rub, "friction rub"; Fig. 50-4) , a hallmark of acute pericarditis, occasionally audible in subacute and chronic pericardial disease, is ascribed to friction between inflamed, scarred, or tumor-invaded serosal surfaces *(endopericardial rub),* including those after sclerotherapy of effusions, or, infrequently, between parietal pericardium and pleura or chest wall *(exopericardial rub)* or both

(endo-exopericardial rub). Endopericardial rubs may also be due to destruction of surfactant pericardial phospholipids. The common endopericardial rub, often monotonal, nearly always disappears with resolution of acute inflammation. Exopericardial rubs sometimes result from penetration by severe acute pericarditis but otherwise are due to direct extension, inflammation, or tumor implants from adjacent structures. They may change radically with respiration, have a musical quality, and seem superficial. Like endopericardial rubs, exopericardial rubs also occur after cardiac surgery and with constrictive and nonconstrictive pericardial scarring; most are from adjacent pleuritis--*pleuropericardial rubs*--due to pleural, or both pleural and pericardial, involvement and have both respiratory and cardiac periodicity. *Conus rubs* accompany pulmonary embolism, thyroid "storm" *(Means-Lerman scratches),* and acute beriberi heart disease; they are ascribed to dilation of the pulmonary conus in a hyperactive heart. In acute pericarditis, rubs usually disappear with accumulation of significant pericardial effusion, but frequently they do not, even during tamponade. Indeed, some rubs, probably exopericardial, "paradoxically" disappear after pericardiocentesis.

Auscultatory Characteristics[9]

Composed of mixed (mainly high) frequency vibrations, most rubs, unlike most murmurs, frequently wax, wane, and transiently disappear. They vary from subtle distant "scrapes" to grating or scratching noises, which may be loud and even palpable. Rubs often give the illusion of "obliterating" or "going through" the heart sounds while seeming superficial. Many change with breathing and body position and do not respect conventional murmur zones of maximum intensity and radiation. Yet, the vast majority of rubs are heard best, or only, along the left mid to lower sternal edge, where palpability is most likely, owing to proximity of the right ventricle to the chest wall. Occasional rubs are sharply localized anywhere along any heart border. Usually loudest in inspiration, particularly with increased pericardial fluid, some rubs have no respiratory predilection; rarely, rubs increase in expiration. Finally, to elicit or accentuate rubs, the examiner should raise all four of the patient's extremities

Figure 50-4 Triphasic pericardial rub: electrocardiogram *(top),* multifilter phonocardiograms *(center)*, and peaks of carotid pulse *(bottom).* S_1 =first heart sound; S_2 =second heart sound. Rub components: DR=diastolic rub; AR=atrial rub; SR=systolic rub. Rub vibrations are mainly high frequency (top two phonocardiograms) and much reduced at lowest frequency (MA/100). This example shows the most common relative intensity: SR louder than AR, louder than DR; only SR remains at lowest filtration. (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

simultaneously to distend the right side of the heart by increased venous return or applying the stethoscope to the precordium while the patient rests on the knee and elbows (Fig. 4-44) .

Components.

Classically described as biphasic ("to-and-fro"), multiobserver investigations revealed, in patients with heart rates less than 120 beats/min, triphasic rub patterns in well over one half of those in sinus rhythm. The rub occurred with atrial systole *(atrial rub),* ventricular systole *(systolic rub),* and early diastole *(early diastolic rub)* (see Fig. 50-4). Only about one third are biphasic (to-and-fro), with some due to absence of atrial systole in rhythm disorders. About 10 percent were monophasic, usually during ventricular systole. At heart rates of more than 100 beats/min the early diastolic and atrial components may fuse *(summation rub).* Some rubs only appear after exercise; others with one or two components may acquire the remaining components on exercise.

HEART SOUNDS.

Pericardial disease can alter heart sounds and their auscultatory appreciation by insulation and particularly by hemodynamic changes.[9] Insulation by pericardial fluid should tend to make heart sounds more distant. Hemodynamic changes common to both tamponade and constriction decrease myocardial compliance and stroke volume, tending to diminish first (S_1) and second (S_2) heart sounds and relatively accentuate the pulmonic component of S_2. Constrictive pericarditis produces its hallmark, the abnormal early diastolic sound[9] --a variant of the third heart sound (S_3; Fig. 50-5) --as well as abnormal splitting of S_2. Effusive constrictive syndromes (simultaneous scar and fluid) produce mixed pictures.

The early diastolic sound of constriction coincides with the abrupt deceleration of excessively rapid early filling[9] [10] and occurs earlier than an abnormal S_3 of myocardial disease and AV valve regurgitation. The early diastolic sound may be the only loud heart sound (sometimes with an intense "knocking" quality) and misinterpreted as S_1, especially during rapid heart rates. At bedside, the S_3 appears after the carotid crest and coincides with the trough of the jugular *y* descent.[9] A faint or absent S_3 may be revealed by prompt squatting. Patients with heavy calcification can have a particularly loud and sharp early diastolic sound, owing to markedly reduced compliance. Like its timing, early diastolic sound intensity varies directly with the abruptness with which ventricular expansion halts; that is, louder third sounds correlate with high diastolic pressures and steepness of reascent from the typical early diastolic "dip" of ventricular pressure and chest wall displacement curves. In sinus rhythm, a fourth heart sound (S_4) is occasionally present and ascribable to high resistance to active filling. Lack of impairment of atrial systole explains why the S_4 is more common in *elastic constriction* (see p. 1849).

CLICKS.

Clicks are high-frequency, discrete vibrations resembling opening snaps of stenosed valves. Classically ascribed to pericardial scarring and articulation of calcifications, this

remains speculative, because most clicks are due to intracardiac phenomena related to valves and chordae.[9] Indeed, pseudoprolapse and true prolapse of mitral and tricuspid leaflets (due to disproportionate shrinkage of ventricular volume in tamponade and constriction) produce clicks.

MURMURS.

Murmurs arise from turbulent flow across orifices and tubes. In pericardial disease they are epiphenomena--due to related or unrelated coincident heart disease or when pericardial scarring narrows a valve ring or portion of the heart, aorta, or pulmonary artery.

Murmurs with inflammatory cysts, hematomas, or abscesses are due to compression or actual physical disruption of valves. AV groove compression has produced annular mitral and tricuspid stenosis with murmurs indistinguishable in quality, timing, and respiratory behavior from those of AV valve disease.[10] Selective scarring has also produced systolic murmurs of aortic supravalvular and pulmonic supravalvular and infundibular stenosis. In constrictive pericarditis, unexplained mitral and tricuspid regurgitant murmurs are common. Some murmurs appear only postoperatively; others arise from local inequality within a generalized constricting scar. Coexisting cardiac disease independently produces murmurs that may become modified by constriction.

AUSCULTATORY EFFECTS OF PNEUMOHYDROPERICARDIUM.

When air or other gas overlies pericardial fluid, due to trauma, gas-producing organisms, or a fistula from adjacent organs, a metallic tinkle synchronous with systole may be heard if the amount of gas is small. Large amounts produce a churning, splashing, "*mill-wheel sound*" from agitation of the gas-liquid interface by the beating heart.[9]

ELECTROCARDIOGRAPHIC ABNORMALITIES IN PERICARDIAL DISEASE (See Chap. 5)

The pericardium produces no detectable electrical phenomenon, yet pericardial disease can significantly modify the electrocardiogram (ECG).[11] Quasi-specific ST-T wave changes follow spread of pericardial inflammation to the subepicardial myocardium; a superficial myocarditis results.[12] Excess pericardial fluid, fibrin, or dense scar may insulate the heart or short circuit cardiac currents, tending to decrease voltage, although hemodynamic impairment may be as or more important than the size of effusion (unless massive) in reducing voltage. ECG effects of constrictive scarring depend additionally on fibrosis and calcification of the subjacent myocardium; any asymmetry of scarring can mimic disease of a cardiac chamber, valve, or great vessel.

Acute Pericarditis

Acute pericardial inflammation with a superficial shell of myocarditis provokes ST-T abnormalities that, in typical three or four-stage sequence (Table 50-2) , are

pathognomonic of acute pericarditis.

STAGE 1.

This stage alone (Figs. 50-6 and 5-47) is quasi-diagnostic. It mimics "early repolarization" and acute

Figure 50-5 Constrictive pericarditis: phonocardiogram showing high-amplitude third heart sound (S_3) larger than S_1 and both components (A_2 and P_2) of well-split second heart sound (S_2). (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

TABLE 50-2 -- ECG: STAGE I PERICARDITIS VS. "EARLY REPOLARIZATION"

	STAGE 1 PERICARDITIS	**"EARLY REPOLARIZATION"**
Sex	Either	Virtually all males
Age	Any	Usually younger than 40 years
Prevalence in mental institutions	Sporadic	Relatively common
J-ST evolution	Yes	No
PR segment deviations	Frequent	Occasional
	Ubiquitous	Restricted distribution
	Often conspicuous	Never conspicuous
R-S slurring	Uncommon	Nearly always
T waves		
Amplitude	Normal	Usually tall
Summit	May be blunt	Peaked
J height/T apex V6 (PR segment as baseline)	Usually 25%	Usually <25%
Tallest precordial R wave	Usually V_5	Usually V_4

Modified from Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

infarction with anterior and inferior ST segment elevation. Characteristic evolution involves the ST junction (J) and T wave. Unless there is a deeper involvement, there are

no QRS complex abnormalities. The entire subepicardial myocardium is involved in generalized pericarditis so that most ECG leads develop simultaneously "in phase" with each other. The mean J-ST vector (axis) is usually directed left and inferiorly ("southeast"), between +30 and +60 degrees in normal hearts. In the thin-walled atrium, myocarditis cannot be superficial and, at least early in acute pericarditis, exaggerates atrial T waves (Ta wave) that appear early, causing PR segment deviations opposite to P wave polarity. Thus PR segment deviations have a vector (axis) 180 degrees opposite to the P axis--usually at -120 to -150 degrees ("northwest") (see Fig. 50-6) . Stage I is virtually pathognomonic of acute pericarditis when it involves virtually all leads. Minimal lead involvement to be considered typical includes I, II, aVL, aVF, and V_3 through V_6 .[11] Leads theoretically reflecting "endocardial" events show depressed J points and elevated PR segments. Thus, the ST segment is always depressed in lead aVR, very frequently depressed or isoelectric in V_1 , and occasionally depressed in V_2 .

STAGE II.

This stage is evolutionary; in early stage II, all ST junctions return to the baseline more or less "in phase" with little change in the T wave; PR segments may now be deviated if they had not been in stage I. In late stage II, the T waves progressively flatten and invert mainly in leads that had shown ST segment elevations.

STAGE III.

This stage shows generalized T wave inversions in most or all leads. If first recorded in stage III, pericarditis cannot be diagnosed by ECG because stage III is also consistent with diffuse myocardial injury, "biventricular strain," or frank myocarditis. Stage III has become less frequent, presumably due to effective early treatment with antiinflammatory agents.

STAGE IV.

In this stage, the ECG returns to its prepericarditis state. Occasionally, stage IV does not occur and there are permanent, generalized or focal T wave inversions and flattenings.

TYPICAL ECG VARIANTS.

Typical variants[11] include the following:

1. In stage I, the ST segment may be isoelectric or slightly depressed in lead III with a horizontal or semihorizontal QRS axis; with a vertical axis, the ST segment is isoelectric or slightly depressed in lead aVL and isoelectric in lead I.
2. There may be rapid evolution of stage I to normality, that is, return of the elevated J-ST to the baseline with little or no T wave change.
3. Any stage may be absent.
4. Stage II may persist indefinitely or for long periods, with T wave flattening or

inversions indicating a more aggressive process or presaging constrictive evolution.

ATYPICAL ECG VARIANTS.

Five atypical variants render the ECG diagnostically nonspecific[11] :

1. There may be no ECG change, either because acute abnormalities are missed (rapid evolution or delayed recording) or because

superficial myocarditis is low-grade or absent. Pericarditis of acute myocardial infarction produces only localized pericardial involvement with no general stage I.
2. PR segment deviations alone are not rare; these are very sensitive (with or without ST deviations) but of undetermined specificity.
3. J-ST changes may be restricted to only a few leads, which is misleading because localized cardiac injury is typical of myocardial ischemia. One may suspect this variant because pericarditic changes lack reciprocal ST deviation.
4. T wave inversions before all ST junctions have returned to the baseline, characteristic of myocardial infarction and myopericarditis (in special cases, patients with preexisting T wave abnormalities, especially digitalis effect, may show J-junction deviation while the original T wave abnormalities persist with or without PR segment deviations) and myopericarditis.
5. In stage III there may be T wave inversions only in some leads (usually V_3 or V_4 to V_6).

Figure 50-6 Acute percarditis: stage 1 ECG. J points are elevated except aVR and V_1 . T waves are essentially normal. PR segments are depressed except aVR and V_1 . Absence of PR deviations in a single limb lead (here, aVL) is common. See text.

Nearly half the ECGs in patients with rubs and corresponding clinical syndromes do not present with or evolve a stage I.[11] The majority with typical ECG changes are always recorded on presentation or the first or second day thereafter. Differentiation from myocardial ischemia is crucial because thrombolytic treatment with unrecognized pericarditis can cause hemopericardium.[11] (see Table 50-5 and Chap. 35) . Differentiation of stage I from the apparently normal variant of "early repolarization" is summarized in Table 50-2.

RATE AND RHYTHM.

Although heart rate is usually rapid (80-130 beats/min), slower rates are noted in patients with autonomic problems--typical of uremic pericarditis. Sinus rhythm is the rule in the absence of heart disease. Indeed, uncomplicated acute pericarditis does not

produce significant rhythm disturbances[11] unless there is underlying cardiac disease either preexisting or related through pericardial inflammation, myocardial or pericardial tumor invasion, or associated metabolic abnormality.[11] [12]

PERICARDIAL EFFUSIONS (see pp. 1831, 1838).

ECG effects of pericardial effusion are difficult to assess. Low-amplitude ECGs are seen in many, but certainly not all, cases with detectable effusion. Chronic effusions with compression atrophy or scarring of the myocardium may cause permanent low voltage.[11] Yet large effusions without voltage or other ECG abnormalities are not uncommon, especially in patients with voltage-increasing heart disease. ST-T wave abnormalities during pericardial effusion can persist or disappear after paracentesis. They may be related to superficial myocarditis, but in some cases they seem to depend on presence of fluid, possibly due to myocardial compression or ischemia.[11] ST segment displacements are more common with rapid fluid accumulation (as in hemopericardium). P wave voltage reduction usually requires truly massive effusions. Tamponade can reduce voltage even with smaller amounts of fluid, partly due to reduced cardiac volume (Brody effect). Hemolysis of red cells in fluid can produce excess potassium concentrations that affect the ST segment and T wave, including T wave peaking and reversal of previous T wave polarity. Pleural effusions, particularly on the left, may contribute to voltage reduction, whereas generalized fluid retention (as in cirrhosis and heart failure) can reduce ECG voltage without pericardial disease.[11] Note that the presence of *more than minimally increased pericardial fluid raises the energy required for defibrillation and cardioversion.*[13]

CARDIAC TAMPONADE (see p. 1841).

Unless massively effusive, chronic pericardial effusion and chronic cardiac tamponade have little ECG effect. In acute tamponade, any ECG stage of acute pericarditis can be found but most often ST (J) segment deviations are absent and T waves are low to inverted. Some patients have nearly normal ECGs. Critical acute hemorrhagic tamponade provokes bradycardia, often of AV junctional origin or with preterminal electromechanical dissociation. QRS-T voltage tends to decrease in tamponade, although the degree of change is unrelated to severity. (Note that preexisting heart disease may account for high or low voltage.) Very few patients have microvoltage, and the P waves usually escape. Whereas purely insulating effects of fluid require large effusions, voltage reduction in tamponade probably is mainly due to angulation and especially to compression of the heart, which reduces its size. (Occasional tamponade patients develop left-axis deviation, possibly due to ventricular displacement or greater compression of the thin right ventricle.) Some T wave abnormalities may be due to reduced coronary flow in previously diseased coronary arteries, owing to low aortic pressure in tamponade plus epicardial compression of the coronary vessels as well as obliteration of the normal transmural myocardial pressure gradient. Pre-tamponade T wave inversions may be pseudonormalized.[11]

ELECTRICAL ALTERNATION.

In the appropriate clinical setting this finding is *almost pathognomonic of tamponade,*

occurring in up to one third of cases because of periodic (nearly always 2:1) oscillation of the heart swinging within the effusion.[4] Although typical of large effusions, alternation can occur with as little as 200 ml of pericardial fluid with a thick parietal pericardium. It reflects alternation of the spatial axis of the QRS complex and other waves due to cardiac movements while the ECG electrodes remain in place. T wave alternation is less easily seen, whereas P waves and PR segments rarely visibly alternate. Removal of a small fluid aliquot usually abolishes alternation, just as the same initial decrement usually produces the greatest relative hemodynamic improvement. Alternation is critically related to heart rate: beta-adrenergic blocking agents can slow the rate and make alternation disappear.

EARLY REPOLARIZATION (see Table 50-2) .

An ECG almost indistinguishable from the J-point deviations of stage I--found mainly in males younger than age 40 and prevalent in mental institutions--may involve most ECG leads and mimic pericarditis. Unlike stage I, this ECG does not acutely evolve and differentiation is sometimes difficult, requiring clinical correlation.[11] In early repolarization, J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point and best seen with tall R and T waves (the largest precordial R wave is usually in V_4 rather than V_5). In general, R wave and T wave voltages are large, and a differential test using the PR segment as a baseline is the height of the J point in lead V_6 . Pericarditis is likely if the J point is more than 25 percent of the height of the T wave apex.[11]

Constrictive Pericarditis

ECG abnormalities in constrictive pericarditis, although often characteristic, are nonspecific. One "typical" ECG would include mildly low voltage QRS and flattened to inverted T waves in all leads of "epicardial" derivation (Fig. 50-7) .[11] (Postoperatively, continued low-voltage predicts reduced survival.) In some patients with chronic and many with acute and subacute constriction, T wave inversions of stage III never improve or regress incompletely. Especially with chronicity, P waves can be wide and bifid (interatrial block), sometimes resembling P-mitrale with P wave axis between +90 and -10 degrees; these predict the future occurrence of atrial fibrillation. The P wave in V_1 may indicate LA enlargement (P-terminal force
4 mV) or RA enlargement (large positive initial component) or both. Yet, many patients have normal ECGs or only nonspecific T wave abnormality. Pleural effusions, ascites, and fluid retention also modify the ECG in constrictive pericarditis. Unlike acute pericarditis, arrhythmias occur in constrictive pericarditis and increase with chronicity (mainly atrial fibrillation and occasionally atrial flutter). Preoperative conversion to sinus rhythm is difficult. Rhythm disturbances are more common with pericardial calcification or an enlarged cardiopericardial silhouette. Arrhythmias always imply cardiac abnormality (see Chap. 25) .

QRS ABNORMALITY.[10] [11]

In chronic constrictive pericarditis, low voltage and myocardial atrophy are common and

probably related. In acute and subacute constrictive pericarditis

Figure 50-7 Constrictive pericarditis (chronic form). Low voltage is evident in ten leads and relatively low voltage occurs in V_2 and V_3 , with flat, -+, inverted, and frankly inverted T waves. P waves are wide (interatrial block [IAB]) with P axis=0 degrees: P wave is flat in aVF, inverted in lead III, and upright in lead I (arrows). Wide negative phase of biphasic P wave in V_1 indicates left atrial enlargement (of which IAB is also a strong correlate). (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

(now the prevalent forms) the QRS axis tends to be normal. In classic chronic constrictive pericarditis, the frontal QRS axis tends to be vertical, in many cases more positive than +60 degrees, and sometimes with right-axis deviation; verticalization increases with chronicity. The vertical tendency may represent disproportionate RV injury and strain or perhaps disuse atrophy of the underloaded left ventricle. Electrical alternation may occur in *effusive-constrictive pericarditis* with dominant parietal pericardial constriction and relatively little effusion. QRS abnormalities typical of RV hypertrophy may evolve in patients with unequal constriction or strategically placed postpericardiectomy scarring affecting the pulmonary artery, the right ventricle, the AV groove, or the mitral valve. Other QRS abnormalities, including abnormal Q waves, reflect myocardial penetration by inflammation, scarring, or focal atrophy. T wave abnormalities are variable. After pericardiectomy, QRS voltage nearly always increases with slow or no evolution in patients with myocardial atrophy. Vertical or right-axis orientation may persist, but there is frequently a limited correction. T wave abnormalities may not change and often temporarily worsen.

CONGENITAL ABNORMALITIES

Most congenital abnormalities of the pericardium are discovered accidentally at cardiac surgery, with routine chest radiography, on fetal echocardiography, or while diagnosing unusual, often unrelated, symptoms.[14] Rarest are *pericardial bands* obstructing the superior vena cava. *Pericardial celomic cysts* are most frequent and usually least important. *Bronchogenic cysts* with congenital partial pericardial defects are important because of potential compression of the heart and vessels.

Congenital Cysts and Diverticula

Cysts occur anywhere on the pericardium (mostly at the right cardiodiaphragmatic angle) and are clinically silent. Usually less than 3 cm in diameter, most are unilocular and smooth and contain clear fluid.[14] Cysts can be associated with chest pain, dyspnea, cough, and significant arrhythmias, probably owing to compression and erosion of adjacent tissues.[15] [16] Rare pedunculated cysts may undergo torsion with chest pain and ischemia-related lesions of the cyst wall. Cysts can become secondarily

infected and can complicate related or unrelated pericardial effusion and tamponade. Rapid enlargement is rare, and "spontaneous" resolution is probably due to traumatic rupture.[14] Intrapericardial rupture of large cysts threatens acute tamponade. Indeed, if very large they can mimic pericardial effusion. The principal significance of unilocular and multilocular congenital cysts is simulation of mediastinal tumors (especially when situated away from the diaphragm), loculated pericardial effusions and hematomas, pericardial diverticula, and ventricular pseudoaneurysms.

Diagnosis.

This is usually by appropriate imaging and, rarely, thoracoscopy or thoracotomy and aspiration.[14] Cyst fluid, which may contain hyaluronic acid, is yellowish or crystal clear. On imaging, tumors with central necrosis may simulate cysts, whereas unusually shaped and internally bleeding cysts may simulate tumors. Occasionally, a bronchogenic cyst will be "trapped" in or on the pericardium. Benign teratomas, which may undergo malignant change, and lymphangiomas have the same differential diagnosis. Usually CT (especially electron beam), MRI, and, with some difficulty, two- and three-dimensional echocardiography, especially transesophageal (TEE), can be diagnostic.[17] Treatment by TEE-assisted open, or video-assisted thoracoscopic, excision is required for symptomatic, locally compressive, and hemodynamically compromising cysts. Aspiration with or without ablation by a sclerosant (e.g., alcohol) is an option. *Pericardial diverticula* are rarer and resemble cysts except that a comparable developmental abnormality has left a communication with the pericardial cavity.

Absence of the Pericardium

Complete *pericardial agenesis* is rare, often discovered accidentally at cardiac operation or during evaluation of unrelated symptoms, and demonstrable by negative imaging. [17] [18] [18A] Partial loss of any part of the pericardium can occur with or without a defect in the adjacent pleura and very often with some kind of associated congenital cardiac, pulmonary, or skeletal abnormality. Most common is absence of the entire left side of the pericardium. Partial left absence and absent right pericardium are uncommon. Absence of the inferior pericardium with or without diaphragmatic defect or aplasia is rare in adults. Associated diaphragmatic defects may permit intrathoracic, including intrapericardial, herniation of abdominal organs.

Absence of the entire right or (especially) left pericardium permits homolateral cardiac displacement, which is visible on imaging and increased with the patient lying on the side of the defect (particularly the left), which accentuates cardiac mobility. Small increases in preload cause undue ventricular dilation, especially of the right ventricle.

Partial absence of the left pericardium potentially permits herniation and entrapment of parts of the heart like the left atrium, LA appendage, right atrium, right ventricle, and, with apical defects, protrusion through the defects of large parts of both ventricles.

Defect edges may compress cardiac chambers, great vessels, and coronary vessels. The phrenic nerves may be displaced to the edges.[19] [20] [21]

SYMPTOMS.

Acute or chronic symptoms like vague chest pain or dyspnea, including trepopnea, may or may not be related to any pericardial defect, but exacerbation in the left lateral decubitus is typical of left-sided defects.[11] [14] [22] Unusual torsion of the great vessels by unrestrained cardiac mobility may affect filling, ventricular ejection, and coronary flow and has been associated with tricuspic chordal rupture. Ischemic pain and myocardial infarction occur when the edge of a defect critically interrupts a coronary artery.

PHYSICAL FINDINGS.[11]

Physical findings usually only support a diagnosis, especially in left-sided absence, and include basal ejection murmurs, wide split S_2 , as well as apical midsystolic clicks and systolic murmurs accentuated by inspiration. Extensive left defects produce conspicuous precordial impulses; the apex, frequently in the anterior or midaxillary line, is hypermobile with changes in body position.

ELECTROCARDIOGRAM. [11]

Sinus bradycardia is common. Usually, with complete left-sided defects, ECG changes reflect posturally changing anatomical abnormalities and relative volume overload of the right side of the heart. Right-axis deviation and incomplete or complete right bundle branch block are the rule. Leftward displacement of the precordial transition zone is common with poor R wave progression and sometimes QS in leads V_1 to V_3 , mimicking anterior infarction: conspicuous single-peaked P waves reflect RA overload.

IMAGING.

In extensive or complete left pericardial absence chest radiographs show leftward displacement of the heart and aortic knob with the trachea midline. The pulmonary artery "segment" bulges or fills in to straighten ("mitralize") the left heart border; the right border can be so levodisplaced that the spine is clearly seen. "Air" (projections of lung) between the aorta and pulmonary artery or between the left diaphragm and inferior cardiac border are common. Herniation of the LA appendage is virtually diagnostic of partial left defect but must be distinguished from congenital LA aneurysm. CT and MRI show all the features and are most reliable for absence of pericardial tissue. MRI is more sensitive and can show the typical absence of the preaortic pericardial recess (almost always present in normal hearts) in both partial and complete absence of the left pericardium.[14] [17]

TREATMENT.

Treatment, reserved for symptoms (unless herniation threatens) includes partial or

complete pericardiectomy, pericardioplasty or extension of the defect to relieve tension on critical structures, and LA appendectomy. Postoperative adhesions help stabilize cardiac position.

ACQUIRED PERICARDIAL DISEASES

Virtually every pathological process, medical and surgical, can involve the pericardium primarily or indirectly.[23] [23A] Thus, freshly diagnosed pericardial disease may or may not be related to other conditions. Classifications in Table 50-3 necessarily overlap; for example, the post-myocardial infarction syndrome belongs both to myocardial/pericardial injury and to the immunopathies. [24] Because of etiopathogenic complexities, protocols for diagnosis and management have been carefully designed and prospectively evaluated.[25]

TABLE 50-3 -- ETIOLOGY/PATHOGENESIS OF ACQUIRED DISEASES OF THE PERICARDIUM*

MAJOR CATEGORIES
I. Idiopathic pericarditis (syndromes)
II. Due to living agents--infectious, parasitic
III. Vasculitis/connective tissue disease
IV. Immunopathies/hypersensitivity states
V. Diseases of contiguous structures
VI. Disorders of metabolism
VII. Trauma--direct, indirect
VIII. Neoplasms--primary, metastatic, multicentric
IX. Of uncertain pathogenesis or in association with various syndromes

Modified from Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

*Considerable overlap (e.g., categories III and IV, V and VIII).

See corresponding chapter sections for detailed outlines.

PERICARDIAL RESPONSES TO INFLAMMATION AND IRRITATION.

Noxious agents contacting the pericardium set up responses producing clinical disease. For example, microorganisms or antigenic material or immunocytes activated elsewhere can reach the pericardium through the bloodstream, lymphatic vessels, or adjacent organs or by traumatic (including surgical) implantation and set up infective pericarditis. When inflammation is intense, the subjacent myocardium becomes involved, permitting ECG diagnosis; pericardial inflammation is mediated by cytokines, such as tumor necrosis factors and interleukins.[23] Inflamed mesothelium produces increased

prostaglandins (inhibition of which may be an effect of antiinflammatory treatment). Intense inflammation involving both myocardium and pericardium produces myopericarditis. Immunopathic mechanisms are increasingly identified in the pathogenesis.[26]

DISEASES OF NEIGHBORING AND CONTIGUOUS STRUCTURES.[23]

Diseases of the myocardium, pleura, lungs, diaphragm, esophagus, and mediastinum involve the pericardium by contiguity or by hematogenous or lymphogenous transmission and may or may not become clinically obvious. Sometimes pericarditis is the first clue to disease in a nearby organ. Transmural myocardial infarction virtually always involves the pericardium, but pericardial involvement is diagnosed in fewer than half of patients. Tuberculous pericarditis when not due to hematogenous or lymphogenous implantation can be introduced by adjacent infected mediastinal lymph nodes. Each of the tissues of the pericardium with the exception of the elastic tissue can give rise to primary malignancies and benign tumors, producing irritative (inflammatory) and physical effects that are usually misinterpreted. This is less true for metastatic malignancy. Pericardial fat necrosis is rare, causing nondescript or sharp pain in the left lower chest, often with pleuritic fluctuation suggesting pleuritis or pericarditis. The chest radiograph may show a particularly smudgy pericardial fat pad. Treatment is with antiinflammatory agents or resection.

PERICARDIAL EFFUSION.

Pericardial effusion is identified as any excessive pericardial contents due to inflammatory exudation, systemic fluid retention, bleeding, gas (including air), pus, or any combination of these. Pericardial exudation arises mainly if not entirely from the visceral pericardium. Hydropericardium is a transudate and can result after systemic fluid expansion, as in cardiac failure and other conditions with solute and water retention. Hydropericardium is first recognized as enlargement of the cardiac silhouette. There are no recognized clinical consequences except with rare massive hydropericardia that compress lung and other adjacent structures. Inflammatory/irritative effusion is produced from an exudate, which appears when the rate of inflammatory exudation exceeds the resorptive capacity of the serosa, particularly its lymphatics and veins. They may be obstructed by inflammatory disease and compression by the effusion itself.[12] [23] Because large molecules are poorly transported by the pericardium, the tendency to fluid accumulation may be exaggerated by the oncotic effect of protein-rich exudates. Pericardial effusions induce four functional states[12] : (1) slow production of undetected fluid; (2) effusion without cardiac compression; (3) effusion at a rate appropriate to compress the heart significantly but checked by compensatory mechanisms; and (4) cardiac tamponade. In the first two states, either the normal residual capacity of the pericardium is not significantly exceeded or the fibrosa can stretch. Many effusions become stabilized at some level by compensatory mechanisms. *Tamponade is a continuum,* even in patients who never develop corresponding clinical syndromes; florid tamponade is an emergency. Bleeding, thrombosis, neoplastic tissue, and pus modify clinical and imaging aspects.

POLYSEROSITIS. [23]

Many conditions causing pericarditis can simultaneously or sequentially inflame other serous sacs. Like pericarditis, polyserositis may appear at any inflammatory state from acute to chronic. Symptoms and signs referable to one or another serosa may dominate the picture. Yet pericardial involvement can be the most distressing because of pericardial pain, emergent tamponade, or the steady deterioration of constriction (e.g., tuberculous serositis); physiologically unimportant pericardial adhesions are common. The vasculitis/connective tissue disease group is most likely to produce true polyserositis (exudates) whereas the acquired immunodeficiency syndrome (AIDS) produces a capillary leak syndrome with noninflammatory

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transudative effusions much more often than true polyserositis.

HEMOPERICARDIUM.

Hemopericardium is always important because of either frank bleeding into the pericardium as in cardiac wounds, erosion of vessels by tumor, an aggressive inflammatory process, or bleeding diatheses, including administration of thrombolytic agents to patients with pericarditis. Detectable bleeding occurs in effusions of almost every etiology. Unless overwhelmed by the rate of bleeding, the fibrinolytic and anticoagulant properties of the pericardial serosa as well as the beating action of the heart (which defibrinates blood) nearly always keeps most or all of the blood liquid and mixed with other pericardial contents. Frank blood and particularly clots, nearly always indicate major bleeding, which must be dealt with at its source. Indeed, clots, recognizable by echocardiography as hyperechoic objects in a pericardial effusion, usually mandate surgical rather than needle drainage. Moreover, any significant amount of blood in the pericardial fluid, especially in the presence of damaged serosa, is the substrate for adhesions and loculations. Malignancy is a major cause of hemopericardium. Subacute and chronic hemopericardium may be "idiopathic" or due to trauma, bleeding disorders, or vascular anomalies. Increasing fluid may be osmotically affected by split proteins (e.g., fibrolysis) and other molecules.

CHYLOPERICARDIUM.

This condition results from extravasation of chyle owing to a neoplasm, particularly lymphangiomatous hamartoma or cystic hygroma, or abnormal communication between pericardium and thoracic duct.[27] Many cases follow cardiac and thoracic surgery, suggesting damage to lymphatic channels; many others are idiopathic. Chylopericardium tends to be large and chronic, with an element of tamponade, and is only rarely constrictive.[10] The fluid is milky and alkaline with electrolyte, protein, glucose, and cholesterol levels similar to those of blood serum. Fat studies are typical of

chyle and include chylomicrons. In neoplasia, the pericardium can refill so rapidly that reaccumulation of chyle may be visible during operation. No visible communication may be demonstrated between the pericardium and the alimentary tract, especially in nonneoplastic patients. Some communication is indicated in chylopericardium by the following tests: (1) intrapericardial appearance of ingested lipophilic dyes, (2) frequent successful treatment by thoracic duct ligation; (3) lymphangiography demonstrating a relationship between thoracic duct and pericardial cavity; and (4) CT or MRI densities consistent with fat (note that if the patient has not eaten for some time, chylous fluid may become clear). "Primary chylopericardium" denotes an unknown cause.[27] Chylopericardium obligates indefinite assessment for constriction. Although chyle is bactericidal, the effusion can become infected. Enhanced CT with lymphangiography should be diagnostic.[28] Conservative management includes pericardial drainage and a low-fat diet with increased medium-chain triglycerides.[23] More often, low thoracic duct ligation plus a pericardial window or resection is required.

CHOLESTEROL PERICARDITIS.

This condition is characterized by high concentrations of cholesterol and other lipids in pericardial fluid and cholesterol crystals in pericardial tissue.[23] Cholesterol effusions tend to be large and subacute or chronic and of multiple etiology. Total pericardial fluid cholesterol approaches or exceeds blood cholesterol (usually normal) with values often more than 500 mg/dl, accompanied by increased total lipids. Cholesterol in most myxedematous effusions lacks crystal formation and usually is in concentrations below the elevated serum level. Cholesterol effusions are turbid, brown, yellow, orange, amber, purple, or coffee color, with a sheen giving a "gold paint" appearance. There may be evidence of recent or remote hemorrhage and leukocytes (mainly lymphocytes). Specific gravity is nearly always greater than 1.020, whereas electrolyte, total protein, and albumin:globulin ratios approximate those of blood. The pericardium is often thickened by scarring, frequently with variable amounts of fibrin and yellowish nodules, plaques, and papillomatous masses of cholesterol. The epicardium may be visibly inflamed, and constrictive epicarditis is not uncommon. Microscopically, there is often intense fibrosis, with inflammation with many cholesterol clefts and crystals and other lipid crystals. Phagocytes take up considerable lipid and some iron pigment; histocytes have foamy cytoplasm. Crystals and clefts are often surrounded by foreign body giant cells and elements of chronic granulomatous inflammation. Examination under polarized light shows cells containing "Maltese crosses."

Cholesterol effusions occur with pericarditis in tuberculosis, rheumatoid arthritis, and after traumatic hemopericardium, as well as myxedema. In the inflammatory lesions, granulomas are probably a source of the cholesterol as is blood. In "formes frustes" high cholesterol concentration is without crystal formation. Any chronic effusion might result in cholesterol precipitation, particularly with a cholesterol source like blood. Unfortunately, pericardiocentesis frequently results in rapid refilling and sometimes epicardial constriction or unremitting chronic cardiac tamponade.[23] [29] Conservative treatment is drainage, but definitive treatment is pericardial resection and management of any underlying diseases.

LYMPHOPERICARDIUM.

This condition is rare and related to local or, more often, generalized lymphangiectasis. Fluid has characteristics of lymph and may contain a predominance of lymphocytes.[23]

PNEUMOPERICARDIUM AND PNEUMOHYDROPERICARDIUM.

In adults, pneumopericardium may be "spontaneous" and usually occurs in conjunction with hemopericardium or some type of effusion.[23] [3] ° It may follow wounds or fistulous communications due to primary disease[31] or instrumentation of adjacent viscera, which can also produce *pyopneumopericardium.* Pericardial infection by gas-producing organisms duplicates the picture. Some cases may be due to malignant destruction of tissue but also to penetrating and nonpenetrating chest and upper abdominal trauma or after single-lung transplantation. Infants and occasional adults on respirators or with severe asthma develop pneumopericardium from alveolar rupture by high-pressure air or oxygen dissecting into the pericardium through weak points in the pericardial reflections over the great vessels.[1] When due to indirect (blunt) trauma, pneumopericardium occurs by three main mechanisms: (1) direct tracheobronchial-pericardial communication; (2) pneumothorax with a pleuropericardial tear; and (3) penetration along pulmonary venous perivascular sheaths from ruptured alveoli to the pericardium. On chest radiography, air-fluid levels indicate pneumohydropericardium. A chest radiograph may show air in the transverse sinus and often subcutaneous emphysema.

TENSION PNEUMOPERICARDIUM.[30]

This condition is due to increasing air, gas, or fluid, which produces pneumotamponade, often with marked cyanosis and hypotension. Pneumopericardium and hydropneumopericardium can produce audible clicks and splashes and an "air gap" sign on M-mode echocardiograms.

PERICARDIAL DISORDERS DURING PREGNANCY.[23]

There is no evidence that pregnancy affects susceptibility to pericardial disease. However, although tamponade has been observed, the physiological 40 to 50 percent increase in blood volume during pregnancy may moderate its physiological and clinical expression. Many pregnant women normally develop a minimal to moderate clinically silent hydropericardium by the third trimester; this could combine with less than usual exudation by any acute pericarditis to cause cardiac compression. Most pericardial disorders run their accustomed courses during pregnancy and are managed as in nonpregnant patients. Unless contraindicated, treatment with antiinflammatory drugs, antibiotics, and drainage for suppurative pericarditis, drainage of tamponading fluids, and pericardiectomy for constriction, recurrent pericardial effusion, and resistant bacterial pericarditis are indicated.

FETAL PERICARDIAL FLUID.

This can be detected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth; more fluid should raise questions of hydrops fetalis, Rh disease, hypoalbuminemia, and immunopathy or maternally transmitted mycoplasmal or other infections. However, "idiopathic" pericardial effusion and tamponade may occur in otherwise normal fetuses (necessitating investigation for infection and neoplasia).[32]

PANCREATITIS.

Acute and recurrent pericarditis, pericardial effusion, and tamponade associated with pancreatitis may be due to simultaneous infection (presumably viral), immunopathy, or chemical

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injury by circulating enzymes and rarely by direct pancreatic-mediastinal communication.[23]

BETA-THALASSEMIA.

Acute and recurrent "idiopathic" pericarditis with all its consequences and complications occur in up to one half of children with thalassemia major (most often silent or mild), suggesting more than a casual relation. This may represent viral susceptibility or an immunopathy with a possible element of tissue injury by hemosiderin.[33]

FAMILIAL MEDITERRANEAN FEVER.[34]

Recurrent pericarditis sometimes accompanies pleuritis and/or peritonitis, making familial Mediterranean fever a polyserositis. Constriction is rare. Treatment is with colchicine.

ACUTE PERICARDITIS

"Dry pericarditis," strictly speaking, indicates pericardial inflammation without effusion, that is, with a fibrinous inflammatory exudate (Fig. 50-8) . Because most pericardial irritation evokes at least some fluid clinically, dry pericarditis encompasses cases in which excess pericardial fluid is virtually absent or clinically unimportant.[35] [36] Virtually all etiological forms can present this way (Table 50-4) . In some conditions, such as rheumatoid pericarditis, the acute phase is usually missed or discovered by accident, so that the history is that of the etiological illness, except when acute pericarditis is its first sign. Infectious pericarditis may be preceded by local and systemic signs of infection.[36] The classic example is acute viral pericarditis, which is responsible for most cases of

"idiopathic" pericarditis and nearly always preceded by a recent respiratory, gastrointestinal, or "flulike" illness. Moreover, symptoms and signs during acute pericarditis may be modified by or coexist with those of an inciting illness. A specific etiological diagnosis (i.e., nonidiopathic) is more easily discovered in "sicker" patients, including those who develop tamponade.[35]

SYMPTOMS.

The onset may be abrupt or insidious. Bacterial and viral pericarditis often strike dramatically, whereas the uremic or tuberculous pericarditis often goes unnoticed. Diagnosis can be suggested by symptoms with an abrupt onset, but it may depend on objective manifestations after an insidious onset. Viral pericarditis, for example, can declare itself by crescendoing pain over several hours, whereas uremic or tuberculous pericarditis often presents as fever of unknown origin.

PAIN (Table 50-5) .

Over the vast range of causes (see Table 50-4) , pain is the most common symptom, although it often is absent; thus, rheumatoid pericarditis is nearly always silent whereas acute infectious pericarditis only occasionally lacks pain. Pain can be due to inflammation of the pericardium itself, the phrenic nerves, the adjacent pleura, sympathetic nerves accompanying coronary vessels in the epicardium, or potentiation of the algesic properties of bradykinin by pericardial prostacyclin.[35] Pain can be sharp, "sticking," dull, aching, and pressure-like in individual cases, with intensities varying from 1 to 10. Initially, it tends to be sharp, precordial, and pleuritic and is exacerbated by inspiration, cough, and recumbency; hence, patients sit up for relief. Pain onset, frequently perceived as sudden, particularly when it interrupts sleep, is occasionally related to exertion, which may be coincidental; once established, it worsens with exertion. Characteristic pain relief from sitting up and leaning forward may be related to the biomechanical characteristics of the parietal pericardium. These maneuvers may relieve increased pericardial tissue tension due to inspiration and truncal extension; they also splint the diaphragm.[35] Pain radiation can follow distributions common to angina as well as to the epigastrium, creating problems in differential diagnosis when the pain is not pleuritic or has a pressing quality, and particularly when it radiates to the jaw or one or both shoulders. Shoulder pain must be distinguished from pain in one or both trapezius ridges, usually the left. Trapezius ridge pain

Figure 50-8 Fibrinous pericarditis. Large fibrinous exudate on anterior epicardium. Minimal pericardial fluid permits delineation of fibrin.

transmitted through the phrenic nerves is virtually pathognomonic for pericardial irritation.[35] Indeed, some patients perceive pain only in a trapezius ridge. Note that patients must be asked to point to the areas of pain perception because patients and most physicians confuse the trapezius ridge with the shoulder. Pain can also occur in the midposterior thorax or below the left scapula. Palpation of the chest wall may elicit local tenderness revealing costochondritis, Tietze syndrome, or other chest wall

syndromes, including rib fractures in patients with traumatic pericarditis.[37] Finally, some patients do not describe "pain" but rather vague precordial distress with or without inspiratory or postural exacerbation. Some patients with myopericarditis (particularly viral) may have skeletal muscle myalgia.

OTHER SYMPTOMS.

A nonproductive cough is common, exacerbates pleuritic pain, and may antedate chest symptoms. Productive cough is due to associated illnesses. Hiccup is relatively rare. Odynophagia, rarely the only sign of pericarditis, occurs because of apposition of the esophagus and posterior parietal pericardium; odynophagia and dysphagia also result from pericardial inflammation or effusion due to spread from esophageal inflammation, trauma, or malignancy. Faintness and dizziness are uncommon in the absence of tamponade but can occur when there is considerable pain, tachycardia, or constitutional reaction.

SYSTEMIC REACTION.

Fever, usually less than 39°C (102.2°F), is common as a result of pericarditis or accompanying diseases and may herald the clinical onset. Elderly patients lacking mechanisms for cytokine liberation may not be febrile, and some with diseases such as renal failure may be hypothermic. Chills (rigors) are likely to accompany spiking fevers in suppurative pericarditis and some cases of idiopathic (presumably viral) pericarditis. Weakness and depression accompany some cases with marked systemic manifestations. Anxiety is common with very painful or disagreeable precordial sensations, especially in those with preexisting heart disease. Pallor may be a clue to systemic illnesses such as tuberculosis, uremia, neoplasia, and rheumatic carditis. In patients severely ill from antecedent or accompanying disease, symptoms and constitutional reaction

TABLE 50-4 -- ETIOLOGIES OF ACUTE PERICARDITIS*

I. Idiopathic Pericarditis

II. Pericarditis Due to Living Agents: Infections, Parasitoses

A. Bacterial

1. Suppurative (any organism)
2. Tuberculous; other mycobacterial

B. Viral

1. Coxsackie virus
2. Influenza virus
3. Human immunodeficiency virus
4. Hepatitis B, A, ?C virus
5. Other

C. Mycotic (fungal)
D. Rickettsial
E. Spirochetal
F. *Spirillum*
G. *Mycoplasma pneumoniae*
H. Infectious mononucleosis
I. *Leptospira*
J. *Listeria*
K. Lymphogranuloma venereum
L. Psittacosis (Chlamydiaceae)
M. Parasitic

III. Pericarditis in the Vasculitis/Connective Tissue Disease Group

A. Rheumatoid arthritis
B. Rheumatic fever
C. Systemic lupus erythematosus
D. Drug-induced lupus erythematosus
E. Scleroderma
F. Sjogren syndrome
G. ? Whipple disease (*Tropheryma whippleii* organisms)
H. Mixed connective tissue disease
I. Reiter syndrome
J. Ankylosing spondylitis
K. Inflammatory bowel diseases
L. Serum sickness
M. Wegener granulomatosis
N. Vasculitis (e.g., temporal/giant cell arteritis)
O. Polymyositis (dermatomyositis)
P. Behcet syndrome
Q. Familial Mediterranean fever
R. Dermatomyositis
S. Panmesenchymal reaction of corticosteroid hormone withdrawal
T. Polyarteritis
U. Churg-Strauss syndrome
V. Thrombohemolytic thrombocytopenic purpura
W. Hypocomplementemic uremic vasculitis syndrome
X. Leukoclastic vasculitis
Y. Other

IV. Pericarditis in Disease of Contiguous Structures

A. Myocardial infarction

1. Acute myocardial infarction
2. Postmyocardial infarction syndrome
3. Postpericardiotomy syndrome
4. Ventricular aneurysm

B. Dissecting aortic aneurysm
C. Pleural and pulmonary diseases

1. Pneumonia
2. Pulmonary embolism
3. Pleuritis

V. Pericarditis in Disorders of Metabolism

A. Renal failure

1. Uremia (chronic/acute renal failure)
2. "Dialysis" pericarditis

B. Myxedema

1. Cholesterol pericarditis

C. Gout
D. Scurvy

VI. Neoplastic Pericarditis

A. *Secondary* (metastatic, hematogenous, or by direct extension): carcinoma, sarcoma, lymphoma, leukemia, carcinoid, Sipple syndrome, other
B.*Primary* mesothelioma, sarcoma, fibroma, lipoma

VII. Traumatic Pericarditis

A. Direct

1. Pericardial perforation (esp. pneumopericardium)

a. Penetrating chest injury
b. Esophageal perforation
c. Gastric perforation

2. Cardiac injury: direct trauma

a. Cardiac surgery (see also V.A3 above) and IX.A below)
b. During catheterization

i. Pacemaker insertion
ii. Catheter ablation for arrhythmias
iii. Diagnostic
iv. Percutaneous transluminal coronary angioplasty with coronary dissection

3. Indirect trauma

a. Radiation pericarditis
b. Nonpenetrating chest injury

4. "Foreign-body" pericarditis

VIII. Pericarditis of Uncertain Pathogenesis and in Association with Various Syndromes

A. Postmyocardial and pericardial injury syndromes (?immune disorders)
B. Pericardial fat necrosis
C. Inflammatory bowel disease

1. Colitis (ulcerative; granulomatous)
2. Segmental enteritis (Crohn disease)
3. Whipple disease
4. Celiac disease

D. Loffler syndrome
E. Thalassemia (and other congenital anemias)
F. "Specific" drug reaction (psicofuranine; ?minoxidil, ? others)
G. Pancreatitis
H. Sarcoidosis
I. Cholesterol pericarditis not associated with myxedema or granulomas
J. Fat embolism
K. Bile fistula (to pericardium)
L. Wissler syndrome
M. "PIE" syndrome
N. Stevens-Johnson syndrome
O. Gaucher disease
P. Diaphragmatic hernia
Q. Atrial septal defect
R. Giant cell aortitis
S. Takayasu syndrome
T. Castleman disease (giant lymph node hyperplasia)
U. Fabry disease
V. Kawasaki disease
W. Degos disease
X. Acute pancreatitis
Y. Histiocytosis X
Z. Campylodactyly-pleuritis-pericarditis syndrome
AA. Farmer's lung
BB. Yellow nail syndrome
CC. Myeloid metaplasia
DD. Afibrinogenemia; hypofibrinogenemia
EE. Juvenile xanthogranuloma
FF. Dermatitis herpetiformis
GG. Hypereosinophilic syndromes
HH. Other

*Most etiologies can cause both "clinically dry" and effusive pericarditis and constriction.

provoked by pericarditis may be submerged in the total picture or suppressed by established treatment.

OBJECTIVE MANIFESTATIONS.

The cardinal sign of pericarditis is the pericardial rub (see Fig. 50-4) --three or fewer friction sounds per cardiac cycle[9] (described earlier). Rubs can be transient or intermittent but often last hours to days. Unusually persistent rubs indicate a tendency to chronicity or continuing pericardial irritation as from malignant

TABLE 50-5 -- PAIN IN ACUTE PERICARDITIS VS. ACUTE ISCHEMIA

	ACUTE PERICARDITIS	ACUTE ISCHEMIA
Onset	More often sudden	Usually gradual, crescendo
Main location	Substernal or left precordial	Same or confined to zones of radiation
Radiation	May be the same as ischemic, also trapezius ridge(s)	Shoulders, arms, neck, jaw, back; not trapezius ridge(s)
Quality	Usually sharp, stabbing; "background" ache or dull and oppressive	Usually "heavy" (pressure sensation) or burning
Inspiration	Worse	No effect unless with infarction pericarditis
Duration	Persistent; may wax and wane	Usually intermittent; <30 min each recurrence, longer for unstable angina
Body movements	Increased	Usually no effect
Posture	Worse on recumbency; improved on sitting, leaning forward	No effect or improvement on sitting
Nitroglycerin	No effect	Usually relief

From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

infiltration. Rubs are common in the presence of even large pericardial effusions. Echocardiograms in patients with clinically dry pericarditis may show fibrin with or without a small effusion or with a ragged "sunburst" appearance. ECG abnormalities range from normal to nonspecific to typical stage I ST segment deviations, usually with PR segment deviations (see Fig. 50-6, Table 50-6) . Like the pericardial rub, the stage I ECG change is virtually diagnostic of acute pericarditis, always requiring differentiation from certain mimics and particularly when there are typical ECG variants. Occasionally, ECG abnormalities are the only evidence of pericarditis. Finally, any arrhythmias are *not* due to the acute pericarditis itself.[11] Pleural effusions, mainly on the left, are frequent in acute pericarditis. Leukopenia is uncommon and may be due to bone marrow

depression by associated disease. Other acute phase reactants,[38] such as the sedimentation rate (ESR) and C-reactive protein (CRP), show mild to marked elevations, the level reflecting the intensity of the process, its inciting disease, or subepicardial myocardial involvement. Serum enzyme elevations derived from myocardium, such as the MB isoenzyme of creatine kinase (CK-MB), aspartate aminotransferase, aldolase, lactate dehydrogenase (LDH), and troponin I, reflect the degree of myocardial involvement by subepicardial myocarditis.[35] Serum myoglobin is usually normal. Patients with the greatest ST segment deviation tend to develop the largest rises, although the correlation is imprecise: some patients do not have significant levels despite ECG changes. Gallium-67 scanning can identify inflammatory and leukemic infiltrations and appears to be superior to scanning with indium-111.[35] [40]

TREATMENT.

Treatment aims to relieve symptoms and eliminate etiological agents. Most patients are hospitalized for complete diagnosis and observation for complications, particularly effusion and tamponade. Antiinflammatory and symptomatic treatments resemble those of other conditions producing comparable pain, fever, and malaise and must be individualized. Nonsteroidal antiinflammatory drugs (NSAIDs) are the mainstay, possibly because many inhibit pericardial synthesis of prostaglandin I_2 . Any effective NSAID may be used. However, indomethacin should be avoided in adults unless all other options fail, because it reduces coronary flow and has marked side effects. Ibuprofen has an excellent side effect profile and increases coronary flow, with the advantage of the largest dose range of the "classic" NSAIDs.[35] [39] Depending on clinical severity and response, treatment may initially require ibuprofen, 300 to 800 mg every 6 to 8 hours, and can be increased. In many mild cases, particularly of "idiopathic" pericarditis, 1 to 4 days of treatment appears adequate. Finally, all patients should be monitored for side effects; because all NSAIDs affect the gastrointestinal mucosa, it is wise to add misoprostol or other mucosal protectants.[41] Anecdotal evidence is increasing that colchicine added to an NSAID or even as monotherapy is effective for the initial attack and to prevent or treat recurrences.[35] It is well tolerated at 0.6 mg every 12 hours with or without a loading dose but must be monitored for side effects. A well-controlled trial is needed. Corticosteroid therapy should be avoided unless required for a specific illness such as a connective tissue disease or when all else fails, and then it should be used in minimally effective doses and carefully tapered. For protracted

TABLE 50-6 -- ECG IN ACUTE PERICARDITIS VS. ACUTE ISCHEMIA

	ACUTE PERICARDITIS	ACUTE ISCHEMIA (AP, MI)
J-ST	Diffuse elevation usually concave, without reciprocal depressions	Localized deviation usually convex (with reciprocals in infarct)
PR segment depression	Frequent	Almost never
Abnormal Q waves	None unless with infarction	Common with infarction ("Q wave" infarcts)

T waves	Inverted after J points return to baseline	Inverted while ST segment still elevated (infarct)
Arrhythmia	None (in absence of heart disease)	Frequent
Conduction abnormalities	None (in absence of heart disease)	Frequent

AP=angina pectoris; MI=myocardial infarction.*From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.*

use of prednisone, ibuprofen or another NSAID should be introduced when tapering; after tapering the prednisone, the NSAID should also be tapered. Colchicine appears to improve therapeutic results and facilitate the "weaning" process.[42] Recovered patients should be observed indefinitely for one or more recurrences or later constriction. If patients require anticoagulants (e.g., those with prosthetic cardiac valves), heparin can be used under strict observation while the pericarditis is in progress.

DIFFERENTIAL DIAGNOSIS.[31]

Acute pericarditis must be differentiated from syndromes producing similar symptoms and signs (Tables 50-5 , 50-6 , 50-7 , and 50-8), bearing in mind that pericarditis may be (1) part of a generalized disease, (2) apparently isolated, or (3) part of a disorder affecting a neighboring organ and (4) occasionally the presenting syndrome of numerous diseases. Pain isolated to or referred to one or both trapezius ridges strongly compels consideration of pericarditis. Central pleuritic chest pain always raises a question of acute pericarditis if pleurisy can be ruled out, but both may occur simultaneously.

When the pain resembles that of cardiac ischemia (see Table 50-8) , it may be longer lasting, sharper, and unresponsive to vasodilator therapy. Purely ischemic pain lacks the frequently pleuritic quality of infarction-related forms of pericarditis. Angina produces ECG changes usually with depressed rather than elevated ST segments. Tables 50-5 , 50-6 , and 50-8 summarize the differentiation of pericarditis from ischemia and infarction. On strictly ECG grounds, up to one third of acute pericarditis cases resemble ischemic heart disease because of atypical ECG evolution (see Chap. 35) . Finally, pulmonary embolism can mimic acute pericarditis, particularly if with pleuritic pain (see Chap. 52) . The ECG is usually nonspecifically altered and the pleural rub, if any, as well as the pain may not be precordial. Rarely, pulmonary embolism provokes a purely pericardial or pleuropericardial rub, pericardial effusion (usually small), or a pericardial response resembling the post-myocardial infarction syndrome.

Monophasic pericardial rubs, particularly the most common one, the ventricular systolic rub,[9] can mimic murmurs of mitral and especially tricuspid regurgitation and also ventricular septal defect, because all rubs tend to be most intense or occur only at the

left mid to lower sternal border where some are palpable.[9] Assisting differential diagnosis are the short-term changeable nature of rubs and their occasionally unpredictable precordial distribution, as well as frequently absent heart disease. A typical stage I ECG is virtually diagnostic, although easily confused with the normal variant "early repolarization." The characteristic widespread ST segment changes are distinguishable from most acute myocardial ischemia and infarctions, which nearly always involve "regional" lead groups with reciprocal ST segment deviations in other leads; reciprocal ST segment depressions virtually never occur in uncomplicated acute pericarditis. Abnormal Q waves do not occur without associated

TABLE 50-7 -- CLINICALLY "DRY" ACUTE PERICARDITIS: PRINCIPAL DIFFERENTIAL DIAGNOSES

MANIFESTATION	TO BE DIFFERENTIATED
Electrocardiogram	
Stage 1	Acute myocardial infarction Early repolarization
Stage 2	Ischemia/infarction
Stage 3	Ischemia/infarction/myocarditis
Pain	Myocardial ischemia
	Angina Infarction
	Pleuritis Pneumonia Chest wall pain Pulmonary embolus (usually small)
Tachypnea	Pleuropulmonary disease Cardiac failure
Pericardial rub	Murmurs Pleural rub Chest wall sounds "Conus rubs"
	Pulmonary embolism Acute hyperthyroidism (Means-Lerman "scratch") Pacemaker rub (endocardial)

From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

or preexisting myocardial disease (see Chaps. 5 and 35) .

Myopericarditis/Perimyocarditis

Pericarditis is often accompanied by some degree of myocarditis and vice versa, with one or the other dominating the clinical picture. Most syndromes are primarily

myocarditic or pericarditic.

PATHOGENESIS.

Systemic disorders with frequent myocarditis, pericarditis, and myopericarditis include immunopathies, the vasculitis/connective tissue disease group, and drug-related pericarditis. Viral and other infections seem most frequent.[43] [44] Cardiotropic viruses can inflame myocardium and pericardium hematogenously, whereas bacterial and other organisms do so through lymphatics or by extension from pericardial infection. In eosinophilic forms, the destructive nature of the eosinophil is evident with high levels of eosinophilic cationic protein.[43] AIDS frequently involves the myocardium, pericardium, or both[45] (see Chap. 68) . AIDS myopericarditis results from infection with the human immunodeficiency virus (HIV) and viral co-infection, damage by CD5 and CD8 lymphocytes, and myocardial Kaposi carditis.[45] Immunological mechanisms appear necessary for persistent and recurrent myopericarditis even in the absence of a viral genome.

TABLE 50-8 -- "CLINICAL FACTORS": ACUTE PERICARDITIS VS. ACUTE ISCHEMIA*

	ACUTE PERICARDITIS	ACUTE ISCHEMIA (AP, MI)
Myocardial enzymes	Normal or elevated	Elevated (infarct)
Pericardial friction	Rub (most cases)	Rub only if with pericarditis
Abnormal S_3	Absent unless preexisting	May be present
Abnormal S_4	Absent unless preexisting	Nearly always present
S_1	Intact	Often dull, mushy after first day
Pulmonary congestion	Absent	May be present
Murmurs	Absent unless preexisting	May be present

AP=angina pectoris; MI=myocardial infarction.*From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.*

*Electrocardiographic differences in Table 50-6 .

Almost any acute pericardial or myocardial damage can induce an immunopathy with recurrences (especially enteroviral and cytomegaloviral infections). Viruses provoke antibodies to myolemmal and sarcolemmal membranes (ALMABs and ASABs) and may be pathogenetic because of their cytolytic or cytotoxic properties.[46] The AMLABs and ASABs are part of B-cell-driven immune responses; for example, IgG-type AMLABs are

diagnostic of perimyocarditis in tuberculous pericarditis. Drug-induced myopericarditis probably is pathogenetically related through "allergic" or hypersensitivity mechanisms. Finally, disease-specific autoantibodies reflect autoimmune involvement, although they correlate poorly with myocardial biopsy.[46] [47]

Many members of the vasculitis/connective tissue disease group (see Chaps. 48 and 67) , classically including acute rheumatic fever, regularly produce myopericarditis.[43] Occasionally, inflammation spreads by contiguity from a primarily pericarditic process to the myocardium or from mediastinitis to the pericardium and myocardium. Pericardial tuberculosis often involves the myocardium, which becomes inflamed and ultimately fibrotic; both active and burned out tuberculosis are evident in tuberculous constriction. In contrast, pure uremic pericarditis may have a brisk inflammatory process in the pericardium and epicardial fat without invading the myocardium.

Evidence of myocardial involvement in pericarditis is summarized in pericarditis (Table 50-9) . During myocarditis, pericardial involvement is mainly recognized by a rub or an effusion.[43] The ECG changes of acute pericarditis, as well as QT prolongation, indicate at least superficial myocarditis even when myocardial involvement is subclinical. Reciprocal and regional J (ST) changes (Fig. 50-9) and abnormal Q waves in the absence of infarction represent significant myocarditis disproportionately involving regions of the myocardium. Arrhythmias or conduction disturbances are absent even in severe pericarditis without independent or related disease of the myocardium or valves; myocarditis qualifies as such a related disease.[38]

After even mild idiopathic (presumably viral) pericarditis, transient myocardial functional and wall motion abnormalities can sometimes be detected for months; in more severe cases, global LV or RV dysfunction or eventual dilated cardiomyopathy are strong evidence of a myocarditic component. Occasional patients who, after drainage of pericardial effusion, develop myocardial dilation and acute cardiac failure ("pericardial shock") in the absence of antecedent heart disease almost certainly have had significant myocarditis.[43] Transient cardiac enlargement, usually recognized by imaging in the absence of increased pericardial fluid, and true dyspnea represents myocarditis. In acute pericarditis, when tachycardia persists after fever and pain subside, a myocarditic component is likely. During acute pericarditis, particularly of viral origin, but also with *Mycoplasma, Leptospira,* and *Borrelia* (Lyme disease) infections and skeletal muscle pain (myalgia)

TABLE 50-9 -- CLUES TO SIGNIFICANT MYOCARDITIS IN PATIENTS WITH ACUTE PERICARDITIS

1. *Any* acute ECG QRS complex change, especially if localized or with atypical evolution. Convex ST segment elevation during acute pericarditis. Atrioventricular or interventricular block.
2. Any significant arrhythmia, especially ventricular (in absence of other heart disease)
3. Evidence of myocardial dysfunction (in absence of other heart disease):

a. Postpericardiocentesis abnormal S_3 (in absence of constrictive pericarditis)
b. Pulmonary edema
c. Postpericardiocentesis cardiac failure, especially pulmonary edema
d. Abnormal imaging and catheterization studies:

(1) Cardiomegaly
(2) Abnormal hemodynamics (in absence of constrictive pericarditis)
(3) Wall motion abnormalities

4. Sinus tachycardia:

a. Out of proportion to fever, anemia, and/or chest pain
b. Persistence after resolution of 6 through 10, below

5. Skeletal muscle myalgias, especially during viral pericarditis (suggests a myotropic organism)
6. Pericarditis with transudative effusion fluid
7. Nonpleuritic substernal chest pain with or without radiation (other than to trapezius ridges)
8. Elevated serum levels of cardiac enzymes, especially in presence of elevated serum myoglobin or troponin
9. Positive antimyosin-indium 111 scintigraphy
10. Myocardial production of tumor necrosis factor in absence of septic shock and congestive heart failure
11. Positive ^{99m} technetium pyrophosphate imaging
12. Positive gadolinium (Gd)-67 scintigraphy; Gd-DTPA-enhanced magnetic resonance imaging
13. Positive fibrinogen polymerization test

Figure 50-9 Perimyocarditis. *Top,* Acute phase with atypical stage III. T wave inversion in inferolateral distribution with J elevation in many leads in (in typical stage III T wave inversions with J on baselines). *Bottom,* Twenty-two days after onset: J on baseline with T wave inversion in inferolateral ("atypical") distribution consistent with myocarditis.

and tenderness, rhabdomyolysis[48] suggests a myotropic organism also involving the myocardium.[43]

Elevations of troponins I and T indicate myocardial damage.[49] Elevated cardiac enzymes with normal myoglobin levels suggest that the pericarditic process has affected only myocardial cell membranes, causing them to leak these substances. This is probably the mildest detectable myopericarditis; elevated serum myoglobin levels may indicate severe (cytoplasmic) damage. Although characteristic ECG changes of acute pericarditis can occur without abnormal enzyme release, in severe cases with significant myopericarditis, CK-MB increases (>10 mug/liter), particularly during ST (J)

deviations.[43] Monoclonal antimyosin antibodies labeled with indium-111 are markers of myocarditis,[45] as is detection of proinflammatory cytokine tumor necrosis factor (TNF) in the absence of congestive heart failure and septic shock.

CLINICAL CONSIDERATIONS.

Pericarditis with pericardial effusions that are closer to transudates, particularly with severe dyspnea, suggests significant myocardial involvement, whereas exudates indicate at least a strong pericarditic component.[43] Imaging and cardiac catheterization demonstrate transiently or permanently reduced myocardial function, that is, diffuse or localized abnormal ventricular wall motion. MRI shows focal myocardial edema in such zones of segmental or general wall motion abnormality. Finally, auscultation of a new S_3 ("ventricular gallop") is evidence either for myocardial inflammation or some degree of constriction.[43] [50]

Although cardiac enzymes and markers (troponin I and T) are released in most patients with myocarditis and ECG abnormalities, cardiac enzymes may be normal or only slightly increased and enzyme levels can fall while the ST (J) segment is still elevated.[51] Another clue to a myocarditic component during pericarditis is the occasionally convexly elevated J-ST segment, in contrast to the concave ST segment characteristic of acute pericarditis. Occasional patients have mixed forms of pain of both "myocardial" and pleuritic types, with dominance of one kind suggesting the dominant lesion (e.g., squeezing chest pain during apparent pericarditis suggesting significant myocarditis).

Any cardiac asynergy is due to myocardial abnormality and mimics acute infarction. A biopsy specimen obtained by catheter (endomyocardial biopsy) or by thoracoscope (epimyocardial biopsy) can identify myocardial inflammation, preferably if taken from the left ventricle, from which specimens are more often positive. Epimyocardial biopsies are much more productive.[49] [52] An active immune process will yield major histocompatibility complex Class I expression and tissue binding of IgG, IgA, IgM, and C3.[46] [47] [53] Finally, such evidence of myocardial inflammation sometimes persists in patients with constrictive pericarditis and may contribute to postpericardiectomy cardiac dilation and failure. In constrictive pericarditis with active myocarditis,[50] differentiation from restrictive cardiomyopathy may be difficult.

MANAGEMENT.

In the absence of myocardial failure, management of myopericarditis is the same as for acute pericarditis.[43] (In both, there are no adequate controlled clinical trials.) Patients may respond to antiinflammatory agents. Corticosteroids should be avoided unless all else fails and the patient is severely ill; near the onset of viral illness, they can stimulate virus replication and paralyze immune responses. Immunosuppressive agents seem useful in autoimmune myocarditis but not conclusively and could be injurious; they appear ineffective for viral (lymphocytic) myocarditis.[54] Interferon may be useful in enteroviral forms. Hyperimmune globulin has been used for cytomegaloviral-associated myopericarditis. Captopril may be of benefit in patients with definite heart failure.[55]

Pericardial effusions must be drained with special care because they may "splint" a myocarditic heart, which drainage permits to dilate.

Prognosis for recovery is generally good if the myocarditis is not intense (it is often focal in myopericarditis[56]), particularly the infective types, although varying degrees of myocardial damage can produce heart failure and, ultimately, dilated or restrictive cardiomyopathy. Rarely, Dressler syndrome (see Chap. 35) ensues.

PERICARDIAL EFFUSION AND HYDROPERICARDIUM

PATHOGENESIS AND CLINICAL CHARACTERISTICS.

Pericardial fluid is in dynamic equilibrium with the blood serum, including free exchange of water and electrolytes with surprising pericardial permeability to some large as well as smaller molecules. However, inflamed pericardium may obstruct these exchanges. Most pericardial effusions "weep" from the visceral pericardium.[57] Irritative and inflammatory effusions are associated with local production of substances such as cytokines, tumor necrosis factors, and interleukins.[58] Exudation of proteinaceous material and larger molecules and dissolution of intrapericardial thrombi osmotically attract additional fluid and impede reabsorption. Large effusions usually follow venous and lymphatic obstruction in the epicardium and often occur in the subjacent myocardium (myocardial lymph drainage normally occurs by means of the pericardium and probably contributes to effusions). Surprisingly small fluid increments and even the normal 15 to 35 ml can be identified by imaging.[57] Asymptomatic effusions are typically first suggested by relatively insensitive radiography (Fig. 50-10); a minimum of about 250 ml is needed to fill the pericardial reserve volume (see earlier) sufficiently to detectably increase the cardiopericardial silhouette. Increased pericardial fluid is either hydropericardium (transudate), "true" pericardial effusion (exudate; pyopericardium if purulent), hemopericardium, or mixtures of these, collectively termed "pericardial effusion." Exudates characteristically have more cholesterol, protein, and LDH than transudates, with cholesterol greater than 45 mg/dl, protein concentration more than half the serum level, and LDH greater than 200 U/liter or more than 60 percent of the serum LDH (the serum-effusion albumin gradient may be more valid).[57] However, the exudate-versus-transudate characterization may be indistinct. Moreover, with improving congestive failure, more rapid reabsorption of water than protein and LDH may convert hydropericardium to a pseudoexudate.

Figure 50-10 Large pericardial effusion. Chest radiograph shows a large, featureless bilaterally distended cardiopercardial silhouette and left pleural effusion. Lung fields are clear. (Patient had a low voltage ECG.)

Excess pericardial contents is loosely associated with vague *chest symptoms* such as

pressure sensations and aches. Rapid exudation can stretch the pericardium, producing "protopathic" pain. Very large effusions can encroach on neighboring structures, manifest as *dyspnea,* especially on exertion, when compression of lung causes a restrictive pulmonary defect; *dysphagia* from esophageal compression; *cough* from bronchial encroachment; *hiccups* from esophageal compression and involvement of the vagi and phrenic nerves; and *hoarseness* from compression of the recurrent laryngeal nerve.[57]

ETIOLOGY.

The causes of exudative pericardial effusion essentially correspond to those of pericardial inflammation and irritation (see Tables 50-3 and 50-4) ; large exudative effusions are most common with tumors, tuberculous pericarditis, cholesterol pericarditis, myxedema, vasculitis/connective tissue disease, uremic pericarditis, and parasitoses.[59] Unusual conditions include the eosinophilic syndromes, endomyocardial fibrosis, and cardiac transplantation (related to chemotherapy, especially cyclosporin or to rejection). Others occur during bone marrow transplant due to graft-versus-host disease.[57] A small to moderate clinically silent hydropericardium develops by the third trimester in many pregnant women (see Chap. 65) . Myopericarditis tends to produce mixed forms, because hydropericardium due to heart failure variably dilutes inflammatory effusions. Drug-related effusions may be difficult to recognize in diseases that can involve the pericardium (e.g., systemic lupus erythematosus [SLE]).

HYDROPERICARDIUM AND CLINICALLY NONCOMPRESSING EFFUSIONS.

Hydropericardium, which is usually small, occurs mainly in conditions of fluid retention but less frequently than pleural effusion. It is usually discovered by accident when imaging the chest or heart. "Noncompressing" exudative effusions due to pericardial lesions produce no significant change in blood pressure or cardiac output and no pulsus paradoxus. They may (1) be asymptomatic, (2) present as pericarditic pain or symptoms and signs of the causative condition, or (3) have asymptomatic but significantly increased respiratory fluctuation in ventricular function. Most have symptoms and signs only of "clinically dry" pericarditis. If the effusion is inflammatory, a pericardial rub usually is audible at some time. Slight exaggeration of the normal inspiratory fall in systolic blood pressure suggests "borderline" tamponade.

The *Bamberger-Pins-Ewart sign* is common with very large effusions and is characterized by a dullness and bronchial breathing between the left (rarely the right) scapula and the spine.[57] Otherwise, physical examination is nonspecific and undependable; even with tamponade, heart sounds may not be muffled and precordial percussion is untrustworthy. The ECG is of little or no direct help, although occasionally very large nontamponading effusions induce *electrical alternation* (see Chap. 5) (otherwise associated with critical tamponade). Reduced ECG voltage is nonspecific and undependable; only massive effusions as in severe myxedema produce true microvoltage that may be equally related to myocardial or hemodynamic abnormality.

IMAGING.

Radiography can only be suggestive. The shape of the heart shadow on fluoroscopy or static films cannot decisively distinguish true cardiomegaly from pericardial effusion. A "water bottle" silhouette or unusually wide mediastinal shadow (see Fig. 50-10) is suggestive, particularly when the lung fields are not congested. Left pleural effusion is common in both "wet" and "dry" pericarditis, whereas bilateral effusion is more common in congestive heart failure.[57] On a well penetrated lateral film, pericardial fluid is suggested by lucent *pericardial fat lines* within the cardiopericardial shadow. Echocardiography, CT, and MRI define heart size; cardiac function can be determined by echo-Doppler, contrast radiography, nuclear scanning, CT, or MRI.

ECHO-DOPPLER CARDIOGRAPHY (see Chap. 7 , Figs. 7-94 7-95 , 7-96 , and 7-97).

Table 50-10 summarizes the results of echo-Doppler investigation of effusions. On the echocardiogram, normal pericardial fluid and small amounts of excess fluid are seen posteriorly, between the LV wall and the parietal pericardium in systole only. With progressive accumulation, posterior fluid appears in both systole and diastole; in larger effusions, fluid appears anterior to the right ventricle. Fluid can be found behind the left atrium (i.e., in the pericardial oblique sinus) but usually with very large often tamponading effusions. *Effusion size* can be estimated by echocardiography: *small:* aggregate echo-free space in systole and diastole less than 10 mm; *moderate:* echo-free space in systole and diastole 10 to 20 mm, at least posteriorly; and *large:* echo-free space or 20 mm or more. As fluid increases, movement of the parietal pericardium decreases. Note that effusion size is a powerful overall predictor of prognosis; large effusions generally mean more serious disease.[57] [58] [59] Anterior fluid is frequently absent after cardiac surgery due to anterior adhesions.[60] With only an anterior echo-free space, posterior adhesions might be present, although epicardial fat is usually more likely; occasionally an infiltrative lesion, often malignant, is responsible. Epicardial fat, occasionally simulating posterior and circumcardiac effusions on echocardiography, must be distinguished by CT or MRI (see Chap. 10) .

With very large effusions, echocardiography may show cardiac oscillation ("swinging") within the pericardium (see Table 50-10) . With some degree of tamponade, often critical, swinging reverses direction on alternate beats instead of on every beat, producing ECG electrical alternation. Large effusions can cause mitral prolapse or pseudoprolapse, as well as midsystolic notching of the aortic or pulmonic valves. TEE is superior to transthoracic echocardiography (TTE), especially for identifying metastases, pericardial thickening, and clots, but it tends to underestimate the volume and distribution of effusions. Three-dimensional echocardiography is promising.[61] Although echocardiography is sufficient in most cases, CT and MRI may be needed if echocardiographic results are equivocal.[57]

MANAGEMENT.

Without tamponade (see p. 1841), hemopericardium, or pyopericardium, there are few

absolute indications for drainage. Very large nontamponading effusions can be drained to relieve symptoms due to compression of lung and other structures. Pericardial drainage occasionally may be required for diagnosis through examining fluid; pericardial biopsy can be obtained simultaneously. Pericardiocentesis by needle alone can be unrewarding diagnostically, although modern bacteriological and immunocytochemical methods are improving the results (Table 50-11) . [59] [62] [63] Adequate fluid with an adequate pericardial biopsy is better and more safely obtained by thoracotomy, subxiphoid incision, or video-assisted thoracoscopic resection and drainage, which also permits efficient and relatively inexpensive removal of thrombi, adhesions, and fibrinous material, minimizing chances for recurrence and cicatrization. Percutaneous balloon pericardiotomy may be used but is best for palliation of malignant tamponade. Loculated effusions may require open surgery or thoracoscopic drainage. The decision for operative intervention depends on (1) urgency of diagnosis and a prognosis requiring aggressive management and (2) probable yield of the diagnostic sample. Thus, persistent illness without an etiological diagnosis warrants obtaining tissue as well as fluid surgically. All patients, especially those with underlying cardiac disease, including myocarditis, should be monitored for postdrainage decompensation.[57]

PERICARDIOCENTESIS.

The precise techniques of needle drainage with and without catheter insertion are explained in detail elsewhere.[64] Techniques for nonsurgical drainage for relief of tamponade have been refined over many years, and imaging methods such as echocardiography and CT are now used routinely to locate the effusion and guide needle insertion.[65] Large effusions are more successfully reached; smaller effusions (<5 mm anteriorly) can be missed by the needle, with more frequent complications such as penetration or laceration of cardiac structures. Thick viscous fluids such as pus and partly clotted blood are difficult to aspirate. Patients with severe hemorrhagic disease may tend to bleed. Sites on the chest wall opposite the deepest anterior and inferior fluid collection (determined by imaging) should be used; echocardiographic studies show the apical approach usually to be best.[66] The procedure is best performed in an environment where resuscitation and monitoring

TABLE 50-10 -- ECHOCARDIOGRAPHIC AND DOPPLER EFFECTS OF PERICARDIAL EFFUSION AND CARDIAC TAMPONADE (VARYING SENSITIVITIES AND SPECIFICITIES)

A. Pericardial effusion

1. Echo-free space:

   a. Posterior to LV (small-to-moderate effusion)
   b. Posterior and anterior (moderate-to-large effusion)
   c. Behind left atrium (large-to-very large effusion and/or anterior adhesion

2. Decreased movement of posterior pericardium-lung interface
3. Brisk RV wall movements unmasked with anterior fluid
4. "Swinging heart" (large effusions, usually tamponade)

a. RV and LV walls move synchronously
b. Periodicity 1:1 or 2:1 (one or two swings per cardiac cycle); 2:1 is characteristic of definite tamponade
c. Pseudoparadoxic motion of LV posterior wall
d. Mitral/tricuspic pseudoprolapse; occasional true prolapse
e. Mitral systolic anterior motion
f. Alternating mitral e-f slope and aortic opening excursion
g. Aortic valve: midsystolic closure movement
h. Pulmonic valve: midsystolic notch

5. Hemopericardium: clotted blood identifiable
6. Inspiratory decrease in LV ejection time (with effusion; greater with tamponade)

B. Cardiac tamponade--**changes of effusion** plus:

1. RV compression

a. RV diameters decreased, especially outflow tract (7 mm)
b. Early diastolic collapse of right ventricle

2. RA free wall indentation (collapse) during late diastole and/or isovolumic contraction lasting at least one third of the cardiac cycle
3. LA free wall indentation (cases with fluid behind left atrium)
4. LV free wall paradoxic motion
5. SVC and IVC congestion (unless volume depletion); IVC >2.2 cm with <50% inspiratory collapse.
6. Exaggerated inspiratory effects (especially with pulsus paradoxus with reciprocal right-heart/left-heart effects during inspiration and expiration)

a. Right ventricle expands
b. Interventricular septum shifts to left
c. Left ventricle compressed
d. Mitral

(1) d-e amplitude decreased
(2) e-f slope decreased or rounded
(3) Open time* decreased; delayed mitral opening

e. Aortic valve: opening decreased*; premature closure*
f. Echographic stroke volume decreased

7. Notch in RV epicardium during isovolumic contraction
8. Course oscillations of LV posterior wall
9. Pseudohypertrophy: apparent wall thickening due to compression

C. Doppler studies: with any degree of tamponade

1. Major changes on first beats during inspiration and expiration
2. Generally reduced flows/stroke volumes
3. Exaggerated inspiratory augmentation of right-sided and decrease of left-sided flows
4. Respiratory variation in superior and inferior vena caval flow velocities marked in tamponade, less increased with effusion; double-peaked superior vena cava systolic wave. Decreased expiratory diastolic SVC flow.
5. Hepatic vein expiratory effect:

   a. Marked atrial reversal (AR wave)
   b. Marked decrease or reversal of diastolic forward flow
   c. (Occasional) systolic flow reversal

6. (Transesophageal echocardiograms): expiratory increase in pulmonary vein diastolic forward flow
7. Marked inspiratory decrease in LV ejection time; increased RV ejection time
8. Marked inspiratory increase in LV isovolumic relaxation time; decreased RV isovolumic relaxation time
9. Hepatic vein velocity difference between systole and atrial reversal <0 cm/sec

SVC and IVC=superior and inferior venae cavae; LA=left atrial; LV=left ventricular; RA=right atrial; RV=right ventricular.
From Spodick DH. The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

*Often difficult to define during pericardial effusion with tamponade; mitral valve opens late and may open only with atrial systole during inspiration.

equipment are available (e.g., the cardiac catheterization laboratory). Cardiac arrhythmias during the procedure will be detected by electrocardiography, but direct monitoring from the needle itself is not an adequate safeguard and may

TABLE 50-11 -- EXAMINATION OF PERICARDIAL FLUID

BASIC TESTS
1. Hematocrit and cell count
2. Stains: Gram, Ziehl-Nielsen, special
3. Cultures
4. Viral cultures; identification of appropriate immunoglobulins
5. Glucose; protein
6. Cytologic examination
7. Immunocytochemistry
ADDITIONAL TESTS FOR ANTICIPATED DIAGNOSES

1. Lactate dehydrogenase
2. Rheumatoid factor; antinuclear antibody
3. Quantitative complement levels
4. Cholesterol
5. Pathologic examination of cell blocks; cytochemical staining
6. pH
7. Amylase
8. Adenosine deaminase
9. Carcinoembryonic antigen

From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.

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be a handicap.[57] [64] [67] Right-sided heart and arterial catheterization are optimal and may reveal unanticipated effusive-constrictive pericarditis (see Chap 11) . Pericardial pressure can be measured through the intrapericardial needle or catheter. An intravenous drip containing isotonic saline or dextrose in water can be used to deliver supporting therapy.

Patients are monitored for cardiac decompensation ("pericardial shock") and for recurrent tamponade due to catheter blockage or reaccumulation of fluid (which is particularly important with bloody fluids or frank hemorrhage because of clotting). Residual clots can later dissolve, producing osmotically active fragments, thus renewing effusion or tamponade.

COMPLICATIONS.

The major complications of needle drainage are caused by needle contact with the heart, particularly laceration of a coronary vessel or chamber wall or myocardial perforation. Injuries to coronary veins, the right atrium, and the right ventricle are most dangerous; these are thin walled and likely to bleed briskly, producing hemopericardium. "Simple" perforation of the myocardium, particularly the left ventricle, without laceration is not rare but is well tolerated. Hypotension, probably reflex, can occur at any point, so that atropine should be on hand. Rare penetrations include stomach, colon, and lung. Arrhythmias occur particularly in patients with preexisting heart disease. Direct contact of the needle with the ventricular surface may produce an injury current or ventricular ectopic beats, and contact with the atrial surface may produce atrial ectopic beats.[57]

CARDIAC TAMPONADE

Pathophysiology

INTERACTION BETWEEN THE PERICARDIUM AND ITS CONTENTS.

To tamponade the heart, pericardial contents must (1) fill the pericardial reserve volume (see Fig. 50-2), then (2) increase at a rate exceeding the rate of stretch of the parietal pericardium, and (3) exceed the rate at which venous blood volume expands to support the small normal pressure gradient for filling the right side of the heart.[68] [69] Increased pericardial fluid causes loss of normal variations in pericardial contact stress (pressures become uniform over all cardiac chambers), increasing both ventricular and AV interaction. Pericardial volume increases partly by reducing cardiac chamber volumes and ultimately equalizes reduced diastolic compliance in all chambers. The resultant operational defect is restriction of cardiac inflows. (Interaction between the rate of fluid accumulation and parietal pericardial stretch determines pericardial stiffness and consequently the shape of the pericardial pressure-volume curve (Fig. 50-11). , With critical tamponade, the heart functions on the steep portion of the pericardial pressure-volume curve so that small fluid increments provoke large pressure increments. With slow fluid accumulation and a yielding pericardium, the initial portion of the pressure-volume curve remains "flat" longer and relatively large fluid volume increases cause relatively little pressure rise (see Fig. 50-11*right*).

Clinically, cardiac tamponade is defined as the decompensated phase of cardiac compression resulting from increased intrapericardial pressure.[68] Physiologically, tamponade is a continuum,[70] because even small increases in pericardial contents couple the pericardium to the heart, producing significantly increased AV and especially ventricular interaction that exaggerates the normal reciprocal respiratory effects on the right and left sides of the heart.[69] If unchecked by compensatory mechanisms, rising pericardial contents, such as effusions, blood, pus, gas, and combinations, ultimately produce critical cardiac compression: florid tamponade.

PATHOPHYSIOLOGICAL CONTINUUM OF TAMPONADE.

The rate of fluid accumulation determines the clinical response. Intrapericardial hemorrhage, as from wounds, rapidly produces "surgical" tamponade in minutes to hours, whereas a low-intensity inflammatory process can require days to weeks before critical cardiac compression ("medical" tamponade). At any rate of accumulation the system is always subject to sudden breakdown of compensation.

PERICARDIAL STRETCH AND PRESSURE-VOLUME RELATIONS.

Pericardial stretch is determined by the rate of increase of its contents and the response of two pericardial "springs": (1) wavy collagen, which tends to be smoothed by expanding pericardial contents, and (2) elastic tissue. Rapid accumulation exhausts these, and the limit of stretch is quickly reached, owing to the pericardium's J-shaped pressure-volume curve (see Fig. 50-11) . The ensuing decompensated tamponade tends to be a "last drop" phenomenon, the last bit of fluid putting the pericardium and consequently the cardiac chambers on the steep portion of their pressure-volume curves. Compression of all heart chambers resists cardiac filling, a form of diastolic

dysfunction in which at any diastolic volume excessive intracardiac pressure keeps pace with excessive intrapericardial pressure.

Pericardial drainage has a reciprocal effect: the first decrement usually produces the largest hemodynamic improvement by shifting the stretched pericardium back toward the less steep portion of its pressure-volume curve and consequently shifts the parallel myocardial pressure-volume relations.[68] [71]

RIGHT-SIDED HEART AND VENOUS FACTORS.

The early point of attack of the rising intrapericardial pressure is on the right atrium and ventricle. The pressures of these thinner chambers equilibrate with rising pericardial pressure before the LA and LV pressures. Normal RA and RV pressures are somewhat lower than in the corresponding left chambers, and the RV wall is much thinner. Thus, rising diastolic pressures paralleling rising pericardial pressure occur first in the right and later in the left sides of the heart.[72] Normally, intrapericardial pressure is lower than RA pressure so that RA (transmural) pressure is normally higher than its cavitary pressure; but with tamponade, rising pericardial pressure progressively reduces, and ultimately makes phasically negative, the transmural pressure of first the right and then the left heart chambers. Cardiac filling is maintained by a parallel rise in systemic and pulmonary venous pressure,[68] the venous beds generating enough pressure to keep both sides of the heart filled.[70] A key factor affecting compensation is the rate of venous volume expansion by fluid transfer from the tissues, from the arterial to the venous side of the cardiovascular system; this requires time and is inoperative in rapid "surgical" tamponade. Finally, diastolic suction probably augments filling.[68]

LEFT-SIDED HEART AND ARTERIAL FACTORS.

Pericardial pressure

Figure 50-11 Cardiac tamponade. Schema of pericardial pressure-volume curves (volume increases over time). At left, rapidly increasing pericardial fluid first fills the pericardial reserve volume (initial flat segment) then rises steeply to exceed the limit of parietal pericardial stretch, causing even steeper rise as smaller fluid increments disproportionately increase the pericardial pressure. At the right, a slower rate of pericardial filling takes longer to exceed pericardial stretch limit because of time available for "give." (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

equilibrates first with RV diastolic pressure also because pericardial stiffness is inherently greater than RV, but not LV, stiffness. As compensatory mechanisms (Fig. 50-12) are defeated, cardiac filling decreases, pericardial pressure equilibrates with LV diastolic pressure, and cardiac output decreases critically (even the left ventricle ultimately equilibrates due to drastic reduction in volume, producing a very low to

phasically negative LV transmural pressure). Eventually, diastolic pressures in both ventricles and the pulmonary artery all equilibrate with mean RA and LA pressures at approximately intrapericardial pressure--the characteristic hemodynamics of "pure" cardiac tamponade.[68] [69] [70] [71] During inspiration, left-right heart pressure differences are least or nil and commonly reversed; circulation is assisted by reciprocal flow changes in inspiration and expiration. During pulsus paradoxus the breathing phases have comparable but exaggerated differential effects; with inspiration, pulmonary wedge pressure falls below pericardial pressure. RA pressure also falls but not below pericardial pressure, enhancing inspiratory RV filling.

Transmural Pressure

The true "filling" (distending) cardiac pressures are the *myocardial* transmural pressures: cavity pressure minus intrapericardial pressure. (Cavity pressures are the sum of transmural pressure and pericardial pressures.) Transient reversal of the transmural pressure gradient (negative transmural pressure) causes RV collapse early in diastole (especially the weak RV outflow tract), and the RA, and sometimes LA, collapse in late diastole[73] (Figs. 50-13 and 50-14 ; see also Figs. 7-95 , 7-96 , and 7-97). (The critical negative transmural pressure buckling pressure for the right ventricle is 0.05 to 0.1 mm Hg; for the left ventricle it is 3.0 mm Hg.[74]) The RV inflow tract continues to fill while the outflow tract collapses, suggesting diastolic suction. The thick left ventricle does not collapse *unless* there is loculated high pressure fluid on its free border, RV hypertrophy, pulmonary artery hypertension, or intrapericardial adhesions. The onset of chamber collapses coincides with a 15 to 25 percent decrease in cardiac output[75] while compensatory mechanisms (see Fig. 50-12) still maintain arterial pressure, mainly due to increased peripheral resistance. Thus, at least in euvolemic and hypervolemic patients, RV collapse tends to occur earlier than pulsus paradoxus.

In tamponade, blood mainly enters the heart when blood is leaving it; pericardial volume and pressure vary continuously during the cardiac cycle, reflecting variations in early cardiac chamber volumes, although pericardial fluid continuously compresses the heart. In early diastole, the peak ventricular filling rate is radically reduced along with the filling fraction, emphasizing the importance of atrial contributions.[68] [69] By end-diastole or earlier, the ventricles are filled and maximally expanded within the pericardial sac, raising intrapericardial pressure to its maximum. Although atrial expansion by filling would tend to raise pericardial pressure at end systole, ventricular ejection is complete so the ventricles are at minimal volume, permitting intrapericardial pressure to fall. As the ventricles contract to eject blood and the pericardial "space" is increased, the atrial "floors" are pulled downward and pericardial pressure falls, increasing transmural pressure

Figure 50-13 Large pericardial effusion (PE) with tamponade. Arrow indicates right ventricular (RV) collapse. LV=left ventricle.

to enhance atrial filling.[69] Atrial cavitary pressure falls at the same time, producing the *x* descent in atrial pressure curves (Fig. 50-15) . Within these dynamics, the ventricles

eject reduced stroke volumes but remain underfilled and therefore operate at the low end of their Frank-Starling curves.

High pericardial pressure prevents normally rapid ventricular filling in early diastole. Moreover, the AV valves tend to close early. These factors progressively amputate the *y* descent of the atrial and venous pressure curves, reflecting curtailed and ultimately absent rapid ventricular filling. (Note that the LA *y* descent may be reduced long after elimination of the RA *y* descent.) Atrial reservoir function has increased importance: in severe tamponade the LA may fill only during expiration and the ventricles only during atrial systole.[69] Decreased filling due to premature AV valve closure exacerbates the reduced ventricular preload (shorter fiber length), further contributing to lower stroke volume and decreased ventricular ejection rate. Ultimately, the aortic valve opens only during expiration. During inspiration,

Figure 50-12 Cardiac tamponade and compensatory mechanisms. Solid arrowheads=tamponade. (From Spodick DH: The Pericarium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

Figure 50-14 Large pericardial effusion with tamponade. Biatrial (RA and LA) collapse (arrows).

leftward shift of the atrial and ventricular septa[68] further reduce LV chamber compliance and obstruct LV filling. Thus, the ventricular pressure curves show an immediate, shallow to barely visible diastolic rise from a slight lowering just after AV valve opening at the high diastolic levels seen with pressure equilibrium--typically 15 to 30 mm Hg in euvolemic patients (see Fig. 50-15) .

CORONARY BLOOD FLOW.

This is reduced primarily by increased subepicardial vascular resistance. Yet with normal coronary arteries coronary blood flow remains adequate to support aerobic metabolism because of proportionate reduction in cardiac work; that is, the ventricles are underloaded.[68] Coronary vasodilator reserve, capacitance, and resistance are not critically impaired. Renal and cerebral blood flow during tamponade, though reduced, are partly supported by autoregulation. However, peripheral vascular resistance is high (response to endogenous angiotensin II) with significant hepatic and mesenteric ischemia.

Despite decreased cardiac output, arterial blood pressure is maintained until relatively late in slowly developing ("medical") tamponade, partly by alpha-adrenergic mechanisms, but thereafter may decline precipitously, owing to falling stroke volume and cardiac output. Good myocardial function permits the ventricles to increase the

amount of blood ejected per beat (increased ejection fraction). Diseased or injured left or right ventricles do not maintain compensation as well as normal hearts.[76] [77]

COMPENSATION AND DECOMPENSATION.

Compensatory mechanisms (see Fig. 50-12) include time-dependent pericardial stretch and blood volume expansion, tachycardia, increased ejection fraction, and peripheral vasoconstriction due to intense adrenergic stimulation responding to falling cardiac output. Adrenergic stimulation, including increased serum catecholamines, produces (1) alpha-adrenergically increased systemic resistance, which maintains central blood pressure and supports the gradient for coronary flow (increased systemic resistance is not affected by beta blockade but is decreased by alpha blockade, which is potentially decompensating); (2) a beta-adrenergic contribution, which increases heart rate; (3) rising pressure in the right atrium, which also induces tachycardia to defend the minute cardiac output; (4) beta-adrenergic stimulation, which augments diastolic relaxation; and (5) increased inotropy, which minimizes ventricular and systolic volume and improves the ejection fraction. In decompensated tamponade, the blood pressure fall is strongly influenced by an opioid-dependent mechanism, as demonstrated by naloxone-induced blood pressure increase without increasing cardiac output, that is, a large additional increase in systemic resistance.[75]

Owing to arterial and atrial baroreceptor unloading, arterial pressure is augmented by neurohormonal activation, with a limited late contribution by the renin-angiotensin-aldosterone system. Renin, angiotensin II, arginine vasopressin, and aldosterone decrease urine flow and renal sodium and potassium excretion (after mean blood pressure decreases by about 30 percent), followed by increased adrenocorticotropic hormone.[69] A neurogenic antinatriuresis reflexly increases renal sodium and fluid retention, which, teleologically, defends cardiac filling by increased blood volume and venous pressure. Unlike cardiac failure at comparable central pressures, atrial natriuretic factor does not increase because tamponade prevents myocardial stretch. (Teleologically, this is also favorable because atrial natriuretic factor would increase renal sodium and water elimination and is harmful to myocytes, depressing contractility.[77A]) Finally, tamponade can produce a profound arterial respiratory alkalosis.[67] Mixed venous (pulmonary artery) blood pH, P_{CO_2} , and serum bicarbonate are relatively unchanged, but as cardiac output falls critically the difference between arterial and mixed venous P_{CO_2} increases.

ATYPICAL CARDIAC TAMPONADE.

This occurs in four forms: low pressure, occult, right-sided, and hypertensive.[69] In volume-depleted patients, hypovolemia attenuates compensatory increases in venous blood volume and pressure so that cardiac output falls at lower ventricular diastolic pressure: *Low pressure tamponade* may occur at mean diastolic pressures as low as 6 mm Hg with few symptoms at rest and with or without significant systemic hypotension; yet both RV collapse and pulsus paradoxus may be present. Although pulse contours tend to be abnormal, it may be necessary to expand blood volume by an intravenous saline challenge to produce diagnostic pulse morphology. In *occult tamponade,* pericardial pressure equilibrates with RV and often LV diastolic pressure without a

compensatory increase in venous pressure. *Right-sided tamponade,* with right diastolic pressures exceeding left, can occur when LV compliance is very low (e.g., LV hypertrophy) or, more commonly, after cardiac surgery, if fluid is loculated over the right side of the heart. In *hypertensive tamponade,* even with significantly low cardiac output there is unusually high (i.e., normal to even hypertensive) systolic arterial pressure, probably due to excessive adrenergic stimulation.[78]

Figure 50-15 Cardiac tamponade; pressure equilibration. Pulmonary artery (PA) diastolic, right atrial (RA) mean, and right ventricular (RV) diastolic pressures are each approximately 15 mm Hg. Respiratory fluctuation of right ventricular systolic pressure is between 23 mm Hg in maximum expiration and 29 mm Hg at peak inspiration. Right atrial pressure has a single conspicuous drop, the *x* descent; there is no *y* descent. Pulmonary artery systolic pressure changes follow the right ventricular systolic pressures at approximately the same levels. (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

Clinical Features

Pericardial disease of almost any etiology can produce cardiac tamponade, defined as significant compression of the heart by accumulating pericardial contents (liquids, pus, blood, clots, and gas singly or combined).[79] In patients who present with tamponade the great range of pericardial disease requires etiological assessment by probability while anticipating pathogenetic and etiological surprises.[64] Because tamponade is a pathophysiological continuum, patients can have mild to florid tamponade, the latter a form of cardiogenic shock and the former a stage that can progress. Symptoms and signs mirror the rate of physiological impairment. Thus, "medical" and "surgical" tamponade are loose labels conveying relative urgency.[79] "Surgical tamponade," typified by intrapericardial hemorrhage, can quickly overwhelm compensatory mechanisms; with cardiac wounds and intrapericardial rupture of dissecting aortic hematoma as little as 150 ml of blood and clots can be rapidly lethal (see Chap. 51) . In contrast, in primarily inflammatory or irritative bloody effusions, slowly escaping blood is prevented from clotting by the pericardium's fibrinolytic activity and defibrinization by the "whipping" action of cardiac beating. (Note that almost every form of pericarditis can provoke variably bloody effusion.) In "medical tamponade" fluid exudes at a wide range of rates so that critical cardiac compression may first appear at anywhere from 200 ml to well over a liter. The volume of fluid causing tamponade varies inversely with both parietal pericardial "give" and thickness: disorders that thicken or scar the pericardium such as intense or repeated inflammation can sharply reduce the amount of effusion and bleeding for critical cardiac compression. The clinical onset, ranging from insidious to rapid to sudden, is related to the tempo of physiological impairment. In a patient first discovered to have hundreds of milliliters of fluid, the interplay of exudation rate and pericardial "compliance" permits compensatory responses to keep effusions tolerable longer than in "surgical tamponade."[80]

SYMPTOMS.

Patients may have symptoms of an inciting pericardial disease, notably chest discomfort, but in those presenting unconscious, obtunded, or with convulsions there may be no useful history. Tachypnea and dyspnea on exertion progressing to air hunger at rest (occasionally orthopnea) are common, partly related to increased pulmonary interstitial water increasing lung stiffness. Cough and dysphagia are not uncommon and are deceptive as early complaints. Most patients become weak and anorectic and have symptoms ranging from feeling faint to having syncope. Anemia, common in malignancies, exacerbates dyspnea and weakness. Finally, insidiously developing tamponade may present as signs of its complications, such as renal failure, abdominal plethora, or hepatic (shock liver[81]) and mesenteric ischemia.

PHYSICAL FINDINGS.

Physical examination is of little use in determining the presence of the pericardial effusion itself, although occasional large effusions produce a Bamberger-Pins-Ewart sign. Tachycardia (>100 beats/min) is the rule, although many patients have heart rates of 90 to 100 beats/min and the rate is lower in hypothyroidism and in many uremic patients. During acute pericarditis with tamponade, uremic pericardial rubs often remain and can even be loud. Heart sounds may be distant, owing to insulation by fluid and reduced cardiac function, sometimes with relative accentuation of the pulmonic component of S_2 . The precordium may be quiet and an apex beat not palpable, although, with preexisting cardiomegaly or anterior and apical pericardial adhesions, active pulsations may be palpated. Significant tamponade produces absolute or relative hypotension; indeed, tamponade is part of the differential diagnosis of unexplained hypotension. In "surgical tamponade," shock levels are usual; but in early "medical tamponade," systolic blood pressure is commonly greater than 90 mm Hg. Occasional patients are hypertensive,[78] especially if they have preexisting hypertension; in these patients "normal" blood pressure may be low. (Note that hypertensive blood pressures characterize patients with exaggerated compensatory adrenergic responses and greatly increased peripheral resistance hypertensive tamponade.) Cool extremities, nose, and ears, sometimes with acral cyanosis, are due to vasoconstriction and relative circulatory stasis. Central cyanosis is rare and may be due to a right-to-left shunt, usually through a patent foramen ovale,[82] that disappears after relief of tamponade. Fever is related to etiology, particularly infections. Febrile tamponade may be misdiagnosed as septic shock.

If the patient is not hypovolemic and especially if fluid accumulates sufficiently slowly for expansion of blood volume, jugular venous distention can be anywhere from just visible to striking. Peripheral venous distention can be seen in the forehead, scalp, and ocular fundi. Rapid "surgical tamponade," especially acute hemopericardium, can induce jugular pulsations without distention (i.e., no time for compensatory blood volume expansion). In "medical tamponade," heart rates between 85 and 120 beats/min may yield jugular pulsations slow enough to determine that there is an *x* descent but absent or greatly attenuated *y* descent. Indeed, if a venous pressure level can be discerned,

this single definitely negative phase can be timed as midsystolic (between S_1 and S_2). These are not outward pulsations; *x* and *y* in compressive pericardial disease are "collapses" from a high standing level. Neck veins may also show the normal falling pressure level during inspiration. An inspiratory increase or lack of fall, the so-called Kussmaul sign, belongs to constriction; when verified with tamponade, or after pericardial drainage, it indicates underlying epicardial constriction.

Pulsus Paradoxus (See also Chap. 4)

This is defined as a systolic drop in arterial pressure of 10 mm Hg or more during normal breathing. Most patients with cardiac tamponade have some degree of pulsus paradoxus, often palpable in peripheral arteries (Fig. 50-16) . At very low cardiac outputs, however, an arterial catheter may be needed. With a pronounced pulsus paradoxus there may be no Korotkoff sound in inspiration--indeed, the aortic valve may not open in inspiration--with complete inspiratory loss of pulsations in muscular arteries like the radial (the more elastic carotid is less easily evaluated). Pulsus paradoxus may first be appreciated by taking the radial pulse and watching the patient's abdomen during normal breathing. Breathing should not be exaggerated because that can exaggerate the pressure drop. As the abdomen rises, the pulse weakens or disappears.

To quantify the blood pressure difference noninvasively, a cuff is inflated to 15 mm Hg above the apparent highest systolic level and slowly deflated until the first beats are heard and then held at that point during normal respiration (the sequence resembles "bump-bump-bump, silence-silence-silence, bump-bump-bump;" the "bumps"--Korotkoff sounds--are expiratory). Deflation is then continued to where all beats are audible. The difference between the pressures when systolic sounds are first heard and then are continuously heard gives the "size" of the pulsus paradoxus. If a patient is first discovered with pulsus paradoxus, the pericardial variety must be differentiated from other conditions that produce pulsus paradoxus, such as massive pulmonary embolism, profound hemorrhagic shock and other causes of acute hypotension, and obstructive lung disease. In conditions altering tamponade physiology and respiratory mechanisms, pulsus paradoxus may be undetectable.

Figure 50-16 Pulsus paradoxus during early cardiac tamponade. Brachial artery systolic pressure falls excessively during normal breathing (142 to 124 mm Hg); diastolic pressure is steady at 76 mm Hg. ECG shows marked PR segment depression. (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

PATHOPHYSIOLOGY.

Cyclic cardiocirculatory changes during normal breathing alternately favor right- and left-sided heart filling and ventricular performance, with corresponding pulmonary artery

and aortic pressures and flows. Pulsus paradoxus is a pulse (pulsus), not a pressure, change.[83] (There were no blood pressure cuffs or catheters; to Kussmaul it was "paradoxic" since the radial pulse disappeared during inspiration while the apex continued to beat.) Pulsus paradoxus is an exaggeration of the normal inspiratory fall in arterial flow and systolic pressure (see Fig. 50-16) (arbitrarily 10 mm Hg). Transmission of pleural pressure variations to the cardiac chambers through the pericardium explains pulsus paradoxus in tamponade whereas their insulation from transmission by scar tends to limit or suppress pulsus paradoxus in constriction. Inspiratory RV volume increase is indispensable for pulsus paradoxus, because when systemic venous return is held constant, tamponade does not cause pulsus paradoxus.[84] Moreover, the right side of the heart is the crux of tamponade dynamics and pulsus can occur in isolated right heart tamponade.[83] [85] Although usually elicited by cuff, pulsus paradoxus is more sensitively revealed by catheter, especially during early tamponade when pericardial pressures are approaching equilibrium with right-sided but not yet with left-sided heart pressures and in low-pressure tamponade. Many such patients have an inspiratory fall in arterial pressure of 10 mm Hg or less that is not quite diagnostic.

Pulsus paradoxus usually signals very large reductions in ventricular volumes and equilibration of mean pericardial and all cardiac diastolic pressures (Fig. 50-17) . [83] Breathing now transiently causes the equilibration pressure level to alternate. *Inspiration* decreases pericardial pressure, favoring right-sided heart filling; *expiration* favors left-sided heart filling. Indeed, pulsus occurs as inspiration depresses pulmonary venous pressure below systemic venous pressure so that pulmonary wedge and LA pressures fall below pericardial pressure and the inspiratory decrease in transmitral flow velocity significantly

Figure 50-17 Physiology of pulsus paradoxus. Complex sequential and simultaneous responses as to inspiratory reduction of pleural pressure produce the inspiratory fall in arterial flow and pressure (see text). (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

exceeds the normal decrease of 15 percent or less. RA atrial pressure falls, but not below pericardial pressure. Inspiration may also transiently reverse pulmonary venous flow in severe tamponade and thus reduce LA flow.

MECHANISMS

Pulsus paradoxus clearly depends on alternate reciprocal exaggeration of ventricular interaction by the respiratory cycle. The inspiratory systolic pressure fall is also related to the pattern and depth of breathing and hence to the degree of pleural pressure fluctuation. Normally, intrapericardial and pleural pressures vary almost equally during breathing, but in tamponade intrapericardial pressure during inspiration decreases somewhat less than pleural pressures; it increases as the right side of the heart fills, partly because the right side of the heart expands into the pericardial fluid, increasing its already high pressure (see Fig. 50-17) . The increased pericardial pressure further compresses the left side of the heart in inspiration, along with a sharp leftward shift of

the atrial and ventricular septa, tending to further impede LV filling.[83] The comparable expiratory decreases in right-sided heart filling and cavitary pressures are reflected on echocardiography as maximum RA and RV diastolic collapses during expiration.

Directional respiratory changes in transmural pressures, flow, and filling remain normal and approximately 180 degrees out of phase, that is, almost perfectly reciprocal for maximal changes. At the low chamber volumes of tamponade, proportional inspiratory pressure increases are very much greater than normal on the right; corresponding left-side inspiratory pressure decreases are relatively less than on the right, although much greater than normal, dramatically reflected by marked respiratory fluctuation of Doppler transvalvular and intravascular flow velocities. Displacement of the ventricular and atrial septa into the underfilled left ventricle and atrium, enlarging the right side of the heart at the expense of the left is a parallel effect due to inspiratory increase in RV transmural pressure and filling. The septal shifts further impede LV filling, which is also opposed by inspiratory reduction of aortic transmural pressure causing the left ventricle to contract against increased aortic impedance. Aortic flow and systolic pressure decrease promptly, within one beat of the onset of inspiration, immediately after inspiratory merging of pulmonary wedge and intrapericardial pressures. Thus, a large component of the change must be left sided, occurring before any series effect of increased RV output can reach the left atrium.[83] Pulsus paradoxus usually disappears with adequate pericardial drainage.

"NONPERICARDIAL" PULSUS PARADOXUS.

Pulsus paradoxus occurs frequently in chronic obstructive airway disease and acute asthma and occasionally in hemorrhagic shock, tension pneumothorax, tracheal compression, RV infarction (possibly due to pericardial constraint), severe pulmonary embolism, restrictive cardiomyopathy, and mediastinal and cardiac compression by mass lesions.

ABSENCE OF PULSUS PARADOXUS.

Tamponade without pulsus paradoxus occurs[83] :

1. When LV diastolic pressures and LV stiffness significantly exceed those of the right ventricle; pericardial pressure may effectively equilibrate only with right-sided heart pressures, a form of RV tamponade.
2. When severe aortic regurgitation damps respiratory fluctuations even without LV dysfunction.
3. With atrial septal defect when inspiratory venous return is balanced by shunting to the left atrium.
4. With extreme hypotension in shock, as in severe tamponade, which can make respiration-induced pressure changes unmeasurable.
5. In some cases of acute LV infarction with tamponading effusion.
6. In local (usually postsurgical) cardiac compression.

7. With pericardial adhesions, especially over the right side of the heart.

RENAL EFFECTS.

Tamponade, like any profound hypotension, induces oliguria because it signals renal sodium and fluid retention. Despite high central circulatory pressures, atrial natriuretic factor cannot increase, owing to the absence of myocardial stretch.

ELECTROCARDIOGRAPHY (see p. 1828 and Chap. 5) .[79]

The ECG can be normal but most often is nonspecifically altered (mainly ST-T wave abnormalities). It may show acute pericarditis at ECG stages 1, 2, or 3. Electrical alternation of the QRS complex, rarely including the T wave, is quasi-diagnostic. P-QRS or P-QRS-T or P-PR segment-QRS-T alternations (panalternation)[86] are seen only in critical cardiac tamponade. Low voltage is usually due to reduced heart size. Significant vagally mediated bradycardia (overriding normal baroreceptor reflexes) and ultimate electromechanical dissociation (pulseless electric activity) occur in end-stage tamponade, especially in rapid hemopericardium in which critical cardiac compression prevents filling (therefore output) while the ECG is continuously generated.

IMAGING.

All imaging methods can demonstrate pericardial effusion. Chest radiographs show an enlarged cardiopericardial silhouette with clear lungs (in the absence of pulmonary disease) (Fig. 50-10 , p. 1838). *Echo-Doppler cardiography,* ideally, although not necessarily, TEE, can eliminate the need for invasive hemodynamic measurement by revealing physiological as well as anatomical abnormalities[87] [88] (see Table 50-10) (Fig. 50-18; see also Figs. 7-95 , 7-96 , and 7-97). Some features are initially blunted in hypervolemic patients.

Echo-Doppler signs are less accurate in patients with pulmonary hypertension and intrapericardial adhesions and of greatly reduced sensitivity after cardiac surgery. If the effusion is large enough, the heart may swing freely in it--the basis of electrical alternation. With large effusions, compression by pericardial fluid permits the entire adult heart to be seen, particularly in the four-chamber scan plane. Cardiac compression may also falsely suggest myocardial hypertrophy (pseudohypertrophy); the left ventricle transiently "remodels."[89]

In the absence of heart disease, systolic function is good, with excellent shortening and ejection fractions, although the ventricles operate at reduced volumes, hence with small stroke outputs. Thus, the heart is underloaded, both "underpreloaded" and "underafterloaded," obviously working hard but prevented by reduced inflow from matching circulatory demand.[79] With hemopericardium, blood and clots are seen,

whereas fibrin is common in inflammatory effusions. Collapse of the RV free wall in early diastole (see Fig. 50-13) correlates with obstruction to the atrial *y* descent (i.e., obstruction to rapid filling); it is earliest and most marked in expiration when RV volume is reduced. RA collapse occurs at end diastole and early isovolumic systole; in about 25 percent of cases the left atrium also collapses (see Fig. 50-14). RV diastolic collapse occurs after a 15 to 25 percent drop in cardiac output and before significant decrease in blood pressure in patients who are normovolemic or hypervolemic; it is more specific than RA collapse and more sensitive and specific than pulsus paradoxus in detecting increased intrapericardial pressure, particularly if RV diastolic collapse lasts at least one third of the cardiac cycle. RV diastolic collapse duration is quantitatively related to the pericardial pressure.[73] It may also occur when unilateral or bilateral pleural effusion causes increased pressure in an insignificant pericardial effusion; this is relieved by pleural drainage. Inferior vena cava (IVC) plethora (diameter
20 mm) and absence of the normal inspiratory IVC collapse (
50 percent) are seen on subcostal echocardiography. Absence of normal inspiratory IVC collapse implies right-sided heart diastolic pressures of 15 mm Hg or more. Respiratory effects parallel pulsus paradoxus reciprocally, with respiration, as shown by atrial and especially ventricular septal shifts from the right into the left atrium and ventricle in inspiration, reversed in expiration. Although total transvalvular blood volume flows are reduced, flow velocity differences between the right and left sides of the heart are enormously magnified during the breathing cycle. Figure 50-18 shows respiratory variation in transmitral flow. Concurrently, respiratory variations of superior vena cava flow velocities are exaggerated in tamponade. Hepatic vein flow velocities increase during inspiration, with retrograde flow in early expiration.

DIAGNOSIS.

Tamponade should be suspected in patients with hypotension and the following findings: elevated systemic venous pressure, falling blood pressure, pulsus paradoxus, tachycardia and dyspnea or tachypnea with clear lungs, chest and abdominal wounds, recent or concurrent evidence of pericarditis, and unexplained "cardiac" enlargement or evidence of pericardial effusion. Moreover, anticoagulant or thrombolytic therapy,[90] certain drugs such as cyclosporine, recent cardiac surgery, blunt chest trauma, malignancies, connective tissue disease, renal failure, and septicemia all precipitate, aggravate, or predispose patients to tamponade. Indwelling instrumentation, particularly of the thin right side of the heart--such as central venous lines, transvenous pacemakers, filtration catheters, and hyperalimentation catheters--can subtly perforate the right atrium or ventricle (see Chap. 11) . Some of these provoke hemopericardium; those delivering parenteral fluids can rapidly fill and overload the pericardial cavity.

Certain conditions inhibit or alter the pattern of chamber collapses and respiratory phenomena[79] [91] just as they limit pulsus paradoxus. These include LV hypertrophy and dysfunction, aortic valve disease, pulmonary hypertension, hypertrophy and reduced compliance of the right ventricle, obstruction of heart valves by intrinsic disease or masses, and intrapericardial adhesions. Finally, LV diastolic collapse occurs with loculated, usually postsurgical, effusions over the left ventricle and, rarely, in circumferential tamponade in patients with intrapericardial adhesions, pulmonary artery

hypertension, or RV hypertrophy.[91] [92]

Figure 50-18 Cardiac tamponade. Transtricuspid flow velocity "paradoxus." Marked increase in flow velocity occurs with inspiration.

VARIANT FORMS OF CARDIAC TAMPONADE

LOW PRESSURE TAMPONADE.[83]

Low pressure tamponade occurs in hypovolemia with severe systemic diseases such as tuberculosis and malignancy as well as in chest trauma with bleeding anywhere. Patients are weak, may seem normotensive, and have dyspnea on exertion, with only mild if any jugular venous distention and no diagnostic pulsus paradoxus. However, they have characteristic respiratory changes in Doppler diastolic inflow signals and isovolumic relaxation time (see Table 50-10) . In low-pressure tamponade the low-pressure pericardial effusion equilibrates with RV diastolic pressure only, as in cases of early tamponade, and equilibration occurs first only in inspiration ("inspiratory tracking").

HYPERTENSIVE CARDIAC TAMPONADE.

This condition has all the features of cardiac tamponade except that these exceptional patients have high (rarely very high--
200 mm Hg) blood pressures.[79] Typically, there was antecedent hypertension. Pulsus paradoxus is demonstrable at high pressure. Attempts to reduce the blood pressure may exacerbate the situation and precipitate or greatly exaggerate pulsus paradoxus.[78]

TAMPONADE WITH VENTRICULAR DYSFUNCTION.[89] [90]

RV or LV dysfunction can reduce or eliminate pulsus paradoxus. LV dysfunction, especially reduced compliance, notably in hypertensive or severe coronary artery disease, uremia, or aortic valve disease, may be associated with RA and RV collapses at relatively small volumes of excess pericardial fluid. They essentially produce a right-sided heart tamponade at lower intrapericardial pressures than with a normal left ventricle.

PNEUMOTAMPONADE: TENSION PNEUMOPERICARDIUM OR PNEUMOHYDROPERICARDIUM.[79] [93] [94]

Increasing air or other gas in the pericardium with or without excess pericardial fluid, blood, pus, or chyle can easily tamponade the heart. Examples include a check-valve mechanism admitting air from lung structures or intrapericardial gas-producing

organisms. Diagnostic and therapeutic principles are the same as in liquid tamponade. There is also a tympanitic precordial percussion and frequently the "mill-wheel sound" of the heart splashing in a fluid-gas interface.

REGIONAL CARDIAC TAMPONADE.[79] [95]

Loculated effusion over any part of the heart can compress that part. Loculation is usually due to localized pericardial adhesions, especially postsurgically, and induces hemodynamic abnormalities consistent with the compressed chambers or zones. For example, after RV infarction, loculated effusion can cause selective RV tamponade with RV diastolic pressure higher than LV diastolic pressure. Loculated effusions compressing the right atrium (often after surgery) may act similarly and can cause a right-to-left shunt through a patent foramen ovale or atrial septal defect. Occasionally, loculated effusion tamponading the right atrium reproduces all the hemodynamic findings of severe generalized tamponade, including pulsus paradoxus.

EFFUSIVE-CONSTRICTIVE PERICARDITIS.

This combination of effusion and constriction with mixed clinical, imaging, and hemodynamic signs can produce tamponade with relatively little fluid when there is a scarred, unyielding parietal pericardium or when a constrictive epicarditis underlies the tamponading fluid.

Cardiac Catheterization

It may be necessary to confirm the diagnosis of tamponade by right heart or complete cardiac catheterization, especially when study of the heart and coronaries becomes desirable. Ideally, catheterization shows high pressures throughout ventricular diastole and near-equilibration (>5 mm Hg) of atrial and ventricular diastolic pressures.[79] [92] Most tamponades equilibrate at 16 to 20 mm Hg (6 to 12 mm Hg in low pressure tamponade). Atrial traces show absent or amputated *y* descent. Arterial and pericardial catheters disclose exaggerated respiratory pressure fluctuations. Absent coronary disease, compression of the epicardial coronary arteries and veins does not result in anaerobic metabolism as measured by coronary sinus lactate level, demonstrating that the tamponaded (consequently underloaded) myocardium has sufficient blood supply to avoid anoxia, despite the usual tachycardia and strong compensatory adrenergic response. Despite very high central circulatory pressures, tamponade does not cause alveolar pulmonary edema.[79] [96] There may be some interstitial lung edema, but neither alveoli nor septa are affected. Subcostal echocardiography shows that the intrahepatic IVC is plethoric--a more reliable sign than jugular venous distention.[87] [88]

Treatment

Definitive treatment is prompt evacuation of pericardial contents. Only in relatively few patients who had dehydration and hypovolemia has it been possible to demonstrate effective cardiocirculatory support by medical measures. Volume infusion may also be diagnostically useful only in hypovolemic patients,[97] by revealing the typical

hemodynamics of cardiac tamponade, which are otherwise well concealed in some hypovolemic patients (occult tamponade; low-pressure tamponade (see p. 1841).

MEDICAL TREATMENT.[79] [98] [99]

Experimental evidence favoring a variety of medical agents is conflicting and investigated in models that do not necessarily apply to human tamponade.[98] [99] Medical treatment may appear temporarily effective (partly because tamponade occasionally remits spontaneously) but usually is ultimately ineffective. It is aimed at supporting compensatory and physiological responses, expanding intravascular volume, increasing or decreasing systemic vascular resistance, and supporting inotropy. The latter is almost predictably useless because most tamponaded hearts without preexisting cardiac disease are under effective endogenous inotropic stimulation with an excellent ejection fraction--but at critically low stroke volume. Supporting filling with various intravenous fluids can help hypovolemic patients but otherwise tends to increase heart volume with a subsequent countervailing increase in pericardial pressure, leaving the patient no better and perhaps worse by decreasing transmural pressure. Agents increasing peripheral resistance to support blood pressure have not been demonstrably effective because tamponade evokes maximal endogenous sympathetic stimulation and perhaps because of untoward cardiac effects. Finally, atropine can be given for depressive vagal reflexes during early and late tamponade.[79]

If drainage equipment is not immediately available, medical measures may be attempted for a transiently favorable effect, perhaps permitting additional pericardial stretch. These include isoproterenol, norepinephrine, dobutamine, and similar agents to support blood pressure and flow. Correction of any metabolic acidosis avoids the myocardial depressant effect of that condition and increases responses to endogenous and exogenous catecholamines. Temporary results may also accrue from vasodilators. Nitroprusside plus blood transfusion improved cardiac output in experimental animals.[98] Hydralazine plus volume infusion appears to raise arterial pressure and cardiac output and improve blood flow to myocardium, central nervous system, and kidney, all locations where slightly improving blood flow has not been critical partly due to autoregulation. Positive-pressure breathing of any kind should be avoided at any stage of tamponade because it will further reduce venous return, RV transmural pressure, and cardiac output. Only after the pericardium is incised or the fluid drained may positive-pressure breathing be used safely.

PERICARDIAL DRAINAGE.

Whenever possible, echocardiographically monitored pericardiocentesis or surgical drainage are treatments of choice. Choice of procedure depends on urgency. When death is impending, the quickest method, percutaneous needle paracentesis, can be unavoidable. Yet, with brisk pericardial bleeding, as in wounds, ruptured ventricular aneurysm, or dissecting aortic hematoma, clotting makes needle evacuation impossible. Moreover, bleeding can be slowed by the tamponade pressure so that surgical drainage with suppression of bleeding sources is safer and surer. Drainage should be as complete and prolonged as necessary, whether by catheter or tube or by a window into a neighboring cavity. The choice must be individualized, but a pericardiostomy,[100] with

suction drainage for at least 3 to 4 days, is often optimal. Preventing recurrence is important in disorders prone to reaccumulation. Treatment of underlying disease with specific agents may suppress reaccumulation. However, resistant processes such as malignancies and stubborn infections can ultimately require pericardiectomy or obliteration of the pericardial cavity using tetracycline, minocycline, bleomycin

(installed with a local anesthetic), or other sclerosants; prolonged tube drainage can stimulate obliterative adhesions and is preferable to use of these painful agents.[79] Traditional percutaneous needle pericardiocentesis[77] is usually effective and relatively safe with inferior fluid accumulation at least l cm deep by echocardiogram. Most effusions can be effectively drained with echocardiographic guidance, which has greatly improved its safety, permitting puncture at any reasonable place on the precordium[101] except over the internal mammary arteries, 2.5 cm on each side of the sternum. An apical or, less often, subxiphoid approach is optimal. Fluoroscopic and even CT guidance are also feasible. Contraindications to thoracotomy, such as pleuropulmonary diseases, which make intolerable even temporary compromise of lung tissue, or extensive pleural adhesions may necessitate prolonged tube drainage or even a pericardioperitoneal shunt performed with special equipment.[79]

SURGICAL DRAINAGE.

Subxiphoid surgical incision and thoracoscopic drainage produces little morbidity and can be done in emergencies with only local anesthesia. It permits direct inspection, biopsy of visceral and parietal pericardium, and resection when that is an option. Video-assisted thoracoscopy gives the operator a wide field of view (although a lung, usually the left, must be collapsed). Other chest conditions or failure of thoracoscopic drainage may mandate an open surgical approach.

EFFECTS OF PERICARDIAL DRAINAGE.

After pericardiocentesis, cardiac pressure and volume corrections reflect the presence and degree of cardiac compression and are not predictable from the amount of fluid removed. However, because critically tamponaded hearts operate on the steep portion of their pericardial pressure-volume curve (see Fig. 50-11) , the initial fluid decrement will produce the greatest improvement in stroke volume. After drainage, RV volume usually increases more than LV volume because the more compliant right ventricle was more compressible. Indeed, the right ventricle occasionally dilates and echocardiography shows abnormal ventricular septal motion characteristic of RV volume overload. Especially if there is myocardial disease, RV dilation may initiate congestive failure. LV dilation can also do this with occasional pulmonary edema ("pericardial shock"). Although pulmonary artery pressure usually falls after drainage, it may rise with a temporary mismatch of ventricular output. Such acute right-sided and particularly left-sided heart failure occurs with ventricles unable to accommodate posttamponade increase in venous return exacerbated by continuing high afterload due

to continuing increased peripheral resistance from compensatory adrenergic responses. Hemodynamic and clinical improvements are related to increased stroke volume. Effective drainage is characterized by[79] (1) disappearance of pulsus paradoxus; (2) frequent relief of dyspnea; (3) disappearance of signs of venous engorgement paralleling falling RA pressure; (4) reappearance of *y* descents; (5) loss of vena cava plethora; (6) loss of diastolic pressure equilibration; and (7) prompt loss of electrical alternation. A pericardial catheter (rarely necessary) documents normalization of pericardial pressure.

NONEFFUSIVE SEQUELAE OF PERICARDIAL INFLAMMATION

PERICARDIAL ADHESIONS AND FIBROSIS.

Pericarditis can heal without detectable residua or with some scarring of one or both pericardial layers. The plastic fibrinous exudate of acute and subacute pericarditis can be adhesive, but its fate is either fibrinolysis and reabsorption or organization with newly formed collagen fibrils as a matrix for invasion by new blood and lymphatic vessels and later fibrous or fibrogranulomatous adhesions.[102] A common denominator for intense scarring is bleeding; blood, particularly blood lipids and thrombi, and especially combined with pericardial injury and exudate, is thrombogenic.[102] Cicatrization is probably intensified by locally produced interleukins and tumor necrosis factors found in abnormal pericardial fluids and mesothelial production of a chemical promotant for fibroblasts. The most common cause of intrapericardial adhesions is cardiac surgery.[103]

Local thickenings are not rare on CT in patients with healed myocardial infarctions, rheumatic heart disease, sarcoidosis, and other conditions. More destructive inflammation in severe infectious pericarditis may heal without further consequences but frequently provokes constrictive scarring involving the entire heart, any portion of the heart, or the great vessels, distorting or compressing structures it entraps. Compressive syndromes arise from primarily pericardial lesions, differing from primarily myocardial lesions (e.g., myocardial infarction) that are usually associated with adhesions and fibrosis of little or no dynamic significance. In effusive pericarditis, intrapericardial bands on echocardiography predict significant scarring.[104] Some pericardial adhesions may buttress myocardial wounds or infarcts and contribute mural and microvascular support. Some seal an otherwise fatal myocardial rupture to form a pseudoaneurysm (see Chap. 37) .

Clinical Considerations.

Adhesions on the outside of the parietal pericardium even when combined with internal adhesions can be due to inflammatory disease of the mediastinum and pleura. Rarely they affect the cardiac silhouette[102] (unusual configurations can be resolved by imaging methods like spin-gated MRI; and CT is optimal for retrosternal adhesions).[105] External adhesions can produce exopericardial rubs and rarely permit systolic tugging on adjacent organs after pleuritis and mediastinitis. On imaging, intrapericardial adhesions modify some effects of tamponade by shifting chamber collapses to unusual locations and restricting swinging.[106] Adhesions are a major problem in the increasing numbers of second and third thoracotomies. Surgical preventive efforts include intrapericardial

absorbable polymer patches, plasminogen activator (rt-PA), and hyaluronic acid. Postoperative pericardial closure decreases adhesions but is usually avoided due to unfavorable hemodynamics.[102]

PERICARDIAL CALCIFICATION (PANZERHERZ: "ARMOR HEART").

Dystrophic calcification (rarely ossification) signifies pericardial injury more destructive than conditions healing without calcification.[102] Yet even extensive calcifications may be well tolerated and asymptomatic. However, any degree of calcification may be found in constrictive pericarditis. Local calcification seems related to involvement of areas of least heart movement and of greatest friction between the epicardium and the parietal pericardium: inferiorly the LV apex, the right atrium, the sternal aspect of the right ventricle, and the AV groove. So many cases, especially those with ECG abnormalities, are associated with constriction that constrictive pericarditis should be ruled in or out when pericardial calcification is discovered. Three-dimensional echocardiography, MRI with tagging, and rapid-acquisition spiral or electron-beam CT can simultaneously map calcifications and indicate any hemodynamic impairment.[107] [108] Calcifications increase the technical difficulties of pericardial resection by requiring special instruments, and where calcification invades the myocardium the procedure is particularly difficult and dangerous.

INFLAMMATORY CYSTS.[98]

These include pseudocysts as well as encapsulated and loculated pericardial effusions. Pericardial scarring may trap portions of an intrapericardial exudate or hemorrhage, producing a pocket or cystlike structure with or without symptoms and signs requiring drainage or resection. Their capsules are scarred parietal and visceral pericardium with persistent inflammatory activity. Chronic inflammatory cysts must be differentiated from ventricular

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pseudoaneurysms and true (congenital) pericardial cysts, which tend to be smooth with a predilection for the low right cardiac border, whereas inflammatory pseudocysts, like parasitic cysts, have variable contours and occur anywhere. *Inflammatory diverticula* are related to encapsulated pericardial effusion; they follow exudative pericarditis, especially tuberculous, but acute idiopathic (presumably viral) pericarditis can be a precursor. Unlike inflammatory cysts, only parietal pericardium is primarily involved, and they communicate with the pericardial cavity. Diverticular contents resemble those of inflammatory cysts. Diverticula, for some reason, tend to be right-sided, perhaps because the fibrosa over the right ventricle is particularly thick.

GRANULOMATOUS PERICARDITIS.

Granulomas are characterized by simultaneous inflammation and repair, producing

subacute and chronic pericardial disease. These are basically nodules or masses composed mainly of vascular fibrous tissue with variable leukocytic infiltration. They can spread throughout the pericardium to form a static, avascular scar, making etiological diagnosis ultimately progressively more difficult. Many granulomas are rich in cholesterol and represent one source of cholesterol pericarditis. There are four main etiological groups of granulomatous pericarditis: (1) of unknown origin; (2) due to systemic diseases such as rheumatoid arthritis (rheumatoid arthritis causes a great number of pericardial adhesions and even pericardial rheumatoid nodules, sometimes with acute or subacute fibrinous pericarditis); (3) infections, particularly tuberculosis and fungi; and (4) foreign-matter reactions, particularly silicosis and asbestosis, which tend to form static scars with uncertain (usually low) constrictive potential.

CONSTRICTIVE PERICARDITIS

CLINICAL CONSIDERATIONS.

Constrictive pericarditis "imprisons" the heart.[109] [110] It has important similarities to and differences from cardiac tamponade.[110] Its dominant etiological spectrum has changed (Table 50-12) and its clinical manifestations have changed due to changing tempo of the disease, that is, the aggressiveness of the inciting processes, the point in its development where it becomes significantly compressive or symptomatic and particularly where it becomes diagnosable. With progress in understanding constrictive and restrictive hemodynamics and in testing, diagnosis is only rarely greatly delayed so that most patients are recognized in earlier rather than truly chronic stages. The traditional "*chronic* constrictive pericarditis" is erroneous in most contemporary cases. There remain variably difficult differentiations from restrictive cardiomyopathy, other causes of systemic congestion, particularly RV failure, and hepatic cirrhosis. Sometimes inspection and biopsy of the pericardium and myocardium are required to rule in or out constriction or one of its variants, especially in the presence of systemic diseases that may be related to it. While obliterative adhesions regularly follow cardiac surgery, constrictive scarring is relatively uncommon.[110] Yet, constrictive scarring may follow pericardial resection or pericardiotomy for any condition, including constrictive pericarditis.

PATHOGENESIS.

Currently, most cases are of undetermined etiology--"idiopathic." The initial acute pericarditis can be silent or clinically apparent. The essential pathological process is healing with a thick *or thin* scar that restricts cardiac filling usually by total or near-total obliteration of the pericardial "space," although often with lacunae of fluid, pus, or blood. (Loculated fluid and bandlike constriction can compress any portion of the heart including any chamber, valve rings, and great vessels, mimicking disease in those structures.[109] [110]) Traditionally, constriction has been chronic, sometimes with surprising pericardial thickness; recently, thin constricting pericardia are increasingly evident. Early diagnosis and shift of most processes such as tuberculosis to "idiopathic" pericarditis, viral infections, and cardiac surgery[109] [111] cause most contemporary cases to be *subacute* (arbitrarily, 3 to 12 months after the pericardial insult). *Acute* constriction occurs soon after acute pericarditis; healing can cause constricting cicatrization within

days after draining tamponade fluid. *Transient constriction* soon after acute pericarditis, usually with effusion, has been observed by echocardiography, inspection of the jugular

TABLE 50-12 -- CAUSES OF CONSTRICTIVE PERICARDITIS (WESTERN NATIONS)

Great Majority: Unknown or uncertain etiology/"Idiopathic pericarditis"
Relatively Common
Infectious
Viral or probable viral
Tuberculous
Pyogenic
Therapeutic irradiation
Cardiopericardial surgery
Relatively Uncommon (increased incidence in special populations)
Neoplasia
Metastatic
Mesothelioma
Pericardial
Pleural
Uremia (on dialysis)
Vasculitis/connective tissue disease group
Especially rheumatoid arthritis, lupus, scleroderma (including CREST syndrome)
Infectious
Fungal
Parasitic
Myocardial infarct-related
Post hemopericardium (from thrombolysis)
Post-myocardial infarction (Dressler) syndrome
Trauma
Blunt
Penetrating
Drugs
Procainamide (lupus)
Methysergide
Practolol
Hydralazine (lupus)
Hemopericardium/encapsulated hemopericardium in hemorrhagic disorders
Rare

Cholesterol pericarditis
Chylopericardium
Intrapericardial instrumentation

- Automatic implantable cardioverter-defibrillator
- Epicardial pacemaker

Whipple disease
Wegener granulomatosis
Hypereosinophilic syndromes
Cardiac transplant
Hereditary: mulibrey nanism
Sarcoidosis
Asbestosis
Pericardial amyloidosis
Dermatomyositis
Lassa fever
Chemical trauma: sclerotherapy of esophageal varices

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veins, venous pulse, and auscultation (transient abnormal S_3) with or without symptoms and resolving in days to weeks.[110] In *chronic* constriction, pericardial tissue usually shows nonspecific fibrosis with few inflammatory cells and frequent myocardial atrophy.

Both subacute and acute constriction show many more inflammatory cells and lighter connective tissue. Depending on etiology there may be giant cells and granulomas.

PATHOPHYSIOLOGY. [109] [110]

Constricting pericardial scar, like tamponading fluid, sharply accentuates ventricular pressure-volume relations (see Fig. 50-11) and increases ventricular coupling (ventricular interaction). It *progressively* restricts ventricular filling to earlier diastole until 70 to 80 percent of the reduced filling occurs in the first 25 to 30 percent of diastole[109] (in contrast, tamponade *continuously* restricts filling from the beginning of diastole). Elevated

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Figure 50-19 Constrictive pericarditis. Dip-plateau of left (LV) and right (RV) pressure curves with diastolic equilibrium are best seen in long diastole (patient with atrial fibrillation).

atrial pressures reflect elevated ventricular diastolic pressures. Moreover, early diastolic filling is at high velocity, owing to (1) high atrial pressure as the AV valves open and (2) diastolic suction,[112] [113] augmented by elastic recoil (conversion of potential to kinetic energy or "rubber bulb" effect[112]), that is, rebound of the ventricular pericardial scar, which had been contracted like a spring by ventricular systole. Such factors produce the

"square root" configuration of ventricular diastolic pressure curves (Fig. 50-19) and other findings (see "Cardiac Catheterization," in Chap. 11) .

All cardiac diastolic pressures are nearly equilibrated as in tamponade. Equilibration may be "unbalanced" by vigorous diuretic therapy. Unlike tamponade, venous and atrial pressure waveforms resemble the normal: the *y* descent is preserved, although deep and usually larger than a more or less deep *x* descent (Fig. 50-19) . (In tamponade the *y* descent is eliminated or truncated.) Venous flow toward the heart occurs with the *x* and *y* descents of venous pressure, with the major acceleration during the *y* descent rather than as normally during the *x* descent. There are no systolic abnormalities except with coexisting myocardial lesions, atrophy, or damage, including antecedent or ongoing myocarditis or ischemia. Myocardial atrophy, fibrosis, and calcification are related to chronicity. Ischemia includes intrinsic coronary disease and compression by constricting scar of coronary arteries, veins, or bypass grafts.[114] In uncomplicated constriction, as in tamponade, coronary blood flow is reduced but adequate for aerobic metabolism.

COMPENSATION.

Compensation for constriction resembles compensation in cardiac tamponade. Heart rate is the major mechanism defending cardiac output, because stroke volume becomes nearly fixed by filling halted in early diastole. Increased heart rate mainly amputates the diastolic pressure plateau after the abbreviated filling period, so that tachycardia is relatively less detrimental than in conditions without early filling. Humoral, hormonal, and renal responses are similar to those of cardiac failure and tamponade with electrolyte and water retention.[109] [115] Yet, as in tamponade, restricted atrial distensibility prevents significant rise in atrial natriuretic factors. Sodium and water retention and high systemic venous pressure contribute to high hepatic vein pressure, ascites, and edema. The attendant blood volume expansion is more important than the simultaneously elevated systemic vascular resistance in maintaining arterial pressure.[110]

RESPIRATORY EFFECTS.

Respiratory responses depend on the effects of pericardial scarring: (1) insulation of the heart from intrathoracic pressure changes and (2) increased ventricular interaction. The heart and pulmonary vessels are intrathoracic. Normally they are simultaneously affected by respiratory pressure changes so that pulmonary venous flow to the left atrium is not significantly changed by breathing. But in classic constriction the heart is totally encased; when inspiration decreases intrathoracic pressure, cardiac pressures remain high. Consequently, pulmonary venous blood cannot easily enter the high pressure left atrium; therefore, total pulmonary venous flow and flow velocity are decreased in inspiration, decreasing LV filling and time to peak filling rate. Respiration does not change superior vena cava pressure or flow velocity. Although the IVC is affected by diaphragmatic movements and abdominal pressure fluctuations, there is diminished (<50 percent) to undetectable respiratory change in IVC diameter.[110] [116] Although inspiration does not greatly increase RV filling volume, filling *velocities* sharply increase and pulmonary artery flow velocity increases, with much less effect in decreasing aortic pressure. Yet, in some cases, inspiration decreases systolic blood pressure more than 10 mm Hg, particularly if there is an element of tamponade

(effusive-constrictive pericarditis) or other cause for pulsus paradoxus, such as pulmonary disease but especially with marked respiratory shifts of the ventricular and atrial septa. Note that both ventricular and atrial septa are free of constriction and respond to pressure differences across them; thus, they often move sharply with respiration.[110]

The *Kussmaul sign,* inspiratory increased venous pressure with jugular venous distention, eliminates the normal inspiratory fall of 3 to 7 mm Hg in mean RA pressure, because the neck veins are extrathoracic and face an impediment to flow into the high pressure right atrium. The right atrium resists inspiratory acceleration of venous blood toward the heart with little or no respiratory variation in RA mean pressure. Other conditions with markedly increased RA and venous pressures that also produce the Kussmaul sign include RV failure, RV myocardial infarct, restrictive cardiomyopathy, chronic cor pulmonale, and acute pulmonary embolism.[110]

Clinical Aspects

CHEST RADIOGRAPH.

The cardiopericardial silhouette is usually normal or only modestly enlarged. Its shape depends on the configuration of scar tissue and any remaining fluid.[102] [110] The superior vena cava (SVC) and azygos vein are dilated. Pleural effusions are frequent and usually bilateral. Occasional *constrictive pleuritis* may be missed and discovered by CT, at operation, or post mortem. The only chamber enlargement recognized by chest radiography is LA, particularly with heavy scarring on the left ventricle or the left AV groove (functional mitral stenosis). Pulmonary blood flow often redistributes with upper-zone vascular dilation and decreased lower-zone vessel caliber, particularly with LA enlargement. Kerley B lines may be present, but alveolar edema is rare and implies either unequal chamber constriction or concomitant heart or lung disease.[110] Previously, one third to one half of cases, mainly chronic, had obvious pericardial calcification (Fig. 8-23); diagnostic efficiency has reduced its incidence due to earlier surgery. Calcification is best seen on lateral films (see Chap. 8) . With appropriate hemodynamic and clinical findings, calcification strongly favors the diagnosis of constriction but is itself not specific.

CT AND MRI (see Figs. 10-16 and 10-45) . [117] [118]

Pericardial thickening is best demonstrated by cine and gated MRI and CT with and without contrast medium enhancement. Each technique has high time and spatial resolutions that dependably identify and measure pericardial thickening and geometric changes and are more specific than TTE in differentiating scarring from fluid or tumor. CT and MRI demonstrate the frequently deformed ventricles and atria

and enlarged venae cavae that contrast sharply to the aorta, which their diameter

normally matches. The atria (particularly the left atrium) may be enlarged and the ventricles narrowed and tubelike. The ventricular septum is frequently sinuous, bowed, or angulated. Pericardial thickness by CT and MRI varies from subtle increase over the normal hairline to 10 to 15 mm (rarely more); any thickening over 3.5 mm helps differentiate constriction from restrictive cardiomyopathy; over 6 mm adds great specificity. However, constricting pericardium may be so thin as not to be recognizable as abnormal by contemporary imaging. CT and MRI permit planning the surgical approach in patients with adequate myocardium by revealing the distribution and varieties of pericardial thickenings and calcifications and any myocardial invasion. Absence of myocardium (especially parts of the LV wall) due to atrophy and fibrosis indicates a poor prognosis, including disastrous postoperative results, particularly irreversible decompensation.[118]

ECHOCARDIOGRAPHY (see Chap. 7) .[109] [110] [119] [120]

In 40 percent of pericardiectomy patients at the Mayo Clinic, the first clue to constriction came from echocardiography, which reflects constricting anatomical changes, accelerated ventricular filling, and restricted diastolic expansion and filling. Transesophageal and three-dimensional echocardiography display pericardial thickening comparably to CT. TTE is not as reliable. Doppler recording is excellent for dynamic changes. No single echocardiographic or Doppler sign is pathognomonic.

The ventricular and atrial septa, which are pliant compared with the constricted walls, shift leftward with inspiration and rightward with expiration. The ventricular septum often shows paradoxic systolic motion: anterior (type A) or flat (type B). It may be accompanied by reduced to absent diastolic ventricular expansion with a "flat" LV posterior wall almost equally distant from the chest wall signals in early and late diastole. This is characteristic but not specific. Normal or paradoxic septal motion is bracketed by the components of septal "bounce" [109] on two-dimensional echocardiography, which can be further analyzed by M-mode. The "atrial" notch begins in the middle of the P wave and is characterized by rapid posterior or anterior motion, or posterior, then anterior, motion after atrial systole. The ventricular notch is often more abrupt: posterior, posterior-anterior, or, occasionally, an anterior-posterior sequence in early diastole. This "ventricular" septal notch coincides with the early diastolic abnormal S3. The aortic root may show abrupt early diastolic posterior motion. TTE and TEE usually demonstrate enlargement of one or both atria with reduced wall excursion and dimensional change (particularly on the right). Both venae cavae and hepatic veins are dilated with restricted respiratory fluctuations.[109] [110] In the IVC these vary from well under the normal 50 percent of diameter to no change, as in cardiac tamponade and other conditions with 15 mm Hg or more of elevated RA pressure.

ECHO-DOPPLER CARDIOGRAPHY (see Chap. 7) .[109] [110] [117] [121]

Transmitral and transtricuspid Doppler recordings show rapid forward flow in diastole and reverse flow in later systole (Fig. 7-98) . The early-filling and A (late filling) waves are characterized by increased filling velocities and abnormally rapid deceleration from their peaks. Pulmonary venous forward flow velocity is reduced with exaggerated respiratory variation of early diastolic peak velocity and time integral that is even more

pronounced than across the mitral valve. Reciprocal respiratory flow changes resemble those in tamponade with decreased left-sided and increased right-sided transvalvular velocities at the very onset (first beat) of inspiration and the reverse at the very onset of expiration. When respiratory variation is blunted or absent due to very high LA pressure, reducing preload by sitting or head-up tilt may unmask it.[122] Doppler tissue imaging shows normal LV expansion velocity and rapid mitral annular velocity. The slope of the color M-mode wave indicates a much more rapid flow from left atrium to left ventricle.

CARDIAC CATHETERIZATION (see Chap. 11) .

Catheterization is required to quantify pressures and identify concomitant cardiac disease if the sum of other findings only suggests constriction. (Diuretics should be withheld because hypovolemia alters the results.) Moreover, coronary angiography should identify atherosclerosis or any unusual distribution of the coronary arteries and minimize operative accidents. Constrictive hemodynamics are "restrictive" and therefore closely resemble those of restrictive cardiomyopathy, often the principal differential diagnosis. The major finding is near equalization (
5 mm Hg) in all diastolic chamber and venous pressures. Both LV and RV traces have a *dip and plateau*, the "*square root*" configuration (see Fig. 50-19), usually more pronounced in the right ventricle, with the sharp short early diastolic fall toward 0 pressure (dip), rising to a restrictive plateau as the relaxing ventricles spring back with and reach the limit of the tight pericardium. Typically, RV and pulmonary artery systolic pressures are 30 to 45 mm (up to 70 mm) Hg with RV end-diastolic pressure at least one third of RV systolic pressure. Negative atrial waves, like negative venous waves, are preserved, with the *y* descent usually deeper than the *x* descent (Fig. 50-20) , although they are often equal. In contrast, when *x* is greater than *y* effusive constrictive pericarditis is suggested. The nadir of the dip of the ventricular "square root" coincides with the atrial *y* nadir, ranging from below 0 to well over 20 mm Hg with fluid-filled catheters. High-fidelity catheters show these to be exaggerated; the nadir is usually 4 to 12 mm Hg. *Angiocardiography* shows normal or decreased LV end-systolic and end-diastolic volumes. The SVC is dilated and continuous with a frequently flat RA border. Coronary arteries are usually well within the cardiopericardial silhouette, that is, deep to their normal superficial location, unless the constricting scar is thin. Epicardial coronaries may display less than normal mobility whereas septal coronaries may appear hypermobile.

HISTORY. [109] [110]

A history of antecedent pericarditis or pericarditis-inducing disease, drugs, or thoracic irradiation may be clues to diagnosis, but absence of any history of a provocative disorder is common. Constriction (especially chronic) may present deceptively as "congestive failure," pleural effusions, RA thrombosis, and even hepatic coma.

Symptoms and Signs.

These reflect the degree of systemic and central venous congestion and fluid retention

and may be subtle or overt. Constrictive pericarditis resembles,

Figure 50-20 Constrictive pericarditis. Characteristic right atrial pressure curve has well-formed *x* and *y* descents and *y*>*x*. Mean atrial pressure is approximately 22 mm Hg. Electrocardiogram shows interarterial block. (From Spodick DH: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997.)

but is not, "heart failure": the heart has not failed; it has been prevented from "succeeding." Venous congestion resembles right-sided heart failure with appropriate compensatory responses. Patients have pedal edema, ascites, and abdominal discomfort due to splanchnic engorgement. Ascites may be conspicuous, often without peripheral edema. At higher central diastolic pressures (arbitrarily >15 mm Hg), "central" symptoms are more prominent, including dyspnea, easy fatigability, and occasional orthopnea. Cardiac output cannot rise adequately with exercise because of the relatively fixed stroke volume, so that at any pressure level, dyspnea on exertion is characteristic and exacerbated by any pleural effusions, a diaphragm limited by ascites, or increased lung stiffness from interstitial (not alveolar) edema.[110]

PHYSICAL EXAMINATION.

Mild tachycardia is the rule, even with light exertion. Chronic or aggressive subacute constriction may be accompanied by atrial fibrillation or other atrial arrhythmias. The blood pressure is normal or relatively low, although occasionally hypertensive. Significant (>10 mm Hg; rarely, 15 mm Hg) pulsus paradoxus occurs if there is effusive-constrictive disease or other extracardiac conditions such as lung disease, or if pliant ventricular and atrial septa have exaggerated respiratory mobility. The Valsalva maneuver produces a square wave response, owing to central vascular congestion.[123] Pedal edema may appear early, or there may be ascites with or without edema. Diminished cardiac output may produce pale, cool extremities with peripheral cyanosis. Jaundice in chronic constriction indicates severe congestive or fibrotic liver impairment. Jugular venous distention is a hallmark, although peripheral venous distention is also easily detected in advanced cases. Neck veins are better seen than in most other conditions because of the high level of venous pressure with sharp *x* and *y* descents. These should be sought as collapses from a high standing level. Retinal veins are engorged. Kussmaul sign is common.[110]

Precordial palpation may be "quiet" with no point of maximal impulse or with paradoxical systolic retraction of the chest wall. A sharp early diastolic thrust is common especially in chronic constriction, corresponding to ventricular rapid filling. It coincides with the loud, often palpable, abnormal S_3 (see Fig. 50-5) , which sometimes has a "knocking" quality; it is easily mistaken for S_1 , especially if the simultaneous diastolic thrust is mistaken for the apex beat.[110] If equivocal or faint, the S_3 is enhanced by squatting,

sitting up, or standing or during contrast medium injection. It follows S_2 closely; when it mimics S_1 , it follows the carotid pulse peak whereas S_1 precedes it. The jugular *x* descent occurs approximately with the carotid peak, and the *y* descent coincides with the S_3 and any diastolic precordial thrust. The liver is often palpable and may have a double pulsation. Ascites is recognized by abdominal protrusion and fluid wave. The spleen may be palpable if portal hypertension ensues.

LABORATORY FINDINGS.[109] [110]

The hemogram may be normal or show a normocytic normochromic anemia. Otherwise, especially in less chronic constriction, blood counts reflect etiological agents or processes. Rarely, congestive hypersplenism causes selective cytopenia or pancytopenia. Liver function tests are likely to be abnormal due to hepatic congestion and late cardiac cirrhosis, including increased conjugated and unconjugated bilirubin to the point of cutaneous and conjunctival icterus. Ascitic fluid may be an exudate (typically >2.5 gm/dl protein) or a transudate, (rarely chylous); with chronicity, protein concentration and specific gravity decrease. The serum-ascites albumin gradient tends to exceed 10 gm/dl.

Hypoalbuminemia is common due to liver impairment, protein-losing enteropathy or a proteinuric nephrotic syndrome, each related to chronically high venous pressure and more prominent in children.

ELECTROCARDIOGRAPHY[109] (see also Chap. 5) .

The ECG is nearly always nonspecifically abnormal, only rarely within normal limits. T waves are almost always low to flat or have general or local inversions; they are usually symmetrical unless digitalis has been given. QRS complex and T wave voltage may be normal or reduced. Interatrial block is common, especially with chronicity, with P waves wider than 100 milliseconds and usually notched. These can resemble P mitrale (which may be present with AV groove constriction). RA enlargement can accompany a large pointed P wave or dominantly positive "±" P in V_1 . Local or unequal constriction causes changes due to overload of "upstream" cardiac structures, producing ECGs consistent with RV hypertrophy or "strain" and may show right-axis deviation. In chronic constriction, myocardial atrophy probably contributes to reduced voltage, as do fluid retention and pleural effusions. Myocardial calcification and fibrosis, especially with reduced coronary flow, can produce AV blocks, intraventricular blocks, and even abnormal Q waves. Mixed ECG patterns are particularly common in constriction after cardiac operations because of frequently localized or unequal postoperative scarring and also whatever heart disease required surgery. Finally, constriction can compress even normal coronary arteries sufficiently to produce a positive ECG response to exercise. Subacute and especially chronic constriction is often accompanied by atrial arrhythmias, particularly atrial fibrillation (interatrial block is predictive).

DIFFERENTIAL DIAGNOSIS.[109] [110] [124] [125]

Because of variability in scarring and its many mimics, constriction requires an impressive number of tests. Congestive failure due to heart disease is the principal functional diagnosis. Restrictive cardiomyopathy, often due to myocardial fibrosis or amyloidosis, may be difficult because of frequently identical hemodynamics and impairment. Note that restrictive cardiomyopathy patients are poor thoracotomy risks, whereas constricted patients may become unstable when intubated. The basic problem is to distinguish between abnormal chamber stiffness and abnormal muscle stiffness. The principal differential points are the usual thickness of constricting pericardium on imaging and timing of respiratory changes in ventricular systolic pressures; these are discordant in constriction and concordant in restrictive cardiomyopathy. These Doppler flow changes occur within one beat of the onset of inspiration and expiration in constriction but on later beats, if at all, in restrictive cardiomyopathy. The atrial and ventricular septa, free in constriction, are usually restricted in restrictive cardiomyopathy and therefore unlikely to show respiratory mobility. Meticulous Doppler-echocardiography combined if necessary with CT nearly always makes the diagnosis, and Doppler tissue imaging, slope of the color M-mode wave, and mitral annular velocity give clear separation.[126] [127] Occasional cases, particularly those constricted by a thin pericardium will be sufficiently confusing to require myocardial and/or pericardial inspection and biopsy.

Venous obstructive syndromes (e.g., SVC obstruction and nephrotic syndromes), especially with gross edema and ascites, are usually differentiated by imaging, as is abdominal disease with ascites, such as ovarian carcinoma and hepatic cirrhosis. RA tumors, especially myxomas, can mimic constriction by compressing the tricuspid valve; any ventricular involvement adds to the mimicry. In any unclear syndrome, imaging, hemodynamic data, and liver biopsy can be decisive. However, a few patients have simultaneous restrictive cardiomyopathy and constrictive pericarditis, usually due to radiation therapy, and also occurring in transplanted hearts; biopsy may be necessary. Quite suggestive for differentiation are a history of acute pericarditis of almost any etiology, especially purulent, hemorrhagic, or tuberculous. Finally, all segments of the autonomic nervous system are dysfunctional in constriction; in restrictive cardiomyopathy,

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dysfunction is localized to the sympathetic efferent pathway.[128]

Variants of Constrictive Pericarditis

A variety of cases are not "typical" or "classic," owing to the unpredictable pericardial scarring process, particularly in contemporary patients after cardiac surgery with variants that can resemble other conditions.[110]

UNEQUAL/LOCAL CONSTRICTION.

Chambers, valves, and great vessels can be individually or unequally affected by pericardial scarring and calcification, producing murmurs due to locally turbulent blood flow and local ECG and hemodynamic changes. Echocardiography (TEE, TTE, and three-dimensional), MRI, or CT may demonstrate thickened or calcified pericardium. With *LV constriction* the atria, SVC, and IVC are dilated, the right ventricle is normal sized, and the ventricular septum is straight or inclined to the left. With *RV constriction,* the right atrium, IVC, and SVC are dilated and the septum is straight or inclined to the right. *Annular constriction*, mainly in the AV groove, enlarges the atria while the ventricles remain normal or relatively small.

EFFUSIVE-CONSTRICTIVE PERICARDITIS.

This form produces symptoms and objective findings due to variable mixtures of effusion or tamponade accompanied by constriction of the visceral pericardium (*constrictive epicarditis*) or constriction with local tamponade of one or more chambers due to loculated effusion. Physical and laboratory findings usually resemble tamponade more than constriction until after the fluid is drained when a constrictive picture emerges.[110] Occasionally, tamponade is suggested by an abnormal S_3 , which is ruled out by pure, classic tamponade dynamics (i.e., no rapid filling period). In contrast to pure constriction, significant pulsus paradoxus is frequent. A large dominant *x* descent (*x* > *y*) in atrial and venous traces also suggests an element of tamponade. After drainage, pericardial pressure drops to near 0, hemodynamic curves become more typical of constriction, and pulsus paradoxus may disappear. Kussmaul sign in what appears to be dominantly tamponade is a clue to effusive-constrictive pericarditis and may be accentuated after the fluid is drained.

ELASTIC CONSTRICTION.

Thick pericardial fluids particularly rich in blood and fibrin may organize and resemble tamponade, owing to continuous elastic compression, usually by clot. The venous and atrial waveforms may show a predominant *x* descent like tamponade, and there is nearly always no S_3 because there is no early rapid filling; there may be an S_4 . Occasionally, malignancies surround the ventricles, producing a similar picture.

LATENT (OCCULT) CONSTRICTION.

Patients with dyspnea, fatigue, and mild edema with or without a history of acute pericarditis and no specific cardiac findings may show excessive rises in heart rate and venous pressure with exercise, which may also induce an S_3 . Some patients are volume-depleted due to diuretics. Administration of fluids may bring out constrictive dynamics. In this respect the situation is analogous to that in low pressure cardiac tamponade.

TRANSIENT CONSTRICTION.

Transient constriction often follows acute pericarditis.

Management

Medical management does not relieve constriction except if with a dynamic inflammatory component responsive to antiinflammatory agents.[109] [110] [129] Any underlying disease should be treated; for specific infection, therapeutic agents should be given before operation and continued afterward. Surgery is definitive and technically easier early before calcification or myocardial abnormalities. Good surgical results follow in patients in better cardiac and systemic condition as well as with less pericardial scarring, calcification, and hepatic congestion. Although AV valve regurgitation (particularly tricuspid) is common in constriction,[110] postoperative regurgitation is a complication.[130]

Currently, most patients respond well. Some have an immediate postoperative diuresis, others a slower recovery over weeks or months. Removal of pericardium should be as extensive as possible (intraoperatively recorded pressure-volume loops clearly reveal the optimal extent[131]), especially the surfaces contacting the ventricles, always taking care to spare both phrenic nerves. A stubbornly adherent epicardial constriction may need to be scored or "meshed," leaving it in place but loosened. Poorer results are seen[131A] with inadequate resection, uncorrected coronary disease, higher New York Heart Association "heart failure" classifications, and older age; after radiation pericarditis; with chronicity, including peripheral organ failure (particularly renal and hepatic[129] ; ascites, edema, or both are ominous); with severe myocardial atrophy and fibrosis; and with significant arrhythmias reflecting myocardial impairment. Preventive therapy (often unsuccessful) depends on adequate treatment of acute pericarditis and drainage of significant collections of blood or pus. *Corticosteroids usually fail to prevent constriction.* Whether colchicine and NSAIDs have a preventive effect is unknown. In specific cases after drainage of bloody fluid, intrapericardial urokinase or streptokinase and, for purulent fluids, streptodornase, may check these substrates for constriction.

INFECTIOUS PERICARDITIS

Infectious agents that reach the pericardium inflame it directly or by various immune responses.[132] While any pericardial infection can be clinically silent, clinical pictures]conform to some degree to the descriptions below, with differences characteristic of particular causes. Acute viral pericarditis is likely to provoke the entire range of subjective and objective acute findings, whereas tuberculous pericarditis can do so but is often overshadowed by systemic disease or complications such as fever or tamponade.

Viral Pericarditis

Viral pericarditis has a wide etiological range, mainly the viruses causing myocarditis, the degree of involvement of either or both tissues depending on host susceptibility, and the particular agent; inflammatory abnormalities are due to immune complexes, direct

viral attack, or both.[132] [133] [134] Early viral replication in pericardial tissue elicits cellular and humoral immune responses against the virus. If inadequate, there is direct tissue damage or a destructive autoimmune reaction. Viral genomic fragments in pericardial tissue may not replicate, yet they serve as a constant source of antigen to stimulate immune responses. Virus-specific IgM, often with IgG and occasionally IgA, can be found in pericardium and myocardium for years.[132] Most cardiotropic viruses involve the pericardium and myocardium hematogenously, although cardiac and thoracic surgery permit direct implantation. A latent period between a recognized viral infection and the onset of acute pericarditis is compatible with both infective and immunopathic induction of pericarditis.

CLINICAL FEATURES.

Most cases of pericarditis of unknown origin, "idiopathic" or "nonspecific," are probably viral; these frequently produce the clinical epitome of acute pericarditis: pain, rub, more or less typical ECG changes, elevated acute-phase reactants (e.g., ESR; CRP), fever, leukocytosis, and variable myocardial enzyme levels. "Variable" ranges from normal to occasionally high levels, reflecting, as does the ECG, variable myocardial inflammation. As with most acute pericarditis, there is a 3:1 to 4:1 male preponderance. Pericarditis may occur during initial viral infection but more often 1 to 3 weeks after an upper respiratory or gastrointestinal syndrome, which is too late to culture the virus.[135] Many patients have pulmonary infiltrates and pleural effusions, often with cough. Any viral pericarditis may be effusive and develop tamponade, although most have little or no effusion.

Clinical illness lasts days to a few weeks, usually resolving within 2 weeks.[132] Complications include unresolved inflammation, particularly recurrent pericarditis due to immunopathy and characterized mainly by pain and often recurrent effusion. One to three recurrences affect up to 50 percent of patients, mainly within 8 months of the initial attack. Typically, recurrences are shorter and milder and usually without ECG changes. They may follow unrelated

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infection or physical (rarely mental) stress. Pleural effusions, particularly on the left, are common. Acute effusive viral pericarditis, particularly after tamponade, is associated with eventual classic constriction more often than is "dry" pericarditis. Occasionally, especially in children, with a significant element of myocarditis, heart muscle disease may proceed after the pericardial manifestations become clinically silent. Arrhythmias or conduction defects indicate independent heart disease or significant myocarditis (see Chap. 25) . Differential diagnoses include acute myocardial infarction, particularly with atypical ECGs. Other conditions include traumatic pericarditis, SLE, and nonviral, especially bacterial, pericarditis. Systemic viral disorders (e.g., hepatitis) should suggest a viral etiology. Infectious mononucleosis usually presents as a severe sore throat, adenopathy, and positive serology; a fourfold increase in neutralizing antibody titer is only supporting evidence.

Newer techniques can identify minute amounts of viral nucleic acid; viral genomes can be demonstrated by the polymerase chain reaction (PCR), which amplifies viral DNA along with in situ hybridization.[133]

Reverse immunoassay (RIA) can demonstrate virus-specific immunoglobulins like IgM, IgG, and IgA. It may not be necessary to use these when the diagnosis seems secure in an otherwise healthy patient, especially since, without tamponade, pericardiocentesis and other invasive procedures add little to management and carry risks.[132]

MANAGEMENT.

Effective antiviral agents are not available or even necessary to manage most viral pericarditis. Treatment is for symptoms and complications. Pain, usually pleuritic and limited to the first day or week, is managed by NSAIDs, notably ibuprofen, at doses sufficient to suppress symptoms and fever. Cough can exacerbate pericardial pain and requires antitussive agents. Nontamponading pericardial effusions do not require drainage unless very large. Tamponade requires prompt evacuation of fluid. Usually acute management succeeds. However, virus-specific immunoglobulins are found in many cases of chronic relapsing pericarditis and dilated cardiomyopathy.

Nontuberculous Bacterial (Suppurative) Pericarditis

Acute suppurative pericarditis *(pyopericardium)* simultaneously threatens tamponade and septicemia and is especially serious in children and immunocompromised patients when due to destructive organisms such as staphylococci. Yet, some may be silent, presenting as tamponade or overshadowed by systemic disease and discovered at autopsy. Although many gram-negative organisms such as *Escherichia coli, Salmonella,* other nosocomially acquired infections, and opportunistic organisms have appeared increasingly, the common forms remain streptococcal, pneumococcal, and staphylococcal.[132] Rarely, gasproducing organisms such as *Clostridium* cause pneumopericardium. In adults, pneumopericardium and bacterial pneumopyopericardium are often due to a fistula between the epicardium and a hollow viscus. Invasion from contiguous foci or traumatic implantation include cardiothoracic surgery, mediastinitis, wound infection, myocardial abscess, infective endocarditis, and subdiaphragmatic abscess. Rarely, pericardial invasion spreads along fascial planes from the oral cavity, particularly periodontal and peritonsillar abscesses. Occasionally, infected mediastinal nodes erode the pericardium. Preexisting nonbacterial pericardial effusion as in rheumatoid arthritis, SLE, sarcoid, or uremia can be infected hematogenously. [132] This is probably the pathogenesis of "primary" bacterial pericarditis in which only the pericardium seems to be affected. For example, *Neisseria,* particularly *N. meningitidis* group C, can occur without meningitis, producing "primary" meningococcal pericarditis. Moreover, the *Neisseria* group and other organisms can evoke a sterile, immunopathic effusion, sometimes accompanied by immunopathic or infectious systemic reactions such as arthritis and ophthalmitis.[136] Similarly, *Salmonella* pericarditis, usually due to bacteremia, can occur with or without an enteritic syndrome.

Antimicrobial therapy has decreased the incidence of the common gram-positive

infections. Yet there is relative and absolute increase, usually nosocomially acquired, of infections with multiple and gram-negative organisms, especially in immunocompromised patients and after thoracotomy.[132] [133] *Haemophilus influenzae* occurs sporadically in adults, but children are particularly susceptible to it; pericarditis occurs during respiratory illness and even after cellulitis. *H. influenzae* typically provokes a thick, fibrinopurulent exudate similar to cottage cheese or scrambled eggs that can defeat attempts at percutaneous drainage.

CLINICAL FEATURES.[132]

Suppurative pericarditis is most often acute and fulminant, arising over several days with rapid development of tamponade or presenting as tamponade. Effusion is the rule; the fluid is a turbid exudate characterized by polymorphonuclear leukocytes, increased LDH, and decreased glucose. There is typically tachycardia, fever, toxicity, chills, and sweating. Chest pain is variable, and a pericardial rub is audible in most patients. Cough is common, especially with pleuropulmonary involvement. In some older patients, infections have a reduced tempo, are often clinically silent, or are overshadowed by systemic disease. Chest radiographs usually show an enlarged cardiopericardial silhouette. With gas-producing organisms there are lucent "bubbles" or an "air"-fluid interface. Leukocytosis with a marked left shift is typical (although limited to absent in debilitated and immunosuppressed patients). Blood and pericardial fluid cultures should disclose organisms. The ECG frequently shows stage I changes, although it may be nonspecifically abnormal if the lesion is discovered late. Imaging will disclose any effusion. Inflammatory infiltration of the pericardium can be identified by scintigraphy with indium-111 or gallium-67 (also responsive to leukemic infiltrations).[137] There may be a tendency to loculation producing pericardial abscesses that may resemble cysts. (Congenital cysts may become infected.) Etiologyspecific diagnosis depends on smears, cultures, and more sophisticated searches--e.g., antigen detection, especially when treatment appears to sterilize the fluid. The principal differential diagnoses include tuberculous and viral pericarditis.

PERICARDITIS WITH INFECTIVE ENDOCARDITIS.[132]

Pericarditis during endocarditis can be dramatic but is more often found at autopsy. Acute endocarditis may provoke an immunopathic pericardial effusion with immune complex deposition, whereas subacute endocarditis usually causes an infective effusion. Bacterial endocarditis involves the pericardium most often by erosion of a valve-ring abscess or by rupture of an aortic sinus or myocardial abscess. The most common organisms are *Streptococcus viridans* and *Staphylococcus aureus.* Bacteremia can infect both endocardium and pericardium simultaneously. Sterile "sympathetic" (parapericarditic) effusions are not rare,[138] presumably immunopathic. Hemorrhagic effusions follow direct pericardial irritation or bleeding from rupture of a mycotic abscess. Clues to accompanying myocardial and valve-ring invasion include degrees of AV and bundle branch block, each most common with staphylococcal endocarditis.

MANAGEMENT.

Systemically administered antibiotics achieve excellent levels in pericardial fluid.[132] Pericardial drainage and exploration, monitored by TEE,[139] are desirable because infections tend to loculate, form adhesions, and constrict. In critical tamponade, simple drainage may first be used for relief, with exploration postponed. Pericardial fluid and tissue should be obtained for gram, acid-fast, and

fungal stains, with cultures for aerobes and anaerobes and antimicrobial susceptibility tests.[52] Surgical drainage is preferable over percutaneous drainage, particularly when etiology is uncertain; it permits pericardiectomy when adhesions and loculations predict constriction. With or without definite surgical intervention, urokinase or streptokinase may be used within the pericardium to destroy clots and fibrinous adhesions.[140] Very thick purulent and sanguinopurulent exudates resisting free drainage may require repeated intrapericardial urokinase or streptokinase (to activate the fibrinolytic system) combined with streptodornase (to liquefy viscous nucleoproteins in pus). A clue to loculation and potential constriction is failure to improve after appropriate treatment.[132]

Tuberculous Pericarditis

Pericarditis due to *Mycobacterium tuberculosis* has decreased due to improved public health and effective antimycobacterial treatments. Recently, atypical mycobacteria along with classic tubercle bacilli are increasing in immunocompromised patients, particularly in AIDS due to HIV,[141] lymphocytotrophic, and other viruses. High incidence continues in poorer nations. In the United States its principal importance is differential diagnosis from other syndromes.

PATHOGENESIS. [129]

The pericardium may be infected by hematogenous, lymphatic, peribronchial, or contiguous spread of tuberculosis. (Hematogenous dissemination occurs during all primary tuberculosis.) Lymphatic spread is from lung, bronchi, and mediastinal nodes. Contiguous infection involves intrapericardial inoculation from mediastinal nodal, pleural, and, rarely, myocardial tuberculosis.[141A] Some of the material penetrating the pericardium undergoes proteolytic degradation and antigen processing of individual peptides, with immune responses causing much of the morbidity. These include antimyolemmal antibodies,[133] which are very common in tuberculous pericarditis and probably pathogenic. Protein antigens of the bacillus induce delayed hypersensitivity responses stimulating lymphocytes to release lymphokines that activate macrophages and influence granuloma formation. There are four classic pathological stages of tuberculous pericarditis[129] : (1) fibrinous exudation with initial polymorphonuclear leukocytosis, relatively abundant mycobacteria, and beginning granuloma with loose organizations of T cells and macrophages; (2) serous, usually serosanguineous effusions with a mainly lymphocytic exudate with monocytes and foam cells; (3) absorption of effusion with organization of granulomas caseation, and pericardial

thickening due to fibrin, collagenosis, and, ultimately, fibrosis (mycobacteria become difficult to find); and (4) constrictive scarring: replacement of fibrinous and granulomatous matter by fibrosis, which contracts on the cardiac chambers (constriction can develop despite effective antituberculous therapy). Calcification can occur at any stage, tending to form sheets, plaques, hoops, and bands of calcium salts over any part of the heart. Tuberculous pericarditis may surface as an acute or chronic pericardial effusion and occasionally a variant of cholesterol pericarditis with or without overt tamponade and usually with considerable fibrin, adhesions, and loculations demonstrable by imaging. That noneffusive or minimally effusive acute tuberculous pericarditis often heals without treatment is suggested by the appearance of constriction without a recognizable acute state.

CLINICAL FEATURES.[132]

Clinical expression of tuberculous pericarditis depends on the tempo of inflammation, which is typically slow and indolent after an insidious onset and often accidental discovery (especially with large effusions).[142] Occasionally, there is an aggressive course with acute tamponade, often mixed with constrictive components. Children and immunocompromised patients more often present with classic acute pericarditis. Yet most patients have no history of an acute phase and often no history of tuberculosis; evidence of pulmonary tuberculosis is exceptional. However, like tuberculous meningitis, tuberculous pericarditis may erupt during appropriate antimicrobial treatment for tuberculosis elsewhere. When the disease is clinically apparent, patients tend to have lymphocytosis in blood and pericardial fluid with increased proportions of small and T lymphocytes. Tuberculosis may also involve the myocardium, usually without distinctive symptoms unless it is extensive. Eight modes of presentation cover almost any "pericardial" syndrome[132] :

1. Painful acute pericarditis with or without minimal to large effusions and with or without fever, cough, and malaise
2. Silent effusion, often large and chronic
3. Tamponade, usually without other signs except fever
4. Acute constrictive pericarditis (i.e., constriction appearing over a period of days to a month), usually after drainage of an effusion or disappearance of fluid under therapy
5. Subacute constriction (a course of weeks or months) with varying amounts of fluid (i.e., effusive-constrictive pericarditis)
6. Chronic constrictive pericarditis
7. Pericardial calcifications with or without hemodynamic consequences
8. Fever of unknown origin, usually with constitutional symptoms such as anorexia and weight loss

Tuberculous effusions typically increase slowly with few or no symptoms, leading to tamponade or, after reabsorption or drainage, effusive-constrictive or constrictive pericarditis. Yet tuberculous pericarditis may become recognizable at any stage, more often with tamponade,[143] constriction, or combinations of the two or their complications, as when clinically silent constriction causes hepatic congestion and ascites, simulating cirrhosis (''Pick disease''). Those presenting with constriction may have few

constitutional signs and symptoms if the inflammatory process has burned out. Moreover, tuberculous etiology may not be clear because so many forms of pericarditis cause constriction. Few patients have rubs and precordial pain; more often there is nondescript precordial discomfort. Dyspnea, particularly on exertion, may follow cardiac compression or pulmonary restriction due to a very large pericardial effusion with pleural effusion. When presenting as fever of unknown origin, the diagnosis is suggested by an enlarged cardiopericardial silhouette, especially if imaging discloses a more or less chronic pericardial effusion. Finally, tuberculous pericarditis must be ruled in or out when any pericarditis does not rapidly resolve on NSAIDs treatment and in tamponade of obscure origin, particularly in immigrants from Third World countries, elderly patients, and immunocompromised patients, in whom pericardial tuberculosis may be the first manifestation[144] (clinically primary tuberculous pericarditis).

DIAGNOSIS.

Identification of *M. tuberculosis* in pericardial fluid or tissue is specific, but negative results do not rule out tuberculous pericarditis.[132] [145] Organisms may be so difficult to find that all fluid drained should be centrifuged and studied by smear, culture, and, if necessary, DNA amplification. Extrapericardial tuberculosis, including lung, pleura, and lymph nodes, indirectly supports the diagnosis, but pericardial tissue should be sampled by subxiphoid incision or pericardioscopy.[52] [132] Yet negative biopsy does not rule out tuberculosis. A positive tuberculin (purified protein derivative [PPD]) skin test can support but not confirm pericardial tuberculosis because it may reflect antecedent extrapericardial tuberculosis, as may positive sputum and gastric aspiration. Negative skin tests imply low risk of tuberculosis but are unhelpful with loss of reactivity in patients with anergy, especially those with severe systemic disease or HIV infection. Early, transiently negative, skin tests may be due to pericardial and pleural sequestration of PPD-reactive T lymphocytes. A "therapeutic test" may be a last diagnostic resort using appropriate antimycobacterial agents for critically ill patients with persistent constitutional signs. Uptake of radionuclides such as gallium-67 and indium-111 indicate pericardial inflammation but are nonspecific because uptake also occurs in purulent and viral pericarditis, leukemic infiltration, and even mesothelioma. High levels (>40 IU/liter) of adenosine deaminase (ADA) activity in pericardial fluid are quasi-specific for tuberculous pericarditis (very high ADA levels appear to predict eventual constriction).[146] Differentiation of neoplastic effusions is virtually absolute, with low levels of ADA accompanying high levels of carcinoembryonic antigen.[132] Complement-fixing antimyolemmal and antimyosin antibodies have been found in most patients with acute tuberculous pericarditis but decrease in late stages and constriction.[52] [133] Mycobacterial antigens have been increasingly detected by enzyme-linked immunosorbent assay (ELISA) with high specificity and sensitivity. Probably optimal is the PCR, which amplifies mycobacterial DNA to "fingerprint" strains of *M. tuberculosis* in pericardial fluid with excellent specificity.[147] [148] It is particularly useful in patients with AIDS/HIV infection who have adenopathy and often atypical mycobacterial infection, especially *M. avium* complex. Moreover, because of 100 percent sensitivity for activity, a negative result excludes *active* tuberculosis. Specificity, virtually 70 percent for active tuberculosis, approaches 90 percent for any tuberculosis infection. False-positive results occur, and blood in pericardial fluid may lead to false-negative results by enzyme inhibition; yet the PCR is superior to bacteriological methods.[147] [148] Cultures should be obtained because of the need for drug susceptibility

testing.[132]

MANAGEMENT.

Antimycobacterial treatment has greatly decreased mortality in tuberculous pericarditis, although frequently not preventing constriction.[148A] All isolates of *M. tuberculosis* should be tested for antimicrobial susceptibility. Effective multiple drug therapy is mandatory, and severely ill patients benefit from prednisone or other corticosteroid, which will shorten the course, dramatically decrease symptoms and signs in the acute phase, and reduce the death rate.[132] [149] However, corticosteroids reduce constrictive evolution only modestly if at all.[149] Some atypical mycobacteria resist chemotherapy, requiring efforts to find appropriate combinations. Tamponade should be relieved under chemotherapeutic "cover" to prevent extrapericardial spread. Persistent hypotension warrants adrenal function testing because of possible adrenal tuberculosis. Tendencies to nonresolution or worsening (over 6 to 8 weeks), significant pericardial

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thickening, or signs of constriction mandate pericardiectomy as soon as possible. Indeed, patients with tuberculous pericarditis must be observed indefinitely to detect reactivation, constriction, or reconstriction.[132]

Fungal Pericarditis

In the United States, fungal pericarditis is mainly due to two "geographical" fungi, *Histoplasma* and *Coccidioides,* and to "nongeographical" fungi, *Candida* and *Aspergillus* (*Blastomyces* and *Cryptococcus* are comparatively rare, as is *Pneumocystis carinii*).[132] [150] [151] [152] [153] To these are added two "semifungi" (between bacteria and fungi), *Actinomyces* and *Nocardia.* Geographical fungi are locally endemic, whereas nongeographical fungi are largely opportunistic, depending on compromised host defense. All fungi occur preferentially in immunocompromised[153] and severely burned patients, debilitated individuals, infants (especially premature), and those taking corticosteroids that impair antifungal defenses and phagocyte activity. Indeed, apparent cardiac decompensation during fungal infections may be due to tamponade, constriction, or fungal myocarditis.[132] Precise diagnosis is crucial, particularly for the nongeographical fungi, because amphotericin B, a principal antifungal agent, is very toxic. Pericardiectomy is usually crucial for survival.

HISTOPLASMOSIS.

This is the most common "naturally" acquired fungal infection. It is frequent in endemic areas of the Ohio and Mississippi River valleys and western Appalachia. Pericarditis usually occurs late after infection elsewhere. Acute fibrinous pericarditis is usually a noninfectious (irritative or immunopathic) complication of infection in adjacent mediastinal lymph nodes that can penetrate the pericardium, causing granulomatous inflammation and occasionally calcification. Pleural effusions are more common with

pericarditis than with pulmonary histoplasmosis. *Histoplasma* pericarditis is relatively common in younger, usually immunocompetent patients, whereas disseminated histoplasmosis, like other fungal infections, is more common with immunosuppression. Pericardial involvement can resemble idiopathic pericarditis, resolving within 2 weeks. However, almost half of *Histoplasma*-induced effusions develop hemodynamic compromise. In contrast to other fungal pericarditides, effusion with or without tamponade can be rapid and massive. The fluid is serous, xanthochromic, or hemorrhagic and predominately leukocytic. Pleuropulmonary involvement produces mixed clinical manifestations: it precedes respiratory illness, pleuritic pain, cough, and dyspnea, resembling viral or tuberculous pericarditis.[151] Only occasionally do patients develop constriction or pericardial calcification (rarely, constriction is the presenting feature). If acute pericarditis resolves, relapses occur variably. The diagnosis must be considered in endemic zones. Rising complement fixation titers and the immunodiffusion test are helpful. Moreover, other causes of pericarditis must also be considered in endemic areas even in seropositive patients.[132] With persistent illness, biopsy of lymph nodes, particularly mediastinal nodes, with cultures and methonium silver stains, may be decisive. *Histoplasma* should be identified, because granulomas alone are nonspecific; indeed, tuberculosis may be associated. The principal differential diagnoses are pericarditis due to viruses, tuberculosis, brucellosis, Hodgkin disease, or sarcoid.

Resolution spontaneously or with antiinflammatory agents without antifungal medication indicates almost certainly "immunopathic" or "irritative" pericardial involvement without infection, even if with tamponade. Unless *clearly* recovering, are in no distress, and have a "dry" pericardium on imaging, patients should be hospitalized because of the (infrequent) possibility of tamponade. Antifungal treatment with amphotericin B or ketoconazole is indicated for disseminated histoplasmosis or severe pericardial inflammation.[132] To reduce chest pain, fever, and effusion and suppress the pericardial rub, NSAIDs usually suffice. Tamponade and constriction require decompression. Corticosteroids predispose to dissemination but may be used for severely ill patients. With disseminated histoplasmosis, adrenal function should be assessed because the adrenals may be involved, requiring corticosteroid treatment.

COCCIDIOIDOMYCOSIS.

This fungal infection is endemic in the southwest, particularly in the San Joaquin Valley. Spores are inhaled from soil. Pericardial coccidioidomycosis is usually a complication of progressive disseminated infection, although it is rarely "primary" (i.e., confined to the pericardium).[132] Hilar node involvement resembles tuberculosis. Infection causes serofibrinous effusion with a potential for adhesion. The clinical spectrum is wide: from classic acute to chronic adhesive pericarditis and rarely to effusive-constrictive pericarditis. Acute pericardial coccidioidomycosis usually accompanies pneumonia from the same organisms, sometimes with systemic adenopathy, osteomyelitis, or meningitis. The main symptoms may be pneumonitic: cough, dyspnea, fever, and pleuritic pain. Patients are usually chronically ill, debilitated, malnourished, and often immunocompromised. Diagnosis requires histological documentation but is suggested by pericarditis in the endemic zone, especially if with disseminated coccidioidomycosis. Pericarditis may resolve without specific therapy, but anticoccidioidal agents such as

fluconazole may be necessary, depending on severity and progress.

"NONGEOGRAPHICAL" FUNGAL INFECTIONS.[132] [150] [152] [153]

These related organisms produce similar clinical pictures. Actinomycosis may cause fistulas and sinus tracts to skin and other organs as well as contiguous spread along thoracic and mediastinal tissue planes. Pericarditis tends to be insidious until tamponade or constriction, but acute pericarditis may be followed by chronic effusion with pericardial thickening and adhesions.[154] Acute tamponade may respond to medical and surgical management, only to be followed by rapid constriction. These "semifungi" also cause endocarditis and myocarditis. Although suggested by infection elsewhere, specific diagnosis is by staining and culturing pericardial fluid. Infection is fatal unless treated medically and surgically. *Actinomyces* responds to penicillin and other antibiotics. *Nocardia* responds to sulfonamides, particularly sulfisoxazole. Optimal therapy is combined antimicrobials, surgical drainage, and pericardiectomy as indicated.

PERICARDIAL DISEASE IN AIDS AND AIDS-RELATED COMPLEX (see alsoChap. 68). [132] [155] [156]

Immunocompromised patients with AIDS and AIDS-related complex respond as do other kinds of immunosuppressed patients, such as those receiving corticosteroids and cytotoxic agents, and include mainly patients on cancer chemotherapy or with serious inflammatory disorders or after organ transplants. AIDS predisposes to infection by multiple organisms, many opportunistic, and to malignancies such as Kaposi sarcoma and non-Hodgkin malignant lymphoma. Complications of AIDS and HIV infection affect the endocardium, myocardium, and pericardium; patients with cardiac involvement have lower T4 cell counts. Pericardial disease, particularly effusion, is relatively frequent but more often discovered by imaging or at autopsy. The most frequent cardiac lesion at autopsy is sterile pericardial effusion.[132] In general, late AIDS-related pericardial effusions imply a grave prognosis, suggesting end-stage HIV disease. Patients with pericarditis often also have myocarditis.

Pericardial involvement in AIDS occurs in six forms[132] :

1. *Silent.* Fibrinous and effusive pericarditis with or without adhesions or apparently sterile pericardial effusion occur as part of a generalized serious effusive process, including ascites and pleural effusion ("capillary leak syndrome"). The specific etiology is often uncertain.
2. *Classic acute pericarditis.* Typically there is pain, rub, and often ECG changes. If effusive, the fluid may be clear, purulent or sanguineous. A search for an infectious etiology is often rewarded. Mycobacteria, fungi, and other opportunistic organisms are frequent.
3. *Cardiac tamponade.* This usually is recurrent with chronicity but it may be the presenting syndrome.
4. *Constrictive pericarditis.*
5. *Neoplasia.* This mainly includes Kaposi sarcoma and aggressive Hodgkin or non-Hodgkin lymphoma.
6. *Myopericarditis*. With definite inflammatory signs there tends to be lymphocytic

pericardial infiltration. Sterile hydropericardium may be due to uremia or congestive failure from associated myocarditis or cardiomyopathy. Pericardial effusions of any size are associated with shortened survival.[132] Large effusions may be tuberculous or fungal. Nontuberculous *Mycobacterium* infection occurs late.

At least two forms of *malignancy* are related to AIDS: Kaposi sarcoma and non-Hodgkin malignant lymphoma[157] ; Hodgkin and other lymphomas also occur. Kaposi sarcoma involves both visceral and parietal pericardium, with particular predilection for epicardium and subepicardial fat; it produces effusion and occasionally constriction. Although usually disseminated, in AIDS it may appear to be primary in the pericardium with a strong tendency for tamponade.[129] *Malignant lymphoma* is usually multicentric and only rarely primary in the heart, where it typically affects the myocardium more often than the pericardium. Occasionally, an Epstein-Barr viral genome may be discovered.

PARASITIC PERICARDITIS

Pericardial parasitoses appear in endemic areas and in travelers from them in whom mild attacks are often mistaken for idiopathic pericarditis.[132] [158] [159] [160] The acute illness typically resembles suppurative bacterial, or occasionally viral, pericarditis. Parasites frequent in the liver such as *Echinococcus* and amebae may also provoke sterile, presumably immunogenic, ("sympathetic") pericardial effusions, which may cause tamponade.[132] Such parasites usually enter the pericardium from perforation through the diaphragm or from secondary lesions in the lung and pleura. Parasitosis elsewhere suggests the diagnosis. In some patients, fluid may be negative for organisms, requiring biopsy. Blood or pericardial fluid *eosinophilia* always suggests parasitic disease.

TOXOPLASMOSIS.[132]

Toxoplasmosis (caused by *Toxoplasma gondii*)

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may be congenital or acquired. Pericarditis is often found at autopsy in patients with more obvious *Toxoplasma* myocarditis. Pericardial affection is mainly chronic, with often a chronic effusion and rarely constriction. Acute pericarditis with or without tamponade is rare and includes fever, rash, and adenopathy; it can resemble SLE. Pericardial involvement may occur during miliary spread, particularly in patients with leukemia and other disorders treated with chemotherapeutic agents or corticosteroids.

ECHINOCOCCOSIS. [159] [160]

Echinococcus granulosus, an invasive and destructive sporozoan, occurs mainly in sheep-raising countries. It produces hydrated cysts of the myocardium, pericardium, and mediastinum, including great vessels. The pericardium is involved from a ruptured

adjacent myocardial cyst or a hepatic cyst penetrating the diaphragm. Chest pain and sharp anaphylactic reactions with eosinophilia are characteristic. Multiple intrapericardial rupture can produce vague to striking symptoms. Pericardial and mediastinal echinococcal cysts also compress the cardiac chambers or great vessels, producing corresponding abnormalities on imaging, which shows well-defined unilocular (occasionally multilocular) cysts with trabeculations due to internal "daughter membranes." Complications include secondary bacterial infection, tamponade, and constriction and even coronary obstruction. Surgical excision (enucleation) may be dangerous due to spillage of active parasites. Evacuation of the cysts and instillation of silver nitrate is usually preferable.

AMEBIASIS.[132]

Amebiasis (caused by *Entamoeba histolytica*) occurs mainly in endemic areas and in travelers from them (in whom the syndrome may appear years later). Although patients may also have intestinal amebiasis, liver abscesses, particularly in the left lobe, typically perforate the diaphragm and involve the pericardium. Mortality is high, especially with missed diagnoses. Serofibrinous ("presuppurative") pericarditis with straw-colored or sanguineous fluid can precede gross rupture into the pericardium and is often suspected to be tuberculous. Frank pericardial rupture can be insidious or dramatic with pain, shock, tamponade, and cyanosis. Fluid is brownish; the pus may simulate anchovy paste, an appearance that is quasi-diagnostic. Secondary bacterial infection must be considered in severely ill patients. Occasionally, there is classic acute pericarditis or subacute effusive-constrictive pericarditis with pericardial thickening. Diagnosis is by fluorescent antibody test or amebic enzyme immunoassay supported by a liver scan with technetium-99m.[132] Medical therapy with antiamebic agents such as metronidazole or dehydroemetine is highly successful in hepatic cases, but pericardial involvement requires drainage and, if necessary, resection.

NEMATODAL PERICARDITIS

Filariasis (caused by *Wuchereria bancrofti*), endemic in Africa and India, produces hemorrhagic effusions in which microfilaria are easily found in nocturnal blood smears.[129] Effusions may be clinically silent or massive with rapid or slow tamponade. Cough and constitutional symptoms are common. Persistent pericardial inflammation produces sanguinopurulent pericarditis with chronic lymphocyte inflammatory changes. Survival may produce rapid constriction, even during chemotherapy. Diagnostic clues include other manifestations of filariasis, such as elephantiasis. *Necator americanus* produces eosinophilic pericardial effusion, possibly an "allergic" effect. *Dracunculus* ("guinea worm") has been found in constrictive pericardial scar.

SPIROCHETAL PERICARDITIS

Except for spirochetes transmitted during Lyme carditis[161] and leptospirosis, spirochetal pericarditis is poorly characterized, owing to extreme rarity of discovery in tissue where its presence may be accidental. *Treponema pallidum* is identified only in the rare involvement of the pericardium by localized or miliary syphilitic gummas with a fibrotic

reaction or accompanying a hemorrhagic effusion.[132] *Lyme pericarditis* can produce acute pericarditis, pericardial effusion, and myopericarditis. Fatal myopericarditis may ensue with myocardial and conducting tissue involvements. Silver stains of sampled material may demonstrate the spirochetes. However, ELISA can detect IgM and IgG antibodies. Indium-111 antimyosin scintigraphy may be helpful.[162] Leptospirosis[132] (caused by *Leptospira icterohaemorrhagiae*) is mainly a tropical disease and is reported at all ages. Most cases are subclinical. Conjunctival suffusion is a clue. Myocardial and pericardial involvement, often mild, is seen more frequently in patients who are anicteric. Typical acute pericarditis including friction rub and ECG changes may be due either to the organism itself or to an accompanying uremia. Diagnosis is by *Leptospira* agglutination test.

RICKETTSIAL PERICARDITIS

Rickettsiae, particularly *Rickettsia rickettsii,* can produce pericarditis,[132] [163] [164] myocarditis, and vasculitis in endemic areas, including South America, Africa, and the South Central and Atlantic States (Rocky Mountain spotted fever [RMSF]). In Africa tic-transmitted *boutonneuse fever* is due to *Rickettsia conorii*. Q fever, due to *Coxiella burnetii*, is transmitted by sheep and cattle in milk and is found worldwide. It appears to produce more obvious clinical pericarditis than does RMSF and may present as a pericardial effusion. In RMSF, myocarditis and pericarditis can occur with or without vasculitis, the latter being a "toxic" or immunogenic process. Cross-reactive antimyolemmal antibodies suggest that apericardial involvement can be immunopathic with pericarditis after extension of myocarditis to the epicardium. Diagnosis is by serological test, including Weil-Felix agglutinins and IgM and IgG antibodies.

CHLAMYDIAL PERICARDITIS

Chlamydiae produce classic acute pericarditis and large effusions.[132] Rare until recently, the Chlamydiaceae, especially *C. trachomatis, C. psittaci,* and *C. pneumoniae,* are increasingly found in immunocompromised patients and patients with malignancies, as well as otherwise healthy hosts. They produce pericarditis, myocarditis, pleuritis, and pneumonitis. Psittacosis follows exposure to psittacine and other birds. (Indeed, pericardial effusion is one of the most common forms in affected birds themselves.) Specific diagnosis is by IgG antibody titers.

PERICARDIAL DISEASE IN METABOLIC DISORDERS

Renal Failure (See Fig. 72-6)

Most *uremic pericarditis* is due to chronic renal failure, which produces all morphological forms of acute pericarditis, effusive and noneffusive, and is usually hemorrhagic, with and without tamponade.[165] [166] *Dialysis pericarditis* accompanies prolonged survival due to effective dialysis, and with it uremic constrictive and effusive constrictive pericarditis have appeared. In acute renal failure, acute uremic pericarditis is usually of less serious significance. Although nitrogen retention is necessary for uremic pericarditis, many patients escape pericarditis so that the pathogenesis is uncertain; "toxic metabolites"

are often invoked. Pericardial involvement is unrelated to the etiology of renal failure. Although blood urea nitrogen levels are customarily over 60 mg/dl, there is no strict numerical relationship; and echocardiography reveals excess pericardial fluid in many asymptomatic patients. The incidence of acute pericardial disease in chronic renal failure has plummeted, owing to effective dialysis, hemoperfusion, and renal transplantation (although pericarditis follows transplant in 2 to 3 percent of patients[167]). Small pericardial effusions and noninflammatory hydropericardium due to volume overload and congestive failure (see Chap. 17) are common and usually insignificant.

Cardiac tamponade is the main danger, often precipitated by critically increased bleeding. It may appear as an unexplained fall in blood pressure to a level that varies widely between high, but lower than previously, and shock level. A change in mental status may be the first clue. Fever is variable in the absence of infection and more common in dialysis pericarditis than uremic pericarditis. Chest pain varies from severe to absent. Uremic pericardial rubs tend to be loud, are often palpable, and frequently persist after biochemical abnormalities improve. In uremic pericarditis due to acute and chronic glomerulonephritis and in dialysis pericarditis (especially when precipitated by viral infections), complement-fixing antimyocardial antibodies appear, including antimyolemmal autoantibodies that may be pathogenetic as well as diagnostic.

Uremic pericarditis resembles the spectrum of viral pericarditis and its acute complications, including the characteristics noted earlier. Despite comparable degrees of renal failure, only some, usually younger, patients develop uremic pericarditis, acute myocardial infarction, or hyperparathyroidism.[166] [167] A constant exacerbating factor is the uremic hemorrhagic diathesis from hematological impairments that promote bleeding and abundantly vascular granulation tissue due to uremic inflammation. Pericardial effusions usually predict tamponade in proportion to their size. Uremic exudates contain considerable fibrin and inflammatory cells. All are serosanguineous and, with tamponade, hemorrhagic.[168] Despite destruction of the pericardial mesothelium and gross hemorrhage, pure, that is uninfected, uremic pericarditis is unique: inflammatory cells do not penetrate

the myocardium, accounting for the customary absence of typical ECG changes. Indeed, if the ECG is typical of acute pericarditis, intercurrent infection must be suspected. Most often, ECGs are grossly unchanged and reflect associated abnormalities such as LV hypertrophy and "strain," coronary disease, and electrolyte abnormalities. Fluid retention and pleural effusion may reduce ECG voltages with or without pericardial effusion.

DIFFERENTIAL DIAGNOSIS.

This may be difficult, especially in mentally confused patients and because nonuremic intercurrent pericarditis of any cause is always possible. For example, when hypertension is not being controlled, dissecting hematoma of the aorta (see Chap. 40)

must be considered. Indeed, uremic tamponade may simulate any cardiocirculatory emergency, especially with marked hypotension (often despite fluid overload).[165] [166] [167] [168] Conversely, tamponade may be disguised by a relatively or absolutely high pressure level (high pressure tamponade). Confusion of tamponade with florid heart failure may arise from LV hypertrophy, which is frequent in uremics, and myocardial failure, each of which can prevent pulsus paradoxus. Unexplained worsening renal function may be a clue to tamponade. Sepsis of nonrenal origin may coexist and precipitate tamponade; blood cultures may be positive for organisms and pericardial fluid negative. Hepatic congestion due to tamponade may be confused with viral hepatitis. Finally, in uremic patients, frequent autonomic impairment occurs, even during tamponade, so that the *heart rate may be deceptively slow* (60-80 beats/min) despite fever and hypotension.

TREATMENT.

This consists of drainage, which should be gradual because of possible "pericardial shock" in patients who may have underlying congestive failure or intercurrent myocarditis that predisposes to postdrainage cardiac dilation. A neurogenic element may also contribute to postdrainage collapse because patients are vagotonic; therefore, during pericardial drainage, patients may need to receive atropine.[166] [169] Intrapericardial hydrocortisone, triamcinolone, or equivalent agents may accelerate improvement by suppressing inflammation. For uremia itself, effective dialysis is mandatory, with careful monitoring of intravascular volume, since with excess pericardial fluid rapid vascular volume reduction can precipitate tamponade.

ACUTE RENAL FAILURE.

Patients with hypotension due to shock, sepsis, trauma, or surgery may develop acute renal failure that can be self-limited; but with the blood urea nitrogen of 100 mg/dl or more, uremic pericarditis may appear. This responds to effective treatment of the etiological condition, circulatory support, and acute dialysis. Pericardial involvement is identified by a rub, effusion, or tamponade.

DIALYSIS PERICARDITIS.

Adequate dialysis effectively ends uremic pericarditis within a few months. While classic uremic pericarditis is reversed by dialysis, *dialysis pericarditis,* by definition, appears despite otherwise successful dialysis, even in stable patients with good biochemical control.[166] Its pathogenesis is unknown, although it is much less common during peritoneal dialysis than hemodialysis. Immune complex-like material is found in the dialysate, and this "loss" may retard pericarditis.[168] [169] A pathogenetic role for "middle molecules" has been proposed. Several factors are associated with precipitating dialysis pericarditis and effusion, above all inadequate dialysis. Infection, particularly viral, is frequent, with hepatitis and cytomegaloviruses common in dialysis units. Such infections are often systemic, and the pericardial fluid is sterile. Constitutional symptoms, especially fever, are more severe and more common than in uremic pericarditis, and dialysis pericarditis may be preceded by weight gain and hypotension.[166] Effusion with or without hemorrhage is the most important complication and tends to recur. As in

classic uremic pericarditis, larger effusions predict tamponade. Survival due to dialysis has allowed uremic constriction to appear.[166]

Treatment is designed to intensify dialysis while avoiding hypotension. Tamponade calls for drainage with maintenance of an intrapericardial catheter for at least 2 or 3 days. While there are no controlled trials, intrapericardial nonabsorbable corticosteroid-like triamcinolone appears to be effective. A trial of peritoneal dialysis for patients who have been on hemodialysis may be therapeutic. For intractable pericardial effusions, pericardial resection is the only effective approach.[166] [167] [168]

OTHER RENAL CONDITIONS.

Although transplantation is usually successful for renal failure, severe transplant rejection is accompanied by acute pericarditis. [167] Patients with a nephrotic syndrome frequently have pericardial effusions associated with fluid retention (hydropericardium) or actual inflammation. Pericarditis in hepatorenal failure occurs at relatively low blood urea nitrogen levels, does not respond to dialysis, and is almost uniformly fatal.[166]

Hypothyroidism (See also Chap. 64)

Severe hypothyroidism produces large usually clear, high-protein, high-cholesterol, high-specific-gravity pericardial effusions.[165] [166] [170] These are constant in experimental and human myxedema and may precede other signs (especially in primary hypothyroidism). Echocardiography reveals them in 5 to 30 percent. Children with Down syndrome are at special risk for congenital or acquired hypothyroidism, which is often unrecognized because excessive weight, hypotension, and dry skin are classic in Down syndrome and hypothyroidism.[171] With tamponade, dyspnea, fatigue, cardiomegaly, and cyanosis may be attributed to their congenital heart disease.

Many effusions in hypothyroid patients are very large, chronic, asymptomatic, and discovered accidentally by chest radiography.[166] Clinical tamponade[171] is rare because the slow tempo permits pericardial stretch. Three factors may precipitate tamponade: (1) intercurrent acute pericarditis; (2) hemorrhage; and (3) rarely, cholesterol pericarditis with an inflammatory reaction to precipitated cholesterol crystals. Moreover, tamponade can occur with high arterial pressure, presumably due to the increased catecholamines of hypothyroidism.

In severe myxedema, pleural effusion, ascites, and anasarca resemble chronic cardiac failure and constrictive pericarditis.[165] Blood volume is usually increased, whereas in uncomplicated myxedema it tends to be decreased. In some cases, high sedimentation rates suggest an inflammatory component that has been seen on electron microscopy,[166] but the fluid typically has few leukocytes. The ECG may not be altered. However, bradycardia is common, and severely myxedematous patients have distinctly low-voltage to microvoltage QRS.[166] Treatment is thyroid hormone replacement, which is nearly always followed by steady regression of the effusion.[170] [171]

OTHER METABOLIC DISORDERS.

Pericarditis has been repeatedly observed during severe crises in patients with *diabetic ketoacidosis* and *adrenal failure* and in some patients with hyperuricemic *gout*.[165] [166] In each case, although bacterial infection, addisonian crisis, or tuberculosis was ruled out, there has not been convincing evidence that pericarditis did not represent an intercurrent inflammation, usually viral, that precipitated that diabetic or adrenal crisis (rarely, tamponade precedes adrenal insufficiency). In Waterhouse-Friderichsen syndrome an accompanying pericarditis is almost certainly meningococcal.[166] In diabetic ketoacidosis, ECGs resembling stage I acute pericarditis have been repeatedly observed both with and without clinical pericarditis.[166] Purely metabolic cholesterol pericarditis occurs in exceptional patients with high serum cholesterol without the usual inciting causes.

NEOPLASTIC PERICARDIAL DISEASE (See Chaps. 49 and 69)

Three types of neoplastic disease affect the pericardium[172] : (1) primary pericardial tumors, benign or malignant (comparatively rare); (2) secondary malignancies--metastatic and/or from neighboring structures; and (3) nonneoplastic pericardial effusions accompanying malignancy elsewhere. In general, demonstrably malignant effusions imply a prognosis for life of months to a year with breast carcinoma among the "better" prognoses.

SECONDARY MALIGNANCIES: METASTATIC AND INFILTRATIVE

Metastasizing and multicentric malignancies affect the pericardium with or without cardiac involvement, are silent more often and for longer than primary malignancies, and may be the initial sign of malignant disease arising elsewhere.[172] [173] [174] [174A] These can present as a pericardial effusion or deceptively when a strong fibrinous reaction mimics acute pericarditis with pain, pericardial rub, fever, and typical or suggestive ECG changes.[172] [173] Usually the ECG is nonspecific even if typical. The J-ST elevations sometimes last for days to weeks, implying persistent pericardial and myocardial injury.[172] In metastatic involvement of the heart by discrete tumors, epicardial lymphatics are nearly always involved. Direct extension occasionally occurs from tumors of the lung, chest wall, or esophagus. Solid tumors may be restricted to the pericardium, invade the myocardium, or appear in both. Lymphomas, Hodgkin disease, leukemias, melanomas, and especially multiple myeloma simultaneously infiltrate the myocardium and pericardium, although each can be isolated to the pericardium. Many of these are associated with local production of cytokines, accounting for associated pericardial inflammation.[175] [176] [177] Melanomas, with frequent cardiac involvement often invade the visceral pericardium.[177]

CLINICAL ASPECTS.[172]

Secondary neoplasia tends to be insidious and difficult to diagnose unless cancer is recognized elsewhere. Effusions are usually large, especially in patients with

hypoalbuminemia, and may be decompensated to tamponade by intrapericardial hemorrhage. Occasional tumors induce constrictive, especially effusive-constrictive pericarditis, with the constriction due to neoplastic tissue, adhesions, or both. Some tumors encase the heart, producing elastic constriction. Occasional tumors involving the pericardium mimic one of the vasculitis-connective disease group. Neoplastic effusions that

become suppurative suggest infectious pericarditis, especially in patients immunocompromised due to treatment or to AIDS; the organisms are either common or opportunistic pathogens, especially atypical mycobacteria and fungi.[172]

Pericardial malignancy should be suspected, particularly in patients with malignancy elsewhere[172] : (1) with any large or recurrent effusion; (2) apparently refractory "heart failure" with very high venous pressure; (3) superior vena cava syndrome; or (4) unexplained hepatomegaly. Dyspnea, orthopnea (the most common symptom), unexplained chest pain, and nonproductive cough suggest pericardial involvement. Facial edema and persistent jugular venous distention after drainage of a pericardial effusion may be due to SVC syndrome.

DIAGNOSIS.

This may be indicated by chest film, echocardiography, MRI, CT, and radionuclide scanning with indium-111, gallium-67, or technetium.[172] [178] CT and MRI can also reveal tumor contents and texture. For malignant melanoma (over 60 percent with cardiac metastases[177]), MRI is particularly suited because of magnetic scanning. Large effusions or tamponade necessitate studying fluid or tissue, best obtained by video-assisted pericardioscopy, so that samples including *epicardial* biopsy may be obtained safely under direct vision.[52] [179] Cytology, cytometric, and immunohistochemical studies are highly sensitive and specific for most metastatic lesions.[180] [181] False-negative cytology is more common with lymphomas and mesothelioma. Normal mesothelial cells proliferate in response to injury and can show many mitotic figures similar to tumor cells, particularly resembling mesothelioma and adenocarcinoma.[172] [182] Differentiation is by immunohistochemical and ultrastructural methods.[52] [179] Mesothelial cells have keratin and vimentin, whereas carcinoma cells contain carcinoembryonic antigen and LeuM1.[181] [182] [183] The ECG is usually abnormal but nonspecific. Malignant effusions usually with tamponade are a common cause of electrical alternation. Fluid obtained by needle or surgical drainage should be studied for cells, including histochemical staining[181] [182] [183] ; carcinoembryonic antigen and neuron-specific enolase should be sought.[184] Unsatisfactory results require biopsy with the largest possible specimen through the subxiphoid route or by pericardioscopy.

PRIMARY PERICARDIAL NEOPLASM

Benign tumors are found especially in infancy and childhood, whereas *primary*

malignancies are discovered mainly in the third and fourth decades.[172] Lipomas and fibromas discovered in mid and later life may grow to giant proportions. Pericardial cysts and particularly hydatid cysts require differential diagnosis, especially if atypically located and if imaging suggests solid tumor.[172] The most important primary malignancies are *mesotheliomas* and *sarcomas* (particularly, *angiosarcoma*), which arise respectively from the pericardial serosa and vasculature and do not metastasize. Pleural mesothelioma can spread to pericardium. They proliferate throughout the pericardium, often invading the myocardium. Mesotheliomas are often related to asbestos or fiberglass exposure, although numerous cases lack either. In general, the signs and symptoms of secondary metastatic and infiltrative malignancies also apply to benign and malignant solid tumors.

CLINICAL FEATURES

Benign tumors usually provoke large effusions even in neonates in whom a cardiorespiratory distress syndrome may appear at or shortly after birth. *Teratomas* are nearly always found in infants with large pericardial effusions; the fluid may be transudate, sanguineous, or, rarely, pyopericardium. [172] Teratomas can compress the right side of the heart and may have detectable calcifications: teeth and bones. Bronchial cysts may resemble teratomas on imaging due to radiopaque contents, but effusions are not common. *Pheochromocytomas* (paragangliomas) and related neurofibromas and neuroblastomas often induce adrenergic hormonal effects, leading to detection by blood and urine tests for catecholamines and localization with iodine-131 metaiodo-benzyl-guanidine. They are hypervascular so that intravenous contrast agents can localize them.[172] *Thymomas* can cause pericardial effusion but may be large enough to be confused with effusion and difficult to identify by imaging if isodense with surrounding structures.[173] [185] Malignant thymomas may present as multisystem disease and autoimmune syndromes as well as cardiac tamponade and SVC obstruction; immunocompromised patients are more susceptible.[172] *Mesotheliomas* may give all the symptoms and signs of metastatic and infiltrate tumors and can mimic idiopathic acute pericarditis with effusion, but with characteristically high levels of hyaluronic acid (hyaluran) in blood and pericardial fluid.[173] [186] They can grow without much exudative reaction to overspread the heart, causing atypical or classic constriction.[173] [181] [182] *Angiosarcomas* grow as blood locules within the pericardial cavity, may or may not deform the cardiopericardial silhouette while enlarging it, and, because of their vascularity, imitate hemopericardium of other origin.[172]

MANAGEMENT

Large refractory and tamponading effusions must be drained. Pericardiocentesis has a high failure rate, except for temporary relief. Percutaneous balloon pericardiotomy[187] [188] or subxiphoid surgical drainage (erroneously termed "window") may be successful in patients with limited survival. Subxiphoid incision permits direct inspection and biopsy; balloon pericardiotomy and pericardiopleural window avoid discomfort and risks of surgery. A pericardioperitoneal shunt may provide prolonged palliation, particularly in children.[172] Extensive pericardial resection is mandatory for persistent recurrence of malignant pericardial constriction; video-assisted pericardio(thoraco)scopic resection is desirable.[172] [173] [179] [189] In patients with very poor prognosis or in whom operation would

be hazardous, sclerosing agents have been palliative, although with considerable initial pain.[190] Fortunately, indwelling pericardial drainage tubes act identically, rendering sclerotherapy unnecessary.[172] Yet, there is no convincing evidence that intrapericardial treatment modifies the prognosis for life, which averages 4 months for secondary malignancies except tumors that are unusually sensitive to radiation or systemic chemotherapy.

PERICARDIAL DISEASE IN THE VASCULITIS/CONNECTIVE TISSUE DISEASE GROUP (See Chap. 67)

Diseases causing pericarditis, effusion, adhesions, and constriction include most of the vasculitis/connective tissue disease group--a heterogeneous category of disorders that have in common inflammation of blood vessels. Only specific histological lesions in the pericardium confirm the etiology, although characteristic pericardial fluid constituents may be adequate and characteristic clinical behavior often suggests the diagnosis.[191] The primary pathogenic event leading to vasculitis is probably deposition of immune complexes; group members have immunopathic, including autoimmune, features based on immunoglobulin or complement deposition and/or inflammatory cell infiltration in blood vessels and pericardium.[191] Increased or decreased pericardial fluid complement components with normal serum complement levels suggest local complement activation or consumption. With arthritis, synovial tissue and joint fluid abnormalities may resemble those of pericardium and pericardial fluid.[191] Some heterogeneity relates directly or indirectly to exposure to infectious agents (e.g., streptococcal antigen in acute rheumatic fever; hepatitis B antigen in polyarteritis), to unrelated pericardial trauma (e.g., arthritic manifestations with pericarditis in postpericardiotomy and post-myocardial infarction syndromes), or to hypersensitivity, such as "allergic" reactions (e.g., drug-induced lupus) provoking immunopathic responses. Some, such as Wegener granulomatosis[192] and rheumatoid arthritis,[193] feature granulomas. Sarcoidosis, also granulomatous, is less well understood and not strictly a vasculitis.[191] Many patients develop serological evidence, including hypergammaglobulinemia, cryoglobulinemia, hypocomplementemia, circulating immune complexes, and rheumatoid factor, each of which may also be in pericardial fluid. Most of this group affect a preponderance of females, yet males form a disproportionately large part of those with pericardial involvement, reflecting male preponderance in almost every form of pericarditis.[191]

Laboratory studies (e.g., antinuclear antibodies [ANAs]) may support or confirm some diagnoses but alone are not entirely specific.[194] [195] Some malignancies provoke both vasculitis and pericarditis, and some benign and malignant cardiac tumors, including myxoma, may be associated with systemic syndromes resembling those of members of this group.[191]

Rheumatoid Arthritis

Rheumatoid arthritis and its juvenile and adult variants is probably the largest "generator" of pericardial disease. Pericardial involvement is most common in middle-aged white men. Almost half of autopsy patients with rheumatoid arthritis have significant pericardial adhesions, and on echocardiography approximately half have

excessive pericardial fluid.[190] Rheumatoid arthritis pericarditis is more common

in patients with advanced rheumatoid arthritis with high rheumatoid factor titers.[194] Clinically significant effusions imply a poor prognosis. All morphological forms of pericarditis are associated with rheumatoid arthritis. Acute fibrinous pericarditis, usually subclinical, is demonstrable mainly in patients dying of any reason during arthritis flares. Pericardial effusions, also usually subclinical and small to moderate, can become large, chronic, and even tamponading. Adhesive pericarditis, usually generalized but occasionally localized or with loculated fluid, can provoke all variants of constriction, which tends to occur within 4 to 5 years of the onset of severe rheumatoid arthritis and is comparatively rare with chronicity.[191] Pericardial disease becomes more overt, with severe rheumatoid arthritis particularly in patients with strong serological evidence and only rarely in quiescent disease.[193] [194] [195] [196] The most common presentation is a pericardial rub lasting days to years and accidentally discovered in patients without symptoms or with asymptomatic effusion on echocardiography.[190] Recognition of RA pericarditis is confounded not only by its many variants but also by intercurrent diseases, such as viral pericarditis and drug-induced pericarditis (e.g., by phenylbutazone), possible increased susceptibility to other infections and the excellent substrate for bacterial infection afforded by chronic pericardial effusions. Unilateral or bilateral pleural effusions, pleural rubs, and lung lesions (e.g., Caplan syndrome) are common with active disease. Patients with rheumatoid arthritis and systemic congestion ("right-sided heart failure") raise the question of rheumatoid arthritis constriction or tamponade, although common causes of systemic congestion such as true heart failure are more likely.[191]

DIAGNOSIS.

Although acute, rheumatoid arthritis pericardial effusions may have more fibrin. Acute and chronic effusions resemble arthritic synovial fluid and rheumatoid pleural effusions.[191] [197] They are mainly serous, often serosanguineous, rarely hemorrhagic, and characterized by low glucose (<45 mg/dl) with a mainly neutrophilic leukocytosis (usually >15,000 cells/mm[3]), with many cells showing cytoplasmic inclusions that stain for IgM and soluble immune complexes including IgG; complement levels are very low; latex fixation titers for rheumatoid factor are high and relatively specific. Protein is usually more than 5 gm/dl; cholesterol, including crystals, is frequently increased.[191] [196] [197] ECG changes are nonspecific. Cases must be differentiated from tuberculous and bacterial pericarditis, malignancy and, rarely, other causes of cholesterol pericarditis.

MANAGEMENT.

Treatment is necessary only for symptomatic pericardial disease. Constriction occurs in rheumatoid arthritis patients despite established antiarthritic treatment with corticosteroids, high-dose aspirin, and other antiinflammatory agents.[191] [198]

ACUTE RHEUMATIC FEVER (See also Chap. 66)

Pericarditis in acute rheumatic fever has declined with decreasing rheumatoid factor in the United States.[191] [198] [199] Mainly a disease of children and adolescents, acute rheumatic fever is associated with antecedent streptococcal infection and has features of immunopathies and other connective tissue diseases. Its pericardial lesions include extensive deposition in the pericardium and in vessels of IgG, IgM, and C3. Most patients have at least discrete fibrotic epicardial milk patches; most of those with chronic valve disease have pericardial adhesions, which frequently are obliterative and which do not appear to constrict. Clinically pericardial involvement is mostly minimal or symptomatic; yet manifest pericardial involvement in acute rheumatic fever usually indicates severe and sometimes fatal pancarditis (almost never without valvulitis[199]), especially if with significant effusion, which may be partly or entirely related to rheumatoid factor myocarditis or heart failure.

Acute pericarditis is a sign of active rheumatic carditis.[192] It usually occurs in the first week after fever and arthritis; chest pain varies from mild to severe; there may be a secondary temperature rise. Disproportionate tachycardia and dyspnea are probably related to myocarditis and pulmonary congestion or edema. The pericardial rub may be intense and last several days. Some degree of effusion is the rule with amber fluid, frequently blood tinged, containing considerable fibrin. Tamponade is rare but must be differentiated from congestive heart failure. Differential diagnosis from other vasculitides is essential, particularly juvenile rheumatoid arthritis in adults who have lymphadenopathy, SLE, and also endocarditis, Lyme disease, and sickle cell crisis. Occasionally, pericarditis is the first sign of acute rheumatic fever. In any child with pericarditis, acute rheumatic fever must be ruled in or out, especially if with a rash and arthralgias, which also occur in viral pericarditis and childhood exanthems.

Without definite carditis, the diagnosis of rheumatic pericarditis is circumstantial and includes (1) fever and arthritis usually preceding pericarditis; (2) relative youth in most cases; and (3) serological positivity for beta-hemolytic streptococci. Nonsteroidal agents may be sufficient treatment. Corticosteroid therapy may be used if nonsteroidal agents fail and may be marginally better.

SYSTEMIC LUPUS ERYTHEMATOSUS

Most patients with SLE develop some form of pericarditis, clinical or subclinical.[191] [194] [200] [201] Pericardial effusion, often large, is common, although tamponade and constriction are comparatively uncommon. SLE pericarditis parallels disease activity[202] [203] and is characterized by epicardial microvasculitis and necrosis and a number of antibodies to nuclear components and phospholipids that form pathogenic antigen-antibody complexes. Immune complexes deposited in the pericardium include IgM, IgG, C3, and, rarely, hematoxylin bodies.[191] [200] [201] SLE causes the entire spectrum and all stages (i.e., acute, subacute, chronic and recurrent) of anatomical and pathophysiological pericardial abnormality. This includes pericarditis; exudative pericardial effusion, which can be serous, serosanguineous, or hemorrhagic; pericardial adhesions; and constrictive pericarditis[191] ; any of these may be the first sign.[201] Males

are relatively overrepresented, especially among patients who develop constriction.

Pericarditis typically accompanies severe SLE and is often diagnosed during an acute flare that can be painful or painless but virtually always with serological evidence of active disease. Lupus nephropathy is frequent so that uremic pericarditis with effusion may be mistaken for or accompany SLE pericarditis. Increased susceptibility to a range of common and opportunistic bacteria and fungi can be due to the effects of antiinflammatory, immunosuppressive, or cytotoxic treatments and lead to contamination of sterile effusions.[191] Even with infective effusions, blood cultures tend to be negative and some grossly purulent sterile fluids are explained by a very high white blood cell content.

DRUG-INDUCED SLE.

This condition is not rare and produces all the pericarditic forms of idiopathic lupus from acute to constrictive but usually spares the kidney.[191] Acute forms clear after discontinuation of offending drugs such as procainamide, isoniazid, hydralazine, methyldopa, or penicillin. Patients with methysergide lupus may develop constriction or, more often, an imitative fibrosing mediastinitis.

MANAGEMENT.

Therapy is as for SLE. Tamponade requires drainage, and constriction requires pericardiectomy. However, occasional patients with less than critical tamponade respond to high doses of corticosteroids and even a trial of NSAIDs.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

Scleroderma provokes uncontrolled fibroblastic activity leading to abnormal collagen deposition in the microvasculature, skin, synovia, gastrointestinal tract, lungs, heart, kidneys, and pericardium occurring diffusely or in limited systemic scleroderma (CREST syndrome).[191] [204] [205] Although myocardial involvement with failure is common, pericardial scleroderma is the most common cardiac form at autopsy.[191] Echocardiography shows pericardial effusion in almost one half of patients. Although relatively few patients have clinical signs of pericardial scleroderma, these extend from acute fibrinous pericarditis to effusions, which may be chronic recurrent or tamponading, to constriction from relentless fibrosis. Rarely, acute and chronic effusions and even tamponade precede the diagnosis.[191] Scleroderma pericardial effusion, frequently bloody, is an exudate contrasting to exudates in other forms of vasculitis because of the absence of autoantibodies, immune complexes, or complement deposition along with very few white blood cells and a variable protein level.[191] [204] Transudates and pleural effusions are more likely to result from heart failure or uremia. Pericardial scarring in scleroderma is typically slow and associated with gradual obliteration of small vessels. Pericardial involvement occurs with or without myocardial scleroderma, but ECGs, almost always nonspecifically abnormal, reflect myocardial involvement. Consequently, a typical stage I ECG of acute pericarditis should raise the question of intercurrent infection. Because scleroderma is systemic, *confounding factors* must be considered.

Hemodynamics may be affected by pulmonary lesions with pulmonary hypertension, RV hypertrophy, and systemic congestion. Myocardial scleroderma occasionally produces a restrictive cardiomyopathy masquerading as pericardial constriction. As in radiation pericarditis, constrictive pericarditis and restrictive cardiomyopathy may coexist. Renal scleroderma can produce uremic pericarditis. Symptomatic pericardial disease is associated with a poor prognosis.

SJOGREN SYNDROME

This "sicca syndrome" (dry eyes and dry mouth due to destructive lymphocytic infiltration of exocrine glands) occurs in isolation or in association with connective tissue disorders such as SLE, rheumatoid arthritis, or scleroderma.[191] [206] Pericarditis is of the types associated with the dominant connective tissue disorder, which is usually severe.

POLYMYOSITIS/DERMATOMYOSITIS

These related chronic inflammatory autoimmune diseases of skeletal muscle and skin also affect the heart and pericardium with or without established skeletal muscle involvement.[191] [207] Cardiac and pericardial involvements are usually asymptomatic. Pericarditis, more common in children, is usually discovered incidentally as an effusion on echocardiography, at autopsy, or, occasionally, as fibrinous pericarditis. As in Sjogren syndrome, pericarditis appears to be more frequent in patients with an "overlap syndrome," that is, complicating manifestations of other connective tissue disorders.[191] Effusions, occasionally large, rarely tamponade; constriction is rare. Like SLE, scleroderma can occur with a predominantly myositic syndrome.[207]

PERICARDITIS IN MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease is a set of "overlap syndromes" with variably combined features of lupus, scleroderma, and dermatomyositis/polymyositis.[191] Pericarditis is the most frequent cardiac finding, particularly at autopsy with pericardial effusions of all sizes.[190] Acute pericarditis or pleuritis can be a presenting feature. Patients have combinations of polyarthritis, Raynaud phenomenon, lymphadenopathy, esophageal dysmotility, skin and muscle involvement, and frequent pulmonary disease with pulmonary artery hypertension; mitral valve prolapse is frequent, often with mitral regurgitation. There are high titers of speckled fluorescent ANA and especially circulating antibodies against nuclear ribonucleoprotein. Echocardiograms frequently show effusion (usually small), and there may be pericardial thickening consistent with postmortem findings of patchy epicardial fibrosis suggesting recurrent episodes. The ECG is nearly always abnormal, frequently showing characteristic ST segment deviations, which is not surprising because of the relative frequency of acute fibrinous pericarditis.[191] Pericardial fluid is serous or serosanguineous but only rarely causes tamponade. Prognosis is surprisingly good in mixed connective tissue disease because pericardial involvement responds to short courses of low-to-moderate dose

corticosteroid therapy.

SERONEGATIVE SPONDYLOARTHROPATHIES

This complex group has in common [191] (1) arthritis with a predilection for sacroiliac apophyseal and lumbosacral joints of the spine and the entheses; (2) absence of rheumatoid arthritis serology; (3) male predominance; (4) extraarticular manifestations, including pericarditis, iritis, uveitis, enteric inflammations, myocarditis, and lesions of the aortic root and valve, often with aortic regurgitation; and (5) association with haplotype histocompatibility antigen B27 (HLA-B27). Iritis and cardiopericardial involvement are found primarily in those with B27 positivity, especially syndromes including particularly ankylosing spondylitis, Reiter disease, and the intestinal arthropathies, all associated with dysentery and sometimes urethritis. Dysentery may be related to specific organisms (not necessarily causative). "Psoriatic arthritis" should be included because it can cause constriction. Ankylosing spondylitis is particularly seen in relatively young males with sacroiliitis. Rubs are discovered, and constriction ensues in those with severe acute toxic polyarthritis episodes. Fibrous pericardial adhesions are seen at necropsy. Some patients have had features of Reiter disease. Cardiac involvement is relatively frequent, particularly acute pericarditis with a friction rub[191] and myocarditis [44] with murmurs, gallop rhythms, and conduction abnormalities, all of which may be accompanied by pericardial effusion with increased complement.

The *intestinal arthropathies* include inflammatory bowel disease. In *Crohn disease* and *ulcerative colitis,* acute pericarditis occurs with or without tamponade. *Whipple disease*, a multisystem disorder, has a high proportion of pericardial lesions at necropsy. Serofibrinous pericarditis, sometimes with pleurisy, may accompany seronegative migratory polyarthritis and gastrointestinal symptoms. Pericardial constriction may precede or follow abdominal complaints but is sufficiently rare to suggest intercurrent primary pericarditis.

SYSTEMIC VASCULITIDES

Giant cell arteritis affects medium and larger arteries in any organ including the heart and pericardium.[191] [208] Concomitant pericarditis with or without effusion is of uncertain pathogenesis and possibly is immunopathic. Infections frequently precede giant cell arteritis so that early pericardial syndromes could be mistaken for viral or other infectious pericarditis.[208] Pericarditis and pericardial lesions accompany *temporal (cranial) arteritis* at necropsy and only occasionally clinically, raising the question of intercurrent infection. *Takayasu arteritis* ("pulseless disease"; aortic arch syndrome) is a chronic, idiopathic inflammation of large vessels occurring in relatively young women, with occasional acute pleuritis and pericarditis, sometimes recurrent; more common is postmortem discovery of pericardial scarring. Tamponade is likely to be due to rupture of a coronary sinus aneurysm. Antiinflammatory, particularly corticosteroid, agents reduce inflammation without effect on ischemia due to arterial lesions.[191]

Polyarteritis (periarteritis nodosa)[209] only occasionally produces acute pericarditis, effusion, or hemopericardium in the absence of uremia. They are more common in patients who are HBsAg positive with associated chronic active hepatitis in some.

Patients with coronary arteritis producing myocardial infarcts can develop epistenocardiac pericarditis.

HYPERSENSITIVITY VASCULITIDES

The hypersensitivity vasculitides include *allergic granulomatosis, ChurgStrauss syndrome,* and various *hypereosinophilic syndromes,* all of which have some relation to polyarteritis and produce acute pericarditis, effusion with, or usually without, tamponade and constriction, congestive failure, and acute myocardial infarction.[191] [205] [210] [211] With persistent hypereosinophilia, restrictive cardiomyopathy may result from endocardial involvement. The Churg-Strauss syndrome is a multisystem vasculitis with necrotizing arteritis and eosinophilic infiltrates including extravascular granulomas, particularly in the epicardium. Epicardial and pericardial involvement is relatively frequent, producing all forms of pericarditis and myopericarditis complicated by ischemia due to vasculitis. Characteristically, patients have a history of asthma and allergic rhinitis, which may be transient and episodic. Both blood and pericardial fluid are eosinophilic.

BEHCET SYNDROME.

This is characterized by painful oral and genital ulcers and recurrent hypopyon iritis, sometimes with skin and central nervous system involvement.[191] Arteritis (and venulitis) reveal its relation to the systemic vasculitides. Some patients develop myocarditis, but the *most common cardiac lesion is acute pericarditis.* It is fibrinous or effusive, including pleuropericarditis, each of which may be recurrent but usually self-limited or responding to antiinflammatory agents used for the disease itself. However, Behcet syndrome sometimes provokes thrombosis of major veins, may mimic constriction, and has been associated with chylopericardium and chylothorax.

WEGENER GRANULOMATOSIS.

Wegener granulomatosis is characterized by necrotizing local and systemic granulomatous vasculitis of the upper and lower respiratory tract and glomerulonephritis.[191] [212] It overlaps polyarteritis and both giant cell and hypersensitivity arteritides. Diagnosis often requires biopsies of lung or kidney. Serological testing includes antineutrophil, cytoplasmic antibody, and plasma thrombomodulin, which reflects vascular injury. Cardiac involvement occurs in up to 20 percent, including granulomatous myocarditis, endocarditis (including valvulitis), and aortitis; pericarditis occurs in at least half of these, ranging from acute fibrinous to serous or hemorrhagic effusion and occasional tamponade or constriction.

SARCOIDOSIS.

Cardiac involvement in sarcoidosis is much more common at necropsy than clinically, because granulomas may be microscopic and not strategically located.[191] Widespread active granulomatous myocarditis and pericarditis, fortunately rare, produce serious and often fatal disease. Pericardial effusions with serous or serosanguineous fluid are relatively common, even during corticosteroid therapy. The majority of pericardial

effusions are transudates due to myocardial disease, including heart failure. Constriction has been reported.

SERUM SICKNESS.

Serum sickness--with fever, urticaria, lymphadenopathy, myalgia, arthritis, neuritis, vasculitis, and glomulonephritis--can provoke acute pericarditis probably related to pericardial deposition of soluble antigen-antibody complexes when there is an excess of antigen.[191]

MYOCARDIAL INFARCTION-ASSOCIATED PERICARDITIS (See Chap. 35)

Both "early" and "delayed" infarct-associated pericarditis are usually distinct but sometimes without absolute temporal separation, either because one continues into the other or because of the unusually early appearance of pericarditis with characteristics of the delayed form, called *post-myocardial infarction (Dressler) syndrome*.[213] [214] Because the true "early" form is confined to the infarct zone it is known as "infarct pericarditis" or *epistenocardiac pericarditis.*[213] It occurs in almost half of transmural myocardial infarctions but is clinically discovered in many fewer, owing to varying diligence in auscultating a rub, which is usually the only sign. The principal confounding factor in distinguishing epistenocardiac pericarditis from the post-myocardial infarction syndrome is uncertainty as to actual age of any acute infarct; recognition of pericarditis on or near the day

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of admission usually means epistenocardiac pericarditis, but behavior of the lesion may reveal post-myocardial infarction syndrome.

Infarct Pericarditis

Myocardial infarction-associated pericarditis occurs with anatomically transmural or nearly transmural infarction and is localized to the infarct's "apex" on the epicardium.[213] [214] [215] Most ECG changes are localized and nearly always overshadowed by myocardial infarction changes. Thus, generalized stage I ECG changes always raise a question of the post-myocardial infarction syndrome. Acute pericarditis accompanying nontransmural infarct is more likely to be early post-myocardial infarction syndrome. The pericardial exudate is fibrinous; late consequence is a collagenized scar overlying the infarct. Because myocardial infarctions causing detectable epistenocardiac pericarditis are transmural and relatively large, ventricular thrombi, especially apical and RV, are relatively common and probably the reason that systemic embolism is more common in patients who have myocardial infarction pericarditis; with RV infarcts, pulmonary embolism can occur. Moreover, there are more ventricular aneurysms in patients with myocardial infarction pericarditis and more thrombi in them. Such complications reflect the strong tendency for myocardial infarction pericarditis to occur with larger myocardial infarctions and, therefore, associated with higher Killip class and more atrial and

ventricular arrhythmias than in patients without pericarditis.[213] [215] [216] Atrial and ventricular arrhythmias are related to heart failure and atrial infarction rather than to pericarditis.[212] Temperature exceeds 37.2°C (99°F) more frequently and lasts longer than without pericarditis.

During the first week of acute myocardial infarction, infarct pericarditis is also a common cause of new chest pain, distinguishable from ischemic pain mainly by its respirophasic and positional ("pleuritic") fluctuations. The importance of larger infarct size with easily discoverable (i.e., rub producing) pericarditis is reflected in late mortality. Despite higher Killip classes, the *in-hospital* prognosis is no different from those without pericarditis. However, *late prognosis* (i.e., 6 months and after) is distinctly worse in those who have myocardial infarction pericarditis.[217] [218]

Patients with infarct pericarditis reflect larger myocardial infarction size by greater (1) myocardial enzyme release, (2) number of ECG leads with elevated ST segments, (3) degree of ST segment elevation, (4) number of leads with infarct Q and QRS abnormality, (5) echocardiographic estimate of myocardial infarction size, (6) aggregate wall motion abnormalities, and (7) radiographic score for extravascular lung water.[213] With infarct pericarditis, anterior and multisite myocardial infarctions are more frequent than with the usually smaller inferior myocardial infarctions. With inferior myocardial infarctions, approximately twice as many patients have pericarditis when there is anterior ST segment depression, which is a sign of a more serious process. Patients have lower ejection fractions that continue to fall up to day 10, whereas without pericarditis depressed ejection fractions tend to rise by 6 to 10 days.[129] [213] [215] With pericarditis there are also more frequent signs of heart failure and increased pulmonary wedge pressure.[216] [217] Early thrombolytic therapy has decreased the incidence of epistenocardiac pericarditis; however, pericarditis appearing despite thrombolysis is a marker of greater damage.[218]

PERICARDIAL EFFUSION.[213] [214] [216] [219] [220]

In acute myocardial infarction, pericardial effusions can be irritative (pericarditic) or due to hydropericardium. Effusions tend to develop early, mainly on days 1 to 3, the majority without evidence of pericardial irritation (hydropericardium) and only small to moderate-sized effusions. Larger effusions indicate some degree of heart failure with fluid retention: there is probably increased microvascular permeability associated in some patients with increased extravascular lung water. Increased myocardial interstitial fluid and obstruction of cardiac lymph and venous drainages probably produce the occasional larger irritative effusions that resemble or coincide with hydropericardium.[213] Hydropericardium is more frequent with larger, Q-wave, anterior, and RV myocardial infarctions; they are associated with higher wedge pressures, LV dyssynergy, increased RA pressures, and increased pulmonary alveolar-arterial oxygen difference; reabsorption takes days to weeks.[213] [214] [215] [216] [217]

Although tamponade is rare in the absence of bleeding, hydropericardium presages increased mortality because of its association with the foregoing factors.

Anteriorly loculated effusions may cause isolated right-sided heart tamponade by

selectively compressing the right ventricle, AV groove, or right atrium; patients develop new hypotension, but pulsus paradoxus usually is absent. The pericardial fluid may contain increased adenosine[219] and beta-fibroblast growth factor.[221] Hemorrhagic pericardial effusion or frankly bloody hemopericardium occurs "spontaneously" or with antithrombotic therapy and, of course, myocardial rupture.[213] [222] [223] Yet any significant pericardial bleeding with myocardial infarction pericarditis is uncommon. However, rapid "cardiac" enlargement, or a loud or persistent pericardial rub or unexplained drop in hemoglobin or hematocrit, with or without tamponade, should be observed for pericardial hemorrhage due to excessive anticoagulation or subacute ventricular rupture. Patients who survive subacute rupture and echocardiography may show echodense material, owing to organizing blood or clots, simulating the texture of intracardiac thrombi but seen between heart and parietal pericardium. Acute ventricular rupture produces rapid tamponade and death, usually with vagally mediated bradycardia culminating in electromechanical dissociation.[213] [224] Because of the frequency of negative taps due to clots and the need to seal the wound, only immediate pericardiotomy and repair offer any faint hope of survival.

PERICARDIAL FRICTION RUB.

Most rubs occur within 4 days of onset.[213] [216] A persistent loud or widespread rub may indicate the post-myocardial infarction syndrome or unusually intense myocardial infarction pericarditis requiring intensified observation in patients on antithrombotic therapy. With myocardial infarction pericarditis, most rubs are monophasic, are usually systolic, and can resemble or coexist with murmurs of mitral and tricuspid regurgitation or ventricular septal defect.[213] Disappearance followed by recurrence of rubs may indicate onset of the post-myocardial infarction syndrome. Pericardial rubs with inferior myocardial infarctions are more frequent with RV infarction.

ECG.

Infarct pericarditis occurs with transmural (usually Q-wave) myocardial infarction and usually not separately detectable by ECG because it is localized.[11] [213] Failure of evolution of acute ST-T wave changes of myocardial infarction or reversals of ST-T wave evolution in the infarct zone have been associated with infarct pericarditis and impending rupture.[225] [226] Atrial fibrillation is more common after PR segment deviations, a sensitive sign of atrial myopericarditis of unknown specificity and not rare during myocardial infarction pericarditis.[215] Patients with myocardial infarction pericarditis ultimately have more second- and third-degree AV block and more bundle branch and other fascicular blocks, all correlated with larger myocardial infarctions.[213] [216]

THROMBOLYSIS EFFECTS.[213] [218] [224]

Effective antithrombotic therapy, administered sufficiently early, usually reperfuses the culprit artery and produces a smaller myocardial infarction, better LV function, and thus less pericardial involvement. Very early thrombolysis decreases the incidence of myocardial infarction pericarditis by at least one half, reduces heart failure among

patients with pericarditis, and decreases the incidence of PR segment depression. The rarity

of significant pericardial bleeding is remarkable, but thrombolysis has increased the incidence of infarct ruptures and made them earlier. Recanalization of an artery supplying a necrotic myocardial infarction can make the infarct hemorrhagic with bloody pericardial effusion and even tamponade.

DIAGNOSIS.

A pericardial rub diagnoses myocardial infarction-associated pericarditis. Pleuritic pain is supporting evidence, whereas pain in one or both trapezius ridges is almost pathognomonic. Stage I ECG changes are uncommon and suggest "early" post-myocardial infarction syndrome,[212] whereas failure to evolve or "resurrection" of previously inverted T waves strongly suggest myocardial infarction pericarditis.[225] [226] Absence of effusion on imaging or a clear pericardial tap exclude subacute ventricular rupture. Dense intrapericardial echoes parallel to the cardiac surfaces suggest subacute rupture.

Conditions to distinguish from myocardial infarction pericarditis (they may coexist) include pulmonary embolism, recurrent ischemia or infarction, acute stress ulcer, mitral and tricuspid regurgitation, ventricular septal rupture, and primary pericarditis without myocardial infarction. "Early" post-myocardial infarction syndrome is distinguished by diffuse ST and PR segment changes and more severe pericarditic symptoms, louder and more persistent rubs, and greater tendency to pericardial effusion and hemorrhage.[213] Primary pericarditis may resemble infarct if the ECG is atypical (see Table 50-5) ; however, in the absence of myopericarditis, any ST segment elevations are not accompanied by reciprocal changes usual with acute myocardial infarction. Pulmonary embolus, which can also accompany an RV myocardial infarction with pericarditis and mural thrombi,[218] may require lung scan or angiography. Recurrent ischemia should respond to nitrates; pain and ST segment changes of pericarditis will not. Acute mitral and tricuspid regurgitation and ventricular septal defects are distinguishable by murmurs, thrills, and imaging. Their murmurs may resemble rubs, but flows should be demonstrable by Doppler imaging.

Tamponade is rare; yet, particularly in patients on antithrombotic therapy, it must be distinguished from circulatory collapse due to shock and myocardial failure. Injured, low-compliance myocardium may prevent pulsus paradoxus. Diagnosing tamponade thus may require imaging or cardiac catheterization. Even if intrapericardial blood is drained, relieving tamponade, pericardial clots seen on imaging presage recurrence and demand special vigilance.[213] New pleuritic pain favors pericarditis, especially after antithrombotic therapy, which usually prevents pulmonary embolus. With large infarcts, unexplained deterioration should suggest tamponade. If the diagnosis of acute myocardial infarction is mistaken, thrombolysis may produce tamponade from inflamed

pericardium[227] or aortic dissection, a mimic of both acute myocardial infarction and acute pericarditis (see Chap. 40) .

MANAGEMENT.

Myocardial infarction-associated pericarditis is usually mild and responds to aspirin, up to 650 mg every 4 hours for 2 to 5 days. Other nonsteroidal agents risk thinning an infarct (not conclusively demonstrated in humans); ibuprofen, which increases coronary flow is the agent of choice. Corticosteroid therapy may be used for refractory symptoms (usually post-myocardial infarction syndrome) but should be avoided owing to delayed myocardial infarction healing, possible side effects, and dependency. Although more frequent with thrombolysis, hemopericardium remains uncommon in myocardial infarction pericarditis; therefore, heparin and other antithrombotic treatments may not be contraindicated unless there is a widespread or intense pericardial rub[213] (risk of hemopericardium is probably outweighed by benefits of preventing myocardial infarction extension and ventricular thrombi). Yet the problem is compounded by possible "early" post-myocardial infarction syndrome with diffuse pericarditis and much greater tendency to bleed. Because pericardial bleeding can occur even with clotting indices in the therapeutic range,[222] these must be monitored and the patient watched for tamponade. Finally, any pericardial effusion increases the energy required for defibrillation.[228]

PSEUDOANEURYSM (FALSE VENTRICULAR ANEURYSM)

Pseudoaneurysms represent contained myocardial rupture, most often posterolaterally, limited by the visceral pericardium, with or without adherent parietal pericardium, or by the parietal pericardium alone.[213] [227] They are uncommon and occur with larger infarcts, usually within 5 weeks of onset. They follow ventricular surgery (especially valve replacement), endocarditis, penetrating wounds, and, rarely, tumor infiltration[229] and suppurative pericarditis.[230] Abundant epicardial fat seems to predispose to cardiac rupture[231] but may buttress a pseudoaneurysm.[213] Pseudoaneurysms have a narrow neck communicating with a ventricular cavity; blood flows into the pseudoaneurysm in systole and out in diastole. The neck may be so narrow as to be visible only on color Doppler imaging. Differential diagnosis includes true aneurysm, pericardial cysts, and loculated pericardial effusions.[213]

THE PERICARDIUM AND RIGHT VENTRICULAR MYOCARDIAL INFARCTION

Pericarditis is relatively frequent when inferior myocardial infarction is accompanied by RV myocardial infarction.[213] [229] [232] However, by means of ventricular and AV interaction both the normal and inflamed pericardium constrain the injured right side of the heart, which tends to dilate. RV dilation raises intrapericardial pressure, which decreases LV transmural pressure, thus reducing LV filling, preload, and stroke volume. (Pulmonary embolism can act similarly, with acute right-sided heart dilation imposing acute pericardial constraint.[233]) These represent relative pericardial constriction with constrictive hemodynamics, reduced blood pressure, jugular venous distention, and occasionally an S_3 or Kussmaul sign. Even pulsus paradoxus can appear, related to increased pericardial fluid or septal hyperresponsiveness to the respiratory cycle. These

signs may individually depend on the pathophysiological "mix," that is, whether relative constriction due to pericardial tightening or increased intrapericardial pressure dominates. The lungs are usually clear. Thus, the clinical picture usually resembles constriction; with a pericardial rub and pulsus paradoxus it suggests tamponade.[213] Tricuspid regurgitation due to RV myocardial infarction may simulate or obscure a pericardial rub.

POST-MYOCARDIAL INFARCTION SYNDROME (DRESSLER SYNDROME)

This myocardial infarction-associated pericarditis does not require transmural infarction.[213] [234] Most patients have fever, a high sedimentation rate, considerable "pericardial" pain, pleuritis, and sometimes pneumonitis. Its usual onset is from 1 week to several months after clinical onset of myocardial infarction. Some patients have a remote history of pericarditis.[213] Like myocardial infarction pericarditis, the post-myocardial infarction syndrome occurs more often after larger, particularly anterior infarcts, inferior myocardial infarctions with RV myocardial infarction, and complicated myocardial infarctions. Post-myocardial infarction syndrome can appear as an extension of epistenocardiac pericarditis, with persistence or recurrence of rub and fever and with considerable malaise in contrast to myocardial infarction pericarditis, which is mild and transient. The usual gap from onset of myocardial infarction symptoms to the post-myocardial infarction syndrome suggests a necessary latent period. (Because approximately 30 percent of Q-wave myocardial infarctions are "silent," following them, post-myocardial infarction syndrome could appear as "idiopathic pericarditis" because post-myocardial infarction syndrome often resembles viral pericarditis.)

The incidence of post-myocardial infarction syndrome remains uncertain, but it is much less than the originally reported 5 percent of acute myocardial infarction.[235] Post-myocardial infarction syndrome occurs with and without antithrombotic treatment but may be more frequent in patients with pericardial bleeding, which can occur during myocardial infarction with or without an antithrombotic regimen.[234]

The post-myocardial infarction syndrome is often considered autoimmune, based on factors in common with other pericardial injury syndromes. These include a latent period, development of antiheart antibodies, and preceding pericardial injury (most cases have had epistenocardiac pericarditis), although it also occurs in nontransmural infarction and, therefore, without direct pericardial injury. Other factors include frequent recurrence; typical prompt response to antiinflammatory agents; frequent associated pleuritis with or without pneumonitis; changes in cellular immunity suggested by altered lymphocyte subsets compared with control patients; and evidence favoring immune complex formation incorporating antibody combined with myocardial antigen, complement pathway activation, and evidence of cellular as well as humoral immunopathic responses.[213]

CLINICAL FEATURES.

There may be considerable malaise, marked pleuritic pain, and frequently a rub, pericardial and pleural effusions, and fever up to 40°C (104°F). The ECG occasionally shows ST segment and T wave changes suggesting pericarditis superimposed on evolving myocardial infarction, but it is usually dominated by evolutionary myocardial infarction changes.[213] [234] Telltale PR segment deviations are a strong clue. Pericardial and pleural effusions may be serous or hemorrhagic. Leukocytosis is typically polymorphonuclear (occasionally eosinophilic). The ESR is virtually always high. Recurrence can be single or multiple over weeks or even years. Complications are uncommon but include tamponade relatively early. Late constriction is not surprising because of intrapericardial organization of exudate and blood that can also produce loculated effusions. Rarely, effusions can look purulent because of high neutrophil concentration; taken with the customary fever this mimics purulent pericarditis, but pericardial fluid is sterile.

MANAGEMENT.[213] [234]

Patients should be hospitalized and observed for tamponade, differential diagnosis, and adjustments of treatment, including rest and NSAIDs. Recurrences may require a corticosteroid, which should be a last resort with early tapering to discontinuance.

TRAUMATIC PERICARDIAL DISEASE (See Chap. 51)

Pericardial Reactions to Physical Trauma

The heart and pericardium are only partly protected by the bony thorax.[236] [237] [238] A broad range of pericardial injuries evoke responses due to disruption of pericardial tissue and often adjacent and remote tissues. These may be immediate (cellular and vascular inflammation); delayed, including immunopathic (the post-cardiac--pericardial and myocardial--injury syndrome); and due to healing (adhesions, constriction, effusive-constrictive pericarditis). The inflammatory response may be sterile or infected with or without significant effusion. Traumatic tamponade, the most common cause of early death from cardiac wounds, usually is due to bleeding, producing early or late cardiac compression.[236] [237] [238] Survival with pericardial adhesions can lead to constrictive or effusive-constrictive pericarditis. Blunt (nonpenetrating) trauma, often more complex than penetrating trauma, occasionally causes cardiac and also pericardial rupture with herniation or entrapment of all or part of the heart. Pericardial laceration is not rare with severe blunt trauma, permitting cardiac displacement.

COMPLICATIONS.

Only occasionally does pericardial injury occur in isolation. Concurrent disease or injury of other organs, particularly the heart, modifies the clinical picture, physiological responses, the ECG, and all imaging modalities. These include injuries of the heart,

great vessels (especially ascending aorta), conducting system, myocardium, mediastinum, and other chest and abdominal organs. Late pericardial and cardiac sequelae are common, including pericardial effusion, hemopericardium and tamponade, post-cardiac injury syndrome, false aneurysm, congestive failure, and constrictive pericarditis. They require monitoring and long-term follow-up.

Penetrating Trauma

TRAUMATIC AGENTS.

Knives, needles, bullets and high-velocity projectiles, intracardiac instrumentation, and cardiac surgery are the most common causes of penetrating trauma.[236] [238] [239] Bullets and shrapnel cause more damage than lacerating and puncturing instruments, the pathways of which may seal over. However, early tamponade is much more common in cardiac stab wounds than bullet wounds. (Nail gun injuries, a new category, require exploration.[240] [241] [242]) Any chambers can be involved, but the right ventricle is more common in anterior chest wounds. RA, RV, and great vessel wounds are quickest to tamponade and exsanguinate. The left atrium can be penetrated by posterior chest wounds and has been ruptured by external cardiac massage because of the pericardium's tight clasp of the left atrium. These wounds tend to bleed more slowly than wounds of other chambers and may produce hemothorax rather than hemopericardium or be localized to the adjacent oblique sinus (which may be hemodynamically significant). Anterior esophageal penetration by instruments or swallowed foreign objects such as bones and contaminated surgical instruments is likely to cause suppurative pericarditis. All bullet wounds are potentially infected.[243]

CLINICAL FEATURES.

With penetrating trauma the most common causes of immediate death are exsanguination or tamponade and often both. Some patients have rubs, but many do not, or rubs appear with pericardial bleeding and effusion (many patients have serous effusions[244]). ECGs are frequently unhelpful in assessing pericardial damage but may show typical or atypical stage I changes early or late (>24 hours). The principal cause of death--"surgical" tamponade due to hemopericardium or hemopneumopericardium--is difficult to diagnose because of blood loss, vasoconstriction, and frequent hemothorax that are not characteristic of "medical" tamponade. Pulsus paradoxus may be absent or disappear with severe hypotension and shock. There may be tachycardia and abnormal rhythms due to concomitant cardiac injury, or terminal electromechanical dissociation.

TAMPONADE AND HEMOPERICARDIUM.

Paradoxically, tamponade can be a correlate of survival.[245] Patients with tamponade reaching emergency departments appear to survive better than nontamponaded patients. The corollary is that untimely release of tamponade without thoracotomy can cause rapid decompensation because clotting of the pericardial hematoma can be hemostatic for cardiac wounds.[246] Thus, especially in unstable patients, thoracotomy in the emergency department or in the operating room is optimal for wound repair.

Pericardiocentesis is a temporizing measure for unstable patients while simultaneously preparing for surgery and administering treatment for shock. In stable patients, thoracotomy, subxiphoid pericardial exploration, or video-assisted thoracoscopy are feasible with the option of extending to a full thoracotomy and, if necessary, laparotomy for abdominal wounds (which can also reach the pericardium).

IATROGENIC PERICARDIAL WOUNDS.

These are produced by cardiac surgery, percutaneous transluminal coronary angioplasty, stenting and pacing instruments, central venous and pulmonary flotation catheters, arrhythmia ablation, and even needles and catheters for pericardial drainage.[247] [248] [249] [250] Pericardial damage during percutaneous transluminal coronary angioplasty can occur with coronary artery dissections, producing local or general pericarditis with or without significant bleeding. Patients may present with new pain, a rub, or tamponade or with hemopericardium. Instruments and pacers may penetrate the right ventricle with or without pericarditic signs or hemopericardium.[246] Central venous catheters tend to penetrate the right atrium and rarely the SVC; fluids administered through them may provoke tamponade or exacerbate tamponade already due to bleeding. *Fetal tamponade* has complicated amniocentesis. Open surgical evacuation is often the optimal management, necessitating rapid transfer to the operating room or thoracotomy in the emergency department.[236]

FOREIGN-BODY AND FOREIGN-SUBSTANCE PERICARDITIS[236]

Smooth-edged foreign bodies less than 1 or 2 cm in diameter may be asymptomatic. Relatively large foreign bodies lying in or near the pericardium, such as metallic fragments, bullets, broken instruments, or needles, are associated with recurrent pericarditis and effusion; they need not penetrate the heart. Asbestos poudrage for coronary disease and cardioverter-defibrillator patches have provoked dense calcification. Silicon-contaminated pacemaker insertion can provoke an exuberant pericardial foreign-body reaction, including giant cells. All can progress to tamponade, adhesions, or constriction. Definitive treatment is removal of the foreign material and any significant adhesions and fluid. Postpericardiotomy syndrome may follow.

SURGICAL PERICARDIAL INFLAMMATION AND EFFUSION[245] [251] [252]

Mild pericarditis and low-grade fever, usually with some bleeding and effusion, are common postoperatively and proportional to the amount of pericardial manipulation, which regularly causes loss of mesothelial cells and provokes fibrinous and leukocyte exudation; significant blood leukocytosis may indicate infection.[245] The ECG tends to reflect

this with minor nonspecific or local ST segment changes, yet often with generalized

changes that usually do not evolve beyond stage I. Early pericardial effusions are common, tend to appear by the fifth postoperative day, are usually small (<1 cm echo depth), are usually benign, and are frequently associated with a left pleural effusion. Moderate effusions (1-2 cm) are less common, and large effusions (>2 cm) are uncommon. Large and especially increasing early effusions, usually due to bleeding and more common after valve surgery, are harbingers of tamponade. Late effusions (6-60 days after surgery) may also be due to bleeding, especially in patients taking anticoagulants[253] or with a coagulopathy or due to the osmotic ("hydrophilic") effect of slow intrapericardial clot lysis or to immunopathic responses to cardiopericardial trauma.[236]

POSTOPERATIVE TAMPONADE

Nearly all clinically significant effusions are present by the fifth postoperative day. Circumferential and especially localized tamponade remain challenging diagnostic and therapeutic problems.[236] Anticoagulation is associated with tamponade at any time; its principal importance is in the first 3 to 5 days when hemopericardium is most common. Late tamponade, often associated with postpericardiotomy syndrome, is probably inflammatory or immunopathic.[253] Although classic diagnostic signs of tamponade may be present postoperatively, familiar clinical signs such as pulsus paradoxus are often absent. Similarly, echocardiographic and Doppler signs retain their specificity but their sensitivity is greatly reduced.[219] ECG changes are common and of no help whereas the swinging heart and electrical alternation are uncommon (probably due to adhesions). Thus, atypical presentations of tamponade should be anticipated by liberal monitoring of vital signs and catheterization data as well as by echocardiography for chamber collapses and other evidence. TEE is superior to TTE for both tamponade and pericardial thickening.[251] [254]

DIFFERENTIAL DIAGNOSIS.

Tamponade must be differentiated from extrapericardial causes of low cardiac output, including[245] (1) ventricular hypokinesis with left, right, or combined ventricular failure; (2) acute LV or RV myocardial infarction; (3) pulmonary embolism; (4) coronary insufficiency; (5) effects of prolonged aortic cross-clamping or inadequate coronary perfusion during cardiopulmonary bypass; (6) severe pulmonary artery hypertension; (7) septic shock; (8) hepatitis (enzyme abnormalities, passive hepatic congestion or injury); or (9) mediastinal hematoma or effusion causing extrapericardial cardiac compression. Apart from elastic constriction[255] by clotted hemopericardium, constrictive pericarditis is not an early consideration but can occur as soon as 2 to 7 weeks (usually much later). Acute cardiac dilatation within a repaired pericardium will have a comparable affect. Each may appear as unexplained dyspnea.[236] [256]

MANAGEMENT. [236]

Operative pericarditis and effusions respond quickly to brief therapy with a corticosteroid or NSAID. Coagulation status and platelet levels should be monitored. Early postoperative tamponade is a surgical emergency usually requiring thoracotomy; later

tamponade may respond to drainage and observation. Either type can present as sudden deterioration so that clinically and hemodynamically significant effusions of any size should be drained; urokinase or streptokinase can be instilled to aid drainage and inhibit adhesions if further bleeding is ruled out. Coronary bypass grafts are endangered by any blind procedure. Surgical drainage or video-monitored thoracoscopy may be optimal, as determined by particular fluid loculations disclosed by TEE.

Postoperative Pseudoaneurysm.[236] [257]

False aneurysms occasionally follow cardiac surgery, especially when a chamber has been vented. These resemble pseudoaneurysms after myocardial infarction.

OTHER. [236] [258] [259]

Open-chest *cardiac massage* traumatizes the epicardium, increasing susceptibility to infection, pericardial effusion, tamponade, and ultimate constriction. Removal of *epicardial pacing wires* is usually effected without untoward event, but an epicardial vein or other structure may be traumatized, producing hemopericardium.

CHEMICAL INJURY.

More or less sterile chemical injury to pericardium may follow unusual communications of the biliary tract, pancreas, and esophagus, particularly after sclerotherapy of esophageal varices.[260] Pancreatitis may be accompanied by pericardial irritation and effusion even without communication; this is ascribed to hematogenous and lymphogenous transport of pancreatic enzymes to the pericardium.

ELECTRICAL TRAUMA. [236] [261]

After lightning strikes, with well-known cardiac consequences, occasional survivors have had pericardial effusion with tamponade or recurrent pericarditis. The latter may be a kind of post-cardiac injury syndrome.

Indirect (Blunt/Nonpenetrating) Pericardial Trauma

Indirect injuries to pericardium, heart, and lung are often more complex than those from penetrating trauma.[236] Blunt trauma to the chest and abdomen follows nonpenetrating thoracic impacts, compression (crush), blast, and traumatic deceleration, producing an injury spectrum from contusion to rupture of the heart, the pericardium, or both.[262] Closed-chest cardiac massage even without rib fractures can also traumatize the heart and pericardium.[259] Any cardiac damage, including exacerbation of antecedent heart or pericardial disease, may complicate a range of pericardial injury, including acute, "clinically dry" pericarditis, or hemopericardium with or without tamponade, pneumopericardium, early and late constriction, and recurrent pericarditis.[236] Indirect forces can displace numerous viscera and may cause the heart and great vessels to acutely "trap" more blood than usual, with directional stresses capable of rupturing the

pericardium and other structures. A common cause is deceleration forces, characteristic of transportation-associated accidents, acting in any plane or tangentially. Death usually follows cardiac rupture with acute hemopericardium or pericardial rupture and acute extrusion (herniation; luxation) of some or all of the heart. In general, the more serious the cardiac injury, the more serious the pericardial injury. This may occur in the absence of significant external marks. Isolated parietal pericardial rupture with or without cardiac contusion from blunt injury or after cardiac resuscitation is not rare at autopsy. Fibrinous pericarditis often with some hemorrhage is common. Subacute or late constriction may follow hemopericardium or purulent pericarditis from days to years after injury.

PERICARDIAL LACERATION. [236] [262]

Parietal pericardial tears are frequent, especially after falls and other deceleration injuries. Lacerations are rarely isolated or clinically silent; characteristically, cardiac injury accompanies the laceration. The most serious consequence is cardiac herniation: extrusion of all or part of the heart in any direction but usually into the left pleural cavity, frequently with mediastinal and tracheal shift. Herniation is characteristically sudden and nearly always a surgical emergency. (After 72 hours, herniation tends to be restrained by adhesions.) Rupture and laceration of the parietal pericardium occur mainly at either its diaphragmatic or pleural abutments or both.

CLINICAL CONSIDERATIONS. [236] [263] [264]

Symptoms occurring after blunt trauma can be nonspecific or multiple, with and without dyspnea or anterior chest or abdominal pain, and may be overshadowed by injuries elsewhere. In hemorrhaging and other hypovolemic trauma patients, an initial favorable response to fluid administration may obscure and delay recognition and treatment of tamponade. All significant or potentially significant chest injuries require careful monitoring for progression or sudden cardiocirculatory deterioration. Nonpenetrating trauma can produce all of the cardiocirculatory physical findings of penetrating trauma and surgical injuries. A pericardial rub, easily missed, may be the only physical sign. Hypotension is the rule, and pulsus paradoxus must be diligently sought but is often deceptively absent. Free air in the pericardium rises to the upper sac. Cardiac contusions may be identified by indium-111 antimyosin scintigraphy. The ECG commonly shows only ST-T wave changes, which occasionally suggest, but only rarely are typical of, acute pericarditis. With cardiac displacement, the QRS axis may shift and occasionally become unusual; there may be altered precordial R wave progression.

IMAGING. [236] 263a

Chest radiographs, preferably with the patient upright, demonstrate any rib and sternal fractures, gas collections, atelectasis, tracheal shift, and displacement

of a herniated heart. There may be intrapericardial migration of abdominal organs with unilateral (usually left) diaphragmatic elevation and unusual supradiaphragmatic densities, lucencies, and organ shadows. Rarely, patients do not develop symptoms for months, years, or ever. Echocardiography, optimally TEE, is indispensable and so sensitive that a negative high-quality study significantly decreases the likelihood of complications and sequelae. It will disclose pericardial effusion and fibrinous exudate, RV dilation, ventricular (especially RV) thrombi, and traumatic true and false aneurysms.[263] CT or MRI can discriminate hemopericardium by its density and disclose other cardiac and vascular injuries, angulations, and dilations as well as acute hepatic lymphedema due to cardiac or inferior vena cava compression.[236] Video-assisted thoracoscopy is most specific for selecting appropriate sites and extent of thoracotomy incision.[262A]

MANAGEMENT.

Repositioning the patient may permit restitution of a herniated heart's position. Definitive treatment is repair of wounds especially of the heart and vessels and repositioning of displaced organs. The pericardium may have to be sutured, patched, or resected; and some pericardial lacerations may be enlarged to reposition the heart, especially if it dilates.[264]

Post-Cardiac Injury Syndrome; Postpericardiotomy Syndrome

The post-cardiac injury syndrome develops days to months after cardiac and pericardial injury.[236] [253] It so strongly resembles the post-myocardial infarction syndrome that they both appear to be variants of a common immunopathic process. The post-cardiac injury syndrome differs from the post-myocardial infarction syndrome because it acutely provokes a much greater antiheart antibody (AHA) (antiactin and antimyosin) response, probably related to more extensive tissue trauma and more concentrated release of antigenic material.[236] Because even surgery limited to the pericardium can cause the post-cardiac injury syndrome, it is commonly denoted "postpericardiotomy syndrome."

PATHOGENESIS.

Myocardial injury releases cellular constituents, possibly autoantigens provoking an autoimmune antibody reaction by AHAs; complement is activated, C3 and C4 levels fall, and leukocytes are mobilized. In the postpericardiotomy syndrome, AHAs appear to be pathogenic in the presence of a dormant or concurrent viral infection that "permits" them to act.[236] (Some trigger is necessary because AHAs alone may not be pathogenic.) A quantitative effect of AHAs is seen in the proportionality between occurrence of the postpericardiotomy syndrome and extent of surgery; correction of congenital defects and of the Wolff-Parkinson-White syndrome have the highest relative incidences. (Postpericardiotomy syndrome after strictly pericardial surgery may challenge the immunopathic hypothesis because no antipericardial antibodies have been identified.) Evidence that post-cardiac injury syndrome/postpericardiotomy is immunopathic includes the following: preceding latent period; frequent recurrences; stimulation of AHAs and complement activation; prompt response to corticosteroids; and clinical characteristics of fever, pulmonary infiltrates, frequent pleuritis (rarely the only sign),[245]

and systemic inflammatory symptoms and signs. The "complete" post-cardiac injury syndrome/postpericardiotomy syndrome correlates well with higher titers of AHAs and is rare in patients younger than age 2, possibly owing to hyporeactivity or carryover protection from the mother's immune defenses. The incidence decreases at advanced ages, possibly related to an immune system that has had more extensive encounters with a variety of microorganisms and/or is senescent and therefore hyporeactive. The extent of myocardial damage is not absolutely correlated with provocation of the post-cardiac injury syndrome/postpericardiotomy syndrome.

CLINICAL ASPECTS.[236] [253]

The post-cardiac injury syndrome and postpericardiotomy syndrome differ from the usually self-limited postoperative or posttraumatic pericarditis in that more patients develop a form of post-cardiac injury syndrome than clinically significant postsurgical pericarditis. The postinjury latent period usually lasts a week to 6 months, with symptoms and signs more severe, disabling, and prolonged (days to weeks per attack) than uncomplicated posttraumatic pericarditis, although few develop tamponade or constriction. Pericardial fluid tends to be serosanguineous. Recurrences are characteristic, mainly within 6 months of the index attack. Among patients without congenital heart disease, the post-cardiac injury syndrome/postpericardiotomy is more frequent in those with a history of either pericarditis or corticosteroid therapy (especially for rheumatoid arthritis), after aortic valve replacement, and in those with B-negative blood. Most patients have tachycardia, malaise, pleuritic pain, new pericardial and sometimes pleural rubs or both, and mild lymphocytosis or granulocytosis; all patients have low-grade fever, which may simulate a continuation of postoperative or postinjury fever.[236] Most postsurgical pericardial rubs should disappear within a week. The post-cardiac injury syndrome/postpericardiotomy syndrome is considered "complete" if fever, pericarditis, and laboratory evidence of inflammation are present and "incomplete" with only two of these.

DIAGNOSIS. [236] [253]

In general, post-cardiac injury syndrome/postpericardotomy syndrome must be considered in patients who after 6 days after surgery or trauma develop fever above 37.8°C (100°F) for over 8 hours with significant pleuritic anterior chest pain and a pericardial rub or two of these, usually with an ESR greater than 40 mm/hr and leukocytosis greater than 11,000 cells/mm[3] . The echocardiogram usually shows a small to moderate pericardial effusion. Chest radiographs show left or bilateral pleural effusion in most patients and right pleural effusion in a few. The cardiopericardial silhouette may be enlarged, and a few patients have pulmonary infiltrates. The ECG usually reflects myocardial abnormalities. Principal differential diagnoses of post-cardiac injury syndrome/postpericardiotomy syndrome include (1) other causes of postoperative fever including infections and pneumonitis, (2) pulmonary embolism, and (3) myocardial infarction. Perhaps half the patients have ECG changes consistent with acute pericarditis. If new changes are inconsistent with infarct or pericarditis, radionuclide scanning or comparable studies may be useful.

MANAGEMENT. [236] [253]

The post-cardiac injury syndrome/postpericardiotomy syndrome usually responds within 48 hours to therapy with aspirin or another NSAID, which should be maintained for 10 days. Corticosteroid therapy is reserved for patients with unresponsive severe symptoms. The unusual tamponading effusion must be drained. Recurrences are often worse than the index attack and should be managed similarly, adding colchicine as tolerated if NSAIDs alone appear ineffective. Pericardiectomy is reserved for intractable effusions that may increase (despite even corticosteroid therapy) and for constriction.

PERICARDIAL SEQUELAE.

Pericardial adhesions are generally proportional to the extent of epicardial and pericardial injury and any residual blood after drainage.[245] Loculated effusion or hemorrhage may become manifest early or months postoperatively. Continued inflammatory activity can induce constrictive pericarditis, usually after months to years. Recurrent pericarditis, probably autoimmune, with or without effusion, may follow any pericardial injury, including radiation pericarditis and even pericardial resection. Pseudoaneurysm is rare.

OTHER PERICARDIAL DISEASES

Aortic Dissection and Intramural Hemorrhage (See Chap. 40)

Aortic dissection, DeBakey types I and II, and aortic intramural hemorrhage often rupture into the pericardium.[213] [265] [266] [267] They are almost indistinguishable clinically; this discussion applies to both. Rupture is the most frequent cause of death due to aortic dissection, usually through tamponade with intrapericardial clotting preventing nonsurgical drainage. There is always over 100 ml of blood and usually 400 to 1500 ml.[235] [266] Subacute and chronic bleeding is tolerated with smaller leaks and mitigation by medical treatment of aortic dissecting and shearing forces.[268] A protracted course may allow dilution by pericardial effusion, owing to pericardial irritation and the osmotic affects of intrapericardial hemolysis.

CLINICAL FEATURES.[213] [266] [267]

The ECG is seldom normal and may show preexisting LV hypertrophy, acute ischemia, or myocardial infarction. Pericardial irritation by blood that first dissects under the epicardium can provoke a rub and occasionally compress coronary arteries, causing myocardial ischemia and infarction. Occasionally, the ECG resembles stage I acute pericarditis. Occlusion of renal arteries combined with hypotension can produce acute uremic pericarditis. Indeed, dissecting hematoma may first present hours to many days

before frank rupture as "acute pericarditis" and without pain typical of dissection,[213] [267] suggesting idiopathic pericarditis, which is much more common. In such relatively slow dissections, misleading ST segment elevations can also be due to release of potassium from intrapericardial hemolysis. In older patients with a history of hypertension, acute pericarditis should always be considered part of another syndrome. In younger patients, in whom idiopathic pericarditis is generally more common, signs of Marfan syndrome[267] or other inherited connective tissues disease or aortic coarctation should be sought. Both aortic regurgitation and dissecting aneurysm are more common in patients with bicuspid aortic valves, congenital aortic stenosis, and coarctation with rib notching on the chest film.

Precise diagnosis as in all acute conditions should be as rapid as practical because of the narrow "windows" for aortic rupture and myocardial salvage. Echocardiography, preferably omniplane TEE (as sensitive as CT and MRI) is optimal to detect pericardial effusion, aortic regurgitation, a false lumen, and an aortic intimal flap. If echocardiography is negative or indecisive, CT, especially helical CT, or spin-echo MRI, which is time consuming and logistically difficult, will usually define aortic mural hemorrhages and intimal flaps.[269] They are safer and more sensitive than aortography (which occasionally becomes necessary[270]). All imaging techniques show pericardial effusions due to aortic dissection usually to be anterior.

MANAGEMENT.

The most efficient management when dissection is likely is to do diagnostic procedures in the operating room. Percutaneous pericardial drainage often gives only temporary or no relief, with increase in blood pressure disrupting sealing clots and accelerating intrapericardial leakage, causing frank hemopericardium, shock, electromechanical dissociation, and death. Definitive treatment is surgical relief of tamponade and repair of the aorta. Rarely, aortic dissection involving the pericardium heals spontaneously. Constrictive pericarditis has resulted as early as 7 months later.

PULMONARY THROMBOEMBOLISM AND PULMONARY HYPERTENSION

Pericardial involvement after pulmonary infarction is uncommon. It can be (1) apparently due to contiguity; (2) a complication of antithrombotic therapy for pulmonary embolism; (3) a simultaneous event in pulmonary embolism after trauma including cardiac or other surgery; and (4) rarely, an apparent immunopathy with a pericardial component closely mimicking the post-myocardial infarction syndrome.[271] [272] Infarction of pulmonary segments adjacent to the pericardium can produce pleuropericardial rubs. These are strictly exopericardial and even classic rubs, which rarely may be the first sign of a pulmonary embolus,[213] with or without pleuritic pain. After blunt or penetrating chest trauma or cardiac surgery the mixed picture may be difficult to unravel. Massive pulmonary embolism, such as primary pulmonary hypertension,[271] has been attended by hydropericardium presumably due to right-sided heart failure; such cases may have a conus rub due to acute cor pulmonale without pericarditis. Finally, since pulmonary embolism can be asymptomatic, signs of acute "idiopathic" pericarditis or effusion should alert physicians to search for it in patients who have risk factors for embolism. In general, disorders dilating the right side of the heart increase pericardial constraint of

the entire heart, mimicking constriction, and with hydropericardium suggest tamponade, especially with left-sided chamber collapses,[272] which can also be associated with purely pleural effusions.[273]

POST-PULMONARY INFARCTION SYNDROME.[274]

Rarely after pulmonary embolism, acute pericarditis with or without effusion appears as a syndrome closely resembling post-myocardial infarction syndrome with strictly pericardial rubs, fever, leukocytosis, elevated ESR, frequent pericardial and pleural effusions, and, rarely, tamponade. Like the post-myocardial infarction syndrome and other immunopathies this syndrome responds to antiinflammatory treatment, particularly rapidly to a corticosteroid. NSAIDs should be tried first.

PERICARDIAL INVOLVEMENT IN GASTROINTESTINAL DISORDERS

ESOPHAGEAL DISEASE.[245]

The esophagus overlies the pericardium covering parts of the left atrium and ventricle. Esophageal disorders can involve the pericardium, often catastrophically, frequently with little or no warning, and almost always confusingly because of what appears to be isolated pericardial or cardiac disease or combined esophageal and cardiopericardial signs and symptoms. Most patients who are "candidates" for pericardial involvement include those who have had esophageal surgery and other trauma, gastroesophageal reflux, Barrett esophagus, hiatal hernia, and esophageal strictures. The pericardium is directly involved by fistulas from processes penetrating the esophageal wall such as inflamed esophageal diverticula. These include inflammation (e.g., esophagitis and peptic, bacterial, viral, and fungal ulcers), neoplasms, perforating foreign bodies, corrosive ingestants, and "spontaneous" esophageal rupture. Esophagopericardial fistulas also develop from inflamed surgical and anastomotic suture lines in the esophagus and in patients with colonic interposition for esophageal lesions, resulting in a "thoracic colon"-to-pericardial fistula.

CLINICAL FEATURES.

Symptoms and signs depend on the structures involved, including the pericardium itself. Patients may have acute pericarditis, pericardial effusion, pneumopericardium, pneumohydropericardium, or pneumopyopericardium with or without tamponade; any may be the presenting syndrome, including purulent pericarditis, preceding discovery of the fistula. Effusions are usually small and often loculated by adhesions from chronic inflammation. Esophagopericardial fistulas also follow chemical and physical trauma of the esophagus as well as malignancies, including esophageal, pulmonary, or rarely metastatic, and their radiation therapy. Usually there is a history of chronic peptic esophagitis, esophagogastric surgery, or malignancy. Pain can be retrosternal, in the left chest, or in the shoulders or interscapular. Most patients have fever, many have rubs, and patients with acute cases have shock, dyspnea, and cyanosis, any of which can be the initial symptom. A clue is discovery of a pneumohydropericardium or pneumopyopericardium with a "splashing mill wheel" sound. Whereas polymicrobial

pericarditis[276] [277] is common, blood cultures may not be positive.

DRUG- AND TOXIN-RELATED PERICARDIAL DISEASE

Certain medications, toxic substances, and some irritants contacting the pericardium can induce acute or subacute pericarditis and effusion, tamponade, adhesions, fibrosis, or constriction (Table 50-13) .[278] Anticoagulants and thrombolytic agents may cause an inflamed pericardium to bleed with tamponade or eventual adhesions and constriction, but this is not a specific "pericardiotoxic" effect. Drug and toxin responses are mostly acute pericarditis, inflammatory effusion, or, less commonly, hydropericardium. The importance of these relatively uncommon "pericardiopathies" is their diagnosis and its corollary: excluding other pericardial diseases. Most agents in Table 50-13 are used to treat specific diseases, many of which themselves can cause pericarditis or effusions. In general, acute reactions to these agents resolve when exposure ceases, but some can go on to constriction or recurrent pericarditis. Disorders for which many are given include malignancies, infections, and renal failure, each of which can cause pericarditis. Moreover, distinguishing drug- or toxin-induced pericarditis from idiopathic pericarditis is crucial so that exposure to a pericarditis-inducing agent must be considered in the differential diagnosis of idiopathic pericarditis. For every new case of pericarditis, a thorough history includes exposure to any drugs or noxious agents. Mechanisms include lupus reactions,[279] idiosyncracy,[280] "serum sickness," [281]

TABLE 50-13 -- DRUG- AND TOXIN-RELATED PERICARDIAL DISEASE

A. Drug-induced lupus erythematosus

- Procainamide
- Tocainide
- Hydralazine
- Methyldopa
- Mesalazine
- Reserpine
- Isoniazid
- Hydantoins (phenytoin, dantrolene)
- ? Quinidine

B. Hypersensitivity reaction (often with eosinophilia)

- Penicillins (ampicillin, procaine penicillin)
- Cromolyn sodium
- ? Praziquantel

C. "Idiosyncratic" or hypersensitivity

Methysergide
Minoxidil (?also lupus)
Practolol
Bromocriptine
Psicofuranine
Polymer fume inhalation
Cytarabine
Phenylbutazone
Amiodarone
Streptokinase
p-Aminosalicylic acid
Thiazides
Streptomycin
Thiouracils
Sulfa drugs
Cyclophosphamide
Cyclosporine
Amiodarone
Mesalazine (Rowasa)
5-Fluorouracil
Vaccines
Smallpox
Yellow fever
Granulocyte-macrophage colony-stimulating factor

D. Anthracycline derivatives

Doxorubicin
Daunorubicin

E. Serum sickness

Foreign antisera (e.g., antitetanus)
Blood products

F. Venom

Scorpion fish sting

G. Foreign-substance reactions (direct pericardial application)

Talc (magnesium silicate)
Silicones
Tetracycline and other sclerosants
Asbestos

H. Secondary pericardial bleeding/hemopericardium

Anticaogulants
Thrombolytic agents

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foreign substance reactions, and immunopathy[282] (see Table 50-13) .

IDIOPATHIC PERICARDITIS: PERICARDITIS OF UNKNOWN ETIOLOGY (NONSPECIFIC PERICARDITIS)

No disease is sui genres (i.e., truly idiopathic); rather, etiology is not demonstrable at the contemporary state of knowledge. "Idiopathic" now means "of unknown etiology," usually a syndrome resembling viral pericarditis.[283] Idiopathic pericarditis, that is, any attack resolving without diagnosis, is the most common form of acute pericarditis. However, many diseases can present first as a pericardial disorder. Examples include the vasculitis/connective tissue disease group in which a pericarditic initial presentation is not recognized, particularly lupus; unrecognized myocardial infarction first becoming symptomatic as myocardial infarction pericarditis or even post-myocardial infarction syndrome; aortic dissection; primary and metastatic malignancies; pulmonary embolism; some forms of acute tuberculous pericarditis; Lyme disease; traumatic pericarditis appearing late after trauma, including radiation pericarditis; the seronegative spondyloarthropathies and intestinal inflammatory diseases; acute pancreatitis first presenting as pericardial effusion. Rare diseases exemplify the extreme etiological range, for example, "yellow-nail syndrome," eosinophilic fasciitis (with pericarditis preceding eosinophilia), and celiac disease with dermatitis herpetiformis[284] (here recurrent pericarditis responds to a gluten-free diet). Whereas undiagnosed acute pericarditis with or without effusion often is safely attributed to viral infection, the remarkable range must be considered. Recurrent "idiopathic" pericarditis tends to follow a pattern seen in viral pericarditis. With a missed, (but nonviral) pathogenesis, the causal disease surfaces after the index pericarditis or during a recurrence.[283] In all large prospective studies of patients with acute pericarditis, the largest single group, often the majority, is "idiopathic," often because there have not been comprehensive searches for evidence of viral infection or systemic diseases such as lupus. Treatment is as usual for acute, clinically dry pericarditis and for effusion and tamponade as needed. Eventual identification of any specific pathogenesis requires adequate follow-up and specific treatment.

RECURRENT AND INCESSANT PERICARDITIS

Perhaps 15 to 20 percent of patients do not recover permanently after an initial attack of acute pericarditis. Although exact incidences and natural histories are uncertain, most patients have had acute idiopathic, presumably or manifestly viral, pericarditis; in them, recurrent pericarditis, or continuously active incessant pericarditis, that is, mainly recurrent or incessant pericardial pain, appear to be immunopathic processses.[285] "Incessant" designates pericarditis (or identical pain) in patients who continuously need treatment to suppress symptoms. This can be extended to those who are free of symptoms for periods of less than 6 weeks, an arbitrary figure because of the usual failure of pericardiectomy to end these painful chronic syndrome. Postoperatively, nearly all patients have a brief, unexplained symptom-free 1- to 6-week period (a few patients either appear to be cured completely or for months to years before symptoms return).[285] It is possible that meticulous removal of nearly all the pericardium (pedestals must be left for the phrenic nerves) may yield improved results, but very long follow-up is needed. Anecdotal evidence suggests better results in the less common cases with recurrent pain who also have recurrent effusions.

INCESSANT PERICARDITIS.

This condition involves continuous activity surfacing when antiinflammatory, usually corticosteroid, therapy is reduced or discontinued. Most such patients may be said to be "steroid hooked," [285] a term of art, more dramatic than "steroid dependent," to reflect their desperation. In a minority, repeated or chronic exposure to the inciting agent or process is clearly responsible for recurrences, such as viral and bacterial reinfection (or reactivation of dormant organisms)[283] [284] [285] and, more commonly, systemic disorders, notably the vasculitis/connective tissue disease group, especially lupus. Certain pathogenetic possibilities may apply to recurrent and incessant pericarditis: (1) inadequate antiinflammatory treatment of the index or subsequent attack; (2) corticosteroid treatment given early during active viral multiplication that promotes and prolongs viral infection; (3) poorly understood cyclic immune or autoimmune responses to specific or nonspecific agents and processes such as respiratory infections or fatigue; and (4) viral RNA sequences in pericardial tissue acting as constant sources of antigen, although not themselves capable of replication.

RECURRENT IDIOPATHIC PERICARDITIS.

"Idiopathic pericarditis" is usually of viral origin because its recurrences are virtually the same syndrome as recurrences after demonstrably viral pericarditis.[262] Recurrent idiopathic pericarditis is perhaps the greatest therapeutic challenge among all pericardial disorders and encompasses both intermittent and incessant forms. Recurrent idiopathic pericarditis and sterile recurrences after viral pericarditis are uncommon without a background of initial or continuing corticosteroid treatment. Characteristically, the incessant form has a threshold level of prednisone below which relapse is certain. Significant effusion is uncommon, and tamponade is rare during recurrences. Constriction appears not to occur in those without effusions.[285] Most recurrent pericarditis seems to represent individual pericardial reactivity to a variety of poorly understood pathogenetic processes and their corticosteroid suppression.

PERICARDIAL IMMUNOPATHY.

Strong evidence that most recurrent pericarditis is immunopathic includes[8] (1) latent period after the index attack lasting days to years but usually months; (2) AHAs in some cases, probably those with significant myopericarditis in the index attack; (3) similarity to illnesses such as the post-myocardial infarction and postpericardiotomy syndromes (related to no. 2); (4) frequent allergic personal and/or family history; (5) rapid response to corticosteroid therapy and relapses with decreasing dose or discontinuance; (6) acute recurrent pericarditis during allergic disorders such as reactions to drugs and in celiac disease and dermatitis herpetiformis to foods with gluten; (7) acute recurrent pericarditis in classic serum sickness, including reactions to immunizations (e.g., for smallpox, yellow fever, hepatitis); (8) recurrent pericarditis in diseases of demonstrably

autoimmune pathogenesis such as lupus; (9) occasional occurrence with other serositis, mainly pleuritis and rarely peritonitis; (10) frequent arthralgias especially in the post-myocardial infarction and postpericardiotomy syndromes as well as arthritis in the vasculitides; and (11) occasional eosinophilia.

CLINICAL ASPECTS.

Recurrences vary from one to dozens over periods of weeks to decades. In no individual cases are patterns of recurrence precisely predictable except during corticosteroid weaning with an established threshold level for recurrence. Some patients can predict a relapse, and symptoms are usually stereotyped for each patient. All have pain resembling pain of the index attack often with strong pleuritic components, which is best described as "annoying" and "disabling" making life unpleasant. Objective manifestations are much less uniform and, while frequently detectable in the first recurrence, often become less common.[285] If significant effusion does not accompany the first recurrence, it is less likely subsequently. Exceptional patients have increasing severity in recurrences during which tamponade may first appear.

Recurrent idiopathic pericarditis is frequently of remote viral origin. Enterovirus-specific IgM responses have been found in many patients with chronic relapsing pericarditis, whereas comparable patients after acute enterovirus, mainly coxsackievirus B, infections elsewhere have only transient evidence of viral infection. Yet, among patients with acute pericarditis the level of IgM antibody was significantly higher in those who later experienced relapse. Host genetic factors are suggested by significantly higher levels of HLA-A2 haplotypes in those who were IgM positive (although extracardiac sites of viral persistence could not be excluded).[285] Thus, many patients with recurrent pericarditis experience persistent viral antigenic stimulation. Recurrences frequently follow new exposure to or infection by viral illnesses. It is not clear why constrictive pericarditis can follow a single attack of viral pericarditis while recurrent pericarditis after repeated comparable "idiopathic" attacks appears not to constrict.

NONIDIOPATHIC RECURRENT PERICARDITIS.

Although rare, it is axiomatic that reexposure of susceptible patients to bacterial, particularly tuberculous, and other infections can result in recurrent pericarditis[285] [286] [287] and constriction can ensue. Hemopericardium, particularly with pericardial injury, can be associated with recurrent pericarditis.[285] The post-cardiac injury syndromes are especially prone to recurrence. The most important systemic disorders are the vasculitis/connective tissue disease group, especially lupus. In young patients with beta-thalassemia, the frequency of recurrent pericarditis remains unexplained. Recurrent pericarditis with inflammatory bowel disease is on a fairly firm immunopathic basis, as is that accompanying dermatitis herpetiformis, with immune complex deposition as a common basis of recurrent pericarditis.[285] The recurrent polyserositis of familial Mediterranean fever involves the pericardium less often than other serosae and only rarely constricts. Recurrences are in the group with hypersensitivity and manifest "allergy" usually after exposures to ingestants, inhalants, and injectants.

MANAGEMENT.

For a confirmed etiology there may be specific therapy. For most patients with recurrent "idiopathic" pericarditis, treatment has been difficult. Patients with the incessant form remain corticosteroid dependent. Patients with the intermittent form require treatment only for relapses. Thus the most important preventive consideration is to avoid corticosteroid therapy if possible and to wean patients judiciously from a corticosteroid, relying on aspirin or other NSAIDs, particularly ibuprofen. Immunosuppressive and cytotoxic drugs used in oncology and organ transplantation[288] have not proved effective for recurrent pericarditis. Any effective NSAID may be tried at the lowest adequate dose. Observation is required for gastrointestinal and other side effects, including renal damage particularly in older patients. The largest challenge, requiring high NSAID doses, its to wean "steroid hooked" patients. Without appropriately designed controlled trials, absolute recommendations cannot be given. "Experience" is a potentially useful alternative. It appears that escalating doses of ibuprofen while slowly reducing prednisone gives good results. Treatment must be individually fine tuned. A "standard decrement" of 1 mg of prednisone permits individualized determination of the intervals between dose reductions (e.g. 1 week to 2 months) while introducing colchicine[289] ; and increasing ibuprofen doses beginning with 800 mg every 8 hours, if the patient can tolerate it under careful observation and gastrointestinal mucosal protection.

Recurrent Pericardial Effusion.

If large or with any degree of tamponade, these should be drained by catheter for several days, while maintaining drug therapy.[285] Failure indicates pericardiectomy.

Exercise Restriction.

Personal experience suggests that exercise contributes to exacerbations and recurrences and that restriction of exercise can be a decisive component of treatment in these difficult cases. Absence of appropriately designed controlled trials limits the objectivity of exercise restriction. It is uncertain exactly how to "prescribe" this, but it seems worthwhile.

Radiation Pericardial Disease

Radiation therapy, particularly for Hodgkin disease and other lymphomas and malignancies of the breast, lung or thyroid, involves the pericardium variably, depending on radiation dose, duration of treatment, volume of heart in the field, and radiation source.[236] [290] [291] Incidence increases with survival and follow-up time. (Improved radiation dosing delivery and subcarinal shielding have decreased pericardial involvement.) Peak incidence remains 5 to 9 months after radiation therapy. Prognosis is generally favorable for the pericardial lesion. But, because most significant pericardial involvement is delayed, irradiated patients remain indefinitely susceptible.

PATHOGENESIS.

Of all cardiac structures the pericardium is most susceptible to radiation injury, with pericardial syndromes sometimes complicated by injury of the myocardium, coronary arteries, or valves. Although direct radiation injury can be demonstrated, most patients escape significant involvement, raising questions of triggering latent antigens or viral infections, particularly in the delayed forms. Effusions may be serous, sanguineous, or serosanguineous with high concentrations of protein and lymphocytes resembling malignant effusion.[245] Late thickening is more conspicuous in the parietal pericardium with or without occult or obvious constriction. Microvascular ischemia and collagenization of fibrinous exudates contributes to pericardial fibrosis. Radiation involving more than 50 percent of heart volume and delivering over 2500 rads, or 40 to 60 Gy, increases risk with increasing dose and volume of heart irradiation.

CLINICAL ASPECTS.[236] [290]

Involvement extends from immediate to variably delayed acute, subacute, and especially chronic syndromes. Acute pericarditis, with or without tamponade, is uncommon, but pericardial rubs are frequent during or within weeks of therapy. Oddly, acute syndromes do not correlate with late disease. Echocardiography shows some effusion in all patients with clinical findings. Subacute disease may appear over months, including effusion, constriction, or effusive-constrictive pericarditis. More common are chronic effusion or constriction, even after years of latency, so that other disease must be considered separately or as a precipitant, raising the question of whether radiation injury makes the pericardium more susceptible to infections. Occult constrictive pericarditis (see p. 1853) is relatively common and identified by catheter monitoring of an intravenous saline challenge.

DIAGNOSIS.

Although CT and MRI are more sensitive and specific, TEE is excellent to define the anatomical lesions.[236] Occult constriction may be overlooked in patients with nonspecific complaints (exertional dyspnea, edema, chest pains), which may be attributed to their primary illness. However, radiation therapy is the major cause of combined pericardial constriction and restrictive cardiomyopathy,

with the latter a notorious cause of a poor result from pericardiectomy (see p. 1853).

TREATMENT.

Mild acute pericarditis and noncompressing effusion do not require specific therapy. Usually, there is no reason to discontinue radiation. Prednisone may be needed for

intractable pain but does not prevent constriction. Overt constriction necessitates pericardiectomy, always considering the patient's prognosis and quality of life. Radiation constriction presents technical challenges to the surgeon, and severe involvement of the pulmonary vessels and heart may make it unsuccessful.

Chronic Pericardial Effusion and Chronic Cardiac Tamponade

Chronic pericardial effusion represents excessive pericardial fluid remaining, arbitrarily, for at least 3 months.[292] [293] The vast majority are "idiopathic," presumably autoimmune, or follow viral or other burnt out infections and are large to massive. Chronicity with slow fluid formation permits greater relaxation of the parietal pericardium so that chronic effusions present for 6 months to many years can reach 3 or 4 liters, particularly if of inflammatory origin. Few patients give a history of acute pericarditis.

ETIOLOGY.

Pyogenic bacteria have been found in chronic pericardial exudates. Tuberculosis and actinomycosis and other fungi can cause chronic effusions including pericardial cold abscesses.[292] Although pericardial trauma can cause acute tamponade or constriction, it may be followed by chronic hemopericardium[294] and also is occasionally associated with some neoplasms, including primary pericardial sarcoma and Kaposi sarcoma, and various hemorrhagic diseases.[293] [294] The main connective tissue and related disorders associated with chronic effusions include lupus, rheumatic heart disease, scleroderma, polyarteritis, and especially rheumatoid arthritis.[295] *Lymphopericardium* is uncommon and follows lymphatic obstruction, lymphangioma, or rarely communication of thoracic duct and pericardium (usually after cardiothoracic surgery; also implicated in *chylopericardium*). Chronic effusive *cholesterol pericarditis* has multiple causes. *Endomyocardial fibrosis* may be accompanied by and present as a large hydropericardium. Congenital heart lesions, especially atrial septal defect, and *atrial thrombi* rarely are associated with massive chronic effusion. *Irradiation* for thoracic and cervical tumors can produce large, slowly absorbed or nonabsorbed effusions. Metabolic causes include *myxedema* and *uremia.* Hematological disorders associated with chronic pericardial effusion include *polycythemia* and severe, mainly "congenital" anemias--notably *thalassemia* and *pernicious anemia;* rarely, *heterotopic myelopoiesis* in the pericardium provokes a large effusion.[292]

PATHOLOGICAL CHARACTERISTICS.

Structural abnormalities and fluid characteristics largely depend on causative disorders. Pericardial tissue usually shows no acute changes and may be strictly fibrotic with adhesions and loculations, sometimes with cyst formation. Specific histological changes are uncommon even in cases related to known diseases.[296] Yet subacute inflammation and fibrinous pericarditis is occasionally superimposed on chronic changes.[292] The fluid, especially in idiopathic chronic effusion, is usually clear and straw colored with mainly exudative characteristics. However, transudate and exudate borderlines may be indistinct. Inflammatory fluids are more often under pressure, producing chronic tamponade with or without associated constriction. Pericardial calcification is occasional and usually confined to the visceral pericardium. Constriction[292] [296] [297] is not rare with

chronic effusions of inflammatory origin. Such effusions may contribute independently to cardiac compression depending on an unyielding scarred parietal pericardium. Moreover, constrictive epicarditis is a principal cause of constriction with chronic effusion (i.e., chronic effusive-constrictive pericarditis). Yet many large chronic effusions, even with pericardial calcification, do not develop significant constriction or tamponade. Constriction sometimes develops rapidly after drainage of long-standing effusions, possibly by exciting previously low-grade inflammation.[292]

PATHOPHYSIOLOGY. [292] [298]

Chronic effusions may have four effects[292] : (1) slow production of small amounts of undetected fluid; (2) demonstrable effusion without symptoms or signs of cardiac compression; (3) smaller or larger effusions compressing the heart but stabilized by compensatory mechanisms; and (4) recurrent or progressive chronic cardiac tamponade. The physiological borderline between a stabilized compressing effusion and progressive tamponade is indistinct; tamponade, acute or chronic, is not "all or none." (In some patients with congestive failure and hydropericardium, drainage decreases both pericardial pressure and cardiac pressures, indicating mild cardiac compression.) If pericardial pressure is elevated but less than RA pressure, drainage reduces only the pericardial pressure. In either case, mean atrial pressures and ventricular diastolic pressures significantly differ from pericardial pressure--in contrast to overt tamponade.[292]

PHYSICAL EFFECTS.[292]

Large effusions may encroach on contiguous structures, causing restrictive pulmonary impairment, dyspnea on exertion, hoarseness, hiccough and dysphagia, and a Bamberger-Pins-Ewart sign.

Chronic Cardiac Tamponade

Chronic tamponade resembles chronic constrictive pericarditis. Diminution of cardiac output is comparable.[292] [293] [294] [295] [296] [297] [298] Compensatory mechanisms resemble acute tamponade, but circulating blood volume is more expanded. Many patients tolerate even massive chronic effusions amazingly well with minimal or no symptoms and signs, at least at rest.[292] [293] Others reach a stage of relentlessly increasing cardiac compression or one of prolonged debility with complications due to chronically diminished cardiac output and congested viscera.

CLINICAL MANIFESTATIONS.

Most symptoms and signs are ascribable to the large pericardial mass, any chronic cardiac compression, and residual pericardial inflammation, modified by any cardiac disease.[272] Chronicity makes symptoms "late" or nil; and such quiet chronic effusions, particularly if "idiopathic," are often accidentally discovered.[292] Symptoms and signs can resemble those of acute effusions or tamponade. However, many patients have vague

chest discomfort and chronic fatigue, anorexia, and weight loss.

COURSE. [292] [293] [294] [295] [296]

The course varies according to pathogenetic factors; bland versus actively inflammatory effusion; pure chronic tamponade; or effusive-constrictive pericarditis. With tamponade, patients tend to develop atrial fibrillation as well as myocardial atrophy (with chronicity); liver congestion,[296] which can ultimately induce "cardiac cirrhosis"; the nephrotic syndrome; or protein-losing enteropathy. Complications may also be precipitated by systemic or respiratory infections.

DIAGNOSIS.[292] [293] [294] [295] [296] [297] [298]

Identifying pericardial fluid and tamponade by clinical and graphic methods is the same as for acute effusion and tamponade. The ECG is of little value. Low voltage is probably related to myocardial atrophy, fluid retention, and any pleural as well as pericardial effusion.[292] Etiological diagnosis is not possible in most "idiopathic" cases. Pericardial fluid and tissue obtained surgically, by biopsy or necropsy, may yield evidence from appropriate bacteriological, immunological, and histological techniques; and histologically "nonspecific" tissue may yield evidence of prior infection such as traces of tuberculous or viral RNA sequences.

MANAGEMENT. [296] [297]

Treatment of chronic effusion is individualized considering presence or absence of (1) cardiac compression, (2) a detectable causative disorder, (3) inflammatory manifestations, and (4) symptoms due to encroachment

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on adjacent structures. In general, inflammatory effusions tend to require surgical intervention sooner or later particularly if with chronic tamponade; noninflammatory effusions usually respond to treatment of associated disease. Aspiration of pleural effusions and ascites can contribute to symptomatic relief as well as preoperative management. Search for a cause is mandatory, particularly for specific therapeutic targets such as tuberculosis, toxoplasmosis, or myxedema. Management in general is the same as for acute pericardial effusion and tamponade and includes fluid and biopsy for diagnosis and biopsy and drainage for relief. However, drainage without resection is seldom adequate, particularly in idiopathic cases where refilling is common. Signs of persistent inflammation call for antiinflammatory therapy, particularly nonsteroidal agents. Nonabsorbable corticosteroids may be given intrapericardially. In patients for whom complete pericardial resection is not contemplated, chronic systemic congestion calls for sodium restriction and diuretics. Pericardiocentesis should be slow and intermittent to avoid cardiac overloading in patients with poor myocardial function[299] ; expanded blood volume and any myocardial atrophy make overloading more likely than

in acute tamponade. After paracentesis, incomplete or tardy improvement in the absence of refilling may be due to myocardial impairment; total failure to improve suggests constrictive epicarditis. While pericardiectomy remains a procedure of choice with or without tamponade, it may be postponed in occasional patients with sustained relief from paracentesis or restricted surgical drainage and appropriate medical measures. However, the tendency of inflammatory chronic effusions to eventually constrict and the morbidity from recurrences favor pericardiectomy.[292] [293] Pleuropericardial fenestration is feasible in patients in whom full thoracotomy or thoracoscopic resection are considered unwarranted, principally because of the patient's general condition. Balloon pericardiostomy has been successful. However, fenestration has important disadvantages, including (1) frequent resealing of the stoma, (2) impossibility of complete dependent drainage, (3) potential constrictive scarring due to irritation by the procedure, (4) inadequate inspection of the epicardium, and (5) incomplete removal of adhesive or inflamed and infected tissue.[292]

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Chapter 51 - Traumatic Heart Disease

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The earliest reports of traumatic injury to the heart discouraged operative repair, asserting high mortality and the hopelessness of cardiorrhaphy.[1] This pessimism persisted until the first cardiorrhaphy was performed by Rehn[2] in 1898. Rehn subsequently compiled his series of 124 cases over the next 10 years, with a survival of 40 percent.[3] The first cardiac repair for injury in the United States was performed by Hill[4] in 1902 on a kitchen table. In 1959, Isaacs[5] reported a remarkable survival of 89 percent for stab wounds and 43 percent for gunshot wounds to the heart among 60 patients. Enthusiasm for the surgical intervention in traumatic heart disease grew from these reported successes.

Most of the early reports involving traumatic heart disease involved penetrating injuries. Crynes and Hunter[6] reported the first blunt cardiac injury in 1939. In 1955, Des Forges and associates[7] reported the first successful repair for blunt cardiac injury.

Incidence

In the United States, trauma is the fourth leading cause of death, and it is the leading cause of death in those younger than 40 years of age. Thoracic trauma is responsible for 25 percent of the annual 50,000 deaths from vehicular accidents. As high as one fourth of these deaths are due to traumatic cardiac injury.[8] The actual incidence of cardiac injury from all of the diverse etiologies and classifications (including the confusing "cardiac contusion") is unknown. It has been estimated that cardiac injury may account for 10 percent of deaths from gunshot wounds.[9] Penetrating cardiac trauma is a highly lethal injury, with relatively few such patients reaching the hospital. In a series of penetrating cardiac injuries in South Africa where both those reaching the hospital and those being taken directly to the morgue were included, only 6 percent of 1,198 patients reached the hospital with any signs of life.[10] With improvements in organized emergency medical transport systems, up to 45 percent of those who sustain significant traumatic heart injury may reach the emergency department.[11]

Blunt cardiac injuries have been reported less frequently than penetrating injuries. In a population-based study, which included autopsied patients, the incidence of blunt cardiac injury is 0.1 percent.[12] In hospital-based studies, 10 to 70 percent of motor vehicle fatalities may have been the result of blunt cardiac rupture.[13] [14]

ETIOLOGY AND PATTERNS OF CARDIAC TRAUMA

Categorization of traumatic heart disease is based on mechanism of injury (i.e., penetrating, nonpenetrating [blunt], iatrogenic, metabolic, and other) (Table 51-1) .

PENETRATING CARDIAC TRAUMA.

Penetrating trauma is the most common cause of significant cardiac injury seen in the hospital setting, with the predominant injury being from guns and knives. Penetrating cardiac trauma is secondary to stab wounds in 35 to 96 percent of patients (depending on the instrument used in interpersonal violence in a geographical location), whereas gunshot wounds account for a reported 39 to 66 percent.[15] [16] [17] Both of these etiologies vary according to the year of the report and location in the world. One might also postulate that economic factors influence the availability of a penetrating wounding agent. Other mechanisms such as shotguns, ice picks, and fence impalement have also been reported.

The location of injury to the heart often correlates with the location of injury on the chest wall. Because of their anterior location, the anatomical chambers at greatest risk for injury are the right and left ventricles. In a review of 711 patients with penetrating cardiac trauma, 54 percent sustained stab wounds and 42 percent had gunshot wounds. The right ventricle was injured in 40 percent of the cases, the left ventricle in 40 percent, the right atrium in 24 percent, and the left atrium in 3 percent. One third of

TABLE 51-1 -- ETIOLOGY OF TRAUMATIC HEART DISEASES

I. Penetrating
A. Stab wounds--knives, swords, ice picks, fence posts, wire, sporting
B. Gunshot wounds--low-high caliber, handgun, rifles, nail guns, lawnmower projectiles
C. Shotgun wounds--close range, distant

II. Nonpenetrating (Blunt)
A. Motor vehicle accident
1. Seat belt
2. Air bag
B. Vehicular-pedestrian accident
C. Falls from height
D. Crushing--industrial accident
E. Blasts--explosives, grenades
F. Assault (aggravated)
G. Sternal or rib fractures
H. Recreational--sporting events (bull goring), baseball

III. Iatrogenic
A. Catheter induced
B. Pericardiocentesis induced

IV. Metabolic
A. Traumatic response to injury
B. "Stunning"
C. Systemic inflammatory response syndrome (SIRS)

V. Others
A. Burn
B. Electrical
C. Factitious--needles, foreign bodies
D. Embolic--missiles

cardiac injuries involve multiple cardiac structures.[17] Significant intracardiac injuries involved the coronary arteries (39), valvular apparatus (mitral) (2), intracardiac fistulas (i.e., ventricular septal defects [VSD]) (14), and unusual injuries (10). Only 2 percent of patients surviving their initial injury and undergoing an operation required reoperation for a residual defect.[17]

BLUNT CARDIAC TRAUMA.

Nonpenetrating or blunt cardiac trauma has replaced the term "cardiac contusion" and ranges from minor bruises of the myocardium to cardiac rupture.[18] [18A] It can be caused by direct energy to the heart or compression of the heart between the sternum and the vertebral column, even including "cardiac contusion" and cardiac rupture during external cardiac massage during cardiopulmonary resuscitation (CPR). Within this spectrum,

blunt cardiac injuries may present as free septal rupture, free wall rupture, coronary artery thrombosis, cardiac failure, complex arrhythmia, simple arrhythmia, and/or rupture of chordae tendineae or papillary muscles.[19] [20] The incidence may be as high as three fourths of the patients with severe bodily trauma. Etiologies include motor vehicle accidents, vehicular-pedestrian accidents, falls, crush injuries, blasts, assaults, CPR, and recreational events. Such injury is often associated with sternal or rib fractures. In one report a fatal cardiac dysrhythmia occurred when the sternum was struck by a baseball,[21] which may be a form of commotio cordis.[22]

Cardiac rupture carries a significant mortality. The biomechanics of cardiac rupture include[23] :

- Direct transmission of increased intrathoracic pressure to the chambers of the heart
- Hydraulic effect from a large force applied to the abdominal or extremity veins causing force to be transmitted to the right atrium, resulting in rupture
- Decelerating force, explaining atriocaval tears, between fixed and mobile areas
- Myocardial contusion, necrosis, and delayed rupture
- Penetration from broken rib or fractured sternum

Blunt rupture of the cardiac septum occurs most frequently in late diastole or early systole near the apex of the heart.[19] Multiple ruptures and disruption of the conduction system have been reported.[24] In an autopsy series of 546 patients reported by Parmley and colleagues, blunt cardiac trauma with ventricular rupture most often involved the left ventricle, followed by the right ventricle, and, least often, the left atrium. Thirty cases of VSD were reported, with the most common tear involving both the membranous and muscular portions of the septum. Injury to only the membranous portion of the septum was the least common blunt VSD. Parmley and colleagues also reported that traumatic rupture of the thoracic aorta was associated with lethal cardiac rupture in 22 percent of the cases.[12]

Blunt pericardial rupture results from pericardial tears secondary to increased intraabdominal pressure or lateral decelerative forces. The location of the tears occurs on the left side parallel to the phrenic nerve (64 percent), the diaphragmatic surface of the pericardium (18 percent), the right of the pleuropericardium (9 percent), and the mediastinum (9 percent).[19] Cardiac herniation with cardiac dysfunction can occur with these tears. The heart can be displaced into either pleural cavity or even the peritoneum. In the instance of right pericardial rupture the heart can become torsed and the pericardial cavity is surprisingly found to be "empty" of a heart at a resuscitative left anterolateral thoracotomy. With a left-sided cardiac herniation through a pericardial tear, a distending heart prevents the heart from returning into the pericardium, and the term "incarcerated heart" has been applied. Venous filling is impaired and unless the cardiac herniation is reduced, hypotension and cardiac arrest can occur.

IATROGENIC CARDIAC INJURY.

Iatrogenic cardiac injury can occur with central venous line insertion, cardiac catheterization procedures, and pericardiocentesis.

Cardiac injuries caused by central venous lines usually occur with placement from either the left subclavian or the left internal jugular vein.[25] Perforation causing tamponade has also been reported with a right internal jugular introducer sheath for transjugular intrahepatic portocaval shunts.[26] Vigorous insertion of left-sided central lines, especially during dilatation of the line tract, can lead to cardiac perforations. Even appropriate technique carries a discrete rate of iatrogenic injury secondary to central venous catheterization. Common sites of cardiac injury include the superior caval-atrial junction and the superior vena cava-inominate junction. These small perforations often lead to a compensated cardiac tamponade. Drainage by pericardiocentesis is often unsuccessful, and evacuation by the subxiphoid pericardial window or full median sternotomy is required. Once access to the pericardial space is gained, the site of injury has often sealed and may be difficult to find.

Complications from coronary catheterization, including perforation of the coronary arteries, cardiac perforation, and aortic dissection can be catastrophic and require emergency surgical intervention. The incidence of coronary perforation with balloon angioplasty is estimated to be 0.1 to 0.2 percent, but with advanced interventional techniques (e.g., rotablation, directional atherectomy, coronary artery stenting, and laser ablation) the incidence may be as high as 3 percent.[27]

Other potential iatrogenic causes of cardiac injury include external and internal cardiac massage, right ventricular injury during pericardiocentesis, and intracardiac injections.[28]

METABOLIC CARDIAC INJURY.

Metabolic cardiac injury (MCI) refers to cardiac dysfunction in response to traumatic injury and may be associated with injuries caused by burns, electrical injury, sepsis, the systemic inflammatory response syndrome, and multisystem trauma.[29] [30] [31] [32] The exact mechanism responsible for this dysfunction is unclear, but responses to trauma induce a "mediator storm," and it is this release of cytokines that may have a direct effect on the myocardium. Endotoxin, tumor necrosis factor-alpha, tumor necrosis factor-beta, interleukin-1, interleukin-6, interleukin-10, catecholamines (epinephrine, norepinephrine), cell-adhesion molecules, and nitric oxide are all possible responsible mediators.[33] [34] [35]

Metabolic cardiac injury may clinically present as conduction disturbances or decreased contractility leading to decreased output. Myocardial depression can occur in response to the "mediator storm" and alter calcium utilization and depression of the myocyte responsiveness to beta-adrenergic stimulation.[36] [37] [38] [39] Horton and coworkers[36] have shown that myocytes have altered calcium utilization in patients with injuries from burns. Ungureanu-Longrois and coworkers[34] reported that the activation of constitutive nitric

oxide synthase appears to modulate cardiac responsiveness to cholinergic and adrenergic stimulation and that production of inducible nitric oxide synthase causes depression of myocyte contractile responsiveness to beta-adrenergic agonists. The myocardial depressive effects appear to be reversible.[32]

Treatment of MCI has been supportive with correction of the initiating insults, but some have attempted to address the involved mediators using intravenous milrinone, corticosteroids, arginine, granulocyte-macrophage colony-stimulating factor, and glutamate.[40] [41] [42] [43] Use of an intraaortic counterpulsation balloon pump can be considered to treat such myocardial depression, but controlled series do not exist to test this hypothesis.

BURNS.

Cardiac complications in the early post-burn period are a major cause of death. The initial cardiovascular

effect of burn injury is attributable to the profound reduction in cardiac output that may occur within minutes of the injury. The overall cardiac response has been described as an *ebb* and *flow* pattern, with the initial *ebb* phase lasting between 1 and 3 days and marked by hypovolemia and myocardial depression and the *flow* phase characterized by a prolonged period of increased metabolic demand with increased cardiac output and peripheral blood flow. The reduction in cardiac output observed in the initial period of burn injury is the result of a dramatic and rapid decrease in intravascular volume due to a "capillary leak" and of a direct myocardial depression. Hypovolemia results from the capillary leak caused by endothelial injury and may be mediated by platelet-activating factor, complement, cytokines, arachidonic acid, or oxygen free radicals. Myocardial depression manifested by a decrease in myocardial contractility and abnormalities in ventricular compliance becomes apparent with total body surface area burn of 20 to 25 percent. Myocardial-depressant factor, tumor necrosis factor, vasopressin, oxygen free radicals, and interleukins may be responsible for the depression.[44]

ELECTRICAL INJURY.

Cardiac complications are the most common cause of death after electrical injury. An estimated 1100 to 1300 deaths occur annually in the United States from electrical injury (including lightning strikes). The cardiac complications after electrical injury include immediate cardiac arrest, acute myocardial necrosis with or without ventricular failure, pseudoinfarction, myocardial ischemia, dysrhythmias, conduction abnormalities, acute hypertension with peripheral vasospasm, and asymptomatic, nonspecific abnormalities evident on an electrocardiogram (ECG). Damage from electrical injury is due to the direct effects on the excitable tissues, heat generated from the current, and the accompanying associated injuries (e.g., falls, explosions, or fires).[45]

OTHERS.

Intrapericardial and intracardiac foreign bodies can cause complications of acute suppurative pericarditis, chronic constrictive pericarditis, foreign body reaction, and hemopericardium.[46] Intrapericardial foreign bodies that have been reported in the literature to result in complications include bullets, hand grenades, shrapnel, knitting needles, and hypodermic needles. Some of these are factitiously inserted by a patient, usually with a psychiatric diagnosis. A report by LeMaire and colleagues[46] advocated removal of intrapericardial foreign bodies that are greater than 1 cm in size, those that are contaminated, and/or those that produce symptoms.

INTRACARDIAC MISSILES.

Intracardiac missiles are foreign bodies that are either embedded in the myocardium, retained in the trabeculations of the endocardial surface, free in a cardiac chamber, or in the pericardium. These are the result of direct penetrating thoracic injury or injury to a peripheral vascular structure with embolization to the heart. Location and other conditions determine the type of complications that can occur and the treatment required. Observation might be considered when the missile is (1) right sided, (2) embedded completely in the wall, (3) contained within a fibrous covering, (4) not contaminated, and (5) producing no symptoms. Right-sided missiles can embolize to the lung, at which point they can be removed, or in rare cases they embolize "paradoxically" through a patent foramen ovale or atrial septal defect.[47] Left-sided missiles can present as systemic embolization shortly after the initial injury. Diagnosis is determined with radiographs in two projections, fluoroscopy, echocardiography, or angiography. Treatment of retained missiles is individualized. Removal is recommended for missiles that are left sided, larger than 1 to 2 cm, rough in shape, or produce symptoms.[47] Although direct approach, either with or without cardiopulmonary bypass, has been advocated in the past, a large percentage of right-sided foreign bodies can now be removed by interventional radiologists.

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

PENETRATING CARDIAC TRAUMA.

Wounds involving the precordial "box," which is the anatomical area that includes the epigastrium and precordium within 3 cm of the sternum, carry a high incidence of cardiac injury. Stab wounds present a more predictable path of injury than gunshot wounds. Cardiac injury may present with a clinical spectrum from full arrest with no vital signs to a patient who is asymptomatic with normal vital signs. Up to 80 percent of stab wounds eventually present with tamponade. The weapon injures the pericardium and heart, but as the weapon is removed the pericardium seals and may not allow blood to escape. Rapid bleeding into the pericardium favors clotting rather than defibrination.[48] As pericardial fluid accumulates, a decrease in ventricular filling occurs, leading to a decrease in stroke volume. A compensatory rise in catecholamines leads to tachycardia and increased right-sided heart filling pressures. The limits of distensibility are reached,

and the septum shifts toward the left side, further compromising left ventricular function. If this cycle persists, this may lead to worsening of the ventricular function and irreversible shock. As little as 60 to 100 ml of blood in the pericardial sac can produce the clinical picture of tamponade.[48]

The rate of accumulation is dependent on the location of the wound. Owing to a thicker wall, right ventricular wounds seal themselves more readily than right atrial wounds. Injuries to the coronary arteries present with rapid onset of tamponade combined with cardiac ischemia. With injuries to the left ventricle, the decompensated state can worsen, leading to cardiac arrest. Injuries to the right side of the heart can compensate, and rapid deterioration may not occur; this subset of patients may benefit from early diagnosis and immediate intervention.

The classic finding of Beck triad (muffled heart sounds, hypotension, and distended neck veins) may be seen in only 10 percent of patients. Pulsus paradoxus (a substantial fall in systolic blood pressure during inspiration) and Kussmaul sign (increase in jugular venous distention on inspiration) may be present but are not reliable[49] (see Chap. 50). A very valuable and reproducible sign of pericardial tamponade is a narrowing of the pulse pressure. An elevation of the central venous pressure often accompanies rapid and cyclic hyperresuscitation with crystalloid solutions, but in such instances there is a widening of the pulse pressure. Elevation of the central venous pressure and narrowing of the pulse pressure represents a pericardial tamponade syndrome until proven otherwise.

In contrast to stab wounds, gunshot wounds to the heart are more frequently associated with hemorrhage than with tamponade. Twenty percent of gunshot wounds to the heart present as tamponade. With firearms, the kinetic energy is greater and the wounds to the heart and pericardium are frequently larger. Thus, these patients present in arrest more often due to hemorrhage.[49]

NONPENETRATING CARDIAC TRAUMA.

As in penetrating cardiac trauma, clinically severe blunt cardiac trauma (e.g., cardiac rupture) presents as either tamponade or as hemorrhage, depending on the status of the pericardium. If the pericardium is intact, tamponade develops; if it is not intact, extrapericardial bleeding occurs and hypovolemic shock ensues. Tamponade may be combined with hypovolemia, thus complicating the clinical presentation.

Blunt cardiac injury can be divided into clinically significant and clinically insignificant injuries. Clinically significant injuries include cardiac rupture (ventricular or atrial), septal rupture, valvular dysfunction, and coronary thrombosis. These injuries present as tamponade, hemorrhage, or severe cardiac dysfunction. Septal rupture and valvular

dysfunction (leaflet tear, papillary muscle, or chordal rupture) may initially present

without symptoms but later present as the delayed sequelae of heart failure.[48]

Blunt cardiac injury may also present as dysrhythmias, most commonly premature ventricular contractions, the precise mechanism of which is unknown. Ventricular tachycardia can occur and degenerate into ventricular fibrillation. Supraventricular tachyarrhythmias can also occur. These commonly occur within the first 24 to 48 hours.

Small isolated tears in the pericardium may lead to cardiac herniation. This is a rare complication of pericardial rupture and depends on the size of the pericardial tear. If large enough, cardiac herniation can occur, leading to acute cardiac dysfunction. [48]

EVALUATION

Evaluation of the patient with suspected traumatic heart injury is divided among those patients who are clinically stable and those who are in extremis.

INITIAL ASSESSMENT.

The diagnosis of traumatic heart injury requires a high index of suspicion (Fig. 51-1) . On initial presentation to the emergency center, airway, breathing, and circulation (ABCs) under Advanced Trauma Life Support (ATLS) protocol are evaluated and established.[50] Two large-bore intravenous catheters are inserted, and blood is typed and cross matched. The patient undergoes a Focused Assessment for the Sonographic examination of the Trauma victim (FAST) and is examined for Beck triad of muffled heart sounds, hypotension, and distended neck veins, as well as for pulsus paradoxus and Kussmaul sign. These findings suggest cardiac injury but may be present in only 10 percent of patients with cardiac tamponade. If the FAST demonstrates pericardial fluid in the patient who is unstable (systemic blood pressure <90 mm Hg), immediate transfer to the operating room for definitive repair or damage control is required.

Patients in extremis require immediate surgical intervention and often require emergent thoracotomy for resuscitation. The clear indications for emergency department thoracotomy include the following[51] :

1. Salvageable postinjury cardiac arrest (e.g., patients who have witnessed cardiac arrest with high likelihood of intrathoracic injury, especially penetrating cardiac wounds)
2. Severe postinjury hypotension (i.e., systolic blood pressure <60 mm Hg) due to cardiac tamponade, air embolism, or thoracic hemorrhage

If after resuscitative thoracotomy vital signs are regained, the patient proceeds to the operating room for definitive repair. The patient with confirmed pericardial fluid by FAST with normal vital signs (systemic blood pressure >90 mm Hg) may undergo a thorough evaluation to identify associated injuries. If other injuries are excluded, then open exploration may be required to exclude cardiac injury. In the absence of known causes of pericardial fluid (e.g., malignant pericardial effusion), a missed cardiac injury may

lead to delayed bleeding, deterioration, or death.

Chest radiograph is nonspecific, but it can identify hemothorax or pneumothorax and demonstrate an enlarged

Figure 51-1 Algorithm for the initial assessment of traumatic cardiac injury.

cardiac silhouette suggesting pericardial fluid. Other possibly indicated examinations include ultrasonography, central venous pressure measurements, subxiphoid pericardial window, thoracoscopy, laparoscopy, and pericardiocentesis.

ULTRASONOGRAPHY.

Surgeons are increasingly performing ultrasonography for thoracic trauma. This increase has paralleled the use of ultrasonography for blunt abdominal trauma. The FAST evaluates four anatomical windows for presence of intraabdominal or pericardial fluid[52] (Fig. 51-2) . Ultrasonography in this setting is not intended to reach the precision of studies performed in the radiology suite but is merely intended to determine the presence of abnormal fluid collections, which aid in surgical decision making.[53] Ultrasonography is safe, portable, and expeditious and can be repeated as indicated.[53] If performed by a trained surgeon, the FAST examination has a sensitivity of nearly 100 percent and specificity of 97.3 percent.[54]

To evaluate more subtle findings of blunt cardiac injury in the stable patient, transthoracic (TTE) or transesophageal echocardiography (TEE) may be used. TEE is useful in identifying and characterizing valvular abnormalities and septal defects.

SUBXIPHOID PERICARDIAL WINDOW.

Subxiphoid pericardial window has been performed both in the emergency department and in the operating room with the patient under either general or local anesthesia. A subxiphoid vertical incision is made and a small hole made in the pericardium, looking for blood. In a prospective study, Meyer and coworkers[55] compared the subxiphoid pericardial window with echocardiography in penetrating heart injury and reported that the sensitivity and specificity of subxiphoid pericardial window was 100 percent and 92 percent, respectively, compared with 56 percent and 93 percent with echocardiography. They suggested that the difference in the sensitivity may have been due to the presence of hemothorax, which may confuse the pericardial and pleural space, or due to the fact that the blood had drained into the pleura.[55]

The disadvantage of subxiphoid pericardial window is that it is an invasive procedure;

and if a major injury is found, a second thoracic incision is required for definitive repair. Although there has been significant controversy in

Figure 51-2 Focused Assessment for the Sonographic examination of the Trauma victim (FAST). *(From Rozycki GS, Feliciano DV, Schmidt JA, et al: The role of surgeon performed ultrasound in patients with possible cardiac wounds. Ann Surg 223:737-746, 1996.)*

the indication for subxiphoid pericardial window, recent enthusiasm for ultrasound evaluation has almost eliminated the role of subxiphoid pericardial window in the evaluation of cardiac trauma.

PERICARDIOCENTESIS (See Chap. 50).

Pericardiocentesis has had significant historic support, especially at a time when the majority of penetrating cardiac wounds were produced by ice picks and the (surviving) patients arrived several hours and/or days after injury. In such instances there was a natural triage of the more severe cardiac injuries and the intrapericardial blood had become defibrinated and was easy to remove. Currently, many trauma surgeons discourage pericardiocentesis for acute trauma. In general, pericardiocentesis has historically been used as a diagnostic or therapeutic maneuver to drain nonclotted pericardial fluid. In the setting of trauma, cardiac tamponade is acute and due to hemorrhage. Clot forms quickly and is not amenable to needle drainage. Recurrence of tamponade and subsequent increase in mortality, as well as a significant incidence of false-negative results and potential for iatrogenic injury, makes pericardiocentesis a far less than optimal diagnostic tool.[28]

Indications for its use may apply in the iatrogenic injury caused by cardiac catheterization, at which time immediate decompression of the tamponade may be life saving, or in the trauma setting when a surgeon may not be available.

EVALUATION OF BLUNT CARDIAC INJURY

ECG.

In blunt cardiac injury, conduction disturbances are common, and, thus, a screening 12-lead ECG may be helpful for evaluation. The most common rhythm disturbance is sinus tachycardia. Other possible disturbances include the following: T wave and ST segment changes (as seen with myocardial bruising), sinus bradycardia, first-degree atrioventricular block, right bundle branch block, right bundle branch block with hemiblock, third-degree block, atrial fibrillation, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation.[56]

Cardiac Enzymes.

Much has previously been written about the use of cardiac enzyme determinations in

evaluating blunt cardiac injury. However, no correlation between serum assays (e.g., creatine phosphokinase myocardial band, cardiac troponin T, or cardiac troponin I) and identification and prognosis of injury has been demonstrated with blunt cardiac injury.[57] [58] Therefore, cardiac enzyme assays should not be obtained unless evaluating concomitant coronary artery disease.[56]

TREATMENT

PREHOSPITAL AND EMERGENCY DEPARTMENT.

Only a small subset of patients with significant cardiac injury ever reaches the emergency department, and expeditious transport to a designated trauma facility is essential to survival. Transport times of less than 5 minutes and successful endotracheal intubation are positive factors for survival.

DEFINITIVE TREATMENT.

Definitive treatment involves surgical exposure through a thoracotomy (Fig. 51-3 *A*) or median sternotomy (see Fig. 51-3 *B*). The mainstay of treatment is relief of tamponade and correction of aberrant physiology. This involves correction of the acidosis and hypothermia and reestablishment of effective coronary perfusion (i.e., resuscitation of the heart).

Cardiorrhaphy should be performed by experienced surgeons (Fig. 51-4) . Poor technique may result in enlargement of the lacerations or injury to the coronary arteries. If one is uncomfortable with the suturing technique, digital pressure may be applied until a more experienced surgeon arrives. Other techniques that have been described include the use of a Foley balloon catheter and a skin stapler[17] (Fig. 51-5) .

Figure 51-3 Incisions for cardiac injury. *A,* Left anterior thoracotomy (extension across the sternum if required). *B,* Median sternotomy (extension to the neck can be performed for exposure of the great vessels).

Exposure to the heart is gained by a left anterolateral thoracotomy, which allows access to the pericardium and heart and exposure for aortic cross-clamping if necessary. This incision may be extended across the sternum to gain access to the right side of the chest and for better exposure of the right atrium or right ventricle. This usually requires ligation of both internal thoracic arteries. Manual access to the right hemithorax from the left side of the chest is achieved through the anterior mediastinum by blunt dissection. This maneuver allows rapid evaluation of the right side of the chest for major injuries without transecting the sternum. Once the left pleural space is entered, the lung is retracted to expose the descending thoracic aorta for cross-clamping of the pericardium

for exposure. It is helpful to note how much blood is present in the left side of the chest, which indicates hemorrhage versus tamponade. The pericardial sac anterior to the phrenopericardial vessels and phrenic nerve is opened, injuries are rapidly identified, and repair is performed.

In selected cases, particularly stab wounds to the precordium, the median sternotomy may be used. This incision allows excellent exposure to the anterior structures of the heart, but difficulty with access to the posterior mediastinal structures and descending thoracic aorta for cross-clamping may be encountered.

Mechanical support is not often used in the acute setting.[17]

BLUNT CARDIAC INJURY.

Much debate and discussion has occurred over the clinical relevance of "cardiac contusion." Most trauma surgeons conclude this diagnosis should be eliminated because it does not affect how one treats these injuries.[18] Thus, a normotensive patient with a normal initial ECG and suspected blunt cardiac injury is managed with emergency department or "chest pain" observation units with no expected clinical significance. Patients with an abnormal ECG are admitted for monitoring and treated accordingly. Patients who present in cardiogenic shock are evaluated for a structural injury, which is then repaired.

Results

Factors that determine survival in traumatic cardiac injury are mechanism of injury, location of the injury, associated injuries, coronary artery involvement, presence of tamponade, length of prehospital transport, requirement of resuscitative thoracotomy, and experience of the trauma team. The

Figure 51-4 Technique of suture repair. Cardiorrhaphy *(A)*. Should reinforcement be required, interrupted pledgeted sutures *(B),* pledgeted sutures around previously placed staples *(C),* or felt strips *(D)* can be used. *(From Wall MJ Jr, Mattox KL, Chen CD, Baldwin JC: Acute management of complex cardiac injuries. J Trauma 42:905-912, 1997.)*

Figure 51-5 Temporary techniques to control bleeding. *A,* Stab wound to left ventricle. *B,* Initial management with interrupted or continuous 4-0 polypropylene sutures tied beneath the surgeon's finger. Additional techniques for complex injuries for temporary control include use of Foley balloon catheter *(C)* or skin stapler *(D)*. *(From Wall MJ Jr, Mattox KL, Chen CD, Baldwin JC: Acute management of complex*

cardiac injuries. J Trauma 42:905-912, 1997.)

overall hospital survival for penetrating heart injuries ranges from 30 to 90 percent.[17] [59]

The survival from a stab wound is 70 to 80 percent, whereas survival from a gunshot wound is between 30 and 40 percent.[49] Cardiac rupture has a worse prognosis than penetrating injuries to the heart. Calhoun and colleagues[14] reported a 70 percent survival in 10 patients, but most series report a survival of approximately 20 percent.[19]

Complications

Primary injury-related cardiac complications include coronary artery injury, valvular apparatus injury (annulus, papillary muscles, and chordae tendineae), intracardiac fistulas, arrhythmias, and delayed tamponade. These delayed sequelae have been reported to have a broad range (4-56 percent), depending on the definition of complication.[60]

Coronary artery injury is a rare complication, occurring in 5 to 9 percent of cardiac injuries, with a 69 percent mortality.[12] [17] This mortality is due to the associated cardiac injury and other associated injuries and the state of physiologic compromise when the patient arrives. A coronary artery injury is most often controlled by simple ligation, but bypass grafting using saphenous vein may be required for proximal left anterior descending injuries (with utilization of total cardiopulmonary bypass).[17] With a resurrection of the old concept of coronary artery bypass grafting without cardiopulmonary bypass ("off-pump" bypass), this technique may theoretically be used for these injuries in the highly unlikely event that the patient is hemodynamically stable.

Valvular apparatus dysfunction is rare (0.2-9 percent) and may occur with both blunt and penetrating trauma.[12] [17] Most frequently, the aortic valve, followed by the mitral and tricuspid valves, is injured.[12] Often these injuries are identified after the initial cardiorrhaphy and resuscitation has been performed. Timing of repair depends on the patient's condition. If severe cardiac dysfunction exists at the time of the initial operation, immediate valve repair or replacement may be required; otherwise, delayed repair is advised.

Intracardiac fistulas include VSDs, atrial septal defects, and atrioventricular fistulas, with an incidence of 1.9 percent among cardiac injuries.[17] Management depends on symptoms and degree of cardiac dysfunction, with only a minority of these patients requiring repair.[28] These injuries are often identified after primary repair is accomplished and can be repaired after recovery from the original and associated injuries. Cardiac catheterization should be accomplished before repair so that specific anatomic sites of injury and incision planning can be accomplished.

Arrhythmias may occur due to blunt injury, ischemia, or electrolyte abnormalities and are addressed according to the injury (Table 51-2) (see Chap. 25).

Delayed pericardial tamponade is very rare. It has been reported to occur as early as 1

hour after initial operation and as long as 76 days from the injury.[28]

Follow-Up

Secondary sequelae in survivors of cardiac trauma include valvular abnormalities and intracardiac fistulas.[61] These abnormalities may be identified intraoperatively by gross palpation of a thrill[17] or with the use of TEE. TEE, however, may not be feasible in the acutely injured patient. Early postoperative clinical examination and ECG findings are unreliable.[17] Thus, echocardiography is recommended during the initial hospitalization to identify occult injury and establish a baseline study. Because the incidence of late sequelae may be as high as 56 percent, follow-up echocardiography 3 to 4 weeks after injury has been recommended.[61]

TABLE 51-2 -- ARRHYTHMIAS ASSOCIATED WITH CARDIAC INJURY

Penetrating Injury
Sinus tachycardia
ST segment changes associated with ischemia
Supraventricular tachycardia
Ventricular tachycardia/fibrillation
Blunt Cardiac Injury
Sinus tachycardia
ST segment, T wave abnormalities
Atrioventricular blocks, bradycardia
Ventricular tachycardia/fibrillation
Electrical Injury
Sinus tachycardia
ST segment, T wave abnormalities
Bundle branch block
Axis deviation
Prolonged QT
Paroxysmal supraventricular tachycardia
Atrial fibrillation
Ventricular tachycardia, fibrillation (alternating current)
Asystole (lightning strike)

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Chapter 52 - Pulmonary Embolism

SAMUEL Z. GOLDHABER

Pulmonary embolism (PE) and deep venous thrombosis (DVT) account for hundreds of thousands of hospitalizations annually in the United States and afflict millions of individuals worldwide. The future holds great promise as advances in molecular biology, diagnostic imaging, and therapy with low-molecular-weight heparin (LMWH) revolutionize our approach to venous thromboembolism. Nevertheless, despite progress in early detection and treatment, the rates of mortality (Fig. 52-1) and recurrent PE remain high.[1] As the population ages, venous thromboembolism will become more prevalent because the incidence of PE increases with age.[1]

Cardiovascular specialists must keep PE in mind when they evaluate patients with unexplained chest discomfort, shortness of breath, and lightheadedness because these symptoms constitute the cardinal clinical presentations for PE. They should implement streamlined diagnostic algorithms and use risk stratification to recommend the most appropriate therapeutic approach. Finally, cardiologists must provide expertise in the treatment of hemodynamically compromised patients with PE as well as those with right ventricular failure who maintain a stable blood pressure and heart rate.

Figure 52-1 Overall cumulative mortality due to PE in the International Cooperative Pulmonary Embolism Registry (ICOPER) of 2454 patients was 11.4 percent at 2 weeks and 17.4 percent at 3 months. After exclusion of patients in whom PE was first discovered at autopsy, the mortality rate was 15.3 percent. *(From Goldhaber SZ, Visani L, De Rosa M, for ICOPER: Acute pulmonary embolism: Clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 353:1386, 1999.*

PATHOPHYSIOLOGY

Hypercoagulable States

In 1856, Rudolf Virchow postulated that a triad of factors leads to intravascular coagulation: (1) local trauma to the vessel wall, (2) hypercoagulability, and (3) stasis. Classically, the pathogenesis of PE was dichotomized as due to either unusual "inherited" (primary) or commonly "acquired" (secondary) risk factors. Now, however, it appears likely that many patients who develop PE are genetically predisposed (Tables 52-1 and 52-2) but often require a precipitating environmental stress (Table 52-3) to elicit overt thrombosis.[2]

TABLE 52-1 -- PRINCIPAL HYPERCOAGULABLE STATES ASSOCIATED WITH VENOUS THROMBOSIS

HYPERCOAGULABLE STATE	CITATION	COMMENTS
Mutation in factor V gene	Bertina et al[3]	Replaces arginine 506 with glutamine, rendering factor V resistant to inactivation by activated protein C
	Ridker et al[5]	
Resistance to activated protein C	Zoller et al[11]	Molecular background for resistance to activated protein C was found to be heterogeneous
Prothrombin gene mutation	Poort et al[9]	G20210A point mutation increases prothrombin levels
Mutation in protein C gene	Allaart et al[12]	Associated with protein C deficiency
Protein S deficiency	Gladson et al[13]	Protein S a cofactor for protein C
Antithrombin III deficiency	Bucciarelli et al[14]	Autosomal dominant inheritance; has a higher risk for venous thrombosis than the other genetic defects
Hyperhomocysteinemia	den Heijer et al[15]	Doubles or triples risk[15] [15A] ; potentiates risk from underlying factor V Leiden[16]
	Langman et al[15A]	

Antiphospholipid antibodies	Ridker et al[16] Greaves [17]	Encompasses anticardiolipin antibodies and lupus anticoagulant; associated with venous and arterial thrombosis

TABLE 52-2A -- FREQUENCY OF CLASSIC COAGULATION PROTEIN DEFICIENCIES AMONG PATIENTS WITH VENOUS THROMBOSIS

ABNORMAL	GLADSON ET AL[13] (N = 141)(%)	HEIJBOER ET AL[18] (N=277)(%)	MALM ET AL[19] (N=439)(%)
Protein C	4	3	2
Protein S	5	2	2
Antithrombin III	3	1	1
Plasminogen	2	1	0.5

TABLE 52-2B -- FREQUENCY OF ACTIVATED PROTEIN C RESISTANCE AMONG PATIENTS WITH VENOUS THROMBOSIS

ABNORMALITY	SVENSSON AND DAHLBACK [20] (N = 104)(%)	KOSTER ET AL[21] (N = 301)(%)
Activated protein C resistance	33	21

PRIMARY HYPERCOAGULABLE STATES (see also Chap. 62).

The identification of a poor anticoagulant response to activated protein C (aPC) is the most exciting and far-reaching development ever to occur in the field of prothrombotic markers. Normally, a specified amount of aPC can be added to plasma and prolongation of the activated partial thromboplastin time (PTT) can be observed. However, patients with "aPC resistance" have inadequate PTT prolongation. In contrast to classical coagulation protein deficiencies, which are rare (Table 52-2) .*A*, aPC resistance occurs frequently among patients with venous thrombosis (Table 52-2) *B*.

The phenotype of aPC resistance is associated with a single point mutation, designated factor V Leiden, in the factor V gene.[3] This mutation results from a single nucleotide substitution of adenine for guanine 1691 that replaces the amino acid arginine with glutamine at position 506. This change eliminates the protein C cleavage site in factor

V.[4]

The allelic frequency of this mutation is about 3 percent in healthy male physicians in the United States. In the Physicians' Health Study, no statistically significant differences were found between the incidence of the mutation among previously healthy men who subsequently developed myocardial infarction or stroke compared with men who remained free of cardiovascular disease. However, the incidence of the factor V mutation was three times higher among men who developed DVT.[5]

In a case-control study of premenopausal women who developed DVT, the risk of thrombosis among users of oral

TABLE 52-3 -- ACQUIRED CONDITIONS THAT MAY PRECIPITATE VENOUS THROMBOSIS

Surgery/immobilization/trauma
Obesity
Increasing age
Cigarette smoking
Systemic arterial hypertension
Oral contraceptives/pregnancy/postpartum
Cancer (sometimes occult adenocarcinoma) and cancer chemotherapy
Stroke/spinal cord injury
Indwelling central venous catheter

contraceptives was increased fourfold. However, the risk of thrombosis among carriers of the factor V Leiden mutation was eightfold that of noncarriers. Among patients with both oral contraceptive use and the mutation, the risk of thrombosis was increased more than 30-fold.[6] The factor V Leiden mutation is also a risk factor for recurrent pregnancy loss[7] and in the Physicians' Health Study is associated with a fourfold increased risk of *recurrent* PE or DVT after completion of a course of anticoagulation.[8]

However, in a cohort of patients with venous thromboembolism in Rome and Milan, the risk of recurrent thrombosis after discontinuing anticoagulation was similar among carriers of factor V Leiden and patients without this mutation.[8A] Furthermore, the prevalence of the factor V Leiden mutation appears to be twice as high in patients with DVT compared with patients with PE. Some investigators speculate that the mutation confers an increased stability and adherence of thrombus to the vein wall, thereby decreasing the frequency of embolization to the lungs.[8B]

A single-point mutation in the 3
untranslated region of the prothrombin gene (G-to-A transition at nucleotide position 20210) is associated with increased levels of prothrombin.[9] In the Physicians' Health Study, the prevalence of the prothrombin gene mutation among control subjects was 3.9 percent, and this G20210A mutation doubled the risk of venous thrombosis.[10] Women

with both factor V Leiden and the G20210A prothrombin-gene mutation have a disproportionately high risk of DVT or PE.[10A] Recently, high levels of coagulation factor XI have been described as doubling the risk of venous thrombosis.[10B]

Although molecular medicine can help elucidate pathogenesis, a careful family history is still the most rapid and cost-effective method of identifying a predisposition to venous thrombosis. Investigation with blood tests (see Table 52-1) to detect a hypercoagulable state can be misleading. For example, consumption coagulopathy due to venous thrombosis may be misdiagnosed as deficiency of antithrombin III, protein C, or protein S. Heparin administration can depress antithrombin III levels, and use of warfarin ordinarily causes a mild deficiency of protein C or S. Both oral contraceptives and pregnancy depress protein S levels.

ACQUIRED CONDITIONS THAT MAY PRECIPITATE VENOUS THROMBOSIS.

Conditions that increase venous stasis or cause endothelial damage (see Table 52-3) are likely to predispose toward venous thrombosis, especially among patients who already have subclinical hypercoagulable states. Even minor events such as travel and minor surgery increase the venous thromboembolism risk.[21A]

The stasis and immobilization associated with postoperative venous thrombosis may increase after hospital discharge, because many patients who are forced to ambulate during hospitalization may become confined to bed on returning home. PE is increasingly likely to occur *after* hospital discharge because of the contemporary emphasis on minimizing the length of stay after surgery. Among 45,000 total hip and total knee replacement operations in a State of California data base, the diagnosis of venous thromboembolism was made after hospital discharge in 76 percent and 47 percent of the total hip and total knee replacement operations, respectively. The median interval until diagnosis was 17 days for total hip and 7 days for total knee replacements.[22]

Coronary artery bypass grafting has been associated with a 4 percent risk of PE [23] and a 20 percent risk of venous thrombosis of the deep leg veins.[24] After *major trauma,* the DVT rate was 58 percent in a prospective study in which contrast venograms were obtained.[25] Among immobilized *patients in a medical intensive care unit,* the rate of venous thrombosis detected with ultrasonography was 33 percent.[26]

OTHER RISK FACTORS FOR PULMONARY EMBOLISM

Marked obesity in women was a strong risk factor for PE in both the Framingham Heart Study[27] and the Nurses' Health Study. [28] Other environmental risk factors for PE in the Nurses' Health Study were *cigarette smoking* and systemic arterial *hypertension.*[28]

With respect to *oral contraceptives,* decreasing the estrogen content has diminished the

risk of venous thromboembolism. However, third-generation oral contraceptives with the new progestogens, desogestrel and gestodene, are problematic, with an approximate doubling in thrombotic risk even though they are less androgenic, have less effect on carbohydrate and lipid metabolism, and may have stronger suppression of ovarian activity than second-generation oral contraceptives.[29] They appear to cause an acquired resistance to aPC.[30]

Even the low dose of estrogen prescribed for *postmenopausal hormone replacement* doubles the risk of PE.[31] The risk is increased for *raloxifene,* a selective estrogen receptor modulator, [32] as well as for the more commonly used conjugated equine estrogens.

PE is the leading cause of maternal mortality during *pregnancy.* Antenatal DVT is usually left sided, involves the iliofemoral system, and occurs about twice as frequently as postpartum DVT. Increasing age and cesarean section are major risk factors for venous thromboembolism.[33] Conversely, women with serious obstetrical complications have an increased incidence of genetic mutations predisposing them to venous thrombosis.[34]

Cancer promotes the synthesis and secretion of procoagulants and is a risk factor for PE; conversely, venous thromboembolism may be the initial manifestation of an otherwise occult cancer. In a Danish registry, there was a threefold increase in cancer diagnoses during the initial 6 months after DVT or PE became evident. The cancers were often widely metastatic at the time of discovery, and the most frequent cancers were pancreatic, ovarian, primary hepatic, and brain.[35]

Patients receiving chemotherapy for metastatic breast cancer are at risk of developing venous thromboembolic disease. In a randomized controlled trial of very low-dose warfarin versus placebo, 4 percent of the placebo group developed venous thrombosis during the average 6-month follow-up period.[36]

Leg DVT is a common complication of *acute ischemic stroke,* particularly in the paralyzed limb. Even when patients receive 5000 units twice daily of unfractionated heparin for prophylaxis, the venous thrombosis rate is as high as 31 percent.[37] With *spinal cord injury,* there is also a high rate of venous thrombosis.[38]

Thrombotic complications due to indwelling central venous catheters are common and are often associated with catheter sepsis.[39] Indwelling vascular catheters can become engulfed ln a thrombin or fibrin sheath that serves as a nidus for subsequent infection.

RELATIONSHIP BETWEEN DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM.

Most PE result from thrombi that originate in the pelvic or deep veins of the leg; occasionally, thrombi in the axillary or subclavian veins embolize to the pulmonary arteries. In a treatment trial of proximal leg DVT, Moser and colleagues found that nearly 40 percent of patients had asymptomatic PE, based on concomitantly obtained ventilation-perfusion scans.[40] There is also an appreciable risk of asymptomatic PE due

to upper-extremity thrombosis.[41] However, many patients with PE do not have detectable DVT.[42]

When venous thrombi detach from their sites of formation, they flow through the venous system toward the pulmonary arterial circulation. If an embolus is extremely large, it may lodge at the bifurcation of the pulmonary artery, forming a saddle embolus (Fig. 52-2 *top*). More commonly, a major pulmonary vessel is occluded (Fig. 52-2 *bottom*).

RIGHT VENTRICULAR DYSFUNCTION.

The extent of pulmonary vascular obstruction is probably the most important factor determining whether right ventricular dysfunction ensues. As obstruction increases, pulmonary artery pressures rise. Moreover, the release of vasoconstricting compounds (e.g., serotonin), reflex pulmonary artery vasoconstriction, and hypoxemia may further increase pulmonary vascular resistance and result in pulmonary hypertension.[43]

VENTRICULAR INTERDEPENDENCY.

The sudden rise in pulmonary artery pressure reflects an abrupt increase in right ventricular afterload, with consequent elevation of right ventricular wall tension followed by right ventricular dilatation and dysfunction (Fig. 52-3) . [44] As the right ventricle dilates, the interventricular septum shifts toward the left ventricle, with resultant underfilling of this chamber due to

Figure 52-2 *Top,* Saddle embolus (arrow) at the bifurcation of the pulmonary artery. *Bottom,* Pulmonary embolus in left lower lobe pulmonary artery, with minimal attachment to the wall of the vessel. The embolus was dark red, typical of venous thrombi, and had indentations believed to represent impressions of the venous valves (arrows). *(From Godleski JJ: Pathology of deep venous thrombosis and pulmonary embolism. In Goldhaber SZ [ed]: Pulmonary Embolism and Deep Venous Thrombosis. Philadelphia, WB Saunders, 1985, p 17.)*

pericardial constraint.[45] In addition, right ventricular contractile dysfunction may decrease right ventricular cardiac output and further reduce left ventricular preload. As the right ventricle distends, coronary venous pressure increases and left ventricular diastolic distensibility decreases.[46]

The reduction in left ventricular preload may also lead to interventricular septal shift toward the left ventricle. With underfilling of the left ventricle, both systemic cardiac output and pressure decrease, potentially compromising coronary perfusion and producing myocardial ischemia, with release of troponin.[47] Elevated right ventricular wall tension following massive PE reduces right coronary flow and increases right ventricular myocardial oxygen demand, which may result in ischemia and possibly cardiogenic shock. Perpetuation of this cycle can lead to right ventricular infarction, circulatory collapse, and death.

Figure 52-3 Pathophysiology of right ventricular dysfunction. PA = pulmonary artery; RV = right ventricle; LV = left ventricle.

SUMMARY OF PATHOPHYSIOLOGY.

PE can have the following pathophysiological effects: (1) increased pulmonary vascular resistance due to vascular obstruction, neurohumoral agents, or pulmonary artery baroreceptors; (2) impaired gas exchange due to increased alveolar dead space from vascular obstruction and hypoxemia from alveolar hypoventilation, low ventilation-perfusion units, and right-to-left shunting, as well as impaired carbon monoxide transfer due to loss of gas-exchange surface; (3) alveolar hyperventilation due to reflex stimulation of irritant receptors; (4) increased airway resistance due to bronchoconstriction; and (5) decreased pulmonary compliance due to lung edema, lung hemorrhage, and loss of surfactant.[43]

DIAGNOSIS

Diagnosis of PE is more difficult than treatment or prevention. For patients with PE, the most dangerous period is that preceding the establishment of the correct diagnosis. Fortunately, reliable noninvasive diagnostic approaches have become increasingly available--particularly venous ultrasound, plasma D-dimer enzyme-linked immunosorbent assay (ELISA) chest computed tomography (CT) scanning, and echocardiography. The contemporary diagnostic strategy integrates clinical findings with various diagnostic techniques.[47A]

Clinical Presentation

Clinical suspicion of PE is of paramount importance in guiding diagnostic testing. Dyspnea is the most frequent symptom, and tachypnea is the most frequent sign of PE (Table 52-4) . In general, severe dyspnea, syncope, or cyanosis portends a major life-threatening PE. However, pleuritic pain often signifies that the embolism is small and located in the distal pulmonary arterial system, near the pleural lining.

PE should be suspected in hypotensive patients when (1) there is evidence of venous thrombosis or predisposing factors for it and (2) there is clinical evidence of acute cor pulmonale (acute right ventricular failure) such as distended neck veins, an S_3 gallop, a right ventricular heave, tachycardia, or tachypnea, especially if (3) there are echocardiographic findings of right ventricular dilatation and hypokinesis or electrocardiographic (ECG) evidence of acute cor pulmonale manifested by a new S_1 -Q_3 -T_3 pattern, new incomplete right bundle branch block, or right ventricular ischemia.

DIFFERENTIAL DIAGNOSIS.

The differential diagnosis of PE is broad and covers a spectrum from life-threatening disease such as acute myocardial infarction to innocuous anxiety states (Table 52-5) . Some patients have concomitant PE and other illnesses. Therefore, for example, if pneumonia or heart failure does not respond to appropriate therapy, the possibility of coexisting PE should be considered.

Distinguishing between PE and primary pulmonary hypertension (see Chap. 53) deserves special vigilance (Table 52-6) . Surprisingly, some patients have a hybrid condition that is similar to primary pulmonary hypertension but that includes thrombi. Among these patients, large central pulmonary artery thrombi can develop.[47B] It is often impossible

TABLE 52-4 -- MOST COMMON SYMPTOMS AND SIGNS AMONG THE 2454 PATIENTS IN THE INTERNATIONAL COOPERATIVE PULMONARY EMBOLISM REGISTRY (ICOPER)

SYMPTOM OR SIGN	PERCENT
Dyspnea	82
Respiratory rate >20/min	60
Heart rate >100 beats/min	40
Chest pain	49
Cough	20
Syncope	14
Hemoptysis	7

Adapted from Goldhaber SZ, Visani L, De Rosa M, for ICOPER: Acute pulmonary embolism: Clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 353:1386, 1999.Congestive heart failure ("left-sided")

TABLE 52-5 -- DIFFERENTIAL DIAGNOSIS OF PULMONARY EMBOLISM

Myocardial infarction
Pneumonia
Congestive heart failure ("left-sided")
Cardiomyopathy (global)
Primary pulmonary hypertension

Asthma
Pericarditis
Intrathoracic cancer
Rib fracture
Pneumothorax
Costochondritis
"Musculoskeletal pain"
Anxiety

to determine whether these thrombi formed in situ or whether they embolized to the pulmonary arteries from a separate site.

Clinical Syndromes of Pulmonary Embolism

Classification of PE into various syndromes (Table 52-7) is useful for prognostication and for deciding on subsequent clinical management.[48]

MASSIVE PULMONARY EMBOLISM.

Patients with massive PE are at risk for cardiogenic shock. They have thrombosis often affecting at least half of the pulmonary arterial system. Clot is almost always present bilaterally. Dyspnea is usually the cardinal symptom, and systemic arterial hypotension requiring pressor support is the predominant sign.

MODERATE TO LARGE PULMONARY EMBOLISM.

These patients have right ventricular hypokinesis on echocardiography but normal systemic arterial pressure. Usually, lung scanning indicates that more than 30 percent of the lung is not perfused. These patients have various degrees of right ventricular hemodynamic instability that is masked by normal systemic arterial pressure. They may be at risk for recurrent (and possibly fatal) PE, even with adequate anticoagulation.[49] Therefore, especially if right ventricular dysfunction persists, one should consider using thrombolytics or embolectomy.

TABLE 52-6 -- PRIMARY PULMONARY HYPERTENSION (PPH) VS. RECURRENT PULMONARY EMBOLISM (PE)

SIMILARITIES	
Symptoms	Fatigue, dyspnea on exertion--most common; chest pain, syncope, hemoptysis, cyanosis--also common
Clinical course	Progressive dyspnea, right-heart failure
Hemodynamics	Elevated right-heart pressures, normal pulmonary capillary wedge pressure

Histology	Thrombotic lesions usually present
Treatment	Includes anticoagulation

DIFFERENCES Variable	PPH	Recurrent PE
Age (years)	20-40	>50
Female/male ratio	4:1	1:1
Clinical course	Continued deterioration	Deterioration, with intermittent stabilization
Perfusion lung scan	No segmental perfusion defects	Segmental or larger perfusion defects
Pulmonary artery systolic pressure	>60 mm Hg	<60 mm Hg
Pulmonary angiogram	"Pruning"	Intraluminal filling defects
Confounding problems with angiogram	Thrombi may occur on or distal to PPH lesions	"Pruning" can also suggest PE
Diagnostic alternatives	Lung biopsy	Pulmonary angioscopy
Therapy	Anticoagulation; high-dose nifedipine or diltiazem; long-term continuous intravenous prostacyclin	Anticoagulation; inferior vena caval interruption; thromboendarterectomy

Adapted from Goldhaber SZ: Strategies for diagnosis. In Goldhaber SZ (ed): Pulmonary Embolism and Deep Vein Thrombosis. Philadelphia, WB Saunders, 1985, p 89.

SMALL TO MODERATE PULMONARY EMBOLISM.

This syndrome is characterized by both normal systemic arterial pressure and normal right ventricular function. Patients usually have a good prognosis if anticoagulation or an inferior

TABLE 52-7 -- SIX SYNDROMES OF ACUTE PULMONARY EMBOLISM

SYNDROME	PRESENTATION	RIGHT VENTRICULAR DYSFUNCTION	THERAPY

Massive	Breathelessness, syncope, and cyanosis with persistent systemic arterial hypotension; typically >50 percent obstruction of pulmonary vasculature	Present	Heparin plus thrombolytic therapy or mechanical intervention
Moderate to large	Normal systemic arterial blood pressure; typically >30 percent perfusion defect on lung scan	Present	Heparin plus or minus thrombolytic therapy or mechanical intervention*
Small to moderate	Normal arterial blood pressure	Absent	Heparin
Pulmonary infarction	Pleuritic chest pain, hemoptysis, pleural rub, or evidence of lung consolidation; typically small peripheral emboli	Rare	Heparin and nonsteroidal antiinflammatory drugs
Paradoxical embolism	Sudden systemic embolic event such as stroke	Rare	Anticoagulation ± closure of right-to-left cardiac shunt
Nonthrombotic embolism	Most commonly air, fat, tumor fragments, or amniotic fluid	Rare	Supportive

Adapted from Goldhaber SZ: Treatment of acute pulmonary embolism. In Goldhaber SZ (ed): Cardiopulmonary Diseases and Cardiac Tumors. In Braunwald E (series ed): Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 7.1-7.12.T wave inversion in leads III and aV_F or in leads V_1 -V_4

*Therapy depends on degree of impairment of right ventricular function and presence or absence of contraindications to thrombolysis or heparin.

vena caval (IVC) filter is used to prevent recurrent PE.

PULMONARY INFARCTION.

This syndrome is characterized by unremitting chest pain, occasionally accompanied by hemoptysis. The embolus usually lodges in the peripheral pulmonary arterial tree, near the pleura and close to the diaphragm.[50] Tissue infarction usually occurs 3 to 7 days

after embolism. The syndrome at that time often includes fever, leukocytosis, and chest radiological evidence of infarction.

PARADOXICAL EMBOLISM.

This syndrome often presents with a sudden, devastating stroke and concomitant PE. Patients often have abnormally elevated pulmonary arterial pressure with a patent foramen ovale evident on echocardiography.[51] Among patients suspected of having paradoxical embolism, occult leg vein thrombosis is frequently present and often is confined to the calves.[52]

NONTHROMBOTIC PULMONARY EMBOLISM.

Sources of embolism other than thrombus are less commonly detected than thrombotic PE. Fat embolism syndrome is most often observed after blunt trauma complicated by long-bone fractures.[53] Among patients with cancer, tumor embolism is more difficult to diagnose clinically than thrombotic PE because presenting symptoms and signs are similar in both conditions.[54] Gas embolism,[54A] particularly air embolus, can occur during placement or removal of a central venous catheter.[55] It has also been described as resulting from presumed inadvertent pressure placed on a partially empty plastic intravenous infusion bag.[56]

Intravenous drug abusers tend inadvertently to inject various substances that contaminate their drug supply. Materials commonly found at autopsy include hair, talc, and cotton. These patients are also susceptible to septic PE, which may be accompanied by endocarditis of the tricuspid or pulmonic valves.

Nonimaging Diagnostic Methods

PLASMA D-DIMER ELISA.

This is the most promising blood test for pulmonary embolism screening. An abnormally elevated level of *ELISA-determined plasma D-dimer* has more than 90 percent sensitivity for identifying patients with PE proven by lung scan[57] or by angiogram.[58] This test relies on the principle that most patients with PE have ongoing endogenous fibrinolysis that is not effective enough to prevent PE but that does break down some of the fibrin clot to D-dimers. These D-dimers can be assayed by monoclonal antibodies in commercially available kits.

Although elevated plasma concentrations of D-dimers are sensitive for the presence of PE, they are not specific. Levels are elevated in patients for at least 1 week postoperatively and are also increased in patients with myocardial infarction, sepsis, cancer, or almost any other systemic illness.[58A] Therefore the plasma D-dimer ELISA is best used in patients who have suspected PE but no coexisting acute systemic illness.

In the past, plasma D-dimer ELISA was a cumbersome test, especially for emergency use. It was designed, like many ELISAs, to be run in batches; furthermore, skilled

technologists were needed to run daily controls and to process the samples. A rapid, individual, and quantitative automated D-dimer ELISA has been validated[59] and approved for use in clinical laboratories. The analytical procedure is straightforward, and turnaround time should be less than 1 hour. This advance in technology promises to expedite the screening of patients with suspected PE.

ARTERIAL BLOOD GASES.

Among patients who were suspected of having PE and who underwent angiography in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) (see p. 1893), determination of the Pa_{O_2} did not discriminate between those with and without PE. There

TABLE 52-8 -- ELECTROCARDIOGRAPHIC FINDINGS IN PULMONARY EMBOLISM

Incomplete or complete right bundle branch block
S in lead I and aV_L > 1.5 mm
Transition zone shift to V_5
Qs in leads III and aV_F but not in lead II
QRS axis > 90 degrees or indeterminate axis
Low limb lead voltage
T wave inversion in leads III and aV_F or in leads V_1 -V_4

Modified from Sreeram N, Cheriex EC, Smeets JLRM, et al: Value of the 12-lead electrocardiogram at hospital admission in the diagnosis of pulmonary embolism. Am J Cardiol 73:298, 1994.

was no difference between the average Pa_{O_2} (70 mm Hg) among patients with PE compared with those without PE (72 mm Hg) at angiography. Importantly, among patients with angiographically proven PE who had no prior cardiopulmonary disease, the Pa_{O_2} was more than or equal to 80 mm Hg in 26 percent.[60] Furthermore, normal values of the alveolar-arterial oxygen gradient did not preclude the diagnosis of acute PE.[61] Therefore, arterial blood gas determinations should not be part of the diagnostic strategy when investigating suspected PE.

ELECTROCARDIOGRAM.

An ECG is useful not only to help preclude acute myocardial infarction but also for rapidly identifying some patients with large PE, who may have ECG manifestations of right-heart strain. In a series of 49 consecutive patients with subsequently proven PE, at least three of seven ECG features suggestive of right ventricular overload (Table 52-8) were identified on 76 percent of ECGs obtained at hospital admission.[62]

IMPEDANCE PLETHYSMOGRAPHY.

This is a very indirect approach to DVT diagnosis; it measures changes in electrical resistance caused by obstruction to venous outflow. Impedance plethysmography (IPG) should not be used routinely to detect DVT. In a study of consecutive patients with suspected DVT who underwent both IPG and contrast venography, IPG failed to identify 35 percent of patients with proximal leg DVT.[63]

Imaging Methods

CHEST ROENTGENOGRAPHY.

The chest radiograph is usually the first imaging study obtained in patients with suspected PE. Although more than half of patients with PE have an abnormal chest film examination, a near-normal radiograph in the setting of severe respiratory compromise is highly suggestive of massive PE. Classical chest film abnormalities are uncommon but include focal oligemia (Westermark's sign) (Fig. 52-4) , indicating massive central embolic occlusion.[64] A peripheral wedge-shaped density above the diaphragm (Hampton's hump) (Fig. 52-5) usually indicates pulmonary infarction.[65] In PIOPED, patients with PE and either a prominent central pulmonary artery or cardiomegaly had higher pulmonary arterial mean pressures than did patients with atelectasis, a pulmonary parenchymal abnormality, or pleural effusion.[66]

One should always search for subtle abnormalities such as distention of the descending right pulmonary artery. The vessel often tapers rapidly after the enlarged portion. The chest radiograph can also help to identify patients with diseases that can mimic PE, such as lobar pneumonia or pneumothorax. Patients with these latter illnesses can also have concomitant PE.[67]

VENOUS ULTRASONOGRAPHY.

The primary diagnostic criterion to establish the presence of DVT by ultrasonography is the loss of vein compressibility (Fig. 52-6) . Normally, the vein collapses completely when gentle pressure is applied to the skin overlying it. Upper extremity DVT may be more difficult to diagnose because the clavicle can

Figure 52-4 *A,* Chest film of a patient with clinical signs of pulmonary embolism; marked oligemia (Westermark's sign) is seen in the entire right lobe. *B,* Arteriogram from the same patient shows massive saddle embolus in the right main pulmonary artery (arrow). *(Courtesy of Dr. Jack L. Westcott, The New*

York Hospital and Cornell University Medical College.)

hinder attempts to compress the subclavian vein. With acute DVT of either the upper extremity or leg, there is associated passive dilation of the vein.[68]

As many as half of patients with PE have no imaging evidence of DVT.[42] Therefore, if clinical suspicion of PE is high, patients without evidence of DVT should still be investigated for PE. For detection of DVT, ultrasound examination is more accurate than IPG.[69]

Ultrasonography is usually reliable in diagnosing proximal leg DVT in *symptomatic outpatients.*[70] The presence of newly detected DVT may sometimes be a useful surrogate for PE. At selected centers with special expertise, ultrasonography may also be dependable for evaluating suspected symptomatic infrapopliteal DVT.[71] Serial ultrasound measurement of thrombus mass after an episode of acute DVT may allow subsequent correct identification of recurrent DVT.[72] Unfortunately, ultrasonography may yield disappointing results when screening *asymptomatic patients* with possible DVT after orthopedic surgery[73] or after craniotomy.[74]

NUCLEAR VENOGRAPHY.

In 1998, the Food and Drug Administration (FDA) approved technetium-99m-apcitide (AcuTect; Diatide, Inc; Londonderry, NH) for the diagnosis of acute leg DVT. A complex of the synthetic peptide apcitide and the radionuclide technetium binds preferentially to the glycoprotein IIb/IIIa receptors found on activated platelets. This diagnostic modality may be complementary to ultrasonography and provide information on pelvic vein thrombosis (not ordinarily imaged by ultrasound), acute DVT superimposed on chronic DVT (not well differentiated by ultrasound), and acute DVT when the ultrasound examination is technically limited owing to body habitus or ambiguous

Figure 52-5 Posteroanterior chest film of a patient with pulmonary embolism shows a "Hampton's hump" in the right lower lung field, a homogeneous, wedge-shaped density in the peripheral field, convex to the hilum. *(Courtesy of Dr. Jack L. Westcott, The New York Hospital and Cornell University Medical College.)*

findings. However, broad clinical experience with this technique has not yet been realized.

CONTRAST PHLEBOGRAPHY.

Although contrast phlebography has traditionally been considered the gold standard for DVT diagnosis,[75] venograms are now being obtained with less frequency because of the widespread availability, convenience, and generally excellent results with ultrasonography. Venography is costly and invasive and occasionally results in contrast allergy or contrast-induced phlebitis. Furthermore, there is considerable disagreement in the interpretation of contrast venograms among experienced readers.[76] Patients with

massive leg DVT often have nondiagnostic venograms because the contrast agent simply cannot reach the totally obstructed deep leg veins. Consequently, we reserve contrast phlebography for situations in which the ultrasound findings are equivocal or, alternatively, when the ultrasound examination result is normal despite a high clinical suspicion for DVT.

LUNG SCANNING.

Although lung scanning remains the principal diagnostic imaging test when PE is suspected, there is increasing dissatisfaction with this approach because the majority of scans do not provide definitive results. Perfusion scintigraphy uses radiolabeled aggregates of albumin or microspheres that are trapped in the pulmonary capillary bed. Six standard views are obtained with a gamma camera. Patients with large PE may have many defects on the perfusion scan. If ventilation scanning is performed on a patient who has PE but no intrinsic lung disease, a normal ventilation study result is expected, yielding a ventilation-perfusion mismatch (Fig. 52-7) and a lung scan interpreted as "high probability for PE."

The utility of the ventilation scan has undergone intense

Figure 52-6 Right common femoral vein (RT CFV) thrombosis (transverse view) diagnosed by compression ultrasonography. The left half of the image is the baseline ultrasound examination demonstrating the artery (A) superior to the vein (V). During the examination, the artery can be seen to pulsate and appears to wink at the examiner. The vein is typically larger than the artery but normally is not severalfold larger. With compression (COMP) in the right half of the image, the artery is deformed (curved upper arrows), but the vein fails to compress (straight lower arrows).

Figure 52-7 A 41-year-old woman presented with sudden onset of shortness of breath and retrosternal chest discomfort. Her heart rate was 168 beats/min, respiratory rate 32/min, oxygen saturation 86 percent, and blood pressure 112/70 mm Hg. She underwent a ventilation (*right panel*)-perfusion (*left panel*) lung scan with xenon-133 gas (26 mCi) and technetium-99m macroaggregated albumin (3.2 mCi) in the left posterior oblique position. Numerous scattered segmental (arrows) and subsegmental perfusion defects with near normal ventilation were found. This ventilation-perfusion mismatch was interpreted as high probability for pulmonary embolism.

scrutiny. [76A] In the PIOPED, the ventilation scan was of questionable incremental benefit in establishing or precluding the diagnosis of PE.[77] The European Cardiology Society's Working Group on Thrombosis and Platelets plans to declare that a ventilation scan is no more useful than a chest radiograph for interpretation of perfusion lung scans.

PE is very unlikely in patients with normal and near-normal scans.[78] High-probability

scans usually indicate acute PE, but fewer than half of patients with PE have a high-probability scan (Table 52-9) . Scans that fall between these extremes of the spectrum should be called intermediate probability.[79] Many patients with low-probability scans but high clinical suspicion for PE do, in fact, have PE at angiography (Table 52-10) . Therefore the term *low-probability* scan is a potentially lethal misnomer.[80]

CHEST COMPUTED TOMOGRAPHY.

Chest CT is being used with increasing frequency as the initial imaging test in patients with suspected PE (Fig. 52-8) . Chest CT is beginning to supplant lung scans because the chest CT result usually is not equivocal. Thrombus is either present or absent, without any "intermediate" or "indeterminate" probability of PE. For patients with intrinsic lung disease and abnormal chest radiograph results, CT scan has the added benefit of potentially suggesting an alternative or concomitant pulmonary disease to explain the clinical presentation.

TABLE 52-9 -- PIOPED: PULMONARY EMBOLISM STATUS

	CLINICAL PROBABILITY (%)			
	80-100 No. PE/PTs (%)	**20-79 No. PE/PTs (%)**	**0-19 No. PE/PTs (%)**	**All Probabilities No. PE/PTs (%)**
Scan category				
High	28/29 (96)	70/ 80 (88)	5/ 9 (56)	103/118 (87)
Intermediate	27/41 (66)	66/236 (28)	11/ 68 (16)	104/345 (30)
Low	6/15 (40)	30/191 (16)	4/ 90 (4)	40/296 (14)
Near-normal/normal	0/ 5 (0)	4/ 62 (6)	1/ 61 (2)	5/128 (4)
Total	61/90 (68)	170/569 (30)	21/228 (9)	252/887 (28)

PIOPED=Prospective Investigation of Pulmonary Embolism Diagnosis; PE=pulmonary embolism; PTs=patients.

80-100, 20-79, 0-19 represent the clinical probabilities of PE.

No. PE/PTS (%) represents the number and percentage of patients in each subgroup with PE.

From the PIOPED Investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA 263:2757, 1990.

TABLE 52-10 -- PIOPED: COMPARISON OF SCAN CATEGORY TO ANGIOGRAM FINDINGS

	PULMONARY EMBOLISM			NO ANGIOGRAM	TOTAL N
	Present	**Absent**	**Uncertain**		
Scan category					

High	102	14	1	7	124
Intermediate	105	217	9	33	364
Low	39	199	12	62	312
Near-normal/normal	5	50	2	74	131
Total	251	480	24	176	931

PIOPED=Prospective Investigation of Pulmonary Embolism Diagnosis.

From the PIOPED investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA 263:2756, 1990.

Figure 52-8 A 62-year-old physician suffered a massive pulmonary embolism 2 weeks after prostatectomy. Spiral chest CT with contrast provided a definitive diagnosis, with a large thrombus burden apparent in the right and left main pulmonary arteries (arrows).

The test requires injection of intravenous contrast but is accomplished quickly, while holding a single breath. Although excellent for central large PE, the examination is not reliable for precluding clinically important smaller PE in peripheral pulmonary arteries.[81] [81A]

MAGNETIC RESONANCE IMAGING.

Gadolinium-enhanced magnetic resonance (MR) angiography appears comparable to conventional contrast pulmonary angiography in preliminary studies.[82] Unlike standard angiography, MR does not require ionizing radiation or injection of iodinated contrast agent. MR can be performed safely in patients with poor renal function. The test itself imposes virtually no risk to the patient. Finally, MR pulmonary angiography can include assessment of ventricular function; therefore, MR testing can diagnose PE and image right and left ventricular size and pattern of contraction.

ECHOCARDIOGRAPHY (see Chap. 7).

Echocardiography is insensitive for the diagnosis of PE but is a rapid, practical, and sensitive technique for detection of right ventricular overload among patients with established and large PE (Fig. 52-9) . The frequency of echocardiographic signs of PE (Table 52-11) depends on the population being studied. For those patients in whom transthoracic imaging is unsatisfactory, transesophageal echocardiography can be carried out.[83]

Echocardiographic detection of right ventricular dysfunction at the time of presentation

with PE is useful for risk stratification and prognostication. Among patients with major PE, echocardiographic evidence of a patent foramen

TABLE 52-11 -- ECHOCARDIOGRAPHIC SIGNS OF PULMONARY EMBOLISM

Direct visualization of thrombus (rare)
Right ventricular dilatation
Right ventricular hypokinesis (with sparing of the apex)
Abnormal interventricular septal motion
Tricuspid valve regurgitation
Pulmonary artery dilatation
Lack of decreased inspiratory collapse of inferior vena cava

ovale signifies a high risk of death and paradoxical arterial thromboembolism.[84]

Right ventricular dilatation and hypokinesis may occur in chronic pulmonary hypertension due to any cause. Long-term elevation of right ventricular afterload is usually accompanied by right ventricular hypertrophy. In patients with chronic pulmonary hypertension, the velocity of the tricuspid regurgitant jet may be elevated to a greater level than in patients with acute PE and no underlying cardiopulmonary disease. Right ventricular infarction, cardiomyopathy, and right ventricular dysplasia may also result in right ventricular hypokinesis and dilatation on the echocardiogram. In these conditions, however, the velocity of tricuspid regurgitation is usually less than in acute PE.

It appears that right ventricular contractile dysfunction following PE has a distinct regional pattern in which wall excursion is hypokinetic from the base through the free

Figure 52-9 *A,* Parasternal short-axis views of the right ventricle (RV) and left ventricle (LV) in diastole (*left*) and systole (*right*). Diastolic and systolic bowing of the interventricular septum (arrows) into the LV is compatible with RV volume and pressure overload, respectively. The RV is appreciably dilated and markedly hypokinetic, with little change in apparent RV area from diastole to systole. PE = small pericardial effusion. *(From Come PC: Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. Chest 101:151S, 1992.) B,* Segmental RV free wall excursion (mean ± SEM) by centerline analysis in patients with acute pulmonary embolism (PE) or primary pulmonary hypertension (PPH) and in normal persons. The acute increase in afterload in PE results in regional RV dysfunction predominantly affecting the mid free wall as it assumes a more spherical shape to equalize wall stress. The RV apex is spared (McConnell's sign). In contrast, the chronic pressure overload of PPH results in more diffuse RV dysfunction, with limited shape change of the hypertrophied RV. *(From McConnell MV, Rayan ME, Solomon SD, et al: Echocardiographic diagnosis of acute pulmonary embolism: A distinct pattern of abnormal right ventricular wall motion. Am J Cardiol 78:469, 1996).*

wall but remains almost normal at the right ventricular apex (McConnell's sign) (Fig. 52-9 *B*) This pattern of right ventricular contractile dysfunction differs from the global dysfunction observed in primary pulmonary hypertension.[85] A possible explanation is that in PE, the left ventricle may tether the right ventricular apex, thereby preserving near-normal wall motion in this region.

PULMONARY ANGIOGRAPHY.

Standard contrast pulmonary angiography has been considered the gold standard for accurate in vivo diagnosis or exclusion of PE. With appropriate techniques and experience, it can be performed expeditiously and safely in most patients. Angiography is most useful when a diagnostic dilemma persists despite the use of noninvasive tests. This situation is most common when the diagnostic test results are negative or ambiguous in the presence of high clinical suspicion for PE. Pulmonary angiography is obviously also required when interventions are planned such as suction catheter embolectomy, mechanical clot fragmentation, or catheter-directed thrombolysis (discussed later).

PREPARATION OF THE PATIENT.

A history of allergy to contrast medium should be sought. If present, high-dose corticosteroids should be administered. Heparin can be discontinued immediately before the procedure, unless the clinical suspicion for PE is very high. Patients should avoid heavy meals for at least 4 hours before angiography.

THE ANGIOGRAPHIC PROCEDURE.

The perfusion lung scan serves as a road map to the angiographer, who performs selective angiography rather than injecting into the main pulmonary artery. Obtaining accurate and high-quality recordings of right-heart pressures and waveforms is of paramount importance. If the pressure tracing "dampens" or "wedges" in the proximal pulmonary artery, anatomically massive PE should be suspected before injection of contrast agent. If the pulmonary artery systolic pressure exceeds approximately 50 mm Hg, the differential diagnosis should include chronic PE or acute superimposed on chronic PE.

Our preferred approach is via the femoral vein, although brachial or internal jugular approaches are alternatives. The best means of identifying the correct level for puncture in the groin is with fluoroscopy; the skin incision site should be at the level of the upper region of the femoral neck. We prefer a single wall puncture to avoid the possibility of passing first through the femoral artery before entering the femoral vein. Once access has been obtained, a guidewire is inserted through the needle, and the needle is exchanged for either a pigtail catheter or a sheath with a side arm. To advance through the cardiac chambers and measure right heart pressures, we use either (1) a pigtail catheter with a tip deflector wire or (2) a Swan-Ganz catheter followed by exchange over a guidewire for a pigtail catheter. The pigtail catheter permits a high contrast

injection rate with considerable safety.

To carry out a complete diagnostic procedure, at least two views of each lung should be obtained. One view on each side should be the *ipsilateral posterior oblique* (approximately 45 degrees), and the other view can be either an *anteroposterior* view or the *ipsilateral anterior oblique* (approximately 45 degrees). Low-osmolar contrast medium is used because it does not cause the severe coughing that occurs with high-osmolar contrast medium and it gives a greater margin of safety among patients with elevated right-sided heart pressures. The contrast medium is injected usually at a rate of 20 to 25 ml/sec for 2 seconds. If the right-sided heart pressures are elevated, the rate of injection can be decreased, depending on the severity of the elevation. If the right ventricular end-diastolic pressure exceeds 20 mm Hg, consider superselective arteriography with a decreased rate and volume of contrast into the lobe that is most likely to yield a positive result.

We now perform all of our filming for pulmonary arteriography using digital acquisition. The filming rate is 7.5 frames/sec for 1 second before injection (to obtain mask images for digital subtraction), followed by 7.5 frames/sec for the first 3 seconds after the beginning of the injection. However, with digital subtraction, one should view the images in the unsubtracted mode, because subtraction may lead to artifacts that can simulate pulmonary emboli. After the initial rapid filming rate, the filming rate can be decreased to 1 to 2 frames/sec for approximately 5 seconds. If the foregoing views are nondiagnostic, selective magnification angiography (also acquired digitally) of any areas in question can be obtained. If these views do not lead to a diagnostic resolution, balloon occlusion arteriography may be performed.

INTERPRETING THE ANGIOGRAM.

A definitive diagnosis of PE depends on visualization in two projections of an intraluminal filling defect in a pulmonary arterial branch or cutoff of a branch with the visualized "tail" of the embolus. Secondary signs of PE reflect decreased perfusion and consist of abrupt occlusion (cutoff) of vessels, oligemia or avascularity of a segment, a prolonged arterial phase with slow filling and emptying of veins, and tortuous, tapering peripheral vessels.[86]

Not all pulmonary artery filling defects or occlusions are due to acute PE. In chronic PE, arteries may appear pouched, and thrombus appears organized with a concave edge. Bandlike defects called *webs* may be present, in addition to intimal irregularities and abrupt narrowing or occlusion of lobar vessels.[87] Other causes of intraluminal filling defects include pulmonary Takayasu's arteritis (see Chap. 40), angiosarcoma, and sarcoidosis.[67]

Overall Strategy: An Integrated Diagnostic Approach

A wide array of diagnostic tests is available for the investigation of suspected PE. Familiarity with each test's strengths and weaknesses (Table 52-12) as well as knowledge of the availability and reliability of specific tests at one's hospital will facilitate

a concise and streamlined work-up.

At Brigham and Women's Hospital, we are initiating an interdisciplinary protocol for patients who present to the emergency department with suspected PE (Fig. 52-10) . The initial assessment includes the history, physical examination, and ECG, with special attention to the patient's clinical milieu and risk factors for venous thromboembolism. Next we obtain a chest radiograph and a rapid plasma D-dimer ELISA. If both are nondiagnostic, then PE is exceedingly unlikely, and we consider the diagnosis excluded at that point. If either result is abnormal, the diagnostic work-up continues. Most patients then undergo lung scanning, despite its limitations. If the chest radiograph appears abnormal, however, the likelihood of a diagnostic lung scan is low, and we usually perform chest CT with contrast in our emergency department scanner in lieu of lung scanning. For those patients in whom the diagnosis is not clarified with lung scanning or chest CT, the next step is venous ultrasonography. If the result is normal and our clinical suspicion remains high, we usually proceed with contrast pulmonary angiography. We do not consider a low-probability lung scan and a nondiagnostic venous ultrasonogram of the leg to be sufficient to preclude PE in the presence of high clinical suspicion.[88]

Using a similar protocol, investigators collaborating in Geneva and Montreal evaluated 918 consecutive patients suspected of having PE or DVT. After 3 months of follow-up, only 2 percent developed clinical evidence of PE. Pulmonary angiography or contrast venography of the legs was required in only 6 percent of the entire cohort.[89]

MANAGEMENT

Rapid and accurate risk stratification is of paramount importance. Patients with PE present with a wide spectrum of illness, and appropriate care can range from prevention of recurrent PE (with anticoagulation alone or insertion of an IVC filter) to clot dissolution or removal with thrombolysis or embolectomy. Anticoagulation with LMWH is being used with increasing frequency as a bridge to full and therapeutic levels of warfarin.

Adjunctive measures include provision of supplemental oxygen and adequate pain relief, usually most effective with nonsteroidal antiinflammatory medications. Patients who appear toxic and hypoxic should be considered for prompt temporary mechanical ventilation. Those with impending hypotension or poor organ perfusion require rapid institution of an inotrope.

Dobutamine--a beta-adrenergic agonist with positive inotropic and pulmonary vasodilating effects (see Chapter 18) should be considered a first-line agent to treat right-sided heart failure and cardiogenic shock.[89A] In general, volume loading these patients is ill advised because ventricular interdependence can lead to even further reductions in

TABLE 52-12 -- ADVANTAGES AND DISADVANTAGES OF DIAGNOSTIC TESTS FOR SUSPECTED PULMONARY EMBOLISM

DIAGNOSTIC TEST	ADVANTAGES	DISADVANTAGES
Plasma D-dimer ELISA	A normal result makes PE exceedingly unlikely	Level is elevated in many systemic illnesses that mimic PE; unless a rapid assay is available, the turnaround time will be long
(ECG)	Universally available; may indicate acute cor pulmonale	Acute cor pulmonale on ECG is not specific for PE; not a sensitive test
Impedance plethysmography	Portable, inexpensive, easy to use	Inaccurate, with failure to detect major nonobstructive proximal DVT
Chest radiograph	Usually has minor abnormalities but occasionally pathognomonic; may suggest alternative diagnoses; may guide work-up toward chest CT rather than lung scan	Not specific
Venous ultrasonography	Excellent for detecting symptomatic proximal DVT; surrogate for PE	Cannot image iliac vein thrombosis; imaging of calf is operator dependent; DVT may have embolized completely, resulting in a normal result
Nuclear venography	Image pelvic and calf veins; differentiate acute versus chronic DVT	Limited experience with this test
Contrast venography	Used to be gold standard; excellent for calf veins	Can cause chemical phlebitis; uncomfortable; costly; may fail to diagnose massive DVT because veins are filled with thrombus and cannot be opacified
Lung scanning	Standard initial imaging test for PE; high-probability scans are reliable for detecting PE; normal/near-normal scans are reliable for precluding PE	Most scans are neither high probability nor normal/near-normal; ventilation scans are falling out of favor; most test results are equivocal
Chest CT	Excellent for PE in the proximal pulmonary arterial tree	Insensitive for important but distal PE
MRI	Excellent for anatomy and cardiac function	In preliminary use; not widely available; experience very limited

Echocardiography	Excellent for identifying right ventricular dilatation and dysfunction that is not obvious clinically, thus providing an early warning of potentially adverse outcome	Not specific; many patients with PE have normal echocardiograms; the test cannot reliably differentiate causes of right ventricular dysfunction
Pulmonary angiography	Considered the gold standard for diagnosis	Invasive, costly, uncomfortable

ELISA=enzyme-linked immunosorbent assay; PE=pulmonary embolism; ECG=electrocardiogram; DVT=deep vein thrombosis; CT=computed tomography; MRI=magnetic resonance imaging.

left ventricular output. For patients with pulmonary hypertension and a patent foramen ovale, inhaled nitric oxide may reverse right-to-left shunting and improve oxygenation.[90]

Figure 52-10 Pulmonary embolism diagnosis strategy: Overall integrated diagnostic approach. CXR = chest radiograph; ELISA = enzyme-linked immunosorbent assay; PA-GRAM = pulmonary arteriogram.

Prevention of Pulmonary Embolism and Deep Venous Thromboembolism

Heparin

UNFRACTIONATED HEPARIN (see also Chap. 62).

Standard, unfractionated heparin is a highly sulfated glycosaminoglycan that is partially purified from either porcine intestinal mucosa or bovine lung. Its molecular weight ranges from 3000 to 30,000 and averages 15,000. Heparin acts primarily by binding to antithrombin III (AT III), an enzyme that inhibits the coagulation factors thrombin (factor IIa), Xa, IXa, XIa, and XIIa. Heparin subsequently promotes a conformational change in AT III that accelerates its activity approximately 100- to 1000-fold.[91] This prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse clot that has already formed. However, heparin does *not* directly dissolve thrombus that already exists. The efficacy of heparin is limited because clot-bound thrombin is protected from heparin-antithrombin III inhibition.[92] Furthermore, heparin resistance can occur because unfractionated heparin binds to plasma proteins.[93]

LOW-MOLECULAR-WEIGHT HEPARINS (LMWHs).

LMWHs are fragments of unfractionated heparin that exhibit less binding to plasma proteins and endothelial cells than unfractionated heparin. Therefore, LMWHs have greater bioavailability, more predictable dose response, and longer half-life than unfractionated heparin.[94]

The introduction of LMWHs for treatment of venous thromboembolism is revolutionizing the management of DVT and PE, especially for the majority of patients who are hemodynamically stable. Many large randomized trials of patients with acute DVT have compared subcutaneously administered

LMWH with continuous intravenous unfractionated heparin as a bridge to full and therapeutic anticoagulation.[95] [96] [97] LMWH was at least as effective and safe as continuous intravenous unfractionated heparin.

A metaanalysis of randomized trials comparing 3674 patients with acute DVT receiving LMWH versus unfractionated heparin[98] demonstrated that LMWH reduced the mortality rate over 3 to 6 months of follow-up by 29 percent. The major bleeding complication rate was reduced by 43 percent. These data were used in a cost-effectiveness analysis that showed that LMWH is highly cost effective compared with unfractionated heparin for DVT management.[99]

The excellent bioavailability and subcutaneous administration of LMWH permit a strategy of weight-based LMWH dosing (without laboratory tests for dose adjustment in most instances) coupled with the possibility of outpatient therapy or an abbreviated hospitalization. With a concerted effort, it appears that the majority of ambulatory patients who present with DVT can be treated as outpatients,[100] as long as an infrastructure has been established to ensure close and meticulous follow-up.[101]

On December 31, 1998, the FDA approved outpatient treatment of DVT *without PE* using enoxaparin 1 mg/kg every 12 hours for a minimum of 5 days. Warfarin is usually begun on the first evening of therapy, and enoxaparin is continued until a stable and therapeutic INR of 2.0 to 3.0 is achieved. The dose of enoxaparin must be decreased in patients with renal insufficiency because LMWH is primarily renally excreted.

The FDA approved the same enoxaparin dosing regimen for inpatient treatment of DVT *with or without PE.* An alternative dosing regimen was also approved for the same indication: 1.5 mg/kg/24 hr of enoxaparin. However, there is less clinical experience with this dosing regimen.[102] Importantly, no trial of patients with symptomatic PE has attempted outpatient or abbreviated hospitalization with LMWH.[103]

MONITORING HEPARIN.

An activated PTT that is at least 1½times greater than the control value should provide a minimum therapeutic level of unfractionated heparin. However, there are many different PTT reagent kits and virtually no standardization of PTT levels.[104] Therefore, an individual hospital's target PTT range for anticoagulation with unfractionated heparin should correspond to a plasma anti-Xa level of approximately 0.4 to 1.0 units/ml. At Brigham and Women's Hospital, we assay the anti-Xa level with a HEPRN pack (Du

Pont) in the automated clinical analyzer used for other chemistry tests. This is a chromogenic assay based on the inhibition of factor X_a by heparin-activated antithrombin III.

The plasma anti-Xa level is particularly useful in three situations: (1) monitoring heparin anticoagulation among patients with baseline elevated PTTs due to a lupus anticoagulant or anticardiolipin antibodies, (2) monitoring heparin among DVT and PE patients who require large daily doses of heparin,[105] and (3) monitoring LMWH, which blunts the elevation in the PTT and in the activated clotting time that occurs with unfractionated heparin.

When LMWH is given for prophylaxis, it is administered in a fixed dose, with no or at most slight adjustments based on weight. However, when LMWH is given to achieve full and therapeutic levels of anticoagulation, the dose is based on weight. Ordinarily, no blood tests are needed to monitor LMWH. However, titration of LMWH is warranted for patients with massive obesity or for patients with renal insufficiency. In both circumstances, the dose of LMWH that is administered needs to be adjusted downward from the calculated weight-based dose.

In general, anticoagulation for prophylaxis can be achieved with an anti-factor Xa level of 0.2 to 0.4 units/ml. Full anticoagulation for therapy can be attained with an anti-factor Xa level of 0.4 to 1.0 units/ml. The level peaks approximately 3 hours after subcutaneous injection,[105] and an anti-factor Xa level is optimally obtained during the plateau phase, 4 to 6 hours after injection.[106]

For patients in whom warfarin therapy has failed or who cannot take warfarin (e.g., pregnant women), we treat with LMWH injected subcutaneously and usually teach self-administration.

INITIATING HEPARIN THERAPY.

Heparin is the cornerstone of treatment for acute PE. Before heparin therapy is begun, risk factors for bleeding should be considered, such as a prior history of bleeding with anticoagulation, thrombocytopenia, vitamin K deficiency, increasing age, underlying diseases, and concomitant drug therapy. The most frequently overlooked portion of the physical examination is a rectal examination for occult blood.

There is a transition toward the use of LMWH for patients who present with acute symptomatic PE, even though this approach is not FDA approved. The conventional treatment strategy uses unfractionated heparin, with an initial bolus of 5000 to 10,000 units, followed by a continuous intravenous infusion based on weight. Most patients require at least 30,000 units/24 hr. There are many nomograms, such as Raschke's,[107] to assist in adjusting the dose of continuous intravenous unfractionated heparin, with guidelines provided by the patient's weight and PTT. An automated heparin-delivery system has been described; it controls the PTT based on a computer-generated algorithm and relies on automated venous blood sampling.[108]

Unless a severe bleeding problem such as active gastrointestinal bleeding is detected, heparin can be started before lung scanning or pulmonary angiography. In cases of severe bleeding, heparin therapy should be withheld, and nonpharmacological treatment (secondary prevention) with insertion of an IVC filter should be considered if the diagnosis of PE is confirmed.

COMPLICATIONS.

The most important adverse effect of heparin is hemorrhage. Major bleeding during anticoagulation may unmask a previously silent lesion, such as bladder or colon cancer. For most cases of moderate bleeding, cessation of heparin will suffice, and the PTT usually returns to normal within 6 hours because the half-life of unfractionated heparin is only 60 to 90 minutes.

Resumption of heparin at a lower dose or implementing alternative therapy depends on the severity of the bleeding, the risk of recurrent thromboembolism, and the extent to which bleeding may have resulted from excessive anticoagulation. Risk factors for major in-hospital bleeding among anticoagulated patients include the presence of comorbid conditions, age greater than 60 years, the intensity of anticoagulation, concurrent medications, or liver dysfunction that worsens during treatment.[109]

In the event of life-threatening or intracranial hemorrhage, protamine sulfate can be administered at the time heparin is discontinued. Protamine, a strongly basic protein, immediately reverses anticoagulant activity by forming a stable complex with the acidic heparin. For life-threatening hemorrhage, the usual dose is approximately 1 mg/100 units of heparin, administered slowly (e.g., 50 mg over 10 to 30 minutes). Protamine sulfate may cause allergic reactions, particularly in diabetic patients who have had prior exposure to protamine after using neutral protamine Hagedorn (NPH) insulin.[91]

HEPARIN-INDUCED THROMBOCYTOPENIA.

This complication is caused by IgG antibodies that recognize complexes of heparin and platelet factor 4, leading to platelet activation via platelet Fc gamma IIa receptors. Formation of procoagulant, platelet-derived microparticles generates thrombin and makes patients especially vulnerable to venous thromboembolism.[110] These clots are often large and bilateral, and they get worse if heparin is continued.

The diagnosis should be suspected if patients develop DVT or PE while receiving heparin, especially if the platelet count decreases to less than 100,000/mm^3 or if it decreases by more than 50 percent of baseline. The peak incidence is 4 to 14 days after initiating heparin. Heparin-induced thrombocytopenia occurs much more commonly with unfractionated heparin than with LMWH.[111] However, LMWH usually cross-reacts with unfractionated heparin after heparin-induced thrombocytopenia occurs and therefore should not be used for treatment.

Patients with heparin-induced thrombocytopenia are especially susceptible to venous

limb gangrene if warfarin is given before several days of effective antithrombotic therapy[112] such as danaparoid,[113] which reduces thrombin generation, or lepirudin,[114] which inhibits thrombin. Lepirudin currently is the only FDA-approved therapy for heparin-induced thrombocytopenia. The weight-adjusted dose must be reduced in the presence of renal insufficiency, and there is no specific antidote if bleeding occurs. Another direct thrombin inhibitor, argatroban, effectively treats heparin-induced thrombocytopenia.[115] Argatroban does not require dose adjustments with renal dysfunction, and FDA approval is imminent.[115A]

HEPARIN-INDUCED OSTEOPENIA.

Patients receiving prolonged heparin therapy may develop osteopenia, osteoporosis, or pathological bone fractures. In most cases, asymptomatic osteopenia is the most severe adverse effect on bone metabolism. This finding is most readily assessed with bone densitometry.[116] Among women who have discontinued heparin after pregnancy, the osteopenia usually resolves within a year.[117] For reasons not well understood, LMWH may cause less osteopenia than does unfractionated heparin.[118]

SPINAL AND EPIDURAL HEMATOMA.

Over a 5-year period, the FDA received reports of 43 patients in the United States who suffered spinal or epidural hematoma after receiving LMWH. Emergency decompressive laminectomy was performed in 28, and permanent paraplegia occurred in 16.[119] Consequently, most patients receiving LMWH during pregnancy are switched to unfractionated heparin for several weeks before their due date. Alternatively, LMWH is withheld for at least 24 hours before a scheduled induction of delivery.

HEPARIN-ASSOCIATED TRANSAMINITIS AND HYPERKALEMIA.

Heparin-associated elevations in transaminase levels occur commonly, have no relation to whether the heparin is of bovine or porcine origin, and are rarely associated with clinical toxicity.[120] [121] Heparin causes aldosterone depression by an unknown mechanism within 4 to 8 days after initiation of therapy. In patients with a normally functioning renin-angiotensin-aldosterone axis, this is probably of no clinical significance, although serum sodium levels may drop slightly. However, it may cause clinically important hyperkalemia in certain patients, such as those with diabetes or renal failure.[122]

Warfarin Sodium (See also Chap. 62)

Warfarin is a vitamin K antagonist that prevents gamma carboxylation activation of coagulation factors II, VII, IX, and X. The full anticoagulant effect of warfarin may not be apparent for 5 days, even if the prothrombin time, used to monitor warfarin's effect,

becomes elevated more rapidly. Elevation in the prothrombin time may initially reflect depletion of coagulation factor VII, which has a half-life of about 6 hours, whereas factor II has a half-life of about 5 days.

OVERLAP WITH HEPARIN.

When warfarin therapy is initiated during an active thrombotic state, the levels of protein C and S decline, thus creating a thrombogenic potential. By overlapping heparin and warfarin for 5 days, the procoagulant effect of unopposed warfarin can be counteracted. In a Dutch study, patients with DVT were randomized to oral anticoagulation alone versus heparin plus oral anticoagulation. The recurrent DVT rate was three times higher in the group that received oral anticoagulation alone.[123] This study demonstrates that warfarin should be given with heparin coverage and overlap to patients with an active thrombotic state.

MONITORING WARFARIN.

The prothrombin time, used to adjust the dose of warfarin, should be reported according to the International Normalized Ratio (INR), not the prothrombin time ratio or the prothrombin time expressed in seconds. Fewer bleeding complications occur when the INR is used to monitor warfarin dosing rather than the prothrombin time ratio.[124]

INTENSITY AND DURATION OF THERAPY.

It is our practice to treat with 5 to 7 days of heparin and to initiate warfarin administration on the first hospital day after documenting a PTT within the therapeutic range[125] or several hours after subcutaneous injection of a therapeutic dose of LMWH. The recurrence rate after completion of anticoagulation is halved by using 6 months of oral anticoagulation rather than 6 weeks.[126] One small study suggests using an indefinite duration of anticoagulation after a first episode of idiopathic venous thromboembolism.[127] However, this approach is not generally accepted. Ongoing trials are investigating the optimal duration and intensity of antiocoagulation among patients at highest risk, those who suffer DVT or PE without recent surgery or antecedent trauma.[128]

There is disagreement about whether patients with venous thromboembolism and factor V Leiden are at increased risk of recurrence after anticoagulation has been discontinued.[8] [8A] The ongoing NIH-sponsored clinical trial, PREVENT, is addressing this issue.[128]

In otherwise healthy patients, I usually initiate warfarin therapy with 5 mg and achieve the target INR in about 5 days.[129] Among systemically ill patients, however, vitamin K deficiency[130] may lead to marked overanticoagulation just after a single modest dose of warfarin. I tend to treat first-time DVT of the calf[131] or upper extremities[132] for 3 months, and proximal DVT or PE for 6 months. The target INR for first-time DVT is 2.0 to 3.0, but I tend to treat PE more intensively, with a target INR of at least 3.0. Whenever possible, patients who have DVT or PE and who also have the antiphospholipid-antibody

syndrome should be maintained with a target INR of at least 3.0.[133]

COMPLICATIONS.

The major toxic effect of warfarin is bleeding. The risk of bleeding increases as the INR increases. Risk factors for hemorrhage include severe hepatic or renal disease, alcoholism, drug interactions (including acetaminophen[134]), trauma, malignant disease, and known previous bleeding sites in the gastrointestinal tract. The incidence of rehospitalization for bleeding after hospitalization for DVT is greatest during the first 30 days after discharge. Women and nonwhite patients appear to be at especially increased risk for anticoagulant-related bleeding.[134A]

About 1 to 2 percent of patients will have an extremely low warfarin requirement of 1.5 mg or less in the absence of liver dysfunction, drug interaction, or concomitant disease. A subset is born with CYP2CP variant alleles that are associated with impaired hydroxylation of S-warfarin. If not recognized when warfarin is initiated, these individuals are at a potentially high risk of bleeding complications.[135]

Major life-threatening bleeding requires immediate treatment with enough cryoprecipitate or fresh frozen plasma (FFP) (usually 2 units) to normalize the INR and achieve immediate hemostasis. To treat less serious bleeding, vitamin K has traditionally been administered parenterally; a dose of 10 mg subcutaneously or intramuscularly usually reverses the effects of warfarin in 6 to 12 hours. However, this approach makes patients relatively refractory to warfarin for up to 2 weeks, so that reinstitution of warfarin becomes more difficult. A novel and alternative approach is to administer a single dose of vitamin K. In a cohort of patients who were not bleeding and who had an INR greater than 5.0, a single average dose of 10 mg of vitamin K sufficed to lower the INR to the targeted therapeutic range, without disrupting the subsequent daily dosing of warfarin.[136]

Minor bleeding with a prolonged INR may merely require interruption of warfarin therapy, without administration of FFP, until the INR has returned to the therapeutic range. If bleeding occurs when the INR is within the therapeutic range, occult malignant disease should be suspected and ruled out. Evaluation of cases of minor bleeding and an INR above the therapeutic range is less productive.

Warfarin-induced skin necrosis[137] is a rare but important complication that may be related to warfarin-induced reduction of protein C. The "purple toes syndrome" is another rare complication of warfarin therapy that appears to be caused by cholesterol microembolization.[137] In this syndrome, crystals are released from ulcerated atherosclerotic plaques. It appears that warfarin may worsen cholesterol microembolic disease by interfering with the healing of ulcerated atherosclerotic plaques.

During pregnancy, heparin should generally be used instead of warfarin because warfarin is associated with a markedly higher rate of congenital anomalies. The fetus is particularly susceptible to warfarin embryopathy during the 6th through 12th weeks of gestation. The main features are saddle nose, nasal hypoplasia, frontal bossing, short stature, stippled epiphyses, optic atrophy, cataracts, mental retardation, and flexure

contractures. Intracranial bleeding may also lead to secondary central nervous system deformities.[138] Women can take warfarin post partum and breast feed safely, but reliable contraception is essential because warfarin is teratogenic.[139] The level of warfarin in breast milk is so low (25 ng/ml)[140] that it cannot be detected in the baby's plasma.[140]

In the office setting, I routinely assess warfarin dosing with a "point-of-care" device that provides the INR result in 2 minutes by use of a drop of whole blood obtained from a fingertip puncture. Substantial time savings have resulted, and patients leave the office with greater peace of mind and with a more accurate understanding of their warfarin dosing regimen. Appropriately selected patients can self-manage their warfarin dosing at home with a point-of-care device. In a randomized trial comparing self-management with conventional management, the self-managed patients more frequently achieved their target INRs and reported an improved quality of life compared with the conventionally managed group.[141]

ASPIRIN (see also Chap. 62).

Aspirin exerts its antithrombotic effect

TABLE 52-13 -- INDICATIONS FOR INFERIOR VENA CAVAL FILTERS

Anticoagulation Contraindicated and PE Documented
Active bleeding that might cause exsanguination (e.g., gastrointestinal)
Feared bleeding that might be catastrophic (e.g., postoperative craniotomy)
Ongoing complications of anticoagulation (e.g., heparin-associated thrombocytopenia)
Planned intensive cancer chemotherapy (with anticipated pancytopenia or thrombocytopenia)
PE=pulmonary embolism.
Anticoagulation Failure Despite Documentation of Adequate Therapy (e.g., Recurrent PE)
Prophylaxis in High-Risk Patients
Extensive or progressive venous thrombosis
In conjunction with catheter-based or surgical pulmonary embolectomy
Severe pulmonary hypertension or cor pulmonale
PE=pulmonary embolism.

by eliminating platelet prostaglandin synthesis, thereby blocking thromboxane A_2

formation and causing a moderate decrease in platelet function and a mild hemostatic defect.[142] Consequently, aspirin has at least a modest role in prevention of venous thrombosis.[143] I prescribe low-dose aspirin, usually 81 mg daily, for some patients who have finished their full course of warfarin. This strategy averts an abrupt transition from full anticoagulation to no anticoagulation.

Secondary Prevention: Inferior Vena Caval Interruption

The major indications for placement of an IVC filter are listed in Table 52-13 . An IVC filter prevents PE, not DVT.[144] Therefore, when a filter is inserted, anticoagulation should also be used, whenever possible, to prevent further thrombosis.[145]

Most IVC filters are placed below the renal veins. For suprarenal vein placement, the largest experience is with the Greenfield filter. At Brigham and Women's Hospital, we primarily use the bird's nest filter for infrarenal placement (Fig. 52-11) .

Primary Treatment

Thrombolysis

Thrombolytic therapy is a useful adjunct to heparin in patients who have PE and who are hemodynamically unstable.[146]

Figure 52-11 Inferior vena caval filters. Most filters are placed percutaneously via the right femoral vein. Our current preference is percutaneous placement of a Bird's Nest Filter (Cook Incorporated, Bloomington, IN), which has a low rate of failure, thrombogenicity, and occlusion. The smallness of its sheath may help minimize the risk of bleeding during and after the procedure. To insert the Bird's Nest Filter, the right-angled handle of the wire guide pusher is rotated counterclockwise for 10 to 15 turns to disengage it from the filter. Then the wire guide pusher is removed first, followed by the empty filter catheter. The introducing sheath is left in place so that a postprocedure venacavogram can be obtained. *(From Goldhaber SZ: Treatment of venous thrombosis. In Goldhaber SZ [ed]: Cardiopulmonary Diseases and Cardiac Tumors. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 12.1-12.14.)*

The definition of "hemodynamically unstable" is controversial and varies from systemic arterial hypotension to normal systemic arterial pressure with moderate or severe right ventricular dysfunction. Rapid improvement of right ventricular function and pulmonary perfusion, accomplished with thrombolytic therapy followed by heparin, may lead to a lower rate of death and recurrent PE.[49] Thrombolysis may (1) prevent the downhill spiral of right-sided heart failure by physical dissolution of anatomically obstructing pulmonary arterial thrombus (Fig. 52-12) ; (2) prevent the continued release of serotonin and other neurohumoral factors that might otherwise lead to worsening pulmonary hypertension; and (3) dissolve much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent large PE.

The potential benefits of immediately reversing right heart failure and preventing

recurrent PE must be balanced by the risk of hemorrhage. Contraindications to thrombolysis,

Figure 52-12 *Left,* A large embolus in the right pulmonary artery (arrow). *Right,* After a 2-hour infusion of tissue plasminogen activator through a peripheral vein, resolution is pronounced, with only a small amount of residual thrombus in segmental branches. *(From Goldhaber SZ, Vaughan DE, Markis JE, et al: Acute pulmonary embolism treated with tissue plasminogen activator. Lancet 2:886, 1986.)*

such as intracranial disease, recent surgery, or trauma, preclude its use in some patients who can safely receive heparin alone. There is a 1 to 2 percent risk of intracranial hemorrhage.[147] Carefully screening patients for contraindications to thrombolysis is the best way to minimize bleeding risk (see Chap. 62) .

At Brigham and Women's Hospital, we have coordinated five trials of PE thrombolysis, including the largest trial of tissue plasminogen activator (t-PA, 100 mg/2 hr) plus heparin versus heparin alone.[148] The initial systemic arterial systolic pressure was at least 90 mm Hg in every patient. Most importantly, no clinical episodes of PE recurred among patients receiving t-PA, but there were five (two fatal and three nonfatal) clinically suspected recurrent PEs within 14 days in patients randomized to heparin alone (p=0.06). All five initially showed right ventricular hypokinesis on echocardiogram. This latter observation suggests that echocardiography may help identify a subgroup of patients with PE at high risk of adverse clinical outcomes if treated with heparin alone. Such patients in particular would appear to be excellent candidates for thrombolytic therapy in the absence of contraindications.

Qualitative assessment of right ventricular wall motion demonstrated that 39 percent of the t-PA recipients improved (Figs. 52-13 *A* and *B*) and 2.4 percent worsened, compared with 17 percent improvement and 17 percent worsening among those who received heparin alone ($p < 0.005$). Quantitative assessment showed that t-PA recipients had a significant decrease in right ventricular end-diastolic area during the 24 hours after randomization compared with none among those allocated to heparin alone ($p < 0.01$). Recipients of t-PA also had an absolute improvement in pulmonary perfusion of 14.6 percent at 24 hours (Fig. 52-13 *C* and *D*), compared with 1.5 percent improvement among heparin-alone recipients ($p < 0.0001$).

Unlike patients with myocardial infarction-thrombolysis, patients with PE have a wide "window" for effective use of thrombolysis. Specifically, patients who receive thrombolysis up to 14 days after new symptoms or signs maintain an effective response,[149] probably because of the bronchial collateral circulation. Therefore, patients suspected of having PE should be considered as potentially eligible for thrombolysis if they have had any new symptoms or signs within the 2 weeks before presentation. Although t-PA 100 mg/2 hr is the only contemporary FDA-approved dosing regimen for PE thrombolysis,[150] other regimens also appear promising, including 1,500,000 units of

streptokinase/2 hr[151] and double-bolus reteplase (r-PA) (10-unit bolus followed 30 minutes later by a second 10-unit bolus).[152]

DVT THROMBOLYSIS

Most patients with DVT have contraindications to thrombolysis.[153] Totally occlusive venous thrombosis usually does not lyse if the agent is administered through a peripheral vein.[154] For patients with iliofemoral venous thrombosis, catheter-directed thrombolysis[155] or thrombolysis plus venous angioplasty[156] may be successful.

VENOUS INSUFFICIENCY.

Many patients with PE are plagued with chronic lower leg swelling and calf discomfort that can become problematic years after an episode of venous thromboembolism. This is known as *venous insufficiency* or *postthrombotic syndrome.* In most situations, the pathophysiology is damage of venous valves from antecedent DVT. Under extreme circumstances, venous ulceration can occur, particularly in the medial malleolus. The condition is usually manageable with below-knee vascular compression stockings. However, the frequency of venous insufficiency can be halved by preventive use of sized-to-fit compression stockings of 20 to 40 mm Hg.[156A]

Embolectomy

The results of embolectomy can be optimized if patients are referred for this procedure before the onset of cardiogenic shock.[156B] Greenfield's embolectomy device is a classical catheter-based method of extracting pulmonary arterial thrombus (Fig. 52-14).[157] It consists of a 10F steerable catheter with a suction cup attached at the tip. Because of the cup's large size, a surgical venotomy is used, usually to access the right internal jugular vein. A steerable handle controls progression of the catheter through the right cardiac chambers and the pulmonary arterial branches.

Alternative catheterization methods[158] include mechanical fragmentation of thrombus with a standard pulmonary

Figure 52-13 Echocardiograms (four-chamber view) and perfusion lung scans (anterior view) in a previously healthy 53-year-old man treated with tissue plasminogen activator (t-PA) for pulmonary embolism. *A,* Enlargement of the right ventricle (RV) before treatment. The RV end-diastolic area was 42.9 cm^2 , and the interventricular septum (arrow) was displaced toward the left ventricle (LV). There was moderately severe RV hypokinesis. *B,* Three hours after initiation of t-PA therapy, the size of the RV normalized (with a planimetered area of 25.7 cm^2) and the interventricular septum resumed its normal configuration. RV wall motion normalized. *C,* The pretherapy lung scan (*left*) shows absence of perfusion in the right middle lobe (lower arrowhead) and in most of the right upper lobe, particularly the apical segment of the right upper lobe (upper arrowhead). The left lung shows absence of perfusion in the lingula and anterior segment of the left upper lobe (horizontal arrowhead) and irregular perfusion in the apical-posterior segment of the left upper lobe. *D,* The posttherapy scan (*right*) shows marked improvement in perfusion. *(From Goldhaber SZ: Treatment of acute pulmonary embolism. In Goldhaber SZ [ed]: Cardiopulmonary Diseases and Cardiac Tumors. In Braunwald E [series ed]: Atlas of Heart*

Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 3.1-3.25.)

Figure 52-14 Philippe Reynaud, M.D., at the Laennec Hospital in Paris, used a Greenfield embolectomy catheter to remove this 17-cm thrombus from a severely compromised patient with PE. Rapid hemodynamic improvement ensued. *(From Meyer G, Tamiser D, Reynaud P, Sors H: Acute pulmonary embolectomy. In Goldhaber SZ [ed]: Cardiopulmonary Diseases and Cardiac Tumors. In Braunwald E [series ed]: Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 7.1-7.12.)*

artery catheter, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy,[159] and pigtail rotational catheter embolectomy.[160] This 5F Teflon catheter has a distal tip that is divided into four 15-mm bends. The high-speed mechanical rotation of the catheter (about 100,000 rpm) causes centrifugal force to open the distal bends and form a soft flexible helical spiral that can disintegrate thrombus into microscopic particles within seconds.[159] Another approach is simultaneous mechanical clot fragmentation and pharmacological thrombolysis (Fig. 52-15 *A* and *B*). [161] Finally, balloon angioplasty has also been used to improve pulmonary arterial flow among patients with PE.[162]

If catheter-based strategies fail, emergency surgical embolectomy with cardiopulmonary bypass can be undertaken (Fig. 52-16) . [163] A nonrandomized comparison of t-PA

Figure 52-15 A 77-year-old woman had right-sided heart failure despite 3 days of full-dose heparin. Therefore, she underwent right heart catheterization and pulmonary angiography. Her pulmonary arterial pressure was 55/30 mm Hg. Seen on her baseline angiogram (*A*) were large right middle and right upper lobe pulmonary emboli (arrows). Because of relative contraindications to full-dose thrombolysis (systemic arterial hypertension and mild dementia), she underwent combined suction catheter embolectomy and catheter-directed thrombolysis with a bolus pulse spray of 8 mg of tissue plasminogen activator followed by an overnight infusion of 1 mg/hr. Her follow-up angiogram (*B*) shows marked improvement and reperfusion.

Figure 52-16 A 52-year-old woman was on the medical service to treat multiple sclerosis when she became short of breath and collapsed. Her echocardiogram showed a dilated right ventricle and collapsed left ventricle. Shortly thereafter, she suffered cardiac arrest and was immediately taken to the operating room with the presumptive diagnosis of pulmonary embolism. She was placed on cardiopulmonary bypass, and massive amounts of thrombus (*shown above*) were removed from her pulmonary arteries. She subsequently recovered uneventfully.

Figure 52-17 Proposed strategy for treatment of pulmonary embolism in which risk stratification, often with echocardiography, is undertaken to determine clinical and hemodynamic stability. This evaluation helps to determine prognosis as well as appropriateness of aggressive intervention with thrombolysis or mechanical measures to remove thrombus. IVC = inferior vena caval.

thrombolysis versus surgical embolectomy indicated that both approaches can be life saving in the majority of patients with massive PE.[164] For patients with PE causing hemodynamic instability, pulmonary embolectomy in the catheterization laboratory or operating room should be considered when there are contraindications to thrombolysis or when thrombolysis has failed.[165]

Management Approach for Acute Pulmonary Embolism

Therapy for PE should be tailored according to the anatomical extent of the embolus, the presence of underlying cardiopulmonary disease, and the detection of right-sided-heart dysfunction.[166] [167] The echocardiogram is becoming increasingly important for determination of hemodynamic stability, risk stratification, and prognostication (Fig. 52-17) . Primary therapy is being used with increasing frequency for patients with moderate or severe right ventricular dilatation and hypokinesis on echocardiogram, even in the presence of normal systemic arterial pressure. Secondary prevention of recurrent PE is directed toward all patients and appears to suffice in those with small to moderate PE in the absence of major right ventricular dysfunction. Before hospital discharge, obtaining a follow-up perfusion lung scan is useful to establish a new baseline, in case the patient subsequently complains of symptoms suggesting recurrent PE.

EMOTIONAL SUPPORT.

Although PE can be as emotionally devastating as myocardial infarction, the psychological burden for patients with PE may be greater. The lay public is not familiar with PE, particularly in terms of the possibility of genetic predisposition, long-term disability, and recurrence of disease. By discussing the implications of PE with patients and their families, the emotional burden may be assuaged. We initiated a Pulmonary Embolism Support Group, co-led by a nurse-physician team, and have been gratified by the experience. Although these sessions have an educational component,[168] the major emphasis is on discussing the anxieties and living difficulties that occur in the aftermath of PE.

Chronic Pulmonary Embolism

Patients with chronic pulmonary hypertension due to previous PE may be virtually bedridden with breathlessness due to high pulmonary arterial pressures. They should be considered for pulmonary thromboendarterectomy, which, if successful, can reduce and at times even cure pulmonary hypertension. The operation involves a median sternotomy, institution of cardiopulmonary bypass, and deep hypothermia with

circulatory arrest periods. Incisions are made in both pulmonary arteries into the lower-lobe branches. Pulmonary thromboendarterectomy is always bilateral, with removal of organized thrombus from all involved vessels.

At the University of California at San Diego, more than 1000 patients debilitated by chronic pulmonary hypertension due to PE have undergone pulmonary thromboendarterectomy with good results and at an acceptable risk (Fig. 52-18) . The two major causes of mortality are (1) inability to remove sufficient thrombotic material at operation, resulting in persistent postoperative pulmonary hypertension and right ventricular dysfunction; and (2) severe reperfusion lung injury.[169]

Prevention

PE is difficult to diagnose, expensive to treat, and occasionally lethal despite therapy. Therefore, preventive measures are paramount.[170] Various mechanical measures and pharmacological agents can be used. The most recent innovation has been FDA approval of two different LMWHs, one (enoxaparin) for use in patients undergoing total hip or knee replacement or general surgery and another (dalteparin) for patients undergoing total hip replacement or general surgery.

American [171] and European[172] consensus conferences have provided detailed guidelines for prevention of venous thromboembolism. The concept of prophylaxis has gained wide acceptance. This is, at least in part, because of the medicolegal liability of physicians who omit prophylaxis among their hospitalized patients with risk factors for venous thrombosis.[173] Furthermore, a policy of prophylaxis is cost-effective. It is estimated that for every 1,000,000 patients undergoing operation who receive prophylaxis against DVT and PE, approximately $60,000,000 can be saved in direct health care costs.[174]

MECHANICAL MEASURES

GRADUATED COMPRESSION STOCKINGS.

These provide continuous stimulation of blood flow and prevent dilation of the venous system

Figure 52-18 A 30-year-old man with chronic pulmonary embolism complained of exercise intolerance. His echocardiogram showed mild to moderate right ventricular dysfunction and enlargement. Lung scan, chest CT scan, and pulmonary angiogram showed numerous thrombi. He underwent pulmonary thromboendarterectomy after insertion of a prophylactic inferior vena caval filter. At surgery, a moderate amount of thromboembolic material (*shown above*) was removed from both lungs. His pulmonary artery pressure decreased from a baseline of 35/10 mm Hg to 18/9 mm Hg before the pulmonary artery catheter was removed. He has enjoyed an excellent and uncomplicated recovery. *(Courtesy of Dr. Kim M. Kerr.)*

in the legs. Graduated compression stockings (GCS) exert more compression at the ankles (usually 18 mm Hg) than at the popliteal fossa or upper thigh (usually 8 mm Hg). In an overview of 12 trials in moderate-risk surgery, GCS reduced the DVT rate by two-thirds.[175] Thus, GCS should be considered first-line prophylaxis for most hospitalized patients and should suffice for prophylaxis among low-risk patients.

INTERMITTENT PNEUMATIC COMPRESSION.

Intermittent pneumatic compression (IPC) devices expel blood from the leg veins and thus prevent venous stasis. The mechanical force of compression appears to enhance systemic fibrinolytic activity.[176] IPC is particularly worthwhile among patients who have an absolute contraindication to anticoagulation. In addition, for patients receiving postoperative warfarin prophylaxis, IPC devices have special utility because they are immediately useful, whereas warfarin requires 4 to 5 days of administration before it is entirely effective as an anticoagulant. IPC devices are, in general, used properly in intensive care units. In one survey, however, they were either not applied or applied improperly in the majority of patients after transfer from an intensive care to a regular general surgery unit.[177]

INFERIOR VENA CAVAL INTERRUPTION.

(see p. 1899). The most invasive mechanical prophylaxis measure that can be implemented is IVC filter placement. Use of an IVC filter might be appropriate for patients with recently diagnosed PE or DVT who must undergo major surgery that places them at high risk for suffering perioperative PE. The filter prevents PE but not DVT.[144]

PHARMACOLOGICAL AGENTS

UNFRACTIONATED HEPARIN.

"Minidose heparin" has traditionally been used to prevent perioperative venous thromboembolism. Unfractionated heparin is administered two or three times daily in a dose of 5000 units subcutaneously. The first injection is usually given 2 hours before the skin incision. An overview of 78 randomized controlled trials with 15,598 patients found a 40 percent reduction in nonfatal PE and a 64 percent reduction in fatal PE.[176] In more recent pharmacological prophylaxis trials, at times, prophylaxis has been deferred until the early postoperative period. Any loss of efficacy resulting from deferring prophylaxis until shortly after surgery is unlikely to be marked.[178]

LOW-MOLECULAR-WEIGHT-HEPARIN.

LMWH has a more predictable dose response, more dose-independent mechanisms of

clearance, and a longer plasma half-life than unfractionated heparin. LMWHs can achieve higher plasma heparin levels with less bleeding than equivalent doses of unfractionated heparin. Because of its favorable profile (see p. 1896), an increasing number of orthopedic and general surgical patients are receiving once-daily fixed-dose prophylaxis with LMWH rather than injections of minidose unfractionated heparin two or three times daily.

DANAPAROID.

Danaparoid is a heparinoid glycosaminoglycuronan that inhibits factors Xa and IIa (thrombin) in a ratio greater than 20.[178A] The active components are heparan sulfate (84 percent), dermatan sulfate (12 percent), and chondroitin sulfate (4 percent). The average molecular weight is about 5500. The only FDA-approved indication is prophylaxis in patients undergoing total hip replacement (in a dose of 750 units administered subcutaneously twice daily).[179] However, it is often used for "off-label" treatment of heparin-induced thrombocytopenia,[180] even though there is about a 10 to 15 percent rate of cross reactivity between unfractionated heparin and danaparoid. Danaparoid can be administered subcutaneously, unlike the only FDA-approved treatment for heparin-induced thrombocytopenia, lepirudin, which can be administered only intravenously.

ASPIRIN.

Although aspirin provides modest pharmacological prophylaxis against perioperative venous thromboembolism,[143] it is too weak an agent to be considered the standard of care for prevention of PE or DVT.

PROPHYLAXIS STRATEGIES FOR SPECIFIC CONDITIONS

Fortunately, numerous prophylaxis options are available for preventing PE and DVT in most patients (Table 52-14) . The specific prophylaxis modality that is chosen is not nearly as important as upholding a standard that virtually all hospitalized patients receive some preventive measure appropriate to their level of risk.

ORTHOPEDIC SURGERY.

Both adjusted-dose warfarin (target INR 2.0 to 3.0) and fixed-dose LMWH effectively prevent most episodes of venous thromboembolism that occur after total hip replacement,[181] total knee replacement, or hip fracture surgery. In one trial, desirudin appeared even more effective than LMWH in preventing venous thromboembolism after total hip replacement[182] ; however, it is not commercially available.

To determine whether low-dose aspirin could prevent PE in patients with hip fracture, a megatrial of 13,356 patients was undertaken. They were assigned to 160 mg of enteric-coated aspirin once daily or its placebo in a randomized controlled design. At 5 weeks, 81 patients in the placebo group suffered PE (43 fatal and 38 nonfatal),

compared with 46 in the aspirin group (18 fatal and 28 nonfatal), for an overall 43 percent risk reduction (p = 0.002) without any increase in major bleeding.[183]

Foot-compression pumps have become popular as a mechanical prophylaxis method, particularly in patients undergoing orthopedic

TABLE 52-14 -- PREVENTION OF VENOUS THROMBOEMBOLISM

INDICATION	POTENTIAL PROPHYLAXIS REGIMEN
Orthopedic surgery	Enoxaparin 30 mg twice daily
	Enoxaparin 40 mg once daily*
	Dalteparin 5000 units once daily*
	Danaparoid 750 units twice daily*
	Warfarin (target INR=2.0-3.0)
	GCS plus IPC
General surgery	Enoxaparin 40 mg daily
	Dalteparin 2500 or 5000 units once daily
	GCS plus IPC
Pregnancy	Enoxaparin 40 mg daily
	Dalteparin 5000 units daily
Medical patients	Enoxaparin 40 mg daily
	GCS plus IPC

GCS=graduated compression stockings; IPC=intermittent pneumatic compression boots; INR=International Normalized Ratio.

*Approved only for total hip replacement prophylaxis.

surgery. However, the effectiveness of these pumps in preventing PE and DVT has not been extensively studied. In one trial of patients receiving foot-pump prophylaxis for total knee replacement, 54 percent had postoperative DVT.[184] Thus, these devices cannot be recommended at this time.

Two important concepts have recently emerged. First, DVT occurs with surprisingly high frequency after knee arthroscopy, affecting 18 percent of patients in one series.[185] Second, patients remain at high risk of venous thromboembolism after hospital discharge following total hip or knee replacement.[186] The median time for diagnosis of venous thromboembolism was 17 days postoperatively for total hip replacement and 7 days postoperatively for total knee replacement in a series of approximately 45,000 patients undergoing surgery in California. The FDA has approved prophylaxis for 3 weeks after hospital discharge with enoxaparin 40 mg once daily for patients

undergoing total hip replacement.

CARDIAC SURGERY.

In a trial of 2786 patients undergoing open-heart surgery, prophylaxis was randomized to pneumatic compression devices plus minidose heparin versus minidose heparin alone. The frequency of PE was 1.5 percent in the combined prophylaxis group versus 4 percent in the group given minidose heparin alone.[187]

MEDICAL PATIENTS.

Medical patients have not been nearly as well studied as surgical patients in terms of prevention of venous thromboembolism. In the MEDENOX Trial of 1102 hospitalized medical patients, prophylaxis with enoxaparin 40 mg once daily reduced by two-thirds the frequency of DVT as assessed by bilateral contrast venography between days 6 and 14.

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Chapter 53 - Pulmonary Hypertension

STUART RICH

Normal Pulmonary Circulation

During the passage of red blood cells through the lungs, hemoglobin is normally oxygenated to nearly full capacity and the blood is cleansed of much particulate matter and bacteria. The lungs, in addition to functioning as a blood oxygenator and filter, play a dominant role in achieving acid-base balance by excreting carbon dioxide, thereby helping maintain optimal blood pH.[1]

PULMONARY BLOOD FLOW, PRESSURE, AND RESISTANCE

PULMONARY CIRCULATION IN THE NORMAL ADULT.

The lung has a unique double arterial blood supply from the pulmonary and bronchial arteries, as well as double venous drainage into the pulmonary and azygos veins.[2] The right and left pulmonary arteries carry the entire output of the right ventricle and follow a course adjacent to the airways. Inside the lung each pulmonary artery accompanies the appropriate-generation bronchus and divides with it down to the level of the respiratory

bronchiole. Additional supernumerary branches originate without relation to bronchial divisions and directly penetrate into the lung parenchyma. The diameter of the arteries decreases more rapidly than that of the airways they accompany, so in the lung periphery the diameters of the arteries are smaller than those of the adjacent airways. Within the respiratory units the pulmonary arteries and arterioles are centrally located and give rise to precapillary arterioles from which a network of capillaries radiate into the alveolar walls. The alveolar capillaries collect at the periphery of the acini and then drain into venules located within the interlobular and interlobar septa.

The pulmonary arteries are classified as elastic or muscular based on the structure of the tunica media. The elastic arteries are conducting vessels, highly distensible at low transmural pressure. As the arteries decrease in size, the number of elastic laminae decreases and smooth muscle increases. Eventually, in vessels between 1000 and 500 mum, elastic tissue is lost from the media and the arteries become muscular. The intima of the pulmonary arteries consists of a single layer of endothelial cells and their basement membrane. The adventitia is composed of dense connective tissue in direct continuity with the peribronchial connective tissue sheath. The muscular arteries are 500 mum in diameter or less and are characterized by a muscular media bounded by internal and external elastic laminae. In normal adults, the lumen is wide and the media is thin and represents less than 10 percent of the arterial cross-sectional area. Arterioles are precapillary arteries smaller than 100 mum in outer diameter and composed solely of a thin intima and single elastic lamina. The alveolar capillaries are lined with a continuous layer of endothelium resting on a continuous basement membrane and focally connected to scattered pericytes located beneath the basement membrane.

The bronchial arteries ramify into a capillary network drained by bronchial veins, some of which empty into the pulmonary veins, whereas the remainder empty into the systemic venous bed. The bronchial circulation therefore constitutes a physiological "right-to-left" shunt. The function of the bronchial circulation is to provide nutrition to the airways. Normally, blood flow through this system is quite low and amounts to approximately 1 percent of the cardiac output[3] ; the resulting desaturation of left atrial blood is usually trivial. However, in some forms of pulmonary disease, e.g., severe bronchiectasis, and in the presence of many congenital cardiovascular malformations that cause cyanosis, blood flow through the bronchial circulation can increase significantly, account for nearly 30 percent of left ventricular output,[4] and produce a significant right-to-left shunt. In pulmonary disease, significant right-to-left shunting through the bronchial circulation may also result in arterial desaturation. In cyanotic congenital heart disease, bronchial blood is not fully oxygenated; it may participate in gas exchange and improve systemic oxygenation.

Normal pulmonary artery pressure in a person living at sea level has a peak systolic value of 18 to 25 mm Hg, an end-diastolic value of 6 to 10 mm Hg, and a mean value ranging from 12 to 16 mm Hg* (see Chap. 11) . Definite pulmonary hypertension is present when pulmonary artery systolic and mean pressures exceed 30 and 20 mm Hg, respectively. Normal mean pulmonary venous pressure is 6 to 10 mm Hg; therefore, the normal arteriovenous pressure difference, which moves the entire cardiac output across the pulmonary vascular bed, ranges from 2 to 10 mm Hg. This small pressure gradient is all the more remarkable when one considers that to move the same amount of blood

per minute through the systemic vascular bed, a pressure

*All pressures discussed here are in reference to atmospheric pressure at the level of the heart. True transmural pressures are more physiologically meaningful, especially when pulmonary parenchymal disease is present, but are rarely measured.
Isolated medial hypertrophy

differential of approximately 90 mm Hg (systemic arterial mean pressure minus right atrial mean pressure) is required.

Pulmonary Vascular Resistance.

Thus, the normal pulmonary vascular bed offers less than one-tenth the *resistance* to flow offered by the systemic bed. *Vascular resistance* is generally quantified, by analogy to Ohm's law, as the ratio of pressure drop (DeltaP in millimeters Hg) to mean flow (Q in liters per minute). The ratio is commonly multiplied by 79.9 (or 80 for simplification) to express the results in dynes-seconds centimeters^{-5} . This conversion to metric units may be avoided, i.e., resistance may be expressed in millimeters Hg per liter per minute, which is sometimes referred to as hybrid units, PRU (peripheral resistance units), or Wood units (after the English cardiologist Paul Wood). The calculated pulmonary vascular resistance in normal adults[5] is 67±23 (SD) dyne sec cm^{-5} , or 1 Wood unit.

Vascular resistance reflects a composite of variables that includes, but is not limited to the cross-sectional area of small muscular arteries and arterioles. Other determinants are blood viscosity, the total mass of lung tissue (i.e., resistance is higher in infants and children than in adults), proximal vascular obstruction (e.g., pulmonary coarctation, pulmonary embolism, peripheral pulmonic stenosis), and extramural compression of vessels (perivascular edema).

The reduction in resistance in a distensible vascular bed that occurs with increased flow has been offered as the explanation for the absence of pulmonary hypertension in many patients with large left-to-right intracardiac shunts, particularly atrial septal defects.

REGIONAL PERFUSION.

A large degree of heterogeneity in regional pulmonary perfusion is characteristic of the pulmonary circulation and can be explained by a fractal branching network.[6] The pulmonary vascular tree can be conceptualized as having a fixed structure that is the primary determinant of overall perfusion and a variable component that can be influenced by passive and active regional factors such as recruitment and/or distention from changing driving or hydrostatic pressures. Active factors such as vasomotion and response to shear stress or hypoxic vasoconstriction influence regional perfusion, which is constantly changing.

PULMONARY CIRCULATION WITH EXERCISE.

With moderate exercise, a large increase in pulmonary blood flow is normally accompanied by only a small increase in pulmonary artery pressure. It is important to note that exercise results in an increase in left atrial pressure that is progressive with exercise intensity and accounts for the majority of the increase in pulmonary arterial pressure that is observed.[7] This marked effect of downstream pressure on upstream pressure is unique to the lung circulation inasmuch as systemic arterial pressure during exercise is largely independent of right atrial pressure. Because of the high vascular compliance in the normal lung microcirculation, an increase in left atrial pressure that results from the increased flow will act to distend the small vessels, thereby accounting for the dramatic fall in pulmonary vascular resistance during exercise. Microcirculatory distention increases the surface area for diffusion and slows passage of red cells through the lung, which facilitates oxygen transfer.

FETAL AND NEONATAL CIRCULATION (see alsoChap. 43) .

In the fetus, oxygenated blood enters the heart from the inferior vena cava and streams across the foramen ovale to the left atrium, left ventricle, ascending aorta, and cranial vessels. Desaturated blood returns from the superior vena cava and passes through the tricuspid valve into the right ventricle and pulmonary artery. Because the resistance of the pulmonary vascular bed in the collapsed fetal lung is extremely high, only 10 to 30 percent of the total right ventricular output passes through the lungs, the remainder being shunted across the ductus arteriosus to the descending aorta and then back to the placenta. An abrupt change in the pulmonary circulation occurs at birth. With the first breath, expansion of the lungs and the abrupt rise in P_{O_2} of blood lead to a release of pulmonary arteriolar vasoconstriction and stretching and dilatation of muscular pulmonary arteries and arterioles, with a marked drop in vascular resistance.[8] This decreased resistance facilitates a large increase in pulmonary blood flow and raises left atrial volume and pressure. The latter closes the flap valve of the foramen ovale, and interatrial right-to-left shunting ordinarily ceases within the first hour of life. Normally, the ductus arteriosus closes over the next 10 hours as a result of contraction of the thick smooth muscle bundles within its wall in response to rising arterial oxygen tension and a change in the prostaglandin milieu. Following the initial dramatic fall in pulmonary vascular resistance at birth, a continuous decline occurs over the first few months of life that is associated with thinning of the media of muscular pulmonary arteries and arterioles until the normal adult pattern is achieved[9] (Fig. 53-1) .

AGING AND THE PULMONARY CIRCULATION.

Pulmonary artery pressure and pulmonary vascular resistance increase with advanced age, similar to increases that occur in systemic vascular resistance.[10] [11] [12] Reduced compliance of the pulmonary vascular bed secondary to intimal fibrosis or increased wall thickness in the muscular pulmonary arteries is a possible cause. It is also possible that some of the changes in the pulmonary arteries relate to reduced compliance of left ventricular filling that is passively reflected back on the pulmonary vascular bed.[11] The

prevalence of mild pulmonary hypertension (mean pulmonary artery pressure 20 mm Hg) may be as high as 13 percent in persons up to 45 years old and 28 percent in those up to 75 years old.[13]

RESPONSE TO HYPOXIA, DRUGS, AND NEURAL AND ENVIRONMENTAL FACTORS

HYPOXIA.

Acute *hypoxia* elicits pulmonary vasoconstriction[14] as a self-regulatory mechanism for adjusting capillary perfusion to alveolar ventilation. Hypoxia in humans (P_{O_2} 55 mm Hg) is associated with rapid onset of vasoconstriction.[15] Potassium, calcium, and probably chloride channels play important roles in determining pulmonary vascular tone.[16] Ionic control over membrane potential and cytosolic calcium regulates the degree of vasoconstriction and influences proliferation of smooth muscle cells. It seems likely that hypoxia inhibits outward potassium currents, thereby resulting in depolarization of the pulmonary vascular smooth muscle cell membrane, which allows calcium entry into voltage-dependent calcium channels, followed by contraction. Hypoxic pulmonary vasoconstriction is widely variable among healthy people. It also varies markedly with the age of an individual and among different mammalian species. (For further discussion, see Chapter 54.)

NEURAL REGULATION.

The media and adventitia of the large elastic pulmonary arteries and the large pulmonary veins are supplied by nerve fibers that influence the distensibility of these capacitance vessels.[3] Although *neural regulation* of pulmonary vascular resistance can be demonstrated[17] and may be particularly important in fetal life, its importance in a normal human adult is less certain.

Figure 53-1 Changes in pulmonary arteries after birth. Comparison of relative medial thicknesses at birth (*A*), at 2 months of age (*B*), and at 7 months of age (*C*). Elastic-van Gieson stain; magnification × 360; reduced 17 percent. (From Petersen RC, Edwards WD: Pulmonary vascular disease in 57 necropsy cases of total anomalous pulmonary venous connections. Histopathology 7:47, 1983.)

ADRENERGIC RECEPTORS.

The pulmonary vasculature expresses both alpha and beta adrenoreceptors, both of which help regulate pulmonary vascular tone by producing vasoconstriction or vasodilatation, respectively.[18] $Alpha_1$ adrenoreceptors in the pulmonary arteries have increased affinity and responsiveness to their agonists when compared with other

vessels.[19] The downstream signaling events in alpha$_1$ -adrenergic stimulation are an increase in ionic calcium levels and activation of protein kinase, which mediate vascular contractile and proliferative responses. The increased sensitivity of alpha$_1$ adrenoreceptors to norepinephrine in the pulmonary arteries may greatly facilitate local regulation of vascular tone in response to acute changes in oxygen concentrations, thereby adjusting regional perfusion. Stimulation of alpha$_1$ adrenoreceptors increases intracellular free calcium levels by at least two mechanisms: (1) coupling to specific G proteins on the cell membrane and (2) blockade of potassium ion channels.[20] [21] Excessive stimulation of alpha$_1$ -adrenergic receptors produces smooth muscle contraction, proliferation, and growth. Factors that produce an increase in alpha$_1$ adrenoreceptor gene synthesis, density, and activity greatly enhance pulmonary artery smooth muscle contractile and proliferative responses. Such factors include norepinephrine, appetite suppressants, and cocaine.[22] [23] It also is plausible that an estrogen-induced increase in the number and affinity of vascular alpha$_1$ adrenoreceptors in women is the explanation for the female preponderance noted in conditions associated with pulmonary hypertension[24] (Fig. 53-2) .

DRUGS.

The alpha-adrenergic blocking agent phentolamine, as well as tolazoline (Priscoline), which also exhibits alpha-adrenergic blocking action, can lower pulmonary vascular resistance. *Beta-adrenergic stimulation* with isoproterenol has been repeatedly shown to cause pulmonary *vasodilatation.* In contrast, beta-adrenergic blockade does not produce any change in pulmonary vascular resistance, which suggests that tonic activation of beta receptors is not necessary for maintenance of the normal low pulmonary vascular resistance. *Acetylcholine* is also a potent relaxant of pulmonary arteries and arterioles and transiently lowers pulmonary vascular resistance in patients with elevated pulmonary vascular resistance with a major reversible component.

PROSTAGLANDINS.

Lung tissue is particularly active in the synthesis, metabolism, and release of a number of *prostaglandins,* some of which may play a role in the regulation of pulmonary vascular resistance. Prostaglandins I_2 (PGI_2) and E (PGE_2) are active pulmonary vasodilators, whereas PGF_2 alpha and PGA_2 are pulmonary vasoconstrictors.[25] Counterregulatory actions have been ascribed to prostacyclin (PGI_2) and thromboxane within the pulmonary circulation. Pulmonary endothelial cells have an abundance of prostacyclin synthase, whereas platelets are replete with thromboxane synthase.[26] [27] Both convert the cyclic endoperoxide precursors PGG_2 and PGH_2 into specific bioactive eicosanoids. Prostacyclin is a powerful vasodilator that also inhibits platelet aggregation through activation of adenylate cyclase. Its metabolic half-life in the bloodstream is less than one circulation time, with its metabolite 6-keto-prostaglandin F_1 alpha having little biological activity.[28]

A variety of drugs with diverse mechanisms of action are reported to encourage

prostacyclin production and include calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and nitrates.[26] Physiologically, prostacyclin is a local hormone rather than a circulating one. Release of prostacyclin by endothelial cells causes relaxation of the underlying vascular smooth muscle and prevents platelet aggregation within the bloodstream. Thromboxane is synthesized in platelets and macrophages.[27] It also has a short half-life. Thromboxane is a potent agonist for platelet aggregation and vasoconstriction, and it may function as a growth factor for smooth muscles by acting via protein kinase C-linked pathways.[29] Because the biological actions of prostacyclin are the opposite those of thromboxane,

Figure 53-2 Signaling pathways of alpha$_1$ -adrenergic receptors in smooth muscle cells that lead to pulmonary hypertension. Alpha$_1$ -adrenergic receptors activate phospholipase C to produce inositol 1,4,5-triphosphate (IP_3), which mobilizes calcium from intracellular stores. Activation of protein kinase C also activates transcription factors such as mitogen-activated protein kinase (MAP kinase) and nuclear factor kappa-B (NFkappaB), which induce DNA synthesis and cell proliferation. By increasing levels of oncoprotein (Bcl-2) to inhibit apoptosis, the survival of vascular smooth muscle cells is promoted. Alpha$_1$ -adrenergic receptors also couple to K^+ channels, which leads to entry of calcium from extracellular sources through voltage-sensitive channels. An increase in intracellular calcium is the major signal transduction mechanism responsible for producing smooth muscle contraction via the calcium calmodulin pathway, and protein kinase C activation is the major signal transduction pathway involved in the proliferation of pulmonary vascular smooth muscle cells. (From Salvi SS: alpha-1 Adrenergic hypothesis for pulmonary hypertension. Chest 115:1708-1719, 1999.)

Figure 53-3 Generation of prostacyclin (PGI_2), endothelial-derived relaxing factor-nitric oxide (EDRF-NO), and endothelin-1 (ET-1) in endothelial cells. Stimulation of receptors on the cells by serotonin (5HT [5-hydroxytryptomine]) or adenosine diphosphate (ADP) released from platelets or by thrombin, bradykinin, or shear stress leads to the release of vasoactive mediators. PGI_2 relaxes vascular smooth muscle and inhibits aggregation of platelets by increasing levels of cyclic adenosine monophosphate (cAMP). EDRF-NO relaxes vascular smooth muscle and inhibits platelet aggregation and adhesion by increasing levels of cyclic guanosine monophosphate (cGMP). The simultaneous increase in cAMP and cGMP inhibits platelet aggregation. (From Vane JR, Anggard EE, Bolting RM: Regulatory functions of the vascular endothelium. N Engl J Med 323:27, 1990. Copyright © 1990 Massachusetts Medical Society. All rights reserved.)

the balance between these two peptides appears to control the local environment within the vascular bed.

NITRIC OXIDE.

The biological action of nitric oxide (NO) is quite similar to that of prostacyclin in that it relaxes vascular smooth muscle. It differs, however, in that its effects are mediated by changing levels of cyclic guanosine monophosphate (GMP).[30] Endothelial NO synthase

is found in the vascular endothelium of the normal pulmonary vasculature, where it is responsible for generating NO to govern vascular tone. Release of NO occurs in response to a multitude of physiological stimuli, which include thrombin, bradykinin, and shear stress.[31] Besides its direct hemodynamic effects, NO inhibits platelet activation and confers an important antithrombotic property on the endothelial surface. NO also inhibits the growth of vascular smooth muscle cells and is probably involved in vascular remodeling in response to injury.[30] NO is also important in the signal transduction of angiogenesis inasmuch as vascular endothelial growth factor receptor activation results in increased NO production[32] (Fig. 53-3) .

OTHER VASOACTIVE SUBSTANCES.

Endothelin is a potent vasoconstrictor peptide that also plays an important role in the regulation of pulmonary vascular tone. Because of its long half-life, subtle disturbances in production or release can lead to sustained vasoconstriction.[33] Several studies have demonstrated an interaction between NO and endothelin-1 (ET-1) in the vascular endothelium.[34] Expression of endothelin is inversely related to that of NO synthase, thus suggesting an opposite regulatory pathway for these two factors. Two types of ET-1 receptor are known: ET_A is expressed mainly on smooth muscle cells and ET_B is expressed on endothelial cells. [34] The former mediates vasoconstriction, while the latter mediates vasorelaxation through release of nitric oxide (Fig. 53-4) .

Serotonin is an important constituent of platelet dense granules and is released upon activation.[35] Normal endothelial cells respond to serotonin by enhancing the release of NO, thereby leading to vascular smooth muscle relaxation and vasodilatation. In the setting of endothelial dysfunction, serotonin is unable to stimulate NO release and increases vascular smooth muscle tone, thereby leading to vasoconstriction.[36] In addition, serotonin can act as a growth factor and contribute to medial hypertrophy and promote vascular remodeling.[37]

Angiotensin II is generated in the lung by means of enzymatic conversion of angiotensin I, a potent pulmonary vasoconstrictor. Angiotensin II stimulates cell proliferation, extracellular matrix proteins synthesis, and smooth muscle cell migration. Elevated plasma renin and angiotensin II levels have been found during acute hypoxia and hypercapnia in CO_2 -retaining patients with chronic obstructive lung disease.[38]

Figure 53-4 Regulation of the effects of endothelin (ET). ET may be active in the final stage of transduction of a number of pulmonary smooth muscle contractile and mitogenic factors. Nitric oxide (NO) and prostacyclin (PGI_2), together with atrial natriuretic peptide (ANP), inhibit expression of ET-1. ET_A receptors are involved in contraction and in mitogenic effects on smooth muscle cells and fibroblasts. The small resistance arteries in humans appear to have contraction-inducing ET_B receptors as well. TGF-beta-transforming growth factor-beta. (From Higgenbottam TW, Laude EA: Endothelial dysfunction providing the basis for the treatment of pulmonary hypertension. Chest 114(Suppl):72-79, 1998.)

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Primary Pulmonary Hypertension

Primary pulmonary hypertension (PPH) is the diagnosis given to patients with pulmonary hypertension of unexplained etiology. Although the name of the disease stems from its distinction from pulmonary hypertension secondary to known cardiac or pulmonary causes, PPH should not be considered as only pulmonary hypertension for which no cause is found. The clinical features, usual age of onset, progression of the disease, and autopsy findings make PPH a distinct clinical entity and distinguish it from many forms of secondary pulmonary hypertension even though its diagnosis requires careful exclusion of secondary causes.[39] The actual incidence of PPH appears to be approximately two cases per million population, thus qualifying it as an orphan disease.[40] [40A]

ETIOLOGY

The precise cause of PPH is unknown, but it probably represents the clinical expression of pulmonary arterial hypertension as the final common pathway from multiple biological abnormalities within the pulmonary circulation. As understanding of vascular biology is improving, many studies point to abnormalities in pulmonary endothelial cell function as causing or contributing to the development of pulmonary hypertension in humans.[41] It is now understood that the endothelial cell regulates pulmonary smooth muscle cell tone.[26] It should be pointed out that even though endothelial cells may appear normal histologically, they may be quite abnormal with respect to function. Dysfunction of the counterregulatory systems within the pulmonary vascular bed seems to be common in pulmonary hypertension. The normal pulmonary vascular endothelial cell maintains the vascular smooth muscle in a state of relaxation.[26] The finding of increased pulmonary

vascular reactivity and vasoconstriction in patients with PPH suggests that a marked vasoconstrictive tendency underlies the development of PPH in predisposed individuals,[42] possibly as a result of loss of endothelial cell integrity.[41] The autonomic nervous system has been considered a contributory factor in the development of PPH through stimulation of the pulmonary vascular bed by either neuronally released or circulating catecholamines. In some patients with PPH, the response to vasodilators such as tolazoline, acetylcholine, or isoproterenol is a reduction in pulmonary artery pressure and pulmonary vascular resistance,[43] which supports the notion that the autonomic nervous system is at least in part maintaining a role in constant elevation of pulmonary vascular resistance.

Reduced expression of NO synthase in the endothelium of patients with pulmonary hypertension has been demonstrated and correlates inversely with the extent and severity of morphological lesions.[45] Although it is unsettled whether reduced NO synthase production is a cause or result of the disease, it is consistent with endothelial dysfunction underlying PPH as part of the disease process. Studies of vasodilators in pulmonary hypertension demonstrate that responsiveness to endothelium-dependent vasodilating agents is impaired before response to endothelium-independent vasodilators.[44] [46] This impaired responsiveness may reflect the underlying severity of vascular damage. Conversely, endothelin, a potent vasoconstrictor peptide, may also play an important role in the regulation of pulmonary vascular tone.[34] Its secretion may be enhanced in the presence of vasoconstriction or in the setting of platelet aggregation. Because it has a long half-life, subtle disturbances in production or release could lead to sustained vasoconstriction. ET_A receptor antagonists have been reported to reduce pulmonary artery pressure in experimental animals.[47] Given that the major resistance vessels in the pulmonary vascular bed are at the arteriolar level, diffuse arteriolar vasoconstriction could easily cause chronically sustained elevations in pulmonary vascular resistance and result in pulmonary hypertension. Elevations in endothelin levels within the pulmonary vasculature of patients with primary and secondary forms of pulmonary hypertension have been documented. [48] This finding would suggest that regardless of whether abnormal endothelial function is the underlying cause of PPH, progression of the disease is invariably accompanied by worsening of endothelial function, which itself can promote disease progression.

A striking feature of the pulmonary vasculature in patients with PPH is intimal proliferation, and in some vessels it causes virtually complete vascular occlusion[49] [50] (Fig. 53-5) . Several growth factors have been implicated in the development of this type of vascular pathology, including basic fibroblast growth factor from the endothelium[51] and platelet-derived growth factor[52] and transforming growth factor-beta [53] from platelets. Enhanced growth factor release, activation, and intracellular signaling may lead to smooth muscle cell proliferation and migration, as well as extracellular matrix synthesis. Even advanced lesions show evidence of in situ activity of ongoing synthesis of connective tissue proteins such as elastin, collagen, and fibronectin.[54] [55]

An equally important etiologic feature of PPH is the widespread development of in situ thrombosis of the small pulmonary arteries with resultant vascular obstruction.[49] [50] [56] [57] [57A] Although it was once believed that recurrent, systemic venous microembolism could be an underlying mechanism in PPH, this theory has been essentially rejected for

lack of both animal and human data to support it as a clinical entity. Animal studies suggest that more than 22 million thromboemboli in the pulmonary arterioles would be required to raise the mean pulmonary artery pressure 5 mm Hg, yet no source of these emboli has ever been found in patients dying of PPH.[56] Various defects in coagulation; including abnormal platelet function and defective fibrinolysis, have been demonstrated in patients with PPH.[57] [58] In situ thrombosis of the pulmonary vascular bed has been proposed as a causative or contributing feature of pulmonary hypertension.[56] [59] Abnormalities in platelet activation and function and biochemical features of a procoagulant environment within the pulmonary vasculature support a role of thrombosis in disease initiation in some patients.[57] [58] [60] [61] Interactions between growth factors, platelets, and the vessel wall suggest that thrombosis may play a fundamental role in many of the pathobiological processes described in PPH and in disease progression.[62] A prothrombotic state can arise as a consequence of fibrinolysis, enhanced coagulation, or increased platelet activation. Platelet activation not only promotes thrombosis but also leads to the release of granules that contain mitogenic agents and vasoconstrictive substances.[63]

Several studies suggest that local hemodynamics can influence pulmonary vascular remodeling.[64] A classic example is the pulmonary hypertension that occurs in congenital systemic-to-pulmonary shunts. It is believed that endothelial cells can release mediators that induce vascular smooth muscle cell growth in response to changes in pulmonary blood flow or pressure. Experimental data suggest that medial hypertrophy can be converted to a neointimal pattern when pulmonary vascular injury is coupled with increased pulmonary blood flow.[65] These neointimal lesions are composed of smooth muscle cells that are immunoreactive to anti-alpha smooth muscle actin antibody. It is now accepted that hemodynamic shear stress acts through the endothelium to regulate vessel tone and in the chronic restructuring of blood vessels.[64] Endothelial denudation also results in platelet adherence to exposed tissue collagen, with release of platelet-derived smooth muscle mitogens that also have vasoconstrictor properties. This process in turn leads to an inflammatory response and thrombosis, thereby narrowing the lumen of pulmonary vessels. In a person who is susceptible--whether on a genetic or an acquired basis--intense vasoconstriction may lead to fibrinoid necrosis of the arteriolar wall and the development of plexiform lesions. Ultimately, the vessels are reduced in number, and the residua of these destroyed vessels can be seen histologically as "ghost vessels." Destruction of large numbers of pulmonary arterioles reduces the cross-sectional

Figure 53-5 Photomicrographs of pulmonary arterial histological lesions seen in clinically unexplained pulmonary hypertension. All slides were stained with Verhoeff-van Gieson stain. *A,* Medial hypertrophy (×100). *B,* Concentric laminal intimal fibrosis--seen most often in association with plexiform lesions (×200). *C,* Plexiform lesion demonstrating obstruction in the arterial lumen, aneurysmal dilatation, and proliferation of anastomosing vascular channels (×200). *D,* Eccentric intimal fibrosis--often seen in association with organized microthrombi but also present in many patients with plexiform lesions (×100). (From Palevsky HI, Schloo BL, Pietria CC, et al: Primary pulmonary hypertension. Vascular structure,

morphometry and responsiveness to vasodilator agents. Circulation 80:1207, 1989.)

area of the pulmonary vascular bed, thereby producing a permanent increase in pulmonary vascular resistance and fixed pulmonary hypertension. The latter in turn damages other blood vessels and initiates a vicious circle, with progressively rising pulmonary arterial pressure (Fig. 53-6) (Figure Not Available) .

Vascular remodeling is becoming recognized as an important component in the pathogenesis of pulmonary hypertension.[64] An essential role of ACE in the pathogenesis of pulmonary hypertension is strongly suggested by the presence of increased ACE immunoreactivity at sites of increased matrix gene expression in human hypertensive pulmonary arteries.[66] Further supporting a role for ACE in pulmonary vascular remodeling are observations that ACE protein and mRNA expression are focally increased in rat pulmonary arteries with medial hypertrophy from chronic hypoxia.[67]
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Increased activity of elastolytic enzymes appears to be important in the pathophysiology of pulmonary vascular disease.[68] High elastin turnover and neosynthesis of elastin have been attributed to degradation of elastin from the increased activity of serine elastase. A cause-and-effect relationship between elastase and pulmonary vascular disease was demonstrated when elastase inhibitors were shown to be effective in attenuating the development and retarding the progression of pulmonary hypertension in monocrotaline-injected and hypoxic rats.[69] Progression of pulmonary hypertension may involve a series of switches in smooth muscle cell phenotype and proliferation to account for the medial hypertrophy and smooth muscle cell migration resulting in neointimal formation. Structural and functional alterations in the endothelial cell could result in loss of barrier function and allow leakage into the subendothelium of a serum factor normally excluded from this region. Enzymes released from precursor or mature smooth muscle cells could activate growth factors normally stored in the extracellular matrix, such as basic fibroblast growth factor and transforming growth factor-beta, which are known to induce smooth muscle cell hypertrophy and proliferation and increase connective tissue protein synthesis. In muscular arteries, release of growth factors would result in hypertrophy of the vessel wall[69] (Fig. 53-7) .

Potassium channels are found throughout the pulmonary vascular bed.[35] They consist of voltage-dependent potassium channels and calcium-dependent potassium channels (see also Chap. 22) . The role of these channels has been studied primarily in the presence of acute hypoxia in animals. It is believed that potassium channels modulate adult pulmonary vascular tone. It is probable that calcium channels also serve a regulatory role in modulating vascular tone, particularly the L-type calcium channel. Inhibition of the voltage-regulated potassium channel by hypoxia or drugs can produce vasoconstriction and has been described in pulmonary artery smooth muscle cells harvested from patients with PPH.[70] It has been suggested that defects in the potassium channel of pulmonary resistance smooth muscle cells are involved in the initiation or progression of pulmonary hypertension. A genetic defect related to potassium channels in the lungs of patients with PPH that leads to vasoconstriction may

be one mechanism for the development of PPH in some patients[70] (Fig. 53-8) .

The dysfunctional pulmonary hypertensive endothelial cell phenotype is characterized by uncontrolled proliferation, increased production of vasoconstrictor mediators such as endothelin, expression of 5-lipoxygenase, and decreased synthesis of prostacyclin. In normal lungs, larger proximal pulmonary arteries express more prostacyclin synthase than do smaller arteries.[71] In patients with PPH, expression of prostacyclin synthase is reduced in pulmonary arteries ranging from 1 mm to less than 100 mum in diameter, which suggests that the reduction in prostacyclin synthesis in otherwise morphologically normal to minimally remodeled vessels may play a role in the early stages of pathogenesis. Alternatively, endothelial cells of pulmonary small arteries may become dysfunctional as the disease progresses and pulmonary artery pressure progressively rises. The decrease in prostacyclin production by pulmonary endothelial cells could predispose the lung vessels to additional vasoconstriction and/or in situ thrombosis from enhanced platelet adhesion. Loss of expression of prostacyclin synthase is one of the phenotypic alterations present in pulmonary endothelial cells in severe pulmonary hypertension.[71]

Serotonin may play a role in pulmonary hypertension. Elevations in serotonin levels have been correlated with the pulmonary vascular pressure gradient in patients with acute respiratory distress syndrome.[72] Children with congenital heart disease and pulmonary hypertension have increased turnover of serotonin.[73] PPH has been reported in a patient with familial platelet storage pool disease, which represents a defect in serotonin handling and release.[74]

One series reported increased serotonin in patients with pulmonary hypertension associated with the use of fenfluramine and with collagen-vascular disease.[75] Of interest is that after six of these patients underwent heart/lung transplantation, they had persistently elevated concentrations of plasma serotonin and decreased platelet serotonin concentrations, thus suggesting that the abnormality in platelet serotonin handling was a primary process in the evolution of their pulmonary hypertension.

Genetics

An important emerging concept in the development of PPH is that the disease develops in patients with an underlying genetic predisposition following exposure to specific stimuli, which serve as triggers. Predisposition to the development of pulmonary hypertension has been noted by the marked heterogeneity in responses of the pulmonary vasculature

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Figure 53-6 (Figure Not Available) Possible pathogenesis of primary pulmonary hypertension (PPH). Endothelial injury or dysfunction sets off a cascade of cellular events that lead to the abnormal pulmonary vascular response seen in PPH and subsequently to a perpetuating vicious circle promoting plexogenic and thrombotic pulmonary arteriopathy. (From Rubin L J: ACCP Consensus Statement: Primary

pulmonary hypertension. Chest 104:236, 1993.)

Figure 53-7 Schema of the pathophysiology of pulmonary hypertension related to elastase activity. Alterations in the endothelium that result in loss of its barrier function may allow leakage of a serum factor that stimulates smooth muscle cell (SMC) production and release of endogenous vascular elastase (EVE). EVE will degrade elastin and proteoglycans, which serve as storage sites for growth factors such as transforming growth factor-beta (TGFbeta) and basic fibroblast growth factor (bFGF). Subsequent stimulation of production of the matrix glycoprotein tenascin leads to an increase in SMC hypertrophy and the synthesis of connective tissue (CT) proteins. The elastin peptides also stimulate production of the matrix glycoprotein fibronectin, which changes SMC from a contractile to a migratory phenotype. (From Rabinovitch M: Pulmonary hypertension: Updating a mysterious disease. Caradiovasc Res 34:268-272, 1997. Copyright 1997, with permission from Elsevier Science.)

Figure 53-8 One proposed cellular mechanism responsible for the development of primary pulmonary hypertension initiated by abnormal gene transcription and expression of voltage-regulated potassium (K_v) channels. Increased calcium influx would raise cytosolic calcium ($[Ca^{2+}]_{cyt}$) and serve to trigger pulmonary vasoconstriction and stimulate cell proliferation with subsequent pulmonary vascular remodeling. Endothelium-derived relaxing factors (EDRFs) also participate in regulating potassium and calcium channels in pulmonary artery smooth muscle cells (PASMCs). (From Yuan JX, Aldinger AM, Juhaszova M, et al: Dysfunctional voltage-gated K^+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. Circulation 98:1400-1406, 1998.)

in a variety of disease states. Examples include the considerable variability among individuals to vasoconstrictive stimuli such as hypoxia or acidosis, which can produce marked pulmonary hypertension in one person and be essentially without effect in another. The pulmonary arterial pressure response to hypoxia is particularly great in individuals with blood group A.[14] This variability in responsiveness of the pulmonary vascular bed undoubtedly accounts for the fact that pulmonary edema develops in only a minority of individuals on exposure to high altitude. Also, the severity of pulmonary hypertension and the level of pulmonary vascular resistance vary considerably among individuals with congenital heart disease and comparably sized ventricular septal defects. Presumably, a genetic basis underlies these differences in pulmonary vascular reactivity, just as there appears to be a genetic basis for the increased reactivity of the systemic vascular bed in essential systemic hypertension.

FAMILIAL PPH.

PPH has been diagnosed in families worldwide. The prevalence of familial PPH is uncertain, but it occurs in at least 6 percent of cases and the incidence is probably higher.[76] Many unique features are associated with the transmission and development of PPH in families.[77] The age of onset is variable and penetrance is incomplete. Many individuals in families with PPH inherit the gene and have progeny in whom PPH never

develops. The observation that fewer males are born in PPH families than in the population at large suggests that the PPH gene might influence fertilization or cause male fetal wastage.

Patients with familial PPH have a similar female-to-male ratio, age of onset, and natural history of the disease as those with sporadic PPH. Documentation of familial PPH can be difficult since remote common ancestry occurs in patients with apparently sporadic PPH and skip generations caused either by incomplete penetrance or by variable expression can mimic sporadic disease. Because the clinical and pathological features of familial and sporadic PPH are virtually identical, it seems likely that the same genes may be involved in both forms of the disease. It also seems likely that the disease will not be due to an abnormal gene product resulting from a mutation but rather due to abnormal production or regulation of a normal gene product.

Vertical transmission has been demonstrated in as many as five generations in one family and is probably indicative of a single dominant gene that is believed to be autosomal for PPH.[78] Genetic anticipation has been described in familial PPH since the early reports. Trinucleotide repeat expansion, originally described in several neurological disorders, remains the only known biological explanation for genetic anticipation in PPH and raises the possibility that the pathogenesis of familial PPH might have a neurological basis (Fig. 53-9) .

The locus of a gene linked to familial PPH has been identified on chromosome 2q31,-33,[78A] and analysis of the genome containing the gene has been reduced to less than 7 million base pairs.[79] PPH-1 is the Human Genome Organization-approved designation DGB:1381541. The low penetrance of this gene confers only about a 10 to 20 percent likelihood of development of the disease.

Risk Factors in the Development of PPH

Although pulmonary hypertension can be the clear result of a disease process affecting the pulmonary parenchyma or vessels directly, a number of conditions have been identified that appear to be associated with the development of primary or unexplained pulmonary hypertension. Risk factors for PPH include drugs, chemical products, and other diseases. Expression of PPH may depend on other clinical features, such as the patient's gender or age at the time of disease expression.[80] The clinical features of PPH in patients with known risk factors are generally determined by the severity of the PPH and whatever influence the risk factor has on the overall medical condition. For example, the association of PPH and cirrhosis would have the combined clinical features of PPH and liver disease.

PORTAL HYPERTENSION

Pulmonary abnormalities have been commonly associated with the development of hepatic cirrhosis and portal hypertension[81] and include hypoxemia and intrapulmonary shunting, portal-pulmonary shunting, impaired hypoxic pulmonary vasoconstriction, and pulmonary hypertension.[82] [83] [84] Studies show that the liver plays an important role in regulating pulmonary vascular tone. Although the relative risk associated with the

development of pulmonary hypertension in patients with portal hypertension is unknown, a large postmortem study from the Johns Hopkins Hospital showed that the prevalence of unexplained or pulmonary hypertension in patients with cirrhosis was 5.6 times higher than that of PPH alone. A modest increase in pulmonary artery pressure is not unusual in patients with cirrhosis and portal hypertension.[83] The increase in pulmonary artery pressure is usually passive and relates to the increase in cardiac output and/or blood volume and is associated with near-normal pulmonary vascular resistance. Published studies indicate a strong association between portal hypertension and pulmonary hypertension regardless of

Figure 53-9 The pedigrees of two families (*A* and *B*) with familial primary pulmonary hypertension (PPH). Shaded symbols represent affected individuals. Genotyped individuals are indicated by the respective pedigree designations. The PPH-1 region on chromosome 2 (2q31-q32) contains a number of candidate genes. (From Morse JH, Jones AC, Barst RJ, et al: Mapping of familial primary pulmonary hypertension locus (PPH-1) to chromosome 2q31-32. Circulation 95:2603-2606, 1997.)

whether liver disease is present.[84] [85] [86] Although the mechanisms are uncertain, several possibilities are consistent. Portal hypertension itself induces numerous modifications in the vascular medium that may trigger a cascade of intracellular signals and/or cause activation or repression of various genes in endothelial and smooth muscle cells.

Pulmonary hypertension may develop in susceptible patients with portal hypertension in response to an increase in vascular wall shear stress caused simply by the increased pulmonary blood flow through the lungs. The presence of a portosystemic shunt may also allow substances normally cleared by the liver to gain access to the pulmonary circulation. Increased levels of several vasoactive mediators, cytokines, and growth factors have been demonstrated in patients with portal hypertension, including serotonin and interleukin-1.[86] Other angiogenic factors such as hepatocyte growth factor or vascular endothelial growth factor may be involved in pulmonary artery remodeling.[87] [88]

Patients in whom PPH develops in association with cirrhosis appear to be similar to patients without cirrhosis with the sole exception that they tend to have higher cardiac output and consequently lower calculated systemic and pulmonary vascular resistance, which is characteristic of the cirrhotic state.[83] Treatment of portal pulmonary hypertension generally follows the guidelines developed for treating patients with PPH. Although severe pulmonary hypertension is considered a contraindication to liver transplantation because of the risk of irreversible right-sided heart failure, successful liver transplantation has been reported in patients with mild pulmonary hypertension.[89] [90] Whether the pulmonary circulation will eventually return to normal posttransplantation remains uncertain.

ANOREXIGENS

Several anorexigens have been demonstrated to cause pulmonary hypertension in humans. The first observation was made in 1967, when an epidemic of PPH was associated with the use of aminorex in Europe coincident with its introduction in the general population.[91] The mechanism by which aminorex causes pulmonary hypertension remains uncertain, but it has similarities to both adrenaline and ephedrine in its chemical structure. The clinical features of pulmonary hypertension were identical to those attributed to PPH.

In 1981 a cause-and-effect relationship between the ingestion of fenfluramine, another appetite suppressant, and the development of pulmonary hypertension was established in a patient in whom PPH developed but reversed upon drug withdrawal and then redeveloped upon rechallenge.[92] The magnitude of the association between the use of appetite suppressants and the development of PPH was clearly defined in the International Primary Pulmonary Hypertension Study (IPPHS), a case-control study conducted in Europe in 1992-1994.[40] In addition to the association between the use of appetite suppressants and the development of pulmonary hypertension, the IPPHS described a dramatic increase in the risk of development of pulmonary hypertension with increased duration of use. The study resulted in severe restriction of the use of appetite suppressants in Europe, only to see their use popularized in the United States. Ultimately, the marked increase in the number of cases of PPH and cardiac valvulopathy ascribed to the use of fenfluramine drugs in the United States led to their withdrawal in 1997. Unfortunately, in the majority of patients the development of pulmonary hypertension has been progressive despite withdrawal of the appetite suppressants.[93] [94] [94A] Although the drugs mainly identified in the IPPHS were the fenfluramines, amphetamine-like anorexigens were also implicated.

The mechanism by which the fenfluramines and aminorex produce pulmonary hypertension has been investigated. Experimental studies have demonstrated that these drugs can cause pulmonary vasoconstriction by inhibiting voltage-gated potassium channels in the smooth muscle cells of resistance-level pulmonary arteries.[95] Although the degree of pulmonary vasoconstriction noted was small, it increased dramatically when NO synthase was inhibited. One recent study compared NO production in patients with PPH and patients with pulmonary hypertension associated with the use of anorexigens.[96] It appears that the latter group had a deficiency in basal NO production when compared with patients with PPH, which suggests that NO may be a compensatory product of the pulmonary arterial endothelium that increases in pulmonary hypertension to counteract the effects of chronic vasoconstriction.

Because of the consistent association with anorexigens and unexplained pulmonary hypertension, clinicians should be exceedingly careful in the use of these drugs in the future, especially in patients who may have increased susceptibility to the development

of pulmonary hypertension (Fig. 53-10) .

HIV INFECTION

Although well documented, it remains unclear how human immunodeficiency virus (HIV) infection results in an increased incidence of PPH in HIV-infected patients.[97] [98] A direct pathogenic role of HIV seems unlikely inasmuch as no viral constituents have been detected in the vascular endothelium of these patients.[99] On the other hand, reports of pulmonary arteriopathy with intimal proliferation in monkeys experimentally infected with the simian immunodeficiency virus and in a murine model of acquired immunodeficiency syndrome suggest a pathogenetic link between infection with an immunodeficiency virus and the development of PPH, possibility mediated by release of inflammatory mediators or by autoimmune mechanisms.[100] A large case-control study of HIV-associated PPH was recently conducted in the Swiss HIV Cohort Study.[101] The cumulative incidence was 0.6 percent within the entire HIV-infected population. PPH was diagnosed in all stages of HIV infection and without an obvious relationship to immune deficiency. The clinical and hemodynamic features of these patients were similar to those of patients with PPH. Of great interest, however, is that antiretroviral treatment seemed to exert a beneficial effect on the course of hemodynamic progression of the disease.

SYSTEMIC HYPERTENSION

Systemic hypertension is two to three times more common in patients with PPH than in an age-matched population.[40] The underlying mechanisms related to the development of essential hypertension are quite diverse, but the possibility exists that in some patients the mechanism that increases systemic vascular resistance similarly affects the pulmonary vascular bed.[102] It has been suggested that neurohumoral factors may play a role[103] or that the pulmonary vasculature is hypercontractile and overreacts to sympathetic stimulation.[104] Given that essential hypertension is extremely common in the general population, other confounding factors probably contribute to the development of pulmonary hypertension in affected individuals.

INCREASED PULMONARY BLOOD FLOW

For many years it has been observed that PPH can develop in adulthood in patients with atrial septal defect.[105] However, the incidence of this combination is extremely low, thus raising the possibility that they are two completely unrelated events. It is possible that chronically increased pulmonary blood flow may have effects on pulmonary endothelium through some type of mechanical means that would cause perturbations in the integrity of the vascular wall and lead to the development of pulmonary vascular disease. Increased pulmonary blood flow from hyperthyroidism and beriberi have been reported to be associated with the development of unexplained pulmonary hypertension, which suggests that high pulmonary blood flow,[106] rather than mere coincidence, is the basis for the development of pulmonary

Figure 53-10 Relationship between duration of exposure to anorectic drugs and the development of primary pulmonary hypertension (PPH). The odds ratio of PPH developing increases with increased duration of use. The number of controls taking anorectic drugs in whom PPH does not develop diminishes over time, which raises the possibility that a marked increase in duration of exposure could eventually convert all the controls into cases. (From Abenhaim L, Moride Y, Brenot F, et al: Appetite suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 335:609-616, 1996. Copyright © 1996 Massachusetts Medical Society. All rights reserved.)

hypertension in patients with pretricuspid shunts such as atrial septal defect or anomalous pulmonary venous drainage.

PATHOLOGICAL FINDINGS

Morphological abnormalities in each cell line have been described in PPH.[3] [49] [50] The endothelium in particular displays marked heterogeneity in the pulmonary vascular bed. Although endothelial dysfunction has been clearly described in PPH, discordance between phenotype and function is commonly noted.[107] It is not known at what stage during the evolution of PPH that endothelial cell proliferation occurs. It has been proposed, however, that a somatic mutation rather than nonselective cell proliferation in response to injury may account for the growth advantage of endothelial cells in PPH.[108] Heterogeneity in the smooth muscle and fibroblast populations also contributes to discordance between phenotype and function. Interconversion between cell types (fibroblast to smooth muscle cell or endothelium to smooth muscle cell) in addition to neovascularization may occur.

In the large muscular and elastic arteries, smooth muscle cell hypertrophy and increased connective tissue and extracellular matrix are found.[68] [69] In the subendothelial layer, increased thickness may be the result of recruitment and/or proliferation of smooth muscle-like cells. It is possible that precursor smooth muscle cells are in a continuous layer in the subendothelial layer along the entire pulmonary artery. These cells are similar to the pericytes that are responsible for the appearance of muscle in normally nonmuscular arteries and that contribute to intimal thickening in larger arteries. Alterations in the extracellular matrix secondary to proteolytic enzymes also play a role in the pathology of

TABLE 53-1 -- HISTOPATHOLOGICAL CLASSIFICATION OF HYPERTENSIVE PULMONARY VASCULAR DISEASE

CLASSIFICATION	CHARACTERISTIC HISTOPATHOLOGICAL FEATURES
Arteriopathy	
Isolated medial hypertrophy*	Medial hypertrophy: increase of medial muscle in muscular arteries, muscularization of nonmuscularized arterioles; no appreciable intimal or luminal obstructive lesions. No plexiform lesions

Plexogenic pulmonary arteriopathy	Plexiform and dilatation lesions. Medial hypertrophy; eccentric or concentric-laminar and nonlaminar intimal thickening; fibrinoid necrosis, arteritis, and thrombotic lesions
Thrombotic pulmonary arteriopathy	Thrombi (fresh, organizing, or organized and colander lesions). Eccentric and concentric nonlaminar intimal thickening, varying degrees of medial hypertrophy. No plexiform lesions
Isolated pulmonary arteritis	Active or healed arteritis. Limited to pulmonary arteries; varying degrees of medial hypertrophy, intimal fibrosis, and thrombotic lesions. No plexiform lesions. No systemic arteritis
Venopathy	
Pulmonary venoocclusive disease	Eccentric intimal fibrosis and recanalized thrombi within pulmonary veins and venules; arterialized veins, capillary congestion, alveolar edema and siderophages, dilated lymphatics, pleural and septal edema, and arterial medial hypertrophy; intimal thickening and thrombotic lesions
Microangiopathy	
Pulmonary capillary hemangiomatosis	Infiltrating thin-walled blood vessels throughout pulmonary parenchyma, pleura, bronchi, and walls of pulmonary veins and arteries. Medial hypertrophy and intimal thickening of muscular pulmonary arteries and arterioles

Reprinted from Pietra GG: Pathology of primary pulmonary hypertension. In Rubin LJ, Rich S (eds): Primary Pulmonary Hypertension. New York, Marcel Dekker, 1997, pp 19-61 by courtesy of Marcel Dekker, Inc.

*Medial hypertrophy includes muscularization of arterioles.

PPH. Matrix-degrading enzymes can release mitogenically active growth factors that stimulate smooth muscle cell proliferation. In addition, elastase and matrix metalloproteinases contribute to upregulation of proliferation. Degradation of elastin has also been shown to stimulate upregulation of the glycoprotein fibronectin, which in turn stimulates smooth muscle cell migration.[68]

The most common vascular changes in PPH can best be characterized as a *hypertensive pulmonary arteriopathy,* which is present in 85 percent of cases (Table 53-1) . These changes involve medial hypertrophy of the arteries and arterioles, often in conjunction with other vascular changes. Isolated medial hypertrophy is uncommon, and when present it has been assumed to represent an early stage of the disease. Plexogenic pulmonary arteriopathy is the most common pattern of hypertensive arteriopathy seen in patients with PPH.[3] [50] It is characterized by medial hypertrophy along with intimal proliferation and other complex lesions. The intimal proliferation may be concentric laminar intimal fibrosis, eccentric intimal fibrosis, or concentric nonlaminar intimal fibrosis. The frequency of these findings differs from case to case and within regions of the same lung in the same patient. In addition, plexiform and dilatation lesions, as well as a necrotizing arteritis, may be seen throughout the lungs. The

fundamental nature of the plexiform lesion remains a mystery.[109] It is possible that it represents endothelial cells that are involved prominently in angiogenesis, perhaps akin to a neoplastic process. Morphologically, they represent a mass of disorganized vessels with proliferating endothelial cells, smooth muscle cells, myofibroblasts, and macrophages. Several studies have demonstrated the involvement of growth factors that have been implicated in angiogenesis.[110] Whether the plexiform lesion represents impaired proliferation or angiogenesis remains unclear. These lesions, however, are not pathognomonic for PPH but representative of a chronic, severe pulmonary hypertensive state.

The other major pattern of vascular changes in PPH is that of a *thrombotic pulmonary arteriopathy.*[111] Typical features include medial hypertrophy of the arteries and arterioles with both eccentric and concentric nonlaminar intimal fibrosis. The presence of colander lesions, which represent recanalized thrombi, is also typical. These lesions are believed to arise as a result of primary in situ thrombosis of the small vascular arteries and not from recurrent pulmonary embolism.

On rare occasion, a diffuse pulmonary arteritis with secondary thrombosis has been reported in patients with PPH, predominantly in children.[112] Although the association has not been reported in patients with underlying collagenvascular disease, it may reflect the vascular response to a specific, but not clearly identified risk factor.

PULMONARY VENOOCCLUSIVE DISEASE

Pulmonary venoocclusive disease is a rare form of PPH observed in approximately 5 percent of cases.[49] [50] The histopathological diagnosis is based on the presence of obstructive eccentric fibrous intimal pads within the pulmonary veins and venules. Arterialization of the pulmonary veins is often present and associated with alveolar capillary congestion. Other changes of chronic pulmonary hypertension such as medial hypertrophy and muscularization of the arterioles with eccentric intimal fibrosis may also be seen. The pulmonary venous obstruction explains the increased pulmonary capillary wedge pressure described in patients in the late stages of the disease and the increase in basilar bronchovascular markings described on the chest radiograph. These clinical findings, along with a perfusion lung scan showing diffuse, patchy nonsegmental abnormalities, is highly suggestive of the diagnosis on a clinical basis.[113] [114] [115]

PULMONARY CAPILLARY HEMANGIOMATOSIS

This extremely rare condition is characterized by proliferation of the thin-walled microvessels that infiltrate the peribronchial and perivascular interstitium and lung parenchyma.[116] On occasion, it may be confused with pulmonary venoocclusive disease. The lesions are often patchy and the proliferating vessels may form small nodules within the alveolar interstitial space. These thin-walled vessels are prone to bleeding and may be manifested clinically as overt hemoptysis in affected patients. The perfusion lung scan in these patients may show "hot spots" reflective of local areas within the lung that have increased vascularity. These areas are typically seen at the lung periphery and can be confirmed by pulmonary angiography.[117] The natural history

of this form of PPH is not yet defined.[118] [119]

CLINICAL FEATURES

NATURAL HISTORY AND SYMPTOMATOLOGY.

The most extensive study on the natural history of PPH was reported from the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension from 1981 to 1987.[76] The study included the long-term follow-up of 194 patients in whom PPH was diagnosed by established clinical and hemodynamic criteria. Sixty-three percent of the patients were female, and the mean age was 36 ± 15 years (range, 1 to 81 years) at the time of diagnosis. The mean interval from the onset of symptoms to diagnosis was 2 years, and

the most common initial symptoms were dyspnea (80 percent), fatigue (19 percent), syncope or near syncope (13 percent), and Raynaud phenomenon (10 percent). No ethnic differentiation was observed, with 12.3 percent being black and 2.3 percent being Hispanic.

Syncope is a characteristic symptom of PPH and is assumed to be due to a fixed cardiac output. A recent study on the systolic function and interactions of the left and right ventricles in patients with PPH revealed an increased right ventricular end-diastolic volume and reduced right ventricular ejection fraction, with a greater stroke volume than in the left ventricle.[120] The mechanism for maintaining cardiac output with exercise was primarily through an increased heart rate inasmuch as stroke volume actually decreased. The right ventricular ejection fraction decreased with exercise, thus suggesting exercise-induced right ventricular failure. This result is expected because pulmonary artery pressure increases with exercise in PPH. The left ventricular ejection fraction is maintained, however, but left ventricular end-diastolic volume decreases and left ventricular end-systolic volume becomes extremely small, which suggests that the left ventricle is shortening to its maximum extent. The fact that left ventricular end-diastolic and end-systolic volumes decreased whereas right ventricular end-systolic and end-diastolic volumes remained unchanged supports the concept that underfilling and not external compression accounts for the small left ventricular chamber size observed in PPH. Syncope occurs because of exercise-induced right ventricular failure whereby the heart rate becomes the only mechanism available to increase cardiac output, which has limited effectiveness.

On *physical examination,* an increased pulmonic component of the second heart sound was the most common finding (93 percent), with tricuspid regurgitation noted in 40 percent and peripheral edema in 32 percent. In 90 percent of patients the chest radiograph revealed enlargement of the main pulmonary arteries, and the electrocardiogram revealed right ventricular hypertrophy in 87 percent. The clinical profiles of these patients were remarkably similar to those in a previously reported

retrospective study of 120 patients from the Mayo Clinic.[57] In the Mayo Clinic series, 75 percent of the patients were women with a mean age of 34 years (range, 3 to 64 years) and a mean interval from onset of symptoms to diagnosis of 1.9 years.

The NIH Registry also revealed that restrictive changes in pulmonary function testing and reduced diffusing capacity for carbon monoxide were very common, with forced vital capacity approximately 80 percent of predicted and diffusing capacity 70 percent of predicted. These changes, however, do not correspond to any measure of severity of the pulmonary hypertension. An additional, virtually universal finding was mild to moderate hypoxemia (mean P_{O_2} of 72 ± 16 mm Hg), which is attributed to the effect of low mixed venous oxygen from low cardiac output amplified by the underlying ventilation-perfusion inequality.

The hemodynamic findings also suggested that the severity of the disease could be related to a rising right atrial pressure and falling cardiac index, both of which reflect underlying right ventricular dysfunction. The fact that the mean pulmonary artery pressure was similar in patients whose duration of symptoms was less than 1 year and those who were symptomatic for more than 3 years suggests that pulmonary artery pressure rises to fairly high levels early in the course of the disease.

Univariate analysis from the NIH Registry pointed to the mean right atrial pressure, mean pulmonary artery pressure, and cardiac index, as well as the diffusing capacity from carbon monoxide, as significantly related to mortality.[121] In addition, the New York Heart Association classification has also been shown to relate very strongly to survival. Based on estimates obtained from the proportional hazards model, a regression equation was developed that describes the relationship between these three hemodynamic variables and subsequent mortality.

where P(t) = percent survival at t years, t = number of years, x = mean pulmonary artery pressure, y = mean right atrial pressure, and z = cardiac index. This equation has since been validated in two subsequent studies,[122] [123] which suggests that baseline hemodynamic characteristics are very predictive of outcome.

The most common cause of death in patients with PPH in the NIH Registry was progressive right-sided heart failure (47 percent). Sudden cardiac death (both witnessed and unwitnessed) occurred in 26 percent. Of interest is that sudden cardiac death was limited to patients who were New York Heart Association Class IV, thus suggesting that it is a manifestation of end-stage disease rather than a phenomenon that occurs early or unpredictably in the clinical course of the disease. The remainder of the patients died of some other medical complication such as pneumonia or bleeding, which suggests that patients with PPH do not tolerate coexistent medical conditions well. In the NIH Registry experience, no deaths or sustained morbidity was associated with the diagnostic evaluation done at baseline assessment. It should be pointed out, however, that these

were university centers with established experience in the management of patients with PPH.

MECHANISMS OF RIGHT VENTRICULAR FAILURE.

It is presumed that right ventricular dysfunction in patients with chronic pulmonary hypertension is a result of chronic pressure overload and associated volume overload with the development of tricuspid regurgitation. However, animal studies suggest that right ventricular ischemia may also be a feature and potentially a very common one.[124] The mechanism of right ventricular failure in pulmonary hypertension is complex. The chronic pressure overload that induces right ventricular hypertrophy and reduced contractility has been shown to cause a reduction in coronary blood flow to the right ventricular myocardium, which can produce right ventricular ischemia, both acutely and chronically. Such right ventricular dysfunction appears to be a result of a reduction in right ventricular coronary artery driving pressure. In an interesting animal study by Vlahakes and colleagues[124] acute right ventricular failure secondary to right ventricular hypertension was overcome by increasing central aortic pressure, which resulted in an increase in right ventricular coronary driving pressure. Murray and Vatner[125] reported that a moderate increase in aortic pressure was accompanied by a large increase in right ventricular myocardial perfusion only when the autonomic nervous system was blocked with an alpha blocker. Because the symptom of angina associated with PPH is characteristic of myocardial ischemia, it probably represents ongoing ischemia caused by this phenomenon.

On occasion, patients with pulmonary hypertension may have a reduced left ventricular ejection fraction and even regional wall motion abnormalities of the left ventricle. In the past, these findings had been attributed to mechanisms related to interventricular dependence, which suggests that in some way a dysfunctional right ventricle can lead to a dysfunctional left ventricle.[126] Clearly, the shared interventricular septum can affect the function of both ventricles. More recently, extrinsic compression of the left main coronary artery by the pulmonary artery in patients with chronic pulmonary hypertension has been described and may be associated with classic angina-like symptoms.[127] [128] It is advisable to look for extrinsic compression of the left main coronary artery with coronary angiography in patients with longstanding pulmonary hypertension who have abnormal left ventricular function.

The clinical course of patients with PPH can be highly variable. However, with the onset of overt right ventricular failure manifested by worsening symptoms and systemic venous congestion, patient survival is generally limited to approximately 6 months. Understanding the clinical course of patients with PPH is important, especially when considering major interventional therapy such as organ transplantation.

PHYSICAL EXAMINATION.

Findings are consistent with pulmonary hypertension and right ventricular pressure overload: a large *a* wave in the jugular venous pulse; a low-volume carotid arterial pulse

with a normal upstroke; a left

parasternal (right ventricular) heave; a systolic pulsation produced by a dilated, tense pulmonary artery in the second left interspace; an ejection click and flow murmur in the same area; a closely split second heart sound with a loud pulmonic component; and a fourth heart sound of right ventricular origin. Late in the course, signs of right ventricular failure (hepatomegaly, peripheral edema, and ascites) may be present. Patients with severe pulmonary hypertension may also have prominent *v* waves in the jugular venous pulse as a result of tricuspid regurgitation, a third heart sound of right ventricular origin, a high-pitched early diastolic murmur of pulmonic regurgitation, and a holosystolic murmur of tricuspid regurgitation. Cyanosis is a late finding in PPH and may be worsened by a patent foramen ovale with right-to-left shunting. Other causes of cyanosis include a markedly reduced cardiac output with systemic vasoconstriction and ventilation-perfusion mismatches in the lung. Uncommonly, the left laryngeal nerve becomes paralyzed as a consequence of compression by a dilated pulmonary artery (Ortner syndrome).

LABORATORY FINDINGS

HEMATOLOGICAL AND CHEMICAL STUDIES.

Results of these studies are usually normal in patients with PPH. If chronic arterial oxygen desaturation is noted, polycythemia may be present. A number of investigators have reported hypercoagulable states, abnormal platelet function, defects in fibrinolysis, and other abnormalities of coagulation in patients with PPH.[58] [59] Abnormal liver function tests results can indicate right ventricular failure with resultant systemic venous hypertension.

ELECTROCARDIOGRAPHY.

The electrocardiogram in PPH usually exhibits right atrial and right ventricular enlargement. A direct correlation between the amplitude of the R wave in V_1 , the R/S ratio in V_1 , and the level of pulmonary arterial pressure has been reported.

ROENTGENOGRAPHY.

Radiographic examination of the chest in patients with PPH shows enlargement of the main pulmonary artery and its major branches, with marked tapering of peripheral arteries. The right ventricle and atrium may also be enlarged. Fluoroscopic examination may disclose exaggerated pulsations of secondary pulmonary arterial branches reflecting an elevation in pulmonary arterial pulse pressure. However, in contrast to the plethoric peripheral lung fields in patients with left-to-right shunts, oligemia is noted in these lung regions in patients with PPH. It has been suggested that survival in PPH

correlates inversely with the size of the main pulmonary artery--a reasonable suggestion because the latter correlates with the height of pulmonary arterial pressure. The diameter of the pulmonary artery may be determined from computed tomographic (CT) scans and used to estimate pulmonary artery pressures.[129]

PULMONARY FUNCTION TESTS.

Pulmonary function tests typically show mild restriction with a reduced diffusion capacity for carbon monoxide (D_{LCO}) and hypoxemia with hypocapnea. Some patients have increased residual volume and reduced maximum voluntary ventilation.

ECHOCARDIOGRAPHY.

Echocardiography usually demonstrates enlargement of the right atrium and ventricle, normal or small left ventricular dimensions, and a thickened interventricular septum. The septal/posterior left ventricular wall ratio may be abnormally increased, as in hypertrophic obstructive cardiomyopathy, but other echocardiographic signs characteristic of that condition are not observed. Systolic prolapse of the mitral valve is frequently present, as well as abnormal septal motion of the ventricular septum, as a result of chronic right ventricular pressure overload and reduced left ventricular filling.[130] Doppler echocardiographic evidence of right ventricular systolic hypertension may be obtained by measuring the velocity of the tricuspid regurgitant jet and using the Bernoulli formula (see Chap. 7) . Doppler techniques have demonstrated left ventricular diastolic dysfunction with marked dependence on atrial contraction for ventricular filling.[130]

LUNG SCINTIGRAPHY.

A perfusion lung scan is an essential component in making the correct diagnosis of PPH. It may reveal a relatively normal perfusion pattern or diffuse, patchy perfusion abnormalities.[131] The severity of the perfusion abnormality in lung scans does not parallel the hemodynamics inasmuch as serial lung scans performed over time in patients with PPH do not show progressive changes consistent with the patients' worsening clinical state. A perfusion lung scan should help distinguish patients with PPH from those who have pulmonary hypertension secondary to chronic pulmonary thromboembolism (Fig. 53-11) . The risk associated with lung scans in PPH has been grossly overstated. The early literature reported three patients with pulmonary hypertension who died following lung scans, but it is not clear that the deaths were caused by the procedure. In the NIH Registry on PPH, not one morbid clinical event was associated with the performance of lung scans in any of the patients with pulmonary hypertension.[76]

PULMONARY ANGIOGRAPHY.

Pulmonary angiography is essential to establish the correct diagnosis in a patient with presumed PPH in whom a perfusion lung scan suggests segmental or lobar defects. Typically, pulmonary angiography demonstrates large central pulmonary arteries with marked peripheral tapering. Postmortem arteriograms demonstrate the absence of

"background haze" secondary to the loss of small, nonmuscular pulmonary arterioles. Although pulmonary angiography carries an increased risk in patients with PPH, it can be performed safely if adequate precautions are taken. The NIH Registry contains no deaths or serious morbidity associated with pulmonary angiography.

Maintenance of adequate oxygenation by the administration of supplemental oxygen and the avoidance of vasovagal reactions (and rapid treatment of those that occur with intravenous atropine) should reduce the associated risk in this patient group. Placement of an arterial line for continuous arterial pressure monitoring is advised, and nonionic contrast agents appear to be better tolerated. Injections are preferably limited to the individual lungs or specific lobes to reduce

Figure 53-11 Perfusion lung scans in patients with pulmonary hypertension. *A,* Patient with primary pulmonary hypertension (PPH). *B,* Patient with pulmonary thromboembolism causing pulmonary hypertension (PTE). Both perfusion scans are abnormal. The scan on the patient with PPH shows a mottled distribution in a nonsegmental, nonanatomical manner. The scan on the patient with PTE reveals lobar, segmental, and subsegmental defects highly suggestive of an anatomical obstruction to pulmonary blood flow.

TABLE 53-2 -- APPLICATIONS OF CATHETERIZATION IN ESTABLISHING THE ETIOLOGICAL DIAGNOSIS OF PULMONARY HYPERTENSION

CONDITION	TEST APPLIED	FINDING
Congenital heart disease	Step-up in O_2 saturation in right heart Step-down in O_2 saturation in left heart Cardiac angiography	Left-to-right shunt and location of shunt Right-to-left shunt and location of shunt Anatomical definition
Peripheral pulmonary artery stenoses	Intrapulmonary arterial pressure Pulmonary angiogram	Intrapulmonary arterial pressure gradients Pulmonary arterial branch stenoses
Proximal pulmonary arterial occlusion by clot or tumor*	Selective or main pulmonary angiography	Intravascular filling defect or narrowing, webs, poststenotic dilatation
Mitral stenosis Cor triatriatum Supravalvular mitral ring	Simultaneous wedge and left ventricular pressure recording	An elevated wedge pressure and mean mitral valve diastolic pressure gradient >3 mm Hg at rest, both of which increase with exercise

Mitral regurgitation	Simultaneous wedge and left ventricular pressure recording Left ventriculogram	Large systolic pressure wave in wedge tracing. Regurgitation of contrast from left ventricular angiogram into the left atrium
Left ventricular diastolic dysfunction Restrictive cardiomyopathy	Left ventricular pressure Right ventricular pressure	LVEDP >15 mm Hg LVEDP response to intravenous fluid challenge: normalization of LVEDP with marked reduction in pulmonary artery pressure with intravenous nitroprusside

LVEDP=left ventricular end-diastolic pressure.
Modified from Reeves JT, Groves BM: Approach to the patient with pulmonary hypertension. In Weir EK, Reeves JT: Pulmonary Hypertension. Mt Kisco, NY, Futura, 1984, p 20.

*Ventilation=perfusion lung scans precede catheterization.

the contrast load. Pulmonary wedge angiography using a segmental angiographic technique with hand injection of small amounts of angiographic contrast through the terminal lumen of a balloon flotation catheter while the balloon is inflated is not a substitute for pulmonary angiography.

COMPUTED TOMOGRAPHY OF THE CHEST.

Chest radiographs, as well as chest CT scans, have been used to determine the presence and severity of pulmonary hypertension based on the diameter of the main pulmonary arteries.[129] [132] This information may be useful when performing chest CT to investigate the lung parenchyma in patients with pulmonary hypertension who are undergoing diagnostic evaluation. In addition, high-resolution chest CT scans have been used successfully in diagnosing chronic thromboembolic pulmonary hypertension.[132] In addition to visualization of thrombi in the pulmonary vasculature with contrast enhancement, a mosaic pattern of variable attenuation compatible with irregular pulmonary perfusion can be determined in the unenhanced CT scan. Marked variation in the size of segmental vessels is also a specific feature of chronic thromboembolic disease. In some institutions, high-resolution CT scanning has replaced lung scintigraphy as a test to make this diagnosis.

EXERCISE TESTING.

The use of a symptom-limited exercise test can be very helpful in the evaluation of patients with pulmonary hypertension. Besides allowing objective assessment of the severity of symptoms, exercise testing has been shown to also be predictive of survival. Two types of exercise testing have recently become popularized. The Naughton protocol uses a treadmill with increases in work of 1-MET increments at 2-minute stages to allow patients with very limited exercise tolerance to perform. In the 6-minute walk

test, patients are instructed to walk down a 100-ft corridor and cover as much ground as possible within the 6 minutes. The total distance walked is determined by a tester. The application of exercise testing has been particularly helpful in evaluating the efficacy of drug therapy.[133]

CARDIAC CATHETERIZATION.

The diagnosis of PPH cannot be confirmed without cardiac catheterization (Table 53-2) . Besides allowing the exclusion of other causes, it also establishes the severity of disease and allows an assessment of prognosis. By definition, patients with PPH should have a low or normal pulmonary capillary wedge pressure. Although it has often been stated that one may be unable to obtain an accurate wedge pressure in these patients, such is rarely the case in experienced hands.[76] However, when an increased wedge pressure is obtained, it must be correlated with left ventricular end-diastolic pressure and not attributed to a "falsely elevated" reading.[134] It has been shown that left ventricular diastolic compliance becomes significantly impaired in PPH and parallels the severity of the disease; thus, pulmonary capillary wedge pressure tends to rise slightly in the late stages of PPH, although it rarely exceeds 16 mm Hg. Measurements of all right-sided pressures are properly made at expiration to avoid incorporating negative intrathoracic pressures.

It can be extremely difficult to pass a catheter into the pulmonary artery in patients with pulmonary hypertension because of the tricuspid regurgitation, dilated right atrium and ventricle, and low cardiac output. Flow-directed thermodilution balloon catheters, which are the proper devices to use, also lack stiffness and can be difficult to place. A specific flow-directed thermodilution balloon catheter has been developed for patients with pulmonary hypertension (American Edwards Laboratories, Irvine, CA); it has an extra port for the placement of a 0.32-inch guidewire to provide better stiffness to the catheter. The risk associated with cardiac catheterization in patients with PPH is extremely low in experienced hands, but deaths have been reported.[76]

DIAGNOSIS (Table 53-3)

It is essential that diagnostic efforts be pursued vigorously in patients with severe pulmonary hypertension to ensure that no patient with secondary pulmonary hypertension is erroneously classified as having PPH. Patients with PPH may tolerate diagnostic procedures poorly. These individuals can experience sudden cardiovascular collapse and even death during or shortly after the induction of general anesthesia for surgical procedures and during cardiac catheterization and angiography.

The *differential diagnosis* of PPH includes a number of well-defined causes of secondary pulmonary hypertension (Table 53-4) . Exclusion of mitral stenosis, congenital cardiac defects (including cor triatriatum, pulmonary thromboembolism, and pulmonary venous obstruction by means of catheterization and angiography is imperative. "Silent" mitral stenosis, i.e., without the characteristic diastolic murmur, can be excluded by means of echocardiographic visualization of the motion of the mitral valve and the absence

TABLE 53-3 -- DIAGNOSTIC STUDIES USEFUL FOR ELUCIDATING CAUSES OF PULMONARY HYPERTENSION

POTENTIAL CAUSE OF PULMONARY HYPERTENSION	DIAGNOSTIC STUDIES
Pulmonary thromboembolic disease	Ventilation/perfusion scans, computed tomography of chest, pulmonary angiography
Pulmonary venous thrombosis or obstruction	Chest x-ray, angiography, computed tomography, magnetic resonance imaging
Congenital intracardiac shunts	Transesophageal echocardiography with contrast
Increased left atrial pressure secondary to mitral or aortic valve disease, left ventricular dysfunction, or systemic hypertension	Pulmonary artery wedge pressure or left atrial pressure (via patent foramen ovale) (>15 mm Hg and LVEDP)
Pulmonary airway disease (e.g., chronic bronchitis and emphysema)	Respiratory function tests (FVC/FEV, chest x-ray)
Hypoxic pulmonary hypertension associated with (1) impaired ventilation, either central (CNS) or peripheral (chest wall problems or upper airway obstruction) and (2) residence at high altitude	Sleep apnea studies and respiratory function tests
Interstitial lung disease, pneumoconioses, and fibrosis (e.g., silicosis, rheumatoid disease, and sarcoidosis)	Chest x-ray, spirometry and carbon monoxide diffusion, high-resolution chest computed tomography
Collagen-vascular disease (e.g., SLE, polyarteritis nodosa, scleroderma)	Serological and immunogenetic studies; skin, muscle, or other tissue biopsy; esophageal motility studies
Parasitic disease (schistosomiasis or filariasis)	Rectal biopsy, complement fixation, skin tests, blood smears
Cirrhosis with portal hypertension	Liver function tests, ultrasonography, computed tomography
Peripheral pulmonary artery stenosis (including Takayasu disease and fibrosing mediastinitis)	Selective pulmonary angiography or pressure gradient at catheterization
Sickle cell disease	Erythrocyte morphology, hemoglobin electrophoresis

CNS=central nervous system; FEV_1 =forced expiratory volume in 1 second; FVC=forced vital capacity; SLE=systemic lupus erythematosus.
Modified from Weir EK: Diagnosis and management of primary pulmonary hypertension. In Weir EK, Reeves JT: Pulmonary Hypertension. Mt Kisco, NY, Futura, 1984, p 141.

of a transvalvular pressure gradient (see Chap. 46) . *Congenital cardiac defects* with Eisenmengers syndrome can usually be ruled out if significant left-to-right or right-to-left shunts are absent, although occasional patients with equal pulmonary and systemic vascular resistance may have no detectable shunt at rest. Transesophageal echocardiography can reliably detect congenital cardiac defects and distinguish an atrial septal defect from a patent foramen ovale.[135] *Cor triatriatum* (see Chaps. 43 and 44) is recognized by appropriate hemodynamic studies and angiographic visualization of the left atrial membrane. This entity has a characteristic left atrial echocardiogram with normal mitral valve motion. Cardiac catheterization reveals a hemodynamic pattern similar in some ways to mitral stenosis, i.e., a diastolic pressure gradient between the left ventricle and the pulmonary capillary bed. *Pulmonary embolism* (see Chap. 52) can be excluded by pulmonary angiography, and *sickle cell disease with in situ pulmonary vascular thrombosis* (see Chap. 69) can be evaluated by hemoglobin electrophoresis. The presence of severe *pulmonary parenchymal disease* can be recognized by the characteristic physical findings, chest radiograph, pulmonary function tests, and high-resolution chest CT. *Collagen-vascular disease* is suggested by the involvement of other organ systems or the presence of abnormal immunological phenomena such as antinuclear antibodies and LE cells (see Chap. 67) .

TABLE 53-4 -- DIAGNOSTIC CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary arterial hypertension	Interstitial lung disease
Primary	Sleep-disordered breathing
Sporadic	Alveolar hypoventilation disorders
Familial	Chronic exposure to high altitude
Secondary	Neonatal lung disease
Collagen-vascular disease	Alveolar-capillary dysplasia
Congenital systemic-to-pulmonary shunts	Other
Portal hypertension	Pulmonary hypertension from chronic thrombotic and/or embolic disease
HIV infection	
Drugs/toxins	Thromboembolic obstruction of proximal pulmonary arteries
Anorexigens	Obstruction of distal pulmonary arteries
Other	Obstruction of distal pulmonary arteries

Persistent pulmonary hypertension of the newborn	Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
Other	In situ thrombosis
Pulmonary venous hypertension	Sickle cell disease
Left-sided atrial or ventricular heart disease	Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
Left-sided valvular heart disease	
Extrinsic compression of central pulmonary veins	Inflammatory
Fibrosing mediastinitis	Schistosomiasis
Adenopathy/tumors	Sarcoidosis
Pulmonary venoocclusive disease	Other
Other	Pulmonary capillary hemangiomatosis
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia	
Chronic obstructive pulmonary disease	

From Rich S (ed): Primary Pulmonary Hypertension: Executive Summary from the World Symposium--Primary Pulmonary Hypertension 1998. Available from the World Health Organization via the Internet (http://www.who.int/ncd/cvd/pph.html).

Figure 53-12 An algorithm for the management of primary pulmonary hypertension. NYHA = New York Heart Association. (From Rubin LJ: Primary pulmonary hypertension. N Engl J Med 336:111-117, 1997. Copyright © 1997 Massachusetts Medical Society. All rights reserved.)

TREATMENT (Fig. 53-12)

LIFE STYLE CHANGES.

The diagnosis of PPH does not necessarily imply total disability for the patient. However, physical activity can be associated with elevated pulmonary artery pressure inasmuch as marked hemodynamic changes have been documented to occur early in the onset of increased physical activity.[136] For that reason, graded exercise activities, such as bike riding or swimming, in which patients can gradually increase their workload and easily limit the extent of their work, are thought to be safer than isometric activities. Isometric activities such as lifting weights or stair climbing can be associated with

syncopal events and should be limited or avoided.

The subject of pregnancy should also be discussed with women of childbearing age. The physiological changes that occur in pregnancy can potentially activate the disease and result in death of the mother and/or the child. Besides the increased circulating blood volume and oxygen consumption that will increase right ventricular work, circulating procoagulant factors and the risk of pulmonary embolism from deep vein thrombosis and amniotic fluid are serious concerns. Syncope and cardiac arrest have also been reported to occur during active labor and delivery, and a syndrome of postpartum circulatory collapse has been described.[137] For these reasons, surgical sterilization should be given strong consideration by women with PPH or their husbands.

DIGOXIN.

Animal studies performed on the utility of digoxin in right ventricular systolic overload show that prior administration helps prevent the reduction in contractility of the right ventricle. Recently, it has been shown that digoxin can exert a favorable hemodynamic effect when given acutely to patients with right ventricular failure from pulmonary hypertension.[138] An increase in resting cardiac output of approximately 10 percent was noted, which is similar to observations made in patients with left ventricular systolic failure. In addition, it was also observed that digoxin causes a significant reduction in circulating norepinephrine, which was markedly increased. Digitalis toxicity in patients with pulmonary hypertension and normal renal function is uncommon. Consequently, digoxin appears to be a potentially useful medication for patients who have right ventricular failure, either with isolated pulmonary hypertension or in combination with left ventricular systolic failure.

DIURETIC THERAPY.

Diuretics appear to be of marked benefit in symptom relief of patients with PPH. Their traditional role has been limited to patients manifesting right ventricular failure and systemic venous congestion. However, patients with advanced PPH can have increased left ventricular filling pressures that contribute to the symptoms of dyspnea and orthopnea, which can be relieved with diuretics. Diuretics may also serve to reduce right ventricular wall stress in patients with concomitant tricuspid regurgitation and volume overload. The fear that diuretics will induce systemic hypotension is unfounded because the main factor limiting cardiac output is pulmonary vascular resistance and not pulmonary blood volume. Patients with severe venous congestion may require high doses of loop diuretics or the use of combined diuretics. In these instances, electrolytes need to be carefully watched to avoid hyponatremia and hypokalemia.

SUPPLEMENTAL OXYGEN THERAPY.

Hypoxic pulmonary vasoconstriction can contribute to pulmonary vascular disease in patients with alveolar hypoxia from parenchymal lung disease. Supplemental low-flow oxygen alleviates arterial hypoxemia and attenuates the pulmonary hypertension in

these disorders; in contrast, most patients with PPH do not exhibit resting hypoxemia and derive little benefit from supplemental oxygen therapy. Patients who experience arterial oxygen desaturation with activity, however, may benefit from ambulatory supplemental oxygen because increased oxygen extraction develops in the face of fixed oxygen delivery. Patients with severe right-sided heart failure and resting hypoxemia resulting from markedly increased oxygen extraction at rest should be treated with continuous oxygen therapy to maintain their arterial oxygen saturation above 90 percent.[139] Patients with hypoxemia caused by a right-to-left shunt via a patent foramen ovale do not improve their level of oxygenation to an appreciable degree with supplemental oxygen.

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VASODILATOR TREATMENT.

Because of early reports showing a reduction in pulmonary artery pressure following the acute administration of vasodilators, it has been presumed that vasodilators are the mainstay of treatment in patients with PPH. This presumption, however, is not supported by the published literature over the past two decades. Vasodilators appear to be effective in a subset of patients with PPH, but many complexities regarding vasodilator administration make their use in these patients very difficult.

The first principle in using vasodilators in patients with PPH is to establish accurate baseline hemodynamics. Because substantial hemodynamic variability has been reported to exist in the pulmonary vascular bed and will produce changes in cardiac output and pulmonary artery pressure from moment to moment, serial baseline recordings are required to evaluate the magnitude of change in hemodynamics that may be attributed to variability rather than to drug effect.[140] The practice of attributing "peak" effect of the drug to an administered agent introduces bias into the assessment. Thus, by choosing the highest level of pulmonary artery pressure as the baseline and the subsequent lowest one as drug effect, one may be misled to attribute a favorable influence from a medication when in fact no effect or even an adverse one is occurring.

It must also be emphasized that hemodynamic assessment of the entire circulatory system is essential when determining the influence of drugs in these patients. Small changes in pulmonary artery pressure are probably due to variability and are not related to direct drug influence. Changes in pulmonary vascular resistance cannot be directly measured but are computed by the change in pulmonary pressure and cardiac output simultaneously. Because thermodilution cardiac output, the method that is most commonly used in these patients, can be associated with large errors in reproducibility, particular care should be taken in the methodology of thermodilution used in these patients. In addition, when an underlying right-to-left shunt exists or severe tricuspid regurgitation is a concern, the Fick determination of cardiac output is preferred.

Changes in pulmonary capillary wedge pressure can have important influences on the determination of pulmonary vascular resistance. A rising capillary wedge pressure secondary to increased cardiac output may be the first sign of impending left ventricular

failure and an adverse effect of a drug, whereas the calculated pulmonary vascular resistance may become lower and suggest a beneficial effect. Right atrial pressure also reflects the filling characteristics of the right ventricle. A right atrial pressure increase in the face of rising cardiac output suggests right ventricular diastolic dysfunction.[141] The resting heart rate is a physiological parameter of marked importance in patients with congestive heart failure, and treatments that cause an increased heart rate are likely to yield deleterious long-term results. Finally, the systemic arterial oxygen content should be evaluated in patients with PPH. Effective vasodilator drugs can result in vasodilatation of blood vessels supplying poorly ventilated areas of the lung and worsen hypoxemia. This effect is particularly noticeable in patients with underlying chronic lung disease. For all these reasons it has been advocated that vasodilators be initiated only in the hospital setting with central catheter placement for direct hemodynamic recordings and never initiated in the outpatient setting.[139] [142]

ACUTE TESTING WITH INTRAVENOUS VASODILATORS (Table 53-5)

Intravenous vasodilators may be of value in the short-term assessment of pulmonary vasodilator reserve in patients with PPH.[139] Historically, tolazoline received attention as an agent to acutely test the responsiveness of the pulmonary vascular bed in patients with pulmonary hypertension from several causes. However, it is poorly tolerated acutely because of its side effects and has largely been replaced by other agents. Acetylcholine was one of the first medications used to evaluate patients with PPH. It is rapidly inactivated by the lung, which explains why intravenous administration seems to produce selective pulmonary vasodilator effects. Although it has been reported to produce substantial acute reductions in pulmonary artery pressure in some patients, chronic therapy with this drug is not feasible. Isoproterenol is a potent beta-adrenergic agent that affects both the systemic and pulmonary vascular beds and increases cardiac output by chronotropic and inotropic mechanisms. It is considered a pulmonary vasodilator because it results in lowering of the calculated pulmonary vascular resistance. However, it rarely results in substantial lowering of pulmonary artery pressure in patients with pulmonary hypertension because of its more direct effect in increasing cardiac output. Phentolamine is a potent alpha-adrenergic blocker that has been shown to cause pulmonary vasodilatation in animals and humans. Its widespread use is limited by the profound systemic hypotension that occurs upon administration, and it is not generally used in the evaluation of PPH. Sodium nitroprusside is a potent vasodilator that acts on arterial and venous beds. Its short half-life is also an advantage because the effects rapidly dissipate when infusion of the drug is stopped. Like phentolamine, its use as a test of vasodilator reserve is limited by the marked lowering of systemic blood pressure that occurs.

ADENOSINE.

This substance is an intermediate product in the metabolism of adenosine triphosphate that has potent vasodilator properties through its action on specific vascular receptors. In addition to pulmonary vasodilatation, it can also produce systemic and coronary vasodilatation. It is believed to stimulate the endothelial cell and vascular smooth muscle receptors of the A_2 type, which induce vascular smooth muscle relaxation by increasing cyclic adenosine monophosphate.[143] In patients with PPH, adenosine has

been shown to be an extremely potent vasodilator and predictive of the subsequent effects of intravenous prostacyclin and oral calcium channel blockers.[144] [145] Adenosine has an extremely short half-life (less than 5 seconds), which provides a safety net by its rapid dissolution should any adverse side effects occur. It is administered intravenously in doses of 50 ng/kg/min and titrated upward every 2 minutes until uncomfortable symptoms develop (such as chest tightness or dyspnea). It should be noted that adenosine is given as an infusion and not as an

TABLE 53-5 -- HEMODYNAMIC ASSESSMENT OF VASODILATORS IN PULMONARY HYPERTENSION

PARAMETER MEASURED	DESIRED ACUTE CHANGES	COMMENTS
Mean pulmonary artery pressure	>25% fall; ideally mean PAP below 30 mm Hg	Must not be any associated significant fall in systemic blood pressure
Pulmonary vascular resistance	>33% fall; ideally, PVR below 6 units	Should be associated with a fall in PA pressure *and* an increase in cardiac output. An increase in cardiac output alone may lead to future RV failure
Right atrial pressure	No change or fall	An increase in RA pressure signals impending RV failure
Pulmonary capillary wedge pressure	No change	An increase in wedge pressure suggests pulmonary venoocclusive disease or coexisting LV dysfunction
Systemic blood pressure	Minimal fall; mean arterial pressure should remain above 90 mm Hg	A significant hypotensive response makes chronic vasodilator therapy contraindicated
Cardiac output	Increase	The increase should be related to increased stroke volume and not solely due to increased heart rate
Heart rate	No significant change	A chronic increased heart rate will result in RV failure. Watch for bradycardia if high doses of diltiazem are used
Systemic arterial oxygen saturation	Increase if reduced on room air, little change if normal	A fall in systemic arterial oxygen saturation suggests lung disease or right-to-left shunting and prohibits chronic use
Pulmonary artery (mixed venous)oxygen saturation	Increase	Should reflect the increase in cardiac output and improved tissue oxygenation

LV=left ventricular; RA=right atrial; RV=right ventricular.

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intravenous bolus as is used to treat supraventricular tachyarrhythmias.

PROSTACYCLIN.

This substance (epoprostenol sodium, or PGI_2) is a metabolite of arachidonic acid that is synthesized and released from vascular endothelium and smooth muscle. Its vasodilatory effects are thought to be mediated by activation of specific membrane PGI_2 receptors that are also coupled to the adenylate cyclase system.[28] Other effects include inhibition of platelet activation and aggregation, as well as leukocyte adhesion to the endothelium.[146] Prostacyclin has been used as an acute test of vasodilator reserve in patients with PPH. Like adenosine, its short half-life allows use of the drug to be discontinued if any acute adverse effects result. Also similar to adenosine, it is administered incrementally, at 2 ng/kg/min and increased every 15 to 30 minutes until systemic effects such as headache, flushing, or nausea occur, which limits the acute dose titration. Favorable acute effects from prostacyclin appear to be predictive of a favorable response to oral calcium channel blockers.[147]

Adenosine and prostacyclin possess potent inotropic properties, in addition to their ability to vasodilate the pulmonary vascular bed. When using these drugs for the acute testing of patients, one needs to pay particular attention to changes in cardiac output that occur in association with the changes in pulmonary arterial pressure. An increase in cardiac output with no change in pulmonary arterial pressure will result in a reduction in calculated pulmonary vascular resistance and may be erroneously interpreted as a vasodilator response. Instead, one should look at the magnitude of change of each individual parameter to determine the effects that the drug is having on the pulmonary circulation, as well as the type of response that it elicits.

NITRIC OXIDE.

This substance, whose activity is identical to that of endothelium-derived relaxing factor, is produced from L-arginine by NO synthase.[148] NO diffuses to vascular smooth muscle and mediates vasodilatation by stimulating soluble guanylate cyclase to produce cyclic GMP. Because it binds very rapidly to hemoglobin with high affinity and is thereby inactivated, inhalation of NO gas results in selective pulmonary vascular effects without influencing the systemic circulation. Inhalation of NO by patients with PPH has been shown to produce a reduction in pulmonary vascular resistance acutely, similar to that achieved with intravenous adenosine, and to also predict the effectiveness of calcium channel blockers.[149] [150] NO has also been shown to be effective in patients with pulmonary hypertension secondary to congenital heart disease and the adult respiratory

distress syndrome.[151] Although NO seems to have similar acute effects on pulmonary arterial pressure that are predictive of the chronic response to oral vasodilator agents, it differs importantly from adenosine and prostacyclin in that it has little effect on cardiac output.

Chronic Treatment

CALCIUM CHANNEL BLOCKERS.

Of the vasodilators tested in patients with PPH, calcium channel blockers appear to have the widest usage. Early studies using conventional doses failed to demonstrate a chronic sustained benefit. Moreover, calcium channel blockers have properties that could worsen the underlying pulmonary hypertension, including negative inotropic effects on right ventricular function (Fig. 53-13) and reflex sympathetic stimulation, which may increase the resting heart rate.[141] It has been reported that patients with PPH who are challenged with very high doses of calcium channel blockers may manifest a dramatic reduction in pulmonary artery pressure and pulmonary vascular resistance, which upon serial catheterization has been maintained for over 5 years.[122] Importantly, the patient's quality of life is restored with improved functional class, and survival (94 percent rate at 5 years) is improved when compared with nonresponders and historical control subjects (36 percent rate) (Fig. 53-14 *A*). This experience suggests that some patients with PPH have the ability to have their pulmonary hypertension reversed and their quality of life and survival enhanced. It is unknown whether the response to calcium channel blockers identifies two subsets of patients with PPH, different stages of PPH, or a combination of both. However, it is essential to point out that patients who do not exhibit a dramatic hemodynamic response to calcium channel blockers do not appear to benefit from their long-term administration. Unfortunately, it is becoming common practice for physicians to prescribe calcium channel blockers at conventional doses to all patients with pulmonary hypertension, often without hemodynamic guidance. This unfortunate practice may result in quicker deterioration in these patients and should be strongly discouraged.

CHRONIC PROSTACYCLIN INFUSION THERAPY.

Continuous-infusion prostacyclin therapy has now been shown in prospective randomized trials to improve quality of life and symptoms related to PPH, exercise tolerance, hemodynamics, and survival.[133] [152] [153] [154] [155] (Fig. 53-14 *B*). The initial enthusiasm for prostacyclin was based on the demonstration of pulmonary vasodilator effects when administered to experimental animals with acute pulmonary vasoconstriction and when subsequently administered to patients with PPH. The long-term effects of prostacyclin in PPH include its vasodilator and antithrombotic effects, but its effects may also be importantly related to its ability to restore the integrity of the pulmonary vascular endothelium. A recent study revealed that significant reductions in pulmonary vascular resistance that go beyond acute vasodilation were the rule in the patients treated with intravenous prostacyclin for 1 year.[155] On average, patients had a reduction in pulmonary vascular resistance of greater than 50 percent which occurred even if no acute hemodynamic effects were noted (Fig. 53-15) .

Prostacyclin is generally administered through a central venous catheter that is surgically implanted and delivered by an ambulatory infusion system. The delivery system is complex and requires patients to learn the techniques of sterile drug preparation, operation of the pump, and care of the intravenous catheter. Most of the serious complications that have occurred with prostacyclin therapy have been attributable to the delivery system and include catheter-related infections and thrombosis and temporary interruption of the infusion because of pump malfunction. Anecdotal reports of rebound pulmonary hypertension occurring in patients in whom the infusion was interrupted suggest

Figure 53-13 Adverse effects of calcium channel blockers in pulmonary hypertension. The hemodynamic effects of verapamil and nifedipine in patients with pulmonary hypertension are shown. An increase in right atrial pressure in association with no significant change in cardiac index as produced by nifedipine suggests that right ventricular dysfunction is occurring. The increased right atrial pressure associated with a fall in cardiac index, as produced by verapamil, suggests that negative inotropic effects are producing overt right ventricular failure. (Adapted from Packer M, Medina N, Yushak M: Adverse hemodynamic and clinical effects of calcium channel blockade in pulmonary hypertension secondary to obliterative pulmonary vascular disease. Am Coll Cardiol 4:890, 1994.)

Figure 53-14 *A,* Effect of high doses of calcium channel blockers on survival over 5 years in patients with primary pulmonary hypertension (PPH). Patients who responded to the high-dose regimen (open circles) had a 95 percent 5-year survival rate, as opposed to the nonresponders (solid line), who had a 36 percent 5-year survival rate. Rates were similar in patients studied in the National Institutes of Health (NIH) Registry on PPH (triangles), as well as patients from the University of Illinois only (solid circles). *B,* Effect of intravenous prostacyclin (PGI_2) on survival in patients with PPH. The survival of patients given a chronic infusion of prostacyclin and monitored for 5.5 years is compared with that of functional Class III and IV patients from the NIH Registry (historical controls). *C,* Effects of anticoagulation on survival in patients with PPH who did not respond to calcium channel blockers. Patients who received warfarin (open circles) had a marked survival advantage over those who received no warfarin. (*A* and *C* from Rich S, Kaufmann E, Levy PS: The effects of high doses of calcium channel blockers on survival of primary pulmonary hypertension. N Engl J Med 327:76, 1992. Copyright © 1992 Massachusetts Medical Society. All rights reserved. *B* from Barst RJ, Rubin LJ, McGoon MD et al: Survival of primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 121:409, 1994.)

that great care must be taken to ensure that the infusion is never stopped.

Side effects related to prostacyclin therapy include flushing, headache, nausea, diarrhea, and a unique type of jaw discomfort that occurs with eating. In most patients, these symptoms are minimal and well tolerated. Chronic foot pain and a poorly defined gastropathy with prolonged use develop in some patients. Tachyphylaxis to the drug develops at low doses and therefore may require a periodic dose increase to maintain its efficacy. To date, chronic prostacyclin has been given to patients with PPH for over

10 years with continued favorable effectiveness. In some patients (Class IV) who are critically ill, it serves as a bridge to lung transplantation by stabilizing the patient to a more favorable preoperative state. Patients who are less critically ill may do so well with prostacyclin therapy that they may delay the need to consider transplantation, perhaps indefinitely.

A high-cardiac output state has been reported in a large series of patients with PPH receiving chronic prostacyclin therapy and is consistent with the drug having positive inotropic effects.[156] Whether the effect is a direct one on the myocardium or indirect via neurohormonal activation has not been determined. Although most patients with PPH have reduced cardiac output on initial examination, the development of a chronic high-output state could have long-term detrimental effects on underlying cardiac function. The follow-up assessment of patients receiving intravenous prostacyclin is quite variable from medical center to medical center, but it does appear important to determine the cardiac output response to therapy periodically to optimize dosing.[157]

Figure 53-15 Long-term reduction in pulmonary vascular resistance (PVR) with chronic therapy with epoprostenol (prostacyclin) for primary pulmonary hypertension (PPH) in relation to the short-term reduction after the administration of adenosine. Although patients with the greatest short-term reduction in PVR had the greatest long-term reduction, patients who had little or no reduction acutely still had a significant reduction in PVR with long-term therapy. This finding suggests that mechanisms other than acute vasodilatation are responsible for the long-term benefit of intravenous prostacyclin therapy in PPH and supports the notion that reversal of pulmonary vascular remodeling is occurring. (From McLaughlin VV, Genthner DE, Panella MM, et al: Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 338:273-277, 1998. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

ANTICOAGULANTS.

Oral anticoagulant therapy is widely recommended for patients with PPH, although its clinical efficacy as a therapy is difficult to prove. A retrospective review of patients with PPH monitored over a 15-year period at the Mayo Clinic suggested that patients who received warfarin had improved survival over those who did not.[57] The influence of warfarin therapy has been investigated in patients with PPH who failed to respond to high doses of calcium channel blockers.[119] Significant improvement in survival was observed in patients who received anticoagulation, with a 1-year survival rate of 91 percent and 3-year survival rate of 47 percent as compared with 1- and 3-year rates of 62 and 31 percent, respectively, in patients who did not receive anticoagulants (Fig. 53-14 *C*). The current recommendation is to use warfarin in relatively low doses, as has been recommended for prophylaxis of venous thromboembolism, with the international normalized ratio maintained at 2.0 to 2.5 times control.[156] Given its inhibitory effects on smooth muscle proliferation, heparin might be a suitable anticoagulant in PPH, although its use is more difficult. With the recent advent of low-molecular-weight heparins requiring once-a-day administration without the need for adjusting the dose to its

antithrombotic effect, treatment with these agents is becoming a more viable alternative. They may be particularly useful in patients who are believed to be at increased risk for pulmonary thromboembolism.

ATRIAL SEPTOSTOMY

The rationale for the creation of an atrial septostomy in PPH is based on experimental and clinical observations suggesting that an intraatrial defect allowing right-to-left shunting in the setting of severe pulmonary hypertension might be of benefit. Although over 60 patients have undergone this procedure worldwide, it should still be considered investigational.[159] [160] [161] [162] Nonetheless, atrial septostomy may represent a real alternative for selected patients with severe PPH. Indications for the procedure include recurrent syncope and/or right ventricular failure despite maximum medical therapy, as a bridge to transplantation if deterioration occurs in the face of maximum medical therapy, or when no other option exists.[162] Because the disease process in PPH appears to be unaffected by the procedure, the long-term effects of atrial septostomy must be considered palliative.

The procedure-related mortality with atrial septostomy in patients with PPH is high, and thus it should be attempted only in institutions with an established track record in the treatment of advanced pulmonary hypertension and experience in performing atrial septostomy with low morbidity.[161] It should not be performed in a patient with impending death and severe right ventricular failure or a patient receiving maximum cardiorespiratory support. Predictors of procedure-related failure or death have been identified and include a mean right atrial pressure of greater than 20 mm Hg, a pulmonary vascular resistance index of greater than 55 units m^2 or a predicted 1-year survival rate of less than 40 percent.

The mechanisms responsible for the beneficial effects of atrial septostomy remain unclear. Possibilities include increased oxygen delivery at rest and/or with exercise, reduced right ventricular end-diastolic pressure or wall stress, improvement in right ventricular function by the Frank Starling mechanism, or relief of ischemia.

HEART-LUNG AND LUNG TRANSPLANTATION. (see also Chap. 20) .

Heart-lung transplantation has been performed successfully in patients with PPH since 1981.[163] Because these patients have pulmonary vascular disease and severe right ventricular dysfunction, it was originally believed that heart-lung transplantation was the only transplantation option. Widespread application of heart-lung transplantation, however, has been limited by the number of centers with expertise to perform the procedure, the scarcity of suitable donor organs, and the very long waiting times required for

TABLE 53-6 -- GENERAL GUIDELINES FOR SELECTION OF LUNG TRANSPLANT RECIPIENTS

Indications

Advanced obstructive, fibrotic, or pulmonary vascular disease with a high risk of death within 2 to 3 yr
Lack of success or availability of alternative therapies
Severe functional limitation but preserved ability to walk
Age 55 yr or less for candidates for heart-lung transplantation, age 60 yr or less for candidates for bilateral lung transplantation, and age 65 yr or less for candidates for single-lung transplantation

Absolute Contraindications

Severe extrapulmonary organ dysfunction, including renal insufficiency with a creatinine clearance below 50 ml/min, hepatic dysfunction with coagulopathy or portal hypertension, and left ventricular dysfunction or severe coronary artery disease (consider heart-lung transplantation)
Acute, critical illness
Active cancer or recent history of cancer with substantial likelihood of recurrence (except for basal cell and squamous cell carcinoma of the skin)
Active extrapulmonary infection (including infection with HIV, hepatitis B, hepatitis C)
Severe psychiatric illness, noncompliance with therapy, and drug or alcohol dependence
Active or recent (preceding 3 to 6 mo) cigarette smoking
Severe malnutrition (<70% of ideal body weight) or marked obesity (>130% of ideal body weight)
Inability to walk, with poor rehabilitation potential

Relative Contraindications

Chronic medical conditions that are poorly controlled or associated with target organ damage
Daily requirement for more than 20 mg of prednisone (or equivalent)
Mechanical ventilation (excluding noninvasive ventilation)
Extensive pleural thickening from prior thoracic surgery or infection
Active collagen-vascular disease
Preoperative colonization of the airways with pan-resistant bacteria (in patients with cystic fibrosis)

From Arcasoy SM, Kotloff RB: Lung transplantation. N Engl J Med 340:1081-1091, 1999. *Copyright © 1999 Massachusetts Medical Society. All rights reserved.*

patients with end-stage right-sided heart failure. More recently, bilateral or double-lung transplantation and single-lung transplantation have been performed successfully in patients with PPH.[164] Hemodynamic studies have shown an immediate reduction in pulmonary artery pressure and pulmonary vascular resistance associated with improvement in right ventricular function.[165]

The ages of recipients of heart-lung and lung transplantation for pulmonary hypertension have ranged from 2 months to 61 years.[166] Operative mortality ranges

between 16 and 29 percent and is somewhat higher for recipients of a single-lung transplant. The 1-year survival rate is between 70 and 75 percent, the 2-year survival rate is between 55 and 60 percent, and the 5-year survival rate is between 40 and 45 percent. Transplantation should be reserved for patients with pulmonary hypertension who have progressed in spite of optimal medical management.[167] (Table 53-6) .

Patients should be referred for evaluation for transplantation at the appropriate time.[168] The course of the disease and the waiting time must be taken into account, as well as other factors such as the anticipated waiting time before transplantation in the region and the expected survival after transplantation. It is generally accepted that patients should be considered for transplantation when they are New York Heart Association Functional Class III or IV in spite of medical therapy or when treatment with prostacyclin is failing or causing intolerable side effects.

The major long-term complications in patients who survive the operation are the high incidence of bronchiolitis obliterans in the transplanted lungs, acute organ rejection, and opportunistic infection.[169] Although several studies have documented significant improvement in quality of life after heart-lung and lung transplantation for pulmonary hypertension, cost-effectiveness has not yet been addressed. In many patients, prostacyclin may prove to be an ideal bridge to keep patients alive and stable until organs become available.[170]

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Secondary Pulmonary Hypertension

Although PPH is relatively rare, with an estimated incidence of 1 to 2 per million in the population, severe pulmonary arterial hypertension associated with other conditions is more common[171] [172] [173] [174] [175] [176] [177] (Table 53-7) . The most common etiology is associated with collagen-vascular disease states, primarily scleroderma, including the CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), and mixed connective tissue disease.[172] Pulmonary arterial hypertension is also relatively common in patients with congenital heart defects, especially those with ventricular septal defects or a patent ductus arteriosus.[174] Other major etiologies include cirrhosis with portal hypertension and HIV infection.[97] [177] In some instances, increased resistance to pulmonary blood flow downstream leads to what has been referred to as "passive" pulmonary hypertension because in many cases, elevation in pulmonary artery pressure but no significant elevation in pulmonary vascular resistance is observed. Reactive pulmonary hypertension often coexists in these states, with pulmonary artery pressure and pulmonary vascular resistance elevated to levels higher than can be accounted for purely by increased downstream resistance to blood flow. In some instances, relieving the downstream obstruction results in normalization of pulmonary artery pressure and pulmonary vascular resistance, whereas in other instances it may not. Failure of normalization has been believed to be related to chronicity of the reactive pulmonary hypertension leading to irreversible vascular changes, although this hypothesis has never been proved. When reactive pulmonary hypertension occurs, it often results in right ventricular failure, which can predominate in the patient's clinical symptomatology and lead to marked deterioration in functional class and death.

PULMONARY HYPERTENSION ASSOCIATED WITH COLLAGEN-VASCULAR DISEASES (see alsoChap. 67)

Scleroderma, either from progressive systemic sclerosis or the CREST syndrome, is the most common etiology of pulmonary hypertension in collagen-vascular disease states.[171] [172] Scleroderma is associated with pulmonary hypertension in as many as one-third of patients, and CREST syndrome in as many as 50 percent.[172] [178] The high incidence suggests that periodic screening with echocardiography in these patients may be a reasonable practice. Although pulmonary hypertension may occur as a result of entrapment and obstruction of the pulmonary microvasculature by interstitial inflammation or fibrosis, patients initially seen with severe pulmonary hypertension usually do not have evidence of interstitial lung disease and have a pulmonary vasculature with histological features that resemble those of PPH.[179] Patients with systemic lupus erythematosus may also have pulmonary hypertension, although less common than in scleroderma. On occasion, pulmonary hypertension may precede the clinical diagnosis of lupus by several years. Mixed connective tissue disease is a less common form of collagen-vascular disease, but pulmonary hypertension may occur in as many as two-thirds of these patients. Pulmonary hypertension has also been described in patients with polymyositis, dermatomyositis, and rheumatoid arthritis.

Because collagen-vascular diseases may have an insidious onset and slowly progressive course, early recognition of the symptoms of pulmonary hypertension may be difficult. Although easy fatigability may be a feature of the collagen-vascular disease, it may also be an initial symptom of pulmonary hypertension. Dyspnea is still the most common initial symptom and should not be attributed to advancing age. Syncope, presyncope, or peripheral edema represents advanced pulmonary hypertension and right-sided heart failure. Physical findings of an elevated jugular venous pressure and an increased pulmonic component of the second heart sound along with a right ventricular fourth heart sound are typical features of pulmonary hypertension and warrant an evaluation for pulmonary hypertension. A murmur of tricuspid regurgitation generally reflects more advanced disease. Arterial hypoxemia is characteristic and should also prompt an evaluation of possible pulmonary hypertension in these patients.

The prognosis of patients with collagen-vascular disease in whom pulmonary hypertension develops is very poor.[179] Conventional therapy with digitalis, diuretics, and supplemental oxygen is used, and

TABLE 53-7 -- ADVANCED PULMONARY HYPERTENSION BY DISEASE CATEGORY

DISEASE	PREVALENCE	PERCENTAGE OF PATIENTS WITH PH	ESTIMATED NUMBER IN NORTH AMERICA AND EUROPE
Systemic sclerosis	190/million	33	37,620
Congenital heart defects (ASD/VSD/PDA)	300/million	15-20	31,500
Cirrhosis	1600/million	0.6	5760
HIV related	2500/million	0.5	7500

Primary PH	7/million	100	4200

ASD=atrial septal defect; PDA=patent ductus arteriosus; PH=pulmonary hypertension; VSD=ventricular septal defect.

Figure 53-16 Mean pulmonary artery pressure (*top*) and pulmonary vascular resistance (*bottom*) before and after prostacyclin therapy in patients with secondary pulmonary hypertension. White bars indicate patients with congenital heart disease, striped bars indicate patients with collagen-vascular disease, and black bars indicate patients with portopulmonary hypertension. *$p<0.01$. $p<0.05$ versus baseline. For all groups combined, mean pulmonary artery pressure fell 23% and pulmonary vascular resistance 50% after chronic (1 year) therapy. (From McLaughlin VV, Genthner DE, Panella MM, et al: Compassionate use of prostacyclin in the management of secondary pulmonary hypertension: A case series. Ann Intern Med 130:740-743, 1999.)

anticoagulation has been recommended to provide a survival benefit similar to the practice in PPH. Although the use of oral vasodilators has been disappointing, intravenous prostacyclin therapy has demonstrated therapeutic efficacy manifested by improved exercise tolerance, hemodynamics, and sense of well-being.[180] [181] Prostacyclin should be considered as a therapeutic intervention as early as possible in patients with pulmonary hypertension secondary to collagen-vascular disease. In patients with associated Raynaud phenomenon, it may provide relief of digital ischemia (Fig. 53-16) .

INCREASED RESISTANCE TO PULMONARY VENOUS DRAINAGE

PATHOPHYSIOLOGY.

Increased resistance to pulmonary venous drainage is a mechanism common to several conditions of diverse cause in which pulmonary arterial hypertension occurs. Altered resistance to pulmonary venous drainage may be the result of diseases affecting the left ventricle or pericardium, mitral or aortic valvular disease, or rare entities such as cor triatriatum, left atrial myxoma, or pulmonary venoocclusive disease (see below).

The magnitude of pulmonary hypertension depends, in part, on the performance of the right ventricle. In response to an acute stress such as pulmonary embolism, the normal right ventricle of an adult living at sea level can achieve systolic pulmonary pressures of 45 to 50 mm Hg, above which right ventricular failure supervenes. Systolic pressures of 80 to 100 mm Hg can be generated only by a hypertrophied right ventricle that is normally perfused. If right ventricular infarction or ischemia has occurred or if the right and left ventricles are both affected by a myopathic process, right ventricular failure occurs at lower pulmonary vascular pressure and severe pulmonary hypertension may not develop despite an increase in pulmonary vascular resistance.

In the presence of a healthy, nonischemic right ventricle, an increase in left atrial pressure from subnormal levels up to 7 mm Hg results in a fall in both pulmonary vascular resistance and the pressure gradient across the lungs. These reductions may reflect distention of a population of compliant small vessels, recruitment of additional vascular channels, or both. With further increases in left atrial pressure, pulmonary arterial pressure rises along with pulmonary venous pressure; i.e., at a constant pulmonary blood flow, the pressure gradient between the pulmonary artery and veins and pulmonary vascular resistance remains constant. Finally, when pulmonary venous pressure approaches or exceeds 25 mm Hg on a chronic basis, a disproportionate elevation in pulmonary artery pressure occurs; i.e., the pressure gradient between the pulmonary artery and veins rises while pulmonary blood flow remains constant or falls, which is indicative of an elevation in pulmonary vascular resistance that is due, in part, to pulmonary vasoconstriction. The latter occurs to a variable extent in response to passive elevations in pulmonary venous pressure and probably reflects the reactivity of the pulmonary vasculature, which may be variable between and within species.

Considerable variability in pulmonary arterial vasoconstriction is listed in response to pulmonary venous hypertension. Marked reactive pulmonary hypertension with pulmonary artery systolic pressures in excess of 80 mm Hg occurs in somewhat less than one-third of patients with pulmonary venous pressures elevated chronically in excess of 25 mm Hg. The fact that severe reactive pulmonary hypertension develops in less than one-third of patients with severe mitral stenosis also argues in favor of a spectrum of pulmonary vascular reactivity to chronic increases in pulmonary venous pressure.

The mechanism involved in elevating pulmonary vascular resistance is unclear. A neural component may be present; also, an elevation in pulmonary venous pressure may narrow or close airways, which may diminish ventilation and lead to hypoxia and, in turn, elevate pulmonary artery pressure. Finally, interstitial pulmonary edema secondary to pulmonary venous hypertension may encroach on the vascular lumen and contribute to the pulmonary arterial hypertension.

PATHOLOGY.

Structural changes in the pulmonary vascular bed develop in association with chronic pulmonary venous hypertension, irrespective of its etiology. At the ultrastructural level, these changes include swelling of pulmonary capillary endothelial cells, thickening of their basal lamina, and wide separation of groups of connective tissue fibrils, indicative of interstitial edema. With persistence of the edema, reticular and elastic fibrils proliferate and the alveolar capillaries become embedded in dense connective tissue. The permeability of interendothelial junctions depends on pulmonary capillary pressure, with leakage of large molecules (40,000 to 60,000 daltons) occurring at capillary pressures in excess of approximately 30 mm Hg.

Light microscopic examination of the lungs of patients with pulmonary venous hypertension shows distention of pulmonary capillaries, thickening and rupture of the basement membranes of endothelial cells, and transudation of erythrocytes through

these ruptured membranes into the alveolar spaces, which contain fragments of disintegrating erythrocytes. Pulmonary hemosiderosis is commonly observed and may progress to extensive fibrosis. In the late stages of pulmonary venous hypertension, areas of hemorrhage may be scattered throughout the lungs, edema fluid and coagulum may collect in the alveolar spaces, and widespread organization and fibrosis of pulmonary alveoli may be present. Occasionally, particularly in patients with chronic pulmonary venous hypertension caused by mitral valve disease, the alveolar spaces become ossified. Pulmonary lymphatics may become markedly distended and give the appearance of lymphangiectasis, particularly when pulmonary venous pressure chronically exceeds 30 mm Hg. Structural alterations in the small pulmonary arteries, arterioles,

and venules include medial hypertrophy, intimal fibrosis, and rarely, necrotizing arteritis. However, plexiform lesions are not seen. The latter characterize the "irreversible" forms of pulmonary arterial hypertension.

PULMONARY HYPERTENSION SECONDARY TO ELEVATION IN LEFT VENTRICULAR DIASTOLIC PRESSURE

LEFT VENTRICULAR DIASTOLIC FAILURE.

This condition may result from hypertension: aortic stenosis; ischemic heart disease; hypertrophic, restrictive, and congestive cardiomyopathies; and constrictive pericarditis. Chronic increases in mean left ventricular filling pressure exceeding 25 mm Hg are uncommon, and the resulting pulmonary arterial hypertension is usually moderate unless reactive pulmonary hypertension also occurs.

Increased pulmonary artery pressure in patients with left ventricular dysfunction is a marker of poor prognosis. Pulmonary hypertension is associated with more frequent episodes of congestive heart failure and excess mortality after heart transplantation.[182] Pulmonary hypertension may result from an increase in left atrial pressure and pulmonary vascular resistance and possibly from the loss of endothelium-dependent vasodilatation of the pulmonary arterial bed. The severity of pulmonary hypertension in patients with left ventricular dysfunction is widely variable and independent of the degree of left ventricular dysfunction or associated functional mitral regurgitation. Many patients will improve considerably if effective medical therapy can be identified that will lower left ventricular end-diastolic pressure.[183] Identifying the basis for the increase in this pressure is essential.

PULMONARY HYPERTENSION SECONDARY TO LEFT ATRIAL HYPERTENSION

Mitral Valve Disease (see also Chap. 46) .

MITRAL STENOSIS.

This valvular lesion represents an important cause of pulmonary hypertension. Although the pulmonary hypertension associated with mitral stenosis is initially a result of an increase in resistance to pulmonary venous drainage and backward transmission of the elevated left atrial pressure, many patients subsequently exhibit marked pulmonary vasoconstriction and anatomical changes in vessels, so the pulmonary hypertension is "reactive" as well as "passive." The elevation in pulmonary vascular resistance and the associated pulmonary hypertension may come to dominate the clinical picture in mitral stenosis. Thus, patients with mitral stenosis often have what might be considered to be a more proximal obstruction at the level of the pulmonary arterioles and small muscular arteries, with resultant pulmonary hypertension equal to or exceeding systemic arterial pressure during exertion and sometimes even at rest. The clinical picture in such patients is characterized by right ventricular failure with distended neck veins, hepatomegaly, and ascites. These patients exhibit marked fatigue, occasionally a more serious complaint than dyspnea. The murmur of mitral stenosis may be soft or even inaudible, and the opening snap of the stenotic mitral valve may be indistinguishable from a loud pulmonic component of S_2 as a result of narrowing of the S_2 opening snap interval. Pulmonary congestion and edema may not be prominent clinically. Cardiac output is usually markedly reduced. This constellation of findings may obscure the underlying diagnosis of mitral stenosis and suggest instead either PPH or pulmonary hypertension secondary to some other disorder.

Diagnostic Studies.

The echocardiogram shows left atrial enlargement and thickened mitral valve leaflets whose mobility is markedly reduced. At cardiac catheterization, the pulmonary arterial hypertension is associated with substantial elevations in pulmonary wedge pressure, and a sizable (>10 mm Hg) pressure gradient is generally noted between pulmonary capillary wedge and left ventricular diastolic pressure. These findings are of key importance in distinguishing mitral stenosis from pulmonary arterial hypertension, a condition in which left atrial size and the wedge pressure are normal and in which no diastolic pressure gradient can be found between the wedge and left ventricular pressure.

Protection Against Pulmonary Edema.

At least three mechanisms that tend to protect against pulmonary edema formation are operative in patients with mitral stenosis and chronic elevations in pulmonary venous pressure in excess of 25 mm Hg (see Chap. 17) . First, lymphatic drainage of the pulmonary interstitium increases abruptly when pulmonary venous pressure is increased to 25 mm Hg. Acute increases in pulmonary lymph flow of up to 8 times the resting level occur when pulmonary venous pressure is raised to 30 mm Hg for a 10-minute interval, and the increased lymphatic flow persists at high levels for 30 to 60

minutes after pulmonary venous pressure has returned to normal. In models of *chronic* pulmonary venous pressure elevation, increases in pulmonary lymph flow of up to 28 times normal have been observed.

Diminished permeability of the capillary-alveolar barrier is a second protective mechanism that might be operative in patients with *chronic* pulmonary venous hypertension in excess of 25 mm Hg. There is morphological evidence of thickening of the layer between the capillary lumen and the alveolar space.[184] A third mechanism operating in patients with chronic increased resistance to pulmonary venous drainage is the reactive constriction of small muscular pulmonary arteries and arterioles. This constriction, which results in considerable elevation in pulmonary artery pressure, is usually associated with a significant decline in right ventricular output and therefore pulmonary blood flow). The lower pulmonary blood flow tends to diminish the formation of pulmonary edema because it results in substantially lower left atrial and pulmonary venous pressure at any given size of the mitral valve orifice or for any given impairment in left ventricular function.

Effects of Surgery.

After corrective surgery on the mitral valve or after mitral balloon valvuloplasty (see Chap. 46) , both pulmonary vascular resistance and pulmonary hypertension decline,[185] the major extent of which is noted within the first postoperative week. The extent of reversal of pulmonary vascular obstruction has varied depending on the adequacy of the procedure in producing an increase in mitral orifice area and whether mitral valve restenosis.[186]

MITRAL REGURGITATION.

Although pulmonary hypertension is widely recognized as developing in patients with left atrial hypertension caused by mitral stenosis, it can also occur in patients with pure mitral regurgitation.[187] In one series, nearly half of a cohort of 41 patients with severe mitral regurgitation had pulmonary artery systolic pressures in excess of 50 mm Hg. In this subgroup of patients, pulmonary vascular resistance was three times normal and cardiac output was substantially depressed when compared with that in patients in whom severe mitral regurgitation was associated with only minimal pulmonary artery pressure elevation.[187] Presumably, the pulmonary hypertension in these patients is reversible, just as it is in mitral stenosis, although data on this point have not been reported.

COR TRIATRIATUM (see also Chap. 43) .

In this malformation, partitioning of the left atrium creates two left atrial subchambers. The posterior subchamber receives the pulmonary venous inflow, which then drains through an opening in the partition into the anterior subchamber and then through the mitral orifice into the left ventricle. When the opening in the partition separating the two left atrial subchambers is small, severe pulmonary venous and pulmonary arterial

hypertension result.

INCREASED RESISTANCE TO FLOW THROUGH THE PULMONARY VASCULAR BED

Pulmonary Parenchymal Disease

This important cause of pulmonary hypertension is discussed in Chapter 54 .

Eisenmenger Syndrome (see also Chaps. 43 and 44)

Decreased cross-sectional area of the pulmonary arteriolar bed with irreversible pulmonary hypertension characterizes the so-called Eisenmenger syndrome. This term was used by Wood[188] to refer to patients with congenital cardiac lesions and severe pulmonary hypertension in whom reversal of a left-to-right shunt has occurred. Left-to-right shunts are usually due to congenital cardiovascular malformations (e.g., atrial and ventricular septal defects, patent ductus arteriosus).

PATHOPHYSIOLOGY.

Pulmonary hypertension in congenital heart disease may occur simply because of increased pulmonary blood flow. When chronic, the increased pulmonary flow is often associated with a passive reduction in pulmonary resistance and little elevation in pulmonary vascular pressure. In a normal adult with pulmonary blood flow (PBF) of 5 liters/min, pulmonary vascular resistance (PVR) of 60 dyne-sec cm^{-5} , and mean left atrial pressure (LA) of 6 mm Hg, the pulmonary artery mean pressure (PA) may be calculated from the expression

If PBF is doubled, a reduction in pulmonary vascular resistance to 30 dyne-sec cm^{-5} maintains pulmonary artery mean pressure at a normal level of 10 mm Hg. However, if PBF is increased fourfold to

sixfold, the reserve capacity of the pulmonary vascular bed is exceeded, and pulmonary artery pressure rises. Thus, if the pulmonary vascular resistance is 30 dyne-sec cm^{-5} , a PBF of 30 liters/min is associated with a mean pulmonary artery pressure that is only minimally elevated at 17 mm Hg, although the high right ventricular stroke volumes associated with the augmentation in PBF result in considerably higher values (40 to 45 mm Hg) for pulmonary artery and right ventricular systolic pressure. If no underlying arteriolar vascular disease exists, abolition of the shunt by corrective surgery restores

PBF and pulmonary artery pressure to normal.

If a congenital cardiovascular defect causes pulmonary hypertension from the time of birth, the small, muscular arteries of the fetal lung may undergo delayed or only partial involution, with subsequent persistently high levels of pulmonary vascular resistance. This is especially true in lesions in which a left-to-right shunt enters the right ventricle or pulmonary artery directly (i.e., a posttricuspid valve shunt, such as ventricular septal defect or patent ductus arteriosus); these patients experience a higher incidence of severe and irreversible pulmonary vascular damage than do those in whom the shunt is proximal to the tricuspid valve (pretricuspid shunts, as in atrial septal defect and partial anomalous pulmonary venous drainage). In the latter category, pulmonary hypertension may result from a large pretricuspid left-to-right shunt, which enhances the risk of pulmonary vascular damage.

PATHOLOGY.

The extent of reversibility of pulmonary vascular obstructive disease in the presence of congenital heart disease varies. From an anatomical point of view, reversible conditions are those in which the decreased pulmonary arteriolar cross-sectional area is the result of medial hypertrophy and vasoconstriction; irreversibility is associated with the presence of necrotizing arteritis and plexiform lesions in these small vessels. The classification by Heath and Edwards[3] of six grades of structural change is widely used to assess the potential reversibility of pulmonary vascular disease and is summarized as follows: *Grade I* is characterized by hypertrophy of the media of small muscular pulmonary arteries and arterioles. In *grade II,* intimal cellular proliferation is added to the medial hypertrophy. *Grade III* is characterized by advanced medial thickening with hypertrophy and hyperplasia, together with progressive intimal proliferation and concentric fibrosis that result in obliteration of many arterioles and small arteries. In *grade IV,* dilatation and so-called plexiform lesions of the muscular pulmonary arteries and arterioles are observed. The latter consist of a plexiform network of capillary-like channels within a dilated segment of a muscular pulmonary artery. The channels are separated by proliferating endothelial cells that often contain thrombi; indeed, the network of capillary channels may constitute recanalization of a thrombus. *Grade V* changes include complex plexiform, angiomatous, and cavernous lesions and hyalinization of intimal fibrosis. Finally, *grade VI* is characterized by the presence of necrotizing arteritis.

The Heath-Edwards classification implies that the morphological alterations are sequential, with grade I being the earliest stage and grade VI being the "end stage" of pulmonary vascular obliterative disease. That such an orderly progression may not in fact occur is suggested by the findings of Wagenvoort, which indicate that plexiform lesions develop gradually in areas affected by necrotizing arteritis. Fibrinoid necrosis of a small segment of a pulmonary arterial branch has been suggested to lead to medial destruction and subsequent aneurysmal dilatation of the vessel, as well as the formation of a fibrin clot in the lumen, often with an admixture of platelets. Organization of the fibrin clot by strands of intimal cells leads to formation of the plexus; the small capillary-like channels within the plexus provide continuity to the distal portion of the artery, which undergoes poststenotic dilatation. With time, the inflammatory component

of the process subsides, fibrin disappears, and the strands of intimal cells become fibrotic. Wagenvoort's view is supported by animal experiments in which end-to-end systemic-pulmonary anastomoses resulted in arteritis and fibrinoid necrosis before the appearance of plexiform lesions. Thus, although Heath-Edwards grades I, II, and III may represent chronological progression, evidence exists that grade VI (necrotizing arteritis) changes appear next, followed by grades IV and V as end-stage alterations.

CLINICAL CONSIDERATIONS.

Eisenmenger syndrome is applied to any anomalous circulatory communication that leads to obliterative pulmonary vascular disease, including pretricuspid and posttricuspid shunts. Health-Edwards grade IV to VI changes are usual in these patients; occasionally, lesser anatomical changes predominate and may be reversible after successful corrective surgery. The long-term prognosis of patients with the Eisenmenger syndrome is substantially better than that of patients with other conditions associated with pulmonary hypertension.[189] Patients with the Eisenmenger syndrome have an 80 percent survival rate at 10 years, a 77 percent survival rate at 15 years, and a 42 percent survival rate at 25 years.[190] [191] Survival is typically related to mean right atrial pressure and pulmonary vascular resistance.

When pulmonary vascular resistance has increased so that it equals or exceeds systemic resistance and the anatomical changes of the pulmonary vessels are predominantly those of grades IV to VI, surgical closure of the anomalous circulatory communication will be associated with a prohibitive immediate risk and, if the patient survives, will usually fail to relieve pulmonary hypertension. Surgery may in fact hasten death in most survivors who had either balanced shunts or predominant right-to-left shunts because closure of the right-to-left communication merely increases the load on an already overburdened right ventricle. Structural changes in the pulmonary vascular bed are evident in pulmonary arteriograms, which reveal dilated central pulmonary arteries and narrowing of the peripheral branches. These changes can be evaluated by means of quantitative analysis of the pulmonary wedge angiogram.[192]

Intravenous prostacyclin therapy is highly effective and has been shown to improve exercise tolerance, quality of life, and hemodynamics in patients with congenital heart disease irrespective of the severity or duration of the condition[181] [193] (see Fig. 53-16) . It is effective in patients who have had previous surgical repair of their defect and in those who have not. No increased incidence of systemic side effects has been noted in patients who have a persistent right-to-left shunt. Long-term prostacyclin therapy may slow the progression of Eisenmenger syndrome and render some patients eligible for partial surgical repair consisting of atrial septostomy.[193] In patients who have bidirectional shunts, the use of prostacyclin may be a therapeutic strategy to enable a patient who is considered inoperable to become eligible for surgery at a later date.

Other Conditions Associated with Decreased Cross-Sectional Area of the Pulmonary Vascular Bed

PERSISTENT FETAL CIRCULATION IN THE NEWBORN (see also Chap. 43) .

This condition has been reported as a cause of severe pulmonary hypertension.[194] [194A] Affected infants exhibit cyanosis, tachypnea, acidemia, normal pulmonary parenchymal markings on chest radiography, and anatomically normal hearts. Cyanosis is the result of right-to-left shunting across the foramen ovale and through a patent ductus arteriosus. The condition may be due to persistence of extremely muscular small pulmonary arteries, a diminution in the absolute number of these resistance vessels, or a combination of the two.[195]

PULMONARY THROMBOEMBOLISM.

This important cause of pulmonary hypertension is discussed in Chapter 52 .

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Chapter 54 - Cor Pulmonale

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Cor pulmonale is defined as right ventricular hypertrophy and dilatation secondary to pulmonary hypertension caused by diseases of the lung parenchyma and/or pulmonary vasculature, unrelated to the left side of the heart. Chronic cor pulmonale traditionally implies pulmonary hypertension related to either obstructive or restrictive lung disease, whereas acute cor pulmonale usually refers to the development of acute pulmonary hypertension from massive pulmonary embolism. The basic anatomy and physiology of the pulmonary circulation is reviewed in Chapter 53 . In this chapter the focus is on chronic pulmonary hypertension primarily related to disorders of the respiratory system and/or hypoxemia, chronic thromboembolic disease, and disorders directly affecting the pulmonary vasculature (see Table 53-4 , p. 1922). The pathogenic mechanisms that can lead to pulmonary arterial hypertension and cor pulmonale are shown in Table 54-1 .

THE EFFECTS OF ALVEOLAR GAS TENSION ON THE PULMONARY CIRCULATION

(see also p. 1909). The hypoxic pulmonary vasoconstrictor response is an important adaptive mechanism in human physiology. [1] Alveolar hypoxia results in local vasoconstriction so that blood flow is shunted away from hypoxic regions toward better-ventilated areas of the lung, improving the ventilation-perfusion matching within the lung.[2] Although the acute effects of this response are undoubtedly beneficial, chronic hypoxemia can result in sustained elevation of pulmonary artery pressure, vascular remodeling, and the development of cor pulmonale.

Hypoxic pulmonary vasoconstriction can be observed in isolated pulmonary vascular smooth muscle cells.[3] The mechanism of hypoxic pulmonary vasoconstriction involves the inhibition of potassium currents and pulmonary vascular smooth muscle membrane depolarization as a result of changes in the membrane sulfhydryl redox status. Potassium, calcium, and chloride channels all play important roles in determining pulmonary vascular tone and are altered by changes in local oxygen tension in the pulmonary circulation.

Increased calcium (Ca^{2+}) entry into the vascular smooth muscle cells appears to mediate hypoxic pulmonary vasoconstriction.[4] The concentration of Ca^{2+} in the vicinity of the contractile machinery represents a balance between inflow and outflow across the cell membrane and intracellular release and uptake. Within the cell, Ca^{2+} can be mobilized from the sarcoplasmic reticulum and mitochondrial membrane, or the inner aspect of the cell membrane.[5] Although most of the evidence favors an influx of Ca^{2+} from extracellular fluid, the relative contribution of differential mobilization from intracellular stores is unsettled. The mechanism responsible for intracellular mobilization of Ca^{2+} is also unclear.[6] [7]

Mechanisms of Hypoxic Vasoconstriction.

The mechanism of acute hypoxic pulmonary vasoconstriction is multifactorial, but the vascular endothelium plays a central role as a mediator of hypoxia-induced pulmonary vasoconstriction. Balanced release of nitric oxide[8] and endothelin [9] by endothelial cells is a key factor in the regulation of tone in the pulmonary circulation. A reduction in nitric oxide production has been demonstrated in the chronically hypoxic piglet[10] and rat,[11] whereas prolonged inhalation of nitric oxide attenuates hypoxic pulmonary vasoconstriction[12] and pulmonary vascular remodeling[13] in rats. Conversely, plasma levels of endothelin-1 are increased in association with hypoxemia in humans.[14] It is believed that endothelin-1 induces a decrease in the calcium-activated potassium current, contributing to hypoxia-induced pulmonary hypertension.[15] Endothelin receptor antagonists have been demonstrated to reduce hypoxic pulmonary vasoconstriction in animals.[16] [17] [18] [19] [20] [21]

Pulmonary vascular remodeling in response to hypoxia is also meditated by a number of growth factors. Platelet-derived growth factor-A (PDGF-A) and PDGF-B are elevated in hypoxic rats,[22] and vascular endothelial growth factor (VEGF), which is an endothelial

cell-specific mitogen, is upregulated during exposure to chronic hypoxia.[23] [24] [25] VEGF is likely involved in pulmonary vascular injury and endothelial cell proliferation in the setting of chronic hypoxic pulmonary vascular remodeling because of its permeability, angiogenesis, proinflammatory properties,[26] and specificity for endothelial cells (Fig. 54-1) .

The roles of angiotensin-converting enzyme (ACE) and angiotensin II in the pulmonary circulation are becoming more established. Local increases in right ventricular ACE activity and expression likely play an important role in the pathogenesis of right ventricular hypertrophy secondary to hypoxic pulmonary hypertension. In chronically hypoxic rats the development of pulmonary hypertension and right ventricular hypertrophy is associated with a significant increase in membrane-bound right ventricular ACE activity.[27] ACE inhibitors attenuate the development of pulmonary hypertension in rats exposed to chronic hypoxia,[28] [29] and acute hypoxic pulmonary vasoconstriction is attenuated by type 1 angiotensin II receptor blockade.[30] Treatment of chronically hypoxic rats with ACE inhibitors also reduces right ventricular hypertrophy and fibrosis.[31]

Hypoxia inducible factor-1 (HIF-1)[32] represents a vital link between oxygen sensing, gene transcription, and the

TABLE 54-1 -- POTENTIAL PATHOGENETIC MECHANISMS LEADING TO PULMONARY ARTERIAL HYPERTENSION AND COR PULMONALE

MECHANISMS	EXAMPLE
Primary	
Anatomical decrease in crosssectional area (vessel destruction; encroachment on lumen by hypertrophy) of the pulmonary resistance vessels	Interstitial fibrosis and granuloma
Vasoconstriction of pulmonary resistance vessels	Hypoxia and acidosis
Contributory	
Large increments in pulmonary blood flow	Exercise
Increased pressures on the left side of the heart and pulmonary veins	Left ventricular failure or pulmonary venoocclusive disease
Increased viscosity of the blood	Secondary polycythemia or chronic hypoxia
Unproved	
Compression of pulmonary resistance vessels by raised alveolar pressures in their vicinity	Asthmatic bronchitis

Bronchial arterial-pulmonary arterial anastomoses	Expanded bronchial circulation

From Fishman AP: Pulmonary hypertension and cor pulmonale. In Fishman AP: Pulmonary Diseases and Disorders. 2nd ed. New York, McGraw-Hill, 1988, p 1001.

physiological adaptation to chronic hypoxia in vivo. One of the classic adaptations to chronic hypoxia is an increased rate of erythropoiesis that is mediated by the glycoprotein growth hormone erythropoietin. HIF-1 has been identified as a nuclear factor that is induced by hypoxia and bound to a site in the erythropoietin response element. HIF-1 expression is tightly regulated by cellular oxygen tension.

Changes in alveolar oxygenation affect the oxygenation of small pulmonary arteries and arterioles by direct gaseous diffusion from the alveoli, respiratory bronchioles, and alveolar ducts in the pulmonary arterioles, even though the latter are "upstream" in relation to the alveoli. This fact, taken together with evidence for a reduction in pulmonary arterial blood volume during hypoxia,[33] supports the view that the small pulmonary arteries and arterioles are the main sites of vasoconstriction and increased resistance in the pulmonary circulation during hypoxia.[33] [34] Although alveolar oxygen tension is a major physiological determinant of pulmonary arteriolar tone, a reduction in the oxygen tension in the mixed venous blood flowing through the small pulmonary arteries and arterioles may also contribute to pulmonary arterial vasoconstriction.[35]

Acidosis significantly increases pulmonary vascular resistance and acts synergistically with hypoxia.[36] In contrast, an increase in arterial P_{CO_2} seems to exert no direct effect but rather operates by way of the induced increase in hydrogen-ion concentration. Hypoxia and acidemia frequently coexist; and their interaction, which is clinically important, follows a predictable pattern.

ALTITUDE.

Life at high altitudes is associated with pulmonary hypertension of variable severity, reflecting the range of reactivities of different persons due to the pulmonary vasoconstrictive effect of hypoxia.[37] Altitude decreases the inspired partial pressure of oxygen (P_{IO_2}) because of a decrease in barometric pressure. At sea level, P_{IO_2} is on average 150 mm Hg. At high altitudes (3000 to 5500 m) P_{IO_2} decreases to 80 to 100 mm Hg, and at extreme altitudes,

Figure 54-1 This diagram demonstrates the existence of phenotypically unique cell subpopulations in the normal vascular media and their contribution to injury-induced vascular remodeling. In response to vascular injury, select cell subpopulations may be activated to migrate, proliferate, and/or change their production of specific matrix proteins. In addition, these cells may also produce autocrine or paracrine growth factors. The selectively activated cell population thus not only expands but also induces changes in other smooth muscle cell subpopulations in the vessel wall. Thus, the final vascular lesion observed in response to physiological stimuli is the collective product of many cell types and several cellular processes. *(From Stenmark KR, Frid MG: Smooth muscle cell heterogeneity: Role of specific smooth*

muscle cell subpopulations in pulmonary vascular disease. Chest 114:82S-90S, 1998.)

5500 to 8840 m, P_{IO_2} decreases to 40 to 80 mm Hg. Corresponding alveolar P_{O_2} (P_{AO_2}) and arterial P_{O_2} (Pa_{O_2}) depend on the hypoxic ventilatory response and associated respiratory alkalosis. Mild pulmonary hypertension in adult natives at high altitude occurs at rest and may increase substantially with exercise. It is not immediately reversed by breathing of oxygen, does not seem to limit exercise capacity, and is rarely the cause of right ventricular failure.[38] [39] Severe pulmonary hypertension may occur with high altitude pulmonary edema, with infantile or adult forms of subacute mountain sickness, and with chronic mountain sickness. Subacute and chronic mountain sickness may be associated with right-sided heart failure. Subjects susceptible to high-altitude pulmonary edema often present with a slight increase in pulmonary vascular resistance at rest and exercise at sea level and with an enhanced pulmonary vascular reactivity to hypoxia. Transient right ventricular dysfunction has also been described with strenuous exercise at high altitude. In one study, 5 of 14 runners who completed an ultra-marathon at high altitude developed marked right ventricular dilation and hypokinesis, paradoxical septal motion, and pulmonary hypertension.[40] These echocardiographic abnormalities had all normalized at 1-day follow-up.

ASSESSMENT OF PATIENTS WITH COR PULMONALE SECONDARY TO LUNG DISEASE

CLINICAL EXAMINATION.

The clinical examination is a relatively insensitive means of detecting pulmonary hypertension

Figure 54-2 Upright chest radiograph in the posteroanterior (PA) projection in a man with severe COPD and pulmonary artery hypertension (mean pulmonary artery pressure = 47 mm Hg). The arrows indicate the widest dimensions of the enlarged right descending pulmonary artery. Note also the enlarged main pulmonary artery in the central left hemithorax. An enlarged right descending pulmonary artery (>16 mm Hg) and an enlarged main pulmonary artery on the PA projection are indicative of pulmonary artery hypertension in patients with COPD.

or right ventricular dysfunction in patients with chronic obstructive pulmonary disease (COPD), because clinical signs are often obscured by hyperinflation of the chest. The jugular venous pressure may also be difficult to assess in patients with COPD because of large swings in intrathoracic pressure. A systolic left parasternal heave indicates right ventricular hypertrophy, whereas the murmur of tricuspid regurgitation suggests right ventricular dilatation, but these are not always present and may be modified by hyperinflation. Accentuation of the pulmonic component of the second heart sound indicating pulmonary hypertension is a specific but insensitive finding in patients with COPD. Peripheral edema can be due to other causes (such as hypoalbuminemia) and

does not always occur in patients with pulmonary hypertension. A progressive decrease in exercise tolerance in the absence of worsening pulmonary function should suggest a cardiovascular cause and prompt a thorough evaluation.

CHEST RADIOGRAPH

(Fig. 54-2) . The presence of pulmonary arterial hypertension in patients with COPD has been shown to be related to the width of the right descending pulmonary artery. A right descending pulmonary artery ranging from greater than 16 mm Hg in its widest dimension[41] to greater than 20 mm Hg has been reported to identify patients with pulmonary arterial hypertension.[42] In addition, a high value for the cardiothoracic ratio was 95 percent sensitive and 100 percent specific for the presence of pulmonary hypertension in patients with COPD.[42] Although measurements on plain chest radiography may be useful as an initial screening test for the presence of pulmonary arterial hypertension, they cannot be used to predict the level of pulmonary arterial pressure in individual patients. Dilatation of the right ventricle gives the heart a globular appearance, but right ventricular hypertrophy or dilatation is not easily discernible on a plain chest radiograph. Encroachment of the retrosternal air space on the

TABLE 54-2 -- FREQUENTLY USED ECG CRITERIA FOR RIGHT VENTRICULAR HYPERTROPHY

Right-axis deviation>110°
R/S ratio in V_1 >1
R wave in V_1 7 mm
S wave in V_1 <2 mm
qR pattern in V_1
R wave in V_1 +S wave in V_5 or V_6 >10.5 mm
R/S ratio in V_5 or V_6 1
Onset of intrinsicoid deflection in V_1 = 0.035-0.055 second
rSR^1 in V_1 with R^1 10 mm
Adapted from Chou T-C: Right ventricular hypertrophy. In: Electrocardiography in Clinical Practice. Philadelphia, WB Saunders 1991, pp 53-68.

lateral film may be a helpful sign to confirm that the enlarged silhouette is a result of right ventricular dilatation.

ELECTROCARDIOGRAPHY.

The detection of right ventricular hypertrophy by the electrocardiogram (ECG) is highly specific but has a low sensitivity (see Chap. 5). Frequently used criteria for the diagnosis of right ventricular hypertrophy are outlined in Table 54-2 . However, these ECG abnormalities are usually less pronounced in COPD than other forms of pulmonary hypertension because of the relatively modest degree of pulmonary hypertension that occurs and because of the effects of hyperinflation (Fig. 54-3) . Butler and coworkers have introduced three criteria for right ventricular hypertrophy: (1) P wave amplitude <0.25 mV in II, III, aVF, and V_1 or V_2 ; (2) R wave amplitude
0.2 mV in I; and (3) A+R -PL
0.7 mV (A = R or R
in V_1 or V_2 ; R = S in I or V_6 ; PL = S in V_2).[43] These three criteria achieve 66 percent sensitivity in a group with right ventricular hypertrophy caused by mitral stenosis and 95 percent specificity in normal controls. When these criteria were evaluated in a population with cor pulmonale, their sensitivity was found to be even higher at 89 percent.[44]

ECHOCARDIOGRAPHY.

Although echocardiography is an invaluable tool in the evaluation of most forms of pulmonary hypertension (see Chap. 7), its utility is more limited in COPD because hyperinflation of the lungs and marked respiratory variations in intrathoracic pressures often result in suboptimal images. Delayed opening of the pulmonic valve, midsystolic closure, and an increase in the ratio of right ventricular preejection time to total ejection time have been described in patients with pulmonary hypertension. [45] Measurement of the velocity of blood flow in the main pulmonary artery can be used to estimate the pulmonary artery pressure.[46] The interval between the onset of right ventricular ejection and peak velocity, known as the time to peak velocity, correlates fairly well with the mean pulmonary artery pressure in patients with COPD (r = 0.7).[47] However, an adequate recording of the flow velocity from the pulmonary valve may be difficult to obtain. The addition of Doppler echocardiography has improved the assessment of right ventricular systolic ejection flow as an estimate of pulmonary artery systolic pressure[48] by adding the mean right atrial pressure to the peak systolic gradient between the right atrium and right ventricle. It is also possible to estimate the pulmonary end-diastolic pressure noninvasively by summing the mean right atrial pressure and the end-diastolic gradient between the pulmonary artery and the right ventricular outflow track using the pulmonary regurgitation jet. Because obtaining the estimates of peak tricuspid regurgitation velocities in patients with COPD can be difficult at times, saline contrast medium enhancement should be used to improve the accuracy of the measurements.[49]

Two-dimensional echocardiography can be used to assess right ventricular dimensions and wall thickening and right ventricular volume overload in patients with COPD. Detection of right ventricular hypertrophy by echocardiography

Figure 54-3 Electrocardiogram in a patient with emphysema and diffuse lung disease; there is right-axis deviation, "P pulmonale," a qR pattern in V_1 and an rS pattern in V_6 . *(From McGowan FX, Wagner GS: The electrocardiogram in chronic lung disease. In Rubin LJ [ed]: Pulmonary Heart Disease. Boston, Martinus Nijhoff, 1984, p 117.)*

is limited by the ability to differentiate the right ventricular wall from its surrounding structures. Moreover, correlations between the thickness of the right ventricular wall and the right ventricular mass are poor, even when measured at autopsy.[50] Measurement of the right ventricular diastolic diameter by echocardiography may be useful in detecting right ventricular enlargement. Right ventricular dysfunction is difficult to quantitate echocardiographically, but the position and curvature of the intraventricular septum gives an indication of right ventricular afterload. The utility of transesophageal echocardiography in the evaluation of pulmonary hypertension has yet to be fully explored, but this technique will usually provide satisfactory imaging of the right-sided heart structures in patients whose transthoracic images are of poor quality.

RADIONUCLIDE VENTRICULOGRAPHY (See also Chap. 9).

Radionuclide ventriculography can provide useful information regarding right ventricular function, provided that adequate separation of the cardiac chambers can be accomplished. Because radioactive counts are proportional to volume, variations in the geometric configuration of the ventricles are less important. Although pulmonary artery pressure can not be estimated with this technique, there is an inverse relationship between pulmonary artery pressure and right ventricular ejection fraction in COPD.[51] In most patients with pulmonary vascular disease caused by COPD, the right ventricular ejection fraction is preserved at rest but fails to increase appropriately during exercise.[51] Contractility appears to be maintained until late in the course of the disease, and the abnormal right ventricular response during exercise is most likely due to increased afterload. Patients in whom the right ventricular ejection fraction is reduced usually have more severe pulmonary hypertension or overt signs of right-sided heart failure.

COMPUTED TOMOGRAPHY (See also Chap. 10).

CT determined pulmonary arterial cross-sectional diameter correlates well with mean pulmonary artery pressure.[52] A high-resolution CT scan of the chest is also the most accurate noninvasive means of detecting emphysema in vivo.[53] The principal manifestation of emphysema is a hyperlucent region of lung tissue with no or only a very thin visible wall. Because CT has 10 times the density resolution of conventional radiography, it more readily distinguishes the emphysematous spaces from surrounding lung tissue. Other findings on high-resolution CT include ground-glass opacity, bullae, bronchial wall thickening, mucous plugging of bronchi and bronchioles, overinflation, air trapping (manifest as a lack of expected increase in lung capacity on exhalation scans), central arterial dilatation reflecting pulmonary arterial hypertension, and modest mediastinal lymphadenopathy. CT may demonstrate emphysema in patients with little or

no abnormality on pulmonary function tests. Because the aggregate cross-sectional area is so large, the respiratory bronchioles contribute only a small portion of the total resistance to air flow, which causes poor sensitivity of pulmonary function tests.

MAGNETIC RESONANCE IMAGING (See also Chap. 10).

MRI is becoming the reference standard for measuring ventricular dimensions because it produces the best images of the right ventricle. This technique is noninvasive and does not impose a radiation burden on the patient, but it is expensive and available only in specialized centers. Studies in patients with COPD have demonstrated a correlation between the right ventricular free-wall volume and both pulmonary artery pressure (r = 0.72, $p > 0.01$) and pulmonary vascular resistance (r = 0.65, $p > 0.01$).[54] Interestingly, the right ventricular free-wall volume as an estimate of wall mass correlates with the Pa_{CO_2} but not with the Pa_{O_2} .[54] MRI can be used to diagnose right ventricular hypertrophy in patients with COPD and to study the effect of therapeutic interventions. It can also be used to quantify regional right ventricular function to determine the impact of chronic pulmonary hypertension on right ventricular performance.[55]

PULMONARY HYPERTENSION ASSOCIATED WITH RESPIRATORY DISORDERS

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States, affecting over 14 million people.[56] The incidence, morbidity, and mortality from COPD is rising and varies widely among countries. In fact, the mortality attributed to COPD in the United States rose by 32 percent during the past decade.[56] This may be related to differences in exposure to risk factors as well as to large variations in individual susceptibility. COPD is a heterogeneous group of diseases that share a common feature: the airways are narrowed, which causes the inability to exhale completely. Although there are numerous disorders that fall under the heading of COPD, the two largest components are emphysema and chronic bronchitis. The American Thoracic Society defines COPD as a disorder characterized by abnormal tests of expiratory flow that do not change markedly either spontaneously over short periods of time or after administration of a bronchodilator.[57] Although clear-cut distinctions can often be made, there is considerable overlap as to the dominant abnormality in the individual patient in whom features of both may be manifest. *Chronic bronchitis* is a condition associated with excessive tracheal bronchial mucous production sufficient to cause cough with expectoration for at least 3 months of the year for more than 2 consecutive years. *Emphysema* is defined as the permanent, abnormal distention of the air spaces distal to the terminal bronchial with destruction of the alveolar septa. In lungs from patients with COPD studied at postmortem, the major site of air flow obstruction has been shown to be in the small airways.

Cigarette smoking is the most commonly identified correlate with COPD and accounts for 80 to 90 percent of the

risk of developing COPD.[58] It has been estimated that 15 percent of one-pack-per-day smokers and 25 percent of two-pack-per-day smokers will eventually develop COPD during their lifetime.[58] [59] Why the proportion is so small is not known, but underlying host factors may play a role. Other potential environmental causes include air pollution, occupational exposures, and infection. Individuals who are homozygous for $alpha_1$-antitrypsin deficiency develop severe emphysema in the third and fourth decades of life. Dusty occupational environments are well-established risks but probably not major factors in North America.

PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION.

Most commonly, pulmonary hypertension in COPD is due to multiple factors, which include pulmonary vasoconstriction caused by alveolar hypoxia, acidemia, and hypercarbia; the mechanical effects of the high lung volume on pulmonary vessels; the loss of small vessels in the vascular bed in regions of the emphysema and lung destruction; and the increased cardiac output and blood viscosity from polycythemia secondary to hypoxia. Of these causes, hypoxia is undoubtedly the most important and is associated with pathological changes that occur characteristically in the peripheral pulmonary arterial bed.[60] The small pulmonary arteries develop accumulations of vascular smooth muscle cells in their intima that are laid down longitudinally along the length of the vessels. Intimal thickening appears to be an early event that occurs in association with progressive air flow limitation.[61] Medial hypertrophy in the muscular pulmonary arteries, and less commonly fibrinoid necrosis in these vessels, has also been reported in patients with COPD with chronic pulmonary arterial hypertension. Thus, structural change, rather than hypoxic vasoconstriction, is required for the development of sustained pulmonary hypertension in patients with COPD.[62]

Changes in airway resistance may augment pulmonary vascular resistance in patients with COPD by affecting the alveolar pressure. The normal linear relationship between pressure and flow in the pulmonary circulation changes when alveolar pressure is increased. The effect of airway resistance on pulmonary artery pressure may be particularly important when ventilation increases (such as in acute exacerbation of COPD). In patients with COPD, even the small increases in flow that occur during mild exercise may increase pulmonary artery pressure significantly. Alveolar hypoxia is a potent arterial constrictor in the pulmonary circulation, which reduces perfusion with respect to ventilation in an attempt to restore Pa_{O_2}. In patients with COPD there is a positive correlation between the Pa_{CO_2} and the pulmonary artery pressure. Polycythemia, which may develop in response to chronic hypoxemia, increases the blood viscosity, which may also contribute to the severity of pulmonary arterial hypertension. Pulmonary arterial thrombosis may also occur in patients with COPD and may be a result of peripheral airway inflammation.

HEMODYNAMIC CHANGES.

The elevation in pulmonary artery pressure tends to be rather mild in patients with COPD. Naeije studied 74 patients with severe, but clinically stable COPD. All presented with episodes of acute and chronic respiratory failure in the past, and almost half presented with peripheral edema.[63] They all had severe air flow limitations (FEV_1 25.7 ± 1 percent of predicted) and hypoxemia (Pa_{O_2} mean 43 mm Hg, range 23 to 67 mm Hg), and the majority were also hypercapnic (Pa_{CO_2} mean 51 mm Hg, range 33 to 68 mm Hg). However, the pulmonary artery pressure was only modestly raised to a mean of 35 mm Hg in this group. Although the pulmonary artery pressure may be normal or only slightly elevated when measured at rest in patients with COPD, it may increase to abnormal levels during exercise.[64]

The progression of pulmonary hypertension seems to be related to hypoxemia. In 93 patients with COPD observed for 5 years, hemodynamic worsening, defined as an increase in mean pulmonary artery pressure by more than 5 mm Hg, was observed in 29 percent of patients.[65] In these patients there was a marked worsening of hypoxemia that was not observed in the others. In patients with mild COPD, right ventricular end-diastolic pressure and right ventricular stroke work, which were normal at rest, increased during exercise due to an increase in work against a higher pulmonary artery pressure.[66]

Severe pulmonary arterial hypertension is uncommon in the presence of COPD. In a review of 500 patients referred with cor pulmonale, only 6 were found to have severe elevation in mean pulmonary artery pressure (>50 mm Hg), which was not related to the severity of their underlying lung disease.[67] This observation suggests that a different biological mechanism results in changes in the pulmonary vascular bed in susceptible patients and that pulmonary hypertension occurs in the presence of lung disease rather than as a *result* of the lung disease. This has important implications with respect to treatment. Patients who present with severe pulmonary hypertension should be evaluated for another disease process that is responsible for the high pulmonary arterial pressures before attributing it to the COPD.

PROGNOSIS AND PREDICTORS OF SURVIVAL.

Although pulmonary arterial hypertension progresses slowly in patients with COPD, its presence confers a poor prognosis. Weitzenblum and coworkers showed a 72 percent 4-year survival rate in those with normal pulmonary artery pressure compared with a 49 percent survival rate in those with an elevated pulmonary artery pressure (mean > 20 mm Hg).[68] Burrows and colleagues studied 50 patients with chronic airway obstruction over 7 years and showed that the pulmonary vascular resistance was the hemodynamic parameter that correlated best with mortality.[69] In this study, none of the patients whose pulmonary vascular resistance exceeded 7 Wood Units survived for more than 3 years. France and colleagues, in a study of 115 patients with COPD, found that a number of variables correlated significantly with mortality, including Pa_{O_2} , Pa_{CO_2} , $FEV_{1,}$ and the presence of peripheral edema.[70] Others have reported that patients with COPD who develop peripheral edema have a 5-year survival rate of only 27 to 33 percent.[71]

A 10-year follow-up study conducted on a cohort of 870 patients with severe COPD concluded that (1) patients with COPD have a high mortality rate from acute respiratory failure, cor pulmonale, and lung cancer; (2) patients' age at the time of diagnosis influences the death hazard; (3) patients who need long-term oxygen treatment have a higher death hazard than those who do not; (4) the higher the FEV_1 or Pa_{O_2} at the time of diagnosis, the lower the death hazard; (5) patients who need and use long-term oxygen treatment have a lower death hazard compared with those who need it but do not use it properly; and (6) patients with a partial reversible airway obstruction who regularly attend the clinic for planned checkups have a lower death hazard compared with those who have the same characteristics but do not show adherence to the care program.[72] In another study, among a cohort of 270 patients with COPD, the median survival was 3.1 years. Death was predicted by the following variables: age, ECG signs of right ventricular hypertrophy, chronic renal failure, ECG signs of myocardial infarction or ischemia, and FEV_1 less than 590 ml.[73] Among 166 patients treated with long-term oxygen therapy, the overall survival rates were 78.3 percent and 67.1 percent at 2 and 3 years, respectively. A multivariate analysis showed an independent predictive power for right ventricular systolic pressure, age, and FEV_1 .[74] Once endotracheal intubation is necessary, the prognosis is usually poor and the survival after 1 year is usually lower than 40 percent.[75] Pulmonary embolism is a common cause of death, with the frequency estimated to be approximately 11 percent.[76]

Among patients with COPD in the intensive care unit, pulmonary embolism was the most frequent cause of death at 40.6 percent.

Treatment

Management goals in COPD are to ameliorate air flow obstruction and improve symptoms, to avoid secondary complications, to maintain functional capacity, and to improve the quality of life. Recent advances in smoking cessation strategies and surgical techniques (lung volume reduction surgery and lung transplantation) and renewed interest in noninvasive positive-pressure ventilation have expanded treatment options to meet the patient's needs. In addition to the specific therapies discussed here, all patients should receive a yearly influenza vaccination and the 23-valent pneumococcal vaccination at least once in their lifetime. For patients who do not receive influenza vaccine and are at risk for influenza type A infection, amantadine, 200 mg/d, or rimantadine, 100 mg twice per day, should be prescribed until the risk of infection has subsided.

SMOKING CESSATION.

The importance of smoking cessation cannot be overemphasized. The annual rate of decline of FEV_1 in smokers is approximately 80 ml per year, in contrast to 25 to 30 ml

per year in nonsmokers. The Lung Health Study reported that patients who stopped smoking had a small improvement in FEV_1 (57 ml) after 1 year. [77] Thereafter, the rate of decline in lung function is similar to age-matched nonsmokers. The short-term success rates with smoking cessation are variable (18-77 percent), but success is more likely if the patient abstains from smoking within the first 2 weeks of entry into a program. The use of nicotine replacement therapy should always include a structured behavioral modification program to increase the likelihood of success. Pharmacological methods to reduce addictive behavior have not been found to be effective in controlled clinical trials.[78] Recently, the novel antidepressant bupropion (Zyban), which enhances noradrenergic activity, was reported to have a successful smoking cessation rate of 44 percent, compared with 19 percent in the placebo group.[79]

PULMONARY REHABILITATION.

Patients with advanced COPD often lead a sedentary lifestyle because of breathlessness during mild to moderate exercise. The lack of exercise leads to deconditioning and worsening dyspnea, even with low levels of activity. The overall goal of a pulmonary rehabilitation program is to maintain the individual's maximal level of independence and functioning in the community. Pulmonary rehabilitation can improve exercise endurance and decrease the sense of breathlessness. Several studies have demonstrated that pulmonary rehabilitation can improve exercise capacity, subjective symptoms, and quality of life.

Because of hyperinflation, deconditioning, and malnutrition, patients with advanced air flow obstruction have weakened ventilatory muscles. Moreover, because of the increased work of breathing, the inspiratory muscles are prone to fatigue. Fortunately, the respiratory muscles can be trained to improve their strength and endurance. Strength training can be achieved by high-intensity, low-frequency stimuli such as inspiring against a closed glottis or shutter valve. Endurance training may also improve inspiratory muscle strength.

OXYGEN.

Hypoxemia is a common finding in patients with advanced COPD and is easily corrected with low-flow supplemental O_2 . In key clinical trials sponsored by the National Institutes of Health (NIH, Nocturnal Oxygen Therapy Trial [NOTT] Group, 1980) and the British Medical Research Council (1981) long-term oxygen therapy clearly improved the survival of hypoxemic patients with COPD (Fig. 54-4) .[80] [81] The British study compared the effect of treatment with oxygen for approximately 15 hours per day with the effects of no oxygen therapy, whereas the NIH

Figure 54-4 Survival curves in the MRC (British) and NIH (US) long-term oxygen therapy trials in patients with severe hypoxemia and cor pulmonale. *(From Flenley DC, Muir AL: Cardiovascular effects of oxygen therapy for pulmonary arterial hypertension. Clin Chest Med 4:297, 1983.)*

study compared nocturnal oxygen therapy (about 12 hours per day) to "continuous" oxygen therapy (at least 19 hours per day). In each study, the mean baseline Pa_{O_2} when the patients were breathing ambient air was 51 mm Hg; the mean FEV_1 was 0.7 to 0.8 liter.

Oxygen therapy was beneficial in both studies (see Fig. 54-4). In the British study, 19 of 42 (45 percent) oxygen-treated patients died within 5 years, whereas 30 of 45 (67 percent) untreated patients died. In the NIH study, the mortality rate after a year was 20.6 percent in the group receiving nocturnal oxygen and 11.9 percent in the group receiving continuous oxygen therapy; and after 2 years, mortality was 40.8 percent and 22.4 percent, respectively. The relative risk of death for nocturnal oxygen therapy compared with continuous oxygen was 1.94. Oxygen therapy is therefore effective, and continuous therapy is more effective than nocturnal therapy only.

HEMODYNAMIC EFFECTS OF OXYGEN.

How oxygen therapy improves survival is unknown. Two major hypotheses have been proposed: (1) oxygen relieves pulmonary vasoconstriction, decreasing pulmonary vascular resistance and thus enabling the right ventricle to increase stroke volume, and (2) oxygen therapy improves arterial oxygen content, providing enhanced oxygen delivery to the heart, brain, and other vital organs. These two hypotheses are not mutually exclusive, and each one has supporting evidence. Oxygen therapy clearly alleviates the progressive pulmonary hypertension of untreated COPD. Patients who exhibit a significant decrease in pulmonary artery pressure (>5 mm Hg) after acute oxygen therapy (28 percent oxygen for 1 day) have better survival than patients who do not respond acutely when both groups of patients are subsequently treated with long-term continuous oxygen therapy.[82] Enhanced right ventricular performance during short-term oxygen therapy may also be the direct result of improved tissue (e.g., myocardial) oxygenation rather than decreased pulmonary vascular resistance.[83]

RECOMMENDATIONS.

Criteria for chronic home O_2 therapy are shown in Table 54-3 . Long-term oxygen therapy is warranted if the resting Pa_{O_2} remains less than 55 mm Hg after a 3-week stabilization period on maximal medical therapy (e.g., bronchodilators, antimicrobial agents, diuretics). Patients with a Pa_{O_2} above 55 mm Hg should be considered for oxygen therapy if they are polycythemic or have clinical evidence (e.g., ECG, physical examination) of pulmonary hypertension.[84] Hypoxemia should be documented after the stabilization period to avoid the cost of long-term

TABLE 54-3 -- INDICATIONS FOR HOME OXYGEN

Absolute

Pa_{O_2}
55 mm Hg or Sa_{O_2}
88%

Pa_{O_2} 55-59 mm Hg or Sa_{O_2} = 89% in the presence of any of the following

Dependent edema suggesting congestive heart failure

P pulmonale on theECG (P wave <3 mm in standard leadsII, III, or aVF)

Erythrocytosis (hematocrit>56%

Specific Situations

During exercise

Pa_{O_2} <55 mm Hg or O_2 saturation <88% with low level of exertion

During sleep

Pa_{O_2} <55 mm Hg or O_2 saturation <88% with associated cpmplications, such as pulmonary bypertension, excessive daytime sleepiness, and cardiac arrhythmias

Adapted from ATS Statement: Comprehensive outpatient management of COPD. Am J Respir Crit Care Med 152(Suppl):S84-S96, 1995.

oxygen therapy in patients who do not require it. In the NOTT study,[81] 45 percent of hypoxemic patients initially selected for study improved enough during 3 to 4 weeks of observation and treatment to suspend plans for long-term oxygen therapy. An even longer observation period of 2 or 3 months may be necessary to exclude patients who eventually achieve acceptable Pa_{O_2} values on medical therapy alone. For sedentary patients already on supplemental O_2 , the resting O_2 requirement may be increased by 1 liter/min during mild activities. Oxygen has been shown to delay the onset of fatigue in exercising muscles, thus improving ventilatory endurance and exercise capacity.[85] In addition, it also decreases dyspnea and minute ventilation for a given workload.[86] Nocturnal oxygen therapy may be important in patients with sleep desaturation. Daily activities, such as walking, washing, and eating, are associated with transient oxygen desaturation in patients with moderate to severe COPD, even in the absence of resting hypoxemia.[87] Ambulatory oxygen therapy in patients with COPD and exercise hypoxemia may improve exercise capacity and breathlessness.[88]

Carbon dioxide retention may occur with supplemental O_2 , especially with higher O_2 concentrations, and is thought to be due to blunting of hypoxemia driven central respiratory drive. This observation may lead some physicians to withhold O_2 therapy. It is now believed that the main mechanism for CO_2 retention in these patients is worsening ventilation-perfusion inequality due to O_2 -induced pulmonary vasodilatation in areas of the lung with poorer ventilation. Ambier and colleagues show that central respiratory drive is normal or slightly increased in patients who develop hypercapnia while on O_2 therapy.[89] If CO_2 retention is associated with systemic acidosis (pH 7.25 or

less) and the patient requires high O_2 flow to maintain satisfactory PaO_2 , mechanical ventilation should be considered.

ANTICHOLINERGICS.

Anticholinergics are the bronchodilators of choice in the management of COPD and appear to be more effective than beta$_2$ agonists. [90] Anticholinergic drugs, typified by atropine, cause bronchodilatation by blocking cholinergic mediated increases in bronchomotor tone. In addition, they also block the afferent limb of the vagally mediated bronchoconstriction induced by nonspecific airway irritants such as cigarette smoke, dust, and fumes. Ipratropium bromide can achieve similar, if not greater, degrees of bronchodilatation than beta agonists and has fewer side effects. It has been suggested that ipratropium bromide should be the initial agent in the chronic therapy for COPD.[91] Combination therapy with anticholinergic and beta$_2$ agonists has been shown to be more effective than either drug alone.[92] Unlike beta agonists, anticholinergic drugs have a slower onset of action and a longer half-life. The usual dose of ipratropium bromide is two puffs every 4 to 6 hours. An investigational agent, ipatropium bromide, gives prolonged bronchodilatation lasting over 24 hours and has the advantage of improved compliance with once-daily dosing.[93]

BETA-ADRENERGIC AGONISTS.

These are important drugs in the management of chronic air flow obstruction. In contrast to asthma, however, a lesser degree of bronchodilatation is seen in COPD. The absence of a significant bronchodilator response on a single spirometry (post-bronchodilator increase in FEV_1 by greater than 15 percent) does not preclude the delayed effectiveness of beta agonists. As many as 70 percent of patients who show no initial response to a beta agonist will show greater than 15 percent improvement in FEV_1 on subsequent spirometry.[91] The increases in vital capacity are usually higher than those observed for FEV_1 , and they are often associated with symptomatic improvement.[94] Recent studies have shown that the long-acting inhaled beta$_2$ agonists salmeterol and formoterol are beneficial in patients with COPD, resulting in improved lung function and symptom control.[95] [96] The side effects of properly used inhaled beta agonists are minimal and limited to skeletal muscle tremors and tachycardia. Although there is no evidence that the regular use of a beta agonist increases mortality in patients as alluded to in asthma, it is generally recommended that a beta agonist should be used on an "as needed" basis. In patients with severe COPD, regularly dosed beta agonists may improve symptoms.[97]

THEOPHYLLINE.

The use of theophylline in COPD has been tempered by its frequent side effects, variable hepatic metabolism, and studies showing little symptomatic benefit. However, theophylline is an effective bronchodilator in COPD and will cause a small improvement in results of pulmonary function tests.[98] [99] Long-term use has been associated with an overall 10 to 20 percent increase in the FEV_1 from baseline, and an improvement in

minute ventilation and gas exchange has also been observed.[98] [100] In addition to improving FEV_1 , theophylline reduces dyspnea,[98] [101] improves exercise performance,[102] and is associated with a subjective sense of well-being in patients with severe COPD, even if the reduction in dyspnea is not accompanied by a change in functional indices such as FEV_1 or arterial blood gases.[101]

CORTICOSTEROIDS.

Because there is continued neutrophilic inflammation in COPD, it was thought that inhaled corticosteroids might prevent the progression of disease. However, there is little evidence that inhaled corticosteroids are of benefit to a large percentage of patients.[103] The few patients (approximately 10 percent) who have some response to corticosteroids have asthma. A large study (the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease [EUROSCOP]) in patients with mild COPD showed no overall effect of an inhaled corticosteroid (budesonide, 400 mug twice daily) on the annual rate of decline in lung function, although some subgroups appear to benefit.[104] A recent trial of even higher doses of inhaled budesonide, 1600 mug/d, versus placebo showed no physiological or functional benefit in patients with advanced COPD after 6 months.[105] A 3-year placebo-controlled, parallel group, randomized, double-blinded trial of inhaled budesonide demonstrated no clinical benefit in COPD patients.[106]

The effects of oral corticosteroids are similarly disappointing. Only 10 to 20 percent of COPD patients with judicious use of oral corticosteroids will show improvement in pulmonary symptoms and FEV_1 by 20 to 25 percent,[107] as well as decreasing the number of acute exacerbations[108] and airway responsiveness. Clinical criteria that may be useful in predicting corticosteroid responders from nonresponders includes a significant bronchodilator response

to a beta agonist, presence of eosinophils in the sputum or blood, and a history of atopy.

DIGITALIS.

The effects of digitalis in cor pulmonale are complex. The cardiac glycosides increase the contractility of the RV myocardium, but they also can produce pulmonary vasoconstriction. Furthermore, Sylvester and associates[109] showed that, in dogs, digitalis can reduce venous return, which may adversely affect cardiac output. Intravenous digoxin may also improve diaphragm strength and blood flow in patients with COPD with acute respiratory failure.[110]

Digitalis therapy is indicated in patients with cor pulmonale and coexistent left ventricular failure. In patients with severe COPD and biventricular failure, an improvement in right ventricular ejection fraction has been observed with digoxin,[111] but not in patients with a reduced right ventricular ejection fraction and normal left

ventricular function.[112] Recently, it was demonstrated that short-term intravenous digoxin improved cardiac output and reduced circulating norepinephrine[113] in patients with right ventricular dysfunction due to primary pulmonary hypertension. Digitalis therapy may cause an increased incidence of adverse side effects (e.g., cardiac arrhythmias) in patients with obstructive lung disease, presumably in part owing to the effect of hypoxia.

VASODILATORS.

No agent other than oxygen has been shown convincingly to vasodilate the pulmonary circulation in patients with COPD. Nonselective beta-adrenergic antagonists may reduce systemic arterial oxygen saturation from intrapulmonary shunting associated with an increase in dyspnea in these patients. Hydralazine and calcium channel blockers have been shown to have essentially no effect on pulmonary hemodynamic measurements in patients with COPD. Currently, there is no role for oral vasodilators in the management of COPD.

NITRIC OXIDE.

Inhaled nitric oxide (NO) has been used as a selective pulmonary vasodilator due to its short duration of action and inactivation in the systemic circulation,[114] but it is difficult to use over a prolonged period. A recent study demonstrated that the combined inhalation of NO and O_2 was associated with reductions of the mean pulmonary artery pressure and pulmonary vascular resistance and a remarkable improvement in arterial oxygen saturation.[115] Other studies have suggested that inhaled NO worsens oxygenation in the setting of COPD, potentially by overriding hypoxic pulmonary vasoconstriction.[116] [117] The role of NO in the therapy for COPD has yet to be defined.

ACE INHIBITORS.

Angiotensin II is a potent pulmonary and airway constrictor acting through angiotensin II receptors. The role of ACE inhibitors and angiotensin II receptor antagonists is still emerging. In one trial, enalapril reduced pulmonary hypertension and improved renal blood flow in 30 patients with COPD.[118] The angiotensin receptor blocker losartan also reduces pulmonary artery pressure in patients with COPD[119] and therefore may be useful in preventing the progression of pulmonary hypertension and cor pulmonale in patients with severe COPD. Further investigation needs to be completed before making generalized recommendations regarding these agents in patients with COPD.

NONINVASIVE VENTILATION.

Noninvasive positive-pressure ventilation (NPPV) has been reported to improve gas exchange, sleep efficiency, quality of life, and functional status in patients with restrictive lung disease and chronic respiratory failure. Its usefulness in patients with COPD is not as well established. The initial interest in using intermittent noninvasive ventilation for patients with severe COPD arose from physiological studies on respiratory muscle function. Hyperinflation in patients with COPD was found to place the respiratory

muscles at a mechanical disadvantage. The flattened diaphragms had shortened sarcomere lengths, diminished maximal force, increased muscle tension, and compromised blood supply. Based on these considerations, investigators hypothesized that noninvasive ventilation would be of value to patients with severe COPD because it would rest the chronically fatigued muscles. Periods of intermittent rest would permit recovery of muscle function, increasing muscle strength, reducing the tendency to fatigue, and improving pulmonary function and gas exchange.

An alternative hypothesis was generated based on sleep studies in COPD. Patients with severe COPD have a high prevalence of sleep-disordered breathing, including not only obstructive sleep apnea but also episodes of hypoventilation associated with oxygen desaturations.[120] Large retrospective analyses have examined outcomes of patients treated with NPPV for periods ranging up to 5 years.[121] [122] Patients with COPD were less likely to continue NPPV treatment than patients with neuromuscular disorders or chest wall deformities, but the average duration of continuation was still 2 to 3 years. Although the survival of patients with COPD treated with long-term NPPV appears to be comparable to that of patients treated with tracheostomies or long-term oxygen therapy, the retrospective and uncontrolled nature of these trials greatly limits any conclusions that can be drawn.

A recent consensus conference suggested that patients with severe CO_2 retention, particularly those with nocturnal oxygen desaturation, appear most likely to respond favorably to NPPV.[123] The statement specifically recommends consideration of NPPV for those patients with COPD and symptoms such as fatigue, dyspnea, and morning headache despite optimal medical management and one of the following physiological criteria: Pa_{CO_2} greater than or equal to 55 mm Hg; Pa_{CO_2} of 50 to 54 mm Hg and nocturnal desaturation (oxygen saturation < 88 percent for 5 continuous minutes while receiving 2 L/min or more of nasal O_2); or Pa_{CO_2} of 50 to 54 mm Hg and hospitalization (two or more times in a 12-month period) related to recurrent episodes of hypercapnic respiratory failure.

LUNG VOLUME REDUCTION SURGERY.

Volume reduction surgery, which was originally described by Brantigan, has been advocated in selected patients with advanced emphysema. The surgical technique involves removing 20 to 30 percent of the volume of each lung by means of sternotomy, sequential thoracotomy, or thoracoscopy to reduce the severe hyperinflation commonly seen in patients with severe COPD. The physiological improvement after excision of large bullae in patients with severe emphysema is easy to understand. The compressed normal lung parenchyma expands after bullaectomy, resulting in improved lung function and exercise capacity. In patients with diffuse emphysema, the exact mechanism of these physiological improvements is less clear. The proposed benefits of surgery include the following: restoration of elastic recoil on small airways leading to decreased airway resistance; restoration of normal outward chest recoil; improved ventilation-perfusion matching; and a reduction in end-expiratory lung volume, thereby returning the diaphragm to a more favorable length-tension precontraction length for optimal pressure generation. There are, however, very strict criteria for lung volume reduction surgery (Table 54-4) . Although the medical selection criteria are less stringent

for lung volume reduction surgery than for lung transplantation, the disease-specific criteria are more restrictive. The residual volume to total lung capacity ratio is the single most important determinant of improvement in pulmonary function after lung volume reduction surgery.[124]

Patients with COPD who are thought to respond best to surgery have the following characteristics: heterogeneous bullous changes within the lung as detected by CT and ventilation-perfusion scan; presence of severe hyperinflation; reduced diaphragmatic excursion; and absence of hypercapnia and pulmonary hypertension. Long-term follow-up data are still not available, and it is not clear how long

TABLE 54-4 -- CRITERIA FOR LUNG VOLUME REDUCTION SURGERY

No age restriction
Marked disability after completing pulmonary rehabilitation (see text)
No tobacco use for at least 4 months
Imaging must show heterogeneous disease (homogeneous disease has more stringent criteria)
Pulmonary function tests (all after bronchodilator administration; lung volumes measured by plethysmography)
Forced expiratory volume in 1 second (FEV_1)
45% if age >70 years, an FEV_1
15% predicted)
Total lung capacity
110%
Residual volume
150%
Diffusing capacity of the lung for carbon monoxide
70%
Absence of bronchodilator response (FEV_1) change
30% and 300 ml
$Paco_2$ <60 mm Hg
Pao_2 >45 mm Hg on room air
Mean pulmonary artery pressure
35 mm Hg or peak systolic pressure
45 mm Hg

Adapted from Dasgupta A, Maurer J: Late-stage emphysema: When medical therapy fails. Cleve Clin J Med 66:415-425, 1999.

the improvement in lung function seen after lung volume reduction will persist. Maximal improvement in lung function indices are seen at 6 months after surgery; and although improvements are maintained at 1 year, there may be a trend toward falling indices compared with the 6-month values.[125] Lung volume reduction is palliative to a procedure that does not halt but only slows the rate of functional decline for COPD. The disease will still progress, and symptoms will likely worsen.

LUNG TRANSPLANTATION.

COPD is the most common indication for lung transplantation worldwide. In 1995, approximately 60 percent of single lung and 30 percent of bilateral lung transplants were performed on patients with COPD.[126] Lung transplantation is a viable treatment option in patients with advanced pulmonary parenchymal or pulmonary vascular disease who have exhausted medical management. Both the number of patients waiting for lung transplantation and the waiting period have increased. Because of the scarcity of organ donors, the waiting time is now approximately 18 to 24 months in the United States. Patient selection and timing of referral for lung transplantation should take into account this waiting period. Selection criteria are outlined in Table 54-5 , although they may differ among lung transplant centers. Currently, both single-lung transplantation and bilateral lung transplantation result in significant improvement in postoperative lung function, exercise capacity, and quality of life.[127] The choice of the procedure needs to be individualized. In general, single-lung transplantation is used for emphysema because of the scarcity of organ donors, lower perioperative morbidity and mortality, and comparable improvement in exercise capacity compared with bilateral lung transplantation.[128] However, postoperative spirometry, single breath diffusing capacity, and arterial oxygen tension are all significantly higher in bilateral lung transplantation compared with single-lung transplantation, which may benefit young patients with emphysema because the higher pulmonary reserve will offset any decline in lung function due to infection or rejection. In most centers, bilateral lung transplantation is reserved for patients with suppurative lung disease or pulmonary vascular disease. The 1-year and 5-year survival for single and bilateral lung transplantation for emphysema is approximately 80 percent and 40 percent, respectively.

Complications associated with lung transplantation recipients are due to infections (i.e., bacterial, viral, or fungal), chronic rejection (bronchiolitis obliterans), and

TABLE 54-5 -- CRITERIA FOR LUNG TRANSPLANTATION FOR COPD

Ambulatory with rehabilitation potential 80-120% of ideal body weight
Approximate maximum age (years)
65 (single-lung recipients)
60 (double-lung recipients)
55 (heart-lung recipients)

Severely ill despite optimal medical therapy
NYHA Class III
FEV_1 <20% of predicted
Rapid decline in FEV_1
Hypoxia
Hypercapnia
Minimal corticosteroid use (15-20 mg qd)
Creatinine clearance >50 mg ml/min
Contraindications
Recent or current malignancy
Significant disease affecting other organ systems
Extrapulmonary infections
Substance abuse (including cigarettes) for more than 6 months
Ventilator dependence
Adapted from Dasgupta A, Maurer J: Late-stage emphysema: When medical therapy fails. Cleve Clin J Med 66:415-425, 1999.

noninfectious complications due to prolonged immunosuppression. Chronic rejection, manifest clinically as progressive deterioration in lung function and pathologically as bronchiolitis obliterans, can occur in 40 percent of lung transplant recipients and is now the most common cause of death among long-term survivors.[129]

Interstitial Lung Disease

Interstitial lung diseases represent a variety of conditions that involve the alveolar walls, perialveolar tissue, and other contiguous supporting structures. Cor pulmonale occurs in a variety of interstitial lung diseases and is often associated with obliteration of the pulmonary vascular bed by lung destruction and fibrosis. The mechanism for pulmonary hypertension may be related to hypoxemia or a loss of effective pulmonary vasculature from lung destruction and/or by indirectly triggering a pulmonary vasculopathy. Interstitial lung disease may be due to environmental inhalant exposures, such as to asbestos, drugs, and chemotherapeutic agents, to radiation, and to recurring aspiration pneumonias. A large number of patients have interstitial lung disease of unknown etiology, the most common being idiopathic pulmonary fibrosis (IPF) and interstitial lung disease associated with collagen vascular diseases.

IDIOPATHIC PULMONARY FIBROSIS.

IPF can be associated with pulmonary hypertension, which is difficult to manage because the current medical therapy for IPF is only minimally effective. Most patients

are older than 50 years of age and usually report an insidious onset of progressive dyspnea and cough from months to years. The physical findings are typified by inspiratory crackles on chest examination and clubbing of the fingers. The chest radiograph may show bilateral peripheral-based opacities and honeycombing predominantly involving the lower lung zones. Pulmonary function tests show reduced lung volumes with restrictive physiology and a diminished diffusing capacity for carbon monoxide. IPF is a diagnosis of exclusion, and other forms of diffuse parenchymal lung disease need to be ruled out. A definitive diagnosis of IPF requires an open-lung biopsy.[130] Other lung diseases that need to be distinguished include bronchiolitis obliterans with organizing pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, acute interstitial pneumonia, lymphocytic interstitial pneumonia, respiratory bronchiolitis-associated

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Figure 54-5 Pathogenesis of pulmonary fibrosis. There are numerous pathways that can lead to pulmonary fibrosis, and none is mutually exclusive. This scheme poses a problem in that specific targeted therapy would likely be ineffective because of the redundancy of pathways toward fibrosis. However, it is likely that only a few of these pathways are critical in human idiopathic pulmonary fibrosis. Studies with keratinocyte growth factor (KGF) in rats and gene deletion studies in mice indicate that a single growth factor or receptor might be highly effective. Therapy need not be directed at the whole inflammatory response as is the current rationale for corticosteroids and cytotoxic agents. IL-4 = interleukin-4; FGF-2 = fibroblast growth factor-2, basic FGF; TGF-beta = transforming growth factor-beta; TNF = tumor necrosis factor; PDGF = platelet-derived growth factor; IL-1 = interleukin-1; IGF-1 = insulin-like growth factor-1; HB-EGF = heparin binding epidermal-like growth factor; IFN = interferon gamma; PGE_2 = prostaglandin E_2 . *(From Mason RJ, Schwarz MI, Hunninghake GW, Musson FA: Pharmacological therapy for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 160:1171-1177, 1999.)*

interstitial lung disease, and chronic hypersensitivity pneumonitis.

The pathogenesis of pulmonary fibrosis has not been well defined because there are numerous pathways that can lead to pulmonary fibrosis that are not mutually exclusive.[131] Although it is believed that inflammatory cells acting directly on fibroblasts in the lung through a variety of inflammatory mediators play a key role, the interaction of the inflammatory cascade with parenchymal lung cells is also important (Fig. 54-5) .

Initial symptoms include dyspnea, effort intolerance, and dry cough without obvious cause. A "ground glass" appearance on high-resolution chest CT is equated histologically with a cellular reaction.[132] A "reticular nodular" appearance denotes more advanced, less cellular fibrotic areas. However, the high-resolution chest CT is normal in approximately 12 percent of biopsy specimen-proven cases of interstitial lung disease.[133]

The major targets of therapy have focused on the inflammatory cells, and this has led to the use of antiinflammatory agents.[134] [135] However, corticosteroids and cytotoxic drugs are only occasionally effective in IPF. Pulmonary hypertension is a complication of

pulmonary fibrosis that may warrant more aggressive therapy. Pulmonary hypertension can become the limiting factor in the dyspnea and exercise limitation of patients with IPF and contributes to its mortality. The therapy for pulmonary hypertension should be directed at the underlying disease process and not toward lowering pulmonary artery pressure. Oxygen is indicated in the presence of hypoxemia. Worsening gas exchange and heart failure can be induced by the use of vasodilators, which appear to have no role in disease management. In such patients, therapy with digitalis and diuretics would be appropriate.

ADULT CYSTIC FIBROSIS.

Cystic fibrosis (CF) is the most common lethal genetic disease in whites and occurs in approximately 1 of every 2000 live births. As the disease progresses, patients develop disabling lung disease and eventually respiratory failure, pulmonary hypertension, and cor pulmonale. The pathophysiology of pulmonary hypertension and cor pulmonale in CF is believed to be related to progressive destruction of the lung parenchyma and the pulmonary vasculature and to pulmonary vasoconstriction secondary to hypoxemia.[136] The development of cor pulmonale in patients with CF carries a grave prognosis. The mean survival time from the onset of cor pulmonale has been reported to be as short as 8 months. Typically, the patients have severe hypoxemia, which may be a result of and a causative factor of the pulmonary hypertension (Fig. 54-6) .

One recent study evaluated patients with CF and cor pulmonale in depth.[137] Right ventricular hypertrophy appears to be a precursor of right ventricular failure and an indicator of the onset of pulmonary hypertension. The severity of the pulmonary hypertension appeared to correlate significantly with declining pulmonary function, as well as with the degree of oxygen desaturation on exercise. In this study, patients who developed pulmonary hypertension had a much worse prognosis (average survival 15 months) compared with those without pulmonary hypertension (average survival 33 months). Once lung function is severely limited (FEV_1 <40 percent predicted), the prevalence of pulmonary hypertension may be as high as 40 percent. Because hypoxemia is universally found, supplemental oxygen

Figure 54-6 The correlation between pulmonary artery systolic pressure (PASP) and FEV_1 , mean oxygen saturation during wakefulness (Sa_{O_2} W), mean oxygen saturation during sleep (Sa_{O_2} S), and mean oxygen saturation at the end of a 6-minute walk test (Sa_{O_2} WT). *(From Fraser KL, Tullis E, Sasson Z, et al: Pulmonary hypertension and cardiac function in adult cystic fibrosis: Role of hypoxemia. Chest 115:1321-1328, 1999.)*

is considered to be the mainstay of treatment in this group.

Sleep-Disordered Breathing

Sleep apnea, defined as repeated episodes of obstructive apnea and hypopnea during sleep together with daytime sleepiness or altered cardiopulmonary function, is common. Epidemiological studies estimate that the condition affects 2 to 4 percent of middle-aged adults.[138] Only a small proportion of the cases in this group of adults have been diagnosed, which is believed to be related to insufficient awareness of sleep apnea among physicians and the public at large.

The incidence of pulmonary hypertension in the setting of obstructive sleep apnea without clinically significant lung disease ranges from 17 to 41 percent, with most studies suggesting an incidence of 20 percent.[139] [140] Pulmonary hypertension is rarely observed in the absence of daytime hypoxemia, and the severity of nocturnal events (i.e., apnea and hypopnea) does not appear to be the determining factor of pulmonary hypertension (Fig. 54-7) (Figure Not Available) . Some studies have demonstrated that a reduced FEV_1 also contributes to pulmonary hypertension in these patients.[141] In most cases, the pulmonary hypertension is mild, similar to COPD.

Patients with sleep apnea also have an increased risk of diurnal hypertension, nocturnal dysrhythmias, right and left ventricular failure, myocardial infarction, and stroke.[142] Symptoms such as sleepiness, fatigue, irritability, and personality change have been attributed to nocturnal desaturation and the chronic sleep deprivation caused by sleep fragmentation. Sleep fragmentation may be the most important predictor of daytime sleepiness. Patient characteristics associated with sleep apnea include male sex, age older than 40 years, habitual snoring, nocturnal gasping, choking, or resuscitative snoring, observed apnea, and a history of systemic hypertension.[143] Symptoms of daytime somnolence, unrefreshed sleep, morning headaches, cognitive impairment, depression, nocturnal esophageal reflux, and nocturia are commonly reported but do not distinguish sleep apnea from other common nonpulmonary, sleep disorders. A sleep study should be performed to confirm the presence of upper airway closure during sleep and to access the patient's level of risk.

Therapeutic strategies for patients with sleep apnea may be grouped into three general categories: behavioral, medical, and surgical. The goals of treatment are to establish normal nocturnal oxygenation and ventilation, abolish snoring, and eliminate disruption of sleep due to upper airway closure. Avoiding factors that increase the severity of upper airway obstruction such as sleep deprivation, the use of alcohol, sedatives, hypnotic agents, and increased weight should be discussed with the patient. In obese patients, weight loss can significantly reduce the severity of the apnea.[144] However, the most important advancement in the medical treatment is positive airway pressure. Positive airway pressure delivered through a mask is the initial treatment of choice in clinically important sleep apnea. Continuous positive pressure is applied to the upper airway with the nasal mask, nasal prongs, or mask that covers both the nose and mouth. The level of positive pressure required to sustain patency of the upper airway during sleep should be determined in the sleep laboratory. Supplemental oxygen can also be used in conjunction with positive airway pressure and assist in maintaining saturation above 90 percent.[145] Patients treated with continuous positive airway

pressure delivered nasally have repeatedly demonstrated improvement in neuropsychiatric function and a lessening of daytime sleepiness.[146] Nocturnal desaturation, ventilatory related arousals, nocturnal dysrhythmias, pulmonary hypertension, and right-sided heart failure have also been effectively treated. Retrospective studies suggest that patients

Figure 54-7 (Figure Not Available) Mean pulmonary artery pressure (P_{pa}) and oxygen saturation by pulse oximetry (SpO_2) is shown during wakefulness in each sleep stage in patients with obstructive sleep apnea. Mean pulmonary artery pressure appears to be highest during rapid-eye-movement sleep, at a time that oxygen saturation is lowest. During wakefulness, when oxygen saturation is higher, the mean pulmonary artery pressures are considerably lower. *(From Niijma M, Kimura H, Edo H, et al: Manifestation of pulmonary hypertension during REM sleep in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 159:1766-1772, 1999.)*

treated with nasally delivered continuous positive pressure or tracheostomy have improved survival.[147] Side effects reported by patients usually involve discomfort or irritation related to the nasal mask.

Surgical treatment includes tracheostomy and palatal surgery. For those with severe apnea who cannot tolerate positive airway pressure, tracheostomy can provide dramatic improvement and be life saving, although additional medical and psychosocial morbidity may be associated with this treatment. The most commonly performed palatal surgery, uvulopalatopharyngoplasty, is curative in less than 50 percent of patients. Of 25 patients observed for 4 to 8 years, about half of the patients were clinically and objectively improved over the long term.[148]

The approach to the patient with severe pulmonary hypertension associated with sleep apnea is controversial. Although it is unlikely a result of hypoxemia alone, it is recommended that these patients have documented effective therapy for at least 3 months, before treating the pulmonary arterial hypertension as a separate entity. In this subset, prostacyclin may prove helpful.

Alveolar Hypoventilation Disorders

CHEST WALL DISORDERS.

Thoracovertebral deformities that can result in restrictive pulmonary syndromes and chronic alveolar hypoventilation include idiopathic kyphoscoliosis, spinal tuberculosis, congenital spinal developmental abnormalities, spinal cord injury and other childhood myelopathies, ankylosing spondylitis, or other congenital and acquired muscular skeletal conditions, such as pectus excavatum. Kyphoscoliosis is a relatively common disorder of the spine in its articulations. When severe, it can have a profound impact on pulmonary function, characterized by a severe restrictive pattern on pulmonary function testing (Fig. 54-8) . In addition, there can be associated inspiratory muscle weakness

that appears related to the increased elastic load from reduced lung and chest wall compliance. Scoliosis that appears before the age of 5 years has the worst respiratory prognosis. An angulation of greater than 100 degrees is considered very severe and is strongly associated with chronic alveolar hypoventilation.[149] Pulmonary compliance is often reduced by 50 percent or more as a result of lung underdevelopment and chronic lung hypoinflation. Patients can also have both central and obstructive apneas and hypopneas.

Pulmonary hypertension and chronic cor pulmonale frequently occur in patients with thoracovertebral deformities. Pulmonary hypertension is related to the reduction of the vascular bed because of hypoventilation and hypoxia. Symptoms are commonly slowly progressive. Hypoxemia may be seen from ventilation-perfusion mismatch or underlying atelectasis. When severe, the hypoxemia can also lead to cor pulmonale. In patients with advanced disease, intermittent positive-pressure breathing and noninvasive ventilation have been used successfully, as well as supplemental oxygen in patients who are hypoxemic.[150]

NEUROMUSCULAR DISEASE.

The development of right-sided heart failure is an unusual manifestation of respiratory failure solely due to respiratory muscle weakness. It usually develops in response to the hypoxic and hypercapnic stimuli in patients with chronic forms of these disorders. Weakness of the respiratory muscles can be caused by either generalized muscle diseases, such as myopathic infiltrating diseases or muscular dystrophy (see Chap. 71), or more commonly by such neurological disorders as a cord lesion at or below the third cervical vertebrae, amyotrophic

Figure 54-8 Pathogenesis of pulmonary hypertension and cor pulmonale in kyphoscoliosis and disorders of ventilatory control. *(From Fishman AP: Pulmonary hypertension and cor pulmonale. In Fishman AP [ed]: Pulmonary Diseases and Disorders. 2nd ed. New York, McGraw-Hill Book Co, 1988, p 1033.)*

lateral sclerosis, myasthenia gravis, poliomyelitis, and Guillain-Barre syndrome. The diagnosis of respiratory muscle weakness is confirmed by the finding of a restrictive ventilatory defect and a marked impairment of maximal respiratory pressures. Nocturnal ventilatory support, with either positive or negative pressure, has become established as effective therapy in appropriate cases, and its beneficial effects are well recognized.[151]

DIAPHRAGMATIC PARALYSIS.

Bilateral diaphragmatic paralysis is an uncommon and rarely recognized cause of cor pulmonale. Diaphragmatic paralysis is a result of phrenic nerve injury, which can be traumatic or secondary to an underlying motor neuron disease. It may occur after

cardiac surgery, as a manifestation of Lyme disease,[152] after radiation therapy,[153] or as a manifestation of other neurological disorders. When an affected patient is upright, ventilation may be normal or almost so, but when the patient is supine, gas exchange deteriorates. The diagnosis may be suspected in a patient with supine breathlessness, a disturbed sleep pattern, paradoxical motion of the abdomen on inspiration, and a low vital capacity in the upright position.

Patients with nontraumatic bilateral diaphragmatic paralysis may go unrecognized until they present either with respiratory failure or cor pulmonale. The diagnosis can be suspected when the vital capacity is reduced greater than 40 percent of predicted and paradoxic motion of the hemidiaphragms is noted on fluoroscopy.[154] Patients can also have unilateral paralysis of the diaphragm, which is more common but associated with less symptoms and physiological abnormalities. The treatment should always be directed toward correcting the underlying chronic neuromuscular disease, if present, and addressing nocturnal hypoventilation with noninvasive ventilatory techniques. Intermittent positive airway pressure is an effective therapy.[155]

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Three forms of persistent pulmonary hypertension of the newborn (PPHN) have been described. In the hypertrophic type, the muscular tissue of the pulmonary arteries is hypertrophied and extends peripherally to the acini. Medial hypertrophy causes narrowing of the arteries and an increase in pulmonary pressure and reduction in pulmonary blood flow. It is believed to be the result of sustained fetal hypertension from chronic vasoconstriction due to chronic fetal distress. In the hypoplastic type, the lungs including the pulmonary arteries are underdeveloped, usually as the result of a congenital diaphragmatic hernia or prolonged leakage of amniotic fluid.[156] [157] The cross-sectional area of the pulmonary vascular bed is inadequate for normal neonatal pulmonary blood flow. In the reactive type, lung histology is presumably normal but vasoconstriction causes pulmonary hypertension. High levels of vasoconstrictive mediators such as thromboxane, norepinephrine, and leukotrienes may be responsible and may result in a streptococcal infection or acute asphyxia at birth.

Although PPHN can vary in severity, severe cases are usually life threatening. It is usually associated with severe hypoxemia and the need for mechanical ventilation. Echocardiographic findings of severe pulmonary hypertension and right-to-left shunting at the level of the ductus arteriosus or foramen ovale are common. Inhaled nitric oxide has provided encouraging results through improvement in oxygenation in these patients (Fig. 54-9) . Intravenous prostacyclin has also been used and may even have additive effects to that of inhaled nitric oxide.[158]

Figure 54-9 The short-term effect of inhaled nitric oxide on systemic oxygenation in infants with severe hypoxemia and persistent pulmonary hypertension of the newborn. As compared with conventional treatment with oxygen and mechanical ventilation without nitric oxide (open bars), nitric oxide therapy (solid bars) rapidly increased postductal Pa_{O_2} from baseline (panel A) and decreased the oxygenation index (a value calculated as $100 \times Fi_{O_2} \times$mean airway pressure and postductal Pa_{O_2}). *(From Roberts JD Jr, Fineman JR, Morin FC III, et al: Inhaled nitric oxide and persistent pulmonary hypertension of the*

newborn. N Engl J Med 336:605-610, 1997.)

ALVEOLAR CAPILLARY DYSPLASIA.

Alveolar capillary dysplasia is a very rare cause for PPHN and is characterized by a developmental abnormality in the pulmonary vasculature. The antemortem diagnosis can only be made with open-lung biopsy. Despite aggressive treatment with nitric oxide, prostacyclin, and even extracorporeal membrane oxygenation, survival in the setting of alveolar capillary dysplasia is rare.[159]

PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOEMBOLIC DISEASE

Thromboembolic Obstruction of the Proximal Pulmonary Arteries (see also Chap. 62)

Pulmonary thromboembolism, as a single event or as repeated events, rarely leads to the development of chronic pulmonary hypertension.[160] However, in a subset of patients (believed to be less than 0.1 percent of all patients suffering from pulmonary embolism), the outcome is unusual.[161] Rather than having inherent fibrinolytic resolution of the thromboembolism with restoration of vascular patency, the thromboemboli in these patients fails to resolve adequately. They undergo organization and incomplete recanalization and become incorporated into the vascular wall. Commonly, they are in the subsegmental, segmental, and lobar vessels, although it is believed that chronic thromboembolism tends to propagate retrograde, leading to slowly progressive vascular obstruction.[160] It appears that the vast majority of these patients have suffered one major thromboembolic event rather than multiple recurrences.

The slowly progressive nature of the course of chronic thromboembolic pulmonary hypertension (CTEPH) allows right ventricular hypertrophy to ensue and compensate for the increased pulmonary vascular resistance. However, owing to either progressive thrombosis or vascular changes in the "uninvolved" vascular bed,[161] the pulmonary hypertension becomes progressive and the patient manifests the clinical symptoms of dyspnea, fatigue, hypoxemia, and right-sided heart failure.

DIAGNOSIS.

The physical examination of a patient with CTEPH is typical of any patient with pulmonary hypertension, with the exception of the following features. These patients tend to have lower cardiac outputs than patients with PPH, which is often reflected by the carotid arterial pulse volume. In addition, on occasion, bruits may be heard over areas of the lung that represent vessels with partial occlusions, but they must be carefully looked for. It is important to make the diagnostic distinction between patients with CTEPH and those with other forms of pulmonary hypertension because the treatment is so different. For the former group, a potentially curative therapy through thromboendarterectomy is available, whereas for the latter group effective

pharmacological regimens are now evolving. The symptoms and physical findings of CTEPH are nonspecific and similar to those patients with primary pulmonary hypertension.

The perfusion lung scan is usually adequate to identify patients with this entity and is an important reason why lung scans are recommended for all patients who present with pulmonary hypertension. However, the lung scan typically underestimates the severity of the central pulmonary arterial obstruction.[162] Therefore, patients who present with one or more mismatched segmental or larger defect should undergo pulmonary angiography. Pulmonary angiography can be performed safely in these patients if careful attention is given to the hemodynamic state. Nonionic contrast medium has been demonstrated to cause no major hemodynamic effects even in patients with severe chronic thromboembolic pulmonary hypertension[163] and is preferred. Hypotension and/or bradycardia should be immediately treated with atropine.

Figure 54-10 Chest CT scans in a patient with chronic thromboembolic pulmonary hypertension. In *A*, a helical scan with contrast medium enhancement of the pulmonary vasculature shows a marked disparity in vessel size between the involved vessels (A), which are enlarged from thrombus, and the uninvolved vessels (B). In *B*, a non-contrast medium-enhanced high-resolution scan illustrates a marked mosaic pattern manifest by differences in density of regions of the lung parenchyma reflecting the perfused areas (B) and the nonperfused areas (A), also consistent with underlying thromboembolic disease.

CT can be a great aid in diagnosing CTEPH (Fig. 54-10) . Using high-resolution nonenhanced CT, areas of increased attenuation that do not obscure the vessels and that have a ground-glass appearance have been characterized as a mosaic pattern corresponding to hypoperfusion of the lung. Although this pattern is consistent with CTEPH, it may also be seen in cystic fibrosis, bronchiectasis, and the lungs of lung transplant recipients. It is virtually never seen in PPH.[164] Marked variation in the size of the segmental vessels is more specific for CTEPH and is believed to represent involvement of the segmental vessels due to thromboemboli. It has been reported that these findings might also be mimicked in patients with fibrosing mediastinitis.

On cardiac catheterization, patients with CTEPH tend to have higher right atrial pressures and lower cardiac outputs than comparable patients with PPH for the same level of pulmonary artery pressure. Because this is a disease that generally is progressive, the hemodynamic indication for

surgical intervention would be an elevation of pulmonary artery pressure and pulmonary vascular resistance for a period of more than 3 months.

TREATMENT.

Patients suitable to undergo pulmonary thromboendarterectomy must have thrombi that

are accessible to surgical removal and demonstrate a significant increase in the pulmonary vascular resistance.[161] The operative mortality is fairly high, approximately 12 percent in experienced centers.[165] The postoperative management of these patients can be extremely challenging. Patients in whom a large volume of central thrombus is removed, associated with back-bleeding from the distal vascular segments and an immediate fall in the pulmonary artery pressure, usually have an extremely good postoperative course and long-term follow-up. Patients in whom small amounts of thrombus can be removed, in whom the thrombus becomes fragmented at the time of thromboendarterectomy, or in whom there is no distal back-bleeding from the segment where the thrombus was removed usually have a difficult postoperative course. In addition, a lack of significant fall in pulmonary artery pressure and an increase in cardiac output portends a difficult postoperative recovery.

These patients may need mechanical ventilation and inotropic support for days to weeks during periods of slow recovery. Much of their mortality appears to be related to severe right ventricular dysfunction, which actually becomes initially worsened during the surgical procedure. Reperfusion injury, which is manifest by profound hypoxemia and pulmonary infiltrates corresponding to the segments where thrombus was removed, has been reported and can be extensive. The only effective management of this complication is sustained assisted ventilation and oxygen supplementation. Attempts to reverse this with corticosteroids or other agents have not been successful.

Those survivors who have a good result, with a significant reduction in postoperative pulmonary vascular resistance at 48 hours, can expect to realize an improvement in functional class and exercise tolerance.[166] [167] Life-long anticoagulation with a goal international normalized ratio of 2.5 to 3.5 is indicated postoperatively. Right ventricular dysfunction of any magnitude is not considered a contraindication to surgery, because right ventricular function has been noted to improve once the obstruction of the pulmonary blood flow is removed. Certain hypercoagulable states such as lupus anticoagulant may be associated with CTEPH.[168] Some of these patients have also been successfully treated with pulmonary thromboendarterectomy.[169]

Sickle Cell Disease

Cardiovascular system abnormalities are prominent as part of the clinical spectrum of sickle cell disease. Evidence of right ventricular dysfunction, presumably resulting from pulmonary hypertension, is a poorly characterized complication. The incidence of pulmonary hypertension in the setting of sickle cell disease in one series of 60 consecutive patients undergoing echocardiography was 20 percent.[170] The mortality was also significantly greater in patients with pulmonary hypertension than those without (42 percent vs. 8 percent, $p = 0.03$). One must always consider left ventricular dysfunction as a cause of pulmonary hypertension in sickle cell disease because the elevation of pulmonary artery pressure is most often associated with elevation of the pulmonary capillary wedge pressure.[171] Patients with sickle cell disease may also have an increased risk of thromboembolism, and pulmonary thromboendarterectomy may be indicated in certain situations.[172] Sickle cell disease can also affect the lungs by causing embolization of bone marrow elements. Generally, the smaller pulmonary arteries, arterioles, and capillaries are affected. It can be associated with pulmonary infarction or

local perivascular fibrosis.

PULMONARY HYPERTENSION DUE TO DISORDERS DIRECTLY AFFECTING THE PULMONARY VASCULATURE

SCHISTOSOMIASIS

Although schistosomiasis is extremely rare in North America, hundreds of millions of people are affected worldwide, particularly in developing countries. The development of pulmonary hypertension almost always occurs in the setting of hepatosplenic disease and portal hypertension.[173] Clinical features appear when ova embolize to the lungs, where they induce formation of delayed hypersensitivity granulomas. In addition, deposition of fibrous tissue causes narrowing, thickening, and occlusion of the pulmonary arterioles. Histologically, focal changes related directly to the presence of schistosome ova may be located either within the alveolar tissue or within the pulmonary arteries, and plexiform or angiomatoid lesions may be found. Fibrosis surrounds most focal lesions.[174] The clinical symptoms and radiographic findings in these patients who develop pulmonary hypertension are not distinctive. In developing countries this condition can be confused with primary pulmonary hypertension.

The diagnosis of schistosomiasis-induced cor pulmonale is confirmed by finding the parasite ova in the urine or stools of persons with symptoms. However, the insidious onset of pulmonary vascular disease years after infection makes finding these parasite ova difficult. Active infections are treated with praziquantel, which kills the adult worms and stops further destruction of tissue by ova deposition.[175] Reversal of pathological lesions in the lungs after therapy has not been documented.

SARCOIDOSIS

Sarcoidosis is a multisystemic granulomatous disease of unknown origin characterized by an enhanced cellular immune response at the sites of involvement.[176] Although any organ can be involved, it most commonly affects the lungs and intrathoracic lymph nodes.[177] The clinical presentation and natural history of sarcoidosis varies greatly, but the lung is involved in over 90 percent of the patients. The most common presenting symptoms are cough and shortness of breath, which is of a progressive nature.[178] As the disease progresses in the lung parenchyma, extensive interstitial fibrosis is the result. In addition, obstructive airway disease, fibrocystic disease, bronchiectasis, endobronchial granulomas, and lobar atelectasis are common consequences of lung involvement.

Cardiac involvement from sarcoidosis appears to be more common than previously thought and may be present in up to one third of the cases (see Chap. 48).[179] Consequently, patients presenting with dyspnea should have a thorough cardiac evaluation for the possibility of cardiac involvement. Noncaseating granulomas may infiltrate the myocardium and leave fibrotic scars; and if enough of the myocardium is involved, the patients will develop clinical features of a restrictive cardiomyopathy. Patients with cardiac involvement from sarcoidosis may also present with varying

degrees of heart block, arrhythmias, and/or clinical features of biventricular diastolic heart failure. Sudden death can be a common manifestation of cardiac sarcoid, and it is one of the most feared sequelae. The prognosis of patients with cardiac involvement from sarcoidosis is variable but can be quite poor. Usually a trial of corticosteroids is given in the hope that it will alter the natural history of the disease.

An echocardiogram will often demonstrate either diffuse or regional wall motion abnormalities in patients with cardiac involvement. It is not uncommon, however, to find the features of pulmonary hypertension. Pulmonary hypertension detected by echo-Doppler techniques may be the result of restrictive cardiomyopathy from sarcoid and needs to be clearly distinguished from patients with pulmonary hypertension from direct pulmonary vascular involvement, because their clinical management will differ dramatically.

Cor pulmonale is most commonly the result of chronic severe *fibrocystic* sarcoidosis.[180] Patients have chronic progressive dyspnea with effort, a chest radiograph demonstrating severe diffuse interstitial fibrotic lung disease, and pulmonary function tests that reflect severe restrictive physiology and hypoxemia. In these cases the resulting cor pulmonale is usually mild to moderate and typical of patients presenting with restrictive lung disease of any etiology. The treatment is generally focused on reversing any acute exacerbations of their lung disease and supplemental oxygen when indicated. Some patients with sarcoidosis, however, have mild to moderate restrictive lung disease with severe pulmonary hypertension, presumed from granulomatous vasculitis of the pulmonary vessels. It is critically important in the cardiopulmonary evaluation of the patient presenting with underlying sarcoidosis and dyspnea to distinguish whether the symptoms are from chronic interstitial lung disease, restrictive cardiomyopathy, or pulmonary vascular disease.[181] Although the traditional treatment of these patients has been unsatisfactory, it has recently been demonstrated that some patients have a very favorable response to intravenous prostacyclin therapy.[182] Although interstitial

lung involvement from the sarcoidosis can result in mild pulmonary hypertension, a subset of patients present with severe pulmonary hypertension believed to be due to direct pulmonary vascular involvement. It appears that, as with other secondary causes, these patients are predisposed to the development of pulmonary vascular disease that is triggered in some way by the sarcoid disease process. Although the use of intravenous prostacyclin chronically may reverse the right-sided heart failure and dramatically improve their pulmonary hemodynamics, it will have no impact on any underlying fibrotic lung disease and/or hypoxemia, which still may render the patients symptomatic and dyspneic.

PULMONARY CAPILLARY HEMANGIOMATOSIS

Pulmonary capillary hemangiomatosis (PCH) was first described in 1978 as a very rare

cause of pulmonary hypertension.[183] Because of the few reports in the medical literature it is hard to characterize this abnormality. The typical chest radiographic appearance is a diffuse bilateral reticular nodular pattern associated with enlarged central pulmonary arteries.[184] Ventilation-perfusion scans are often abnormal and may show matched or unmatched defects. The most characteristic finding on high-resolution CT is diffuse bilateral thickening of the interlobular septa and small centrilobular poorly circumscribed nodular opacities.[185] Diffuse ground-glass opacities have also been described. Histological findings often include irregular small nodular foci of thin-walled capillary sized vessels, which diffusely invade the lung parenchyma, the bronchiolar walls, and the adventitia of large vessels. These nodular lesions are often associated with alveolar hemorrhage. Changes of hypertensive arteriopathy manifest by intimal fibrosis and medial hypertrophy are also common. Most patients appear to be young adults and present with dyspnea and/or hemoptysis. It is very difficult to distinguish PCH from PPH clinically. A hereditary form with probable autosomal recessive transmission has been reported.

The clinical course of these patients is usually one of progressive deterioration leading to severe pulmonary hypertension, right-sided heart failure, and death. Intravenous prostacyclin has been used, but it has been reported with the association of the development of severe pulmonary edema.[186] The only definitive treatment for these patients is bilateral lung transplantation.

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Part VI - MOLECULAR BIOLOGY AND GENETICS

1955

Chapter 55 - Principles of Cardiovascular Molecular Biology and Genetics

JEFFREY M. LEIDEN

During the first half of the 20th century revolutionary studies of human and animal physiology led to an elegant understanding of the anatomical, electrical, and mechanical properties of the cardiovascular system. As we enter the new millennium, we are in the midst of a second and equally exciting revolution in cardiovascular medicine--one that involves the application of recent advances in molecular and cellular biology to understanding both normal cardiovascular function and the pathophysiological bases of human cardiovascular disease.

Applications of modern molecular and cellular biology already permeate both

cardiovascular diagnostics and therapeutics. During the past 10 years a rapidly expanding list of genes that are involved in the etiology of cardiovascular diseases, including hypertrophic and dilated cardiomyopathies, hypertension, and atherosclerosis, have been identified. Recombinant proteins and antibodies made from cloned genes such as tissue plasminogen activator (t-PA) and glycoprotein IIb/IIIa monoclonal antibodies are currently used to treat or prevent acute coronary thrombosis. Novel gene therapies are being tested for the treatment of ischemic cardiomyopathies and vascular proliferative syndromes such as restenosis after balloon angioplasty or arterial stenting.

Although significant, these advances represent just the beginning of a new era of molecular medicine that promises to fundamentally change the way we practice cardiovascular medicine over the coming decades. In 2000, the sequences of all of the genes in the human genome were reported. This enormous accomplishment will provide a wealth of new information about basic cardiovascular biology as well as large numbers of new diagnostic tools and potential drug targets. Given this rapidly expanding mass of molecular information, it is clear that the practicing cardiologist will soon need to understand as much about the basic principles of molecular biology and human genetics as he or she currently knows about coronary anatomy or cardiac hemodynamics.

In this chapter an overview is provided of the basic terminology, principles, and techniques of molecular and cellular biology. The reader is referred to several excellent texts and in-depth reviews for more detailed information about these topics.[1] [2] [3] [4] [5]

ANATOMY OF THE MAMMALIAN CELL

The mammalian cell is a highly dynamic, compartmentalized, and specialized structure that has evolved to carry out a number of functions that are important for survival, replication, and the proper functioning of individual organs and the organism as a whole (Fig. 55-1) (see also Chap. 14). [6] [7]

All human cells share a number of common structures and properties. The outer cell membrane (plasma membrane) is composed of a lipid bilayer studded with extracellular receptors. This membrane provides protection from the extracellular environment while simultaneously enabling the cell to respond to extracellular signals such as hormones, drugs, toxins, or other cells that bind to or otherwise perturb membrane-associated receptors. Mitochondria are specialized subcellular organelles present in all human cells that generate energy in the form of adenosine triphosphate from the oxidation of carbon-containing compounds such as sugars or fats.

The genomic deoxyribonucleic acid (DNA) organized into chromosomes is contained within the membraneencapsulated cell nucleus. The chromosomes are collections of genes that store the genetic information needed to synthesize all of the component proteins that constitute the

Figure 55-1 Anatomy of the mammalian cell. Schematic illustration of an idealized mammalian cell demonstrating structures that are common to most cell types. Note that lineage-specific cell structures, such as sarcomeres, are not included in this illustration. See Figure 14-1 (Figure Not Available) for the latter.

cell and its organelles. As described in more detail later, this DNA is copied or transcribed into ribonucleic acid (RNA) in the nucleus. This RNA is then transported to the cytoplasm (i.e., the nonnuclear portion of the cell), where it is used as a template to direct the synthesis of proteins on specialized synthetic organelles called ribosomes. Newly synthesized proteins are sorted into the cytoplasmic compartment, inserted into membranes, or incorporated into specialized granules for secretion from the cell. These proteins play diverse roles in the physiology of the cell, including functioning as major structural elements; serving as enzymes that catalyze biochemical reactions; and functioning as cell surface receptors that sense and send extracellular signals and as hormones, growth factors, cytokines, or other secreted molecules that help integrate the function of multiple cells and organs within the organism.

In addition to these common structures and organelles, many cells express cell lineage-specific proteins and structures that enable them to carry out their specialized functions within the organism. Thus, for example, striated cardiac muscle cells express a set of contractile proteins assembled into sarcomeres that allow their rhythmic contraction whereas neurons express lineage-specific neurotransmitters and receptors that allow them to interpret and respond to diverse environmental stimuli.

GENETIC MACHINERY AND FLOW OF INFORMATION IN THE CELL

DNA

Despite its remarkably simple structure and limited four-letter alphabet, deoxyribonucleic acid represents one of the most sophisticated and foolproof information storage systems ever discovered.[7] [8] Given its elegant simplicity, it is not surprising that the basic structure and information storage rules of DNA have been highly conserved during evolution from the most simple viruses and bacteria to humans.

DNA is composed of two long strands of polynucleotides wound around each other in a clockwise double helix (Fig. 55-2 *A*). Each strand can contain an unbroken array of millions of nucleotides. The backbone of each strand of the DNA helix is composed of a linked array of identical deoxyribose phosphate groups, with the phosphate group forming a 5
-3
phosphodiester bond between the fifth carbon of one pentose ring and the third carbon of the adjacent ring. Each deoxyribose sugar on each strand is attached to one of four nucleic acid bases: two purines, adenine and guanine (A and G), and two pyrimidines,

cytosine and thymine (C and T). These nucleic acids project at right angles toward the center of the DNA helix and pair with each other according to a very specific set of rules: an A from one strand can only pair with a T from the opposite strand, whereas a C from one strand can only pair with a G from the opposite strand. This nucleic acid pairing, which is stabilized by hydrogen bonding between the two complementary nucleic acids, serves to hold the two strands of the helix together. Of equal importance, the two strands of the helix, which have opposite polarities (one is oriented in the 5 to 3 direction, whereas the other is oriented in a 3 to 5 direction), are complementary copies of each other. Therefore, the sequence of one strand of the helix can be used to easily predict or program the sequence of the opposite strand. This important property of complementarity allows the enzymatic machinery of the nucleus to copy faithfully one strand of DNA into a daughter strand during cell replication and also allows the DNA sequence of a gene to be easily copied into RNA that can be used to program the synthesis of cellular proteins (Fig. 55-2 *B*) (see later).

Chromosomes and Genes

Within the nucleus, the DNA is compacted by being wound around specialized structures called nucleosomes and organized into packages called chromosomes.[9] [10] [11] The human genome contains approximately 3×10^9 pairs of nucleotides (called base pairs) organized into 23 pairs of chromosomes.[12] [13] [14] One member of each pair of chromosomes is inherited from each parent. Remarkably, almost all of the cells in the human body contain a copy of the entire human genome or all of the instructions necessary to specify the entire organism (erythrocytes and platelets are notable exceptions).

Within a single chromosome, the DNA is organized into individual packets of information called genes[12] [13] [14] (Fig. 55-3) .

Figure 55-2 Flow of genetic information within a eukaryotic cell. *A,* Schematic illustration of the structure of eukaryotic DNA. The double helix at the right edge of the illustration is unfolded to allow visualization of the deoxyribose-phosphate backbone of each strand as well as base pairing between complementary nucleotide bases. *B,* Schematic illustration of transcription and translation of a eukaryotic gene. *Top right,* Genomic DNA being transcribed into messenger ribonucleic acid (mRNA) in the nucleus. *Bottom right,* mRNA being translated into a polypeptide in the cytoplasm. Transfer RNAs (tRNAs) loaded with amino acids are shown binding to the mRNA on a ribosome.

Each gene is composed of a unique sequence of nucleotides that comprises the information needed to encode one protein. The capacity of a unique sequence of bases within a gene to encode a unique protein is somewhat analogous to the letters of the

alphabet that when assembled in different combinations uniquely define the meaning of individual sentences. The human genome contains an estimated 80,000 to 150,000 distinct genes.[14] The protein coding information contained within a single gene is not continuous but instead is encoded in multiple discontinuous packets called exons.[15] Between these exons are variable-sized stretches of DNA called introns. The function of these introns, which can be thought of as "junk" DNA and which are interspersed in the genes of all eukaryotic cells, remains unclear. However, it has been suggested that they may have facilitated the creation of new genes during evolution by enabling the duplication, shuffling, and divergence of functional domains of different genes.[15]

In addition to its coding sequence (i.e., the sequence that determines the structure of its encoded protein), each gene also contains regulatory DNA sequences that control its spatial and temporal patterns of expression within different cell types and in response to different extracellular signals. These regulatory sequences, called promoters, enhancers, and silencers, are recognized and bound by a set of specialized nuclear proteins called transcription factors that can promote or inhibit the copying of a gene into an RNA template that can then program the synthesis of its encoded protein.[16] [17] [18] [19] [20] [21] [22] [23] Promoters are typically located immediately upstream (or 5
) of the coding region of the gene. Enhancers on the other hand can be located upstream (5
), downstream (3
), or even within the introns of a gene.

Figure 55-3 Transcription and processing of eukaryotic RNA. *Top,* Structure of a prototypical eukaryotic gene with a 5
promoter, three exons (exons 1-3), and a 3
enhancer. This gene is transcribed into a primary RNA transcript, which is then processed by splicing and addition of a 5
cap and 3
polyA tail. The resulting mature mRNA molecule is exported to the cytoplasm where it is translated into protein on a ribosome.

TRANSCRIPTION.

The genes themselves can be thought of as the code stored in a basic computer program. To be functional, these genes must first be interpreted or translated into the proteins that they specify. This is a complex and highly regulated process that involves (1) the initial copying of the DNA copy of the gene into RNA in the nucleus, (2) processing and transport of this RNA copy to the cytoplasmic compartment (i.e., across the nuclear membrane), (3) translation of the RNA into its encoded protein on ribosomes, and, in some cases, (4) posttranslational modifications of the proteins

themselves (see Figs. 55-2 and 55-3). In the first of these steps the antisense strand (3 -5
 strand) of the gene is copied base by base into a single-stranded complementary RNA molecule by cellular RNA polymerases.[19] Like DNA, RNA is a polynucleotide strand composed of a backbone of ribose sugars linked to one of four nucleic acid bases (A, G, C, and U [uracil], instead of T [thymidine]). Thus the sequence of the RNA copy of the antisense strand is identical to the sense strand of the DNA (except that *U*s replace the *T*s). Because this RNA copy contains both the exons (protein coding blocks) and introns (interspersed junk DNA) it must be processed (spliced) to remove all intron sequences and precisely join the exons into a single messenger RNA (mRNA) containing a contiguous region of sequence encoding its cognate protein.[24] Both ends of this single-stranded mRNA are then modified (a cap is added to the 5
 end of the mRNA while the 3
 end has a string of adenine bases added to produce a polyA tail), and the RNA is exported from the nucleus into the cytoplasm, where it is bound by ribosomes in preparation for translation into protein.[25] [26] [27]

THE GENETIC CODE.

Because DNA and RNA are linear arrays of nucleotides, whereas proteins are linear arrays of amino acids, there must be a code by which the linear sequence of the four nucleotides of the RNA molecule can be translated into the linear sequence of amino acids of its encoded protein. This "genetic code" turns out to be remarkably simple and has been conserved in most (but not all) organisms from viruses to humans.[28] [29] Every three contiguous nucleotides or triplets in the RNA specify a single amino acid (Fig. 55-4) . Because there are four nucleotide possibilities at each position, there are 4×4×4 or 64 different triplet possibilities. One of the triplets, AUG, specifies methionine, which is the amino acid that starts each protein; three other triplets, UAA, UGA, and UAG, program the ribosome to end translation and are therefore called stop codons. The remaining 60 triplets or codons specify one of the 20 amino acids. Because there are 60 codons and only 20 amino acids some amino acids can be specified by two or more different triplets (e.g., cysteine=UGU or UGC). Thus, it is possible to read the sequence of the protein encoded by a gene by simply reading its triplets in order (e.g., ATG TCC TGG TCC=Met Ser Trp Ser).

TRANSLATION.

The conversion of the single-stranded mRNA into protein on the ribosome requires special adapter molecules called transfer RNAs (tRNAs) (see Fig. 55-3). One portion of these tRNAs is complementary to the triplet corresponding to the single amino acid it adds to the growing protein chain (e.g., the tRNA for methionine contains a triplet RNA sequence, UAC, that can base pair with the triplet AUG that encodes methionine in the mRNA). A second portion of the tRNA molecule can bind specifically to that amino acid. By docking on the triplet in the mRNA by base pairing, the tRNA brings the correct amino acid into proximity with the growing protein chain, allowing the ribosome to specifically couple it to the carboxy terminus of the nascent polypeptide. The ribosome and tRNAs can therefore be thought of as a reading machine that scans the sequence

of the mRNA and converts it into a protein.

EVOLUTIONARY CONSERVATION.

The remarkable evolutionary conservation of the structures of DNA, RNA, and

Figure 55-4 The genetic code. The amino acids corresponding to each nucleotide triplet in the mRNA are shown. Note that there are three stop codons (UAG, UAA, and UGA) and a single start codon (AUG).

proteins as well as the genetic code and much of the machinery for RNA and protein production has profound implications for molecular geneticists. It means, for example, that human genes can be transferred into bacteria, yeast, or insect cells where they will be faithfully replicated and copied into RNA and protein. This property constitutes the basis of the recombinant DNA technology used to produce many therapeutic proteins such as t-PA. Similarly, human genes can be spliced into viruses that can be used to infect human cells to transfer genes for therapeutic purposes. Finally, many of the genes involved in human cardiovascular development and function have been highly conserved in mice, fish, and even flies. Thus, these simple organisms can serve as powerful model systems for studying human cardiovascular development and function and for testing novel genetic or pharmacological therapies for human cardiovascular diseases.

Regulation of Gene Expression

Only a small fraction of the genes within the human genome is expressed in any given cell at any given time. These genes can be divided into several subsets based on their patterns of expression. One subset of genes is constitutively expressed in most, if not all, cells. The products of these so-called housekeeping genes are necessary for basic functions of cell survival, replication, and energy generation. A second subset of genes is expressed in a lineage-restricted fashion, for example, only in a cardiomyocyte or an endothelial cell. In fact, it is the precise regulation of expression of this subset of lineage-specific genes that determines the unique identity and function of a particular cell type. A final subset of genes is expressed only in response to a specific environmental stimulus. Given the necessity for these complex and dynamic patterns of differential gene expression, human cells have evolved sophisticated molecular mechanisms to regulate lineage-specific gene expression and to allow rapid and precise changes of gene expression in response to various organismal and environmental signals.

The expression of a specific gene can be regulated at many levels including transcription of the gene into RNA,[16] [17] [18] [19] [20] [21] [22] [23] processing and transport of the mRNA into the cytoplasm,[24] [25] [26] [27] stability of the cytoplasmic mRNA,[30]

translation of the mRNA into protein,[31] [32] posttranslational modification of the protein,[33] [34] [35] [36] [37] subcellular localization of the protein, [38] and protein stability.[37] Although each of these mechanisms plays important roles in regulating some genes, two of these, the regulation of gene transcription and protein phosphorylation (and dephosphorylation), appear to represent the major mechanisms used by the cell to control the expression and activity of proteins. Indeed, in many cases these two mechanisms have been linked into distinct signaling pathways that allow cells to respond to developmental, environmental, and organismal signals with complex and precisely orchestrated changes in gene expression. An example of one such signaling pathway is shown in Figure 55-5 . In this example, stimulation of a G protein-coupled beta-adrenergic receptor in the plasma membrane by beta-adrenergic agonists such as norepinephrine results in the activation of the enzyme adenylyl cyclase and in the increased production of cyclic adenosine monophosphate (cAMP) in the cytoplasm.[39] This increase in cAMP in turn activates the protein serine kinase, protein kinase A, which migrates to the nucleus where it phosphorylates the transcription factor CREB on a single serine residue (Ser133).[40]

Figure 55-5 Schematic illustration of a beta-adrenergic signaling pathway. Binding of a beta-adrenergic agonist to the transmembrane beta-adrenergic receptor (betaAR) results in the release of the active G protein, G_S. G_S activates adenylate cyclase, which causes increased production of cyclic adenosine monophosphate (cAMP). cAMP in turn activates protein kinase A (PKA), which migrates to the nucleus where it phosphorylates the CREB transcription factor on serine 133. The phosphorylated transcription factor CREB binds as a homodimer to a cAMP response element (CRE)-binding site (TGANNTCA) and activates transcription of a CREB-responsive gene. (See also Figures 14-15 to 14-17 .)

Phosphorylated CREB then binds to its specific recognition sequence (TGANNTCA), which is present in the promoters of a set of cAMP-responsive genes, and activates their transcription and expression.[41] Similar types of signaling pathways have evolved to regulate gene expression in response to hormones, cytokines, hypoxia, cell-cell signals, and mechanical stretch.[33] [34]

GENETIC BASES OF HUMAN CARDIOVASCULAR DISEASE

Mutations are alterations in the structures of individual genes that result in corresponding structural changes in the proteins they encode (see also Chap. 56). Because many individual proteins play critical roles in the development and function of the cardiovascular system, such mutations leading to quantitative and qualitative defects in protein function can result in a wide variety of human cardiovascular diseases. Indeed, the preponderance of evidence suggests that genetic mutations often in combination with environmental factors are responsible for the majority of human cardiovascular diseases, including both classical congenital disorders of the heart and vasculature as well as "acquired diseases" such as hypertension, cardiomyopathies,

and atherosclerosis.

Different types of mutations affect their encoded proteins in very different ways (Fig. 55-6) . "Missense mutations" result from the substitution of one or more nucleotides in such a way as to change the primary sequence of the encoded protein (e.g., mutation of TTT to TTG causes a single amino acid change of phenylalanine to leucine). Such missense mutations do not typically alter the level of protein expressed but can alter the function of the protein by altering its structure. In contrast, "nonsense mutations" (e.g., TAT to TAA) introduce a premature stop codon into a gene, resulting in a truncated protein product that can display alterations in function or can be unstable. Insertions or deletions of nucleotides can add or subtract amino acids from the resulting proteins if they result in the addition or deletion of triplets of amino acids (i.e., if they occur in multiples of three) or alternatively can result in "frameshifts" in which the codons of the gene are read in the wrong reading frame. Such frameshift mutations typically cause abnormal protein structures that often terminate prematurely, owing to the introduction of out-of-frame termination codons. Mutations in both exons and introns can cause splicing errors that result in alterations in protein structure and/or frameshifts. Finally, mutations in the promoters or enhancers of genes can lead to alterations (either increases or decreases) in the levels of expression of a given protein or, alternatively, can change the temporal or spatial patterns of expression of that protein. In addition to single gene mutations, rearrangements of genes on the same or different chromosomes can also result in human disease. For example, the "in frame" fusion of two different genes by chromosomal rearrangement can result in a fusion protein

Figure 55-6 Different types of mutations alter the structure and expression of human genes. *A,* An example of a wild-type gene sequence is shown in the top panel. The bottom panel shows examples of different types of nucleotide mutations and the resulting alterations in the amino acid sequences of the corresponding protein. Mutations are underlined; deletions are noted by a dot. Polymorphism is a nucleotide substitution that does not alter the primary amino acid structure of the resulting protein. *B,* Splice mutations: an example of a mutation in the 3
splice acceptor sequence that disrupts splicing, resulting in read-through into the intron and premature termination of the protein.

with a novel and sometimes deleterious function. Similarly, fusion of the promoter of one gene to the coding sequence of a second can lead to an abnormal spatial and temporal pattern of expression of the second gene and protein.

These different types of mutations also lead to different types of diseases (see also Chap. 56). For example, the functional inactivation, deletion, or premature termination of a single gene often results in a "loss of function" of its encoded protein that is manifest as an autosomal recessive trait. That is, only homozygous patients who inherit two copies of the mutated gene (and therefore have a severe deficiency in the amount of protein expressed) manifest the disease. In contrast, heterozygous "carriers" express 50 percent of the normal level of the protein and therefore are usually (but not always)

asymptomatic. In contrast, some mutations result in the production of a dominant negative protein that inhibits the function of the normal protein expressed by the other copy of the gene in the patient's cells. Such mutations are often inherited in a dominant fashion; that is, one mutant copy of the gene (allele) is sufficient to produce disease. Similarly, some mutations can result in a gain of function, that is, in constitutive activation or superactivation of the function of the encoded protein. Once again, such mutations are often inherited in an autosomal dominant fashion. Finally, mutations of genes on the X chromosome are often inherited in an X-linked fashion. That is, the disease is only manifest in boys (who have a single X chromosome and therefore are functionally homozygous for the mutation) and is usually inherited from an unaffected mother.

Examples of Genetically Determined Cardiovascular Diseases

Familial Hypertrophic Cardiomyopathy: Genetic Diseases of the Sarcomere (See also Chap. 48)

Familial hypertrophic cardiomyopathy (FHC) is an autosomal dominant inherited disorder with a prevalence of approximately 1 per 500 live births that is characterized by progressive left ventricular hypertrophy, diastolic dysfunction, arrhythmias, and often heart failure and premature death.[42] This disease unfortunately often presents as sudden death in young adults. FHC is genetically heterogeneous; that is, linkage studies in humans demonstrated that the disease maps to a number of different chromosomal loci in different families.[43]

A major breakthrough in cardiovascular genetics occurred when Christine and Jon Seidman and their coworkers identified mutations in the beta-myosin heavy chain (beta-MHC) in some families with FHC.[44] The majority of these were missense mutations, that is, they produced a full-length protein with single amino acid substitutions (e.g., in one common beta-MHC mutation, the arginine 403 was mutated to a glutamine). In these cases it is likely that the mutant protein serves as a dominant negative inhibitor of sarcomere function--that is, the mutant protein oligomerizes with the normal protein expressed from the wild-type allele and in some way impairs the normal protein's contractile function. This overall impairment in function then stimulates a hypertrophic response (through unknown signaling pathways) that leads to increased diastolic pressures and ultimately to congestive heart failure and arrhythmias.[43] This type of dominant negative phenotype explains how one mutant copy of the gene produces the human disease and is consistent with the dominant pattern of inheritance seen in this disorder.

Subsequently, several groups have identified mutations in other sarcomeric protein genes as the cause of FHC in other families. These include the troponin T gene,[45] the alpha-tropomyosin gene,[45] and the myosin-binding protein C gene.[46] Thus, a picture is now emerging in which many different disruptions of the sarcomeric proteins can lead to cardiac hypertrophy and heart failure.[43] [47] It will be of great interest to understand the molecular pathways by which the cardiomyocyte senses defects in contractile function in patients with FHC and then initiates the hypertrophic program because similar pathways may underlie pathological hypertrophy in patients with acquired hypertrophic cardiomyopathies such as those associated with hypertension and valvular heart

disease.

One of the most interesting stories to emerge from the genetic analyses of FHC patients was the notion that one could begin to predict clinical outcomes based on the nature of the mutation causing the disease. Thus, for example, patients with the arginine 403 to glutamine mutation tended to display markedly increased mortality rates, whereas patients with a valine 606 to methionine mutation had normal life expectancies.[48] [48A] This type of genetic prognostication will likely play an increasingly important role in risk stratification in patients with inherited cardiovascular disorders (see Fig. 48-11 (Figure Not Available)). By use of genetic engineering, mutant myosins can be expressed in vivo, permitting functional analysis of the isolated mutant proteins by biophysical techniques in vitro.[48B]

Congenital Long QT Syndrome: A Disease of Cardiomyocyte Ion Channels (See also Chap. 25)

The congenital long QT syndromes are autosomal dominant inherited disorders characterized by repolarization abnormalities (manifest by prolonged QT intervals on an electrocardiogram) and torsades de pointes.[49] Like patients with FHC, long QT syndrome patients often present with syncope and sudden death. Our understanding of both the genetic and pathophysiological bases of this disease were significantly enhanced by Keating and coworkers, who first demonstrated linkage of the disease to three chromosomal loci (LQT1, LQT2, and LQT3) and then cloned the genes responsible at each locus.[50] [51] [52] [53] Interestingly, in each case the defective gene encoded a cardiac ion channel: LQT1 is caused by mutations in the *KVLQT1* cardiac K channel gene,[53] LQT2 by mutations in the *HERG* (Human Ether a-go-go Related gene) K channel gene,[51] and LQT3 by mutations in the *SCN5A* sodium channel gene on chromosome 3p21-24.[52] In the case of the *SCN5A* gene, in-frame intragenic deletions were shown to disrupt the inactivation of the channel, resulting in enhanced activity during repolarization. Thus, this was essentially a gain of function mutation also consistent with its dominant pattern of inheritance.[54] As in FHC, it appears that mutations in multiple genes involved in regulating the cardiac action potential can give rise to the long QT syndrome.

In addition to inherited long QT syndrome there are a number of environmental long QT syndromes, such as those associated with cardiac ischemia, hypokalemia, type I antiarrhythmic drugs, and certain drug interactions. It is tempting to speculate that polymorphisms (silent mutations or variations) in the same ion channel genes that cause congenital long QT syndrome might confer susceptibility or resistance to these environmental insults. In this regard it will be of interest to sequence these ion channel genes in patients who are very sensitive (or resistant) to hypokalemia or drug-induced QT prolongation.

BASIC TECHNIQUES OF MOLECULAR BIOLOGY

Cloning and Recombinant DNA

Because every human cell contains 3×10^9 base pairs or 80,000 to 150,000 human

genes, it is difficult if not impossible to study the structure and function of a single human gene in the context of an intact human cell. To circumvent this problem, molecular biologists have developed simple and elegant techniques for isolating, sequencing, and mutating single genes and copying them millions of times either in simple organisms like bacteria or in the test tube in vitro.[55] Indeed, such gene cloning techniques in many ways represent the foundation of modern molecular biology. As described earlier, the power of gene cloning derives from the fact that bacterial, yeast, and mammalian cells use common mechanisms for copying and expressing DNA. Thus, human genes can be inserted into bacteria, yeast, fruit flies, or mice, where in most cases they are faithfully replicated and expressed into their cognate proteins.

RESTRICTION ENDONUCLEASES.

Restriction endonucleases are bacterial proteins that recognize and cleave or cut specific palindromic sequences in DNA.[56] For example, the EcoRI restriction endonuclease from the bacteria *Escherichia coli* recognizes the sequence GAATTC, which occurs approximately every 3000 to 4000 base pairs in human DNA. After recognition of its cognate sequence EcoRI cleaves the two strands of the double helix asymmetrically after the GA to produce overhanging single-stranded sticky ends of ATTC (Fig. 55-7) . Three properties of such restriction endonucleases make them extremely useful tools for molecular biologists. First, because the sequence of any gene is unique and generally identical among all members of the species, such endonucleases can be used to reproducibly cleave a given gene at a specific location, thereby resulting in predictably sized cleavage products containing that gene. Second, because there are hundreds of distinct restriction endonucleases each with its own unique recognition sequence, any gene can be reproducibly cut into pieces of almost any size (and the sizes of these fragments

Figure 55-7 Recombinant DNA technology can be used to amplify a human gene. Shown is ligation of a human DNA fragment digested with the restriction endonuclease HindIII into a HindIII-digested bacterial plasmid vector. Hybridization of complementary sticky ends on the two HindIII-digested DNAs allows precise ligation of the two fragments. Ab^R =an antibiotic resistance gene used to select bacteria transformed with the recombinant plasmid. The recombinant plasmid is used to transform bacteria. Bacteria containing the plasmid are selected by growth in antibiotic, resulting in the exponential amplification of the recombinant DNA molecule.

can be predicted in advance from the known sequence of the DNA). Finally, the existence of complementary sticky ends on fragments cut by a single restriction endonuclease allows molecular biologists to join together or "ligate" any two fragments of DNA that have been cleaved by that endonuclease. Thus, for example, a human gene fragment digested with EcoRI can be easily ligated to a bacterial gene cut by the same endonuclease. Similarly, a human gene can be ligated into an adenovirus vector after cleavage of both pieces of DNA with a single restriction endonuclease.

GENE CLONING.

Plasmids are small circular pieces of DNA that replicate autonomously to high copy number in bacteria.[57] Such plasmids often contain genes encoding antibiotic resistance in bacteria, allowing the selection of bacteria containing them by growth in antibiotic-containing medium. This type of drug resistance plasmid can be cleaved once with a restriction enzyme and a single human gene cut with that same enzyme ligated into the plasmid DNA to produce a plasmid copy of the human gene (see Fig. 55-7) . The resulting plasmid can then be introduced into bacteria. Growth of such genetically modified bacteria in the presence of the appropriate antibiotic yields an essentially pure culture of bacteria, each of which contains between 10 and 500 copies of the single cloned human gene. Because the doubling time of bacteria is on the order of 20 minutes, inoculation of a 1-liter culture of bacterial broth with a single bacterial cell containing 500 copies of a human gene at 6 P.M. results in a culture containing 10^{11} copies of that same gene the next morning. The bacterium serves as a logarithmic gene-duplicating machine with a short replication time--the ideal tool for copying genes.

RECOMBINANT PROTEINS.

In addition to their ability to copy genes rapidly and accurately, bacteria can also be used to express the human proteins encoded by cloned genes. By pasting the cloned human gene into a bacterial plasmid containing bacterial transcriptional regulatory sequences, the bacteria can be programmed to make large amounts of the human protein.[58] As long as the protein folds correctly and does not need to be posttranslationally modified by human enzymes (e.g., by adding sugar moieties or phosphate residues), such recombinant proteins made in bacteria will function normally both in vitro and after infusion into patients. In other cases, yeast or mammalian cells can be programmed to synthesize large amounts of recombinant proteins for human therapy.[59] [60]

Example of a Genetically Engineered Protein Used in Therapy: Production of Tissue Plasminogen Activator Using Recombinant DNA Technology

The use of thrombolytic agents has revolutionized the care of patients with acute myocardial infarction (see Chap. 35).[61] [62] Thrombolytic proteins are produced naturally by a wide range of organisms from bacteria to humans. One of the most potent agents, t-PA, was first isolated and purified in substantial amounts from human melanoma cells. However, such cells did not produce sufficient quantities of the active protein for widespread human therapy. Accordingly, there was great interest in using recombinant DNA technologies to engineer the production of large quantities of biologically active and pure t-PA. Although some human proteins such as growth hormone can be produced in their active form from bacteria like *E. coli,* bacteria often cannot properly fold or modify complex human proteins. This proved to be the case with t-PA. After cloning of the gene from melanoma cells[63] (using synthetic oligonucleotides based on the sequence of the purified protein as probes to pick the proper clones), the t-PA complementary DNA (cDNA) was cloned into a restriction endonuclease-digested plasmid containing a drug resistance gene *DHFR),* and a eukaryotic promoter.[64] After

amplification in bacteria this plasmid was transfected into Chinese hamster ovary cells, and clones expressing t-PA were selected by growth in HAT media, which only allowed the survival of cells with large numbers of copies of the *DHFR*-bearing plasmid. These clones of transfected cells were then grown in large numbers in cell fermentors, and the recombinant t-PA that was secreted from the cells was collected and purified from the tissue culture medium.

Nucleic Acid Hybridization

Because the two strands of the DNA helix are complementary to each other, they tend to specifically find and anneal to each other if mixed together under appropriate temperature and salt conditions. Such annealing is stabilized by hydrogen bonding between the complementary base pairs present on each strand of the helix. The annealing of complementary DNA strands is called hybridization and is the basis of many of the techniques used to identify specific genes in large mixtures of genetic material (see blotting techniques and array technologies, later). Hybridization is also employed to specifically join together two pieces of DNA containing complementary single-stranded ends such as occurs after cleavage with a single restriction enzyme and to anneal synthetic single-stranded oligonucleotides to genes during amplification by the polymerase chain reaction (PCR).

The Polymerase Chain Reaction

As described earlier, bacterial cloning represents an elegant biological solution to the problem of the clonal amplification of genes. An even more rapid technique has been described that allows the clonal amplification of any specific fragment of DNA in less than 2 to 3 hours in a test tube[65] [66] [67] [68] [69] (Fig. 55-8) . In the PCR a mixture of double-stranded DNA from as little as a single cell is mixed with synthetic oligo

Figure 55-8 Gene amplification by the polymerase chain reaction (PCR). Synthetic oligonucleotide primers corresponding to the 5
and 3
ends of the DNA sequence to be amplified are chemically synthesized. The double-stranded DNA is melted by heating to 92%C, and primers are annealed by cooling the DNA solution to 72%C. A thermostable DNA polymerase then amplifies each strand of the target sequence, producing two copies of the gene segment. This process is repeated to produce an exponential amplification of the target sequence.

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nucleotide primers (small pieces of DNA that are complementary to the ends of the

sequence to be amplified). The mixture is heated to melt apart or separate the two strands of human DNA and then cooled to allow the complementary oligonucleotide primers to hybridize or specifically anneal to their complementary sequences, flanking the gene of interest on the single-stranded human DNA. A purified DNA polymerase is then used to synthesize a complementary copy of the fragment of interest. The mixture is again heated to melt apart the complementary strands of human DNA, and the process is repeated. The special heat-stable DNA polymerase used for PCR amplification derives from a bacterium adapted to live in hot water (*Thermus aquaticus,* hence "Taq" polymerase). Each such cycle of PCR, which takes only 3 minutes or so, produces a doubling of the quantity of the gene fragment of interest. Thus, beginning with the DNA from a single cell, in 30 cycles one can produce 2^{30} copies of any gene, more than enough to clone, sequence, or manipulate in vitro. The entire amplification is carried out in a sealed test tube or well in a specially designed machine that can be programmed to automatically heat and cool the sample. This ingenious and simple technology has revolutionized our ability to copy, sequence, mutate, and clone genes beginning with only tiny amounts of a DNA sample.

DNA Sequencing and the Human Genome Project

The human genome contains all of the information necessary for the development and function of the organism. Of equal importance, variations and mutations in the human genome are important determinants of disease susceptibility. Thus, obtaining the sequence of the human genome has been one of the major goals of molecular biology and medicine during the past 20 years. During the 1970s several groups described techniques for sequencing short stretches (several hundred base pairs) of cloned human DNA.[69] [70] The problem was then how to scale up this technology to accomplish the sequencing of the 3×10^9 base pairs contained in each human cell. This scale up has been accomplished in a remarkably short time, particularly considering that a single sequencing reaction still typically generates less than 1000 base pairs of readable DNA sequence. During the past several years the complete sequences of bacteria, yeast, worms, and flies have been determined.[71] [72] [73] [74] The sequencing of the entire human genome was completed in 2000. Now that this sequence is in hand, the challenge will become how to organize, search, and manage this vast amount of new information and how to begin to understand the variabilities in sequence between human populations and individuals and how such genetic variability translates into phenotypic variation.

Monoclonal Antibodies

Antibodies recognize and bind to epitopes, specific shapes of molecules such as those assumed by a particular sequence of amino acids or sugars. A single plasma cell produces one antibody with a unique recognition site for a single protein or sugar epitope. However, in a typical immune response after vaccination with a foreign protein, the mammalian organism produces thousands of different plasma cells that secrete thousands of distinct antibodies into the serum. Although such polyclonal antisera are useful, it would clearly be desirable to identify a renewable cell source that could be used to produce a single homogeneous (monoclonal) antibody that is specific for a single epitope on a functionally important human protein. Unfortunately, it is not possible

to clone and grow normal plasma cells in tissue culture for long periods of time.

The problem of monoclonal antibody production was solved by Kohler and Milstein,[75] who discovered that they could fuse a normal antibody-producing plasma cell to an immortalized myeloma cell to produce a continuously growing fusion cell that would in many cases continue to produce and secrete large amounts of the plasma cell's antibody. This technique has subsequently been used by many investigators to produce immortalized plasma cells that produce antibodies to proteins of the cardiovascular system. Such monoclonal antibodies are useful for identifying and purifying individual proteins, for diagnostic tests designed to identify and quantify those proteins in cells, tissues, and serum, and in some cases as therapeutic reagents.[17] [76] [77] [78]

Example of a Monoclonal Antibody Use in Therapy: Monoclonal Antibody Directed Against the Platelet Glycoprotein IIb/IIIa in the Treatment of Thrombotic Coronary Syndromes (See also Chaps. 35 , 36 , 38 , and 62)

Platelet adhesion, aggregation, and secretion play an important role in the etiology of myocardial infarctions and strokes. Thus, there has been a great deal of interest in developing novel therapeutic reagents that can be used to inhibit platelet function in patients with these disorders. The platelet-specific glycoprotein (GP) IIb/IIIa is a cell surface molecule composed of a 136-kDa A chain and a 100-kDa B chain.[79] GP IIb/IIIa is a member of the integrin family of cellular adhesion receptors. Binding of GPIIb/IIIa to ArgGlyAsp (or RGD) peptide sequences in fibrinogen results in platelet cross-linking, adhesion, spreading, and secretion, and subsequent thrombus propagation.[79]

The importance of the GP IIb/IIIa molecule was demonstrated using RGD (or KGD) containing peptide inhibitors and monoclonal antibodies specific for the fibrinogen binding site of GPIIb/IIIa, both of which were shown to potently inhibit platelet aggregation and function in vitro.[80] These findings led directly to the idea of using such monoclonal antibodies as antiplatelet reagents in patients suffering from unstable coronary syndromes and those undergoing percutaneous revascularization. To avoid immune responses, a high-affinity murine monoclonal antibody directed against the human GP IIb/IIIa molecule (that also recognized the $alpha_V$ $beta_3$ vitronectin receptor) was "humanized" using recombinant DNA techniques to render the murine monoclonal antibody less immunogenic and to produce it in large quantities in the supernatants of cultured myeloma cells.

The resulting purified monoclonal antibody abciximab (or ReoPro) was then tested for efficacy in clinical trials in patients undergoing percutaneous coronary revascularization by either balloon angioplasty or stenting.[81] [82] [83] [84] These studies have shown a consistent 50 to 60 percent reduction in acute ischemic complications (death, myocardial infarction, and emergency revascularization) in the treated patients. Abciximab appears to be even more efficacious in patients with unstable coronary syndromes undergoing percutaneous revascularization.[85] Small molecule or peptidic GP IIb/IIIa antagonists have similar effects (see also Chaps. 38 and 62). The success of these clinical trials not only has provided us with important new therapeutic reagents for patients undergoing percutaneous revascularization but also has raised the level of enthusiasm concerning the development of additional monoclonal antibody drugs for

patients with cardiovascular diseases.

Blotting Techniques

A typical human cell contains thousands of genes, mRNAs and proteins. Blotting techniques allow the identification of single genes, RNAs, or proteins based on their size and sequence without the need to purify individual molecules. Southern blotting begins with the cleavage of human genomic DNA with one or more restriction enzymes, thereby producing a mixture of thousands of DNA fragments of all sizes.[86] These DNA fragments are subsequently separated by size using electrophoresis in an agarose gel. In such a gel the smallest fragments migrate most quickly to the bottom of the gel whereas the larger fragments migrate more slowly and remain near the top of the gel. The fragments are then denatured (separated into single strands) and transferred to a sheet of filter paper to produce a replica of the gel. This filter is then exposed to a radioactive DNA probe (a radiolabeled single-stranded DNA fragment) that is complementary to the gene of interest. Such a probe hybridizes specifically to its complementary gene fragment on the filter and sticks to the filter during washing to remove unbound radioactivity. Because a given gene will only be contained in one or at most a few fragments whose size is based on the occurrence of restriction enzyme sites in and around the gene, the probe will only anneal to a few bands on the filter. Autoradiography of the hybridized and washed filter will

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allow visualization of these bands and determination of their sizes.

Northern blotting is used to detect specific mRNAs and is based on principles similar to Southern blotting[55] (Fig. 55-9) . The mRNA corresponding to each gene displays a characteristic size or sizes. Therefore, a mixture of cellular RNAs of different sizes is separated by electrophoresis on agarose-containing gels, transferred to a filter, and hybridized to a radiolabeled DNA probe complementary to the mRNA of interest. After hybridization the radiolabeled bands are visualized by autoradiography.

Western blotting is an electrophoretic technique used to identify specific proteins. Once again it is based on the principle that different proteins display characteristic sizes and can be recognized specifically by antibodies. A mixture of proteins is separated by size by electrophoresis through a polyacrylamide gel and transferred to a filter. This filter is then incubated with an antibody that is specific for the protein of interest coupled to a radioactive isotope or an enzymatic marker. Specific bands corresponding to the protein of interest are then visualized by autoradiography or colorimetric or photometric reactions.[55]

In addition to allowing the identification of genes, RNAs, and proteins, these blotting techniques allow quantitation of the levels of specific biomolecules in different cell types, in cells from patients with disease, and in response to different developmental or

environmental stimuli.

Gene Array Technologies

Blotting techniques allow quantitation and comparison of the levels of expression of a single gene between various cell samples. However, in many cases it would be desirable to compare the expression profiles of hundreds or even thousands of genes in two cell types or tissue samples. For example, it would be fascinating to understand the patterns of expression of all of the genes in the human genome in cardiomyocytes from failing as compared with normal hearts or in vascular smooth muscle cells immediately before and after mechanical injury such as balloon inflation. This type of gene profiling study has become increasingly powerful as the number of sequenced human genes increased over the past several years. Gene array technologies developed during the past 5 years allow the highly accurate and simultaneous quantitation of levels of mRNA expression from thousands of genes.[87] [88] [89] [90] [91] Although these technologies differ in their experimental details, they are all based on arraying cDNAs or oligonucleotides corresponding to known gene sequences on a grid of some sort (from a piece of filter paper to a glass slide or a silicon chip) and then hybridizing radiolabled or fluorescent cDNAs (DNA copies of RNA) from different cell samples to the grid. Computer software is then used to analyze the intensity of hybridization to the individual spots on the grid, and statistical analysis can be used to estimate the likelihood of significant changes in the levels of gene expression between the samples.

GENETICALLY MODIFIED MICE AS A MODEL SYSTEM OF HUMAN CARDIOVASCULAR DISEASE

One of the most surprising findings to emerge from molecular genetic studies of the cardiovascular system is the remarkable evolutionary conservation of the molecular pathways that control cardiovascular development and function. It is now clear that similar genes and signaling pathways regulate the development of the heart and vasculature in mice and humans.[2] In some cases these same pathways

Figure 55-9 Northern blot analysis. Cellular mRNAs of different sizes are separated by agarose gel electrophoresis and transferred to a filter membrane. The membrane is incubated in a solution containing a single-stranded radiolabeled DNA probe complementary to the mRNA of interest. This radiolabeled probe hybridizes only to the single band containing the complementary mRNA. Nonspecific binding of the probe is removed by washing the filter, and the band is visualized by exposure of the filter to x-ray film. As shown in the figure, the intensities of the resulting autoradiographic bands correspond to the abundances of the mRNA in the original samples. Hence, the technique can be used to quantitate the levels of gene expression in two different tissue samples.

have even been conserved in reptiles and insects. Thus, we can gain important insights into human cardiovascular biology and disease by studying these processes at the

molecular level in lower organisms. In many ways, mice represent an ideal model system for studies of human cardiovascular biology and disease. The mouse is a small animal with a short gestation period (21 days). A great deal is known about murine embryology and genetics. The mouse genome is being sequenced as a part of the genome initiative. Therefore, it will soon be possible to compare the structures of all of the mouse and human genes. Perhaps most importantly, elegant techniques for gene insertion, inactivation, and modification have been devised that allow genetic manipulation of the mouse almost ad libitum.

Transgenic Mice

Overexpression of a wild-type or mutant gene in a mouse represents a powerful tool for understanding both the function of that gene in normal mouse development and, in some cases, its role in specific disease states. The production of a transgenic mouse involves (1) the cloning of the gene of interest, (2) fusion of that gene to transcriptional regulatory sequences that program its expression either in all tissues of the mouse or in specific tissues, (3) injection of the purified transgene into the male pronucleus of a fertilized one-cell mouse embryo, and (4) reimplantation of the injected embryo into a foster mother[35] [92] [93] (Fig. 55-10) . In many cases the injected transgene is randomly integrated into a chromosome of the fertilized embryo, resulting in a founder mouse that not only will express the injected transgene but also will pass that transgene on to 50 percent of its progeny. By comparing the phenotype of the transgenic animals with that of their nontransgenic (but otherwise genetically identical) siblings, one can draw firm conclusions about the effects of transgene overexpression on development and function at the cellular, tissue, and organismal levels. Although the production of transgenic animals was originally a technically difficult procedure that could only be carried out in a few specialized research laboratories,[94] it is now possible to produce routinely multiple transgenic founders in less than a month after a single day of embryo injections with the appropriate transgene DNA construct. Thus, the production of transgenic mice has become a standard procedure carried out in many laboratories throughout the world. Moreover, similar techniques have recently been used to produce transgenic rats, rabbits, and pigs.

Promoters have recently been characterized that program transgene expression exclusively in cardiomyocytes, endothelial cells, and vascular smooth muscle cells.[35] [95] Thus, it is now possible to restrict transgene expression to specific cell types in the cardiovascular system. In addition to producing gain-of-function animals by overexpression of the wild-type or even a superactivated mutant gene, it is also possible to use transgenic techniques to eliminate the function of a single gene by overexpressing a dominant negative mutant of that gene whose encoded protein interferes with the function of the wild-type protein.[96] [97] Recently, it has also become possible to produce transgenic mice in which expression of the transgene is turned on or off by administration

Figure 55-10 Production of transgenic mice. The transgene of interest is coupled by recombinant DNA technology to a transcriptional regulatory sequence that directs its expression either in all cells or in specific tissue types of the mouse. This transgene construct is microinjected into the pronucleus of a

fertilized mouse egg, which is then implanted into the uterus of a foster mother. Twenty-one days later, this mother gives birth to a litter containing one or more transgenic founder mice that have integrated the transgene cassette into their genomic DNA. Breeding of these founders to wild-type mice results in transmission of the transgene to 50 percent of the resulting offspring. Transgenic mice are shown in black. Nontransgenic mice are shown in white.

of a simple drug like tetracycline.[98] Such mice allow precisely timed transgene expression as well as a comparison in the same animal of the phenotypes of transgene-positive and transgene-negative states.

Example of the Use of Genetically Altered Mice to Investigate Cardiovascular Pathophysiology: Transgenic Mice Reveal the Role of Beta-adrenergic Receptor Downregulation in Congestive Heart Failure (See also Chap. 16)

Chronic overstimulation of beta-adrenergic receptors as is seen in patients with congestive heart failure leads to the downregulation of beta-adrenergic receptor (betaAR) signaling in cardiomyocytes.[99] Recent studies have demonstrated that this downregulation results from phosphorylation of the betaAR by beta-adrenergic receptor kinase (betaARK) and subsequent receptor internalization and uncoupling.[100] Receptor uncoupling, in turn, leads to decreased contractility and an exacerbation of heart failure. Thus, prevention of receptor phosphorylation and internalization might be beneficial in patients with congestive heart failure.[101] [101A]

During the past 5 years, several mouse models of dilated cardiomyopathy and heart failure have been described.[97] [102] [103] [104] [105] To ask if the prevention of betaAR uncoupling could ameliorate the progression of congestive heart failure in these models, Lefkowitz and colleagues produced transgenic mice that overexpressed a truncated form of betaARK (called betaARKct).[101] betaARKct was known to function as a dominant negative inhibitor of betaARK, that is, it prevented betaARK from phosphorylating the betaAR and therefore prevented betaAR internalization. To be certain that the effects of the betaARKct transgene were due to its activity in cardiomyocytes, Lefkowitz and colleagues linked the betaARKct transgene to the cardiomyocyte-specific alpha-myosin heavy chain (alpha-MHC) promoter using standard recombinant DNA techniques. After injection of the betaARKct transgene into fertilized mouse embryos, Lefkowitz and colleagues produced several lines of transgenic mice that expressed high levels of betaARKct only in cardiomyocytes. These betaARKct transgenic mice demonstrated increased basal heart rates and contractility as well as enhanced responses to betaAR stimulation.[101] To test the effects of betaARK inhibition on the progression of heart failure, the betaARKct transgenic mice were bred with MLP knockout (KO) mice[102] that develop dilated cardiomyopathy and heart failure. Remarkably, the betaARKct transgene prevented the development of congestive heart failure in the MLP KO mice, demonstrating directly that betaAR downregulation plays a key role in both the development and progression of heart failure in the MLP KO mice.[106] This exciting genetic experiment confirmed the important role of betaARK in this model of heart failure and suggested that drugs that inhibit betaARK activity may be

useful new therapeutic reagents in patients with congestive heart failure.

Targeted Gene Inactivation ("Knockout") Technologies

Gene knockouts represent a complementary approach to transgenesis for studying the role of a specific gene in mouse development and physiology[107] [108] [109] [110] [111] [112] [113] [114] (Fig. 55-11) . Unlike transgenic experiments that typically result in overexpression of the transgene product (and hence produce a gain-of-function mouse), gene knockouts eliminate the expression of one or more genes to produce a loss-of-function mutant animal. The classical knockout approach involves transfection of a pluripotent mouse embryonic stem (ES) cell with a targeting construct or copy of the gene of interest containing a deletion or nonsense mutation.[108] Homologous recombination between the targeting construct and one copy of the endogenous gene produces an ES cell with a heterozygous deletion of the gene of interest. This mutant ES cell is then injected into a fertilized mouse blastocyst, which in turn is implanted into a foster mother. The resulting mouse is a chimera in which all tissues (including the gonads) are derived in part from the mutant ES cells and in part from the wild type cells of the injected blastocysts. This chimeric animal is then bred to a wild-type animal. Fertilization of a wild-type egg with a mutant sperm from the chimera produces a heterozygous KO animal in which one copy of the gene of interest in all cells is mutant and the other copy is wild type. Such heterozygous animals can be bred to produce homozygous knockouts that lack active copies of the gene of interest in all cells. The phenotype of such gene KO animals reveals the essential function(s) of that gene in both normal development and physiology. Unlike transgenesis, gene knockouts are difficult, time consuming, and expensive to produce. It typically takes a skilled investigator 6 to 12 months to produce a single KO mouse strain.

Example of Targeted Gene Deletion to Produce a Disease Model: Apolipoprotein E-Deficient Mice: A Murine Model of Atherosclerosis

Unlike humans, mice are remarkably resistant to atherosclerosis, even when maintained on a high-cholesterol diet.[115] This fact has limited our ability to use mouse models to study the pathogenesis and treatment of atherosclerotic vascular disease. It has been hypothesized that the resistance of mice to atherosclerosis may be due in part to the fact that most of the cholesterol in mouse serum is present in the high-density lipoprotein ([HDL], as opposed to the low-density lipoprotein [LDL]) fraction.[115] [116] To alter the lipoprotein pattern in mice and directly test the function of apolipoprotein E (apoE) in cholesterol metabolism, two groups independently used gene targeting to inactivate the apoE gene in mice.[117] [118] Due to delayed clearance of very low density lipoprotein (VLDL) particles lacking apoE, the mutant mice displayed marked elevations in VLDL-like particles and reciprocal decreases in HDL cholesterol (see also Chap. 31). Interestingly, these disorders in lipid metabolism were associated with the development of extensive atherosclerosis when these mice were maintained on a diet similar to those consumed in westernized countries.

These results not only proved the important role of apoE in determining sensitivity to atherosclerosis, but also provided a new animal model of the disease, which could be used to study both pathogenesis and treatment. For example, recent studies have

demonstrated that the development of late atherosclerotic lesions in the apoE-deficient mice can be significantly reduced by breeding them to mice deficient in CD154 (or CD40 ligand)[119] or by administration of antibodies against CD154,[120] [120A] a proinflammatory receptor present on T cells, macrophages, vascular smooth muscle cells, and endothelial cells. These findings directly implicated the CD40/CD40L interaction in the progression of atherosclerosis in this model and suggested that strategies to block this pathway may represent novel approaches for the treatment of atherosclerosis.

Newer Gene-Targeting Approaches

Because many genes are required for the early development of multiple cell types and tissues, classical gene knockout approaches can often result in early embryonic lethal phenotypes that are difficult to analyze and understand. Thus, it would be desirable to be able to delete genes in a tissue-specific fashion and/or to inactivate them at different times in development. Moreover, in some cases it is of interest to produce specific mutations of genes rather than to eliminate their expression completely. Recently developed technologies have begun to address these issues.[110] [111] [112] [113] [114]

The same types of homologous recombination methods that are used to knockout genes by deletion can be used to introduce specific mutations into wild-type genes. The only major difference in technique is that such "knock-ins" use a targeting construct containing a mutant gene rather than a gene deletion. Moreover, it is possible using homologous recombination to introduce a distinct or unrelated gene into a foreign genetic locus and to thereby regulate the new gene under the control of the promoter of the targeted locus.

Gene deletion can also be carried out in a tissue-specific manner by using an elegant bacterial phage recombination system called Cre-lox.[112] [121] The P1 bacteriophage encodes an enzyme called Cre that catalyzes recombination of DNA between two specific sequences (called loxP sites) that signal recombination.[121] This system can be used in mice by

Figure 55-11 Gene targeting in mice. *A,* A schematic illustration of a wild-type prototypical eukaryotic gene with three exons *(top),* a targeting construct in which exon 2 has been replaced with a neomycin resistance gene (neo^R) under the control of the phosphoglycerate kinase (PGK) promoter *(middle),* and a targeted allele in which the wild-type gene has been replaced with the targeting construct by homologous recombination *(bottom). B,* Production of gene-targeted mice. The targeting construct produced in *A* is introduced into murine embryonic stem (ES) cells by electroporation. Cells containing the targeted allele produced by homologous recombination are identified by Southern blot analysis and injected into a fertilized mouse blastocyst. Injected blastocysts are implanted into a foster mother, that gives birth 21 days later to chimeric mice in which all of the tissues are derived in part from the targeted ES cells and in part from wild-type cells within the blastocysts. Breeding of the chimeric mouse to a wild-type mouse results in germline transmission of the targeted allele, producing heterozygous mice that contain one targeted and one wild-type allele. Interbreeding of two heterozygous mice produces a litter composed of

one-fourth wild-type (+/+) mice, one-fourth homozygous targeted (-/-) mice, and one-half heterozygous (+/-) mice. *C,* Southern blot analysis of a cross between two heterozygous gene-targeted mice. The wild-type (WT) and targeted (T) alleles can be distinguished by their different sizes on Southern blot. The genotypes of resulting mice can be deduced from the patterns of the wild-type and targeted alleles. Wild-type (+/+) mice contain two copies of the wild-type allele. Heterozygous (+/-) mice contain a single copy of the wild-type allele and a single copy of the targeted allele. Homozygous deficient mice (-/-) contain two copies of the targeted allele.

producing a targeting construct in which the gene of interest is flanked by loxP sites (a so-called floxed allele).[112] [121] Mice homozygous for the floxed allele can then be bred with transgenic mice that express the Cre recombinase in a tissue-specific manner. Such mice will then delete the gene of interest only in the tissue expressing the Cre recombinase. By placing the Cre transgene under the control of a tetracycline-responsive promoter it is also possible to program gene deletion only after tetracycline feeding.

By using combinations of transgenesis, gene knockout, and new gene targeting approaches it is now possible to produce gain-of-function and loss-of-function mice in a temporally and spatially regulated fashion. In addition to identifying the function of individual genes at the organismal level, such studies often produce new animal models of human cardiovascular disease that are useful for studies of molecular pathogenesis and therapy. For example, such approaches have already produced mouse models of hypertrophic[122] [123] and dilated cardiomyopathy,[96] [97] [102] [103] [104] [105] familial hypercholesterolemia,[124] and congenital cardiac disorders. The completion of the human genome project, announced in June of 2000,[124A] [124B] will lead to the identification of large numbers of variations in gene sequence (polymorphisms), some of which will be associated with specific human diseases. Homologous recombination-mediated knock-ins of these mutations into mice will become an important tool for validating the role of these polymorphisms in the etiology of these diseases.

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Advances in Mouse Physiology

To harness the full power of mouse genetics, it is important to be able to perform accurate physiological studies of the cardiovascular system in genetically modified animals. Until recently, the ability to analyze the mouse cardiovascular system was severely limited by both the small size of the heart and vessels in the mouse and by the resting murine heart rate of greater than 500 beats/min. During the last several years, a number of groups have solved this problem by developing miniaturized instrumentation and microsurgical techniques.[3] [96] [125] Using these approaches it is now possible to obtain a wide variety of physiological measurements in anesthetized and intubated closed-chested animals. Such parameters include aortic blood pressures, real-time left ventricular pressure tracings, dP/dt_{max} and dP/dt_{min} , and arterial blood gases and pH both at baseline and after the infusion of pressors such as dobutamine or isoproterenol. In addition, by using high-frequency transducers and customized software it is possible to obtain high-resolution M mode and two-dimensional echocardiograms from mice.

These images can be used to determine end-systolic and end-diastolic left ventricular dimensions, left ventricular wall thickness and mass, shortening fraction, and wall stress rate-corrected velocity of fiber shortening (Vefc) relationships. It is also possible to produce myocardial infarctions by coronary artery ligation with or without reperfusion injury and to induce left ventricular hypertrophy by aortic banding or chronic infusion of angiotensin II. Finally, it is now possible to obtain 24-hour electrocardiographic recordings on conscious mice using implanted transducers and to perform limited electrophysiological studies to detect inducible cardiac arrhythmias in these animals.[126] Taken together, these advances make it possible to use the mouse as an accurate and convenient model system for studies of cardiovascular physiology and pathology and, when combined with the genetic manipulations described earlier, suggest that the mouse will become an increasingly useful system for studies of the genetic bases of human cardiovascular disease.

GENE- AND CELL-BASED THERAPIES FOR HUMAN CARDIOVASCULAR DISEASE

Somatic Gene Therapy for Cardiovascular Disease

Somatic gene therapy can be defined as the ability to introduce genetic material into non-germline cells to produce a therapeutic effect at the level of the intact organism. The recent rapid increase in the number of cloned and characterized human genes when coupled with an improved understanding of the genetic pathways involved in normal and pathological cell function has increased the potential usefulness of somatic gene therapy approaches for the treatment of a wide variety of human cardiovascular diseases.[127] [128] [129] [130] Indeed, human gene therapy trials have recently been initiated for the treatment of patients with chronic myocardial ischemia[131] and vein graft stenoses.[132]

Gene therapy strategies can be divided into two categories based on the location of cell transduction. Ex vivo approaches are those in which cells or tissues are removed from an animal or patient, transduced with the therapeutic gene in vitro, and then retransplanted into the recipient host. In contrast, in vivo gene therapies involve the transduction of the appropriate cell type in vivo without the need for cell isolation or transplantation. During the past 5 years there has been a paradigm shift in our thinking about gene therapy approaches for human disease. Initial studies focused on the correction of inherited genetic disorders such as familial hypercholesterolemia or muscular dystrophy and often employed ex vivo methods. More recently, it has become clear that gene therapies may also be quite useful for the treatment of acquired disorders such as cardiac ischemia or restenosis and that particularly in the cardiovascular system it is often preferable to develop and employ in vivo gene transduction strategies.[127] [128] [129] [130]

Like any successful therapeutic strategy, gene therapies must be tailored to the patient and the patient's disease. Relevant considerations in this design process include an understanding of the cell type that must be transduced and the efficiency of transduction that is needed to correct or prevent the disease. Different disorders require different stabilities of transgene expression. Thus, for example the treatment of an inherited

metabolic disorder such as familial hypercholesterolemia requires long-term stable transgene expression (or alternatively the ability to readminister the transgene on a regular basis), whereas the treatment of restenosis likely only requires transient expression of an appropriate transgene. Moreover, some gene therapies such as those designed to treat diabetes mellitus with transgene-encoded insulin clearly require regulated transgene expression whereas others such as the treatment of hemophilia with transgenes encoding coagulation factors XIII or IX simply require constitutive transgene expression. Finally, as with any new therapy it is important to carefully consider the potential risks of any gene therapy, including the effects of overexpression or ectopic transgene expression, the possibility of germline transmission of the transgene, risks associated with the vector used to introduce transgenes into cells (this is particularly true of viral vectors), the chance of mutagenesis of the host genome, and the potential for stimulating host inflammatory and immune responses to the vector or the transgene itself.

Most cardiovascular gene therapy approaches require at least three separate but related components: (1) an appropriate therapeutic transgene, (2) a vector for introducing that transgene into the relevant cell type such as a cardiomyocyte or a vascular smooth muscle cell, and (3) a device (e.g., a catheter or stent) for efficient delivery of the vector to the appropriate location in the cardiovascular system (e.g., to a localized segment of the vasculature or myocardium).

Vectors for Cardiovascular Gene Therapy

To date, five different vector systems have been tested or show promise for cardiovascular gene therapy (Fig. 55-12) : (1) "naked" plasmid DNA,[133] (2) synthetic oligonucleotides,[134] (3) replication defective adenoviruses,[135] [136] [137] (4) replication defective adeno-associated viruses,[138] and (5) retroviruses/lentiviruses. [135] [136] [137] Each of these vectors displays unique advantages and disadvantages, which define their usefulness for the treatment of different cardiovascular diseases (Table 55-1) .

"NAKED" DNA.

Naked plasmid DNA vectors (i.e., purified plasmids containing only a transgene and an appropriate transcriptional regulatory element) (see Fig. 55-12) are taken up and expressed by small numbers of cardiomyocytes after direct intramyocardial injection.[133] [139] The advantages of such vectors include the simplicity of their production and administration, the stability of their expression (at least 19 months in rodents),[140] and their inability to transduce most other cell types in vivo after intramyocardial injection. However, these advantages are offset by the extremely low efficiency of cardiomyocyte transduction (less than 0.01 percent of the cells in the area of injection),[133] [139] [140] the requirement for direct injection into the myocardium, and their inability to appreciably transduce endothelial cells and smooth muscle cells in the vasculature. Thus, such vectors will likely only be useful for gene therapy strategies that require local expression of transgenes in very small numbers of cardiomyocytes after direct intramyocardial injection. An example of such an approach

Figure 55-12 Commonly used gene therapy vectors. The structures of retroviral, adenoviral, adeno-associated viral (AAV), and plasmid gene therapy vectors are shown. Viral and bacterial sequences are crosshatched. Transgene, promoter/enhancer, and selectable marker sequences are shown as unshaded boxes. LTR=long terminal repeat from the retroviral genome; Pr/E=an eukaryotic promoter/enhancer; ITR=inverted terminal repeat from either the adenoviral or AAV genomes; Ab^R =an antibiotic resistance gene for selection of plasmid-containing bacteria. Arrows show the direction of transcription of transgenes and selectable markers.

in which plasmid vectors are currently being tested in humans is the localized expression of vascular endothelial growth factor (VEGF) to induce angiogenesis after direct injection into regions of ischemic myocardium.[131]

OLIGONUCLEOTIDES.

Synthetic oligonucleotides are short (10 to 50 base pair) pieces of chemically synthesized single- or double-stranded DNA that can be used to inhibit the expression of one or more genes after their introduction into cells. The mechanism of action of these oligonucleotides is complex and not fully understood. However, in some cases the single-stranded antisense oligonucleotides (i.e., oligonucleotides whose sequence is complementary to the coding sequence of an mRNA molecule) appear to base pair through hybridization with their complementary mRNAs and thereby to promote their degradation.[74] Double-stranded oligonucleotides corresponding in sequence to the recognition site of a specific transcription factor can serve as decoys that bind and sequester their cognate transcription factor, thereby inhibiting its ability to activate its normal set of target genes.[141] The advantages of such oligonucleotides for gene therapy include their ease of production and their relative safety. Disadvantages include significant batch-to-batch variability in activity, the fact that they are generally limited to turning target genes off as opposed to augmenting the expression of therapeutic transgenes, their nonspecific activities in cells, and their short half-lives (on the order of hours to days) in vivo. In addition, the ability of oligonucleotides to transduce cells in vivo is quite limited, necessitating the use of lipid-viral conjugates to enhance transduction.[142] Thus, such oligonucleotide-mediated approaches of gene therapy will likely be useful only for transiently turning off the expression of specific genes in localized areas of the cardiovascular system. Indeed, such approaches have been successful in inhibiting vascular smooth muscle cell proliferation and intimal thickening in animal models of balloon angioplasty.[134] [142] [143]

ADENOVIRUS.

Adenoviruses are double-stranded DNA viruses that can be used to efficiently transduce a wide variety of tissues and cell types in vivo.[144] These viruses can be genetically engineered to render them replication-defective (i.e., to render them capable of infecting a normal human cell once but incapable of generating infectious progeny and spreading

the infection beyond the initial site of administration) and to allow them to program high-level transgene expression in vivo (see Fig. 55-12). The advantages of adenovirus vectors include their very high efficiency of transduction of resting cells (including cardiomyocytes, vascular smooth muscle cells, endothelial cells, and hepatocytes) in vivo, the relative ease of producing large amounts of virus, the ability to deliver the vectors through a catheter, and their relative safety.[145] These vectors have not been associated with persistent infection or malignancy, and they generally do not integrate into the host genome, minimizing the risk of insertional mutagenesis. Unfortunately, these advantages are offset by the fact that adenovirus vectors generally produce potent inflammatory and immune responses both to themselves and to the transgenes that they express.[146] [147] [148] [149] These responses produce local tissue damage and usually eliminate virus-transduced cells, thereby limiting the duration of transgene expression to 2 to 3 weeks.[135] [146] [147] [148] [149] Moreover, adenovirus vectors generate neutralizing antibodies that prevent readministration of the virus,[148] and in some cases these vectors can break tolerance to self proteins that are related to the transgene protein, thereby producing autoimmunity and/or precluding future gene therapies involving the same transgene.[149] Thus, in their present form these vectors will likely only be useful for gene therapy approaches requiring high-level and efficient but transient transgene expression in vivo. Examples include their use in gene therapy strategies designed to inhibit restenosis and to program myocardial angiogenesis after injection into the myocardium.

Despite the apparent limitations on the use of current-generation adenovirus vectors, recent studies have suggested that in some cases it may be possible to obtain long-term transgene expression in vivo with first-generation adenoviruses (e.g., in the case of expression of a self transgene after injection into skeletal muscle and in the case of adenovirus perfusion of the donor heart before transplantation).[138] [149] Moreover, newer versions of adenovirus vectors in which all of the viral genes have been deleted (so-called helper dependent or gutted adenoviruses) also appear to yield stable transgene expression in vivo.[150] [151] [152] Thus, future developments may result in adenovirus vectors that are useful for a wider range of cardiovascular gene therapies.

ADENO-ASSOCIATED VIRUS.

Adeno-associated viruses (AAVs) are single-stranded DNA viruses that are nonpathogenic in humans.[153] By replacing all of the viral genes in these vectors with a transgene and promoter cassette it is possible to produce replication-defective AAV vectors that are quite useful for cardiovascular gene therapy[153] (see Fig. 55-12). Like adenoviruses, AAV vectors efficiently infect many resting cell types in vivo, including cardiomyocytes and hepatocytes.[138] [154] Their efficiency of transduction of vascular endothelial and smooth muscle cells remains less clear.[155] [156] Unlike adenoviruses, AAV vectors do not cause significant inflammatory or immune responses. Thus, these vectors can be used to program transgene expression in vivo that is stable for at least 1 year.[157] [158] Cardiomyocytes can be efficiently transduced after either intramyocardial injection or coronary artery perfusion.[138] Moreover, these

TABLE 55-1 -- COMPARISON OF DIFFERENT CARDIOVASCULAR GENE THERAPY VECTORS

VECTOR/TRANSGENE	ADVANTAGES	DISADVANTAGES
Retroviruses		
	Stably integrate into host genome	Low titers
	Easily manipulated viral genome	Capacity for insertional mutagenesis
	No viral gene products; relatively nonimmunogenic	In vivo instability
		Transcriptional shut off in vivo
	Highly efficient transduction of many cell types	Require cell proliferation for infection
Adenoviruses		
	Maintained as an episome	Evoke potent host inflammatory and immune responses that eliminate transgene expression and preclude repeated administration
	Highly efficient transduction of replicating and nonreplicating cells	
	Stable in vivo in absence of immune response	
		Difficult to target to specific cell types

Adeno-associated virus	High-level transgene expression in vivo	Relatively difficult to manipulate viral genome
	Relatively nonpathogenic	
	High titers	
	Infects replicating and nonreplicating cells	Can accept only small transgenes
	Potential for site-specific integration	Difficult to produce in large quantities
	Relatively nonimmunogenic	Does not appear to stably transduce all cell types in vivo
	High titers	
Plasmid DNA	Nonpathogenic in humans	Potential for insertional mutagenesis
	Easy to manipulate and produce in large quantities	Very low transduction efficiency
	Nonpathogenic	
	Relatively nonimmunogenic	
	Does not require an infectious vector	
	Maintained as an episome	
	Can program long-term gene expression in postmitotic cells in vivo	

Synthetic oligonucleotides	Easy to synthesize in large quantities	Can only reduce or ablate gene expression
	Relatively high transduction efficiencies if delivered with viral liposomes	
		Large number of nonspecific and nonreproducible biological effects
		Cannot target specific cell types
		Relatively short half-life in vivo
Ribozymes	Can specifically and effectively target mRNAs	Can only reduce or ablate gene expression
		Difficult to deliver to cells in vivo
		Stability in vivo unclear

vectors appear to be quite safe, because they do not produce human disease even in their wild-type form.[153] Limitations of AAV vectors include the difficulty to date in producing large amounts of high-titer vector, the limitation on the size of the transgene that they can accommodate (less than 4.5 kb), and their potential for integration into the host genome.[153] These vectors will quite likely be very useful for gene therapy approaches that require efficient and stable transgene expression in the heart, including the treatment of myocardial ischemia, heart failure, and cardiac arrhythmias.

OTHER VIRAL VECTORS.

Retroviruses and lentiviruses are single-stranded RNA viruses that integrate into the host genome after infection[159] [160] [161] [162] (see Fig. 55-12). Retroviruses are unlikely to be useful for most cardiovascular gene therapies because they require cell proliferation for efficient infection.[162] Most cardiovascular cell types do not proliferate in vivo. In contrast, lentiviruses based on human or animal immunodeficiency viruses are capable of efficiently transducing many nonproliferating cell types in vivo.[160] [161] [162] [163] Like AAV vectors, lentiviral vectors can have most of their viral genes removed and do not appear to trigger inflammatory and immune responses.[163] These vectors can program stable transgene expression in neurons in vivo.[160] Their usefulness in the heart and vasculature has not yet been fully evaluated. Potential disadvantages of these vectors include difficulties producing high-titered virus stocks and the risk of recombination with

human immunodeficiency virus or endogenous retroviruses to produce replication-competent pathogenic viruses.

Recent Advances in Vector Development

During the past several years a number of advances have been made that have improved both vector efficacy and safety. These include the use of cell-type specific transcriptional regulatory sequences to produce vectors that express their transgenes in a tissue-specific manner[164] (e.g., smooth muscle cell-specific vectors) and structural modifications of vector coat proteins that enhance their infection of specific cell types.[165] In addition, several systems have been described that allow the regulation of transgene expression in response to exogenously administered drugs.[166] [167] Finally, there has been a great deal of interest in developing systems that will allow the repair of mutant genes in cells in vivo or in vitro. One such system has recently been described that uses chemically synthesized RNA/DNA oligonucleotides called chimeroplasts to direct the cell-mediated repair of single base mutations.[168] The usefulness of this and related gene repair systems for the treatment of inherited cardiovascular diseases will require additional investigation.

Devices for Gene Delivery

The development of devices that can be used for gene delivery has not advanced as quickly as vector development. The design specifications for such gene delivery devices include the ability to efficiently deliver a gene therapy vector to a localized area of the cardiovascular system with minimal invasiveness and no adverse effects on vector viability or efficiency.[169] A variety of catheters have been

tested for local vascular gene delivery. These include double-balloon catheters,[128] hydrogel catheters, [170] and porous and microporous balloon catheters.[171] [172] Each of these catheters has been plagued with specific problems, including inefficient or nonuniform transgene delivery, leak of vector into the systemic circulation, and vascular injury due to balloon inflation and/or jetting of vector solution. Similarly, catheters have been described for direct intramyocardial injection. However, to date such devices produce local tissue damage and can result in significant leak of vector into the left ventricular cavity. Importantly, many of these devices have not yet been carefully tested for compatibility with the different vector systems described earlier. Indeed, recent studies have suggested that many of these catheters efficiently and rapidly inactivate adenovirus vectors.[172A] Areas that require more investigation include the use of gene- or vector-coated stents for gene delivery to the vasculature, production of delivery systems that will facilitate intracoronary perfusion with gene therapy vectors, and iontophoresis to enhance the efficiency of localized gene delivery to the heart and vasculature.

Cell-Based Therapies

A variety of cardiovascular cell types including vascular endothelial cells, vascular smooth muscle cells, and embryonic cardiomyocytes can be cultured in the laboratory in vitro. This finding has suggested the possibility of using either wild-type or genetically modified cardiovascular cell transplantation to treat a variety of cardiovascular disorders. Cultured endothelial cells have been used to seed synthetic grafts in an attempt to reduce graft thrombosis.[173] [174] Similarly, endothelial cells genetically modified to produce tissue plasminogen activator have been suggested as a therapy to reduce the thrombotic potential of grafts and native injured coronary arteries.[175]

Cardiomyocytes are terminally differentiated cells that do not retain the capacity to proliferate. Therefore, the heart lacks the capacity for regeneration after ischemic, toxic, or infectious injury. Accordingly, there has been a great deal of recent interest in developing gene- or cell-based therapies for myocardial repair and regeneration.[176] Potential gene-based approaches to this problem include the use of transgenes to stimulate cardiomyocyte proliferation or to program the differentiation of cardiac fibroblasts into cardiomyoctyes. Unfortunately, genes with these activities have not yet been discovered. Alternative cell-based approaches would include the injection of either cultured cardiomyocytes or skeletal myocytes into the damaged myocardium. Recent studies have demonstrated that skeletal myocytes injected into the myocardium form a stable graft that may improve global hemodynamics after myocardial injury in rodents.[177] [178] [179] However, to date there is no evidence that such grafts form the electrical or functional junctions with the endogenous myocardium that would be required to initiate synchronous contraction of the graft. In contrast, studies from a number of groups have demonstrated stable engraftment of embryonic cardiomyocytes injected into the myocardium with formation of intercalated discs and gap junction between the injected cells and the endogenous cardiomyocytes.[180] [181] [182] These findings suggest that such engrafted cells might be capable of forming beating grafts. However, the efficiency of engraftment of such embryonic cardiomyocytes has been low (less than 0.1 percent). Moreover, it will be important to identify a nonembryonic renewable source of such transplantable cardiomyocytes. In this regard it is of interest that recent studies have suggested that such cells can be derived from embryonic stem cells in vitro as well as from adult bone marrow.[181] [182] [183] Indeed, adult bone marrow appears to contain pluripotent mesenchymal stem cells with the capacity to differentiate into a variety of cell types, including skeletal and cardiac muscle, hematopoietic cells, cartilage, and fat.[184] Such cells have been reported to repopulate damaged skeletal muscle after intravenous injection.[185] It will be of interest to determine if these cells can similarly repopulate the damaged myocardium after systemic administration.

Example of the Use of Gene Therapy for Cardiovascular Disease: Gene Therapy Approaches for Vascular Proliferative Disorders

Vascular smooth muscle cell (VSMC) migration, proliferation, and extracellular matrix deposition are thought to play important roles in vascular proliferative syndromes such as restenosis after balloon angioplasty or stenting.[186] [187] Despite numerous clinical trials with new drugs and devices, restenosis rates of 20 to 40 percent are still seen with

most, if not all, percutaneous coronary revascularization procedures.[188] Thus, there has been interest in developing gene therapy approaches that could be used to treat the vascular proliferative syndromes. Such approaches would require (1) a vector that could efficiently transduce VSMCs at the site of revascularization after delivery through a catheter, (2) an appropriate cytotoxic or cytostatic gene that could either kill or inhibit the proliferation of VSMCs after vessel injury, and (3) a device that could be used to deliver this vector to a localized area of the vasculature.

During the past several years a number of successful gene therapy approaches to this problem have been developed. Nabel and coworkers demonstrated that adenovirus-mediated gene transfer of the herpes simplex virus thymidine kinase (HSV-tk) gene followed by systemic ganciclovir therapy killed proliferating VSMCs and inhibited restenosis by more than 50 percent in a pig model of iliofemoral balloon injury.[130] [189] Using a cytostatic approach, Leiden and coworkers demonstrated that adenovirus-mediated gene transfer of a constitutively active retinoblastoma (Rb) transgene (that inhibits the G1-S transition) or the cyclin-dependent kinase (CDK) inhibitor p21 that prevents Rb phosphorylation prevents smooth muscle cell proliferation and inhibits intimal thickening by 40 to 60 percent in both the rat carotid and porcine iliofemoral models of balloon injury.[189] [190]

Dzau and coworkers demonstrated that double-stranded decoy oligonucleotides containing an E2F binding site (E2F is a transcription factor that is released and activated upon Rb phosphorylation and is needed to drive cells through the G1-S transition) also inhibit restenosis in the rat carotid artery model of balloon injury by more than 70 percent.[143] These investigators have recently gone on to use these same decoy oligonucleotides in a phase I clinical trial of peripheral vein grafting and have reported a statistically significant reduction in graft occlusion after treatment with the E2F decoys.[132] Taken together, these studies suggest that both viral and oligonucleotide-mediated gene therapies may be useful adjuncts to percutaneous and surgical revascularization approaches in patients with atherosclerotic vascular disease.

FUTURE DIRECTIONS OF MOLECULAR CARDIOVASCULAR MEDICINE

Advances in molecular and cellular cardiology have already had a profound impact on cardiovascular biology and medicine. These advances, however, represent only the beginning of a set of revolutionary discoveries that will fundamentally change our understanding of normal cardiovascular function and thereby enhance our ability to diagnose and treat cardiovascular disease. It is impossible to predict the future of this scientific revolution. However, several implications are clear.

The determination of the sequence of all of the genes in the human genome along with the characterization of the role of specific genetic variations in cardiovascular diseases will provide a powerful new set of genetic diagnostic tools. Within 10 years, genetic analyses of a simple blood sample from a child will allow the accurate prediction of the susceptibility of that child to a wide variety of diseases from hypertension, atherosclerosis, and diabetes to cancer and neuropsychiatric disorders. This type of genetic susceptibility testing will fundamentally change the practice of medicine. Rather than treating patients only after they develop symptoms of cardiovascular disease it will

be possible to identify those patients at high risk in childhood and intervene to reduce risk factors before disease develops. In addition, it will be possible to predict accurately the response of an individual patient to different drugs. Thus, susceptibility

testing will allow the development of a new genetically based preventive medicine.

From the standpoint of basic investigation, the cloned genes and their encoded proteins can be structurally analyzed by nuclear magnetic resonance and crystallographic techniques. The resultant structures will produce important clues about the function of these proteins and will also provide that basis for the rational development of drugs designed to augment or inhibit those functions. Biochemical technologies to unravel protein-protein interactions (for example, one known as the yeast two-hybrid system) will be used to place the newly cloned genes (and proteins) into their intracellular pathways. Such approaches will help to define critical domains in molecules that should help to identify new targets for the development of drug- and gene-based therapies. Finally, newly cloned genes emerging from the genome project will be used in transgenic, knockout, and knock-in strategies in mice to determine, more precisely, their functions, to discover the effects of mutations, and to produce new animal models of human diseases for studies of pathogenesis and new therapies ("functional genomics").

From a therapeutic standpoint, the newly cloned genes will be used to design new in vitro or cell-based strategies that can be used by pharmaceutical companies to screen large libraries of compounds for new drugs. Of equal importance, these genes will form the basis for the development of novel genetic therapies for cardiovascular disease.

Like any powerful new technology, molecular genetics will also raise important ethical questions. Which genetic traits are appropriate for modification? What is the role of germ-line gene therapies that modify the genome in a genetically transmissible fashion? How is the confidentiality of genetic susceptibility data about individual patients guaranteed? And how do we handle information about susceptibility to a disease for which we lack an effective treatment? These questions and many others will be actively debated by physicians, patients, ethicists, and politicians for years to come. Despite these thorny problems, the potential for benefit from molecular genetics significantly outweighs the potential for harm. It is safe to predict that the era of molecular medicine will revolutionize the ability to diagnose and treat patients with cardiovascular diseases.

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Chapter 56 - Genetics and Cardiovascular Disease

REED E. PYERITZ

GENETIC FACTORS IN DISEASE

Genes contribute to both the cause and the pathogenesis of virtually any abnormality of human physiology and behavior, including, of course, disorders of the heart and vascular system (see Chap. 55) . This statement carries two messages in addition to the obvious one. First, the pathology associated with even the most "environmental" of causes, such as trauma, malnutrition, and drug abuse, can be defined only in terms of the human body's response to the insult. How the stress of the initial insult is expressed (the *phenotype*) and how the patient suffers and perhaps recovers depend, to various and yet often poorly defined degrees, on the patient's *genotype.* This idea seems self-evident and verges on the trite, but it is frequently neglected. Some environmental insults, such as massive trauma or poisoning, are lethal to all, regardless of genotype. Nonetheless, as developments in fields such as *pharmacogenetics* and *ecogenetics* are defining genetic susceptibilities to human disease better and more simply, physicians must become increasingly attuned to the importance of the genotype.[1]

Second, the introductory statement emphasizes that genetic factors have roles in *both* cause and process; etiology and pathogenesis, although related, are conceptually

distinct.[2] For example, the cause of sickle cell anemia is clearly a single mutant gene, whereas whether a patient homozygous for this mutation expresses all, some, or none of the manifestations of the disease depends on many other genetic and nongenetic factors. Conversely, the cause of pneumococcal pneumonia is equally evident, but the severity and resolution of the disease depend on the patient's immune competence (which in turn depends on genetic and nongenetic factors) as much as on treatment with an antibiotic.

The genotype, therefore, can be detrimental in at least two distinct ways. First, mutant genes can so upset embryology or physiology that a clinical abnormality occurs. Whereas the phenotype of any particular mutation depends on a host of factors, including which homeostatic systems are available to modulate the action of the defect, the genotype has the principal role in causing the disease. It is this class of mutations that are usually referred to as genetic diseases. Second, a mutation can facilitate the action of an extrinsic cause in producing disease. Inherited susceptibilities are part of the pathogenesis of disease and are one reason for taking a patient's family history. Until recently, clinicians could do little to pursue tantalizing facts, such as several relatives' suffering myocardial infarction before age 50. The long-touted prospect of detecting a patient's inherited susceptibilities and intervening before irreversible clinical sequelae occur is becoming reality.

Disorders Due to Microscopic Alterations in Chromosomes

Estimates of the total number of human genes range between 50,000 and 100,000. Two copies (termed *alleles*) of each gene are arrayed along 23 pairs of *chromosomes.* Twenty-two of the chromosomes are called *autosomes* (numbered 1 through 22), and the 23rd pair are the *sex chromosomes,* X and Y. Females have two X chromosomes and males have an X and a Y chromosome. Both autosomal alleles are potentially active in specifying RNA copies of their DNA sequences; whether a gene is active depends on the cell type, the developmental stage of the organism, and the regulatory molecules that interact with promoter and enhancer nucleotide sequences that control transcription of the gene. In cells with two X chromosomes (i.e., in all females, in Klinefelter syndrome in which two Xs and one Y occur, and in other rare conditions), only one X is entirely active after early embryogenesis.

Human chromosomes can be examined by culturing cells capable of mitosis; T lymphocytes obtained from venous blood are the usual source, but fibroblasts, cells from chorionic villi, amniocytes, and leukocyte precursors present in bone marrow are also used clinically. Chromosomes are distinguished from one another by their size,

shape (determined by the position of a constriction called the *centromere,* which functions as the attachment of the mitotic apparatus), and characteristic banding pattern as revealed by any of several staining techniques. The chromosomes are photographed, cut out, and arranged in pairs, from 1 through 22 and the sex

chromosomes, in a display called the *karyotype.* This display and its interpretation are the end results of a clinical study of a patient's chromosomes. The chromosome constitution of a cell is designated by first specifying the number of chromosomes present (46 being normal in diploid cells), then specifying the sex chromosomes, and finally describing any abnormalities. For example, a normal male is designated 46,XY, and a female with an extra chromosome 21 is designated 46,XX,+21.

ANEUPLOIDY.

Chromosome aberrations, especially too many or too few chromosomes (*aneuploidy*), are extremely common in human embryos; more than one-half of all conceptuses are spontaneously aborted in early pregnancy, and at least one-half of them are aneuploid. Among live-born infants, about 0.5 percent have a chromosome aberration.

Gain or loss of chromosomes generally happens by nondisjunction, or the failure of a homologous pair of chromosomes to separate. Absence of one chromosome is termed *monosomy;* all autosomal monosomies are embryonic lethals, as is presence of only a Y sex chromosome. Presence of three chromosomes is *trisomy,* and presence of an entire extra set of chromosomes (for a total of 69) is *triploidy.* The most common autosomal aneuploidy, trisomy 21 associated with Down syndrome, and aneuploidy for sex chromosomes all are compatible with survival into adulthood.

CHROMOSOME REARRANGEMENTS.

A chromosome can break and rejoin within itself, potentially giving rise to an *inversion* of genetic material. Often no apparent phenotypic effect is seen in people with an inversion, but because inversions may disrupt chromosome pairing during meiosis, their offspring may have more profound aberrations.

DELETIONS AND DUPLICATIONS.

Just as their names imply, these aberrations are losses or gains of chromosomal material. Many clinical syndromes have been associated with aberrations of specific chromosome regions.[3] [4] The smallest deletion detectable by light microscopy is associated with loss of considerable DNA, on the order of one million base pairs, so more than one gene is potentially disrupted or lost.

A number of conditions, each initially thought to be due to a mutation in a single locus, are associated with small interstitial chromosome aberrations affecting a cluster of genes (Table 56-1) . So rather than pleiotropic manifestations of one mutation, these conditions are likely to be due to the effects of several, and perhaps many, mutations and are therefore called *contiguous gene syndromes.* [5] Such defects are potentially heritable, and the occurrence of the disorder in a family behaves as a mendelian dominant.

Disorders Due to Changes in Single Nuclear Genes (See also Chap. 55)

Mutations of genes located on the 22 pairs of autosomes and the two sex chromosomes produce phenotypes inherited according to the two principal tenets of Mendel: alleles segregate and nonalleles assort. The first statement refers to gametes receiving only one of the two alleles at a given locus as a result of meiosis. The second statement describes the results of recombination, the meiotic process of rearranging DNA between the two chromosomes of the pair (*homologous chromosomes*); if two loci are widely spaced along a chromosome, their chances of being separated by recombination are 50-50, and they are said to be *unlinked.*

The Human Genome Project, begun in 1990, has set goals to map all expressed genes, to create a physical map of overlapping pieces of DNA composing the entire genome, and, finally, to sequence all 3 to 3.5 billion nucleotides in the haploid complement of human DNA.[6] The project is well ahead of schedule, and a "rough draft" of the entire sequence became available in 2000. The beginnings and ends of more than 100,000 expressed sequences, most representing genes, have been identified out of a total of perhaps 125,000 genes. More than 10,000 individual loci have been identified on the basis of the phenotype that mutations in single genes produce. The presumption of single-gene defects is based in most instances on the pattern of inheritance in families; segregation of the phenotype according to mendelian principles is the central piece of evidence. For an increasing number of loci, however, molecular genetic techniques have mapped the phenotype to a narrow chromosome region, to a single gene, or even revealed the actual alteration in nucleotide sequence (see also Chap. 55) [7] (Table 56-2) . The range of known mendelian variation in humans and information about gene mapping and molecular defects are routinely catalogued and available on-line.[8]

Of the more than 10,000 loci that have been clearly identified on the basis of either an abnormal phenotype or a normal product, 9.1 percent involve the heart.[8] Many others involve other parts of the cardiovascular system. Thousands of loci have been mapped to a restricted region of the genome. Many of these loci cause specific mendelian disorders, and the genetic map of these loci represents the "morbid anatomy of the human genome." Many of the cardiovascular and hemostatic disorders that were mapped by the end of 1999 are shown in Figure 56-1 .

DOMINANCE AND RECESSIVENESS.

These related concepts are characteristics of the phenotype, *not of the gene.* A phenotype is dominant when the patient is *heterozygous* for a mutation, i.e., when one copy of the mutant allele and one copy of the normal allele are present; this holds for genes on both autosomes and the X chromosome. A phenotype is recessive when the patient has two mutant alleles at the locus causing the condition. If the mutant alleles are identical, the patient is *homozygous* at that locus, a situation usually present either when the allele is identical by descent through both parents (i.e., the parents had a common ancestor and are *consanguineous*) or

TABLE 56-1 -- CONTIGUOUS GENE SYNDROMES

	REGION	LOCUS	CARDIOVASCULAR ABNORMALITIES
Syndromes with Cardiovascular Involvement			
Arteriohepatic dysplasia	AHD	del 20p11.23-p12.2	Peripheral pulmonic stenosis/hypoplasia
Cat-eye syndrome	CES	dup22q11	Total anomalous pulmonary venous return
DiGeorge sequence	DGS	del 22q11	Truncus arteriosus, right aortic arch, TOF, PDA
Miller-Dieker syndrome	MDS	del 17p13	PDA ± complex anomalies
Prader-Willi syndrome	PWS/AS	del 15q12	Cor pulmonale (secondary to obesity and central apnea)
WAGR syndrome		del 11p13	Hypertension (secondary to Wilms tumor)
Syndromes Without Frequent Cardiovascular Involvement			
Angelman syndrome		del 15q12*	
Smith-Magenis syndrome		del 17p11.2	

TOF=tetralogy of Fallot; PDA=patent ductus arteriosus; WAGR=Wilms tumor, aniridia, genitourinary, and retardation.

*The deletion is often indistinguishable at the cytogenetic level from that of the Prader-Willi syndrome; genetic imprinting of locus *UBE3A* is thought to account in part for the phenotypic differences. In Prader-Willi Syndrome, the deleted chromosome is always the chromosome 15 inherited from the father, whereas in Angelman syndrome, the deletion affects the maternal chromosome 15.

TABLE 56-2 -- MENDELIAN CONDITIONS THAT INVOLVE THE CARDIOVASCULAR SYSTEM WITH KNOWN GENETIC DEFECTS OR GENE MAPPING OF THE PHENOTYPE

PHENOTYPE	GENE SYMBOL	OMIM NO.*	GENE MAP Locus
Cardiomyopathies			

Adhalinopathy, primary	*SGCA*	600119	17q12-q21.33
Arrhythmogenic RV dysplasia-1	*ARVD1*	107970	14q23-q24
Arrhythmogenic RV dysplasia-2	*ARVD2*	600996	1q42-q43
Arrhythmogenic RV dysplasia-3	*ARVD3*	602086	14q12-q22
Arrhythmogenic RV dysplasia-4	*ARVD4*	602087	2q32.1-q32.3
Arrhythmogenic RV dysplasia-5	*ARVD5*		3p23
Arrhythmogenic RV dysplasia-6	*ARVD6*		10p12-p14
Becker and Duchenne muscular dystrophies	*DMD*	310200	Xp21.2
Emery-Dreifuss muscular dystrophy	*EMD*	310300	Xp28
Emery-Dreifuss muscular dystrophy	*LMNA*	150330	1q21.2-q21.3
Endocardial fibroelastosis-2	*TAZ*	302060	Xq28
FDC	*ACTC*	102540	15q14
FDC-1A	*CMD1A*	115200	1p11-q11
FDC-1B	*CMD1B*	600884	9q13
FDC-1C	*CMD1C*	601493	10q21-q23
FDC-1E	*CMD1E*	601154	3p25-p22
FDC-1F	*CMD1F*	602067	6q23
FDC-1G	*CMD1G*	604145	2q31
FDC-1H	*CMD1H*		2q14-q22
FDC-2	*CMD1D*	601494	1q32
FDC, X linked	*DMD*	310220	Xp21.2
FDC-3A	*TAZ*	302060	Xq28
FHC-1	*MYH7*	160760	14q12
FHC-2	*TNNT2*	191045	1q32
FHC-3	*TPM1*	191010	15q22.1
FHC-4	*MYBPC3*	600958	11p11.2
FHC	*TNNI3*	191044	19q13.4
FHC with WPW	*CMH6*	600858	7q3
FHC, mid-LV type	*MYL2*	160781	12q23-q24.3
FHC, mid-LV type	*MYL3*	160790	3p
Friedreich ataxia	*FRDA*	229300	9q13
Muscular dystrophy, Duchenne-like	*SGCA*	600119	17q12-q21.33
Myotonic dystrophy	*DMPK*	160900	19q13.2-q13.3
Myotonic dystrophy 2	*DM2*	602668	3q

Noncompaction of LV	*TAZ*	302060	Xq28
Developmental Disorders			
Alagille syndrome	*JAG1*	601920	20p12
Atrial septal defect, secundum	*ASD1*	108800	6p21.3
Atrial septal defect with AV conduction defects	*CSX*	600584	5q34
AV canal defect-1	*AVSD*	600309	1p31-p21
Bannayan-Zonana syndrome	*PTEN*	6011728	10q23.3
Cardiac valve dysplasia-1	*CVD1*	314400	Xq28
Cat-eye syndrome	*CECR*	115470	22q11
Conotruncal cardiac defects	*CTHM*	217095	22q11
DiGeorge syndrome and velocardiofacial syndrome	*DGCR*	188400	22q11
Down syndrome	*DCR*	190685	21q22.3
Ellis-van Creveld syndrome	*EVC*	225500	4p16
Goldenhar syndrome	*GHS*	141400	7p
Heterotaxy, X-linked visceral	*ZIC3*	306955	Xq26.2
Holt-Oram syndrome	*TBX5*	601620	12q24.1
Keutel syndrome	*MGP*	154870	12p13.1-p12.3
Left-right axis malformation	*TGFB4*	601877	1q42.1
Noonan syndrome	*NS1*	163950	12q24
Total anomalous pulmonary venous return	*TAPVR1*	106700	4p13-q12
Turner syndrome	*RPS4X*	312760	Xq13.1
Werner syndrome	*WRN*	277700	8p12-p11.2
Williams syndrome	*ELN*	130160	7q11.2
Wolf-Hirschhorn syndrome	*WHCR*	194190	4p16.3
Disorders of Blood Pressure			
Bartter syndrome	*SLC12A1*	600839	15q15-q21.1
Bartter syndrome with deafness	*BSND*	602522	1p31
Bartter syndrome, type 2	*KCNJ1*	600359	11q24
Bartter syndrome, type 3	*CLCNKB*	602023	1p36
Dysautonomia, famial	*DYS*	223900	9q31-q33
Hypertension, essential	*SAH*	145505	16p13.11
Hypertension, essential	*PNMT*	171190	17q21-q22

Hypertension, essential	*AGTR1*	106165	3q21-q25
Continued on following page			
Hypertension, essential	*GNB3*	139130	12p13
Hypertension, essential	*AGT*	106150	1q42-q43
Hypertension, low renin	*HSD11B2*	218030	16q22
Hypertension, salt resistant	*NPR3*	108962	5p14-p12
Hypertension, with brachydactyly	*HTNB*	112410	12p12.2-p11.2
Liddle syndrome	*SCNN1B*	600760	16p13-p12
Liddle syndrome	*SCNN1G*	600761	16p13-p12
Mineralocorticoid excess	*HSD11B2*	218030	16p22
Orthostatic hypotensive disorder	*OHDS*	143850	18q
Pheochromocytoma	*PCHC*	171300	1p
Polycystic kidney disease, adult 1	*PKD1*	601313	16p13.3-p13.12
Polycystic kidney disease, adult 2	*PKD2*	173910	4q21-q23
Preeclampsia, susceptibility to	*NOS3*	163729	7q36
Preeclampsia, susceptibility to	*AGT*	106150	1q42-q43
Preeclampsia/eclampsia	*PEE*	189800	4q25-q34
Pulmonary hypertension, familial	*PPH1*	178600	2q31-q32
Disorders of Coagulation and Thrombosis			
Antithrombin III deficiency	*AT3*	107300	1q23-q25
Antithrombin Pittsburgh defect	*PI*	107400	14q32.1
Coumarin resistance	*CYP2A6*	122720	19q13.2
Defective thromboxane A2 receptor	*TBXA2R*	188070	19p13.3
Dysfibrinogenemia, alpha type	*FGA*	134820	4q28
Dysfibrinogenemia, beta type	*FGB*	134830	4q28
Dysfibrinogenemia, chi type	*FGG*	134850	4q28
Dysprothrombinemia	*F2*	176930	11p11-q12
Factor H deficiency	*HF1*	134370	1q32
Factor V deficiency	*F5*	227400	1q23
Factor VII deficiency	*F7*	227500	13q34
Factor X deficiency	*F10*	227600	13q34
Factor XI deficiency	*F11*	264900	4q35
Factor XII deficiency	*F12*	234000	5q33-qter
Factor XIIIA deficiency	*F13A1*	134570	6p25-p24

Factor XIIIB deficiency	*F13B*	134580	1q31-q32.1
Glanzmann thrombasthenia, type A	*ITGA2B*	273800	17q21.32
Glanzmann thrombasthenia, type B	*ITGB3*	173470	17q21.32
GNAQ deficiency	*GNAQ*	600998	9q21
Hemophilia A	*F8C*	306700	Xq28
Hemophilia B	*F9*	306900	Xq27.1-q27.2
PAI1 deficiency	*PAI1*	173360	7q21.3-q22
Plasmin inhibitor deficiency	*PLI*	262850	17pter-p12
Plasminogen activator deficiency	*PLAT*	173370	8p12
Plasminogen deficiency	*PLG*	173350	6q26
Platelet alpha/delta storage pool deficiency	*SELP*	173610	1q23-q25
Platelet disorder, familial with myeloid malignancy	*FPDMM*	601399	21q22.1-q22.2
Platelet glycoprotein IV deficiency	*CD36*	173510	7q11.2
Platelet-activating factor acetylhydrolase deficiency	*PAFAH*	601690	6p21.2-p12
Protein C inhibitor deficiency	*PCI*	601841	14q32.1
Protein S deficiency	*PROS1*	176880	3p11.1-q11.2
Thrombocythemia, essential	*THPO*	600044	3q26.3-q27
Thrombocytopenia, neonatal	*ITGA2B*	273800	17q21.32
Thrombocytopenia, Paris-Trousseau	*TCPT*	188025	11q23
Thrombocytopenia, X-linked	*WAS*	301000	Xp11.23-p11.22
Thrombophilia	*HRG*	142640	3q27
Thrombophilia	*PAI1*	173360	7q21.3-q22
Thrombophilia	*HCF2*	142360	22q11
Thrombophilia	*THBD*	188040	20p11.2
Thrombophilia	*PLG*	173350	6q26
Thromboxane synthase deficiency	*TBXAS1*	274180	7q34
Vitamin K-dependent coagulation defect	*GGCX*	137167	2p12
von Willebrand disease	*VWF*	193400	12p13.3
Warfarin sensitivity	*CYP2C9*	601130	10q24
Disorders of Lipid Metabolism			
Abetalipoproteinemia	*MTP*	157147	4q22-q24
Abetalipoproteinemia	*APOB*	107730	2p24

ApoA-I and apoC-III deficiency	*APOA1*	107680	11q23
ApoA-II deficiency	*APOA2*	107670	1q21-q23
ApoB-100 ligand defect	*APOB*	107730	2p24
Cerebrotendinous xanthomatosis	*CYP27A1*	213700	2q33-qter
Combined familial hyperlipidemia	*LPL*	238600	8p22
HMG-CoA synthetase-2 deficiency	*HMGCS2*	600234	1p13-p12
Hypercholesterolemia, familial	*LDLR*	143890	19p13.2-p13.1
Hypercholesterolemia, familial 3	*FH3*	603776	1p34.1-p32
Hypertriglyceridemia	*APOC3*	107720	11q23
Hypertriglyceridemia	*APOA1*	107680	11q23
Hypoalphalipoproteinemia	*APOA1*	107680	11q23
Hypobetalipoproteinemia	*APOB*	107730	2p24
Sitosterolemia	*STSL*	210250	2p21
Tangier disease	*HDLDT1*	205400	9q31
Wolman disease	*LIPA*	278000	10q24-q25
Metabolic Disorders with Primary Effects			
Carnitine acetyltransferase deficiency	*CRAT*	600184	9q34.1
Carnitine deficiency, systemic	*SLC22A5*	603377	5q33.1
Metabolic Disorders with Secondary Effects			
Amyloidosis	*APOA1*	107680	11q23
Amyloidosis, cerebroarterial	*APP*	104760	21q21.3-q22.05
Cerebral amyloid angiopathy	*CST3*	105150	20p11.2
Cerebrovascular disease, occlusive	*AACT*	107280	14q32.1
Coronary spasm, susceptibility to	*NOS3*	163729	7q36
Fabry disease	*GLA*	301500	Xq22
Gaucher disease with calcification	*GBA*	230800	1q21
Glycogen storage disease II (Pompe)	*GAA*	232300	17q25.2-q25.3
Hemochromatosis	*HFE*	235200	6p21.3
Homocystinuria	*CBS*	236200	21q22.3
Homocystinuria, MTHFR deficiency	*MTHFR*	236250	1p36.3
Menkes syndrome	*ATP7A*	300011	Xq12-q13
Mucopolysaccharidosis I	*IDUA*	252800	4p16.3
Mucopolysaccharidosis II	*IDS*	309900	Xq28
Mucopolysaccharidosis IVA	*GALNS*	253000	16q24.3

Mucopolysaccharidosis IVB	*GLB1*	230500	3p21.33
Mucopolysaccharidosis VI	*ARSB*	253200	5q11-q13
Mulibrey nanism	*MUL*	253250	17q22-q23
Pseudoxanthoma elasticum	*PXE*	264800	16p13.1
Neoplastic Disorders			
Carney (NAME) complex	*CNC*	160980	2p16
Paraganglioma, familial nonchromaffin 1	*PGL1*	16800	12q23
Paraganglioma, familial nonchromaffin 2	*PGL2*	601650	11q13.1
von Hippel-Lindau syndrome	*VHL*	193300	3p26-p25
Primary Disorders of Rhythm and Conduction			
Heart block, progressive familial-1	*HB1*	113900	19q13.2-q13.3
Jervell and Lange-Nielsen syndrome	*KCNQ1*	192500	11p15.5
Jervell and Lange-Nielsen syndrome	*KCNE1*	176261	21q22.1-q22.2
Long QT syndrome-1	*KCNQ1*	192500	11p15.5
Long QT syndrome-2	*KCNH2*	152427	7q35-q36
Long QT syndrome-3 and ventricular fibrillation, idiopathic	*SCN5A*	600163	3p24-p21
Long QT syndrome-4	*LQT4*	600919	4q25-q27
Long QT syndrome-5	*KCNE2*	603796	21q22.1
Ventricular tachycardia, idiopathic	*GNAI2*	139360	3p21
Primary Disorders of Vasculature			
Aneurysm, familial and Ehlers-Danlos, Vascular	*type*	COL3A1	1201802q31
Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy	*NOTCH3*	600276	19p13.2-p13.1
Cerebral cavernous malformations-1	*CCM1*	116860	7q11.2-q21
Cerebral cavernous malformations-2	*CCM2*	603284	7p15-p13
Cerebral cavernous malformations-3	*CCM3*	603285	3q25.2-q27
Fibromuscular dysplasia of arteries	*COL3A1*	120180	2q31
Hemangioma, capillary infantile	*HC1*	602089	5q31-q33
Hemiplegic migraine, familial	*CACNA1A*	601011	19p13
Hemiplegic migraine, familial 2	*MHP2*	602481	1q21-q23
Hemiplegic migraine, familial, susceptibility to	*MFTS*	300125	Xq
Hereditary hemorrhagic telangiectasia-1	*ENG*	131195	9q34.1

Hereditary hemorrhagic telangiectasia-2	*ACVRL1*	601284	12q11-q14
Lymphedema, hereditary	*FLT4*	136352	5q35.3
Continued on following page			
Marfan syndrome	*FBN1*	134797	15q21.1
Moyamoya disease	*MYMY*	252350	3p26-p24.2
Supravalvular aortic stenosis	*ELN*	130160	7q11.2
Venous malformations, multiple	*TEK*	600221	9p21

Disorders may have been mapped by the phenotype, by the gene, or both; (?) after a disorder indicates the mapping data are still in limbo. The annotations p and q refer to band patterns in chromosomes detected cytochemically that mark specific regions.

AV=atrioventricular; FDC=familial dilated cardiomyopathy; FHC=familial hypertrophic cardiomyopathy; LV=left ventricle; RV=right ventricle.

*Refers to the entry for the locus in http://www.ncbi.nlm.nih.gov/htbin-post/Omim.

when the mutant allele is common in the population (e.g., the most prevalent mutation for cystic fibrosis and the mutation for sickle cell anemia). Biochemical and molecular genetic assessment of mutant alleles has shown that the majority of recessive phenotypes are due to two distinct mutant alleles, a situation termed a *genetic compound,* indicative of the widespread heterogeneity in mutations at each locus. Males have but one X chromosome, and each locus is therefore *hemizygous;* a mutant locus is always expressed in the phenotype of a male. Dominance and recessiveness for X-linked traits refer to expression in heterozygous and homozygous women, respectively.

Whether a disorder is called dominant or recessive depends on how carefully the phenotype is assessed and how it is defined. For example, familial hypercholesterolemia is a relatively common hereditary disorder due to defects in the receptor for low-density lipoprotein (see LDL, see also Chap. 31) . The vast majority of patients are heterozygous for a mutant allele at the *LDLR* locus on chromosome 19, and the disease is inherited as a mendelian dominant trait. However, if a man and a woman, each heterozygous for an *LDLR* mutation, produce a child, that child has a 25

percent risk of inheriting both of the mutant alleles and thereby is either homozygous or a genetic compound for *LDLR.* Such a child has a much more severe form of familial hypercholesterolemia that is inherited as a mendelian recessive trait. Similarly, homozygosity for the sickle hemoglobin mutation at the beta-globin locus on chromosome 11 produces the familiar autosomal recessive disease sickle cell anemia. However, heterozygosity for the same mutation rarely produces disease but produces sickling of erythrocytes if they are examined under conditions of low oxygen tension; this phenotype is transmitted as a dominant trait.

AUTOSOMAL RECESSIVE INHERITANCE.

Nearly all deficiencies of enzymatic activity--the classic inborn errors of metabolism first defined by Archibald Garrod in 1903--cause recessive phenotypes. Most homeostatic systems, which include all metabolic pathways, have sufficient flexibility to function well if one of the enzymatic steps functions at half-normal efficiency, as would occur in heterozygosity for a mutant allele at a structural gene for an enzyme. However, homeostasis cannot cope if two mutant alleles cause a reduction in enzymatic activity to a few percent or less of normal activity. The characteristics of autosomal recessive inheritance, features common to such phenotypes, and a typical pedigree are shown in Figure 56-2 .

AUTOSOMAL DOMINANT INHERITANCE.

Only a few enzyme deficiencies, but many disorders of development and structure, are inherited as dominant traits. The reasons for this are several. One possibility is that developmental homeostasis has a limited repertoire of responses to stress, and when a structural or regulatory macromolecule is reduced to only one-half normal amount, the system cannot cope. Another possibility, illustrated by mutations in procollagen molecules, pertains to gene products that must interact before becoming functional; an aberrant protein combined with a normal one would be a defective multimer, and the effect of being heterozygous for a mutation would be magnified--a *dominant-negative effect*[2] [9] The characteristics of autosomal dominant inheritance, features common to many such phenotypes, and a typical pedigree are shown in Figure 56-3 .

Most human dominant traits are *incomplete,* in that the heterozygote is less severely affected than the homozygote. Defects of *LDLR* are illustrative, in which the heterozygote has classic type IIa hyperlipidemia whereas the homozygote has a quantitatively worse form of the same disease. It may well be that homozygosity for most alleles that cause dominant disorders is incompatible with life.

X-LINKED INHERITANCE.

The characteristics of X-linked inheritance, features common to such phenotypes, and a typical pedigree are shown in Figure 56-4 . Whereas virtually all diseases due to mutations on the X chromosome are more severe in hemizygous males, women heterozygous for the same mutations often show some manifestations, albeit less severe and of later age of onset. For example, most women carriers of

alpha-galactosidase A deficiency (Fabry disease) eventually develop cerebrovascular disease or renal failure due to accumulation of sphingolipid.

MITOCHONDRIAL INHERITANCE.

Energy generation through oxidative phosphorylation occurs in mitochondria in the cytoplasm of most cell types. Numerous mitochondria, each containing a single chromosome, exist in each cell. Some of the enzymes of oxidative phosphorylation are encoded by genes on the nuclear chromosomes and the proteins transported into the mitochondrion; the rest of the proteins are encoded by genes on the mitochondrial chromosome. Thus, genetic defects of oxidative phosphorylation can be due to mutations of genes on the autosomes or the X chromosome, and the resulting diseases behave as mendelian recessive traits, or mutations of genes on the mitochondrial chromosome, in which case the resulting diseases do not behave as mendelian traits.[10] [11] The differences are explicable by the events of conception. The spermatocyte contributes virtually no mitochondria to the zygote, and the entire complement of mitochondria that will ever be present in the fetus is derived from the mitochondria already present in the cytoplasm of the oocyte. Thus, phenotypes due to mutations of the mitochondrial chromosome show *maternal inheritance,* the characteristics of which are shown in Figure 56-5 .

Principles of Clinical Genetics

PLEIOTROPY.

Most mutant alleles have effects on more than one organ system, and a mendelian phenotype frequently displays numerous, often diverse manifestations. For example, Marfan syndrome (see p. 2000) is defined by abnormalities in the eye, skeleton, skin, heart, and aorta, and until the recognition of a defect in extracellular microfibrils, the findings could not be linked either etiologically or pathogenetically.[12]

VARIABILITY.

The effects of the same mutant allele on phenotype can be different among people heterozygous (for dominant traits), homozygous (for autosomal recessive traits), or hemizygous (for X-linked traits) for the allele. Variability can be described in terms of the frequency of a particular pleiotropic manifestation among patients with the mutation; the severity of the phenotype; and the age of onset of manifestations. If a person has the mutant allele(s) but shows no phenotypic effect, the trait is called *nonpenetrant.* To an important degree, whether or not a clinical phenotype is called nonpenetrant depends on the sensitivity of the techniques used for detection. For example, two decades ago, based on bedside examination, cardiovascular abnormalities were thought to affect about half of people with Marfan syndrome; echocardiography now reveals aortic dilatation in more than 90 percent. The term *incomplete penetrance* should not be used with reference to individuals but to mean a prevalence of the phenotype is less than 100 percent of people known to carry the mutation(s). The Holt-Oram syndrome (see Chap. 43) is an instructive example. In this autosomal dominant syndrome of reduction

anomalies of the upper limb and congenital heart defect, patients in the same family can have only arm anomalies, only a heart defect, or both. Moreover, the severity of the reduction defect varies widely, from a proximally

Figure 56-1 Chromosomal location of human genes associated with some disorders of the cardiovascular system. These genes affect the structure, function, and metabolism of the heart and blood vessels and hemostasis and have been identified by the deleterious effects of mutations. Numerous additional genes that encode structural proteins important to the cardiovascular system have been identified but not yet associated with disease. In the figure, brackets next to the chromosome show the regional localization of the gene causing a particular disorder. Brackets next to two or more disorders indicate that all of the genes causing the disorders map to the same region. Disorders surrounded by boxes are caused by different mutations at the same gene.

placed thumb to near total absence of the arm. The cardiac feature is incompletely penetrant because only about 50 percent of patients have it, but in any individual with the Holt-Oram allele, the heart is either structurally normal or not.

Numerous genetic and environmental factors can affect expression of a gene (Table 56-3) , and it is often impossible to determine which of these factors are most important in a specific patient or particular disease. However, the pervasiveness of variable expression emphasizes that phenotypes determined by single genes are to some extent really "multifactorial."

GENETIC HETEROGENEITY.

Similar or even identical phenotypes can be due to fundamentally distinct mutations, a phenomenon termed *genetic heterogeneity.* For example, Marfan syndrome and homocystinuria were long thought to be the same disorder, despite what now appear in retrospect to be obvious differences in inheritance pattern and intelligence.[13] As in the case of these two disorders, the causes may lie in two different genes whose products are

Figure 56-2 *Characteristics of autosomal recessive inheritance:* A single generation is affected.
Both sexes are affected equally frequently.
Each parent is heterozygous (a carrier).
Each offspring of two carriers has a 25 percent chance of being affected, a 50 percent chance of being a carrier, and a 25 percent chance of inheriting neither mutant allele.
Two-thirds of clinically normal offspring are carriers.
The rarer the phenotype, the greater is the likelihood of consanguinity.
Characteristics of autosomal recessive phenotypes:
Often due to enzyme deficiencies.
Often more severe than dominant disorders.
Often early age of onset.

functionally distinct. Osteogenesis imperfecta exemplifies a disorder in which mutations in two genes, alpha1(I) and alpha2(I) procollagen, can each produce the same phenotype because the two proteins interact to form type I collagen.[14] Genetic heterogeneity is pervasive at the intragenic level of analysis; except for sickle cell anemia, hemochromatosis, and achondroplasia, virtually all single-gene disorders are due to a wide variety of mutations at a given locus.

Nonpathological Variation in the Cardiovascular System

CARDIAC STRUCTURE AND PHYSIOLOGY.

All aspects of the ontogeny of the cardiovascular system are dictated by the genome. If, as seems most credible, few genes have a large effect and many have small contributions, any specific aspect of "normal" cardiovascular phenotype--size, shape, function--exhibits multifactorial inheritance. In other words, to the extent that any given phenotype can be quantified,

Figure 56-3 *Characteristics of autosomal dominant inheritance:* Several generations are affected.
Both sexes are affected equally frequently.
In familial cases, only one parent need be affected.
Male-to-male transmission occurs.
Offspring of an affected parent has a 50 percent chance of being affected.
The frequency of sporadic cases is higher, the more severe the condition.
Paternal age has an effect in sporadic cases.
Characteristics of autosomal dominant phenotypes:
Often associated with malformations.
Often pleiotropic.
Usually variable.
Often age dependent.

Figure 56-4 *Characteristics of X-linked inheritance:* No male-to-male transmission.
All daughters of affected males are carriers.
Sons of a carrier mother have a 50 percent chance of being affected; daughters have a 50 percent chance of being carriers.
Some mothers of an affected male are not heterozygotes in all cells of their body, but they may have more affected sons if germinal mosaicism is present.

Characteristics of X-linked phenotypes:
More severe in males.
Heterozygous females may be unaffected.
Variable, especially in females.

Figure 56-5 *Characteristics of disorders due to a mutation of the mitochondrial chromosome:* Both sexes are equally frequently and severely affected.
Transmission is only through women; offspring of affected men are unaffected.
All offspring of an affected woman may be affected.
Variability of expression can be extreme in a family, including apparent nonpenetrance.
Phenotypes may be age dependent.

TABLE 56-3 -- CAUSES OF VARIABILITY OF GENE EXPRESSION

Genetic background
Age dependence
Sex influence
Sex limitation
Modifying loci: hypostasis and epistasis
Gene alteration
Somatic mutation
Somatic amplification
Transpositions and rearrangements
Mutations
Physiological rearrangements
Variation in X inactivation*
Endogenous complementation*
Maternal factors
Effects of mitochondrial genome
Intrauterine environment
Imprinting
Exogenous and ecological factors
Ecology--temperature, diet
Teratogens
Medical intervention
Chance

*Pertains to female heterozygotes for X-linked disorders.

it shows a normal distribution within the population, and near-relatives are more similar to each other than they are to distant relatives and the rest of the population. The twin method should demonstrate a higher concordance of the trait in monozygotic than dizygotic twins. However, surprisingly few phenotypes have been examined.

Preliminary data on left ventricular dimensions measured echocardiographically showed higher correlations between parent and child than between matched controls, suggesting a genetic contribution[15] ; however, as in many such studies, the effect of shared environment was not estimated. In an attempt to minimize environmental contributions, left ventricular sizes of twins who were not exercise trained were compared; the mean intrapair differences in echocardiographic dimensions were less in the monozygotic than in the dizygotic twins and nontwin sibs.[16] The caliber and branch geometry of coronary arteries show familial resemblance, and both parameters are much more similar in monozygotic twins than in other relatives.[17] Further support for the importance of genetic factors in normal development derives from studies that demonstrate ethnic differences in structure. For example, the thickness of the intima and the media of coronary arteries of children who died of noncardiovascular causes varied significantly with the ethnicity of the child.[18]

Measures of cardiac electrophysiology show familial resemblance. Studies of both nuclear families[19] [19A] and twins[20] [21] suggest a genetic contribution to resting heart rate, conduction times, and repolarization time. Genetic control of normal cardiovascular function has been especially difficult to study because of the multitude of environmental (training, diet), stochastic (age), and clinical (subtle, unrecognized pathology) issues that confound comparisons of relatives and controls. Thus far, no strong genetic contribution to an individual's response to physical conditioning has emerged.[16]

VASCULAR SYSTEM.

All members of certain inbred animal strains show little variation in arterial anatomy, especially branch angles, and considerable variation with other strains of the same species. Except for the studies of coronary arterial anatomy already noted,[17] similar studies of humans have not been reported.

One intriguing question of clinical importance is whether certain individuals are predisposed to arterial spasm and whether this susceptibility has a genetic basis. An examination of hereditary pathological and polymorphic variation in factors elaborated by endothelial cells, platelets, and leukocytes to maintain patency of blood vessels, such as prostacyclin, endothelium-derived relaxing factor (nitric oxide), or endothelin-1, may prove enlightening.[22] [23] [24] [25] Similarly, is there genetic contribution to arterial stiffness

or its variation with age and conditioning?

CARDIOVASCULAR DISORDERS ASSOCIATED WITH CHROMOSOME ABERRATIONS

Chromosome aberrations occur in 0.5 percent of the population at birth and are common findings in tumors.[26] Visible alterations of the amount of chromosomal material cause primarily structural defects of the cardiovascular system that are evident in the newborn. The frequency of chromosome aberrations among live-born children with congenital heart defects has been found to range from 5 to 13 percent.[27] [28] Upward of 40 percent of all fetuses with heart defects detected by ultrasonography at 18 to 20 weeks' gestation have chromosome aberrations; most are spontaneously aborted. Most forms of aneuploidy and most duplications and deletions of more than a chromosome band are associated with defects of the cardiovascular system[29] (see Tables 56-1 and 56-3) . Exceptions are 47,XXX, 47,XYY, and 47,XXY (Klinefelter syndrome), in which the incidence of congenital heart disease is probably not elevated over the population baseline.

ANEUPLOIDY.

How the abnormal phenotypes caused by autosomal aneuploidy develop remains controversial. One view holds that disturbance of the dosage of the genes present on the specific aneuploid chromosome segments is the central issue. The other view is that any aneuploid state disturbs developmental homeostasis in a nonspecific manner. The former theory predicts some distinctiveness of phenotype among the trisomy syndromes that occur in live-born children, whereas the latter predicts shared manifestations. At a coarse level, the clinical pictures are similar, with grave problems of the craniofacies, central nervous system, genitalia, distal limbs, and heart usually present. But when a more refined examination of the phenotypes is obtained, considerable distinctiveness emerges.

The three most common autosomal trisomies--13, 18, and 21--can be readily distinguished at the bedside. In all three, membranous ventricular and atrial septal defects are common. However, the detailed accounting of cardiovascular lesions among large numbers of patients with these trisomies reveals important differences that suggest aneuploidy exerts more than a global effect on development. In this and most other analyses of congenital heart defects, the system of classification based on the presumed pathogenetic mechanisms proves most instructive and is a useful approach to comparing different causative factors (Table 56-4) .

About one-quarter of the defects in trisomies 13 and 18 are due to cell migration abnormalities, and two-thirds are flow lesions; when combined, these two mechanisms account for considerably more of these classes of defects than in the general population with congenital heart disease. By contrast, in trisomy 21, left-sided flow lesions are much less common, whereas abnormal closure of endocardial cushions is strikingly frequent. Indeed, in contrast to endocardial cushion defects without a chromosome 21 anomaly, left-sided flow lesions are rarely seen in patients with Down syndrome and endocardial cushion defects.[27] [30] Furthermore, the high incidence of endocardial

cushion defects and low incidence of conotruncal and distal aortic anomalies have suggested a distinct pathogenetic mechanism in trisomy 21, potentially involving cell adhesiveness and the extracellular matrix.

TRISOMY 21--DOWN SYNDROME.

This most common phenotype due to a human chromosome aberration occurs about once in every 600 births.[31] Most patients have trisomy 21, and the risk of this aberration is exponentially related to maternal age; the risk is lowest for young women and rises steeply after age 35, reaching 4 percent for women older than 45. A small minority (3 percent) of Down syndrome results from an extra copy of all or part of the long arm of chromosome 21 translocated to another chromosome. This situation is relatively more common in mothers younger than 30 years. The phenotypes of the two forms of Down syndrome do not differ. The phenotype tends to be less severe if the trisomy is mosaic (3 percent of Down syndrome) as a result of a mitotic nondisjunctional error in the embryo.

The most common causes of morbidity and mortality in patients with Down syndrome are congenital heart defects (present in 40 to 50 percent of cases),[32] hematological malignant disease, and duodenal atresia. If patients either escape or survive these problems, survival into the fifth decade and beyond is likely but is complicated by progressive dementia of the Alzheimer type. Premature aging may also affect the vasculature, although definitive studies are lacking.

The most characteristic cardiac anomaly in Down syndrome is a defect of closure of the endocardial cushions (see Chap. 43) . Complicating the clinical problems in such patients and those with simple septal defects is a seeming predisposition to pulmonary hypertension in the presence of elevated pulmonary blood flow.[33] About one-third of congenital heart defects are complex, and affected individuals tend not surprisingly to be the most ill patients. Mitral valve prolapse (MVP) is found with a frequency exceeding that in age- and gender-matched controls.[34] The aortic and pulmonary valve cusps seem predisposed to fenestrations in adulthood.

Through the study of individuals trisomic for only a portion of the long arm of chromosome 21, the region crucial to the development of heart defects has been narrowed to 1.5 to 2.0 megabases (mb) of DNA in bands 21q22.2-q22.3 out of about 35 mb DNA on the entire long arm of chromosome 21.[35]

Medical treatment of patients with Down syndrome has undergone evolution to more aggressive measures in recent years. Objections and hesitations on medical, societal, and ethical grounds to operative repair of heart defects in Down syndrome have been mollified substantially.[31] [36] More follow-up data are becoming available, and early and late postoperative survival in patients with Down syndrome appears to be comparable to that in other patients with similar defects.[36]

TRISOMY 18.

Edwards syndrome is the second most common autosomal trisomy. Most cases are due to meiotic disjunction, and there is a strong relationship to maternal age. Routine prenatal diagnostic testing of women older than 34 years would detect all aneuploid fetuses in them, but this would represent only one-third of all autosomal

TABLE 56-4 -- CARDIOVASCULAR MANIFESTATIONS ASSOCIATED WITH CHROMOSOME ABERRATIONS

CHROMOSOME ABERRATION	EPONYM	CARDIOVASCULAR MANIFESTATIONS
Triploidy		
69,XXX (or XXY or XYY)		>50% have CHD: ASD and VSD
Aneuploidy		
+13	Patau	~80% have CHD; 75% of CHD is complex: PDA, VSD, ASD, PS, AS, dextrocardia, CoA
+18	Edwards	~90% have CHD: most CHD is complex: VSD, PDA, ASD, bicuspid PV and AV, CoA
+21	Down	~40% have CHD: ECD, TOF: MVP in ~20%; AR
+8 mosaicism		~25% have CHD, most of little clinical consequence: VSD, PDA, CoA, PS
+9 mosaicism		~70% have CHD, usually complex: VSD, PDA, PLSVC
45,X	Turner	~10% have clinically important CHD: 50% of these have CoA; mild CoA is likely much more common; also AS, ARD, VSD, ASD, dextrocardia
47,XXX		CHD not increased
47,XXY	Klinefelter	CHD possibly slightly increased; ? mild conduction changes; venous thromboembolic disease
47,XYY		CHD not increased; ? mild conduction changes
Deletions		
4p-	Wolf-Hirschhorn	~50% have CHD, usually complex: VSD, ASD, PDA, PS

5p-	Cri du chat	~20% have CHD, usually single: VSD, PDA, ASD, PS
7q-		~20% have CHD, various, often complex
13q-		CHD common, often severe, but depend on region deleted
18p-		CHD uncommon
18q-		~25% have CHD, usually single, of little consequence: VSD, PDA, ASD, PS
ring 18		~20% have CHD: CoA, PA hypoplasia, HLH, PLSVC
Duplications		
4p trisomy		~10% have CHD, usually single: no defect predominates
9p trisomy		<10% have CHD: VSD, ASD, AS, PS
10 p trisomy		~30% have CHD, usually single: no defect predominates
10q24-qter trisomy		~50% have CHD, usually complex: ECD, VSD, TOF
22pter-q11 trisomy or tetrasomy	Cat eye	~50% have CHD, usually complex: TAPVR, VSD, TOF
Other Aberrations		
Marker Xq27.3	Fragile X syndrome	~50% have aortic root dilatation, MVP, or both

CHD=congenital heart defect(s); ASD=atrial septal defect; VSD=ventricular septal defect; PDA=patent ductus arteriosus; PS=valvular pulmonic stenosis; AS=aortic stenosis; CoA=coarctation of aorta; PV=pulmonic valve; AV=aortic valve; ECD=endocardial cushion defect; TOF=tetralogy of Fallot; MVP=mitral valve prolapse; AR=aortic regurgitation; PLSVC=persistence of left superior vena cava; ARD=aortic root dilatation; PA=pulmonary artery; HLH=hypoplastic left heart; TAPVR=total anomalous pulmonary venous return.

trisomies; in the United States, less than one-half of all women of this advanced age undergo definitive testing. Prenatal detection of trisomies followed by termination of pregnancy is currently having a small but measurable impact on decreasing the incidence of *Down, Edwards,* and *Patau* syndromes.

Although the severity of the phenotype rarely enables survival beyond a few months, 10 percent of patients live to 1 year, and a few survive to adulthood, perhaps because of undetected mosaicism for a chromosomally normal cell line. However, central nervous system function is far less than that in Down syndrome and leads to complex medical management and supportive care for long-term survivors.[37]

Cardiovascular defects occur in at least 90 percent of cases and contribute to death. Complex lesions, usually involving septal defects, dysplastic valves that are rarely hemodynamically important, patent ductus arteriosus (PDA), and persistence of the left superior vena cava are common.[38] [39] Right ventricular enlargement is common and may indicate not only shunting from left to right but pulmonary hypertension due to anomalies of the pulmonary vasculature.[38] As in Down syndrome, transposition of the great arteries is virtually unknown in trisomy 18.[39] Rarely should invasive diagnostic procedures or aggressive supportive measures be undertaken in Edwards syndrome.

TRISOMY 13.

Patau syndrome occurs in about 0.01 percent of live births and in progressively higher frequencies in stillbirths and spontaneous abortions. The external phenotype is usually severe but occasionally not as characteristic as other trisomies; survival beyond a few weeks is rare, and the causes of death involve several organ systems, especially the heart. Cardiovascular anomalies are a bit less frequent than in trisomy 18 and have a slightly different spectrum.[31] [38] Septal defects are the most common isolated lesions; dextrocardia and bicuspid semilunar valves occur in association with other anomalies.

Patients who survive beyond 1 month often are mosaic for a chromosomally normal cell line; thus, prognosis is fraught with uncertainty until detailed analysis is completed. Whether invasive cardiological studies are performed or aggressive management is undertaken can be determined by the severity of involvement of other organ systems, especially the brain, pending cytogenetic investigation.

TURNER SYNDROME.

About one in every 2500 females lacks an X chromosome and has a 45,X karyotype, which is by far the most common cause of Turner syndrome. The frequency of a nonmosaic 45,X karyotype is much higher in spontaneous abortuses than in live-borns, and probably less than 2 percent of such conceptuses come to term. The clinical phenotype is variable and often mild; the diagnosis is often not suspected until a child's short stature is evaluated or a woman complains of amenorrhea. Many cases are mosaic for cell lines with 46,XX or 46,XY constitutions. Various structural aberrations involving the X chromosome can cause partial or complete Turner's syndrome.

Among patients with the 45,X karyotype, reported frequencies of congenital cardiovascular defects vary from 20 to 50 percent, depending on how patients were ascertained.[40] Fifty to 70 percent of those with cardiovascular defects have clinically important aortic coarctation, usually of the postductal form.[41] As noninvasive imaging studies of asymptomatic patients became routine, the frequency of coarctation may increase. Various other cardiac malformations may occur, either singly or combined with coarctation. However, there is strong support for left-sided flow abnormalities as a major pathogenetic mechanism. Bicuspid aortic valve and dilatation of the ascending aorta (with a risk of dissection and histopathology showing elastic fiber disruption) occur even in the absence of coarctation,[42] and hypoplastic left heart has been reported.[43] Partial

anomalous pulmonary venous drainage without an atrial septal defect is fairly common and should be suspected when right ventricular overload is detected on echocardiography.[44]

Postmortem examination of midtrimester abortuses with 45,X showed a higher incidence of left-sided flow lesions than found at

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birth, suggesting an association between the pathogenesis of the cardiovascular anomalies and the uniform presence of lymphatic obstruction at the base of the heart.[41]

Blood pressure elevation is common, even without coarctation or after its repair; a high frequency of renal anomalies is one likely cause but not the sole explanation for the prevalence of hypertension.

In about two-thirds of cases, the retained X chromosome derives from the oocyte (maternal X). Because entire chromosomes or regions of a chromosome may be differentially regulated (imprinted)[45] by passage through oogenesis versus spermatogenesis, could some of the variability in phenotype among patients with Turner syndrome be due to the origin of the retained X or the origin of the lost X? In a study of 63 patients, 10 had severe cardiovascular features, and 9 of them had retained the maternal X.[46] This is an idea worthy of further investigation. Women with mosaic karyotypes are less likely to have cardiovascular defects. Some studies also suggest a "critical region" of the X chromosome, which, when deleted, results in most of the features of Turner's syndrome.[47]

CONGENITAL HEART DISEASE (See Chaps. 43 and 44)

In the past few decades, the reported incidence of structural heart defects in newborns has increased from 5 to 7 per 1000 live births, probably as the result of increased diagnostic sensitivity (especially cross-sectional and Doppler echocardiography and magnetic resonance imaging).[48] [49] [50] [51] [52] Supporting this explanation is the lack of change over the same period in the incidence of critical defects diagnosed neonatally at 3.1 to 3.5 per 1000.[48] [53] This enhanced resolving power of noninvasive methods should prove particularly useful in the study of familial structural defects, because apparently unaffected relatives can be evaluated for subclinical evidence of anomalies. Few investigations to date have capitalized on this approach.[54] [55]

As is evident from the previous section, gross aberrations of chromosomes produce an extensive and varied array of structural heart disease, an observation as true for spontaneous abortuses as for live-born children.[56] Unfortunately, cytogenetic aberrations have provided few clues about etiology and pathogenesis of congenital malformations.[57] [58] Better understanding comes from investigating the other two mechanisms by which genes cause congenital heart defects--multifactorial processes

and mutations of single genes. In addition to the mendelian syndromes discussed later, evidence for the involvement of genes of large effect derives from studies of incidence of congenital heart disease in populations with a high rate of inbreeding. The increased occurrence of defects in offspring of consanguineous matings suggests that mutations in one or more genes, when homozygous, strongly predispose to abnormal cardiovascular development.[59]

MULTIFACTORIAL PROCESSES.

The empirical risks of recurrence of congenital heart defects have increased in recent years,[60] [61] in keeping with the overall higher incidence noted earlier. However, this conclusion has been criticized because the studies focused on the offspring of women probands, in whom the recurrence risk appears higher than in men with congenital heart defects.[62] In addition to this unexplained maternal influence, other factors may be at work. For example, improved detection of subtle lesions, more faithful reporting of patients, and the assiduousness of epidemiologists may have shown a systematic variation. More patients with cardiovascular problems now survive[61] [62] [63] [64] to bear children because of improved medical and surgical care; their offspring might be at increased risk because of the severity of the parents' problems, but some evidence refutes this idea.[65]

The familial aggregation of congenital heart defects supports many of the predictions of the threshold liability model of multifactorial inheritance.[53] [66] [67] In most studies, whether focused on populations or families, defects were classified by their pathology; for example, all ventricular septal defects were considered as one group. There has been bias in reporting families in which one type of defect aggregates, which has led to many reports of "familial atrial septal defect," "familial cardiomyopathy," and so on, without regard to the fact that not all septal defects or cardiopathies have the same structure on careful scrutiny, let alone the same cause.[68] [69]

A major advance has been the movement to examine familial aggregation of defects based on presumed pathogenesis.[52] [70] The scheme developed by Clark[71] and since modified and expanded[72] (Table 56-5) , has become widely used. Under this approach, some anatomically distinct lesions are related by common pathogenesis; if the pathogenetic mechanism has substantial genetic control, then the occurrence of distinct defects in the same family would still be consistent with a genetic model. Alternatively, defects unrelated by pathogenesis would require a different interpretation. This model rationalizes examination of apparently unaffected relatives, which increases the chances of detecting subtle manifestations of defective development of cardiovascular structures.

ERRORS IN MESENCHYMAL TISSUE MIGRATION.

Included in this category are a wide range of anomalies of the outflow tract, some due to failure of fusion and others due to failure of septation. Relatives of probands with interruption of the aortic arch type B or truncus arteriosus, both uncommon conotruncal malformations, had 2.5 percent and 6.6 percent incidences, respectively, of congenital heart defects.[73] Both recurrence rates were higher than expected. The frequency of

congenital malformations was much lower in relatives of patients with other forms of interrupted aortic arch. Moreover, relatives of probands with truncus arteriosus and other defects had a recurrence rate of 13 percent, the majority in the spectrum of conotruncal lesions. Here is an instance in which refined empirical risk data should improve the accuracy of genetic counseling.

Categorizing anatomical defects by presumed pathogenesis emphasizes that all ventricular septal defects are not alike. However, even within an embryologically circumscribed category, the situation is complex. Many perimembranous ventricular septal defects can be considered errors in mesenchymal tissue migration. Evidence exists for the effects of major genes (e.g., as yet unidentified ones in the 22q11 region[74] and *Jagged1,* the gene that when mutated also causes Alagille syndrome[75] and for multifactorial effects.[76]

Conotruncal Development.

Considerable progress has been made during the past few years in identifying a region of chromosome 22 that has a major role in development of the conotruncus, the branchial arches, and the face. Interest was first stimulated by detection of small deletions involving 22q11 in patients with *DiGeorge sequence.*[77] This condition includes developmental anomalies of the fourth branchial arch and derivatives of the third and fourth pharyngeal pouches. Hypoplasia of the thymus and parathyroids causes immune deficiency and hypocalcemia. The cardiac defects range from tetralogy of Fallot to ventricular septal defect, truncus arteriosus, interrupted aorta type B, and right aortic arch and are often lethal. Deletion of 22q11 accounts for about 90 percent of instances of DiGeorge sequence.

TABLE 56-5 -- CLASSIFICATION OF CONGENITAL HEART DEFECTS BASED ON PATHOGENETIC MECHANISMS

PATHOGENETIC MECHANISM	EXAMPLES OF DEFECTS
Embryonic blood flow defects	
Left-sided lesions	HLH; bicuspid aortic valve; IAA type A; CoA; PDA
Right-sided lesions	Secundum ASD; PS
Mesenchymal tissue migration defects	TOF; D -TGA
Extracellular matrix defects	ECD
Abnormal cellular death	Ebstein anomaly; muscular VSD
Defects of looping and situs	l -TGA
Abnormalities of targeted growth	TAPVR

HLH=hypoplastic left heart; IAA=interrupted aortic arch; CoA=coarctation of aorta; PDA=patent ductus arteriosus; ASD=atrial septal defect; PS=valvular pulmonic stenosis; TOF=tetralogy of Fallot; TGA=transposition of great arteries; ECD=endocardial cushion defect; VSD=ventricular septal defect; TAPVR=total anomalous pulmonary venous return.

Subsequently, patients with *velocardiofacial syndrome* (VCF, also called Shprintzen syndrome) and what has been called in Japan the *conotruncal anomaly face syndrome* were found to have deletions in the same region, albeit generally smaller ones than in DiGeorge syndrome.[78] Because the deletion is often too small to be detected by routine cytogenetics, fluorescent in situ hybridization (FISH) with a DNA probe for the region is the assay of choice. The VCF syndrome is unlike DiGeorge syndrome and includes an abnormal but characteristic facies, cleft palate, pharyngeal insufficiency, and conotruncal cardiac defects.

This same region of chromosome 22 has been examined in patients with familial occurrence of various congenital cardiac defects and in patients with nonfamilial occurrence, nonsyndromic conotruncal defects, and an important fraction of patients in both categories have submicroscopic deletions of 22q11.[74] [79] Thus, a gene or genes in this region account for much of the recurrence risk of defects due to mesenchymal tissue migration abnormalities. Further, accurate counseling about recurrence risks for this broad range of defects necessitates FISH or molecular analysis for the presence of a deletion in the proband and, if present, in both parents. Deletion of 22q11 occurs in about 13 per 100,000 live births and is, after trisomy 21, the second most common genetic cause of congenital heart disease.[80]

Investigation of a strain of Keeshond dogs prone to conotruncal defects has shown that a single gene can be responsible for pathogenetically related defects of widely varying severity.[81]

FLOW DEFECTS.

Left-sided flow lesions comprise a spectrum that includes hypoplastic left heart, congenital aortic stenosis, bicuspid aortic valve, interrupted aortic arch type A, and aortic coarctation. Various components of this spectrum can be present in the same patient. Data from the Baltimore-Washington Infant Study,[52] a population-based case-control study of congenital cardiovascular malformations, were used to show that in first-degree relatives of probands with isolated hypoplastic left heart, the incidence of bicuspid aortic valve was 12 percent; most of the cases were asymptomatic and unrecognized before they were detected by echocardiography as part of this investigation.[59] In an exceptional family, four instances of aortic coarctation occurred in four generations.[82]

The association of coarctation of the aorta, bicuspid aortic valve, and dilatation of the

ascending aorta, which may occur as part of *Turner syndrome,* is well known in the general population.[83] Several intriguing questions about the genetics and pathogenesis of this association need to be addressed. To what extent is the ascending aorta intrinsically abnormal and hence predisposed to dilate, and to what extent is the dilatation simply a result of abnormal turbulence created by a bicuspid aortic valve? The fact that some patients with this association also have subtle evidence of a systemic connective tissue abnormality, reminiscent of Marfan syndrome, supports the former hypothesis. It will be of interest to extend the study of left-sided flow lesions to include probands with coarctation or congenital aortic stenosis and to evaluate close relatives with techniques capable of detecting the entire range of flow defects.

EXTRACELLULAR MATRIX ABNORMALITIES.

Enough is known about the biochemistry and cell biology of cardiac embryology to state with some confidence that the extracellular matrix ("connective tissue") has an important role. The endocardial cushions have received the most attention as an area where defects in the extracellular matrix might produce malformations.[71] The high frequency of endocardial cushion defects and atrioventricular septal defects in Down syndrome has been noted (see p. 1986). Of interest is the finding of increased adhesiveness of fibroblasts from patients with trisomy 21, a phenomenon that could reflect interaction with the extracellular matrix.[84] The distinctiveness of endocardial cushion defects in patients with normal chromosomes and in those with trisomy 21 has been suggested because of differences in associated cardiovascular malformations.[68] However, of six families in which the proband had an endocardial cushion defect, three had recurrence of the same type of defect in a relative, including two with trisomy 21.[85]

SITUS AND LOOPING DEFECTS.

This is an area fraught with difficulties of nomenclature, diagnosis, and heterogeneity of both etiology and pathogenesis. In analysis of clinical data, the most informative approach, but clearly arduous because of the large amount of data required, would be to categorize probands and their relatives by the type of situs (solitus, inversus, dextroversion, and levoversion: see Chap. 43) and each of those by presence or absence of other cardiac and visceral defects. This has not been done on epidemiological cohorts, and in family studies relatives have rarely been subjected to evaluations sufficient to characterize their phenotypes in detail. These variable phenotypes are grouped in a category, *heterotaxy,* that accounts for 3 to 4 percent of all congenital heart defects.

Several mendelian phenotypes point to single genes that have a major effect on determining laterality. In the autosomal recessive *Kartagener syndrome,* a randomization of lateralization of the heart (situs solitus and situs inversus are equally likely in homozygotes)[86] coexists with a defect in ciliary motility, which leads to sinusitis, bronchiectasis, and sperm immotility.[87]

Heterotaxy with splenic and other cardiac defects, particularly of the position of the great vessels, can be inherited as an autosomal recessive, as an autosomal dominant,[88] and as an X-linked recessive.[89] Some of the families with these apparently single-gene

disorders have concordance of phenotype, but many do not, suggesting that in some cases various types of situs defects, polysplenia, and asplenia are different manifestations of the same mutation.[90] [91]

In recent years, investigation of molecular embryology has shed increasing light on cardiovascular development and maldevelopment.[92] The determination of laterality and defects involving heterotaxy have been especially revealing, in both mice and humans.[93] [94] In mice, the *inv* locus has long been associated with left/right asymmetry, and the gene was recently cloned.[95] In humans, mutations of two genes thus far, one encoding the activin receptor type IIB[96] and one encoding the connexin43 gap junction protein,[97] both have been associated with defects of laterality.

Few data define the recurrence risks of defects in the *cell death* (e.g., Ebstein anomaly) and *abnormal targeted growth* (e.g., anomalous pulmonary venous return) categories. Data from the Baltimore-Washington Infant Study do not show an increased risk of any cardiovascular defect in the relatives of a proband with a defect in either of these categories.[52]

DISORDERS OF UNCLEAR CAUSE.

A number of disorders include an important likelihood of malformation of the cardiovascular system but are of unclear cause (Table 56-6) . Familial recurrence is low enough to be *incompatible* with multifactorial inheritance. Several of these disorders deserve comment.

Certain congenital cardiac defects and other malformations occur together more frequently than expected by chance; this *association* of defects suggests a common cause, pathogenesis, or both, but the following disorders and those in Table 56-7 remain enigmatic on most of these counts. Designation as a *sequence* implies that some evidence exists for a common developmental problem to account for the features.

CHARGE Association

(see Table 56-6) . Patients with this condition by definition have congenital heart defects.[98] [99] The spectrum of cardiovascular malformations suggests not so much a common pathogenetic scheme as a common time of abnormal development. During gestational days 32 to 45, cardiac septation, fusion of the endocardial cushions and membranous ventricular septum, and formation of the outflow tracts and valves occur. An environmental insult or a breakdown in developmental homeostasis during this period could result in the malformation spectrum of this disorder. The defects in other systems could also arise during this embryological window and would be consistent with either environmental or intrinsic factors.

VACTERL Association

(see Table 56-6) . This condition has expanded over the years to include *v*ertebral, *v*entricular septal, *a*nal, *c*ardiac *t*racheo*e*sophageal, *r*enal, and *l*imb defects. Omitted

from the mnemonic is the single umbilical artery often present.[100] Cardiac defects are present in about one-half of patients with more than two components of this association but usually are not life threatening. VACTERL association occasionally occurs in relatives.[101] Although infants with this condition often fall to thrive initially, the long-term prognosis for health and mental function is good, so aggressive management of the multiple malformations is warranted. It is important to separate as soon as possible those patients who have the features of trisomy 18 or 13q chromosome aberrations, as prognosis in these cases is distinctly unfavorable.

Mendelian Disorders

Some congenital cardiovascular defects segregate in occasional families as predicted of a mendelian phenotype. Strong bias favors reporting such occurrences, and equally strong is a temptation to conclude that, at least in some cases, the defect is caused by mutation in a single gene. However, rarely and by chance alone, a multifactorial trait recurs in a family in a pattern mimicking mendelian segregation. This potential confusion and the resultant uncertainty in counseling patients and families pertains equally well to disturbances of conduction and rhythm, to various cardiomyopathies, to vascular anomalies, and to hypertension, all discussed subsequently. The true cause of the cardiovascular diseases in such families may not become clarified until each is investigated in detail, in concert with efforts to map and sequence the entire human genome.

The subject of this section can therefore be parsed into three broad classes of conditions: congenital cardiac defects that occasionally seem to be inherited as mendelian traits (Table 56-7) , pleiotropic mendelian syndromes that always or frequently affect the structure of the cardiovascular system (Table 56-8) , and mendelian syndromes that occasionally affect the cardiovascular system (Table 56-9) .

PATENT DUCTUS ARTERIOSUS.

Most instances of PDA are sporadic occurrences, and a strong association with prematurity

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TABLE 56-6 -- DISORDERS OF UNCERTAIN CAUSE AND INHERITANCE THAT ARE ASSOCIATED WITH A HIGH INCIDENCE OF CARDIOVASCULAR ABNORMALITIES

DISORDER AND PHENOTYPE	OMIM NO.*	CARDIOVASCULAR ABNORMALITIES
Aase syndrome (congenital anemia, triphalangeal thumbs)	205600	VSD

Bilateral left-sidedness sequence (polysplenia syndrome)	208530	ASD
Bilateral right-sidedness sequence (asplenia syndrome; Ivemark syndrome)	208530	Situs inversus, ECD, VSD
CHARGE association (*c*oloboma, *h*eart anomaly, choanal *a*tresia, *r*etardation, *g*enital, and *e*ar anomalies)	214800	TOF, PDA, ECD, VSD
Cornelia de Lange syndrome(short stature, retardation, synophrys, hypertrichosis, micromelia, genital anomalies)	122470	~20% have CHD: VSD, PDA, ASD, PLSVC, TOF
DiGeorge sequence (abnormalities of derivatives of 3rd and 4th pharyngeal pouches and 4th branchial arch: hypoplastic thymus with cellular immune deficiency, hyoplastic parathyroids with hypocalcemia)	188400	CHD in ~100%: aortic arch anomalies (especially IAA type B and right-sided aortic arch); PDA, TOF
Goldenhar syndrome (abnormalities of derivatives of 1st and 2nd branchial arch: hemifacial microsomia, microtia, vertebral anomalies)	141400,164210,257700	~50% have CHD: VSD, TOF, PDA, CoA, right-sided aortic arch, PLSVC
Klippel-Feil sequence (short neck, limited rotation of the head, cervical anomalies)	118100, 148900,214300	Variable estimates (5-70%) of CHD: VSD, dextrocardia
"Kabuki make-up" syndrome (dwarfism, peculiar facies, scoliosis, mental retardation)	147920	30% have CHD: ASD, VSD, TOF, CoA, PDA
Pallister-Hall syndrome (hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly)	146510	ECD
Poland sequence (unilateral absence of sternocostal pectoralis major, ipsilateral synbrachydactyly)	173800	~10% have dextrocardia or dextroversion

Rubinstein-Taybi syndrome (short stature, retardation, microcephaly, characteristic facies, broad thumbs)	268600	~20% have CHD: ECD, ASD, TOF, PDA, VSD
VATER association (*v*ertebral defects, *a*nal atresia, *t*racheo-*e*sophageal fistula, *r*adial dysplasia, *r*enal anomaly)	192350	VSD

VSD=ventricular septal defect; ASD=atrial septal defect; TOF=tetralogy of Fallot; PDA=patent ductus arteriosus; ECD=endocardial cushion defect; CHD=congenital heart defect(s); PLSVC=persistence of left superior vena cava; IAA=interrupted aortic arch; CoA=coarctation of aorta; VSD=ventricular septal defect.

*None of these disorders is evidently due to a mutation in a single gene; however, most are listed in Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim)[9] and the OMIM no. is provided as a ready source to the literature.

Cardiovascular defects listed in approximate order of decreasing frequency.

90% of cases associated with del(22q11); likely a contiguous gene deletion defect.

TABLE 56-7 -- CONGENITAL HEART DEFECTS OCCASIONALLY SHOWING FAMILIAL AGGREGATION CONSISTENT WITH MENDELIAN INHERITANCE

DEFECT	OMIM NO.*	DEFECT	OMIM NO.
Aneurysm, intracranial berry	105800	Hypoplastic left heart	140500, 241550
Aneurysm, abdominal aortic	100070	Hypoplastic right heart	277200
Angioma	106050, 106070, 206570	Lymphedema, congenital	153000, 153100, 153400, 214900, 247440
ASD, ostium primum	209400		
ASD, ostium secundum	108800, 108900, 178650	Mitral valve prolapse	157700
Bicuspid aortic valve	109730	Patent ductus arteriosus	169100
		Pulmonary venous return, anomalous	106700
Conotruncal defect	231060	Pulmonic stenosis	126190, 178650, 193520, 265500, 265600, 270460

Dextrocardia	244400, 304750		
Ebstein anomaly	224700	Subaortic stenosis	271950, 271960
Endocardial fibroelastosis	226000, 227280, 305300		
Hemangioma	106070, 140800, 140900, 234800	Tetralogy of Fallot	187500
Hemangioma, cavernous	116860, 140850	Ventricle, single	234750

ASD=atrial septal defect.

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

TABLE 56-8 -- MENDELIAN DISORDERS WITH CONGENITAL DEFECTS OF CARDIOVASCULAR STRUCTURE AS FREQUENT MANIFESTATIONS

DESCRIPTIVE NAME	EPONYM	OMIM NO.*	CARDIOVASCULAR ABNORMALITIES
Adult polycystic kidney disease		173900	MVP, dilated aortic root, intracranial berry aneurysm
Arteriohepatic dysplasia	Alagille syndrome	118450	PPS
Cataract and cardiomyopathy		212350	HCM
Chondroectodermal dysplasia	Ellis-van Creveld syndrome	225500	ASD (ostium primum), common atrium
Deafness, mitral regurgitation, and short stature	Forney syndrome	157800	MR
Familial collagenoma syndrome		115250	DCM
Heart-hand syndrome	Holt-Oram syndrome	142900	ASD (ostium secundum), VSD, MVP, HLH
Keratosis palmoplantaris	Mal de Meleda	248300	DCM, dysrhythmia
Malignant hyperthermia and skeletal defects	King syndrome	145600	Malignant hyperthermia cardiac arrest
	Noonan syndrome	163950	PS, HCM

Pulmonic stenosis and deafness		178651	PS
	Smith-Lemli-Opitz syndrome	270400	PDA, ASD, VSD, TOF, ECD, CoA
Velocardiofacial syndrome	Shprintzen syndrome	192430	TOF, tortuous retinal vasculature

MVP=mitral valve prolapse; PPS=peripheral pulmonic stenosis; HCM=hypertrophic cardiomyopathy; ASD=atrial septal defect; MR=mitral regurgitation; DCM=dilated cardiomyopathy; VSD=ventricular septal defect; HLH=hypoplastic left heart; PS=valvular pulmonic stenosis; PDA=patent ductus arteriosus; TOF=tetralogy of Fallot; ECD=endocardial cushion defect; CoA=coarctation of aorta.

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

and all of its antecedents is noted. However, in a number of families that have been described, PDA occurs as an autosomal dominant trait.[102] In some pedigrees, mild facial dysmorphism segregates with PDA; because the facial features differ among families, the number of syndromes remains unclear.[103] [104]

FAMILIAL ATRIAL SEPTAL DEFECT.

Two mendelian forms of atrial septal defect exist as autosomal dominant traits. One has no associated problems and has been described in few pedigrees.[105]

The second, more common condition is associated with atrioventricular conduction delay.[106] [107] The defect is of the secundum type, and relatives do not seem to be at increased risk of other cardiac malformations. The severity of heart block rarely progresses to third degree. The electrocardiographic abnormality in a patient with apparently sporadic atrial septal defect should prompt a detailed family history and evaluation of close relatives. Attention should be directed to the upper limbs, particularly the thumbs, to rule out the Holt-Oram syndrome; radiographic examination of the upper limbs of the proband is helpful on this account.

In patients with atrial septal defect due to aneuploidy (a syndrome with extracardiac features), when one of the autosomal dominant forms is excluded, the recurrence risk of secundum atrial septal defect is about 3 percent, a value that conforms closely to the multifactorial threshold model. Several pleiotropic mendelian conditions have defects of the atrial septum as frequent manifestations.

HOLT-ORAM SYNDROME.

This autosomal dominant condition, first elaborated in 1960, shows marked variability within a pedigree.[108] The cardinal manifestations are dysplasia of the upper limbs and atrial septal defect. In heterozygotes for the mutation, arm deformity ranges from

undetectable through distally placed thumbs and hypoplastic thenar eminences, triphalangeal thumbs, anomalies of the carpus, and radial aplasia, to phocomelia and hypoplasia of the clavicles and shoulders. Upper-extremity deformity is usually bilateral but may be asymmetrical in severity, with the left side more affected. Similarly, the atrial involvement ranges from none to a large secundum defect with early, severe hemodynamic compromise. Other cardiac malformations have been reported, with ventricular septal defects and PDA the most frequent.[109] The skeletal and cardiac manifestations are not correlated in individuals, and how a parent is affected is not a reliable predictor of effects on offspring.[110] Prenatal diagnosis by ultrasonography was reported in a fetus with severe limb abnormalities; a large septal defect could presumably be detected as well. Other manifestations include dermatoglyphic abnormalities, pectus excavatum, hypoplastic peripheral arteries, and cardiac conduction disturbance, the last usually involving the atrioventricular node and present in patients with septal defects. Although the Holt-Oram syndrome bears some resemblance

TABLE 56-9 -- MENDELIAN DISORDERS WITH CARDIOVASCULAR ABNORMALITIES AS OCCASIONAL MANIFESTATIONS

SYNDROME	EPONYM	OMIM NO.*	CARDIOVASCULAR ABNORMALITIES
Acrocephalosyndactyly type I	Apert syndrome	101200	PS, PPS, VSD, EFE
Acrocephalopolysyndactyly type II	Carpenter syndrome	201000	PDA, VSD, PS, TGA
Hereditary angioedema		106100	Coronary arteritis
Imperforate anus with hand, foot, and ear anomalies	Townes-Brocks syndrome	107480	Sporadic cases have CHD: VSD, ASD
Mandibulofacial dysostosis	Treacher Collins syndrome	154500, 248390	10% have CHD: variable
Neuronal ceroid lipofuscinosis	Batten disease	204200	HCM
Orofacial digital syndrome type II	Mohr syndrome	252100	Variable
Short rib-polydactyly syndrome	Saldino-Noonan syndrome	263530	TGA, ECD, hypoplastic right heart
Thrombocytopenia--absent radius syndrome		274000	TOF

PS=valvular pulmonic stenosis; PPS=peripheral pulmonic stenosis; VSD=ventricular septal defect; EFE=endocardial fibroelastosis; PDA=patent ductus arteriosus; TGA=transposition of great arteries; CHD=congenital heart defect(s); ASD=atrial septal defect; HCM=hypertrophic cardiomyopathy; ECD=endocardial cushion defect; TOF=tetralogy of Fallot.

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

to the VACTERL association, the clear mendelian nature and lack of more extensive organ system involvement of the former indicate that the two conditions do not represent a pathogenetic spectrum.

The diagnosis of Holt-Oram syndrome is most likely to be missed in a patient with an unknown or unremarkable family history, a secundum septal defect, and minimal or no thumb anomaly. In any "sporadic" case of an atrial septal defect, the patient and the parents should be carefully examined for limb malformations and the family history studied in detail. Detection of a subtle limb defect alters the recurrence risk in offspring of the proband from the empirical risk of an isolated septal defect of 3 percent to the 50 percent of an autosomal dominant trait.

Mutations in the *TBX5* gene, which is a transcriptional regulator, cause one form of Holt-Oram syndrome.[111] Different mutations have more or less effect on limb and cardiac development, which accounts for much of the interfamilial variability. Not all families with Holt-Oram syndrome are linked to this locus at 12q2, so at least one additional gene can cause this spectrum of defects.[112] [113]

ELLIS-VAN CREVELD SYNDROME

(Fig. 56-6) . This rare autosomal recessive chondrodysplasia is found among the old order Amish because of a founder effect and consanguinity. Short stature, metaphyseal dysplasia, dysplastic nails and teeth, and postaxial polydactyly are the pleiotropic manifestations in addition to congenital heart disease.[114] The last is present in more than one-half of homozygotes, and most of the defects affect the atrial septum. The majority are defects of endocardial cushion closure, including ostium primum defects of widely varying size up to a single atrium. This disorder has long been thought to be due to a yet unknown defect in the extracellular matrix, which would fit with the high frequency of endocardial cushion lesions. However, defects thought due to abnormal embryonic flow (coarctation, hypoplastic left heart, and patent ductus arteriosus) occur in about 20 percent of cases. The gene maps to 4p16 in patients of all ethnic derivations.[115] A gene of unknown function within this locus has been called *EVC*, with the finding of pathological mutations in a number of patients.[115A] Ellis-van Creveld syndrome can be diagnosed prenatally by detection of polydactyly by ultrasonography.

FAMILIAL ATRIOVENTRICULAR CANAL DEFECTS.

This spectrum of defects occasionally occurs in an autosomal dominant pattern in families and is unassociated with features in other systems. Because the cardiac defect is suggestive of that in Down syndrome, linkage to chromosome 21 markers was pursued, to no avail. In a large kindred that showed variable expression of nonsyndromic atrioventricular canal defects, analysis of shared markers among those clearly affected identified a region on chromosome 1 (1p31-p21) that must harbor a

gene that effects susceptibility to failure of closure of the endocardial cushions.[116]

VENTRICULAR SEPTAL DEFECT.

This malformation does not seem to be inherited as an isolated mendelian malformation, and no syndromes include it as a common, isolated manifestation.

SUPRAVALVULAR AORTIC STENOSIS.

This congenital lesion, which may be asymptomatic and detected long after birth because of an ejection murmur, occurs in at least three settings. It can be a sporadic anomaly, a component of Williams syndrome, or an autosomal dominant trait associated with peripheral pulmonic stenoses and a diffuse arteriopathy.

Williams syndrome is usually sporadic but, in more instances than previously recognized, is a highly variable autosomal dominant condition. The full spectrum includes infantile hypercalcemia, abnormal (elfin) facies (see Fig. 43-35) , mental deficiency, short stature, numerous peripheral pulmonic stenoses, and supravalvular aortic stenosis.[117] [118] [119] Although patients usually survive the problems of infancy and show catch-up growth, progressive problems of joint contractures, genitourinary and gastrointestinal dysfunction, hypertension, and psychosocial adjustment define the long-term prognosis.[120] [121] [122]

Supravalvular aortic stenosis (SVAS) is due to heterozygosity for a mutation in tropoelastin (discussed later). Because elastic fibers are

Figure 56-6 Ellis-van Creveld syndrome in a young woman. *A,* Note short stature, joint contractures at the elbows, and marked genu valgum. *B,* The fingers are short and the nails dysplastic. Note the protuberances along the ulnar edges of the hands where sixth digits were amputated.

intrinsic to the media of elastic and muscular arteries, a diffuse, progressive arteriopathy develops, with thickening of the wall and reduction of the lumen. The natural history of the arterial disease is just emerging as patients with Williams syndrome live longer and are monitored prospectively.[123] A predisposition to cerebrovascular disease seems certain.[124] [125]

Virtually all patients with Williams syndrome who have been tested have a deletion of the long arm of chromosome 7.[126] [127] Those with SVAS have a deletion that involves the tropoelastin locus. The crucial gene(s) involved in the rest of the Williams phenotype lie telomeric to the tropoelastin locus; considerable effort is currently being directed at identifying these gene(s) that have a role in development of the face, in calcium

metabolism, and in development of personality and cognitive capability.

Autosomal dominant SVAS is an entity distinct from Williams syndrome,[128] [129] [130] although some patients have subtle defects in personality and intelligence. Peripheral pulmonary artery stenoses may be present but rarely cause hemodynamic problems. The aortic lesion requires surgery in less than half of patients.

MITRAL VALVE PROLAPSE.

(see Chap. 46) . This trait is of heterogeneous cause and pathogenesis; although it has been called the most common abnormality of human heart valves.[131] MVP is equally clearly not always an abnormality.[132] [133] Here only the heritable forms of MVP are discussed. These can be classified into three groups. The first is a familial form with minimal extracardiac involvement. The second is an autosomal dominant condition that is clinically variable and at one end of its spectrum merges with Marfan syndrome; it could just as well be discussed as a heritable disorder of connective tissue. The third category is composed of the various mendelian syndromes that include MVP as a pleiotropic manifestation. In all of these categories, prolapse of the tricuspid valve is a frequent accompaniment.

The first category, which some have called MVP syndrome or familial MVP,[134] includes a condition that is centered on the mitral valve. The development of actual prolapse shows the age- and gender-dependent behavior characteristic of the idiopathic form.[134] [135] Formal genetic studies in most families confirm *autosomal dominance with variable expression.* This category has been partitioned into those patients with billowing of the mitral leaflets and those with excessive systolic mitral annular expansion; because this phenotype breeds relatively true, two distinct autosomal dominant forms may exist.[136] The cause(s) of these entities is unknown. Moreover, when and how the phenotype of this condition can be distinguished from the sporadic cases of MVP and the cases with obvious evidence of a systemic disorder of connective tissue are unclear. The only consistent extracardiac manifestations are excessive arm span in women and relatively low body weight and systolic pressure.[137] [138] Susceptibility to myxomatous degeneration of all cardiac valves can be inherited as an X-linked trait that maps to Xq28.[139]

Many clinical geneticists and cardiologists have referred patients with a suspicion of Marfan syndrome (see p. 1983) or Ehlers-Danlos syndrome (see p. 1986). Some of these patients do not meet minimal diagnostic criteria for a recognized connective tissue disorder[140] [141] but clearly have extracardiac features consistent with a defect of the extracellular matrix described later. MVP is commonly but not always present; when it is and when evidence of a systemic abnormality of connective tissue is lacking, the patient should be considered to have the condition described in the preceding paragraph, what some call primary MVP.[142] The clinical spectrum of the patients with syndromic MVP includes abnormal striae atrophicae, excessive arm span and leg length, joint hypermobility, pectus excavatum, scoliosis, reduction in thoracic kyphosis ("straight back"), myopia, and mild aortic root dilatation.[143] Aortic dilatation beyond 3 SD above the mean for body surface area, aortic dissection, ectopia lentis, or a family history of any of these three features *removes* a patient from this category. For the remainder of

patients, the acronym MASS phenotype, for *m*itral *v*alve, *a*orta, *s*kin, and *s*keletal, describes what certainly is a heterogeneous grouping of patients and families. The aorta is mentioned specifically because of the appropriate concern that progressive dilatation and dissection will occur; in fact, neither has been the case, although prospective evaluation has been unsystematic. Many of the associations between MVP and deformity of the thoracic cage and spontaneous pneumothorax are explained by the MASS phenotype.[144]

Finally, as described later, MVP frequently accompanies Marfan syndrome, several of the Ehlers-Danlos syndromes, and cutis laxa and occurs more often than expected in osteogenesis imperfecta, Larsen syndrome, pseudoxanthoma elasticum, and other mendelian syndromes (Table 56-10) . In addition, occasional families with otherwise unclassified heritable disorders of connective tissue have prominent involvement of the mitral apparatus, with myxomatous deterioration, calcification, or both.[145]

NOONAN SYNDROME.

Among the pleiotropic mendelian syndromes that have frequent cardiovascular involvement, Noonan syndrome is important because of its relatively high prevalence and clinical variability. This autosomal dominant condition has been called the male Turner syndrome in the past because of the short stature, cubitus valgus, neck webbing, congenital lymphedema, and congenital heart defects that coexist in the 45,X Turner syndrome. However, Noonan syndrome is distinct, not simply because both men and women are affected. Patients with Noonan syndrome often have an unusual deformity of the sternum, mental dullness, hypertelorism, ptosis, and cryptorchidism.[146] The cardiovascular defects, although widely varied, do not include an increased incidence of coarctation of the aorta. Because of the dysmorphism of the facies and the cardiac involvement, Noonan syndrome is often classified, along with William, leopard, King, and Watson syndromes, as a cardiofacial syndrome.

The entire phenotype of Noonan syndrome is highly variable, and affected persons can escape clinical problems (or accurate diagnosis) even if they have obvious manifestations.[147] Similarly, a wide range of cardiovascular involvement can occur. *Valvular pulmonic stenosis* was the first defect identified, and Noonan syndrome should always be considered in a patient with this lesion.[148] The valve cusps are thickened and dysplastic, even in the absence of hemodynamic compromise. Obstruction to right-sided flow can also occur in patients with Noonan syndrome because of pulmonary artery hypoplasia or infundibular subvalvular changes. The latter finding reflects a generalized predisposition to hypertrophic cardiomyopathy, often asymmetrical, that can affect either ventricle.[149] *Atrial septal defect* occurs in about one-third of patients, usually in association with pulmonic stenosis.

TABLE 56-10 -- CARDIOVASCULAR DEFECTS ASSOCIATED WITH PRENATAL EXPOSURE TO TERATOGENS

TERATOGEN	CARDIOVASCULAR ABNORMALITIES*
Ethanol	~50% have CHD: VSD (~50% close spontaneously), TOF, ASD, ECD, absence of a pulmonary artery

Hydantoin	~10% have CHD: VSD, ASD, PS
Lithium	<3% have Ebstein anomaly
Phenylalanine	~20% have CHD: TOF
Retinoic acid	>50% have CHD: TGA, TOF, VSD, IAA
Rubella	>50% have CHD: PDA with or without ASD, VSD, PPS, IAA
Trimethadione	~50% have CHD: complex combinations most frequent (involving VSD, ASD, PDA, AS, PS), VSD, TOF
Valproic acid	>50% have CHD: left- and right-sided flow lesions: CoA, HLH, ASD, VSD, pulmonary atresia
Vitamin D	Supravalvular aortic stenosis is the cardinal manifestation; PPS
Warfarin	~10% have CHD: PDA, PS; rarely, intracranial hemorrhage.

CHD=congenital heart defect(s); VSD=ventricular septal defect; TOF=tetralogy of Fallot; ASD=atrial septal defect; ECD=endocardial cushion defect; PS=valvular pulmonic stenosis; TGA=transposition of great arteries; IAA=interrupted aortic arch; PPS=peripheral pulmonic stenosis; PDA=patent ductus arteriosus; AS=aortic stenosis; CoA=coarctation of aorta; HLH=hypoplastic left heart.

*Among patients with the full clinical spectrum associated with each teratogen; cardiovascular defects listed in decreasing order of prevalence.

Ventricular septal defects and patent ductus arteriosus each occur in about 10 percent. Congenital anomalies of coronary arteries are occasionally and unexpectedly found during evaluation of more obvious defects. The electrocardiogram often shows left anterior hemiblock and a deep precordial S wave, a pattern not common in pulmonic stenosis of other causes.

Lymphatic dysplasia, especially of the lower limbs, is common but causes clinical difficulties in less than 20 percent.[146] Although evidence of lymphedema often disappears during childhood, chylothorax and a protein-losing enteropathy represent the severe end of the spectrum.[150]

Noonan syndrome shares features with other cardiofacial syndromes, and in sporadic cases (which account for 50 percent of Noonan syndrome) diagnosis can be difficult. All are *autosomal dominant,* so genetic counseling is somewhat easier. Affected males have reduced reproductive capabilities because of testicular abnormalities. Susceptibility to malignant hyperthermia can be detected by family history, elevated skeletal muscle creatine kinase levels, or muscle biopsy. Despite the relatively high frequency of Noonan syndrome, estimated to be as great as 1 per 1000, neither its cause nor its pathogenesis is clear. One gene has been mapped to 12q24.2-q 24.31,

but interlocus genetic heterogeneity is likely.[151] [152] Intriguing issues that may shed light on these uncertainties are the overlap in phenotype with type I neurofibromatosis[153] [154] (the gene for which is on chromosome 17), and the frequent coexistence of Noonan syndrome and deficiency of coagulation factor XI.[155]

Teratogenic Effects

A teratogen is any agent that adversely affects embryonic or fetal development, such as infectious vectors, radiation, drugs, and other chemicals (see Table 56-10) .[156] Teratogenic effects on the cardiovascular system are considered in this chapter for several reasons: First, the phenotypes are often reminiscent of those due to chromosomal aberrations and single-gene mutations. Second, clinical geneticists and dysmorphologists are involved in diagnosing, managing, and investigating both teratogenic and genetic syndromes. Finally, how the organism responds to an encounter with a potential teratogen is largely determined by its genome. The entire field of ecogenetics and part of pharmacogenetics are concerned with these issues.

The abilities to resist disruption of normal human embryogenesis and development involve systems quite distinct from physiological homeostasis and related only in part with developmental homeostasis. Genetic susceptibilities to teratogens can be illustrated by diverse mechanisms: reduced or inaccurate repair of radiation-induced DNA damage; enhanced receptiveness to viral entry or replication; immune deficiencies that prevent inactivation of infectious vectors or maintenance of immunity; slow inactivation of a compound that exerts a direct deleterious effect; or rapid conversion of an inoffensive drug to a teratogenic metabolite. These types of hereditary variation may be determined by single genes, with susceptibility inherited as a mendelian trait, or by many genes, each of small effect. Either situation can account for the well-known fact that only a fraction of pregnancies exposed to a given agent are affected adversely. Variation in dose and timing of exposure also confound interpretation of epidemiological and family data. It is not surprising, then, that the actual appearance of the abnormal phenotype is not amenable to traditional pedigree analysis. Rather, examination of the biochemical susceptibilities have proved, and will continue to prove, more enlightening.

Some teratogens, such as *warfarin,* have a clear action that explains how the pleiotropic manifestations emerge. The action of other teratogens, such as alcohol, is obscure. Finally, in some teratogenic syndromes, such as that in offspring of women with diabetes mellitus, the actual offensive agent is unclear, and numerous pathogenetic mechanisms seems to pertain.[157] [158] Regardless of cause and pathogenetic mechanism, the phenotypes of many teratogens often share manifestations, especially prenatal growth retardation, abnormalities of the craniofacies, and mental retardation.[159] The following syndromes have prominent consequences on the cardiovascular system.

FETAL ALCOHOL SYNDROME.

Ethanol is the most common teratogen to which the human embryo and fetus are exposed. The period of greatest vulnerability is the first trimester, and the risks are clearly related to the amount of alcohol consumed; the risk of the fetal alcohol syndrome's occurring in an offspring of a chronic alcoholic woman is 30 to 50 percent.

The features are highly variable and include growth retardation, mild to moderate mental retardation, hyperactivity, short palpebral fissures, a smooth philtrum with a thin upper lip, and small distal phalanges.[160] [161] Congenital heart defects occur in more than one-half of children with the full spectrum of the phenotype; ventricular septal defects are most common and often insignificant, but atrial septal defects, tetralogy of Fallot, and aortic coarctation can occur.

FETAL HYDANTOIN SYNDROME.

Virtually all antiseizure medications can affect the fetus. Hydantoin was the first to be identified as a teratogen. The risk to the fetus depends in part on the genotype of the fetus; defects in arene oxidase predispose to the full syndrome.[162] [163] The features include prenatal and postnatal growth retardation, mild mental retardation, a broad face with a short nose, short distal phalanges with small nails, and hip dislocation. Cardiovascular defects, which are an inconstant part of the syndrome, include septal defects, right- and left-sided flow defects, and a single umbilical artery.

RETINOIC ACID EMBRYOPATHY.

Isotretinoin was not recognized as a teratogen until after it was licensed for the treatment of acne. The vulnerable period extends from the first week through the fourth month of gestation. Isotretinoin increases the risks of miscarriage and stillbirth. The phenotype includes anomalies of the craniofacies and gross neuroanatomical disruption. Cardiovascular defects are common and emphasize various conotruncal malformations.[164] Live-born infants often succumb to the cardiac and brain anomalies. Although the mechanism of action is not certain, vitamin A derivatives such as retinoic acid function as *morphogens* during embryogenesis, serving as signals for cell migration. The fact that the cardiovascular defects are primarily those of rotation and folding suggests disruption of a normal developmental homeostatic system.

WARFARIN EMBRYOPATHY.

Coumarin-related vitamin K antagonists are usually prescribed for various cardiovascular problems to women of childbearing age and can cause diverse cardiovascular and other organ damage to the fetus. Coumarin interferes with embryogenesis directly when administered during gestational weeks 6 through 9. The most pronounced effects are on cartilage because of inhibition of enzymes of extracellular matrix metabolism. Congenital cardiac defects are perhaps increased in frequency but fit no specific pathogenetic mechanism.[165] The second pattern of coumarin effects involves exposure during the second and third trimesters and includes spontaneous abortion, stillbirth, and various central nervous system defects. The last are not due simply to intracranial hemorrhage as was once assumed.[165]

What predisposes to the adverse fetal effects of coumarin remains to be discovered. First, more than 75 percent of women who take coumarin derivatives throughout pregnancy have normal offspring; reassuring most women while identifying those at risk for adverse effects has obvious advantages. Second, placing all pregnant women on a

regimen of heparin is not an acceptable solution, because heparin can cause stillbirth or premature fetal loss in about 20 percent of exposures, is not as effective as coumarin in some indications for anticoagulation, and is more trouble to administer and regulate.

MATERNAL PHENYLKETONURIA.

The inborn error of metabolism phenylketonuria (PKU), produces severe mental retardation unless the phenylalanine content of the diet is markedly reduced soon after birth.[166] Deficiency of phenylalanine hydroxylase in the fetus produces no harm because fetal blood levels of phenylalanine are regulated by the heterozygous mother's enzyme. Because neonatal screening for this disease is now routine in all states, virtually all patients receive treatment and grow to adulthood with average intelligence. Many patients discontinue the rigorous dietary therapy during adolescence when the elevated phenylalanine levels have far less deleterious effects. The embryopathy occurs when a woman with homozygous deficiency for phenylalanine hydroxylase becomes pregnant and her fetus is exposed to high levels of the amino acid, which overwhelm its ability to metabolize. The result is highly predictable if the mother does not restart dietary restriction of phenylalanine for the entire gestation: moderate to severe mental retardation, prenatal and postnatal growth retardation, microcephaly, and various cardiovascular defects in 15 to 20 percent.[167] This condition can largely be prevented by effective counseling of female patients with PKU.

FETAL RUBELLA EFFECTS

(see Chapter 29) . About 50 percent of fetuses become infected with the rubella virus when the mother is infected during the first trimester. An infected fetus not only suffers varied and severe interference with development and organogenesis but acquires a chronic viral illness that can persist for years. The most common features of the embryopathy are mental deficiency, deafness, cataract, and cardiovascular defects. PDA is common, as are septal defects. Peripheral pulmonary stenosis and fibromuscular proliferation of medium and small arteries often improve postnatally.

CARDIOMYOPATHIES (See also Chap. 48)

Each of the three clinical categories of primary cardiomyopathy--hypertrophic, dilated, and restrictive--can be caused by mutations in single genes as judged by mendelian inheritance of a consistent phenotype in numerous families. Many other mendelian and mitochondrial disorders also cause cardiomyopathies as a secondary consequence of their basic metabolic disturbance.

Hypertrophic Cardiomyopathy

In the more than four decades since the recognition of hypertrophic cardiomyopathy as

a clinical entity, many aspects of its natural history, pathology, and management have been substantially clarified.[168] [169] The phenotype is most clearly defined anatomically and histologically and consists of myocardial hypertrophy without secondary cause; cellular and myofiber disarray; myocardial fibrosis; and mediointimal proliferation of small coronary arteries. None of these features is pathognomonic; for example, myofiber disorganization is present in the normal human heart during embryogenesis and in congenital heart defects that place strain on the right-sided circulation.

About half of probands with idiopathic hypertrophic cardiomyopathy of any segment of the left ventricle have affected first-degree relatives, and in those families the phenotype is inherited as an autosomal dominant, familial hypertrophic cardiomyopathy (FHC). There is wide variability of expression within a family, in part because of age dependence of the trait.[168] Later generations of relatives in adolescence and childhood may not have developed echocardiographic evidence of hypertrophy. Hence, pedigree screening by phenotype for clinical, counseling, or investigative purposes should not be considered complete until the following criteria are satisfied: Two-dimensional echocardiography is used to ensure that segmental hypertrophy is detected; a person at risk has normal echocardiographic findings and no evidence of electrocardiographic abnormality or important dysrhythmia after about age 20; and a person of any age has left ventricular hypertrophy without any other explanation, such as hypertension or aortic stenosis.

FHC is a disease of the sarcomere, with primary defects of thick and thin filaments now defined. Mutations of at least six and perhaps more loci cause FHC (see Table 56-2) . The first gene identified was the cardiac beta-myosin heavy chain gene (*MYH7*). Depending on the population studied, about 50 percent of all FHC mutations occur in *MYH7,* and many mutations have been described.[169] [170] Patients with neither parent affected may also have *MYH7* mutations, suggesting that the genetic alteration occured in the egg or sperm of a parent.[171] The likelihood of germline mosaicism is strongly suggested by two sibs with FHC and the same mutation in *MHY7*, even though neither parent shows the mutation in leukocyte DNA[171A] Mutations that alter charge of the beta-myosin heavy chain generally carry a worse prognosis in terms of age of detection, electrocardiographic abnormalities, and sudden death.[172] [173] [174] Thus, defining the specific gene involved, followed by the specific mutation, has likely clinical importance.[175] However, because of the substantial technical challenges and expense of identifying the specific mutation in any given patient with FHC, genetic testing is not yet routine.[176] How the mutant protein interacts with other components of the sarcomere of both cardiac and skeletal muscle to produce the phenotype is another area of active research, as is the generation and characterization of animal models of FHC.[177]

Although intergenic and intragenic heterogeneity account for much of the interfamilial variability in the FHC phenotype, considerable variation remains among relatives who share the same mutation. Both environmental and genetic factors have impacts. A possible example of the latter is the angiotensin I-converting enzyme (ACE) genotype, with different polymorphic variants of ACE associated with more or less hypertrophy.[178]

The importance of presymptomatic and even prehypertrophy diagnosis through

mutation analysis in families will become more important as improved methods of therapy evolve.[178A]

Dilated Cardiomyopathy

The prevalence of idiopathic dilated cardiomyopathy is about double that of the hypertrophic form, or about 2 to 8 per 100,000.[179] [180] [181] Although numerous occurrences of familial dilated cardiomyopathy (FDC) are reported, few investigations have been conducted of an unselected series of probands for clinical and subclinical evidence of cardiac disease.[182] Thus, it is unclear what fraction of patients with idiopathic dilated cardiomyopathy have a mendelian disease, how many have a new mutation for a mendelian disease, and how many have phenocopies of nongenetic causes. Estimates of a positive family history, which could suggest a mendelian condition or a shared environmental cause, range from 7 to 30 percent.[168] [169] [182]

Because of the risk of severe dysrhythmia in dilated cardiomyopathy, early detection of individuals with the disorder can be life saving. Two-dimensional echocardiography is a sensitive method for detecting affected relatives with subclinical disease. Individuals who have equivocal left ventricular enlargement or dysfunction can have ambulatory electrocardiographic monitoring and, if the diagnosis is still uncertain, can have serial examinations. Certainly every patient with idiopathic dilated cardiomyopathy should have a detailed family history; about 20 percent reveal an affected relative.[182] If any close relative has a history consistent with cardiomyopathy, dysrhythmia, or sudden death at a relatively young age, counseling about the risk of a familial disease and the potential benefits of pedigree screening should be offered.

The majority of instances of FDC fit autosomal dominant inheritance, but X-linked, autosomal recessive, and mitochondrial forms exist.[168] [183] [184] [185] Clinical variability characterizes virtually all pedigrees; variation in severity, clinical phenotype, and age of onset is typical.

In late 1999, the causes of most of the autosomal dominant forms of FDC were unknown. Mutation of the cardiac actin gene (*ACTC*) causes one uncommon form of FDC.[186] In some families with autosomal dominant disease, a mild proximal skeletal myopathy of type I fibers coexists with cardiac involvement.[187]

In one family, cardiomyopathy developed only in association with pregnancy.[188] Although peripartum cardiomyopathy is a well-recognized, usually sporadic disorder, its occurrence in five women in two generations suggests a hereditary predisposition.

Histological examination of myocardium generally shows nonspecific hypertrophy and fibrosis. By electron microscopy, however, mitochondria are distinctly abnormal, a finding not seen in congestive heart failure due to other causes.[189] Although various mutations of the mitochondrial chromosome can cause dilated cardiomyopathy, including of childhood onset, the inheritance pattern in most cases does not suggest maternal transmission.[185]

Some pedigrees show convincing evidence of X linkage of dilated cardiomyopathy. At least three loci have been identified. In *Barth syndrome,* cardiac involvement is associated with skeletal myopathy, proportionate short stature, and neutropenia. The cause is mutation of the (*TAZ*) gene at Xq28.[189] [190] Mutations of this gene can also cause isolated FDC and noncompaction of the left ventricle.[168] [191]

Many males with *Duchenne* and some with *Becker muscular dystrophy* develop myocardial dysfunction (see Chap. 71) .[192] In the Becker form, right ventricular involvement may be unassociated with left ventricular dysfunction.[193] Deletion of exon 49 of the dystrophin gene predisposes to cardiomyopathy. This pleiotropic feature in a disease that presents as a skeletal myopathy prompted evaluation of the dystrophin locus in pedigrees with apparently isolated cardiomyopathy. Mutations in the 5 end of the dystrophin gene have been found to account for some instances of X-linked dilated cardiomyopathy.[194] [195] Why some dystrophin mutations are selectively expressed in cardiac muscle (and other in brain) is unclear.

Emery-Dreifuss muscular dystrophy (see Chap. 71) is distinguishable clinically from the Duchenne and Becker forms by absence of pseudohypertrophy of skeletal muscle, early involvement of the arms with elbow contractures, and early onset of cardiac conduction abnormalities and atrial dysrhythmia.[192] [196] Autosomal dominant and X-linked recessive forms occur. In the latter, female heterozygotes are also commonly affected, albeit more mildly than males.[197] The disease was mapped to the distal region of Xq28, and a previously unknown gene, called emerin, was found to be mutated.[198] Hearts show replacement of myocardium, especially in the atria, with fat and fibrosis. Even though the conduction system is not primarily affected histologically, sudden death is common in both hemizygous men and heterozygous women; thus, carrier detection can be life saving.

The dominant form of Emery-Dreifuss muscular dystrophy is caused by mutations in the lamin A/C gene.[199] Both emerin and lamin A/C are expressed in the nuclear membrane of skeletal and heart muscle.

An autosomal recessive form of limb-girdle muscular dystrophy with dilated cardiomyopathy has been found to be due to mutations in the gene encoding beta sarcoglycan.[200] In a number of families with severe, adult-onset autosomal dominant skeletal myopathy, cardiac conduction defects, and cardiomyopathy have been due to mutations in the gene encoding the intermediate filament protein, desmin.[200A]

Restrictive Cardiomyopathy

The pathogenesis of the majority of cases of restrictive cardiomyopathy involves infiltration or replacement of the myocardium or both. The causes are varied and can be nongenetic or genetic; the latter are mostly metabolic diseases with secondary effects on the heart and are summarized in Table 56-9; some are reviewed subsequently. One

form of restrictive cardiomyopathy that has primary genetic forms among many other causes is endocardial fibroelastosis. Other mutations produce restriction through pericardial constriction. Isolated pedigrees of primary myocardial fibrosis without secondary cause and leading to restrictive hemodynamics are not classifiable.[201] [202]

ENDOCARDIAL FIBROELASTOSIS

(see Chap. 48) . This abnormality is characterized by thickening of the endocardium, which leads to decreased compliance and impaired diastolic function. Primary forms, discussed here, are unassociated with other cardiac anomalies (see Table 56-9) . In infants there is often an indolent course of failure to thrive, tachypnea, and tachycardia, until a precipitant such as an upper respiratory infection leads to rapid cardiac decompensation. Treatment of children with primary endocardial fibroelastosis is ineffective; cardiac transplantation now offers some hope. Autopsy shows enlargement of the left ventricle and perhaps other chambers, no abnormality of lung vessels, and collapse of the left lower lobe. Histopathological study reveals extensive deposition of extracellular matrix, primarily collagen and elastic fibers, in the endocardium.

X-linked recessive inheritance is the most firmly established of the single-gene causes. Some pedigrees show mainly small, contracted cardiac chambers, whereas others have chamber dilatation; both are compatible with the functional pathophysiology described by the term "restrictive." Males are affected earlier and more severely by both forms, and death in infancy is not unusual.[203] The condition must be distinguished from X-linked dilated cardiomyopathy and Barth syndrome (see also earlier on this page).[189] Morphological abnormalities of mitochondria occur on ultrastructural studies of heart and leukocytes. Insufficient longitudinal experience is recorded to know whether females heterozygous for this mutation develop a dilated or restrictive cardiomyopathy later in life.

Several pedigrees suggestive of autosomal recessive inheritance of primary endocardial fibroelastosis were reported before the routine availability of laboratory methods to diagnose metabolic derangements, especially defects in fatty acid catabolism.[204] The occurrence of hydrocephalus, endocardial fibroelastosis, and neonatal cataracts may be due to a single gene mutation but could represent sequelae of a viral infection.[205] Endocardial fibroelastosis can be a prominent finding at autopsy in patients with autosomal dominant dilated cardiomyopathy[206] , whether the endocardial changes are primary, representing yet another mendelian form of this disorder, or whether they are secondary is unclear.

Restrictive cardiomyopathy often occurs with both hemodynamic evidence of impaired diastolic filling and wall thickening; any of the conditions causing pseudohypertrophy of the myocardium can eventually exhibit restrictive pathophysiology. Hemochromatosis and the amyloidoses, both hereditary and acquired forms, are especially likely to present in this manner. Connective tissue replaces myocytes or infiltrates the interstitium in a number of conditions. Fibrosis of the myocardium may cause pseudohypertrophy, but the clinical consequences are more those of restriction. Restrictive pathophysiology often accompanies fibrosis of the myocardium, at least in the early stages. Replacement of myocytes or infiltration of the interstitium by collagen

and proteoglycan occurs in various conditions, such as muscular dystrophies and disorders that predispose to ischemia due to coronary artery occlusion, such as diabetes mellitus, hemoglobinopathies associated with sickling, Fabry disease, and the mucopolysaccharidoses. Severe fibrosis may produce considerable thickening of the myocardium, or pseudohypertrophy. Finally, a number of hereditary conditions are associated with endocardial fibroelastosis (Table 56-11) .

CONSTRICTIVE PERICARDITIS

(see also Chap. 50) . Two rare autosomal recessive disorders include fibrous thickening of the pericardium as a manifestation. In both, signs and symptoms of constrictive pericarditis develop insidiously, and treatment by pericardiotomy is life saving. One condition was first described in Finland and given the name *MULIBREY nanism,* a combination of a mnemonic for *muscle, liver, brain,* and *eye* and an archaic word for dwarfism (nanism). Growth failure from an early age is common, and growth does not improve once pericardial constriction is abated. Subsequently, more than a dozen patients, generally with consanguineous parents, have been reported from around the world.[207] The disease locus has been mapped to 17q.[208]

The *arthropathy-camptodactyly syndrome* previously had been reported because of the skeletal and rheumatological manifestations before pericardial effusion and fibrous thickening of the pericardium were recognized as manifestations.[209] The disease locus was mapped in consanguineous kindreds by homozygosity by descent to 1q25-q31, and mutations occur in the gene, *CACP,* that encodes a secreted proteoglycan.[210] [211]

TABLE 56-11 -- DISORDERS ASSOCIATED WITH RESTRICTIVE CARDIOMYOPATHY

	OMIM NO.*
Primary Endocardial Fibroelastosis	
Familial endocardial fibroelastosis	226000, 305300
Faciocardiorenal syndrome	227280
Secondary Endocardial Fibroelastosis	
As a Relatively Common Manifestation	
Maternal lupus erythematosus	
Pseudoxanthoma elasticum	177850, 264800
Systemic carnitine deficiency	212140
Trisomy 18	
As a Relatively Infrequent Manifestation	

Cornelia de Lange syndrome	122470
Rubinstein-Taybi syndrome	268600
Secondary Infiltrative Cardiomyopathy	
Familial amyloidoses I and III	176300
Fabry disease	301500
Gaucher disease type I	230800
Glycogen storage disorder II	232300
Glycogen storage disorder III	232400
Hemochromatosis	235200
Mucopolysaccharidosis IH	252800
Mucopolysaccharidosis II	309900

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

Cardiomyopathies Secondary to Other Causes

INBORN ERRORS OF METABOLISM.

These can affect the left ventricle by various mechanisms (Table 56-12) and produce diverse anatomical, histological, and functional disturbances. The most common anatomical result is an apparent hypertrophic cardiomyopathy, which is actually *pseudohypertrophic* because the thickened walls are not due to myocardial cell hypertrophy but to cellular or interstitial infiltration by metabolites. Abnormalities of both systolic and diastolic function result, outflow obstruction may occur, and in some cases the hemodynamic characteristics resemble a restrictive cardiomyopathy. The offending metabolite may be an incompletely degraded macromolecule such as glycogen (*glycogen storage disorder II* [Pompe disease] and *glycogen storage disorder III*), proteoglycan and glycosaminoglycan (*mucopolysaccharidoses I, III, IV, VI,* and *VII*), sphingolipid (*Fabry disease, Tay-Sachs disease, Farber disease, Refsum disease,* and *Gaucher disease*), glycoprotein (*fucosidosis* and *mannosidosis*), and amyloid (*familial amyloidoses I* and *III*) or a small molecule such as iron in *hemochromatosis.* Some of these disorders are discussed later. True myocardial hypertrophy occurs as a part of mendelian syndromes, such as *Noonan syndrome, von Recklinghausen neurofibromatosis*,[212] and *leopard syndrome*,[213] [214] and monogenic errors of metabolism, notably those producing *hyperthyroidism* and *pheochromocytoma.* Any of the mendelian disorders that cause hypertension may, over time, produce true myocardial hypertrophy.

Dilated cardiomyopathy often results from inborn errors of energy production, especially fatty acid metabolism. Various disorders associated with *carnitine deficiency, mitochondrial* and *peroxisomal dysfunction,* and *muscle dysfunction* can present with

symptoms of congestive heart failure or dysrhythmia.

PRIMARY DISORDERS OF RHYTHM AND CONDUCTION

Virtually every dysrhythmia and conduction abnormality has been reported to occur in relatives.[215] [216] For example, *familial disturbance of conduction* occurs, without evident cause, at the sinus node,[217] [218] atrioventricular node,[219] [220] and bundle branches.[221] [222] However, understanding the genetics of cardiac electrophysiology has been hampered by several characteristics of this extensive literature: Most families have been small, so that mode of inheritance, or even whether the inheritance is mendelian, is uncertain; many of the families show a mixture of different defects, partly because the disease is progressive[223] [224] ; and some specific conduction defects are associated with hereditary myocardial diseases, such as familial cardiomyopathy,[168] [225] atrial cardiomyopathy,[226] and familial amyloidosis.[227] As noted earlier, there seems to be genetic control of normal electrical conduction, so it would not be surprising to find mutations in single genes that produced clinically important disturbance.

Several important causes of complete heart block, although not mendelian, nonetheless involve genetic factors. The association between rheumatic diseases and heart block was clearly established when the offspring of mothers with acquired disorders of connective tissue, especially lupus erythematosus, were found to have complete heart block.[228] [229] [230] Many examples of "autosomal recessive" congenital heart block represent this familial but nonmendelian etiology. The risk is not related to severity of the maternal disease but is highest in children of women with antibodies to ribonucleoprotein (anti-Ro[SS-A])[231] and at least one allele for HLA-DR3.[232] Thus, it may be the maternal genotype that determines susceptibility to inflammation of the fetal heart at vulnerable periods, such as gestational weeks 3 to 4, when the atrioventricular node is forming. Also, genetic susceptibility to inflammation of the atrioventricular node of patients themselves is suggested by the relatively high association of HLA-B27 in adults requiring permanent pacemakers[233] ; not all of these patients have overt evidence of HLA-B27-associated rheumatic diseases.

Familial dysrhythmia is also not uncommon.[215] Nodal rhythm,[234] ventricular irritability,[235] and tachydysrhythmia associated with accessory atrioventricular pathways[236] [237] have been reported in families. Familial atrial fibrillation has been genetically mapped to 10q22-q24.[238] In one family, three generations were affected by a syndrome of ventricular extrasystoles and tachydysrhythmias with recurrent syncope, hypoplasia of the distal toes, and hypoplasia of the mandible (Robin sequence).[239]

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA.

Hereditary cardiomyopathies are another cause of familial dysrhythmia, and a notable example is arrhythmogenic right ventricular dysplasia (ARVD), an autosomal dominant condition with variable expression[240] [241] (see also Chap. 25) . Although ARVD is uncommon, the familial form shows clusters of high incidence (0.4 percent) in some regions of Italy and is an underappreciated cause of life-threatening dysrhythmia.[242] The right ventricle is involved primarily in most cases, with thinning and replacement of myocardium by fat and fibrosis.[243] [243A] Dysrhythmia, usually ventricular but occasionally

supraventricular, may precede signs of right ventricular dysfunction. About one-third of cases are familial, generally in an autosomal dominant pattern. At least six loci can cause ARVD (see Table 56-2) .[244] [244A] Whether the pathogenesis is homogeneous or not and whether true dysplasia, degeneration (due to a metabolic defect or muscular dystrophy), or inflammation has the leading role are unclear.

LONG QT SYNDROME

(see Chap. 26) . Familial syncope and sudden death have long been associated with ventricular dysrhythmia, but a distinct syndrome was not recognized until Ward[245] and Romano,[246] working independently three decades ago, reported the characteristic prolonged QT interval. Subsequent investigations of numerous families have clearly established that the defect in repolarization is inherited as an *autosomal dominant.* Although a long QT_c is consistently present, other abnormalities of conduction also occur, although they may not be evident on the resting electrocardiogram.[247] Long QT syndrome is generally unassociated with systemic abnormalities, but three patients with a negative family history for long QT had syndactyly of multiple fingers and toes.[248]

TABLE 56-12 -- MENDELIAN ERRORS OF METABOLISM WITH MANIFESTATIONS

DISORDER	EPONYM OR COMMON NAME	OMIM NO.*	PATHOGENESIS	CARDIOVASCULAR INVOLVEMENT
Aminoacidopathies				
Alkaptonuria	Ochronosis	203500	Deposition of homogentisic acid in connective tissue	AS; atherosclerosis
Cystinosis, nephropathic type		219800	Lysosomal storage	Hypertension from renal failure, vascular wall thickening
Homocystinuria		236200	Unknown	Early CAD; venous thrombosis; pulmonary embolism
Oxalosis I	Hyperoxaluria	259900	Vascular and tissue accumulation of oxalate	Conduction defect; vascular occlusions; Raynaud's phenomenon
Defects in Fatty Acid Metabolism				

Carnitine transport defect	Primary carnitine deficiency	212140	Lipid myopathy; defective energy generation	DCM: ECF
MCAD deficiency		201450	Lipid myopathy; defective energy generation	DCM
LCAD deficiency		201460	Lipid myopathy; defective energy generation	DCM
Glycogen Storage Disorders				
GSD I	Pompe	252300	Lysosomal storage	Pseudohypertrophic CM; short PR interval; ECF
GSD II	Adult acid maltase deficiency	232300	Lysosomal storage	Primarily skeletal muscle; respiratory insufficiency; cor pulmonale
GSD III	Forbes; debrancher deficiency	232400	Intracellular glycogen accumulation fibrosis	Pseudohypertrophic CM
Phosphorylase kinase deficiency	GSD of the heart			DCM
Glycoproteinoses				
Fucosidosis, severe		230000	Lysosomal storage	Myocardial thickening
Fucosidosis, mild		230000	Lysosomal storage	Angiokeratoma
Mannosidosis		248500	Lysosomal storage	Myocardial thickening; valvular thickening; conduction disturbance
Aspartylglycosaminuria		208400	Lysosomal storage	Valvular thickening
Mucolipidoses				
ML II	I-cell	252500	Lysosomal storage	Same as MPS IH
ML III	Pseudo-Hurler polydystrophy	252500	Lysosomal storage	Valvular thickening and dysfunction, esp. AS, AR

Mucopolysaccharidoses (MPS)

MPS IH	Hurler	252800	Lysosomal storage	Early CAD; PH and OAD CP; valvular dysfunction, esp. MR, AR; pseudohypertrophic CM
MPS IS	Scheie	252800	Lysosomal storage	Valvular dysfunction, esp. AS
MPS IH/S	Hurler-Scheie	252800	Lysosomal storage	Same as MPS IH
MPS II	Hunter	209900	Lysosomal storage	Same as MPS IH; less severe in mild MPS II variant
MPS III A	Sanfilippo A	252900	Lysosomal storage	Valvular thickening and occasional dysfunction
MPS III B	Sanfilippo B	252920	Lysosomal storage	Valvular thickening and occasional dysfunction
MPS III C	Sanfilippo C	252930	Lysosomal storage	Valvular thickening and occasional dysfunction
MPS III D	Sanfilippo D		Lysosomal storage	Valvular thickening and occasional dysfunction
MPS IV A	Morquio A	253000	Lysosomal storage	Valvular dysfunction, esp. AR
MPS IV B	Morquio B	253010	Lysosomal storage	Milder than MPS IV A
MPS VI	Maroteaux-Lamy	253200	Lysosomal storage	Same as MPS IH
MPS VII	Sly	253220	Lysosomal storage	Valvular thickening

Sphingolipidoses

alpha-Galactosidase A deficiency	Fabry	301500	Cellular accumulation of trihexosyl ceramide, esp. endothelium	Early CAD, valvular thickening and dysfunction; pseudohypertrophic CM; short PR interval; arteriolar occlusion; angiokeratoma
Ceramidase deficiency	Farber	228000	Histiocytic infiltration	Nodular thickening of valves
Glucocerebrosidase deficiency	Gaucher, adult form	230800	Cellular accumulation of glucocerebroside	PH CP; interstitial infiltration of myocytes by Gaucher cells; constrictive pericarditis
Miscellaneous Disorders				
Acid lipase deficiency	Wolman	278000	Cholesterol; foam cell infiltration	Atherosclerosis
Acid lipase deficiency	Cholesterol ester storage disease	278000	Cholesterol; foam cell infiltration	Atherosclerosis; PH
Geleophysic dysplasia		231050	Lysosomal storage	Valvular dysfunction
Hereditary angioedema		106100	Complement and kinin activation	Angioedema

CAD=coronary artery disease; DCM=dilated cardiomyopathy; ECF=endocardial fibroelastosis; CM=ca
regurgitation; PH=pulmonary hypertension; OAD=obstructive airway disease; CP=cor pulmonale; MR

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

Gene symbol; for chromosomal locus see Table 56-2 .

Naturally occurring mutants; does not include transgenic and knockout rodent models.

Long QT syndrome is genetically heterogeneous, and mutations of at least 5 loci can produce similar disorders (see Table 56-2) . Each gene identified encodes a protein involved with a cation channel.[249] Most mutations in individuals with an autosomal dominant form of long QT occur in potassium channel, rather than sodium channel gene.[250] Long QT syndrome should be suspected as a cause of sudden death, especially in young people without other evident cardiovascular risk factors, and especially when the death is associated with exercise or fright.[251] A positive family history of sudden death would obviously heighten the suspicion of long QT, but in many families penetrance is reduced.[252] Use of genotype to determine unequivocally who is heterozygous for the mutation has permitted assessment of both penetrance and the reliability of electrocardiographic criteria for diagnosis.[253] Not unexpectedly, the criterion of a corrected QT interval greater than 0.44 second is good, but it is less than 90 percent sensitive and specific. Treatment with beta-adrenergic blockade or an automatic implanted defibrillator is effective. Individuals heterozygous for the mutant gene should be identified through a detailed family history, clinical assessment, and, if necessary, DNA testing, and counseled appropriately. In some instances, the nature of the mutation has prognostic implications and can be used to guide the aggressiveness of therapy.[254] [255] However, given the extensive intergenic and intragenic heterogeneity, molecular testing, especially of a person with no family history, is not warranted, given the current technology.[176]

The association of familial syncope, sudden death, and congenital deafness was codified by Jervell and Lange-Nielsen in 1957,[256] although as with most eponymous syndromes, reports of affected individuals occurred previously. As would be expected for a rare autosomal recessive condition, the parents of affected children are more likely than average to be consanguineous. The frequency of a long QT_c among deaf children is about 1 per 100, so routine electrocardiographic screening of anyone with congenital deafness is warranted. Fright and rage clearly precipitate syncope and sudden death.

Patients with this disorder are homozygous or compound heterozygotes for mutations of several of the same cation-channel genes that cause dominant long QT syndrome.[257]

DISORDERS OF CONNECTIVE TISSUE

The two broad classes of disorders of connective tissue are those due to mutations in single genes that determine or somehow affect components of the extracellular matrix and those due to extrinsic factors affecting the extracellular matrix, such as rheumatoid arthritis and systemic lupus erythematosus. The former category includes many disorders that affect the cardiovascular system. Susceptibility to so-called acquired disorders of connective tissue is, in part, determined by genes, and this specific aspect is reviewed.

Close to 200 distinct phenotypes now compose this category, which was first defined less than four decades ago with fewer than 10 disorders.[258] Several reviews and textbooks describe the phenotypes, genetics, and causes of many of the conditions (Table 56-13) .[14] [259] [260] [261] [262]

Marfan Syndrome

This *autosomal dominant* disorder is relatively frequent (
1 per 10,000), occurs in all races and ethnic groups, and is often not diagnosed during life.[262] In light of the classical

TABLE 56-13 -- CARDIOVASCULAR MANIFESTATIONS OF HERITABLE DISORDERS OF CONNECTIVE TISSUE

DISORDER	OMIM NO.*	CARDIOVASCULAR MANIFESTATIONS
Cutis laxa	219100	PS, PPS, CP
	123700	MVP
Ehlers-Danlos I	130000	MVP
II	130010	MVP
III	130020	MVP
IV	130050	Arterial rupture, MVP
VI	225400	MVP
VIII	130080	MVP
X	225310	MVP, aortic root dilatation
Osteogenesis imperfecta I	166200	MVP, mild aortic root dilatation
II	166210	CP, arterial calcification
III	259420	MVP
IV	166220	Aortic root dilatation
Marfan syndrome	154700	MVP, aortic root dilatation, aortic dissection
MASS phenotype	157700	MVP, mild aortic root dilatation
Pseudoxanthoma elasticum	177850	Arteriolar sclerosis, claudication, myocardial infarction, endocardial fibroelastosis

PS=valvular pulmonic stenosis; PPS=peripheral pulmonic stenosis; CP=cor pulmonale; MVP=mitral valve prolapse.

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

phenotype, failure to diagnose Marfan syndrome may seem surprising; however, marked clinical variability, age dependence of all of the manifestations, and a high (30 percent) rate of new mutation all conspire to make detection of mildly affected, young, sporadic patients challenging.[262A] Even with the discovery of the genetic and biochemical bases of the condition, the diagnosis of Marfan syndrome outside of families with the classical phenotype remains entirely clinical. Current criteria (Table 56-14) depend on the manifestations in the cardinal organ systems--the eye, the skeleton, the heart, and the aorta--and other systems, as well as the family history[141] [176] (Fig. 56-7) . The presence of manifestations more specific for Marfan syndrome, such as aortic dilatation, aortic dissection in a nonhypertensive young person, ectopia lentis, and dural ectasia, clearly is more important diagnostically than features common in other connective tissue disorders and in the general population, such as scoliosis, joint hypermobility, myopia, and MVP.

The most common cardiovascular features are MVP and dilatation of the sinuses of Valsalva.[263] [264] Associated clinical problems of mitral regurgitation, aortic regurgitation, and aortic dissection account, if untreated, for most of the early mortality that results in an average age of death in the fourth and fifth decades of life.[265] Children tend to be more severely affected by mitral valve disease,[266] [267] whereas aortic problems are progressive and more likely in adolescence and beyond.

MITRAL VALVE INVOLVEMENT.

MVP (see also Chap. 46) is age dependent and more common in women with Marfan syndrome. The incidence reaches 60 to 80 percent when patients are studied by two-dimensional echocardiography,[142] and the valve leaflets generally have an elongated and redundant appearance. Progression of severity, as judged by appearance or worsening of mitral regurgitation by clinical and echocardiographic criteria, occurs in at least one-quarter of patients,[268] a much higher rate than in MVP found in the general population.[133] The mitral annulus dilates

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TABLE 56-14 -- DIAGNOSTIC CRITERIA FOR MARFAN SYNDROME PHENOTYPIC MANIFESTATIONS*

Skeleton
Joint hypermobility, tall stature, pectus excavatum, reduced thoracic kyphosis, scoliosis, arachnodactyly, dolichostenomelia, pectus carinatum, erosion of the lumbosacral vertebrae from dural ectasia
Eye

Myopia, retinal detachment, elongated globe, ectopia lentis

Cardiovascular

Mitral valve prolapse, endocarditis, dysrhythmia, dilated mitral annulus, mitral regurgitation, tricuspid valve prolapse, aortic regurgitation, aortic dissection , dilatation of the aortic root

Pulmonary

Apical blebs, spontaneous pneumothorax

Skin and Integument

Inguinal hernias, incisional hernias, striae atrophicae

Central Nervous System

Attention deficit disorder, hyperactivity, verbal-performance discrepancy, dural ectasia , anterior pelvic meningocele

If the family history is positive for a close relative clearly affected by Marfan syndrome, to make the diagnosis in the patient, a major criterion should be present as well as findings in one other system.

If the family history is negative or unknown, to make the diagnosis, the patient should have one major criterion and manifestations in two other systems.

*Manifestations are listed within each organ system in increasing specificity for Marfan syndrome, although none is completely specific; those indicated by are the most specific and constitute major criteria.[141]

and contributes to the regurgitation, as do stretching and occasional rupture of chordae. About 10 percent of patients with marked prolapse have calcification of the mitral annulus. Standard treatment for chronic mitral regurgitation is indicated, but coexistent aortic root dilatation usually requires that increasing inotropy be avoided. When mitral regurgitation becomes severe enough to warrant surgical intervention, two considerations must be added to the balance: (1) Repair of the mitral apparatus is often successful and durable in Marfan syndrome.[269] [270] Repair is less easily accomplished when the cusps are extremely redundant, there is marked chordal damage, or the annulus is heavily calcified. (2) The aorta may be enlarged enough to permit concomitant repair. In Marfan syndrome, as in virtually all of the heritable disorders of connective tissue, there is an increased susceptibility to dehiscence of prosthetic mitral valves, regardless of the care taken in placing them.

AORTIC ROOT INVOLVEMENT (See also Chap. 40) .

The sinuses of Valsalva are often dilated at birth, and the rate of progression varies widely among patients in general and also among relatives (Fig. 56-8) . Thus, predicting

long-term risks of developing aortic regurgitation (which clearly is positively associated with aortic root diameter[271]), suffering aortic dissection (which is less clearly associated with diameter), or requiring aortic surgery is fraught with uncertainty. Transthoracic echocardiography is sufficient for detecting and monitoring changes in diameter, because in the absence of dissection, dilatation is limited to the proximal ascending aorta, and the rate of change is slow, measured in millimeters per year. Rare exceptions of principal dilatation of the thoracic aorta can be monitored with transesophageal echocardiography or magnetic resonance imaging. Patients with dilatation less than 1.5 times the mean diameter predicted for their body size[272] can be observed annually; as the diameter increases, more frequent evaluation is necessary. Aortic regurgitation often appears in adults at a diameter of 50 mm but may be absent at diameters of more than 60 mm.[271] [272] The risk of dissection increases with the size of the aorta and fortunately occurs infrequently below a diameter of 55 mm in the adult. Many physicians have adopted the criterion of a 50 to 55 mm maximal aortic root dimension for performing elective surgery in adult patients with Marfan syndrome, regardless of the severity of the aortic regurgitation,[270] although patients with a family history of aortic dissection should have surgery at the lower end of this range. The perioperative results of both elective and emergency repair of the aortic

Figure 56-7 External phenotype of a patient with Marfan syndrome, showing long extremities and digits, tall stature, and pectus carinatum.

Figure 56-8 Dilatation of the aortic root in Marfan syndrome. *A,* Lateral angiogram of the ascending aorta showing dilatation of the sinuses of Valsalva and proximal ascending aorta and relatively normal caliber of the ascending aorta. *B,* Lateral magnetic resonance imaging of the same patient.

root have been excellent and a marked improvement from the pre-composite graft era that ended in the mid 1970s. Long-term results of operation are limited by the problems of endocarditis and anticoagulation, common to all prosthetic valves, but in the absence of chronic aortic dissection appear favorable for patients with Marfan syndrome.[270] [273] [274] [275]

Several approaches to repairing the dilated or dissected aortic root while preserving the native aortic valve have been developed.[276] Both short- and now long-term follow-up of patients with Marfan syndrome who have undergone this repair have been quite favorable.[270] [276A] The operation must be performed before the root is widely dilated and the valve commisures and cusps markedly stretched. This approach is increasingly being taken in all patients when the maximal root dimension reaches 50 mm, and it is an especially suitable procedure for women of childbearing age who want to consider pregnancy, as well as for all others in whom anticoagulation is contraindicated.

THORACIC ABNORMALITIES.

Severe *pectus excavatum* may complicate cardiovascular surgery by hampering exposure of the heart by median sternotomy. For elective cardiovascular surgery, repair of the sternal deformity some months in advance permits sufficient healing of the costochondral junctions that a stable and functionally and cosmetically improved thoracic cage will facilitate further surgery and postoperative recovery.[277] Simultaneous repair of cardiac and sternal defects, although possible, is a long procedure, and intraoperative bleeding from bone can be considerable because of the anticoagulation associated with cardiopulmonary bypass.

AORTIC DISSECTION

(see also Chap. 40) . This complication usually begins just above the coronary ostia (type A in the Stanford scheme) and extends the entire length of the aorta (type I in DeBakey scheme). About 10 percent of dissections begin distal to the left subclavian (type B or III), but rarely is dissection limited to the abdominal aorta. Angiography, magnetic resonance imaging, and transesophageal echocardiography all have a role in the diagnosis of acute dissection in Marfan syndrome, with the capabilities and experience of the medical center and the stability of the patient important determinants of the approach. Because many acute dissections of the ascending aorta in Marfan syndrome have a stuttering course that culminates in death due to rupture or hemopericardium, rapid transfer to a facility prepared to perform immediate repair is essential.

Not all acute dissections in Marfan syndrome involve severe, tearing chest pain that radiates to the back; indeed, some extensive dissections have been occult. This experience reinforces the need for a high index of suspicion by physicians whenever a tall, nearsighted young person with a thoracic cage deformity arrives at an emergency department with vague complaints of lightheadedness, chest or abdominal discomfort, or a murmur of aortic regurgitation. Similarly, patients known to have Marfan syndrome and their close relatives need to be educated about the signs and symptoms of aortic dissection. In general, the management of acute and chronic dissection in Marfan syndrome follows standard practice, with several departures. First, all dissections of the ascending aorta should be repaired promptly, preferably with a composite graft. Second, regular evaluation with magnetic resonance imaging is important, as the diameter of any region of dissected aorta is likely to expand over time.[278] [279] Third, reduction of systolic blood pressure and administration of negative-inotropic doses of beta-adrenergic blockers should be even more strictly adhered to than in dissections without a connective tissue abnormality. In most instances, any region of the aorta should be repaired when complications of further dissection, branch vessel occlusion, or dilatation beyond about 50 mm occur. A staged approach to total replacement of the Marfan aorta is now both feasible and successful.[280]

DYSRHYTHMIAS.

Some patients develop serious ventricular or supraventricular dysrhythmia. The latter often accompanies chronic mitral regurgitation, but the former may be of high grade and difficult to suppress when only MVP is present. Some patients have the syndrome of autonomic dysfunction, atypical chest pain, and palpitations seen in some patients with MVP unassociated with a flagrant connective tissue abnormality.

MANAGEMENT.

Routine cardiological management of Marfan syndrome is multifaceted: regular clinical and echocardiographic examinations; routine endocarditis prophylaxis for dental and other procedures; restriction of activity from heavy weightlifting, contact sports, and any exertion at maximal capacity; and long-term beta-adrenergic blockade form the basic approach, with individual variation often appropriate. Support for the role of beta blockade comes from several prospective studies that show a reduction in the rate of aortic dilatation and the risk of aortic dissection in patients treated with negatively inotropic doses of propranolol or atenolol.[281] [282] However, short-term administration of propranolol to patients with large sinus of

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Valsalva aneurysms, although reducing heart rate and peak systolic pressure, did not improve the impedance characteristics recorded in the ascending aorta. However, in the presence of studies that emphasize the importance of central pulse pressure to aortic dilation,[284] use of beta blockade seems warranted.[283]

A woman with Marfan syndrome has two concerns about pregnancy (see also Chap. 65) . The first is the 50:50 risk that any child will inherit the condition; prenatal diagnosis can currently be attempted in selected situations. The second is the risk of dissection that the hemodynamic stresses of pregnancy place on the aorta. Several dozen case reports attest to the heightened incidence of dissection during the third trimester, parturition, and the first month post partum.[285] [286] However, in the majority of instances, serious aortic dilatation was present. Prospective evaluation of 21 women through 45 pregnancies confirmed our earlier recommendation that the cardiovascular risks are relatively low if the aortic diameter does not exceed 40 mm and cardiac function is not compromised[286] , a view shared by others.[287]

ETIOLOGY.

Marfan syndrome is caused by mutations in the gene that encodes fibrillin-1 (*FBN1*), the major constituent of microfibrils, components of the extracellular matrix that are widely dispersed and perform numerous functions.[262] [288] [289]

Microfibrils and tropoelastin form elastic fibers. Fragmentation and disorganization of elastic fibers in the aortic media have long been a histological marker (inappropriately

called cystic medial necrosis) of Marfan syndrome,[263] although similar microscopic pathology occurs in familial aortic aneurysms and aging aortas of the normal population. A defect in microfibrils explains all of the pleiotropic manifestations of Marfan syndrome.[262] [290]

More than 100 distinct mutations in *FBN1,* the gene that encodes fibrillin-1, have been found in different families, and only a few have occurred, by chance, in unrelated patients.[290] [291] Because *FBN1* is such a large gene (9000 nucleotides in the mRNA), finding a mutation is still not a simple matter.[176] [292] Once the mutation is identified, diagnosis in that family is straightforward. In families with several alive and cooperative affected members, linkage analysis can be used for presymptomatic and prenatal diagnosis. The use of molecular testing is confounded, however, by the discovery that autosomal dominant ectopia lentis, familial tall stature, MASS phenotype, and familial aortic aneurysm all are phenotypes found to be due to mutations in *FBN1* and are exactly the conditions clinicians are interested in excluding in their patients of questionable diagnosis.[290]

Mutations in *FBN1* have distinct effects on microfibril formation: Some affect synthesis, others secretion, and others incorporation of fibrillin-1 monomers into the extracellular matrix.[293] [294]

MITRAL VALVE PROLAPSE AND THE MASS PHENOTYPE.

This heterogeneous group of conditions, described earlier (see p. 1993) likely contains large numbers of patients and families who have a defect of the extracellular matrix underlying the phenotypes. Some but not all have mutations in *FBN1.*[262] [290]

Ehlers-Danlos Syndrome

This group of heterogeneous conditions is linked by variable involvement of the skin and the joints, with hyperelasticity and fragility of the former occurring with hypermobility of the latter[261] [295] (Fig. 56-9) . Mitral valve prolapse is clearly increased in frequency in most of the clinical types,[296] but aortic root dilatation is an uncommon finding.

The most serious cardiovascular problems occur in the *vascular form of Ehlers-Danlos syndrome* with spontaneous rupture of large- and medium-caliber arteries.[296A] Various defects of type III collagen are the cause of the phenotype in virtually all patients studied.[297] Analysis of collagen production by cultured skin fibroblasts should be

Figure 56-9 Legs of a patient with Ehlers-Danlos syndrome type IV who died of rupture of the subclavian artery. Note the mild joint hypermobility and the striking dermal abnormalities--elastosis perforans serpiginosa and thin, atrophic scars over areas of recurrent trauma.

used to confirm the diagnosis.[14] True aneurysms rarely form; rather, a rupture without dissection usually occurs as a catastrophic event. Most prone are the abdominal aorta

and its branches, the great vessels of the aortic arch, and the large arteries of the limbs. False aneurysms and fistulas[298] may be one result in those patients who do not die of the initial rupture. Vascular surgery is difficult, as the normal-appearing vessels around the rent fall to hold sutures. As a consequence, elective surgery to repair vascular anomalies, such as false aneurysms, that are causing no immediate problem is contraindicated in most cases. The vascular form of Ehlers-Danlos syndrome is often sporadic but, when familial, is usually autosomal dominant.[298A] Prenatal diagnosis is possible by examining collagen production in amniocytes. However, pregnancy is particularly hazardous to women with this condition because of vascular rupture, although some mutations may not be as dangerous.[297] [299]

Pseudoxanthoma Elasticum (PXE)

This is a clinically variable and genetically heterogeneous disorder of unknown cause. Histopathological examination of affected tissues shows fragmentation and calcification of elastic fibers. The skin, the eyes, the gastrointestinal system, and the cardiovascular system are the organs most severely affected.[261] [300] The skin shows highly characteristic raised yellowish papules (pseudoxanthoma) overlying areas of flexural stress, such as the neck, cubital and popliteal fossae, and groin (Fig. 56-10) . Breaks in the elastic lamella, Bruch membrane of the choroid, produce the funduscopic finding of angloid streaks. Gastrointestinal hemorrhage is common and potentially fatal; mucosal arterioles bleed, and because the calcified elastic fibers prevent effective vessel retraction, hemostasis is difficult. Selective arterial embolization was life saving in one instance.[301] The heart is affected in a number of ways. Endocardial fibroelastosis is common, but because primarily the atria are involved, a restrictive cardiomyopathy is uncommon. One patient with marked endocardial fibroelastosis was helped by resection of calcified elastic bands within the left ventricle.[306] Mitral valve prolapse may be increased in frequency[302] [303] but is rarely a clinical problem. Coronary artery disease with myocardial ischemia and infarction is a common cause of early death.[304] [305]

Elastic and muscular arteries, including the coronaries, develop a type of arteriosclerosis similar to Monckeberg; progressive luminal narrowing occurs and can produce complete occlusion. This is initially most evident at the radial and ulnar arteries, where absence of pulses

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Figure 56-10 Skin of a young man with pseudoxanthoma elasticum. The neck is a typical location to notice the raised, yellowish papules from which the name of the condition derives.

and a positive Allen test result are noted early in the course.[304] Because narrowing progresses slowly, collaterals form, and peripheral ischemia is a late complication. Because the arterial stenoses tend to be diffuse, bypassing them often involves extensive surgery. Because of a positive association between phenotypic severity and dietary calcium intake, patients can be advised to restrict consumption of dairy products

and to avoid calcium supplements.[307] Hypertension and all risk factors for atherosclerosis should be aggressively controlled.

Through linkage analysis, both the recessive and dominant forms of PXE have been mapped to the same region of chromosome 16.[308]

Genetic Susceptibility to Acquired Disorders of Connective Tissue

Genetic factors are clearly implicated in the susceptibility to many of the rheumatic disorders and to specific complications of specific conditions.[233] The cardiovascular manifestations of these disorders are particularly interesting in this regard. For example, study of HLA-DR antigen frequencies suggests that immune-response factors are involved in the pathogenesis of chronic rheumatic heart disease in blacks.[309]

INBORN ERRORS OF METABOLISM THAT AFFECT THE CARDIOVASCULAR SYSTEM

Hundreds of biochemical defects that affect human metabolism have direct or secondary impact on the cardiovascular system (see Table 56-12) . Several examples are reviewed, selected for their relevance to clinical practice or their instructive lessons about pathophysiology.

Aminoacidopathies

Inborn errors of amino acid metabolism result in the accumulation of precursors and a deficit of end products, either or both of which can be detrimental.

Alkaptonuria

An intermediate of tyrosine catabolism polymerizes to homogentisic acid, which readily accumulates in the extracellular matrix.[310] Over many years, connective tissue of cartilage, heart valves, and arteries becomes increasingly abnormal. Aortic stenosis and arteriosclerosis are the cardiological sequelae.

Homocystinuria

This condition is caused by a deficiency of cystathionine beta-synthase; the pathogenesis of the pleiotropic manifestations is largely unknown.[13] [311] [312] Perhaps the amino acid sulfhydryl groups bind to collagen, fibrillin, and other macromolecules and interfere with cross-linking. The clinical features, once confused with Marfan syndrome, include tall stature, skeletal deformity, ectopia lentis, mental retardation, psychiatric disturbances, and a predilection for venous and arterial thromboses. Those patients with mutations that render the enzyme activity able to be increased by pharmacological doses of pyridoxine are less severely affected; early treatment can prevent most aspects of the phenotype.[313] [313A] Patients unresponsive to pyridoxine can be helped by a low-protein diet to reduce intake of methionine and by oral betaine, a co-factor

essential for remethylation of homocysteine.

Myocardial infarction, pulmonary embolism, and stroke are the most common causes of death. The pathogenesis of the vascular complications was once thought to involve abnormal platelet function, but platelet survival in untreated patients is normal.[314] Growing evidence supports a susceptibility of heterozygotes, who have none of the external phenotype of the disease, to atherosclerosis.[315] [316] [317] Various actions of homocysteine on endothelial receptors, stimulation of smooth muscle growth, and production of extracellular matrix components are being explored for clinical relevance.[318] [319] Current therapeutic approaches are focused on maintaining physiological levels of the co-factors involved in metabolism of sulfurated amino acids--folate and vitamins B_6 and B_{12} .[320]

Disorders of Fatty Acid Metabolism

Although most organs can metabolize fatty acids when faced with hypoglycemia, only the heart depends on fatty acids as the primary source of energy generation. Thus, it is not surprising that virtually all genetic defects in fatty acid metabolism, including generalized defects in mitochondria and peroxisomes, are associated with myocardial dysfunction. Other substrates--glucose, lactate, and oxaloacetate--also generate energy in myocardial cells by entry into mitochondria and the tricarboxylic acid (Krebs) cycle. Thus, defects in conversion of pyruvate to acetyl coenzyme A and in any point along the tricarboxylic acid cycle and the respiratory chain have a major impact on myocardial energy generation. Quite likely, some sporadic and familial instances of idiopathic cardiomyopathy may represent undiagnosed or undefined metabolic disorders.

CARNITINE DEFICIENCIES.

Carnitine is a required co-factor for entry of long-chain fatty acids into mitochondria and is both synthesized endogenously and available from dietary sources.[321] Deficiency of carnitine effectively blocks metabolism of long-chain fatty acids throughout the body and hepatic metabolism of ketones. Because of their relative dependence on fatty acids, muscle cells, including myocytes, suffer out of proportion to other tissue when carnitine levels are low for any reason. Cytoplasmic inclusions of lipid are characteristic findings in myocytes and hepatocytes.

Several mendelian defects produce primary or secondary carnitine deficiency. An autosomal recessive defect in carnitine palmitoyltransferase I leads to increased plasma carnitine and a skeletal muscle myopathy with little effect on the heart.[321] So-called systemic carnitine deficiency can have various causes: primary deficiency of intake, synthesis, or function, and secondary deficiency, the majority now known to be a result of defects in fatty acid metabolism. The latter group of conditions usually does not respond to pharmacological doses of carnitine.[321] [323]

Primary carnitine deficiency usually presents in infancy with hypoglycemia, coma, and congestive heart failure due to dilated cardiomyopathy. In the few cases reported, problems largely resolve with carnitine treatment; they can be prevented from recurring

by oral supplementation with L-carnitine. [323] [324] Primary systemic carnitine deficiency is due to a defect in carnitine transport, which leads to excessive urinary loss and which affects muscle but not liver.[322] Thus, muscle cells still may be relatively deficient in carnitine, despite supplementation, and long-term prognosis is uncertain.

DEFECTS OF BETA-OXIDATION.

At least 20 steps are involved when a molecule of free fatty acid leaves the plasma, enters beta-oxidation in the mitochondrion, and generates electrons and acetyl-CoA[321] At each turn of the oxidation spiral, two carbons are removed from the fatty

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acid, and the enzymes involved in this step are specific for substrates of only certain chain length: long-chain, medium-chain, and short-chain acetyl-CoA dehydrogenases, or LCAD, MCAD, and SCAD. Thus far, patients with defects in nine of the steps have been characterized.

Patients homozygous for these generally autosomal recessive disorders develop episodic hypoketotic hypoglycemia, usually associated with fasting or intercurrent illness. Deficiency of MCAD is the most common cause and occurs in about 1 of every 7000 newborns in the United States. Hypoglycemic crises can rapidly progress to coma and death, and 50 to 60 percent of affected infants die in the first 2 years of life.[325] Because infants between episodes or before a fatal crisis appear normal, MCAD deficiency accounts for a proportion of so-called sudden infant deaths.[326] Histopathological examination shows microvesicular accumulation of fat in cardiac and skeletal muscle. One mutation in MCAD (A985G) accounts for a large percentage of all alleles that predispose to this lethal disorder, and various approaches to newborn screening are being investigated.

MITOCHONDRIAL MYOPATHIES.

All of the enzymes of fatty acid oxidation are encoded by genes located on nuclear chromosomes, but the components of the electron transport chain are encoded by both nuclear and mitochondrial genes. Several syndromes involving various types of myopathies have been shown to be due to mutations in the mitochondrial chromosome.[10] [11] The *Kearns-Sayre* syndrome includes pigmentary degeneration of the retina, ophthalmoplegia, and cardiomyopathy as its most prominent manifestations; all of the affected tissues rely nearly exclusively on oxidative phosphorylation for energy generation.

The *MELAS syndrome* (*m*yopathy, *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes) is due to mutations in mitochondrial transfer RNA genes.[328] [329] In addition to the features that define the acronym, hypertrophic cardiomyopathy and diffuse coronary angiopathy are common. Various other mtDNA mutations are associated with

hypertrophic or dilated cardiomyopathy.[185] [330]

Variations in both the actual mutations and the fraction of abnormal mitochondria in the cells of the different organs (heteroplasmy) account for many of the clinical differences in phenotype, severity, and age of onset among patients with this disorder. Inheritance is maternal for patients with mitochondrial mutations; apparent autosomal recessive and dominant inheritance may indicate that mutations of nuclear genes can impair electron transport similarly to mitochondrial mutations. Some patients have been treated with moderate success over the short term with coenzyme Q[331] and with cardiac transplantation in one case.[332]

Glycogenoses

Three of the glycogen storage disorders affect cardiac muscle.

GLYCOGEN STORAGE DISEASE II.

This autosomal recessive condition is due to deficiency of the lysosomal enzyme alpha-1,4-glucosidase and results in the lysosomal accumulation of glycogen in most tissues. Several allelic variants occur.[333] The condition with infantile onset is called *Pompe disease,* and cardiac involvement is profound.[334] Infants with Pompe disease appear well initially but soon fail to thrive and develop hypotonia, tachypnea, and tachycardia; the disease progresses during the first year to irreversible congestive heart failure and death due to pneumonia or cardiopulmonary failure. Auscultation typically reveals no murmurs until late in the course when obstruction develops, and hypoglycemia does not appear because the nonlysosomal pathway of glycogen catabolism is intact. The diagnosis is suggested by massive cardiomegaly on examination and chest radiography and by characteristic echocardiographic abnormalities of a short PR interval and markedly increased QRS voltage.[335] Echocardiography shows tremendously thickened (pseudohypertrophic) ventricles, and Doppler interrogation or catheterization may reveal subaortic and subpulmonic pressure gradients characteristic of obstructive cardiomyopathy.

Reduced diastolic function of a restrictive cardiomyopathy develops eventually, and endocardial fibroelastosis is common.[335] [336] With these findings, the diagnosis of Pompe disease is virtually certain, but it can be confirmed by analysis of alpha-1,4-glucosidase activity in cultured fibroblasts. Prenatal diagnosis is possible by enzymatic assay of amniocytes. Treatment is supportive, but cardiac transplantation could correct the cardiac problem; unfortunately, involvement of other organs, including the lungs, liver, and skeletal muscle, might eventually prove just as serious as the cardiomyopathy. Bone marrow transplantation might be a solution if performed early in the course. An animal model of alpha-1,4-glucosidase deficiency exists in cattle and develops cardiac pathology typical of human Pompe disease.[337]

Cardiomyopathy may develop in the juvenile-onset form of alpha-1,4-glucosidase deficiency,[338] but it is not invariable because of allelic heterogeneity. In one sibship without cardiac involvement, three brothers had extensive hepatic, skeletal muscle, and arterial smooth muscle accumulation of glycogen, and each died of rupture of a basilar

artery aneurysm.[339] The adult-onset form usually presents with insidious onset of respiratory insufficiency, and clinically important cardiac disease is rare.[340]

GLYCOGEN STORAGE DISEASE III.

The striking clinical variability in phenotype associated with deficiency of alpha-1,4-glucosidase is due in large part to the extensive array of mutations that occur at the *GAA* locus.[341] This autosomal recessive deficiency of amylo-1,6-glucosidase results in infantile- and juvenile-onset syndromes of muscle weakness, wasting, and hepatomegaly. Clinical cardiac disease is not common, although both cytoplasmic (nonlysosomal) and intermyofibril glycogen is routinely present in the heart and causes pseudohypertrophy and increased voltage on electrocardiography. The diagnosis has been established by enzymatic assay of an endomyocardial biopsy specimen.[342] [343] [344]

GLYCOGEN STORAGE DISEASE IV.

This is caused by deficiency of alpha-1,4-glucan: alpha-1,4-glucan 6-glycosyl transferase. It usually causes a fatal disorder of early childhood characterized by hepatic failure; although extensive deposition of polysaccharide occurs in the heart, death intervenes before cardiac symptoms appear. In the most severe form, the fetus has hydrops and generalized muscle degeneration.[345] As with all of the glycogen storage diseases, extensive allelic heterogeneity results in milder forms of the classic disorders. Patients with diagnosis later in adolescence tend to have more severe cardiomyopathy.[346] [347] Liver transplantation has been life saving in some cases and has, somewhat surprisingly, resulted in a reduction of glycogen deposits in the heart and skeletal muscles.[348] [349]

CARDIAC PHOSPHORYLASE KINASE DEFICIENCY.

Few cases of this enzyme deficiency have been reported: deposition of glycogen is confined to the heart, which may be massively thickened and enlarged, and leads to early death.[350] [351]

GLYCOPROTEINOSES.

This group of disorders results in the lysosomal accumulation of various compounds that cannot be catabolized further because of the specific enzyme deficiency (see Table 56-12) . Some have prominent cardiac pathology, generally of pseudohypertrophy and valvular thickening, which present with congestive failure, valvular dysfunction, conduction defects, or dysrhythmia.[352]

Hematological Disorders (See Chap. 69)

HEMOCHROMATOSIS.

This autosomal recessive disorder of unknown cause results in iron deposition in many

tissues, including the myocardium. The manifestations include diabetes mellitus, skin hyperpigmentation, hypogonadism, hepatic failure with cirrhosis, hepatoma, and congestive heart failure; severity is less, and age of onset later in women because of the autophlebotomy provided by menstruation.[353] The cause of the most common form of hereditary hemochromatosis is a gene, *HFE,* that is closely linked to the major histocompatibility locus on chromosome 6. One specific mutation accounts for a large proportion of the mutant alleles among whites.[354] Fully 10 percent of the population is heterozygous for a hemochromatosis mutation, suggesting that at an incidence of 2 to 3 per 1000, this disease is underdiagnosed. This frequency has given rise to interest in population screening by molecular genetic techniques, but for now traditional clinical laboratory approaches are appropriate.[355] Diagnosis depends on finding increased serum iron, ferritin, and, especially, transferrin saturation in the absence of any obvious cause of excessive iron intake.[356]

Cardiac involvement often appears first as dysrhythmia or congestive heart failure. Dysrhythmia, conduction abnormalities, and low QRS voltage are typical electrocardiographic findings; cardiomegaly is seen on chest radiography, and a dilated cardiomyopathy with reduced systolic

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function can be documented on echocardiography.[357] [358] Occasional patients have a restrictive pattern on cardiac catheterization.[359]

Treatment by repeated phlebotomy is most effective if begun before organ damage is irreversible. If a patient with congestive heart failure has not yet developed serious compromise in other organs, cardiac transplantation may be contemplated, as may combined heart-liver replacement.

HEMOGLOBINOPATHIES (See also Chap. 69) .

Sickle cell disease and other hemoglobinopathies associated with sickling can produce ischemia and infarction in numerous organs by occlusion of small vessels[360] ; however, the heart is relatively resistant.[361] Nonetheless, the combination of chronic hypoxemia and anemia produces a sustained high-output state that leads to congestive heart failure in many adults. The cardiovascular system can also be compromized by systemic hypertension due to renal infarction, pulmonary embolism and infarction (the chest pain of which often causes concern about myocardial ischemia), pulmonary hypertension,[362] stroke,[360] and hemosiderosis from chronic transfusions.

In addition to a hyperdynamic congestive failure, iron overload is the principal risk to the myocardium in other causes of decreased erythrocyte production *(thalassemias)* and increased erythrocyte consumption *(hemolytic anemias)* requiring repeated transfusions. Treatment with daily injections of deferoxamine can, if begun early, prevent the development of severe cardiac and hepatic disease.[363] Development of an oral iron chelator would greatly improve compliance and efficacy. Various approaches to

management of sickle cell disease, including hydroxyurea, show promise.[364] Combined heart-liver transplantation has been used in a case of end-stage organ failure with homozygous beta-thalassemia.[365]

Mucopolysaccharidoses and Disorders of Targeting Lysosomal Enzymes

Many of the specific disorders in these two groups share phenotypical manifestations and are caused by various defects in the ability of lysosomes to catabolize proteoglycan and glycosaminoglycan. Short stature, progressive coarsening of facial features, a skeletal dysplasia termed dysostosis multiplex, corneal clouding, and protean effects on the cardiovascular system are common[366] [367] [368] [369] [370] (Fig. 56-11) . Only MPS IS (Schele syndrome), the mild form of MPS IH (mild Hunter syndrome), MPS IV (Morquio syndrome), and MPS VI (Maroteaux-Lamy syndrome) have minimal or no mental impairment.

CARDIOVASCULAR MANIFESTATIONS.

The cardiovascular complications (see Table 56-12) , which are all progressive and usually insidious, arise from engorgement of cells and tissues with macromolecular storage material.[371] First, the ventricular walls become pseudohypertrophic, and systolic function gradually deteriorates. The electrocardiogram shows reduced QRS voltages; rarely is any conduction disturbance present. Second, coronary arteries narrow because of intimal and medial thickening.[372] Myocardial infarction is common in MPS IH and the severe form of MPS II, although the patients are usually too retarded to complain of classical symptoms, and the diagnosis is made post mortem.[373] Third, valve leaflets thicken and cause progressive dysfunction that is oddly specific for individual disorders. For example, aortic stenosis is common in MPS IS, and mitral regurgitation is frequently found in MPS IH and MPS IV. Finally, narrowing of the upper and middle airways causes obstructive apnea, chronic hypoxemia and hypercarbia, pulmonary hypertension, and eventually cor pulmonale.[374] [375]

MANAGEMENT.

Treatment of children with those conditions that caused mental retardation has in the past been supportive. Increasing experience with bone marrow transplantation in many of the conditions shows that in the survivors of the transplant, somatic accumulation of mucopolysaccharide can be reduced, with clinical improvement in cardiopulmonary function.[366] [376] [377] However, improvement of central nervous system function has been marginal or absent. Nonetheless, bone marrow transplantation may have a role, especially in MPS IV and MPS VI, in which cardiopulmonary compromise can greatly shorten otherwise productive lives. Attempts at cardiovascular surgery, indeed of any procedure requiring general anesthesia, are fraught with risks of difficult intubation, hyperextension of the neck with cervical cord damage (the odontoid process is often hypoplastic), and prolonged efforts to wean from mechanical ventilation.[374]

Figure 56-11 Hurler syndrome in a 4-year-old girl. Note short stature and coarse facial features.

Sphingolipidoses

FABRY DISEASE.

This X-linked condition deserves comment because the diagnosis is often not made until adulthood, when serious end-organ damage has occurred.[378] As a result of deficiency of alpha-galactosidase A, ceramide trihexoside and other glycosphingolipids accumulate in lysosomes of many cells and organs, especially endothelial cells, glomerular and tubular cells of the kidneys, and the heart. Microangiopathy causes the characteristic skin lesion, angiokeratoma, and may contribute, along with primary nerve involvement, to acroparesthesias and painful crises. Proteinuria and hypertension precede renal failure, which has often led to death in males and often leads by the fourth decade to the need for long-term dialysis or renal transplantation. A successful kidney allograft does not correct the systemic metabolic defect,[379] and the disease usually progresses in other organs.[380] Infusion of purified human alpha-galactosidase A shows promise of reducing tissue storage of glycosphingolipid.[380A]

CARDIAC MANIFESTATIONS.

Structural and functional cardiac involvement is qualitatively similar to that in the mucopolysaccharidoses. Thickening of the myocardium is pseudohypertrophy due to deposition of glycosphingolipid in lysosomes; the diagnosis has been made by endocardial biopsy during the evaluation of unexplained ventricular hypertrophy or frank obstructive cardiomyopathy.[381] [382] [383] [384] Chronic hypertension can exaggerate left ventricular dysfunction, as can ischemia and infarction due to diffuse luminal narrowing of the coronary arteries. Echocardiography is useful for serial documentation of myocardial function.[385] Although valvular thickening and MVP are common, hemodynamically important mitral regurgitation is not.[386] The pulmonary vasculature becomes narrowed and right-sided pressures rise, but cor pulmonale is rarely a problem. The electrocardiogram often shows a shortened PR interval, increased left ventricular voltages, and dysrhythmia. Medium-sized arteries throughout the body develop luminal narrowing, with cerebrovascular disease the most common cause of death after renal failure.

Heterozygous females generally show some clinical manifestations, especially in the eyes, and at much later ages than hemizygous males develop renal, cerebrovascular, and cardiac disease.[378] [385] [386] [387] Prenatal diagnosis is possible, and a detailed family history and genetic counseling are essential whenever the disease is found. Various mutations occur in the gene for alpha-galactosidase A and account for much of the clinical variability.[382] [384] [388]

Familial Amyloidoses (See also Chap. 48)

Various disorders, defined initially by clinical phenotype and due to progressive accumulation of amyloid in organs and tissues, are beginning to be categorized by the

underlying biochemical and genetic defects.[389] The several conditions termed familial amyloidosis with polyneuropathy and originally classified as separate autosomal dominant disorders are now known to be due to different mutations in the

same gene encoding transthyretin, a thyroxine- and retinol-binding protein also called prealbumin. Although polyneuropathy dominates the early course during young adulthood, renal failure and restrictive cardiomyopathy supervene later and cause death in most cases. The age of onset, severity, and predilection for kidney and cardiac involvement are determined by the type of mutation, with males affected earlier and more severely.[390] [391] [392]

Liver transplatation can prevent progression of the disease and potentially reverse some tissue accumulation[393] ; when the myocardium is severely infiltrated, combined liver-heart transplant offers the only hope.

NEUROMUSCULAR DISORDERS (See Chap. 71)

CARDIAC TUMORS (See also Chap. 49)

The three most common tumors that originate in the heart are myxomas, fibromas, and rhabdomyomas. All occur as part of hereditary syndromes and as sporadic events. The new occurrence of any of these tumors, especially in a child, may represent the first manifestation of a systemic condition, so a detailed general examination and family history are always indicated.[394] [395] [396] [397] For example, 51 to 86 percent of cardiac rhabdomyomas occur because of tuberous sclerosis.[398] [398A] Tumors due to hereditary disorders tend to be multiple and to recur after resection. An example is the NAME syndrome (for *n*evi, *a*trial myxoma, *m*yxoid neurofibromata, and *e*phelides; the acronym ignores the numerous endocrine tumors) also called Carney complex, in which many myxoma can occur throughout the myocardium. [399] [400] [401] [402] [403] [404]

INHERITED DISORDERS OF THE CIRCULATION

Hereditary Hemorrhagic Telangiectasia

This autosomal dominant condition, often called Osler-Rendu-Weber disease, is more common than appreciated. Because of marked intrafamilial and interfamilial variability, the condition may remain undiagnosed in affected patients for years despite mild manifestations.[405] [406] [406A] Mucocutaneous telangiectases, 0.5 to 3 mm in diameter, occur on the tongue, lips, and fingertips most commonly. Small and moderate-sized arteriovenous fistulas occur in the nose, leading to recurrent epistaxis, in the gastrointestinal system, where they cause recurrent bleeding and occult anemia, and in the lungs, resulting in hypoxemia, hemoptysis, polycythemia, clubbing, paradoxical embolization through the right-to-left shunt, and a hyperdynamic circulation. Less

common sites of vascular malformations are the brain,[407] [408] liver,[409] and the kidneys.[410] Diffuse ectasia of the coronary arteries was noted in one patient.[411] and hemorrhagic pericarditis with tamponade in another.[412] Bleeding is facilitated, even in the presence of normal platelet function and clotting function, because of the lack of resistance channels in the telangiectatic lesions.[413]

Patients with hereditary hemorrhagic telangiectasia (HHT) and their close relatives should be screened for pulmonary arteriovenous malformations through auscultation, arterial blood gas analysis, and chest radiography. A low Pa_{O_2} should prompt consideration of angiography and therapeutic balloon occlusion of the feeding arteries of any sizable malformation to prevent systemic embolization, especially to the brain.[414] In a few patients, epistaxis and gastrointestinal blood loss have been reduced by antifibrinolytic therapy with danazol or aminocaproic acid.[415] [416] [417] Controlled trials of various approaches to chronic management, taking into account clinical and genetic variables, are sorely needed.

At least three genes are capable of causing HHT, and two have been mapped, to 9q33-q34 and to 3p22. The former locus encodes a transforming growth factor-beta-binding protein called endoglin, and various mutations segregate with HHT in different families.[418] The other locus encodes an activin receptor-like kinase 1 gene,[419] which is a member of the serine-threonine kinase receptor family, expressed in endothelial cells. This suggests that defects in this gene might affect development or repair of vessels. Yet a third locus is likely.[420] Thus, by mutation detection or linkage analysis, presymptomatic and prenatal diagnosis is available to a large number of patients with a potentially life-threatening disorder.

Von Hippel-Lindau Syndrome

The features of this autosomal dominant condition involve malformations and abnormal growth of small blood vessels. Retinal angioma, hemangioblastoma of the cerebellum, and hemangioma of the spinal cord occur in association with renal cell carcinoma, pancreatic and epididymal cystadenomas, and pheochromocytoma.[421] [422] Secondary hypertension due to renal disease and pheochromocytoma, which is often bilateral, occurs and predisposes to subarachnoid hemorrhage. The cause is a tumor suppressor gene, *VHL,* at 3p26-p25. [423] Patients inherit a germline mutation (and there is great diversity among families in the actual mutations)[424] that is present in all cells. When a somatic mutation in the normal allele occurs in a susceptible cell, such as in the renal parenchyma or adrenal medulla, the cell becomes functionally homozygous for a lack of the gene product, and the cascade toward neoplasia is initiated.[425] How this gene product stimulates or permits angiomatous malformations is unclear.

Disorders Primarily Affecting Arteries

Mendellan disorders are associated with a diverse array of arterial pathology, and some were described or catalogued earlier in this chapter. This section deals with two categories of disorders caused by a single mutant gene: pleiotropic syndromes better known for affecting organ systems other than the vasculature, and primary

abnormalities of arteries.

ADULT POLYCYSTIC KIDNEY DISEASE (APKD).

This relatively common autosomal dominant disease affects 0.5 million people and accounts for 8 to 10 percent of all long-term hemodialysis in the United States. Development of renal cysts is age dependent, and presymptomatic detection of heterozygotes, even by ultrasonography, can be uncertain into adulthood.[426] [427] About one-half of patients are hypertensive, one-half have hepatic cysts, one-half eventually develop severe renal failure, and an unknown (but probably high) fraction have colonic diverticula. Elevated plasma renin levels contribute to hypertension long before renal failure occurs.[428] The cardiovascular manifestations include MVP in one-quarter, mild dilatation of the aortic root, occasional thoracic and abdominal aneurysms, and a predisposition to regurgitation of the aortic, mitral, and tricuspid valves.[429] [430] [431] The association of diverticula, organ cysts, and cardiovascular lesions reminiscent of but milder than Marfan syndrome suggests some involvement of the extracellular matrix.

The most serious vascular problem is typical berry aneurysms of the cerebral circulation, which occur in about 10 percent of heterozygotes but may remain asymptomatic throughout life. Hypertension predisposes to subarachnoid hemorrhage. How to screen for and treat intracranial aneurysms in patients without neurological symptoms remains controversial. Cerebral angiography carries higher risks in patients with APKD because of dissection and heightened vascular reactivity.[432] Magnetic resonance imaging detects most saccular aneurysms down to 2 to 3 mm in diameter. Whether to attempt prophylactic repair when a small aneurysm is detected has not been investigated systematically. Without question, aggressive blood pressure control is indicated in any patient with APKD.

At least three genes cause APKD. The greatest portion of cases are due to mutations in a gene called *PBP* at the *PKD1* locus (16p13.3).[432A]

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In most of the rest of families, the disease maps to the *PKD2* locus in the region 4q23-q23. Families affected by mutations in *PKD2* tend to develop renal failure later and have a milder course.[433] In both *PKD1* and *PKD2,* the multiorgan cysts develop when a somatic mutation occurs in the normal allele at the respective mutant locus, analogous to the two-hit model so familiar with tumorigenesis.[434] [435] A French Canadian family with disease typical of *PKD1* is unlinked to either locus, indicating that a *PKD3* gene exists.[436]

ARTERIOHEPATIC DYSPLASIA.

An autosomal dominant disorder of marked variability, *Alagille syndrome* causes neonatal jaundice due to aplasia of intrahepatic bile ducts and congestive heart failure in the most severely affected infants but may be asymptomatic in heterozygous

relatives.[437] [438] The cardiovascular findings include peripheral pulmonic and systemic arterial stenoses in the majority, occasionally associated with septal defects or PDA. A diffuse vasculopathy is present in some patients.[439] Renal disease may produce hypertension. The locus was initially mapped by studying chromosomes and finding in some patients that part or all of band 20p12 was missing (an interstitial deletion). The *Jagged1* gene, which mapped to this exact region, was then identified as the cause.[440] [441]

ARTERIAL ANEURYSM, ECTASIA, OR DISSECTION

(see also Chaps. 30 , 40 , and 41) . Pedigrees abound in which dilatation of the aortic root, aneurysm of the abdominal aorta, aortic dissection without dilatation, or a combination of these problems occurs in an autosomal dominant pattern without evidence of a recognized heritable disorder of connective tissue.[442] [443] [444] Because of the variable presentation and natural history of the aortic disease, presymptomatic detection of presumed heterozygotes is uncertain, as is reassurance of relatives at risk who are of childbearing age and would prefer not to pass this condition to offspring.

The association of dissection of the ascending aorta with bicuspid aortic valve and aortic coarctation is well known, although the cause and pathogenesis remain unclear. In such cases, the aortic wall shows abnormalities of elastic fibers.[445] A person with a congenitally bicuspid aortic valve or aortic coarctation should be screened for dilatation of the aortic root, and first-degree relatives should be screened for both lesions. This recommendation is based, in part, on bicuspid aortic valve being a congenital heart defect of the left-sided flow category, with a relatively high recurrence risk.

In two families with autosomal dominant transmission of arterial aneurysms and mild increased skin fragility and bruisability, different mutations in the gene encoding type III procollagen occurred.[446] [447] Thus, depending on the mutation, deficiency of type III collagen can cause the vascular form of Ehlers-Danlos syndrome (see p. 2003) or a form of the much subtler but just as deadly syndrome, familial arterial rupture. For these families in which the mutations have been defined, reliable presymptomatic and prenatal diagnoses are at hand. However, suggestions that mutations in type III collagen would account for the majority of aortic aneurysms, including abdominal aneurysms in the elderly, have proved unfounded.[448]

A predisposition to cervical arterial dissection in young people was found to be associated with diffuse lentiginosis in several families, with a suggestion of autosomal recessive inheritance.[449] An association is also noted between cervical dissection and intracranial hemorrhage, which is increased when congenital casdiovascular defects are present, especially bicuspid aortic valve or aortic coarctation.[450] [451]

Formal genetic analysis of 91 families ascertained through a proband with *abdominal aortic aneurysm* suggests that an autosomal recessive predisposition exists for late-onset aneurysms.[452] This study and others [453] provide a rationale for offering ultrasound screening to sibs of patients with abdominal aortic dilatation.

FAMILIAL ARTERIAL TORTUOSITY.

This is a rare, possibly autosomal recessive condition of unknown cause. Diffuse ectasia of all systemic arteries occurs with, paradoxically, peripheral pulmonic stenoses.[454]

FAMILIAL INTRACRANIAL HEMORRHAGE.

In addition to APKD, three syndromes predispose to subarachnoid or cerebral hemorrhage. *Berry aneurysms* without pleiotropic manifestations in other organs are a rare but well-documented autosomal dominant trait.[455] How aggressively near relatives should be screened for intracranial aneurysms remains controversial because of the relatively low risk of hemorrhage compared with the morbidity and mortality of current surgical techniques for repairing defects.[456] [457] [457A] A defect in type III collagen was suggested by linkage analysis, but sequence analysis of the gene in 55 unrelated patients found no mutations.[458]

The *cerebral arterial type of familial amyloidosis* (type VI) is an autosomal dominant condition due to a defect in the proteinase inhibitor cystatin O.[459] This disease is rare outside of Iceland and Holland. The walls of cerebral arteries are thickened by a material resembling amyloid, and the vessels become tortuous and fragile. Recurrent cerebral hemorrhage is common in the fifth and sixth decades of life.[460]

Familial hemangiomas have been reported infrequently to occur as an autosomal dominant condition.[461] The brain and retina are the principal sites of vascular malformation, although in some pedigrees, cutaneous lesions occur. The intracranial hemangioma can be large and present with varied neurological symptoms, including hemorrhage. A more benign familial disorder of primarily isolated cutaneous hemangiomas also exists.[462]

FAMILIAL ARTERIAL OCCLUSIVE DISEASES[463]

Fibromuscular dysplasia of the renal and other arteries occurs in *von Recklinghausen neurofibromatosis* and, along with pheochromocytoma, can be a cause of hypertension.[464] [465] Severe deficiency of alpha$_1$ -antiprotease is another cause of fibromuscular dysplasia.[466] The arterial lesion can occur by itself in families and produce stroke, myocardial infarction, intermittent claudication, and hypertension at young ages, as early as childhood.[467] Inheritance is most consistent with autosomal dominance.[468]

Familial hypoplasia of the carotid arteries,[469] *familial arteriopathy* caused by concentric thickening of systemic and pulmonic arteries,[470] familial moyamoya disease (which has been mapped to 3p24.2-p26),[471] and generalized *arterial calcification of infancy*[472] all are rare, possibly mendelian, syndromes of unknown cause.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is due to mutations in the *NOTCH3* gene.[472A] Characteristic inclusions occur in vascular smooth muscle cells, and the deep, perforating cerebral arterioles develop occlusions that produce insidious onset of symptoms and transient ischemic attacks.

FAMILIAL HEMIPLEGIC MIGRAINE.

The migraine syndrome is commonly familial and occurs in many generations. A severe form, associated with recurrent hemiplegia, is inherited as an autosomal dominant trait and is due to mutations in a sodium channel gene.[473] [474] However, some families with hemiplegic migraine and others with simple migraine are unlinked to this locus.[475] [476] In the same region of 19p is a locus causing autosomal dominant cerebral arteriopathy with subcortical infarcts.[477] Whether the two conditions are related through allelism is unclear.

FAMILIAL PULMONARY HYPERTENSION

(see also Chap. 53) . Primary pulmonary hypertension (PPH) is occasionally familiar.[478] [479] [480] Inheritance is most consistent with an autosomal dominant predisposition with sex influence favoring expression in females. A locus for PPH occurs in the region 2q31-q32 and the defect in some way leads to monoclonal proliferation of endothelial cells.[481] [482] [483] Molecular defects favoring recurrent microemboli to the pulmonary circulation afford another area to explore.

Pulmonary hypertension can occur in *neurofibromatosis* due to pulmonary fibrosis. [484]

Disorders Primarily Affecting Veins

VARICOSE VEINS.

Although a familial susceptibility to varicosities of the lower extremities clearly exists and favors women in a ratio of 2:1, mendelian inheritance has not been confirmed. *Marfan syndrome,* various *Ehlers-Danios syndromes,* and an autosomal recessive condition featuring distichiasis (a double row of eyelashes)[485] predispose to varicose veins.

ATRETIC VEINS.

Some patients with the *Klippel-Trenaunay-Weber syndrome* of cutaneous hemangioma and hemihypertrophy have atresia of the deep venous system.[486] The concomitant superficial varicosities should not be stripped, lest the remaining venous drainage of the lower extremity be removed. This is a confusing syndrome that overlaps with several others; mendelian inheritance is uncertain. Renal arterial aneurysm and hemangioma occurred in one patient.[487]

CAVERNOUS ANGIOMAS.

Cavernous angiomas represent at least 15 percent of vascular malformations of the central nervous system, and familial occurrence is common.[488] These are not arteriovenous malformations but primarily a tortuous collection of veins. Seizure is the most common presenting feature, followed by headache, stroke, and progressive neurological deficit. Magnetic resonance (T_2 -weighted) imaging is the procedure of choice because it is sensitive, and arteriography is not likely to detect the venous malformation. In some families, hepatic angiomas are an important feature.[489] The cause of one form has been identified as a gene, *KRIT1,* of unclear function. [490] [491] [492]

ARTERIOVENOUS MALFORMATIONS.

The most common mendelian cause of arteriovenous malformations (AVM) is the various forms of hereditary hemorrhagic telangiectasia. However, AVM, especially of the brain, are relatively common findings,[493] and other genetic susceptibilities may exist.

Disorders Primarily Affecting Lymphatics

Several forms of *hereditary lymphedema* exist, with the best studied inherited as autosomal dominants. An early-onset form bears the eponym *Nonne-Milroy lymphedema* and can cause a protein-losing enteropathy and pleural effusion. *Meige lymphedema* does not appear until about the time of puberty and is most severe in the legs, although one family with late-onset edema had involvement of the arms

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and face.[494] Considerable intrafamilial variability in age of onset is noted, however, and whether two or more distinct conditions exist remains unclear. Mutations in one of the receptors for vascular endothelial growth factor, *FLT4,* have been found in some families.[495] [496]

GENETIC FACTORS PREDISPOSING TO ATHEROSCLEROSIS (see also Chap. 31)

Various genetic factors, in addition to the well-studied errors of lipid metabolism, clearly predispose to atherosclerosis. Few genes outside of those involved in lipid metabolism have such an overwhelming impact as to be identifiable from the family history. However, genes that predispose to hypertension and diabetes mellitus; control arterial diameter, reactivity, and branching angles; affect platelet adhesiveness, thrombosis, and fibrinolysis; and regulate endothelial and smooth muscle function all can be considered candidate genes for study in families predisposed to atherosclerosis.[497] [498] [499] Screening numerous genes for common mutations and polymorphisms that convey risk information will be increasing possible.[501] [502]

ABNORMAL REGULATION OF BLOOD PRESSURE (see also Chap. 28)

Blood pressure is a quantifiable trait that shows continuous variation within the population. Although many genes and environmental factors undoubtedly affect a person's blood pressure, familial transmission of some arbitrarily defined disease "hypertension" follows neither mendelian nor multifactorial inheritance.[503] [504] [505] Various cybernetic systems operate to maintain the blood pressure within tolerable limits. When this physiological homeostasis goes awry or its limits are too lax, pathological and clinical consequences occur.[509] For example, sensitivity of the baroreflex was impaired in patients who had untreated essential hypertension and a positive family history of hypertension compared with hypertensive patients with no family history and to nonhypertensive controls.[506] The complexities of such systems are considerable, and two approaches have been taken in recent years to focus the analysis.[505] [507] [508] [509] One involves a candidate-gene approach in humans, based on loci known to be involved in physiological pathways, and the second involves naturally occurring and experimentally created strains of animals.

STUDIES OF HUMANS.

All of the classical approaches to detecting genetic influences in diseases--twin studies, familial aggregation, adoption--confirm that genes have a role, but less than 5 percent of patients with hypertension have a defined genetic cause.

Occasional families show striking mendelian segregation of hypertension without being associated with one of the identifiable syndromes listed in Table 56-13 . One example, in which early, severe hypertension is inherited as an autosomal dominant trait, is *Liddle syndrome.*[510] [511] Because of hypokalemia, aldosteronism was suspected, but both aldosterone and renin levels were low. Attention then focused on sodium resorption in the distal nephron and its regulation. Mutations discovered in the beta subunit of the epithelial sodium channel render the channel insensitive to the usual regulators.

Another example of successful application of the candidate gene approach is investigation of *glucocorticoid-remediable aldosteronism.*[512] The phenotype was mapped to chromosome 8q21, a region already known to contain two candidate genes, aldosterone synthase and 11beta-hydroxylase. By honing in on these loci, mutations creating a chimeric gene by unequal recombination were found to be the cause.[513] As a result of the fusion, aldosterone synthase comes under regulation of adrenocorticotropic hormone. The actual frequency of such mutational events is considerably higher than suspected in the population, and the molecular means are now available to assess the epidemiology of what will likely be a common cause of early hypertension.

Angiotensinogen, the gene for which is in the region 1q42-q43, is a logical candidate gene to investigate because of the central role of its product in blood pressure regulation. Several polymorphic variants involving single amino acid substitutions occur; at positions 174 and 235, either methionine (M) or threonine (T) can exist. The special effects of these polymorphisms on activity, if any, are unclear, but persons homozygous for the 235T allele have plasma angiotensinogen levels 20 percent higher than those

with the 235M alleles. Some but not all studies have found an association between the 174M and 235T alleles and hypertension.[514] [515] [516] The importance of these polymorphisms seems to depend on the ethnic background.[517]

The ACE gene, at 17q23, contains a common insertion/deletion polymorphism, termed I and D, respectively, that permits both association and linkage studies. The three possible genotypes are DD, ID, and II, and the plasma level of ACE is highest, for unclear reasons, in persons who are DD and lowest in those who are II. The DD genotype has been associated with predisposition to coronary artery disease and to myocardial infarction, which may account for a relative decrease of hypertensive patients with the DD genotype at older ages.[518] [519]

Pregnancy is a clear risk factor for hypertension. A susceptibility locus for preeclampsia has been identified.[520] [521]

The opposite of hypertension, inappropriate control of pressure on the low side, also has numerous genetic bases (Table 56-15) . [504] [522] [523]

STUDIES IN ANIMALS.

The stroke-prone spontaneously hypertensive (SHRSP) rat is an example of an animal model for a human disease that arose in nature. The phenotype of the rat is clearly polygenic and is thus particularly relevant to much of essential hypertension in humans. Using polymorphic markers spread throughout the rat genome, it has been possible to conduct linkage analyses of hundreds of markers with hypertension when SHRSP animals were crossed with a nonhypertensive strain. Two loci have been identified, and one lies close to where ACE maps.[524] This general approach, called quantitative trait mapping or linkage (QTL), is increasingly being applied to various phenotypes in animals and humans. Determining the actual gene involved in the animal model should then suggest that the homologous locus in the human is a candidate for participation in normal and abnormal regulation of the trait.

A second approach in animals involves transgenic or knockout techniques to create and breed a new, specific genotype. In simplest terms, a given gene can be eliminated, can be mutated in a specific way, can be moved to a different strain (genetic background), or can be overexpressed (See also Chap. 55) . For example, eliminating function of the gene that encodes atrial natriuretic peptide in the mouse resulted in moderate elevation of blood pressure when sodium intake was low or somewhat high. Mice heterozygous for the mutation had normal blood pressure on these salt loads but became abnormally hypertensive when fed a high-salt diet.[525] [526]

A number of mendelian conditions, most of which are rare, cause major deviations of blood pressure from an appropriate physiological range (see Table 56-15) . These disorders are likely to be underdiagnosed.

TABLE 56-15 -- MENDELIAN DISORDERS ASSOCIATED WITH ABNORMAL BLOOD PRESSURE

DISORDER	OMIM NO.*	PATHOGENESIS
Primarily elevated blood pressure		
Adrenal hyperplasia IV	202010,	11-beta-hydroxylase deficiency 11-deoxycorticosterone
Adrenal hyperplasia V	202110,	17-alpha-hydroxylase deficiency 11-deoxycorticosterone
Aldosteronism	103900,	Aldosterone
Alport syndrome	104200,	Renal failure
301050,		
Amyloidosis, familial visceral (amyloidosis VIII)	105200,	Nephropathy
Arterial calcification of infancy	208000,	Arteriosclerosis
Arterial fibromuscular dysplasia	135580,	Renal artery stenosis renin
Arteriohepatic dysplasia	118450,	Renal dysplasia; renal arterial stenosis
Bartter syndrome	241200,	Secondary to hyperaldosteronism
Fabry disease	301500,	Renal failure; renal arterial stenosis; arteriolar stenosis peripheral resistance
Liddle syndrome	177200,	Defective epithelial sodium channel k^+ aldosterone, renin, angiotensin

Multiple endocrine neoplasia I	131100,	Adrenocortical adenoma Cushing syndrome
Multiple endocrine neoplasia II	171400,	Pheochromocytoma catecholamines
Nail-patella syndrome	161200,	Nephropathy
Neurofibromatosis type I	162200,	Pheochromocytoma catecholamines; and renal arterial fibromuscular dysplasia
Paraganglioma	168000,	Catecholamines
Pheochromocytoma, familial	171300,	Pheochromocytoma catecholamines Catecholamines
Polycystic kidney disease, adult	173900, 173910	Renin; renal failure
Porphyria, acute intermittent	176000,	?, but only during acute attacks
Pseudohypoaldosteronism, type I	264350,	Aldosterone receptor deficiency
Pseudohypoaldosteronism, type II	145260,	Defective renal secretion of potassium
Pseudoxanthoma elasticum	177850,264800,	Arteriosclerosis
Riley-Day syndrome	223900,	Dysautonomia
von Hippel-Lindau syndrome	193300,	Pheochromocytoma catecholamines
Wilms tumor	194070, 194071, 194090,	?
Primarily low blood pressure		
Dopamine beta-hydroxylase deficiency	223360,	Synthesis of epinephrine
Fabry disease	301500,	Peripheral vascular tone

Hyperbradykininism	143850,	Bradykinin
Pelizaeus-Merzbacher, late-onset	169500,	?
Peripheral motor neuropathy and dysautonomia	252320,	?
Pheochromocytoma, familial	171300,	Catecholamines (epinephrine)
Shy-Drager syndrome	146500,	Primary autonomic insufficiency

**Data from Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim).*

Does not include hypovolemia, obstruction of blood flow, and cardiogeneic causes of hypotension, each of which subsumes numerous hereditary disorders as primary causes.

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Part VII - CARDIOVASCULAR DISEASE IN SPECIAL POPULATIONS

2019

Chapter 57 - Cardiovascular Disease in the Elderly

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PATHOPHYSIOLOGY

The age at which patients become "elderly" is difficult to define because aging is a continuum, with blurred boundaries between middle and old age. Ideally, the term "elderly" should be marked by distinct changes in physiology, but the rate of physiological aging varies and may not advance in lock step with chronological changes, so that one can be physiologically young but chronologically old, and vice versa. In some reports the elderly are defined by eligibility for Medicare benefits (65

years). In others, age cutoffs of 70 or even 75 years are used.

Aging is characterized by a gradual loss of function in many organ systems, unrelated to a pathological condition. Certainly, in many old individuals comorbid diseases complicate the aging process; but independent of associated diseases, aging produces major cardiovascular changes, including decreased elasticity and compliance of the aorta and great arteries.[1] These alterations result in a higher systolic arterial pressure and an increased impedance to left ventricular (LV) ejection, and subsequent mild LV hypertrophy and interstitial fibrosis.[2] A decrease in the rate of myocardial relaxation also occurs. As a result, the LV becomes stiffer and takes longer to relax and fill in diastole, thus increasing the importance of a properly timed atrial contraction in contributing to a normal LV end-diastolic volume (Fig. 57-1) and forming the basis for diastolic dysfunction and congestive heart failure (CHF).[3] There is also a 50 to 75 percent loss of pacemaker cells in the sinus node, accompanied by a decrease in intrinsic and maximum sinus rate. The number of atrioventricular (AV) nodal cells seems to be preserved, although an increase in AV nodal delay (PR interval) is common. Increased fibrosis of the fibrous skeleton of the AV annuli occur, along with fibrosis and loss of specialized cells in the His bundle and bundle branches that can result in heart block. Heart valves thicken, and calcification results at the base of the aortic valve and mitral annulus.[4] Aging causes a decreased sensitivity of the heart to beta-adrenergic agonists and a diminished reactivity to chemoreceptors and baroreceptors.[5] There is no decrease in myocardial contractility solely as a result of aging, but diseases that do result in decreased contractility, such as hypertension (HTN) and coronary artery disease (CAD), are common in this age group.

Figure 57-1 Effect of age on early diastolic filling and on atrial contribution to diastolic filling by echo-Doppler in healthy Baltimore Longitudinal Study on Aging (BLSA) participants. *(From Geokas MC, Lakatta EG, Makinodon T, et al: The aging process. Ann Intern Med 113:455-466, 1990.)*

Figure 57-2 Exercise-related changes in heart rate *(A),* end-diastolic volume *(B),* end-systolic volume *(C),* and stroke volume *(D)* in young (ages 25-44 years) *(triangles)*, middle-aged (ages 45-64 years) *(open circles)*, and elderly (ages 65-80 years) *(closed circles)* healthy men, according to increasing cardiac output with exercise. All groups had similar increase in cardiac output up to a workload of 150 watts. Note that the elderly increase cardiac output by increasing end-diastolic volume and stroke volume with exercise. *(From Gerstenblith G, Renlund DG, Lakatta EG: Cardiovascular response to exercise in younger and older men. Fed Proc 46:1834-1839, 1987.)*

Cardiac output remains normal at rest, but with a slower heart rate there is an increased reliance on the Frank-Starling mechanism to increase stroke volume and keep the cardiac output normal.[6] With exercise, a decrease in the ability to achieve maximum heart rate and oxygen consumption is seen in older as compared with younger patients. However, ejection fraction (EF) is kept normal by the increased stroke volume sustained

by the larger LV diastolic volume seen with exercise[6] (Fig. 57-2) .

Many of these alterations can be explained at cellular and subcellular levels. Cardiac fibrosis, reduction in the number of cardiac myocytes, increase in cell size and capacitance by 20 to 80 percent, and decreased responsiveness to beta-adrenergic receptor stimulation are typical changes found in older animal hearts. Interestingly, some of the same structural alterations parallel those that occur during development of myocardial hypertrophy. Aging hearts recapitulate the fetal phenotype in many aspects. Aging increases the magnitude of the L-type calcium current (ICa-L) in parallel with enlargement of cardiac myocytes, which may be important to help preserve contractile function (see Chaps. 14 and 15) . The increase in ICa-L is balanced by the enlarged cell size in aged myocytes so that, despite the increase in the numbers of ICa-L channels, the overall density becomes normalized by the increase in cell size and capacitance. However, ICa-L inactivation is slowed so that larger calcium influx can occur with each heartbeat.[7] Altered calcium homeostasis predisposes to calcium overload. Both the amplitude and the density of the transient outward current (Ito) are decreased with aging.[8] These changes in Ito, together with the delay in ICa-L inactivation, may largely account for prolongation in action potential duration as hearts age.

Drug Metabolism

The elderly consume a large percentage of all drugs prescribed. Three fourths of those 75 years of age and older receive drugs of some kind. Elderly outpatients in the community take 2 or 3 medications per day, and institutionalized geriatric patients take 3 to 8 or as many as 15 per day.[9] The pharmacokinetics of drugs have been evaluated mostly in the 65- to 75-year age group, and this information is extrapolated to old and very old patients of ages 80 to 85, because few studies in this age group have been done. Aging affects both the pharmacodynamics and pharmacokinetics of drugs (see Chap. 23) .

PHARMACOKINETICS

ABSORPTION.

Although drugs can be given intravenously, subcutaneously, or intramuscularly, most cardiovascular drugs are given orally and are absorbed by passive diffusion through the intestinal mucosa rather than by active transport. Aging decreases gastric acidity, slows intestinal motility, and decreases by 30 percent the mucosal area for absorption in, and decreases the blood flow to, the small intestine; yet none of these seems to affect cardiovascular drug absorption significantly.

DISTRIBUTION.

With aging, there is a decrease in lean body mass, and therefore a decrease in the volume of total body water. Diuretics, by decreasing the extracellular fluid, further decrease the volume of distribution and reduce the loading dose of the drug needed to

achieve therapeutic levels.

With illness comes a decrease in serum albumin level, counterbalanced partly by an increase in alpha-acid glycoprotein.[10] Although these changes may not be of major importance to a drug's effect, diseases that result in the loss of all plasma proteins such as renal failure can have a major effect. Furthermore, highly protein-bound drugs that compete for binding sites on the albumin can displace other drugs, increasing the free-drug plasma concentration and increasing the effect of the drug. This explains why warfarin, which is 98 percent protein bound, has so many drug-drug interactions.

ELIMINATION.

The major sites of drug elimination are through the kidney and metabolism by liver enzymes. Hepatic metabolism biotransforms the drug to a biologically inactive or a hydrophilic polar compound, cleared by the kidney. There are two phases of liver metabolism: Phase I reactions are discrete oxidative pathways of cytochrome P450 (CYP) occurring in the endoplasmic reticulum, whereas phase II reactions, those of conjugation, including glucuronidation, sulfation, and acetylation, occur in the cytosome. Aging results in a

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decrease in liver mass, and often also in the activity of the most important CYP enzymes involved in drug metabolism. Phase II conjugative reactions do not decrease with age.[11] Obviously, liver disease can affect the capacity of the liver to metabolize drugs.

Biotransformation can be influenced by drugs that either inhibit or cause induction of the CYP syndrome. Common drugs such as cimetidine, macrolide antibiotics, and quinidine inhibit the system, and drugs such as phenytoin and glucocorticoids induce the enzymes. For drugs metabolized by this CYP system, inhibition causes an increase in the plasma concentration and half-life, whereas induction causes a decrease.

Aging results in a decrease in the number of renal glomeruli and tubules, as well as in renal blood flow and glomerular filtration rate (GFR).[12] With a decrease in GFR, the dose of renally excreted drugs must be reduced parallel to this decline in GFR. Digoxin is an excellent example of a renally excreted drug.

Another important renal effect of aging involve angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory agents (NSAIDs). ACE inhibitors reduce conversion to angiotensin II and increase levels of bradykinin; aldosterone excretion is also decreased. This serves to decrease the constriction of the glomerular efferent arterioles and can result in decreasing renal function and even renal failure in the presence of renal artery stenosis. The decrease in aldosterone secretion with ACE inhibitors can increase serum potassium levels and result in hyperkalemia. These

effects are exaggerated in the elderly patient.

NSAIDs inhibit the synthesis of prostaglandins, which are responsible in part for regulating renal blood flow. In elderly patients with a low GFR, CHF, or liver disease, NSAIDs can further reduce renal function, causing hyperkalemia or frank renal failure from tubular necrosis or interstitial nephritis.[13] In the elderly patient using ACE inhibitors or NSAIDs, reduced doses of these drugs, with careful monitoring of renal function and serum electrolytes, are required.

PHARMACODYNAMICS.

Aging is associated with a decrease in cardiovascular responsiveness to $beta_1$-adrenergic stimulation, probably related to a decrease in adrenergic receptors[5] and in baroreceptor sensitivity. In the elderly patient, this accounts for less bradycardia with beta blockers than is seen in younger patients. The decrease in baroreceptor and $beta_1$-adrenergic responsiveness can result in a lack of compensatory tachycardia and exaggerated hypotension with the use of vasodilators and nitrates in elderly patients. Sensitivity to various calcium channel blockers appears to be increased in elderly patients, with a greater decrease in heart rate and blood pressure (BP) to the same serum concentration of verapamil or diltiazem than seen in the younger patient.[14]

Drug Interactions and Adverse Drug Effects

Age brings an increased incidence of adverse drug effects, occurring in one fourth of older patients and accounting for 3 to l0 percent of all hospital admissions for elderly patients.[15] Elderly patients often take multiple drugs; the number of medications taken is the most important risk factor for adverse drug reactions.[16] This polypharmacy results in noncompliance, because the elderly often confuse the drug schedule, especially for drugs given more than once a day. Another reason for noncompliance is the high cost of drugs, which may result in patients electing not to have prescriptions filled. Polypharmacy also results in adverse drug reactions from drug-drug interactions, owing to the interference of the pharmacokinetics of one drug on another. Another common reason for drug-drug interaction is competition between two highly protein-bound drugs for receptor sites, with displacement of one drug and a resultant increase in free drug in the plasma and drug effectiveness.

Other factors predicting poor compliance include a complicated drug regimen, multiple drugs, noncomprehension of instructions, mental impairment, visual or hearing disabilities, and no helper or relative at home. Legible instructions in the patient's language on easily opened bottles, certain memory aids, and the aid of visiting nurses can all improve compliance.

Drugs with similar effect can produce an additive pharmacological action (e.g., excessive bradycardia from a combination of verapamil and digoxin). Cardiovascular drugs that cause the most drug interactions are digoxin, warfarin, lidocaine, quinidine, and amiodarone.[17]

Basic principles of therapeutics in the elderly are as follows:

1. Know all the drugs the patient is taking.
2. Regularly review the drug regimen; insist that the patient bring all medicines to the next visit.
3. Take a careful drug history because of multiple drugs from multiple sources, including self-medication with over-the-counter drugs.
4. Know the pharmacokinetics and side effects of the drugs.
5. Start the drugs in the elderly at a low dose and increase in small increments and larger intervals than in younger patients until the desired effect is obtained.
6. Use the simplest drug regimen possible.
7. Adjust the dose by the patient's response.
8. Educate patient, family, and friends about the medicines, what they are for, and how to take them; also tell them about the major side effects. Be alert to drug-induced illness; in the elderly, this can be subtle or mistaken for symptoms due to the patient's disease. Drug-related effects can present as somnolence, confusion and even delirium, nausea, frequent falls, or urinary incontinence.
9. Expect noncompliance, and tell the patient what to do if the dose is missed or in cases of confusion about whether or not the drug was taken.

EPIDEMIOLOGY

Average life expectancy has risen from 47 years in the United States in 1890 to 72 years for men and 79 years for women by the end of the 20th century. At present, a person reaching the age of 65 has an average life expectancy of 18 more years; at age 85, this is 7 years.[18] The average maximum length of life, however, is 85 to 90 years and has not changed much.[19]

The population 65 years and older has grown from 20 million in 1970 to 35 million in 2000, and it is estimated that there will be 69 million by the year 2030 (20 percent of the U.S. population, up from 13 percent in 1997). By 2030, the fastest-growing segment of that elderly population will be those aged 85 and older,[18] growing from 2 million in 1970 to 4.5 million in 2000, and 8 million (estimated) by 2030.[18] The number of persons in the world who are 60 years old or older is estimated to be nearly 600 million in 1999 and is projected to be about 2 billion by 2050. At that time, the elderly population will exceed that of children from birth to 14 years of age for the first time in human history. At present, one in every 10 people is 60 years or older. By 2050, this is projected to become 1 in every 5. The percentage is growing fastest in the developed regions of the world. The older population itself is aging: currently, the oldest old (80 years or older) comprise 11 percent of the population 60 and older; by 2050, they are projected to comprise 19 percent. The number of those 100 years and older is projected to increase from 145,000 in 1999 to 2.2 million by 2050.[19] The aging pyramid, instead of becoming smaller in number as the age groups increase, will become more of a trapezoid, especially as the "baby boomers" become the elderly population.

In this older population cardiovascular disease plays a significant role and is the most common cause of morbidity and mortality.[20] Heart failure (HF) is the most common

diagnostic-related group in the Medicare population 65 years old and older. In the Framingham Heart Study, 44 percent of men and 28 percent of women aged 75 to 84 had cardiovascular disease; in the 85 to 94 age group, the prevalence was 48 percent in men and 43 percent in women.[21] CAD and HTN (especially isolated systolic HTN) increase as the population ages. In the United States, in people older than 65, HTN is present in about half the patients (Fig. 57-3) .[22]

The overall cost of treating cardiac disease in people older than the age of 65 years was estimated at $58 billion in 1995.[18] Hospital and nursing home care is the largest proportion of this cost. A recent study in 80- to 98-year olds found that most would rather extend their lives in

Figure 57-3 Prevalence of isolated systolic hypertension by the midpoint of the age classes reported in various studies. As shown by the unweighted regression line, the prevalence of systolic hypertension increases curvilinearly with age. The 95 percent confidence interval for the prediction of individual points is presented for the age range of 50 to 90 years. *(From Staessen J, Amery A, Fagard R: Isolated systolic hypertension in the elderly. J Hypertens 8:393-405, 1990.)*

their present state of compromised health than live shorter lives in excellent health.[23]

VALVULAR HEART DISEASE (see also Chap. 46)

Although any valve lesion can be seen in the elderly population, the most common valve diseases are calcific aortic stenosis (AS) and mitral regurgitation (MR) due to myxomatous mitral valve. MR due to ischemia, or previous myocardial infarction, resulting in a failure of the papillary muscle/LV complex to allow proper coaptation of the mitral leaflets, is also a common cause, along with LV failure for any reason. Mild to moderate MR usually occurs in patients with calcification of the mitral annulus. Ruptured chordae, endocarditis, trauma, and aortic dissection are other causes of aortic regurgitation (AR) and MR.

Aortic valve sclerosis, as a result of stiffening and calcification of the aortic annulus and base of the semilunar cusps, causes an early-peaking systolic ejection murmur that is short and grade III-VI or less in loudness. It does not represent significant obstruction. No physical findings of obstruction are present, nor is LV hypertrophy, but it is associated with other manifestations of atherosclerotic disease, especially CAD,[24] and indeed it may result from the atherosclerotic process. It can be found in about 30 percent of the elderly, whereas significant AS is seen in 2 to 3 percent.[24] The cause of AS in the older age group is calcific or degenerative, almost always on a normally tricuspid semilunar valve. Calcification is at the base and body of the semilunar cusps, and the commissures are not fused. Rheumatic heart disease is much less common, as is congenital AS. Patients with a bicuspid aortic valve are seen in the elderly age group, but most who develop calcification and severe obstruction do so between the ages of 40

and 60.[25] In the elderly AR can be due to rheumatic heart disease, but more often it is due to myxomatous changes and prolapse of the aortic cusp, aneurysmal aortic root dilation, infective endocarditis (possibly on a bicuspid aortic valve), or dissecting aorta.

Primary valve disease in the elderly rarely causes tricuspid and pulmonic valve regurgitation, which is usually secondary to pulmonary HTN and dilatation of the right ventricle. Pulmonary HTN can be due to LV diseases such as ischemia or cardiomyopathy, mitral stenosis, or intrinsic pulmonary disease. Primary tricuspid regurgitation due to infective endocarditis almost always occurs in intravenous drug users, who are rare in this age group. Primary tricuspid valve regurgitation (TR) can rarely be seen in elderly patients after trauma. Infrequently, an elderly patient is found with Ebstein disease and TR, or pulmonic valve regurgitation after tetralogy of Fallot repair with a patchenlarged pulmonary outflow tract and annulus.

DIAGNOSIS.

The diagnosis of significant valve disease can be difficult in the elderly population; echocardiographic-Doppler imaging can be of great help (see Chap. 7) . The loudness of an aortic stenotic murmur depends on the generated LV systolic pressure as well as on the stroke volume and the loudness of MR murmur on the regurgitant volume. If the cardiac output is low, the murmur of AS or MR may be soft or even absent. The loudness of the murmur also depends on the nearness of the site of origin of

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the murmur to the chest wall. Accompanying clues to severity can also be absent or confusing in the elderly. For instance, an S_4 gallop or the presence of LV hypertrophy in a young person with AS is a sign strongly suggesting hemodynamic severity of the AS. In the older patient, an S_4 is often present without AS, as is LV hypertrophy, especially in those patients who have had a long history of systolic HTN. In the elderly, the carotid upstroke can feel normal in severe AS because of the stiff aorta.

The severity of AR can be difficult to judge by physical examination in the elderly because of the frequent occurrence of a wide pulse pressure due to a stiff atherosclerotic aorta rather than to severe AR. Acute AR masks many of the peripheral signs of severe AR, because the LV filling pressure is high and the forward effective stroke volume is low, thus decreasing the rise of the systolic aortic pressure, increasing the diastolic pressure, and narrowing the pulse pressure. If the AR is very severe, the diastolic regurgitant gradient between the aorta and LV is small, and with tachycardia there may be little or no diastolic murmur. The collapsing quality of the carotid pulse and Duroziez sign, that is, the systolic and diastolic bruit heard on compression of the femoral artery by the bell of the stethoscope, remain as signs of severe AR.

Treatment

A problem with selecting therapy for the elderly is that, until recently, they have been excluded from most controlled trials, and information about treatment comes mostly from registries and observational studies. Medical therapy for elderly patients with valve disease is generally similar to that for younger patients.[26] In elderly patients, even with mild mitral valve disease, atrial fibrillation (AF) is common, and represents a markedly increased threat of systemic embolization and stroke. Anticoagulation, unless absolutely contraindicated, is essential.

VALVE SURGERY.

Deciding to send an elderly patient with significant valvular stenosis or regurgitation to surgery can be difficult and must be individualized because of the diversity of problems found in this age group. Generally, the patient younger than 75 has a similar morbidity and mortality to a younger patient with a similar problem. As the patient enters the late 60s and early 70s, a higher prevalence of comorbidity exists, with increased coronary, cerebrovascular, renal, hepatic, and pulmonary disease that add to surgical morbidity and mortality.[27] After age 75 to 80, surgical morbidity and mortality are increased, even beyond the impact of comorbidities, because age per se becomes an increasing risk factor for valvular surgery. In patients older than 75, the risk of neurological problems and stroke with cardiopulmonary bypass surgery increases.[28] The elderly have more problems than younger patients with mechanical valve replacement, mostly because of the increased complications from anticoagulation.[29]

The goals of valve surgery in the elderly are somewhat different from those in younger patients. In the older patient the major goal becomes relief of symptoms, with improvement in activity and quality of life rather than prolongation of life.

Aortic Stenosis.

After the occurrence of symptoms of HF, exertional syncope, angina, or myocardial infarction without obstructive CAD, mortality in patients with severe AS increases rapidly, so that the mean survival is 3 years for symptomatic patients, shorter with HF symptoms, and somewhat longer with angina. In all probability, survival is even less in the elderly. Also, the incidence of sudden death increases in the symptomatic patient with AS, accounting for one fifth to one fourth of all deaths (see Chap. 46) . Surgery should be recommended once symptoms begin, depending on the overall status of the patient and the number and severity of comorbidities. Only in the presence of a decreasing EF, or possibly with increasing runs of nonsustained ventricular tachycardia, should a patient not complaining of symptoms be offered surgery.[26]

Patients with AR who undergo aortic valve replacement do not fare as well as patients with AS, especially if they are in New York Heart Association (NYHA) Class III or IV or have a decreased LV EF.[30] Long-term morbidity and mortality are increased in patients with moderate to severe AR if they have symptoms, an EF less than 50 to 55 percent, comorbidities, or an increased LV end-systolic diameter by echocardiography (>25

mm/m^2).[26] [31] Surgery is, therefore, indicated in these patients.

Aortic Valve Replacement.

In younger patients who have pliable valves and AS due to commissural fusion, successful commissurotomy, either surgically or by balloon valvotomy, is possible, with good results lasting 15 to 30 years.[32] In elderly patients with AS of whatever cause, the aortic valve is always severely calcified, and valvotomy, either by surgery or balloon, has a limited, short-lived success. With severe AR, valve replacement is the rule, except for ascending aortic aneurysm or AR with aortic dissection, in which ascending aortic grafting with valve resuspension can be done with long-term success.[33]

In most series of patients older than 70 years, perioperative mortality varies from 2.4 to 12.4 percent, depending on comorbid conditions, increasing patient age, the presence of other cardiac lesions or concomitant operations such as mitral valve repair or replacement, or coronary artery bypass graft (CABG).[34]

As experience has increased, perioperative mortality has fallen to 6 to 10 percent for aortic replacement and CABG[35] and 4 to 7 percent with isolated aortic replacement. Factors that predict perioperative mortality in patients older than 75 years are NYHA functional therapeutic Class IV, decreased LV EF, chronic HF, the presence of comorbid diseases such as pulmonary or renal disease or diabetes, and concomitant procedures such as mitral valve surgery, coronary artery surgery, or surgery performed as an urgent procedure. Other independent predictors of hospital mortality include cardiomegaly, serum creatinine level greater than 150 mmol, and operation as an emergency procedure. Predictors of late mortality are comorbid diseases such as severe renal, pulmonary, or coronary disease and poor LV function.[30] [36] Patients with coexisting minimal-to-moderate AS or AR who have cardiac surgery for other than aortic valve disease (e.g., coronary surgery or mitral valve replacement) generally experience very slow progression of the aortic valve disease. Consequently, there is no indication to replace the aortic valve at that time.[37] However, the higher the aortic valve gradient and the heavier the aortic valve calcification, the more likely the AS will progress, and therefore the more reasonable it becomes to replace the aortic valve at the time of the primary surgery.

As many as 40 percent of patients with AS in the elderly age group have at least one significantly obstructed coronary artery.[38] The presence of atheromas in the descending aorta by transesophageal echocardiography is a good predictor of CAD.[39] Although stress echocardiography has been recommended to detect CAD in patients with AS,[40] stress testing is generally unnecessary, because in this age group coronary arteriography is justified preoperatively to assess the status of the coronary arteries[26] (see Chaps. 6 and 7) . Aortic valve debridement can result in relief of severe calcific AS; however, it has been abandoned by most surgeons because there is a rapid restenosis and, with some techniques, a high incidence of increased AR (see Chap. 46) . Occasionally it can be beneficial. [41]

A biological tissue valve, rather than a mechanical valve, is most often placed in this elderly age group because of their shorter life expectancy, because biological valves are

less subject to tissue failure in elderly patients,[27] [42] and because of the dangers of anticoagulants in the elderly.[29] For most tissue valves, even in younger patients, there is no significant failure for 5 to 10 years, long enough to last the natural life of the elderly patient.[42] With aortic valve replacement, operative mortality is slightly increased with age and more markedly increased with comorbidity and severity of disease; however, the results of surgery are excellent, with a definite increase in quality of life.

Mitral Valve Repair/Replacement.

With MR, because of multiple causes and especially CAD causing severe MR, the results of valve replacement are not as good as with AS; 5-year survival after both coronary surgery and mitral valve replacement is only about 50 percent.[43] With mitral valve replacement, the major risk factor for mortality is the presence of CAD.[44] Patients do well after repair of MR, with

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perioperative mortality of 4 percent and 25 months late mortality of 6 percent.[45] Thus, the elderly undergoing mitral valve surgery do not do as well as those having aortic valve replacement or younger patients and fare better with mitral valve repair than with replacement.

Balloon Valvotomy.

For calcific AS, balloon valvotomy increases aortic valve area, but rapid restenosis follows. Because balloon valvotomy is not an alternative to valve replacement, its use is restricted to very old, extremely symptomatic patients who are poor candidates for surgery, where the procedure might improve cardiac output and peripheral organ perfusion, and relieve afterload on the LV enough to allow surgical valve replacement at a later time. It can also be useful in those patients who are not candidates for surgery because of comorbid problems and who are repeatedly hospitalized for HF. Balloon valvotomy can keep these patients out of the hospital for a variable period of time, and improve quality of life.[46] Balloon valvotomy for MS has become the procedure of choice when the valve is not heavily calcified and MR is absent or minimal. The results of balloon valvotomy are equivalent to those of open commissurotomy, and both are better than closed commissurotomy.[47] Mitral valve calcification, frequent in the elderly, reduces the success rate and increases mortality and complications.[48]

CORONARY ARTERY DISEASE (see also Chaps. 35 , 36 , and 37)

PREVALENCE AND INCIDENCE.

As the population ages, the prevalence and annual incidence of the development of overt CAD increases substantially with age, as does the total number of people with clinical CAD (Fig. 57-4) . The severity and diffuse distribution of the coronary obstruction

also increases, presumably as a result of prolonged exposure to atherosclerotic risk factors. There is a striking gender difference, with men developing CAD at a younger age than women (37 percent in men aged 65 to 74 vs. 22 percent in women of the same age range). The prevalence of CAD in the Framingham cohort aged 75 to 84 years was 44 percent in men and 28 percent in women. In the 85- to 94-year age range, the prevalence of CAD was 48 percent in men and 43 percent in women.[49] The lifetime risk of developing CAD at age 40 is 49 percent for men and 32 percent for women, decreasing to 35 percent for men and 24 percent for women at age 70, or 1 in 3 for men and 1 in 4 for women.[50]

MORTALITY.

Almost 85 percent of people who die of CAD are age 65 or older. According to data from the Health Care Financing Administration, in 1995, $98 billion ($3,769 to $11,110 per discharge) was paid by Medicare to Medicare beneficiaries for CAD. Of 2.3 million Americans discharged from hospitals with a first-listed diagnosis of CAD in 1996, 57 percent were 65 years of age or older.[51] CAD mortality is about twice as high in men as in women and higher in blacks than in whites. After age 70, mortality in white men is higher than in black men. In women, mortality in blacks exceeds that in whites until age 85.[52] Although mortality from CAD has been declining since 1970, the decline is greater in white men and women than in blacks (average annual percentage change 3 to 4 percent vs. 2 to 3 percent), more robust than in the age groups up to 85 but still 1 to 2 percent in even the oldest age groups.[52] After adjustment for major risk factors, with each decade of advancing age, a twofold to threefold increase in coronary vascular mortality persists.

RISK FACTORS (See Chaps. 31 , 32 , and 39)

The impact of many risk factors for CAD, such as HTN, diabetes, and LV hypertrophy, increases with age. Although the benefits of risk-factor reduction in the elderly for some risk factors is incomplete, excellent evidence exists that control of BP, for example, reduces cardiovascular events even in the older age group.

HYPERTENSION (see Chaps. 28 & 29).

Because HTN is so common in the older population, and the number and type of effective drugs so numerous, this is one of the most controllable of the risk factors. Fifty-seven percent of men and 61 percent of women aged 65 to 74 and 64 percent of men and 77 percent of women aged 75 and older have HTN, as defined by at least one ambulatory BP reading of 140 mm Hg systolic or 90 mm Hg diastolic or higher.[18] Both systolic and diastolic elevation of BP is associated with an increased risk of CAD in men and women. People older than 65 years with systolic pressure greater than 180 mm Hg have a threefold to fourfold increase in risk of CAD compared with people with a systolic pressure of less than 120 mm Hg. A diastolic pressure greater than 105 mm Hg increased the risk two to three times compared with a diastolic pressure of less than 75 mm Hg.[53]

Isolated systolic HTN (systolic pressure greater than 140 mm Hg with a diastolic pressure less than 90 mm Hg)[54] is very frequent in the elderly and is partially related to the loss of elasticity and compliance of the aorta and arterial branches. The risk of stroke, CHF, renal disease, renal insufficiency, and probably coronary artery events decreases with a decrease in the degree of systolic HTN, as shown in the Systolic Hypertension in the Elderly Program (SHEP trial) (see Chap. 29) . Treatment of HTN in the elderly population reduces the risk of cardiovascular events, especially stroke and CHF, and probably decreases the incidence of myocardial infarction.[55]

Figure 57-4 Prevalence of coronary heart disease by age and sex. (NHAHES III, US 1988-1991.) *(From Kannel WB, Wilson WF, Larson MG, et al: Coronary risk factors and coronary prevention in octogenarians. In Wenger NK [ed]: Cardiovascular Disease in the Octogenarian and Beyond. 1st ed. London, Martin Dunitz, 1999, p. 143.)*

SMOKING (see Chaps. 31 , 32 , and 39) .

Cigarette smoking declines in prevalence with advancing age to about 15 percent of men and 11.5 percent of women age 65 and older.[56] Although smoking is a powerful risk factor in the younger patient, it is unclear if smoking exerts the same risk in the older population[57] and whether smoking cessation in elderly patients decreases the incidence of coronary events. In the Coronary Artery Surgery Study (CASS) registry, patients older than age 70, all of whom had CAD, who continued to smoke, had three times the risk of death or myocardial infarction during a 60-year follow-up period compared with those who stopped smoking. In the British Physicians' Study[58] and the U.S. Nurses' Health Study,[59] smoking was an independent risk factor for coronary events in both younger and older age groups. However, the Framingham Heart Study showed that in individuals older than age 65 the incidence of lung cancer is accelerated, but there was no correlation between the incidence of smoking and CAD.[60] The explanation for the latter may be that, although there is increased risk of CAD from smoking, there is increased mortality from other smoking-related diseases in this age group. It is also possible that those susceptible to CAD from smoking died at a younger age, and among the persons who survive to age 65, fewer patients are susceptible to CAD from smoking.

HYPERLIPIDEMIA (see Chap. 31) .

Serum cholesterol concentration increases progressively until age 50 in men and age 65 in women and then begins to decline. High-density lipoprotein value is higher in both men and women and stays constant with aging.[61] Among people 65 to 74 years of age, 22 percent of men and 41 percent of women have a total serum cholesterol value of greater than 240 mg/dl; for those older than 75 years, 20 percent of men and 38 percent of women have cholesterol levels greater than 240 mg/dl.[18] Although the association

between the risk factor of an elevated serum cholesterol level and the development of CAD is less striking in the elderly, the ratio of total to high-density lipoprotein cholesterol remains a strong predictor of CAD in the elderly.[62] Elevated triglycerides have been independently associated with an increased risk of CAD in elderly women but not men.[63] Treatment with HMG-CoA reductase drugs can reduce the incidence of acute cardiac events in patients up to 75 years of age; older patients have not been studied.[64]

DIABETES MELLITUS (see Chap. 63) .

In 1996, there were 503,000 Americans discharged from the hospital with a first-listed diagnosis of diabetes mellitus. Of these, 39 percent were older than 65 years of age. The prevalence of physician-diagnosed diabetes in patients aged 60 and older is 12 to 13 percent for men and women. The vast majority of patients older than age 70 have non-insulin-dependent (type II) diabetes. Its presence doubles the risk of CAD and, when combined with hyperlipidemia, increases the risk 15-fold.[65]

PHYSICAL INACTIVITY.

Approximately one third of men and women aged 65 to 74, and 38 percent of men and 51 percent of women aged older than 75 years, report no leisure-time physical activity. Frequent exercise raises high-density lipoprotein cholesterol, controls obesity, and lowers systolic and diastolic BP even in patients 60 to 80 years old and reduces insulin resistance.[66] Even moderate amounts of exercise have been shown to protect against CAD events in middle-aged and older men in the Framingham Heart Study.[67]

Other risk factors for CAD, such as lipoprotein (a) and other apolipoproteins, are still being investigated. A high homocystine level is not uncommon in elderly men and is strongly associated with increased prevalence of coronary heart disease and cerebrovascular disease.[68] After an acute myocardial infarction (AMI), patients with depression who are socially isolated have an increased recurrence rate and mortality[69] (see Chaps. 39 and 70) . This social isolation is more common in the elderly.

Clinical Presentation

Elderly patients have more multivessel disease and lower EF than do younger patients.[70] Although angina pectoris is a common first presentation of CAD in the elderly, angina may not occur until the CAD is well advanced because of often markedly decreased activity. For this reason, acute ischemic syndromes are common initial presentations of CAD.[70] Also, many symptoms of discomfort that would alert a younger person are explained away in the elderly patient as a consequence of "getting old."

When angina occurs, the precipitating factors and the description, with radiation and its relief by rest, are similar to that in younger patients. However, with advancing age, a frequent presenting symptom is increasing fatigability and shortness of breath during activity because of the ischemic effects on systolic and diastolic myocardial function. In patients with documented CAD, anginal pain without dyspnea is reported in 25 to 43 percent of persons older than age 65, dyspnea without chest discomfort in 8 to 25

percent, and both dyspnea and angina in almost 50 percent.[71] Others have reported the initial manifestation of CAD in the elderly to be angina in 80 percent.[72] As many as 30 percent have silent ischemia.

With increasing age, the gender composition of patients with AMI changes from 80 percent men younger than 55 to about 50 percent men aged 75 to 84 and only one third men aged older than 83.[73] Sudden pulmonary edema is a common presentation of AMI in the elderly, but chest pain is still the most common, as it is in younger patients. Neurological symptoms as a presentation of AMI, such as syncope, stroke, or confusion, are more likely seen in the elderly, as is painless AMI. Non-Q-wave myocardial infarctions are more common in the elderly. Physical examination, especially during the ischemic episode, can be very helpful. Unlike younger patients, an S_4 gallop rhythm is very common in elderly patients with and without CAD; however, the appearance or increase in the loudness of an S_4 or S_3 gallop or MR murmur during the chest discomfort or dyspnea and its disappearance with relief of the chest discomfort or dyspnea are strong evidence in favor of a transient decrease in diastolic ventricular function, the most common cause of which is CAD. For the same reason, an electrocardiogram (ECG) taken during the time of the discomfort that shows definite ST segment elevation or depression, or marked T wave inversion, which reverses after the discomfort abates, is excellent evidence of severe CAD. Because LV hypertrophy is common in elderly patients, ST segment/T wave changes can be present chronically on a resting ECG and are of limited help in diagnosing myocardial ischemia unless the ST segment/T wave changes are transient and associated with chest discomfort.

SILENT ISCHEMIA.

The presence of significant CAD without symptoms increases with age. Because only about 20 percent of people older than 80 have clinically evident CAD[74] and over 50 percent have significant CAD at autopsy,[75] a large number of elderly people must have significant CAD without symptoms. About one third of asymptomatic hypertensive elderly patients have a myocardial infarction discovered incidentally on ECG. An equal number have silent ischemia. The reason for increased silent ischemia in the elderly patient is not known, but it may be related to mental status changes impairing perception or recall of ischemic pain, to the development of collaterals that reduce the severity of the myocardial ischemia, to autonomic dysfunction, or to increased sensitivity to endogenous endomorphins.[76] Although the presence of silent ischemia may not predict a worse prognosis for the patient with CAD than its absence, most people with silent ischemia have a positive exercise test result and so probably have more extensive CAD.

Diagnosis

The diagnosis of CAD in the elderly can be suspected by finding a history of typical angina or atypical symptoms related to exertion, and by a careful physical examination, as indicated earlier. Stress testing is done to establish the diagnosis and to determine risk stratification and prognosis (see Chap. 6) . The high prevalence and increased severity of CAD in the elderly, by Bayesian principles, increases the sensitivity of stress

testing but makes it harder to exclude significant disease because of more false-negative test results.[77]

The criteria for a positive exercise test result in the elderly do not differ significantly from those in the younger patient.[77] As in younger patients, the test is less likely to be positive with single-vessel disease but is 80 to 85 percent sensitive in identifying patients with three-vessel or left main CAD. In patients older than 60 to 65 years, the sensitivity for diagnosing the presence of significant CAD varies from 62 to 84 percent, and the specificity from 56 to 93 percent, depending on the population studied. The ability to walk through the second stage of Bruce protocol (>6 minutes) predicts low risk.[77]

The increased number of false-positive test results seen in the elderly is probably attributable to an abnormal resting ECG, the presence of LV hypertrophy from HTN or valve disease, or intraventricular conduction defects. Prognosis depends on the amount of ischemic and nonfunctioning myocardium, reflecting the effect of severity and extent of CAD on LV function. For risk stratification, attention should be paid to the chronotropic and inotropic responses to exercise, exercise-induced arrhythmias, and the duration of exercise. Arrhythmias are common in the elderly, especially at high workloads, but are not necessarily an adverse feature unless they occur with other signs of ischemia.[77] Inability to increase the heart rate to 85 percent of age-predicted maximum, or a hypotensive response to exercise, are poor prognostic factors, similar to those seen in younger patients.

PROGNOSTIC VALUE OF STRESS TESTING.

Stress testing offers challenges to the elderly. Many have orthopedic or neurological problems that prevent active walking on a treadmill. Many are physically deconditioned and may have an abnormal resting ECG, making criteria of ST segment shifts for positivity less reliable. In a study of patients older than 65 years observed for 2 years, those with ST segment depression during stress testing had a 17 percent cardiac death rate, whereas the incidence was only 2 percent in those without ST segment depression. [78] In patients older than 70 years who had exercise stress testing 3 weeks after an AMI and were observed for a mean of 4.5 years, of those who failed to increase double product from rest to exercise by more than 1500, and also developed ventricular arrhythmias with exercise, only 25 percent were still alive at the end of the follow-up time, whereas in the absence of either response, 77 percent were still alive.[78A] Patients after AMI who are unable to increase systolic BP with exercise greater than 30 mm Hg have a 1-year mortality of 15 percent compared with 2 percent for those who did increase their BP.[78B] Using the Duke treadmill score combining ST segment depression, chest pain, and exercise duration is useful to predict significant (>75 percent) stenosis and severe three-vessel or left main disease.[77]

When the patient can exercise, but the resting ECG is abnormal or has a feature that

makes it impossible to diagnose ischemia (left bundle branch block, pacemaker, or marked ST segment changes), then myocardial perfusion study at rest and after exercise, using tracers such as thallium-201, technetium-99m sestamibi or technetium-99m tetrofosmin single-photon emission computed tomographic imaging (see Chap. 9) , or stress echocardiography (see Chap. 7) can be used to detect areas of scarring or ischemia. When exercise cannot be done, pharmacological tests using dipyridamole or adenosine to vasodilate coronary arterioles and increase coronary blood flow maximally to areas without stenotic arteries, or dobutamine to increase myocardial oxygen demand and create ischemia, can be used. Dobutamine stress testing is safe in the elderly. These techniques are more sensitive than exercise testing in identifying single- and two-vessel disease, and, like exercise testing, are also useful for risk stratification. With the use of thallium-201 perfusion tests on 120 patients older than 70 years with known or suspected CAD, three variables were associated with a cardiac event: (1) a maximum ST segment depression of
2 mm (27 percent with vs. 6 percent without), (2) peak exercise beyond stage 1 of the Bruce protocol (18 percent event rate in those who could not go beyond this stage vs. 6 percent in those who could), and (3) the presence of either a fixed or a reversible thallium defect (18 percent event rate with vs. 2 percent without). The combination of inability to attain peak exercise beyond stage 1 and the presence of any thallium defect were the most powerful predictors, with a relative risk of 5.3 at 1 year.[79]

Acute Myocardial Infarction (see also Chap. 35)

In the elderly, AMI results in an increase in mortality compared with younger patients. Eighty percent of all deaths due to AMI occur in those 65 years of age and older.[74] In a population-based study over a 20-year period between 1975 and 1995, patients aged 55 to 64 were 2.2 times more likely to die of AMI during hospitalization than were patients younger than 55, whereas patients aged 65 to 74, 75 to 84, and older than 85 years were at 4.2, 7.8, and 10.2 times greater risk of dying.[73] In the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO)-I study of 41,021 patients, in-hospital mortality from AMI younger than age 65 was 3 percent as opposed to 9.5 percent at age 65 to 74, 19.6 percent at age 75 to 85, and 30.3 percent in those older than 85 (Fig. 57-5) . [80] Age alone can result in changes that increase mortality from AMI due to increasing diastolic dysfunction, altered baroreceptor and beta-adrenergic receptor responsiveness, and age-related decreases in renal and pulmonary function, all of which make the patient vulnerable to increased complications. Older patients have an increased comorbidity with pulmonary, renal, and hepatic disease. A more adverse baseline status in AMI prevails with higher NYHA functional class, prior history of CHF, prior myocardial infarction, angina, HTN or diabetes mellitus, low EF, and cardiovascular disease; and more of the elderly are women.[81] Complications of myocardial infarction are also more frequent in the elderly, including

Figure 57-5 Effects of age on mortality and stroke, GUSTO-1 trial. Of 41,021 patients, 24,708 were younger than 65 years, 11,201 were 65 to 74 years, 4625 were 75 to 85 years, and 412 were older than 85 years. All patients had ST segment elevation and were treated with thrombolytic agents. Postdischarge 1-year mortality remained high in the oldest groups (6.1 percent and 10.3 percent, respectively) and continued to be low (1.5 percent) in the younger than 65 group. *(From White HD,*

Barbash GI, Califf RM, et al for the GUSTO-1 Investigators: Age and outcome with contemporary thrombolytic therapy: Results from the GUSTO-1 Trial. Circulation 94:1826-1833, 1996.)

CHF, atrial arrhythmias, cardiogenic shock, and cardiac rupture.[82]

Management

Management of AMI

MEDICAL TREATMENT.

Treatment of patients with angina, acute ischemic syndromes, and AMI is similar to that in younger patients (see Chaps. 35 and 36) . For angina and acute ischemic syndromes, aspirin, nitrates, beta-blockers, calcium-channel blockers, ACE inhibitors, and anticoagulants such as heparin have all been found to be as effective in elderly as in younger patients.[83] In the older population, attention should be paid to impaired baroreceptor reflexes, decreased beta-adrenergic responsiveness, and stiff aorta. With ACE inhibitors or nitrates, especially short-acting nitroglycerin with venodilatation, postural hypotension can result in falls and injury. Combinations of digoxin, amiodarone, and calcium channel blockers can also produce profound bradycardia more easily in the elderly. These drugs should be initiated cautiously, beginning with lower doses than in younger patients and carefully watching for toxicity.[84]

In a study of 10,018 patients older than 65, after an AMI with no absolute contraindication to aspirin use, aspirin was associated with a 22 percent reduction in 30-day mortality.[85] Beta blockers are the antiischemic drugs of choice in elderly patients with stable angina,[86] and all appear to be equally effective in controlling angina.[87] Many studies demonstrate the effectiveness of beta blockers in reducing mortality after AMI, including in patients older than age 65.[88] Beta blockers are often not given to patients with chronic obstructive pulmonary disease, type I diabetes mellitus, a low LV EF, or a history of HF, even though they have been shown to reduce mortality in these groups also. Despite evidence of effectiveness, aspirin and beta blockers are underprescribed in the elderly, and patients with the highest risk for in-hospital death appear to be least likely to receive beta blockers. ACE inhibitors have also been shown to reduce mortality, and to prevent LV remodeling and the onset of CHF in patients after a large AMI[89] (see Chaps. 35 and 39) . Calcium channel blockers are equally effective, as are beta blockers, in controlling anginal pain.[87] Because of the tendency of rapid-acting calcium channel blockers to cause vasodilation, a drop in BP, and increased sympathetic tone, short-acting calcium channel blockers should be avoided. The use of slow-release, or new-generation long-acting, dihydropyridines are the calcium antagonists of choice.[87] After an AMI, however, calcium channel blockers have not been shown to decrease mortality; and in certain patients there is evidence that they are harmful, especially in those with decreased ventricular function, CHF, or bradyarrhythmias.[84] It is a consensus of the American College of Cardiology/American Heart Association AMI

group that calcium channel blockers are used too often in patients with AMI and that beta blockers are the more appropriate choice.[84] [90]

Heparin is recommended in acute ischemic syndromes and has been shown to decrease the development of AMI and/or mortality in patients given aspirin compared with those given aspirin alone.[91] Most studies have not investigated patients older than age 75, where the incidence of intracranial bleeding is higher than in younger patients. No trial has specifically investigated fractionated or low-molecular-weight heparin, with varying molecular weights that bind specifically to antithrombin III in patients 75 years of age and older.[91] Two major trials of the platelet glycoprotein IIb-IIIa inhibitors have been reported, with reduction in combined endpoints of myocardial infarction and death, but the number of patients older than 65 was small and no specific comments can be made.[91]

FIBRINOLYTIC THERAPY.

There is evidence that the older population with AMI benefits from fibrinolytic drugs with reduced mortality and preserved LV function. Pooled results from five major thrombolytic trials showed an absolute reduction in mortality of 3.5 percent in patients older than age 65 compared with 2.2 percent in the younger population.[92] There was also an absolute excess of strokes and other bleeding complications of less than 1 percent. Elderly patients take longer to reach the hospital after the onset of chest pain and are less likely to receive thrombolysis.[93] [94] Depending on the study, 10 to 50 percent of the elderly are excluded from thrombolytic therapy solely on the basis of age.[95] Observational studies indicate that older patients are at slightly greater risk of hemorrhagic stroke after fibrinolysis than younger patients.[96] In the elderly, especially those older than age 75, the incidence of serious bleeding, especially intracranial bleeding, must be balanced against any possible benefit derived from the use of fibrinolytics during an AMI.

THROMBOLYSIS VERSUS PRIMARY ANGIOPLASTY.

Several trials have shown no advantage to early angioplasty compared with medical management in patients with non-ST segment elevation myocardial infarction, except for those with ongoing ischemia.[91] However, none of these has addressed the elderly specifically. In patients with ST segment elevation AMI, percutaneous transluminal coronary angiography (PTCA) can restore antegrade flow in the infarct-related occluded artery, with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in 90 percent of patients.[84] In a post-hoc analysis of high-risk patients (those older than age 75 with anterior myocardial infarction or tachycardia on presentation), mortality was only 2 percent in those with primary angioplasty, and 10 percent in those receiving thrombolysis ($p < 0.01$).[97] The difference was in part related to an excessive incidence of cerebrovascular hemorrhage with death in the thrombolytic group. The cardiac-related deaths were similar in the two groups.

Management of CAD

PERCUTANEOUS CORONARY INTERVENTION (PCI).

Coronary arteriography is more likely to be performed in elderly patients who are symptomatic and have CAD than in younger patients.[98] Elderly patients with high-risk CAD or angina not responding to medical management are being sent for PCI in increasing numbers because it is a less invasive procedure than coronary bypass surgery.[99] Although patients in general do very well, some studies document increasing procedural morbidity and mortality with advancing age, particularly past 80 years.

Multivessel PCI is successful in patients aged 65 and older, with an overall angioplasty success rate of 96 percent. Complete revascularization was accomplished in 52 percent, and 3.2 percent had a myocardial infarction or other major in-hospital complications. Independent predictors of mortality were EF less than 40 percent ($p < 0.001$), three-vessel disease ($p < 0.01$), female gender ($p < 0.02$), and PTCA from 1985 or earlier.[100] In one study, the octogenarian was more likely to be a woman and have multivessel disease, with high-grade stenoses and more complex lesions than the younger patient.[101] Procedural mortality rose fivefold in those older than 80 years compared with those younger than 60 years. The rate of postprocedural myocardial infarction was also one and one-half times higher in the elderly than in the younger patients. Angiographic success was equal to that in younger patients, and the rate of in-hospital bypass surgery after intervention was less than that in younger patients.[101]

CORONARY ARTERY BYPASS SURGERY.

There are no randomized studies comparing surgery to medical management in patients older than 65 years. Although there is limited information from randomized studies of coronary

surgery compared with angioplasty that have included elderly patients,[102] and many reports of elderly patients from the same institution who had either CABG or angioplasty,[103] the conclusions from such studies are limited. With medical advances in the treatment of CAD, and with more patients with lesser degrees of CAD receiving angioplasty, coronary surgery is being done more often than in the past on older patients with more complicated CAD. As age increases, the proportion of men to women undergoing CABG increases, as does the prevalence of severe angina and CHF. The severity of the distribution of coronary stenoses also increases with age, as well as the incidence of complications, including neurological events, wound infections, and death, increasing in every decade after age 40. In most surgical series, morbidity and mortality are greater in the elderly, particularly in those older than 75 years. [104] Perioperative mortality in the elderly patient varies in different studies, from less than 2 percent to 10 percent.[102] [104] Morbidity and mortality depend on the presence of comorbidity, the EF, and the diffuseness of the CAD but are generally higher in the elderly.[104] The elderly patient also has a higher incidence of complications such as stroke, renal failure,

prolonged ventilation, and postoperative cardiac arrest.[104] [105] Carotid artery disease is also more common in the elderly.

In the Bypass Angioplasty Revascularization Investigation (BARI) trial, 709 patients aged 65 to 80 with multivessel CAD were randomized to bypass surgery or angioplasty.[102] Mortality at 30 days was 0.7 percent for PTCA and 1.1 percent for CABG. For patients both older and younger than 65, it was 1.7 percent. CABG resulted in greater angina relief and fewer repeat procedures in both younger and older patients. In older patients compared with younger patients, stroke was more common after CABG than after PTCA (1.7 vs. 0.2 percent), and HF and pulmonary edema were more common after PTCA (4.0 vs. 1.3 percent). The 5-year survival rate was 91.5 percent after CABG and 89.5 percent after PTCA in the younger patients and 85.7 percent after CABG and 81.4 percent after PTCA in the older. Stents[106] and minimally invasive or "off-pump" coronary artery surgery[107] offer advantages in the elderly for low risk revascularization. There is evidence of substantial improvement in health-related quality of life after PTCA in the elderly similar to that seen in the younger patients.[107A]

CARDIAC REHABILITATION (see Chap. 39) .

Fewer than half of eligible patients, and most elderly patients after a myocardial infarction or CABG do not participate in rehabilitation programs.[108] Because exercise capacity is reduced in the elderly after a cardiac event, exercise rehabilitation is especially important in this age group. Women and older patients are less likely to participate, as are those with lesser degrees of education and employment.[109]

Psychological depression is common after AMI and coronary surgery, especially in the elderly.[69] [110] Education and reinforcement that this reaction is a normal response to a major cardiovascular event, and mostly transient, can be very helpful. Erectile dysfunction is especially common after coronary surgery or AMI and should be inquired about. The energy used during sexual activity is usually less than 5 METs.[111] Most patients can return to normal sexual activity within 3 to 4 weeks after an acute event. If erectile dysfunction is a problem, encouragement to resume sexual activity gradually should be given; and drugs such as sildenafil, or intracavernosal or intraurethral prostacyclin, can be very effective. The patient should be cautioned about the need to avoid taking nitrates within 24 hours of taking sildenafil.[111]

Exercise prescriptions designed for the individual show substantial evidence for benefit of exercise in the elderly, with an increase in exercise tolerance and capacity, obesity indices, lipid profile, overall levels of physical fitness, and quality of life.[112] The greatest reduction in mortality with exercise training may occur in elderly men.[113] The benefits of cardiac rehabilitation have been shown to occur equally well in elderly women.[114] Rehabilitation programs for the elderly are safe. Data from 57,000 patients with over 2 million exercise hours identified only 21 cardiac events, including three fatal and eight nonfatal myocardial infarctions, during exercise training, or one cardiac event per 100,000, one AMI per 300,000, and one death per 1 million exercise hours.[115] [116]

HEART FAILURE

Heart failure is the leading first-listed diagnosis among hospitalized older adults[117] (Fig. 57-6) . Among an estimated 4 million U.S. residents with HF, 70 percent were older than 60 years. The National Hospital Discharge Survey estimated 871,000 hospital admissions annually with a first-listed diagnosis of HF from 1985 to 1995; the numbers of hospitalizations for any diagnosis of HF increase to 2.6 million, or 53 percent, over the 10-year period in question. About 78 percent of men and 85 percent of women hospitalized with HF were older than 65 years.

The etiology of HF in the elderly is the same as that in the younger populations. In the Framingham Heart Study, the prevalence of HF increased from 0.8 percent in the 50- to 59-year age group to 9.1 percent in the population 80 years and older.[118] Also in the Framingham study, the annual incidence of HF in men increased from 0.2 percent in the 45- to 54-year age group to 1.4 percent in the 75- to 84-year age group to 5.4 percent in the 85- to 94-year age group.[118] Whereas the majority of patients with HF younger than 65 years are men, of those over that age 60 percent are women, and the proportion increases with age.[119] Furthermore, there was a 27 percent increase in the incidence of initial hospitalization for HF in those 65 years and older from 1986 to 1993.[120]

The mortality from HF is very high in the elderly, particularly with advanced HF, and may be 10 to 15 percent at 1 month and as high as 30 percent or more at 1 year. Mortality rate increases exponentially after age 65 in both men and women.[120A] HF is not only an important reason for

Figure 57-6 Incidence of heart failure by age and sex: 30-year follow-up from the Framingham Heart Study. *(From Kannel WB, Belanger AJ: Epidemiology of heart failure. Am Heart J 121:951-957, 1991.)*

hospitalization but also is second only to HTN as a reason for outpatient physician visits, accounting for 12 million office visits per year in the United States.[121] HF in the older population consumes the most resources, with an estimated annual expenditure of $40 billion.[121]

PATHOPHYSIOLOGY (see Chap. 16) .

With aging, LV hypertrophy occurs as a result of increased afterload, a slowing of LV muscle relaxation, and stiffening of the LV, all of which lead to diastolic dysfunction as a prominent feature of HF. With a stiff LV, atrial contraction becomes most important in delivering a normal LV diastolic volume and keeping stroke volume normal (see Fig. 57-1) . Therefore, AF often precipitates, or markedly increases, symptoms of HF in the elderly population.[122] In fact, with advancing age, the proportion of people with LV failure but normal systolic function approaches 50 percent or more.[123] Diastolic dysfunction as a pathophysiological function of HF occurs more often in women than in

men and also more often with hypertensive cardiovascular disease and diabetes.

DIAGNOSIS.

The diagnosis of HF can be difficult in the older individual. Symptoms of dyspnea on exertion or easy fatigability are often taken as signs of "getting older" or deconditioning or can result from other diseases, especially pulmonary disease, thyroid abnormality, anemia, or depression. Edema of the lower extremity is not unusual in older patients, because the skin turgor decreases and the patient is increasingly sedentary, with legs dependent much of the time. Edema-related liver and renal disease is also not uncommon. Symptoms of increasing orthopnea or development of nocturnal cough, shortness of breath, or paroxysmal nocturnal dyspnea should alert the clinician to the possibility of the diagnosis of HF.

Physical examination is particularly helpful with the findings of rales, tachycardia, and an S_3 gallop rhythm; with right-sided HF, an elevated jugular venous pressure or positive hepatojugular reflux can be seen, as well as a right-sided S_3 gallop rhythm. Chest radiography showing cardiomegaly, pulmonary congestion, or vascular redistribution confirms the diagnosis.

Echocardiography is especially helpful in identifying the presence of a dilated, hypokinetic LV. With pure diastolic dysfunction as a cause of HF, the patient often has LV hypertrophy, although LV systolic function may appear to be normal, with normal or near-normal EF. An S_4 gallop rhythm and echo-Doppler signs of delayed LV filling and diastolic dysfunction are frequently present. Clinical signs and symptoms of HF in the presence of a normal EF makes the diagnosis of pure diastolic dysfunction.

Management (see also Chaps. 18 , 19 , and 21)

The management of HF in the elderly follows the same principles as those in younger patients[124] (see Chaps. 18 and 21) . The goals of therapy are also the same, including a decrease or elimination of symptoms, reduction in rehospitalization, and improvement in quality of life. Prolongation of life is desirable but of lower priority in the aged person with HF. Treatment requires consideration of the etiology of the heart disease, the factors that can precipitate HF, and the medical management. For instance, the patient with HF due to AS requires aortic valve replacement; HF due to ischemic but viable myocardium requires revascularization. Managing problems that precipitate HF in patients with underlying heart disease can be important in their medical management. For example, in the patient with diastolic dysfunction who develops HF along with AF, conversion to normal sinus rhythm or, less desirable, control of ventricular rate is the most important treatment.[125]

Noncompliance with medical therapy, excessive salt intake and volume overload in the patient with renal failure, and infection are all causes of exacerbation of HF requiring rehospitalization. These factors contribute to 30 to 50 percent of recurrent episodes of HF in the elderly[126] and are the major reasons why between one third and one half of all

patients hospitalized with HF are readmitted within 3 to 6 months of initial discharge.[126]

An effective way of managing elderly patients with HF is through a multidisciplinary approach and follow-up of patients at home through telephone calls, home visits by nursing personnel, and other patient contacts between office visits. Such an approach decreased the 90-day readmission rate by 32 percent in a group of 137 patients 80 to 96 years of age,[127] with improved quality-of-life scores and decreased overall cost. This multidisciplinary approach involves ongoing patient education, dietary consultation, medication review, daily weighings, and help with psychosocial problems and results in better compliance with medication[128] and overall cost reduction due to decreased rehospitalization.[129]

Although medications for HF are the same as those for the younger population, care must be taken not to cause hypovolemia, with marked reduction in stroke volume. Also, electrolyte levels should be monitored closely, especially in those patients taking digoxin and ACE inhibitors, because of the danger of renal dysfunction, hypokalemia, and hyperkalemia. A danger of hypovolemia is precipitation of falls in elderly patients, with subsequent hip fracture.[130] Another problem in elderly patients is that many are receiving NSAIDs, which can increase the risk of HF in elderly patients taking diuretics.[131]

DRUG THERAPY

ACE inhibitors, underprescribed in the elderly, are as effective in improving quality of life and reducing mortality as in younger patients.[132] Digoxin is useful in patients with HF who are in AF and/or are symptomatic on diuretics and ACE inhibitors.[133] However, in the elderly, lean body mass is decreased and renal function frequently is impaired; digoxin dosage is therefore lower than in the younger patient, and the danger of toxicity is greater. The Digitalis Investigation Group (DIG) reported that there was no decrease in overall mortality, but there was a decrease in hospitalization and mortality due to HF in patients receiving digoxin. Older age was an independent risk factor for all-cause mortality and rehospitalization, as well as for HF rehospitalizations and deaths.[134]

Angiotensin II type 1 receptor antagonists are probably as effective as ACE inhibitors, but they are still being evaluated in the elderly, although side effects are probably less often noted.[135] Candesartan was effective in improving exercise tolerance, as well as symptoms and signs of HF.[136] In patients unable to take ACE inhibitors or angiotensin II type 1 receptor blockers, hydralazine and isosorbide have been shown to reduce mortality in patients with HF (see Chap. l8) .

Beta blockers, if started in the usual dosage in patients with HF, will worsen the patient's clinical status; however, beta blockers started in small doses with titration upward have been shown to be very effective in improving quality of life of patients with HF, as well as increasing EF and exercise tolerance.[137] In the U.S. carvedilol study, patients with chronic HF and EF less than 35 percent were randomized to carvedilol versus placebo. Mortality was 65 percent lower in the carvedilol group in a 6.5-month follow-up.[138] Patients older than 60 years had results similar to younger patients. In this study, few patients were older than age 75 years. After AMI, beta blockers have been shown to

decrease late mortality in the elderly population.[139]

In general, first-generation calcium channel blockers have been associated with adverse effects in patients with HF and as a result are usually contraindicated. If calcium channel blockers are indicated for ischemia, then those with little negative inotropic effect, such as amlodipine or felodipine, should be used.

DIASTOLIC DYSFUNCTION

The treatment of diastolic dysfunction in the elderly has not been well studied. If the symptoms are predominantly pulmonary congestion, then treatment with diuretics and/or long-acting nitrates will lower the filling pressure and decrease shortness of breath. However, overdiuresis can markedly drop the stroke volume and cause hypotension and prerenal azotemia. Beta blockers, by slowing the heart rate and increasing the diastolic filling period, can lower the filling pressure and improve LV compliance by decreasing LV hypertrophy. Similar benefits can result from ACE inhibitors and calcium channel blockers, and all of these drugs have been used in patients with HF and EF greater than 40 percent. Verapamil has been shown to improve symptoms in exercise capacity and diastolic function in older patients with HF and EF less than 45 percent.[140] Whether results with spironolactone will be similar in patients older than age 75 years is unknown but likely (see Chap. 18) .

HYPERTENSION (see also Chaps. 28 and 29)

Both essential and secondary HTN, especially with renoarterial disease, are found in the elderly (see Fig. 57-3) . Isolated systolic HTN, as defined by a systolic BP greater than 140 mm Hg and a diastolic BP reading less than 90 mm Hg, is especially prominent in the elderly as a result of the decrease in arterial compliance and concomitant LV systolic stiffening.[3] The diagnosis of HTN should be made only after the BP is found to be elevated on three separate occasions. In the elderly, there are several problems in obtaining a correct BP using the BP cuff.[141] With noncompliant arteries, changes in stroke volume can result in wide variations in systolic BP. The patient should therefore be allowed to rest for 3 minutes before BP is taken.[141] Each time, BP should be taken two or three times and the results averaged. The "white coat" effect can be seen in 15 to 20 percent of all hypertensives, and it is especially common in the elderly.[142] Systolic BPs can vary as much as 20 to 40 mm Hg. For this reason, home or ambulatory BP recordings can be helpful in ascertaining the patient's usual BP.[143]

Another problem, termed "pseudohypertension," is caused by a brachial artery that is calcified and sclerotic and therefore not easily compressed by the BP cuff. The diagnosis of pseudohypertension can be made for certain only by comparing cuff systolic BPs to intraarterial pressures. Recently, doubt has been cast on the validity and usefulness of "Osler's maneuver," that of continuing to palpate a radial pulse with the BP cuff above auscultated systolic BP.[144] Falsely low systolic BPs can also occur

because of the "auscultatory gap" in 20 percent of the elderly.[145] Here, Korotkoff sounds may be heard at 180 mm Hg, disappear, and then reappear at 130 mm Hg. If the BP cuff is not inflated to more than 180 mm Hg, the systolic BP will be incorrectly read as 130 mm Hg. This auscultatory phenomenon, the cause of which is unknown, is associated with age, female gender, increased arterial stiffness, and increased prevalence of carotid atherosclerotic plaques.[145] Pseudohypotension occurs when the BP is measured in an arm with an atherosclerotic obstruction proximal to the brachial artery. It can be suspected when there is a 30 mm Hg difference in BPs between the arms. A unilateral supraclavicular bruit is often heard. BP should always be taken initially in both arms and followed in the arm with the higher pressure.

HYPOTENSION.

Orthostatic hypotension, defined as a drop of more than 20 mm Hg in pressure on going from a supine or sitting to a standing position for 1 to 3 minutes, was present in the Systolic Hypertension in the Elderly Program (SHEP) study before therapy in one of every six elderly patients with HTN.[146] Orthostatic HTN is more likely to occur in an elderly person because of the noncompliant vessels and is especially likely to occur with hypovolemia due to diuretics or drugs interfering with vasoconstriction, such as alpha-adrenergic blockade given for HTN or benign prostatic hypertrophy.

Postprandial hypotension is especially common in elderly patients, occurring 30 to 120 minutes after a meal and causing drops in BP of more than 20 mm Hg. It is associated with lightheadedness, syncope, and falls and may be caused by vasodilation associated with excessive insulin response to a glucose load.[147] Decisions regarding BP control or change in therapy for HTN should take into account how long after the last meal the BP is taken.

EPIDEMIOLOGY

HTN is more common in blacks than in whites: About 45 percent of white, but 60 percent of black, men and women have HTN at ages 65 to 74.[148] In a study from a university geriatrics practice of 459 men and 1360 women, mean age 80 ± 8 years (range 59 to 101 years), HTN was present in 58 percent.[149] Because of its prevalence in the elderly, isolated systolic HTN was thought to be a natural consequence of aging. To the extent that there are changes in the arterial wall with aging that lead to less compliant vessels, a rise in systolic BP is a consequence of aging. That isolated systolic HTN is not a normal consequence of aging is reflected in the fact that epidemiological studies show a rise in systolic BP with age occurring only infrequently in most nonindustrialized societies. In a study in which participants at ages 50 to 89 were surveyed as to leisure activity (classified into light, moderate, heavy, and no physical activity), BP decreased with increasing levels of activity.[150] It appears, therefore, that there are environmental and life-style influences on the late rise in systolic BP with aging.

HTN remains the most common cause of HF, both with systolic and diastolic dysfunction. It is a strong risk factor for the development of CAD in both men and women. The Framingham Heart Study found that people 65 to 94 years of age with

systolic BPs greater than 180 mm Hg had a threefold to fourfold increase in the risk of CAD compared with those whose systolic BP was less than 120 mm Hg.[53] A diastolic BP greater than 105 mm Hg caused a twofold to threefold higher rise in CAD than in those with a diastolic BP less than 75 mm Hg. Mortality is increased in elderly patients with HTN, mainly owing to HF and CAD.[53] In addition to mortality, the complications of HTN can be especially devastating: almost two thirds of those older than age 60 with untreated HTN will have a cerebrovascular accident, HF, myocardial infarction, or aortic dissection within 5 years.[151] Similar morbidity and mortality have been shown to occur in patients with isolated systolic HTN as in those with systolic and diastolic HTN.[152]

Although there is no doubt that lowering BP will reduce mortality, in old patients aged 80 to 85, there is paradoxical evidence of higher mortality with lower than with higher systolic or diastolic BP.[153] In one study of 561 people, including 82 percent of women aged older than 85, the 5-year mortality was lower in hypertensive (41 percent) than normotensive (72 percent) patients. It was highest in those with the lowest systolic BP (<120 mm Hg) or diastolic BP (<70 mm Hg) and was lowest in those with systolic BP greater than 160 mm Hg or diastolic BP greater than 90 mm Hg.[153] Another study found that patients with a mean age older than 75 with the lowest diastolic BP (<75 mm Hg) had the highest cardiovascular disease and all-cause mortality, whereas the highest diastolic BPs predicted higher survival.[154] The higher mortality in patients with the lowest diastolic BP suggests the possibility of decreased coronary perfusion pressure and subendocardial ischemia. This paradox of increased mortality in very old patients with a lower systolic BP and diastolic BP has been termed the "J curve,"[155] which is probably related to the effects of cardiac, respiratory, and neoplastic disease in those with low BP versus good myocardial function in those with HTN. Therefore, one cannot conclude that patients older than 75 to 80 years will not benefit from BP reduction. The SHEP study found no evidence of a J curve in treated patients with isolated systolic HTN.[156] However, a recent population-based cohort study[157] reported a risk of myocardial infarction in elderly patients with treatment of diastolic BP to less than 90 mm Hg, after adjusting for all other coronary risk factors.

Treatment (see also Chap. 29)

The recommendations for the treatment of HTN in the elderly do not differ from those for younger patients.[54] [158] Lowering even isolated systolic HTN decreases cardiovascular and total mortality, as well as hypertensive complications of HF, renal failure, and stroke.[55] [156] The goal of treatment of HTN in elderly patients should be a lowering of systolic BP to less than 140 mm Hg without creating postural hypotension or symptoms of organ hypoperfusion, such as elevated blood urea nitrogen or renal insufficiency.[158] If this is not possible, lowering systolic BP by 20 mm Hg is considered an acceptable response and has been associated with useful reduction in clinical cardiovascular events.[64] Benefits occur regardless of the class of antihypertensive drugs used.

The Swedish Trial in Old Patients with Hypertension (STOP-H) randomized 1627 patients with systolic/diastolic HTN, aged 70 to 84, to placebo versus atenolol, metoprolol, pindolol, or hydrochlorothiazide and amiloride. In a 25-month follow-up, a 28 percent decrease in fatal myocardial infarction, a 67 percent decrease in sudden death,

and a 47 percent decrease in stroke resulted.[159] A meta-analysis of

1670 patients aged 80 or more, from randomized controlled trials of antihypertensive drugs, suggested that treatment prevented 34 percent of strokes and decreased the incidence of major cardiovascular events by 22 percent and HF by 39 percent. However, there was no treatment benefit for cardiovascular or total deaths. This suggests, in patients older than age 80, that there is benefit in reducing nonfatal cardiovascular events but not total mortality.[160]

Because of the expense and potential benefit in patients with CAD, diuretics and beta blockers are often the first choice in antihypertensive treatment in the elderly. In the patient with HF, ACE inhibitors should be used together with other drugs to decrease BP. Nitrates have recently been advocated in patients with isolated systolic HTN because they have an effect on arterial distensibility, reducing systolic BP without affecting mean BP or diastolic BP.[161] This has the theoretical benefit of not decreasing myocardial perfusion and would benefit those patients with HTN and concurrent CAD and cerebrovascular disease.

Nonpharmacological therapy, consisting of increased exercise, salt restriction, weight loss, and limited alcohol intake can be useful for patients with mildly elevated BP.[54] [158] There are few studies in elderly hypertensives of the effectiveness of this approach in decreasing BP and no evidence (unlike in pharmacological therapy) that it would decrease complications of HTN and mortality. The elderly have increased sensitivity to salt, so that salt loading increases BP and salt restriction reduces it.[162] In a meta-analysis of 11 randomized controlled trials, 5 included patients older than 60 years of age and 6 included patients with a mean age of 60. When all trials were pooled, a chronic high sodium chloride intake significantly increased systolic BP and diastolic BP by 6 and 3.5 mm Hg, respectively, and there was a significant association between salt intake and systolic BP. A high sodium chloride diet in elderly patients with essential HTN is associated with a higher systolic BP and diastolic BP, and the effect is more pronounced in the older patient.[163] In 300,000 elderly nursing home patients (mean age, 83 years), HTN was diagnosed in 27 percent. About one fourth had six or more comorbid conditions. Seventy percent of these patients were receiving antihypertensive drugs, with calcium channel blockers the most common (26 percent), followed by diuretics (25 percent), ACE inhibitors (22 percent), and beta blockers (8 percent). The oldest subjects (>85 years) and those with marked physical or cognitive impairment were less likely to receive treatment.[164]

CARDIOMYOPATHY (see also Chap. 48)

Both dilated (DCM) (congestive) and hypertrophic (HCM) cardiomyopathy occur in the elderly. Most DCMs are of unknown etiology, just as they are in younger patients.

Amyloid Cardiomyopathy

Amyloid DCM is noted primarily in older people. Although small deposits of amyloidosis (senile amyloidosis) are often seen at autopsy, they are of no clinical significance in people younger than 85 years. Reactive amyloidosis, seen in chronic rheumatoid arthritis or bronchiectasis, usually does not involve the heart. In amyloid heart disease the amyloid, an abnormal fibrillar protein, is deposited intercellularly and in the walls of small coronary arteries[165] (see Chap. 48) .

The amyloid can involve only certain organs, or it can be a generalized disorder. The heart and tongue, with and without skeletal involvement, and the autonomic nervous system, are frequently involved. Amyloid infiltration of the heart causes thickening of the ventricles, which become less compliant to diastolic filling, resulting in the picture of restrictive cardiomyopathy. Senile amyloidosis, in the past thought to be a consequence of aging without clinical significance, is now known to contribute to HF in patients older than 85.[166] Of 142 men and 90 women with primary immunoglobulin light-chain amyloidosis, the median age at diagnosis was 59 years, with a range of 29 to 85 years, and was unusual in those younger than 40 (3.0 percent) and in nonwhites (6.5 percent). Macroglossia was seen in 27 percent. Patients most often demonstrated features of multisystem dysfunction, and cardiac amyloidosis was seen in isolation in only 3.9 percent. With cardiac involvement, the median survival was 1 year from diagnosis; and with the onset of HF, it was 9 months. Cardiac amyloidosis should be suspected in elderly patients with HF and a hypertrophied LV, possibly with "sparkling" myocardial characteristics and normal chamber sizes on echocardiography (see Chap. 7) , low ECG voltage (see Chap. 5) , and evidence of multisystemic disease.[167] An abnormal echocardiogram and signal-averaged ECG predict both all-cause and sudden cardiac death mortality, whereas an abnormal signal-averaged ECG independently predicts SD in those patients with an abnormal echocardiogram.[168]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is another important disease that is being diagnosed increasingly in the elderly patient.[169] HCM in elderly patients has been found in 4 percent of an unselected population of 379 elderly patients (mean age = 83 years) in a long-term health care facility.[170] In an echocardiographic survey of 15,137 people in a 33-month period, 44 patients with HCM (0.29 percent) were found, aged 16 to 87 years (mean age 57), 14 of whom were older than 60 years. Eighty-three percent had few or no symptoms; in 8 patients, symptoms began at age 70 or older. Resting systolic gradients were found in 38 percent of the patients. It is clear that HCM can remain clinically silent and undetected for many years, often to an advanced age.[171]

Compared with younger patients, the elderly with HCM have more mild HTN and fewer have a history of syncope. Echocardiography shows that the elderly have relatively mild LV wall thickening, generally confined to the basilar septum.[172] Another study showed that elderly patients with HCM had more concentric hypertrophy than younger ones. Microscopically, there is less marked septal myocyte disarray and intramural coronary artery thickening and less sudden cardiac death (see Chaps. 26 and 48) in older

patients with HCM than in younger patients.[173]

In the symptomatic patient, beta blockers and calcium channel blockers are still the first line of treatment. Controlled trials with synchronous AV pacing have yielded mixed results, although most find a moderate to marked decrease in systolic LV outflow tract gradient. Some note a decrease in symptoms, increased quality of life measures, and increased exercise capacity[174] ; but others find no subjective or objective benefits.[175]

When medical management fails, surgical septal myomectomy has proven successful over the years, with an early mortality from isolated myomectomy of 3.6 percent. During the past 10 years, mortality was only 1.9 percent.[176] In 346 patients followed up to 26 years after surgery, the annual mortality was 0.6 percent compared historically to an annual mortality in unoperated patients that varied from 1.7 to 4 percent. The surgical patients also had long-lasting improvement in symptoms, exercise capacity, and quality-of-life indices.

Alcohol-induced transcoronary ablation of septal hypertrophy has been reported, with low mortality and significant improvement manifested by reduction in septal thickness, LV outflow tract gradient, and improvement in NYHA functional class and exercise capacity. There is also a significant improvement in LV passive filling volume,[177] a decrease in LV filling pressures at rest, and during exercise.[178] High-grade AV block can result.[178]

In those patients surviving a cardiac arrest or who have ventricular tachycardia (see Chap. 25) , or those judged to be at high risk for a life-threatening cardiac arrhythmia, an implanted cardioverter-defibrillator (see Chaps. 24 and 26) has proven to be very effective.[179]

ARRHYTHMIAS (see also Chaps. 23 , 24 , and 25)

Supraventricular Arrhythmias

The frequency of both supraventricular and ventricular arrhythmias increases with age. Premature atrial complexes (PACs) are extremely frequent in elderly people. Isolated PACs can be seen in resting ECGs of 5 to 10 percent of normal people older than age 60. With 24-hour ambulatory ECGs, the majority of patients older than age 65 have PACs, and even short runs of supraventricular tachycardia (SVT) of mostly three to five beats.[180] In mostly healthy subjects 65 years of age and older in the Cardiovascular Health Study, short runs of paroxysmal SVT (PSVT) were seen in about 50 percent of subjects, nearly doubling in prevalence from the late 60s age group to the 80s.[180] Both isolated PACs and short runs of PSVT have no prognostic significance for CAD in elderly patients over a 10-year follow-up period in the Baltimore Longitudinal Study of Aging Project.[181]

In general, patients with PACs or short runs of asymptomatic PSVT need no treatment except reassurance. If the patient is unpleasantly symptomatic, type IA or IC antiarrhythmic drugs are effective but should not be given to patients with underlying heart disease. Amiodarone or sotalol can be tried. PSVT, either AV nodal reentry, atrial tachycardia, or SVT associated with a bypass tract, is treated just as in younger patients. Adenosine can be used effectively and safely in elderly patients.[182] Although beta blockers, calcium channel blockers, and type IC antiarrhythmic drugs are effective for patients with repeated prolonged episodes of some SVTs, radiofrequency catheter ablation is done with success rates similar to that seen in younger patients.[183]

ATRIAL FIBRILLATION.

This is the most common chronic arrhythmia and increases with age. It is seen in 3 to 4 percent of subjects 60 to 65 years of age, a prevalence 10 times as high as that in the general population. The incidence doubles for each decade after age 60,[184] reaching 8.8 percent of the population older than 80 years.[185] About one third of patients with AF have paroxysmal episodes on 24-hour ambulatory ECG, and two thirds have chronic AF.[184] The prevalence of AF in men and women without cardiovascular disease in the Cardiovascular Health Study was 1.6 percent, rising to 4.6 percent in patients with subclinical, and to 9.1 percent in those with overt, cardiovascular disease.[186] Age-adjusted prevalence of AF increases strikingly in men with a prior myocardial infarction (4.9 to 17.4 percent).[187] AF most often occurs with underlying heart disease such as HTN, CAD, mitral valve disease, and HF. The presence of any cardiovascular disease increases the risk of AF by twofold to fivefold.[188] In elderly patients, thyrotoxicosis can manifest mainly by the onset of AF with a rapid ventricular response, so-called apathetic thyrotoxicosis.[189]

Symptoms and morbidity occur in older patients with AF. The rapid ventricular response can cause unpleasant palpitations; but also, with loss of atrial contraction, the booster-pump function of atrial systole is lost and stroke volume decreases (see Fig. 57-1) . If the rate is very rapid, BP may drop significantly. In the elderly, because of the less compliant LV, loss of atrial contraction is especially important. Uncontrolled rapid ventricular response can lead to HF or "tachycardia-mediated cardiomyopathy." In elderly patients with sick sinus syndrome, paroxysmal AF can result in syncope when the arrhythmia terminates and there is a long pause before sinus node function returns or if the subsequent rhythm is marked bradycardia (see Chaps. 23 and 25) . A most important problem associated with AF is that of thromboembolism, because of stasis of blood flow, especially in the atrial appendage, with thrombus formation and possible thromboembolism. In the Framingham Heart Study, the incidence of stroke in patients with AF rose from 1.5 percent in the 50- to 59-year age group to 23.5 percent in those older than age 80.[190]

A small number of older patients with AF have neither HTN nor any other cardiovascular disease and represent cases of so-called "lone" AF. The Framingham study found lone AF in 17 percent of men and 6 percent of women, with a mean age of 71 and 68 years, respectively. Follow-up for new cardiovascular events over a mean of 16 years revealed similar rates of CAD and HF as in control patients without AF, but a fourfold increase in

the rate of stroke.[191] Patients younger than 60 years with lone AF do not have an increased risk of embolic stroke,[192] but increasing age increases the risk.[193] Risk factors that increase the incidence of thromboembolism and stroke during AF include diabetes, HF, advanced age, smoking, recent myocardial infarction, HTN, and enlarged left atrial diameter greater than 40 mm.[185] Patients older than age 75 years with diabetes, HTN, or prior transient ischemic attack/stroke have an annual stroke incidence of 8 to 12 percent.[192]

Warfarin reduces the incidence of stroke in patients with nonvalvular AF (see Chap. 25) , but the risk of bleeding, particularly intracerebral hemorrhage, is higher, especially in patients older than 75.[194] Nevertheless, in elderly patients it appears safe to use adjusted-dose warfarin with a low risk of major hemorrhage, if the international normalized ratio (INR) is maintained in the 2 to 3 range.[195] [196] Therefore, it is recommended that all elderly patients with AF without contraindications (active ulcer, recent surgery, bleeding diathesis, dementia, frequent falls or trauma) be anticoagulated to an INR between 2 and 3, with avoidance of higher INRs. In those who cannot take warfarin, an antiplatelet drug such as aspirin, 325 mg/d, although clearly not as effective as warfarin, is recommended.[197] Patients younger than 65 with lone AF can be treated with aspirin, or without antithrombotic therapy. In those older than age 75, therapeutic benefit must be balanced against the risk of intracerebral bleeding, but anticoagulation with INR between 2 and 3 is recommended with risk factors present that increase the chance of stroke. In others, aspirin should be considered.

In elderly patients with AF, an attempt to convert to sinus rhythm, preferably by direct-current cardioversion after 3 to 4 weeks of anticoagulation, can be made. Maintenance of sinus rhythm is most successful if the AF is not long standing (i.e., less than a year) and with minimal left atrial enlargement.[198] If this is not possible, or if the patient reverts to AF despite antiarrhythmic drug therapy, control of ventricular response is necessary with beta blockers, calcium channel blockers, or digoxin. If drugs fail to slow the ventricular rate, modification of AV nodal conduction by radiofrequency catheter ablation is successful. Radiofrequency ablation can also be used to eliminate rapidly discharging foci causing AF (see Chap. 25) .

Atrial flutter responds to low-energy direct-current cardioversion, which is the procedure of choice when the ventricular response is rapid. It can be an unstable rhythm, reverting to sinus rhythm or AF. If atrial flutter persists, RF catheter ablation can eliminate further episodes (see Chap. 25) . Although the incidence of thromboembolism is lower than with AF, anticoagulation is generally indicated for patients with atrial flutter, as in patients with AF.[199]

Ventricular Arrhythmias

Premature ventricular complexes (PVCs), like PACs, increase in prevalence and frequency with age and include simple and complex PVCs, ventricular couplets, and short bursts of ventricular tachycardia.[180] [184] [200] With exercise, PVCs increase in prevalence from 11 percent in the third decade to 57 percent in the ninth.[200] The prognostic significance of isolated or even complex PVCs depends on the presence or

absence of underlying cardiovascular disease.[201]

The treatment of PVCs, even complex PVCs, is not indicated in asymptomatic patients who have no underlying cardiac disease. In symptomatic patients, beta blockers are often the initial drug of choice. Treatment of nonsustained and sustained ventricular tachyarrhythmias in the elderly in general is no different than in younger patients (see Chap. 25) . [202]

Conduction Defects

The changes in the sinus and AV nodes due to aging, along with the decreased sensitivity to adrenergic stimulation, create an increased incidence of sick sinus syndrome, as well as AV and bundle branch conduction disease. Individuals older than 80 years without cardiovascular disease are reported not to have sinus bradycardia less than 43 beats/min or pauses of more than 2 seconds.[180] Consequently, sinus bradycardia less than 40 beats/min or sinus pauses of more than 2 seconds may be manifestations of sick sinus syndrome. However, pacemaker implantation is not indicated in asymptomatic patients with these findings. In contrast, in the patient with syncope or presyncope or taking medications that aggravate the sick sinus syndrome, a pacemaker is indicated.

With aging, the incidence of AV and bundle branch block is increased, possibly as a result of increasing fibrosis and calcification of the fibrous skeleton of the heart.[201] Types 1 and 2 degree AV block can be benign unless associated with digitalis toxicity or symptoms and are usually the result of enhanced vagal tone. The presence of Mobitz type II and third-degree AV block is unusual, even in older patients,[201] and is always associated with advanced conduction system disease, requiring pacemaker implantation[203] (see Chaps. 23 , 24 , and 25) . In paced patients 65 to 79 years of age with isolated AV block, the survival rate was similar to matched individuals without AV block, whereas in those older than 80 years, the survival rate was lower than in matched controls.[204]

The QRS axis shifts leftward with age, becoming -30 degrees in 20 percent by age 90, perhaps due to increased LV mass or interstitial fibrosis of the anterior fascicular radiation. Right bundle branch block is found in 3 percent of healthy people older than 85 years, and in 8 to 10 percent of those with heart disease.[201] [205] The presence of left bundle branch block correlates strongly with age and may be a marker of slowly progressive degenerative disease affecting the myocardium. In 855 men older than 50 years observed for 30 years, 1 percent of those aged 50 and 17 percent at age 80 developed bundle branch block. No relationship between bundle branch block and ischemic heart disease or mortality was found. Men who developed bundle branch block had a larger-volume heart at age 50 and developed diabetes and HF during follow-up more often than control subjects.[206] In the Framingham Heart Study, 2 percent of subjects older than age 70 developed a nonspecific intraventricular conduction defect

exceeding 120 milliseconds, which was associated with the presence of organic heart disease.[207] The presence of bundle branch block should lead to a search for underlying cardiac disease, but unless it progresses to advanced heart block it needs no therapy.

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Chapter 58 - Coronary Artery Disease in Women

PAMELA S. DOUGLAS

Approximately one third of all deaths in women are attributed to coronary artery disease (CAD), making it the most common cause of death in women as well as in men (Fig. 58-1) . The proportion rises to over half of all deaths if all forms of cardiovascular disease are included, and CAD is increasingly important as longevity is enhanced and the population ages.[1] [2] Yet, in contrast to the dramatic decrease in cardiovascular mortality achieved for men in the past 20 years, there has been little improvement for women.

An enormous amount of scientific investigation is directed at understanding the causes and cures of CAD. Recognizing the influences of gender on basic biology may provide important keys to cardiovascular pathophysiology that may eventually benefit both sexes. In the clinical arena, CAD is increasingly thought of as a preventable disease as medicine acquires the knowledge and tools to reduce its incidence and modify its consequences. However, the benefits have not been as readily extended to women. This chapter addresses the similarities and differences in CAD risk factors, symptoms, diagnosis, and treatment between men and women. Knowledge of these and their incorporation into clinical practice will improve care for women and reduce the large

health risk and burden of CAD.

RISK FACTORS FOR CAD IN WOMEN AND THEIR MODIFICATION

Perhaps the most important risk factor for CAD in women is the misperception that coronary artery disease is not a woman's disease--that it is somehow more benign or less important in women than in men.[3] This misconception, shared by both patients and providers, is gradually being corrected but still has important influences on all aspects of prevention, diagnosis, and treatment. If CAD is not believed to pose a significant risk, it is unlikely that patients will implement difficult life-style changes to prevent it or seek emergency care on development of symptoms. This underestimation of risk extends to offspring of women with CAD, who, despite a significant burden of modifiable risk factors, perceive their risk of CAD as being below average.[4] Similarly, providers have been shown to underestimate the likelihood of CAD presence, leading to neglect of formal risk assessment and failure to aggressively treat CAD once it has been detected. In addition, a woman's presentation style alters physicians' estimates of the likelihood of CAD, so that an actress whose demeanor was more business-like was judged to have a much higher probability of disease than one who behaved histrionically, despite identical histories and test results.[5] To reduce CAD mortality in women, it is critical that patients, providers, and the public recognize the importance of CAD and its prevention and treatment.

Factors associated with higher cardiac risk in men, including age, family history, smoking, hypertension, lipoproteins, and diabetes mellitus (see Chap. 31) , are also associated with increased cardiac risk in women[6] [7] [8] [9] [10] ; however, they may have a different relative importance. Moreover, additional factors such as hormonal status are equally powerful predictors of CAD in women. These differences have been formally incorporated into a variety of gender-specific risk assessment algorithms published by the American Heart Association (AHA) and others.[1] [7] [11] Furthermore, the

Figure 58-1 Number of deaths due to the seven leading causes of death in women and men in the United States in 1997, ranked in order for women. *(Data from National Vital Statistics Report 47[June 30], 1999.)*

approach to management of CAD risk differs somewhat in women. In recognition of this, the AHA and American College of Cardiology have published comprehensive guidelines for primary and secondary prevention of CAD in women.[7]

LIPIDS

(see also Chaps. 31 , 32 , and 33): Elevated total cholesterol and low-density lipoprotein (LDL) levels are only weakly associated with CAD in women and only in

women 65 years old or younger.[8] [9] [10] [11] [12] [13] Instead, high-density lipoprotein (HDL) cholesterol is closely and inversely associated with CAD risk.[10] [14] Triglycerides are an independent predictor of CAD, particularly in older women.[10] [15] [16] Lipoprotein(a), a composite of LDL, apolipoprotein B-100, and apoliprotein(a), is also associated with higher cardiac risk in women.[17] [17A]

Treatment of dyslipidemia is generally accomplished by the same life-style changes and medications in men and women, although dietary interventions may be less effective in women.[18] Although clinical trials have generally not included women in sufficient numbers for independent prospective analysis, several recent studies employing aggressive, multifactorial treatment for lipid lowering have documented an equal or greater effect in women, for both primary and secondary prevention,[19] [20] [21] and after bypass surgery (see Chap. 33) .[22] Women, as well as men, display angiographic regression of coronary atherosclerosis and reduction in coronary events and death, even with normal baseline cholesterol levels.

In general, recommended dietary and pharmacological lipid-lowering strategies are similar in men and women and should be as aggressively employed. However, hormone replacement therapy may be a preferred primary therapy for postmenopausal women with low HDL[8] [23] (Table 58-1) . Effects of estrogen may be additive to or even supplant those of conventional lipid-lowering medications,[24] [25] because they include other beneficial effects in addition to lipid lowering, such as coronary vasodilation and antioxidant properties (see later).[26] [27] However, estrogen increases triglycerides in 20 to 25 percent of women, particularly those with elevated baseline levels,[28] who may therefore be less likely to benefit from hormone replacement therapy. An elevated baseline level therefore mandates careful monitoring of lipid levels after institution of hormonal therapy and consideration of transdermal rather than oral administration. Newer regimens include selective estrogen receptor modulators (SERMs), soy compounds such as isoflavenoids, and phytoestrogens, all proven to have beneficial effects on serum lipids in women,[29] [30] [31] but their place in the therapeutic armamentarium has not been established by large-scale randomized clinical trials.

Current recommendations for initiation of treatment and therapeutic goals (National Cholesterol Education Program [NCEP]-II) are similar in men and women and are based on LDL levels.[23] Despite the fact that HDL is a more powerful determinant of CAD risk in women, the NCEP-II guidelines do not include HDL except as a modifying factor, and then at a fairly low level for women. Similarly, triglycerides are not considered as a primary indication for treatment. Strong arguments have been made to alter these recommendations in favor of more aggressive therapy for indications other than LDL-lowering in women, particularly because it is not clear how well NCEP-II guidelines address the needs of women or the very elderly, who are predominantly female. The strikingly positive results achieved in recent statin trials suggest that these agents should be included in most lipid-lowering regimens designed for primary or secondary prevention of CAD for women.

DIABETES

(see also Chap. 63) . Diabetes is a risk factor for the presence and severity of coronary

artery disease in both men and women but carries a greater incremental risk in women, completely eliminating the "female advantage."[6] [9] [11] [32] The AHA awards twice the weight to diabetes in women in calculating CAD risk,[11] similar to that of a systolic blood pressure of 173 mm Hg or above or a cholesterol level of 316 mg/dl or above. Even more than in men, diabetes dramatically increases the mortality of myocardial infarction in women.[9] [33]

Non-insulin-dependent diabetes is associated with obesity, abdominal and upper body fat distribution, hypertension, and insulin resistance, all of which have been associated with higher coronary artery disease risk.[32] This complex of abnormalities may be causally related to high circulating insulin levels. More so than in men, obesity and body fat distribution appear to be independent coronary artery disease risk factors in women.[6] [32] Diabetes is also linked with the presence of hyperlipidemia (elevated triglycerides, reduced HDL), especially in women,[32] although the lipoprotein response to adequate diabetic treatment is variable.[34] Finally, diabetes is associated with a variety of platelet abnormalities and endothelial dysfunction, additional contributors to CAD.[35] Regardless of mechanism, recent data from the Diabetes Control and Complications Trial suggest that intensive diabetes therapy reduces cardiovascular complications in young (younger than age 40) men and women.[36]

HYPERTENSION

(see also Chaps. 28 and 29) . The prevalence of hypertension in women greatly increases with age so that nearly 80 percent of women older than age 75 are hypertensive.[37] Hypertension carries an independent coronary artery disease risk for both men and women and substantially enhances the risks associated with hyperlipidemia, smoking, obesity, and diabetes. Antihypertensive treatment reduces both overall mortality and cardiac morbidity as well as the incidence of stroke; these effects are most striking in the elderly.[37] [38]

TABLE 58-1 -- EFFECT OF HORMONE REPLACEMENT THERAPY ON LIPOPROTEIN LEVELS (% INCREASE OR DECREASE)

	PLACEBO	E ALONE	E+PA (CYCLIC)	E+PA (CONTINUOUS)	E+PA (CYCLIC)
TC	-11	-20	-36	-36	-20
LDL	-11	-37	-46	-43	-38
HDL	-3	+14	+4	+3	+11
Triglycerides	-4	+15	+14	+13	+15
LP(a)	0	-17	-26	-20	-22

E=conjugated equine estrogen 0.625 mg daily; E+PA (cyclic)=conjugated equine estrogen 0.625 mg daily plus medroxyprogesterone acetate, 10 mg/d for 12 days each month; E+PA (continuous)=E+PA 2.5 mg/d; E+P (cyclic)=E+micronized progesterone, 200 mg/d for 12 days each month.

Adapted from The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial: Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. JAMA 273:199, 1995. Copyright 1995, American Medical Association. Additional data from Espeland MA, Marcovina SM, Miller V, et al: Effect of postmenopausal hormone therapy on lipoprotein(a) concentration. Circulation 97:979, 1998.

SMOKING.

Smoking is a strong independent risk factor for coronary artery disease in both men and women; although smoking rates in the United States are falling overall, they are currently increasing among young women.[39] This risk is present even with minimal exposure (
5 cigarettes/day) and is not improved by use of low-yield cigarettes. Smoking risk is strikingly synergistic with that of oral contraceptive use, especially in women older than age 35, and leads to an earlier menopause, another coronary artery disease risk unique to women.[40] Cessation of smoking appears to gradually eliminate the excess risk in women,[41] although women more often smoke to lose or maintain body weight and find it harder to quit than do men.

HEMOSTASIS.

Elevated fibrinogen levels appear to be an independent cardiac risk factor in men and women, although women have not been as well studied.[42] The mechanism(s) by which fibrinogen enhances risk are poorly understood, although high fibrinogen levels have been associated with other CAD risk factors, including hypertension, diabetes, smoking, obesity, hyperlipidemia, and menopause, and lower levels have been associated with exercise, hormone replacement therapy, and high HDL.[43] Gender differences in platelet function and hemostasis are virtually unexplored. Factor V Leiden mutation may be a marker for atherothrombotic risk in postmenopausal women taking estrogen replacement or, conversely, may identify those who can take such medication without such side effects.[44]

EXERCISE.

A sedentary life style is associated with CAD in both men and women, although the data for women are sparse.[45] The reported beneficial effects of exercise on CAD risk profile are less marked in women compared with men, with lesser increases in HDL and less weight loss resulting from similar exercise training.[18] In prospective observational studies, a lower fitness level has been associated with a 4.7-fold increased risk for all-cause mortality in women,[46] and higher activity levels have been associated with decreased relative risks for CAD (0.44) and stroke (0.51), independent of other vascular risk factors.[47] Recent data from the Nurses' Health Study defines the amount of

exercise needed to prevent CAD, with a convincing dose-response relationship between the intensity of exercise and the reduction in risk.[48] Two aspects of this study were particularly important: brisk walking conferred the same benefit as vigorous exercise, and sedentary women who became active late in life reaped similar benefits as those who remained active throughout.

PSYCHOSOCIAL FACTORS

(see also Chap. 70) . The interaction of psychosocial and biobehavioral factors and heart disease is complex but perhaps has been more extensively studied in women than in men.[49] [50] Several of the cardiovascular risk factors discussed earlier are related to behavior (obesity, smoking, exercise) and are optimally treated with its modification. Perceived stress and its balance with situational control have been found to affect CAD risk in women as well as in men. Acute and chronic stress are thought to "trigger" myocardial infarction in both sexes by contributing to plaque rupture.[51] Social networks and support influence CAD outcome both independently and through the likelihood of compliance with therapeutic strategies (e.g., cardiac rehabilitation). The lack of social support has been associated with a worse outcome in both men and women, but its impact may be greater in women and women are more likely to survive their partners and live alone. Depression appears to be an independent risk factor for poor outcome after cardiac events or surgery in women, and cardiovascular outcome can be improved by specific therapy.[52]

INFLAMMATION

(see also Chap. 31) . Inflammation is increasingly recognized as a risk factor for CAD in women. In the Women's Health Study, C-reactive protein was as powerful an independent predictor as any other single factor.[52A] [52B] Women with the highest quartile of C-RP had a fivefold to sevenfold increased risk of cardiac and vascular events over a 3-year follow-up period. Other markers with lower, but still significant, risk include serum amyloid A, soluble intercellular adhesion molecule-1, and interleuken 6.

HORMONES: RISKS AND BENEFITS OF ESTROGEN

The ovary produces both estrogenic and androgenic hormones until menopause, when production decreases gradually over several years but does not fully cease. The risk of CAD in women rises thereafter, equaling that in men by age 75. Women who have an early menopause and/or bilateral oophorectomy experience a higher risk of CAD. Menopause, or estrogen deprivation, is associated with detrimental changes in cardiovascular risk factors, including an increase in LDL cholesterol, a small decrease in HDL, and an increased total ratio of cholesterol to HDL.[53] [54] Furthermore, menopause decreases aortic root elasticity and blunts nocturnal reductions in blood pressure, in association with the more subtle changes of concentric left ventricular remodeling and reduced contractility.[55] [56] Natural menopause seems to have little immediate effect on blood pressure, glucose tolerance, insulin levels, body weight, or physical activity other than that of advancing age.[54]

ORAL CONTRACEPTIVES.

Current low-dose oral contraceptives generally contain a synthetic estrogen, such as ethinyl estradiol, and a synthetic progestin, and pose only a very negligible cardiovascular risk for most patients.[53] [57] [58] The risk of arterial and venous thrombosis is low but is magnified by advancing age and especially by smoking. The risk of myocardial infarction is not increased by oral contraceptives unless the patient is older than age 35 and/or smokes cigarettes, and it appears to be entirely caused by thromboembolism rather than by coronary atherosclerosis, because the angiographic coronary plaque burden is actually lower in oral contraceptive users than in age-matched nonusers with myocardial infarction.

Because most regimens employ a combination of hormones, the effect of any given oral contraceptive on circulating lipoproteins represents the sum of estrogenic effects (higher HDL and triglycerides, lower LDL) and progestogenic effects (higher LDL, lower HDL). Newer agents such as norethindrone, gestodene, desogestrel, and norgestimate have beneficial effects on lipoprotein levels but may increase thromboembolic complications.[58]

ESTROGEN AND CARDIAC RISK FACTOR MODIFICATION.

Observations of the low risk of CAD in premenopausal women led to the hypothesis that estrogen is protective and led to clinical trials of estrogen therapy in men in the 1950s and 1960s. These studies used high-dose conjugated estrogens (up to 10 mg/day) and generally resulted in poor drug tolerance, little in the way of favorable risk factor modification, and an excess of thrombophlebitis, cholecystitis, and embolic events without evidence of cardioprotection. Large, randomized trials in women have only begun recently; results from many trials will not be available for several years. Currently, our knowledge of the value of hormonal replacement therapy in women is based on its prospectively demonstrated beneficial effects on cardiac risk factors, observational evidence of primary and secondary protection, and the negative results of the one secondary prevention trial published to date (Heart and Estrogen/Progestin Replacement Study [HERS]).[59]

In postmenopausal women, exogenous estrogen results in higher HDL (especially HDL_2) and apolipoprotein A1, and lower LDL, apolipoprotein B-100, and Lp(a),[17A] [53] [60] [61] [62] (see Table 58-1) . Importantly, the Postmenopausal Estrogen/Progestin

Interventions (PEPI) trial showed that the addition of a progestin to estrogen did not interfere with the LDL cholesterol-lowering effect of the latter but reduced endometrial hyperplasia. The use of micronized progestin was associated with an increase in HDL cholesterol.[60] Triglycerides and LDL are often increased in a dose-dependent manner;

and although these increases are highly variable in magnitude, they may limit the use of estrogen in some patients. Transdermal estrogens appear to have lesser effects on all lipoproteins, suggesting that first-pass liver metabolism is important in mediating these effects. This mode of drug delivery may be preferred in women with marked triglyceride elevations at baseline or in response to the oral route.[63] Indeed, the alterations in lipoprotein metabolism result largely from estrogen receptor-mediated actions on apolipoprotein gene expression in the liver.

Actions of Estrogen

Estrogen was once thought to mediate all of its beneficial effects through alterations in lipid metabolism; however, this mechanism accounts for only one fourth to one third of its actions. The other, multiple beneficial effects provide additional "biological plausibility" for the observed reduction in CAD among premenopausal women or postmenopausal women taking hormone replacement therapy.[64] [65] Estrogen mediates most of its effects through specific receptors (at least two types, alpha and beta, have been described) that function as transcription factors altering gene expression when they are activated. Estrogen receptors are found throughout the vasculature as well as in reproductive tissues, bone, liver, and brain. Estrogen decreases the atherogenic oxidation of LDL both in vivo and in vitro and decreases the incorporation of lipids into the vessel wall, both protective mechanisms for estrogen replacement.[66] [67] Data from the Atherosclerosis Risk in Communities (ARIC) study suggest that estrogen's effect is largely physiological and not structural or anatomical.[61] [68] In support of this, estrogen is a direct vasodilator, with effects on nitric oxide release and calcium and potassium ion channels. Estrogen acutely decreases the paradoxical coronary vasoconstriction response to acetylcholine[69] and potentiates the endothelium-dependent vasodilation of conductance and resistance coronary beds and forearm vessels in women.[70] This effect may account for its symptomatic benefit in women with Syndrome X.[71]

Estrogen also regulates expression of a variety of vascular-related genes important in CAD. These include prostacyclin, endothelin-1, collagen, matrix metalloproteinase 2, E-selectin, vascular adhesion molecule, and vascular endothelial growth factor. A similar array of actions is noted on nonvascular genes, also deemed to be important in CAD, including growth and development genes (TGF-beta, epidermal growth factor, platelet-derived growth factor, flt-4 tyrosine), coagulation- and fibrinolysis-related genes (tissue factor, fibrinogen, protein S, coagulation factors VII and XII, PAI-1, tPA, and antithrombin III) and signaling-related genes. Together, these actions suggest a powerful role for estrogen in regulating vascular tone, the response to injury and repair, atherosclerosis, and coagulation. Clinical studies confirm estrogen's association with many of these systems. These effects include a decrease in thrombotic potential,[60] [72] enhanced fibrinolysis,[73] and lowered serum angiotensin-converting enzyme activity.[74] Reports of an idiosyncratic elevation in blood pressure and improved insulin sensitivity have not been confirmed by more recent clinical studies.[60] [61] At present, which of the many beneficial effects of estrogen are most important for the prevention of CAD has not been determined. An active area of research, this knowledge is critical to future development of clinical tools for the prevention and treatment of CAD in both men and women.

CAD Prevention with Estrogen

More than 30 epidemiological studies have examined the utility of estrogen in the primary prevention of CAD, and the vast majority report a significant benefit.[53] [75] [76] [77] [78] [79] [80] [81] The largest of these studies, the Nurses' Health Study, reported a relative risk of 0.56 for myocardial infarction or death in women currently using estrogen and 0.83 in everusers, after adjustment for age and risk factors.[81] Metaanalyses[75] [77] [80] have determined composite relative risks of 0.50 to 0.65 for both the development of and death from CAD in estrogen users.

Other documented benefits of estrogen therapy include the alleviation of menopausal symptoms, including vasomotor instability, prevention of urogenital atrophy and urinary tract infections, prevention of osteoporosis and fatal hip fracture (relative risk for death is 0.75 for users of estrogen), and prevention of colon cancer (relative risk 0.80).[53] [75] [79] A possible protective effect against stroke has been noted in several studies[82] but is not significant in others, including the large Nurses' Health Study (relative risk 0.97 for current users) and another recent meta-analysis.[75] It is possible that the relatively young cohorts examined may have influenced these findings (median age for stroke in women is 83 years). Estrogen replacement may also have beneficial effects on cognitive function, particularly in symptomatic women.[83]

The beneficial effect of reproductive hormones also extends to selective estrogen receptor modulators (SERMs). Tamoxifen, a first-generation estrogen agonist/antagonist with selective tissue effects, has been shown to have salutary effects on circulating lipoproteins[84] and to reduce the number of hospital admissions resulting from CAD and deaths due to myocardial infarction and vascular causes.[85] Raloxifene, a second-generation SERM, also has a beneficial effect on cardiac risk factors[29] [86] and does not cause breast or uterine hyperplasia, although its clinical cardiovascular benefit is unproven. In rabbits, it is a nitric oxide-dependent coronary vasodilator acting through estrogen receptor binding.[87] Studies in monkeys fed an atherogenic diet showed that, whereas raloxifene reduced LDL, it did not prevent plaque formation, as conjugated estrogens did.[88] The data regarding phytoestrogens and soy products (isoflavenoids) are even less clear. However, some women may prefer these agents, because they are seen as dietary supplements rather than pharmacological interventions, and the U.S. Food and Drug Administration has approved labeling of soy products as possessing efficacy in lipid lowering. These are very active areas of investigation and drug development, and many new prescription and over-the-counter compounds will be introduced in the near future, including those suitable for use in men. Ultimately, recommendations regarding their use await performance of randomized trials with clinical (and not surrogate) endpoints and demonstration of relative merit to conventional estrogen replacement therapy.

A smaller number of studies have evaluated the utility of estrogen in the secondary prevention of coronary artery disease. Women who were current or ever-users of estrogen had less severe angiographic coronary artery disease than never-users, even after correction for age, cholesterol, smoking, diabetes, and hypertension.[89] Long-term survival in women with a similar extent of angiographically documented coronary

disease or after coronary artery bypass grafting is greater in women taking estrogen,[90] [91] and restenosis is reduced after angioplasty.

Although these observations are compelling, completion of the first randomized prospective trial of hormone replacement

therapy, HERS, has caused a dramatic rethinking of the potential benefit.[59] Contrary to expectations, there were no reductions in nonfatal myocardial infarction, coronary death, and overall mortality during 4.1 years of follow-up in 3763 postmenopausal women with CAD (Fig. 58-2). Instead, there was an excess of thrombotic events, particularly in years 1 and 2. As an alternative to abandonment of the hypothesis that estrogen is protective, investigators have cited the possible mitigating effects of concomitant progestin. However, the hormone replacement therapy regimen used (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone daily) did have beneficial lipid effects, raising HDL 10 percent and lowering LDL 11 percent, but also caused more thromboembolic events and

Figure 58-2 Coronary artery disease (CAD) events *(left)*, nonfatal myocardial infarction *(center)*, and CAD deaths *(right)* in the Heart and Estrogen/Progestin Replacement Study (HERS): Kaplan-Meier estimates of the cumulative incidence of events. The number of women observed at each year of follow-up and still free of an event are provided in parentheses. Log rank *p* values are 0.91 for primary CAD events, 0.46 for nonfatal myocardial infarction, and 0.23 for CAD death. *(From Hulley S, Grady D, Bush T, et al: Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 280:609, 1998. Copyright 1998, American Medical Association.)*

gallbladder disease. Another possible explanation is attrition of women with an early increased risk, such as for thromboembolism.[92] This hypothesis is supported by close examination of the time trends that reveal excess CAD events early and fewer later in the follow-up period. Further, there are questions regarding the statistical power of the HERS population and follow-up.[92A] A final hypothesis, that estrogen may increase vascular inflammation, is supported by several recent studies showing increased C-reactive protein among estrogen users,[93] [94] which may override antiinflammatory effects of lowered E-selectin in some individuals and is associated with increased cardiovascular risk.[52A]

In the light of these data it is hard to recommend initiation of estrogen replacement therapy for secondary prevention of CAD, yet patients currently on therapy should probably continue. Many questions remain.[92] [92A] [95] Some have suggested that use of a lower dose or different hormone regimen or the addition of aspirin would modify the early thromboembolic side effects. It is also unclear how these results should be applied to decisions regarding use of estrogen replacement therapy for primary prevention. Trial participants are currently being followed for longer term results, and other studies are in

progress.

In addition to the questions HERS raises about efficacy, and the methodological limitations in other available studies, there are significant risks associated with estrogen use and logistic problems with its prescription. Chief among the risks of estrogen use is endometrial cancer, for which unopposed estrogen therapy carries a fivefold to eightfold increased risk, associated with an estimated threefold increased risk of death.[75] [78] Women without a uterus obviously do not share this risk, and it has been proposed that the addition of a progestin nullifies it. A potential detrimental effect on the cardioprotective action of estrogen of adding progestins has been anticipated because of their androgenic effect on circulating lipids; however, recent studies suggest that this factor may have negligible effects or may even be beneficial.[60] [80]

BREAST CANCER.

Estrogen may increase breast cancer risk, with meta-analyses showing little increased risk for short-term therapy, whereas a higher relative risk, up to 1.5, has been associated with long-term use (over 10 years) in the Nurses' Health Study.[75] [96] [97] This a strong psychological, if not biological, deterrent to estrogen replacement, especially in women with a personal or family history of breast cancer and a low likelihood of developing (i.e., no risk factors for) CAD. Women with established CAD or with risk factors and no family history of breast cancer would remain good candidates for estrogen replacement, and SERMs, which may actually reduce breast cancer risk,[98] could be preferred agents in others. The effects of the addition of progestins to estrogen on the incidence of breast cancer are unknown, but they appear to be minimal.[97]

WEIGHING RISKS AND BENEFITS OF ESTROGEN.

Three recent meta-analyses of estrogen replacement reviewed all available data on its effects on endometrial and breast cancers, hip fracture, stroke, and coronary artery disease.[75] [76] [77] [80] Combining these data with other information regarding the incidence and mortality of these diseases, detailed estimates of the gain/loss in life expectancy or assessment of summed risk weights with hormone therapy were derived. In these analyses, for most women, estrogen replacement enhanced longevity somewhat and SERMs added little benefit. However, simple life expectancy calculations may not address some women's concerns adequately.[99]

Other considerations in the decision to use estrogen replacement include the drug's side effects, such as vaginal bleeding, the need for careful monitoring for breast and uterine cancers and endometrial hyperplasia, and the costs of therapy and of monitoring.[75] [76] [77] The risk of thrombophlebitis is unclear at the doses currently employed,[100] but

it is likely elevated[59] ; it is unclear if aspirin use offsets this risk or if testing for prothrombotic tendencies, such as factor V Leiden mutation, can be used to exclude

women at higher risk.[44] Finally, compliance with estrogen replacement therapy taken to relieve menopause symptoms is poor; there is no reason to think that this will improve in asymptomatic women taking estrogen for the prevention of future disease.[95]

A full evaluation of the risks and benefits of estrogen replacement cannot be made without considering the methodological flaws inherent in all available data and those crucial areas in which information is lacking. For primary prevention, the reliance on observational studies in the absence of randomized trials raises issues of selection bias, especially because women using estrogen are more likely to see their physicians frequently, to adopt healthy behaviors such as exercise, prudent diet, and smoking cessation, and to be of higher socioeconomic status.[101] For any woman, patient preference after careful counseling should be a dominant factor. Published patient algorithms are helpful in this regard.[76] [99] [102]

The most commonly used estrogen is conjugated equine estrogens at a daily dose of 0.625 mg. There is no evidence that cardioprotection is enhanced or even preserved at a higher dose, and side effects are often worse; indeed there is evidence that a dose of 0.3 mg is equally cardioprotective.[102A] Similarly, the optimal formulation, dosage, and regimen for progestins are unclear. The optimal timing of estrogen replacement is also unknown. Some workers suggest starting the drug at menopause and continuing indefinitely for women at high risk. The usefulness of beginning therapy at a more advanced age (e.g., with the first manifestation of CAD) is unknown, particularly in light of the HERS study.

ESTROGEN REPLACEMENT THERAPY GUIDELINES.

The American College of Physicians and others have published guidelines for counseling postmenopausal women about primary preventive hormone therapy that are well grounded in available knowledge.[76] [102] These guidelines suggest that, based on available data, estrogen replacement is likely of value in women with a high risk of developing osteoporosis or CAD. This proposal represents an enormous potential change in cardiovascular therapeutics and practice, as yet unsupported by data from randomized controlled trials, such as the Women's Health Initiative, which will not become available until 2005. It is important to recognize that whereas salutary effects of estrogen replacement on lipids have been demonstrated in prospective randomized trials, clinical benefits in primary prevention thus far are limited to observational studies and secondary prevention was not beneficial in the single large study completed to date.[59] It may be that untested, newer agents such as the SERMs or phytoestrogens[102B] may ultimately be preferred treatment. Ongoing randomized trials of primary and secondary prevention will prove whether the use of estrogen replacement in postmenopausal women is a viable strategy.

EVALUATION OF CHEST PAIN IN WOMEN

Clinical Syndromes and Natural History

It has long been assumed that the clinical expression of CAD is similar in men and

women, yet available information suggests that gender differences in presentation and disease manifestations exist and should be considered in the evaluation of the patient with chest pain. Several studies document that women are more likely than men to present with angina and less likely to present with a concrete event such as myocardial infarction as either the first

Figure 58-3 Prevalence of angiographically documented coronary heart disease (CHD) in men and women according to age and chest pain syndrome. *(Modified from DeSanctis RW: Clinical manifestations of coronary artery disease: Chest pain in women. In Wenger NK, Speroff L, Packard B [eds]: Cardiovascular Health and Disease in Women. Greenwich, CT, Le Jacq Communications, 1993, p 68.)*

or subsequent manifestations of CAD.[3] Furthermore, women are on average 5 to 10 years older at the time of presentation. Perhaps even more than in men, the prevalence of angiographic coronary disease varies dramatically according to the nature of the chest pain, the patient's age, and the presence and type of coronary risk factors[103] [104] [105] (Fig. 58-3) . This underlines the importance of good history taking and careful cardiovascular risk factor assessment in the evaluation of women with chest pain.[106]

A variety of factors influence the evaluation of chest pain in women, including patient and physician perception of disease risk (see earlier). Compared with men, women with chronic stable angina are older and more likely to have hypertension, diabetes, and congestive heart failure but are less likely to have had a prior myocardial infarction or revascularization.[107] Although equally likely to have effort angina, such women are more likely to experience pain at rest, during sleep, or with mental stress. Similarly, women undergoing a myocardial infarction are more likely to have nausea and jaw, back, or neck pain, or palpitations, and are less likely to report diaphoresis than men.[108] [109] These differences make the evaluation of a new symptom or disability more complex and make essential a gender-based approach to education of both lay and health personnel in the presentation of acute ischemic syndromes.

The reasons for these differences in symptoms are unclear. Women with acute myocardial infarction have similar angiographic findings, suggesting that the mechanism of infarction does not vary by gender.[110] However, women do have higher prevalences than men do of vasospastic angina and of microvascular angina,[104] [105] both of which are associated with atypical chest pain patterns, are often treated differently, and have a more favorable prognosis than epicardial coronary disease. Recent data suggest that such chest pain syndromes are related to myocardial ischemia with altered phosphocreatine metabolism documented by PET scan.[110A] Even in the presence of angiographically documented disease, gender differences in plaque components (more cellular and fibrous tissue in women), endothelial function (estrogen-induced coronary vasodilation), and hemostasis (higher fibrinogen and factor VII levels in women) may influence the pathophysiology and, therefore, the clinical manifestations of coronary disease.[43] [111] Finally, women more commonly have noncoronary chest pain syndromes, further complicating their clinical assessment.

Women with chest pain are less likely to experience a subsequent myocardial infarction or coronary death than men.[3] [112] [113] Although overall age-adjusted rates of death or myocardial infarction in women with angina are less than those in men,[112] of subjects older than age 65, women and men with exertional chest pain have the same relative risks of CAD death (2.7 vs. 2.4).[114] Other data suggesting that the prognosis of coronary disease is not more benign in women include the similar (if not worse) early mortality after myocardial infarction in women.[115]

Thus, determination of the etiology of chest pain in women can be difficult, hampered by the onset of CAD later in life, a setting of greater frailty and concomitant disease, the more common appearance of symptoms such as rest angina in patients with otherwise stable patterns, and the higher likelihood of alternative mechanisms of chest pain.

NONINVASIVE DIAGNOSTIC TESTING

(see also Chaps. 6 , 7 , 9 , and 13) . Although noninvasive diagnostic testing for CAD does not fully resolve the difficulties inherent in evaluating chest pain in women, careful test selection and interpretation can provide valuable information regarding the presence and severity of CAD in women. The general principles underlying noninvasive diagnostic testing do not differ in men and women.[116] The simplest diagnostic test, the resting electrocardiogram, reveals a higher prevalence of repolarization (ST-T wave) abnormalities in women with suspected coronary disease than in men (32 vs. 23 percent).[103]

Treadmill exercise testing carries a higher false-positive rate in women (38 to 67 percent) than in men (7 to 44 percent) in the same studies, in part because of a lower pretest likelihood of disease.[104] However, women have a low false-negative rate (12 to 22 percent) that compares favorably to that in men (12 to 40 percent) and suggests that routine testing reliably *excludes* the presence of CAD in women with negative tests. The exercise electrocardiogram also provides useful prognostic information in women.[117] [118] Variables contributing to test accuracy are resting ST-T wave abnormalities, peak exercise heart rate, number of diseased vessels, typical angina, age, gender, drug use (digitalis, diazepam), hyperventilation, conduction abnormalities, left ventricular hypertrophy, mitral valve prolapse, vasospasm, and hormonal influences. Although less common in women, false-negative studies may be contributed to by gender-specific characteristics, including reduced exercise tolerance and the higher prevalence of single-vessel disease in women.

The addition of imaging to electrocardiographic stress testing markedly improves its accuracy in women, as noted by recent meta-analyses[119] [120] and reviews[121] (Fig. 58-4; Table 58-2) . Planar thallium scans during treadmill exercise testing suggest moderate increases in sensitivity and specificity in women.[118] [119] [121] The use of single-photon emission computed tomography (SPECT) may not improve accuracy in women as it does in men.[122] Much of the inaccuracy of thallium scanning in women has been

attributed to breast attenuation, which is reduced by use of higher-energy isotopes such as technetium-99m-sestamibi and by newer algorithms for attenuation correction (see Chap. 9) . [123] Coupling exercise testing with echocardiographic visualization of wall motion (i.e., exercise echocardiography) also improves diagnostic accuracy in women,[119] [121] [124] even more so than in men.[120] Similarly, the use of pharmacological stress agents (e.g., adenosine, dipyridamole, dobutamine) in women coupled with either echocardiographic or nuclear imaging shows substantial improvements in test performance over electrocardiographic results alone.[121]

Because few direct comparisons between exercise echocardiography and exercise-thallium or sestamibi testing have been reported, the objective basis for selecting one

Figure 58-4 Posttest likelihood of coronary artery disease (CAD) in a 55-year-old woman, depending on test results (positive, top; negative, bottom), type of chest pain (CP), and pretest probability of disease (in parentheses) as described in CASS (Edmond M, Mock MB, Davis KB, et al: Long-term survival of medically treated patients in the coronary artery surgery study [CASS] registry. Circulation 90:2645, 1994) and type of stress test performed (exercise electrocardiogram [ECG], thallium perfusion [Thal], echocardiographic imaging [Echo]). *(Data from Kwok Y, Kim C, Grady D, et al: Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 83:660, 1999.)*

modality over another must rely on meta-analysis and cost-effectiveness modeling. Recent meta-analyses[119] [120] have shown exercise echocardiography to have similar sensitivity and superior specificity to nuclear perfusion studies, with the accuracy of exercise ECG and exercise nuclear studies showing gender dependence, whereas that of exercise echocardiography is similar in men and women. Several formal cost-effectiveness models show stress echocardiography to dominate over nuclear techniques,[124] [125] [126] suggesting that diagnostic testing strategies employing exercise echocardiography as the first test might be superior.

CORONARY ANGIOGRAPHY.

Few studies have examined gender differences in invasive diagnostic testing. Women are more likely than men to experience vascular and renal complications from diagnostic angiography, possibly due to more advanced age, higher prevalence of diabetes, and smaller body size; the incidence of myocardial infarction, stroke, and death are similar.[127]

GENDER BIAS.

A 1987 study reporting that men with positive nuclear exercise tests were 6.3 times more likely to

TABLE 58-2 -- WEIGHTED MEAN TEST CHARACTERISTICS FOR EXERCISE STRESS TESTING IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE IN WOMEN

EXERCISE TEST	NO. WOMEN	SENSITIVITY	SPECIFICITY	LIKELIHOOD RATIO (+)	LIKELIHOOD RATIO (-)
ECG	3721	61%	70%	2.25	0.55
Thallium	842	78%	64%	2.87	0.36
Echo	296	86%	79%	4.29	0.18

Modified from Kwok Y, Kim C, Grady D, et al: Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 83:660, 1999.

be referred to cardiac catheterization than women[128] gave rise to concerns that female patients were receiving inadequate or inappropriate care, a conclusion that has been supported by several subsequent studies. Coronary angiography is performed 28 to 45 percent more often and revascularization 15 to 27 percent more often in men than in women with a diagnosis of CAD.[129] Although awareness of gender differences is growing, these discrepancies still exist, such that both gender and race influence management of chest pain.[130]

It is clear that less aggressive treatment strategies in women do not represent optimal care even for patient groups with differences in disease prevalence, nor do they accurately reflect the difficulties in diagnosing coronary disease in women. Although women undergoing diagnostic stress testing[131] were equally likely to have a positive stress electrocardiogram (29 percent in women vs. 30 percent in men) or stress thallium examination (23 vs. 27 percent), they were less commonly referred for additional noninvasive testing (4 vs. 20 percent) or catheterization (34 vs. 45 percent). However, subsequent event rates were higher in women, whether they had a normal initial test (1.6 percent/yr death or myocardial infarction vs. 0.8 per cent in men) or an abnormal one (14.3 vs. 6.0 percent/yr). Both male and female patients who did undergo revascularization had no events, whereas women who were not revascularized had a worse prognosis than similarly untreated men. These data demonstrate not only a gender-based difference in clinical practice but a worse patient outcome in women treated less aggressively.

MANAGEMENT OF CHRONIC CAD IN WOMEN

MEDICAL THERAPY.

Because fewer studies have examined the medical treatment of chronic CAD in women, there is less evidence as to whether women respond similarly to men to conventional therapy. A recent review of gender differences in the efficacy of CAD treatment found

evidence for similar benefit of antiplatelet therapy, beta blockade, nitroglycerin, thrombolytics, and angiotensin-converting enzyme inhibitors[132] (Fig. 58-5). Calcium channel blockade was not effective in either men or women. Although early data regarding aspirin were conflicting, newer observational studies suggest benefit but still await confirmation by a randomized clinical trial. The Nurses' Health Study showed that women older than 50 taking one to six aspirin per week had a 32 percent lower likelihood of myocardial infarction, [133] a borderline significant reduction that did not apply to younger women or higher doses. Another observational study in women with CAD revealed reduced adjusted relative risk for cardiovascular (relative risk 0.61) and all-cause (0.66) mortality. Diabetic, elderly, and symptomatic women benefited most, as did women with prior myocardial infarctions.[134] Aspirin and other antiplatelet agents also reduced vascular events in women.[135]

Interestingly, glycoprotein IIb-IIIa inhibitors provide additional benefit over aspirin in unstable coronary syndromes in women but not in men.[136] This finding suggests that, in women, platelets may play a more important role or may require more aggressive inhibition.

Cross-sectional studies reveal that women with CAD are more likely than men to be receiving nitrates, calcium channel blockers, sedatives, diuretics, and other antihypertensive agents but are equally or less likely to have been prescribed aspirin and beta blockers.[107] [131] Although this has improved somewhat, treatment levels are not yet equal, especially in older patients. The impact, if any, of these differences on the prognosis of coronary disease is unknown. Although the Coronary Artery Surgery Study (CASS) shows that women treated medically had better 12-year survival with angiographically documented zero-, one- or two-vessel disease than did men with similar anatomy,[137] other studies suggest that undertreatment of women is related to a worse outcome.[138]

REVASCULARIZATION.

Many studies have addressed the relative effectiveness of revascularization procedures (angioplasty and coronary artery bypass grafting [CABG]) in men and women. Unfortunately, comparisons of the results of medical management and percutaneous and operative revascularization are few. Instead, these studies have focused on gender differences in the population under study, making difficult the application of these data to the optimal care of individual patients. Virtually all data for both angioplasty and CABG have been derived from post hoc subgroup analyses of studies designed to address other issues.

Percutaneous Coronary Intervention (PCI) (see also Chap. 38) .

Virtually all PCI studies note a greater prevalence of comorbidities in women, including advanced age, hypertension, congestive heart failure, diabetes, severe concomitant noncardiac disease, and hypercholesterolemia.[138] [139] [140] [141] [142] [143] [144] [145] [146] The severity of angina is also greater in women, the condition being more likely to be

unstable or to be of Canadian Class III or IV severity.[139] [141] [142] [143]

The likelihood of *angiographic success* of the application of balloon angioplasty or of new devices is similar in men and women in current series,[141] [142] [143] with lower success rates in women reported only in the older studies. In contrast, in most balloon angioplasty series, women experience higher complication and mortality rates, including groin complications, acute closure, and death, but not myocardial infarction or emergency coronary artery bypass grafting[140] (Table 58-3) . Indeed, the proportional risk of death from procedural complications is greater in women.[145] [146] The difference in outcome has been variously attributed to women's older age, smaller body size, greater severity of angina, more fragile vessels, and greater burden of comorbidity.[143] [147] More recent preliminary data from the National Heart Lung and Blood Institute (NHLBI) Dynamic Registry (1997-1998) and Northern New England Data Bases (1990-1993 and 1994-1996) suggest that the gender gap is narrowing, particularly with the growing use of new devices.[145] [148] [149]

The late outcome of PCI appears to be similar in men and women, with women more likely to experience angina

Figure 58-5 Proportional effects of treatment strategies on morbidity and mortality in women versus men from randomized controlled trials. Antiplatelet trials evaluated aspirin, dipyridamole, ticlopidine, sulfinpyrazone, or suloctidil versus active or placebo control in vascular disease (not coronary artery disease); beta blocker trials assessed atenolol, metoprolol, or propranolol versus control; calcium channel blocker studies evaluated diltiazem or verapamil versus control; the nitroglycerin trial assessed transdermal glyceryl trinitrate versus control; fibrinolytic trials tested streptokinase, anistreplase, urokinase, or alteplase versus control; comparative thrombolytic trials assessed streptokinase versus alteplase; and angiotensin-converting enzyme (ACE) inhibitor trials assessed captopril, lisinopril, or enalapril versus control. Unless otherwise specified, summary frequencies and odds ratios with 95 percent confidence intervals (C.I.) are presented. Asterisk indicates multivariable-adjusted odds ratio, percentages of patients only.*(Modified from Fetters JK, Peterson ED, Shaw LJ, et al: Sex-specific differences in coronary artery disease risk factors, evaluation, and treatment: Have they been adequately evaluated? Am Heart J 131:804, 1996.)*

and men more likely to experience cardiac events (myocardial infarction, revascularization or death).[140] [141] [142] [143] [146] [147] Two observational studies have suggested that estrogen use in postmenopausal women reduces restenosis,[150] [151] perhaps through acceleration of endothelial repair.

Coronary Artery Bypass Grafting (see also Chap. 37) .

Gender differences in outcome after CABG are well established and remain present even in the mid 1990s.[152] [153] [154] As with angioplasty, virtually every study has shown women to have more comorbidities and less favorable patient characteristics preoperatively. Women are also more likely than men to undergo urgent or emergent

surgery. Women and men undergoing CABG are equally symptomatic, but women are more likely to have preserved ventricular function and less likely to have multivessel or three-vessel disease.

The mortality of women is higher than of men, with risk ratios of 1.4 to 4.4. This is particularly true for low- and medium-risk patients, with no difference in highest-risk patients, suggesting that other factors predominate.[154] In addition, women are less likely to receive internal mammary grafts or undergo complete revascularization and are more likely to experience the complications of heart failure, perioperative infarction, and hemorrhage.[152] [153]

The causes of this higher mortality appear to be multiple, including technical factors such as smaller body size and coronary diameter, advanced age, comorbidities such as diabetes and hypertension, and clinical factors such as the urgency of the procedure. Disease-related factors such as the extent and severity of angiographic stenoses and left ventricular dysfunction are also important in determining outcome, yet these factors tend to be more favorable in women. As with angioplasty, patient-related factors and comorbidities seem increasingly important to outcome, with more recent studies reporting continuing gender differences in outcome.[154] The impact of new techniques such as minimally invasive bypass surgery and grafting performed without circulatory arrest is unknown, but it may be greater in the frailer, older female population.

Women have a lower likelihood of being free of angina than do men and experience greater physical disability and less return to work. Rates of long-term survival, infarction, and reoperation are similar.

ACUTE CORONARY SYNDROMES (see also Chaps. 35 and 36)

Women have a different clinical presentation and hospital course after acute coronary syndromes and acute myocardial infarction and respond differently to both medical and

TABLE 58-3 -- GENDER DIFFERENCES IN EARLY OUTCOME OF ELECTIVE ANGIOPLASTY

STUDY, YEAR, REFERENCE	SERIES	ANGIOGRAPHIC SUCCESS (%)		COMPLICATIONS (%)		MORTALITY (%)	
		Women	Men	Women	Men	Women	Men
Cowley, et al., 1985[139]	NHLBI 1978-1982	56.6	56.6	27.2	19.4	1.7	0.3
Kelsey, et al., 1993[140]	NHLBI 1985-1986	89	89	29	20	2.6	0.3

Arnold, et al., 1994[141]	Cleveland Clinic 1980-1988	93.6	93.3	9	7	1.1	0.3
Weintraub, et al., 1994[142]	Emory 1980-1991	90.8	89.7			0.7	0.1
Bell, et al., 1993[143]	Mayo Clinic 1979-1987	83	82			1.0	1.2
	Mayo Clinic 1988-1990	87	90			2.9	1.4
Welty, et al., 1994[144]	Deaconess 1981-1989	89.6	91.2			0.6	0.9
Malenka, et al., 1999[145]	Northern New England 1990-1993					0.6	2.2
Keelan, et al., 1997[146]	Mayo Clinic 1981-1993 (unstable angina)	87.9	87.2	8.3	7.8	4.1	3.2
O'Connor, et al., 1999[147]	Northern New England 1994-1996					1.3	0.96

procedural therapies. Gender differences in acute myocardial infarction have been reviewed.[155]

CLINICAL SYNDROMES.

Women suffering from an acute coronary syndrome or myocardial infarction are likely to be older and more likely to have a history of hypertension, diabetes, unstable angina, hyperlipidemia, and congestive heart failure, and they are less likely to be smokers than their male counterparts.[155] [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] [167] [168] [169] [170] [171] Women are also more likely to experience neck and shoulder pain, abdominal pain, nausea, vomiting, fatigue, and dyspnea in addition to chest pain.[163] [164] It is unclear if they are more likely to have silent infarctions.[3] Perhaps due in part to these more atypical symptoms, women seek medical attention more slowly[166] and even after hospital arrival may experience greater delays in receiving care.[157] [159] [163]

Women admitted to a hospital for acute coronary syndromes are more likely to have experienced a prior nontransmural infarction.[161] Women with infarction have more serious presentations, with greater prevalences of tachycardia, rales, heart block, and a higher Killip class on initial presentation.[157] [159] [161] [164] [166] Nevertheless, women are less likely to receive thrombolysis (even after controlling for eligibility)[156] [163] [164] [166] [167] and receive it later than do men.[159] [162] Women are also less likely to be admitted to a coronary care unit[166] [168] or to be hospitalized in an institution in which catheterization is available.[161] Most[161] [163] [165] [168] but not all[169] [170] studies find that women with acute

infarction are less likely to undergo diagnostic catheterization during their hospital stay, even after controlling for age and a variety of clinical characteristics. Some studies have reported equal or near-equal rates of angioplasty and bypass surgery among catheterized patients,[159] [160] [165] [169] suggesting that differences in treatment disappear once disease is documented angiographically.[169] [171] However, this is not true in all series.[163] [164]

Women have higher rates of in-hospital complications from infarction, including bleeding, stroke, shock, myocardial rupture, and recurrent chest pain, than do men, although most of these differences disappear on correction for controlling for age and comorbidities.[159] [160] [172] Women with acute infarction are more likely to be treated with nitrates, digoxin, and diuretics than are men and are less likely to receive thrombolytics, antiarrhythmics, antiplatelet agents, and beta blockers.[158] [162] [166] Even after discharge, women are less likely to be scheduled for exercise tests or referred for cardiac rehabilitation, and recovery from infarction appears delayed with slower return to work and full resumption of all activities, with more sleep disturbance and psychiatric and psychosomatic complaints experienced. [173]

MORTALITY.

Mortality in non-Q-wave myocardial infarction appears to be similar to that in men, whereas women with unstable angina are less likely to have angiographic CAD or reinfarction and death.[174] [175] In acute myocardial infarction, early or in-hospital mortality in women is greater than in men, and adjustment for age and/or clinical characteristics serves to reduce this difference but not to eliminate it fully. This is particularly true in younger women (Fig. 58-6) . [115] [156] [176] [177] Analysis of a very large scale, population-based data set (as opposed to post hoc analysis of thrombolytic trial study populations[178]) indicated that gender differences in mortality decrease with age.[177] In part, this gap may be due to a higher rate of prehospital sudden death in men,[164] but this cannot explain the twofold greater mortality in women younger than 50 years of age compared with similarly aged men. Mortality 1 to 3 years after hospital discharge is similar in men and women, when adjustments are made for age and other baseline characteristics.[115] [179]

TREATMENT.

The reduction in mortality from thrombolysis in men and women with acute myocardial infarction is likely similar.[110] [163] [176] [179] The efficacy of thrombolysis also appears similar in men and women with similar rates of intracoronary thrombosis on pretreatment angiography[110] and of thrombolytic-induced, infarct-related artery patency and left ventricular function.[157] [160] However, complication rates, particularly hemorrhagic stroke and recurrent myocardial infarction, appear to be higher in women.[159] [160] [180] [181] Primary angioplasty is equally, if not more effective in women, as demonstrated by the Primary Angioplasty in Myocardial Infarction (PAMI) trial, in part due to the reduction in hemorrhagic stroke.[182] [183]

Medical treatment after hospital discharge appears to carry somewhat different benefits for men and women. Aspirin likely prevents reinfarction in women[134] ; calcium channel

blockers are not of benefit. Two studies suggest

Figure 58-6 Odds ratios for death during hospitalization for myocardial infarction in women as compared with men, according to age. *A,* The unadjusted odds ratios were derived from the model that included sex, age, the interaction between sex and age, and the year of discharge. *B,* The adjusted odds ratios were derived from the model that also included race, insurance status, medical history, severity of clinical abnormalities at admission, type of management in the first 24 hours after admission, and time to presentation.*(From Vaccarino V, Parsons L, Every NR, et al: Sex-based differences in early mortality after myocardial infarction. N Engl J Med 341:220, 1999. Copyright 1999, Massachusetts Medical Society.)*

that men may experience more benefit than women when treated with angiotensin-converting enzyme inhibitors post-infarction.[184] [185] In contrast, beta blockade clearly provides a substantial improvement in postinfarction survival in women that is equal to, if not greater than, that seen in men.[186] [187] [188] Unfortunately, women are less likely to be discharged on beta blockers.[158] [162] [166]

CONCLUSIONS

Although gender differences in the epidemiology of CAD have long been appreciated, we have only recently begun to critically examine and analyze differences in heart disease between men and women. Application of this new knowledge to patient care requires education of both patients and providers, yet it is essential for optimal medical practice. Although the diagnostic and therapeutic management of CAD are based on principles common to men and women, differences exist in risk factors, hormonal influences, clinical presentation, diagnostic evaluation, treatment, and outcomes of interventions for coronary artery disease. Similar differences exist in heart failure.[189] The astute practitioner will be able to incorporate knowledge of these differences into the care of each individual.

In the past 5 years, knowledge of gender-based cardiovascular pathophysiology and therapeutics has dramatically increased and will continue to grow as the many studies in progress close the gaps in our understanding of CAD in women. In particular, hormones and hormone replacement therapy, central to women's care, remain a large and unresolved area awaiting further elucidation of the basic biology and its translation into clinical care.

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Chapter 59 - Cardiovascular Disease in Athletes

BARRY J. MARON

During the past several years, the medical community and the lay public have become increasingly interested in and concerned about the causes of sudden and unexpected deaths in young trained athletes.[1] Such catastrophes are always unexpected events and, though relatively uncommon,[2] [3] nevertheless achieve high visibility and have a particularly tragic and devastating impact on the community.[4] As a consequence, the cardiovascular diseases[4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] and circumstances[16] [17] [17A] responsible for sudden death in athletes participating in sporting activities have been the subject of several reports, and a large measure of clarification has resulted.

CAUSES OF SUDDEN DEATH

Several autopsy-based studies have documented the cardiovascular diseases responsible for sudden death in young competitive athletes or youthful asymptomatic individuals with active sports-related life styles.[2] [5] [6] [7] [8] [9] Of note, these structural abnormalities should not be confused with the normal physiological adaptations in cardiac dimensions evident in many trained athletes and consisting of increased left ventricular mass with end-distolic cavity enlargement or occasionally increased wall thickness.[18] [19] [20] It is also important to be cautious in assigning frequency estimates

for various cardiovascular diseases as causes of sudden death in athletes; patient selection biases unavoidably influence the acquisition of such data in the absence of a systematic national registry.

Young Athletes

It has been convincingly demonstrated that the vast majority of sudden deaths in young athletes (age
35 years) are due to various congenital cardiovascular diseases (>20) (see Figs. 59-1 , 59-2 , 59-3 , and 59-4 .) [2] [4] [5] [6] [7] [8] [9] Indeed, virtually any disease capable of causing sudden death in young individuals may also do so in young athletes. It should be emphasized that all of these diseases are uncommon within the general population and do not occur with the same frequency as causes of sudden death in young athletes; indeed, most of the diseases are responsible for just 5 percent or less of all athletic field deaths.[4] [5]

HYPERTROPHIC CARDIOMYOPATHY (HCM) (see Chap. 48) .

The majority of studies show HCM to be the single most common cause of sudden death in young athletes, accounting for about one-third of these catastrophes.[5] HCM is a primary and familial cardiac malformation characterized by asymmetrical left ventricular hypertrophy and nondilated ventricular cavities[21] [22] [23] [24] (Fig. 59-2) , with heterogeneous expression and diverse clinical course. Disease-causing mutations in nine genes encoding proteins of the sarcomere (and >100 mutations) have been reported.[23] [24] HCM is a relatively common genetically transmitted disease, occurring in about 0.2 percent (1 in 500) of the general population.[25]

Not uncommonly, HCM is responsible for sudden cardiac death in young and asymptomatic individuals and frequently occurs during moderate or severe exertion.[21] [22] Indeed, the stress of intense training and competition (and associated alterations in blood volume, hydration, and electrolytes) undoubtedly increases that risk to some degree.[26] In HCM, particularly strenuous physical activity may act as a trigger mechanism for generating potentially lethal ventricular tachyarrhythmias, given the underlying electrophysiologically unstable myocardial substrate composed of replacement fibrosis (which is probably the consequence of

Figure 59-1 Causes of sudden cardiac death in young competitive athletes (median age, 17 years) based on systematic tracking of 158 athletes in the United States, primarily 1985-1995. In an additional 2 percent of the patients, no evidence of cardiovascular disease sufficient to explain death was identified at necropsy.
(increased) cardiac mass = hearts with increased weight and some morphological features consistent with (but not diagnostic of) hypertrophic cardiomyopathy. *(From Maron BJ, Thompson PD, Puffer JC, et al: Cardiovascular preparticipation screening of competitive athletes. Circulation 94:850-856, 1996. Adapted and reproduced with permission of the American Heart Association.)*

Figure 59-2 Morphological components of the disease process in hypertrophic cardiomyopathy (HCM), the most common cause of sudden death in young competitive athletes. *A,* Gross heart specimen sectioned in a cross-sectional plane similar to that of the echocardiographic (parasternal) long axis; left ventricular wall thickening shows an asymmetrical pattern and is confined primarily to the ventricular septum (VS), which bulges prominently into the left ventricular outflow tract. The left ventricular cavity appears reduced in size. FW = left ventricular free wall. *B-D,* Histological features characteristic of left ventricular myocardium in HCM. *B,* Markedly disordered architecture with adjacent hypertrophied cardiac muscle cells arranged at perpendicular and oblique angles. *C,* An intramural coronary artery with thickened wall, due primarily to medial hypertrophy, and with apparently narrowed lumen. *D,* Replacement fibrosis in an area of ventricular myocardium adjacent to an abnormal intramural coronary artery, and probably a consequence of ischemia. Ao = aorta; LA = left atrium; RV = right ventricle. *(From Maron J: Hypertrophic cardiomyopathy. Lancet 350:127-133, 1997.)*

ischemia) and disorganized cardiac muscle cells (see Fig. 59-2) .

Disease variables that appear to identify those individuals at greatly increased risk include prior aborted cardiac arrest or sustained ventricular tachycardia, family history of sudden or other premature HCM-related death (or high-risk genotype), multiple-repetitive nonsustained ventricular tachycardia on ambulatory Holter electrocardiographic (ECG) recording, recurrent syncope particularly when exertional and in the young, massive degrees of left ventricular hypertrophy, and possibly hypotensive blood pressure response to exercise.[22] Patients who have HCM and who are judged to be at high risk for sudden death may be considered for primary prevention of sudden death with prophylactic cardioverter-defibrillator implants.[27]

Although HCM may be suspected during preparticipation sports evaluations by the prior occurrence of exertional syncope, a family history of HCM or premature cardiac death, or the presence of a heart murmur, these features are relatively uncommon among all individuals affected by the disease.[22] Consequently, screening procedures limited to customary history and physical examination cannot be expected to identify HCM reliably and consistently.[28]

In some young athletes, segmental ventricular septal thickening (13 to 15 mm) consistent with a relatively mild morphological expression of HCM may be difficult to distinguish from the physiological and benign form of left ventricular hypertrophy that represents an adaptation to athletic training (i.e., "athlete's heart").[28A] [28B] Athletes within this morphological "gray zone" present an important and not uncommon clinical problem in which the differential diagnosis between HCM and athlete's heart can often be resolved by noninvasive testing[29] (Fig. 59-3) . This distinction may have particularly important implications, given that young athletes with an unequivocal diagnosis of HCM are discouraged from participation in most competitive sports to minimize risk (with the possible exception of those sports considered to be of low intensity).[30] Conversely, improper diagnosis of cardiac disease in an athlete may lead to unnecessary withdrawal

from athletics, thereby depriving that individual of the varied benefits of sports.

In addition, hearts encountered at autopsy not infrequently have increased mass (and left ventricular wall thickness) and nondilated ventricular cavities suggestive of HCM, but with other objective morphological findings not sufficiently striking to permit a definitive diagnosis.[5] It is

Figure 59-3 Chart depicting the criteria used to distinguish hypertrophic cardiomyopathy (HCM) from athlete's heart when the left ventricular (LV) wall thickness is within the shaded gray zone of overlap (13 to 15 mm), consistent with both diagnoses. *Assumed to be the nonobstructive form of HCM in this discussion, because the presence of substantial mitral valve systolic anterior motion would confirm, per se, the diagnosis of HCM in an athlete.
May involve various abnormalities, including heterogeneous distribution of left ventricular hypertrophy (LVH) in which asymmetry is prominent, and adjacent regions may be of greatly different thicknesses, with sharp transitions evident between segments. Also, patterns in which the anterior ventricular septum is spared from the hypertrophic process and the region of predominant thickening may be in the posterior portion of the septum or anterolateral or posterior free wall.
= decreased; LA = left atrial. *(From Maron BJ, Pelliccia A, Spirito P: Cardiac disease in young trained athletes: Insights into methods for distinguishing athlete's heart from structural heart disease with particular emphasis on hypertrophic cardiomyopathy. Circulation 91:1596-1601, 1995. Reproduced with permission of the American Heart Association.)*

uncertain whether some of these cases represent mild morphological expressions of HCM or, conceivably, unusual examples of marked physiological left ventricular hypertrophy associated with deleterious consequences.

CONGENITAL CORONARY ARTERY MALFORMATIONS (see Chaps. 43 and 44) .

Second in importance and frequency to HCM are the congenital coronary artery anomalies of wrong aortic sinus origin (occurring in about 20 percent).[5] The most common of these lesions causing sudden death in athletes appears to be anomalous origin of the left main coronary artery from the right (anterior) sinus of Valsalva,[31] [32] [33] although the mirror-image malformation, anomalous right coronary artery from the left aortic sinus, has also been incriminated in these catastrophes[33] (Fig. 59-4). Such malformations are difficult to recognize during life because they are usually unassociated with symptoms (e.g., exertional syncope or chest pain) or alterations in the 12-lead or exercise ECG; therefore, diagnosis requires a high index of suspicion.[31] Indeed, occurrence of one or more episodes of exertional syncope in a young athlete

Figure 59-4 View of the aortic root in wrong sinus origin of the right coronary artery from the left sinus of Valsalva in a 22-year-old man who died suddenly during a soccer match. Incision has been carried out into the right sinus of Valsalva, but no coronary ostium was found. Both the anomalous right coronary artery (arrowhead) and the left main coronary artery originate from the left sinus of Valsalva. The left main

trunk has been opened and divides into anterior descending and left circumflex branches. (From Basso C, Corrado D, Thiene G: Cardiovascular causes of sudden death in young individuals including athletes. Cardiol Rev 7:127-135, 1997.)

necessitates definitive exclusion of a coronary anomaly. It may also be possible to identify (or raise a strong suspicion of) anomalous coronaries of wrong sinus origin using transthoracic or transesophageal echocardiography,[4] [34] which can then lead to anatomical confirmation with coronary arteriography. However, congenital coronary artery malformations cannot be reliably identified by standard preparticipation athletic screening.

These coronary malformations should result in exclusion from intense competitive sports to reduce the risk of a cardiac event.[26] Also, wrong sinus anomalies are amenable to surgical correction with bypass grafting, which is the most common approach to restore distal coronary flow.[4] [31] [32] [33]

Myocardial ischemia (see Chap. 34) in young individuals with coronary artery anomalies involving wrong sinus origin probably occurs in infrequent bursts, cumulative with time, ultimately resulting in patchy myocardial necrosis and fibrosis; this process could predispose to lethal ventricular tachyarrhythmias by creating an electrically unstable myocardial substrate. Potential mechanisms that have been advanced include (1) acute angled takeoff and kinking or flaplike closure at the origin of the coronary artery and (2) compression of the anomalous artery between the aorta and pulmonary trunk during exercise. Furthermore, the proximal portion of the artery may be intramural (i.e., within the aortic tunica media), which could further aggravate coronary obstruction, particularly with aortic expansion during exercise.

Other unusual causes of exercise-related sudden deaths in young athletes include hypoplasia of the right coronary and left circumflex arteries, left anterior descending or right coronary artery origin from the pulmonary trunk, virtual absence of the left coronary artery, and spontaneous coronary arterial intussusception and coronary artery dissection.[5] [8] [9]

CORONARY ARTERY DISEASE (see Chaps. 35 , 36 , and 37).

Atherosclerotic coronary artery disease may be responsible for sudden death during physical exertion in youthful athletes[2] [5] [6] [7] [8] [9] and can be associated with acute plaque rupture[35] (Fig. 59-5) . Indeed, Corrado and colleagues [36] have emphasized the occurrence of premature atherosclerotic coronary disease as a prominent cause of sudden death in young persons (including some competitive athletes) in the Veneto region of northeastern Italy. The coronary disease is usually confined to the left anterior descending coronary artery and is due to obstructive fibrous and smooth muscle cell plaques in the absence of acute thrombus. In one study of sports-related sudden deaths, not limited to competitive athletes, atherosclerotic coronary artery disease (as well as HCM) was the leading cause of sudden death.[6]

MYOCARDITIS (see Chap. 48) .

Although myocarditis is an acknowledged cause of sudden death in young athletes, with or without prior symptoms, definitive diagnosis may be difficult clinically (and at autopsy), particularly in the healed phase.[30] Indeed, the importance of myocarditis as a cause of sudden death in the young may have been previously exaggerated owing to overinterpretation of histological data[37] or the lack of standardized morphological criteria[30] ; others have suggested that this diagnosis is now probably underestimated.[4] In a large autopsy-based series of 134 competitive athletes, only 6 percent showed areas of myocardium with acute inflammatory changes, consistent with acute myocarditis,[5] or areas of idiopathic myocardial scarring possibly representing healed myocarditis. The inflammatory process of myocarditis (see Fig. 59-5) is usually triggerred by several viral agents, often enterovirus but

Figure 59-5 Cardiac morphological findings at autopsy in four competitive athletes who died suddenly. *A,* Gross specimen from an athlete with greatly enlarged ventricular cavities, consistent with dilated cardiomyopathy. *B,* Histological section of the left anterior descending coronary artery (*left*) and diagonal branch (*right*) showing severe (>95 percent) cross-sectional luminal narrowing by atherosclerotic plaque. *C,* Foci of inflammatory cells consistent with myocarditis. *D,* Histological section of the right ventricular wall showing islands of myocytes within a matrix of fatty and fibrous replacement characteristic of arrhythmogenic right ventricular cardiomyopathy. *(Adapted from Maron BJ, Shirani J, Poliac LC, et al: Sudden death in young competitive athletes: Clinical, demographic, and pathological profiles. JAMA 276:199-204, 1996. Reproduced with permission of the American Medical Association.)*

also adenovirus.[38] Chronic cocaine use may provoke a similar clinical and pathological profile.[39]

Myocarditis does not necessarily require permanent withdrawal from competitive athletics. Athletes should, however, undergo a prudent convalescent period of about 6 months after the onset of clinical manifestations and should be allowed to resume competition when ventricular function and cardiac dimensions have returned to normal and clinically relevant arrhythmias are absent on ambulatory monitoring and stress testing.[30]

INTRAMURAL CORONARY ARTERY (see Chaps. 34 and 37) .

It is unresolved whether the presence of short segments of the left anterior descending coronary artery (1 to 3 cm), tunneled and completely surrounded by left ventricular myocardium (i.e., myocardial "bridges"), constitutes a potentially lethal anatomical variant responsible for sudden unexpected death in otherwise healthy young individuals during exertion.[40] Some regard muscle bridges to have the potential for producing critical systolic arterial narrowing (and residual diastolic compression), resulting in myocardial ischemia and, in one report, increased risk for cardiac arrest in young patients with HCM.[41] Short-acting beta blockers may alleviate anginal symptoms and

ischemia by increasing luminal diameter of tunneled coronary segments and normalizing flow velocities, thereby suggesting that myocardial bridges may have pathophysiological significance.[42] Nevertheless, coronary blood flow occurs predominantly during diastole, and necropsy studies have frequently documented tunneled coronary arteries in patients who had not died suddenly.

AORTIC RUPTURE (AND MARFAN SYNDROME) (see Chaps. 40 and 56) .

Young athletes uncommonly die suddenly as a result of rupture of the aorta,[2] [5] [8] [9] including some with the physical stigmata of Marfan syndrome, in whom disruption of the aortic media with decreased numbers of elastic fibers is usually evident at autopsy (i.e., cystic medial necrosis). Certain individuals with Marfan syndrome may successfully participate in strenuous competitive sports for many years without experiencing a catastrophic event, presumably before the time aortic dilatation becomes marked and predisposition for dissection or rupture increases critically. Indeed, the presence of aortic dilatation is the primary determinant of whether athletes with Marfan syndrome should be judged medically ineligible for competition.[26]

VALVULAR HEART DISEASE (see Chap. 46) .

Aortic valvular stenosis has proved to be an uncommon cause of sudden death in young athletes,[2] [5] [6] [8] [9] although older hospital-based studies suggested that this lesion much more frequently caused sudden unexpected death in children and young asymptomatic adults.[37] This is probably because aortic stenosis is likely to be identified early in life (including during preparticipation screening), by virtue of the characteristically loud heart murmur, thereby leading to disqualification from competitive sports.[28] Despite its frequency within the general population (probably <3 percent),[43] mitral valve prolapse appears to be a very uncommon cause of morbidity or sudden death in young competitive athletes.[30] [43] [44]

CARDIAC CONDUCTION SYSTEM ABNORMALITIES (see Chap. 25) .

A spectrum of congenital or acquired abnormalities confined to the cardiac conduction system (in the absence of other structural cardiac abnormalities) has occasionally been regarded as the cause of sudden death in competitive athletes and other young people, presumably by producing heart block and bradyarrhythmias.[45] [46] These

Figure 59-6 Arrhythmogenic right ventricular cardiomyopathy in a 25-year-old man who died suddenly at rest. *Top panel,* Heart specimen is sectioned in a four-chamber plane viewed from the posterior aspect. Fatty replacement of the anterior right ventricular free wall and infundibulum is demonstrated by transillumination. *Bottom panel,* Macrohistological section confirming that fatty replacement of myocytes is confined to the right ventricular wall, sparing the ventricular septum and left ventricular free wall.

Heidenhain trichrome stain ×3. (Reproduced with permission from Basso C, Corrado D, Rossi L, Thiene G: Arrhythmogenic right ventricular cardiomyopathy/dysplasia. *In* Nava A, Rossi L, Thiene G [eds]: Morbid Anatomy. Amsterdam, Elsevier Publishers, 1997, pp 71-86.)

include malformations of the atrioventricular conduction tissue, such as accessory atrioventricular pathways, or morphologically abnormal small intramural arteries to the sinoatrial node or atrioventricular nodes with thickened vessel walls and narrowed lumen. Such vascular abnormalities have been incriminated as determinants of sudden death and myocardial ischemia by virtue of tissue degeneration, scarring, and hemorrhage in the surrounding conducting tissue.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC) (seeChaps. 25 and 48) .

ARVC is an unusual, often familial condition that may be associated with important ventricular or supraventricular arrhythmias and has been cited as a cause of sudden death in young individuals, including athletes.[47] [48] [49] ARVC is characterized morphologically by cell death in the right ventricular wall, in which myocytes are replaced by fibrous or adipose tissue, often associated with myocarditis and evidence of programmed cell death (Fig. 59-6 ; see Chap. 48). This disease process may be segmental or may diffusely involve the right ventricle. In several autopsy studies of sudden death of young athletes, ARVC is uncommon (i.e., <5 percent).[4] [5] [6] [9] An exception is reports from the Veneto region of Italy, where ARVC is the single most common cause of sudden death in competitive athletes (and HCM is uncommon),[7] because of either a unique genetic substrate or the longstanding Italian national screening program for competitive athletes,[50] which has probably identified and disqualified far greater numbers of athletes with HCM than ARVC.[51]

APPARENTLY NORMAL HEARTS.

Occasionally, no evidence of structural cardiovascular disease is demonstrable in athletes dying suddenly even after careful examination of the heart. In such instances (about 2 percent of athletic field deaths),[4] [5] it may not be possible to preclude with certainty noncardiac factors, such as substance abuse (see Chap. 70).[39] It is also possible that such deaths are due to either occult conduction system disease,[45] [46] clinically unidentified Wolff-Parkinson-White syndrome, rare conditions in which structural cardiac abnormalities are characteristically lacking at necropsy such as idiopathic ventricular fibrillation[52] and long QT syndrome,[53] or unrecognized segmental ARVC (see Chap. 25) .[47] [49]

Older Athletes

Older athletes (age >35 years) may also harbor occult cardiac disease and die suddenly and unexpectedly while participating in intense (often competitive) athletic activities. Unlike in youthful athletes, in older conditioned athletes, the cause of death is usually atherosclerotic coronary artery disease (see Chaps. 35 to 37) . The remaining deaths in older athletes are due to diseases unrelated to atherosclerosis, such as HCM or valvular heart disease.[30] [54]

Older trained athletes who have died suddenly of coronary heart disease, reported in several necropsy-based investigations,[10] [11] [13] [14] [15] compose a heterogeneous athletic population including runners training for competitive long-distance races and recreational joggers, as well as participants in sports such as rugby, squash, and golf. Most of these deaths occur during or just after physical activity. In contrast to young competitive athletes, most older athletes who have died of coronary heart disease had either known risk factors, cardiovascular symptoms, or prior myocardial infarction, with severe coronary artery involvement (atherosclerotic narrowing of two or three major extramural coronary arteries) and myocardial scarring.

PROFILE AND DEMOGRAPHICS

Prevalence and Significance

In young athletes, the frequency of sudden unexpected death that occurs during competitive sports and is due to cardiovascular disease appears to be low, occurring in about 1:200,000 individual student-athletes per academic high school year[3] and in 1:70,000 during a 3-year career. In comparison, older athletes have somewhat higher rates of exercise-related sudden death, reported to be 1:15,000 to 1:50,000 per year, usually in apparently healthy male athletes,[12] joggers, [11] and marathon racers.[15] Such estimates may suggest that the intense and persistent public interest in these tragic events in young individuals is perhaps disproportionate to their overall numerical significance. However, the emotional and social impact of athletic field catastrophes remains high because competitive athletes, to much of the lay public and physician community, intuitively represent the healthiest element of society.[1] [4]

Demographics

Based primarily on data assembled from broad-based United States populations,[2] [3] [4] [5] [6] [9] a profile of young competitive athletes who die suddenly has emerged. Athletes had participated in a large number and variety of sports, the most frequent being basketball and football (about 70 percent[5]), probably reflecting the relatively high participation level in these team sports as well as their intensity. In European studies, the most common sport associated with sudden death is soccer.[47] [51] The vast majority of athletic field deaths occurred in males (about 90 percent), largely of high school age (about 60 percent[5]); however, others achieved collegiate or even professional levels of competition.

The vast majority of athletes who incur sudden death are free of cardiovascular symptoms during their lives, with their underlying cardiovascular disease completely unsuspected. Sudden collapse has been associated with exercise in 90 percent of athletes, predominantly in the late afternoon and early evening hours, corresponding to the peak periods of competition and training (particularly for organized team sports).[5] These observations substantiate that, in the presence of certain structural cardiovascular diseases, physical activity represents a trigger and an important

precipitating factor for sudden death on the athletic field.

Although the majority of reported sudden deaths in competitive athletes have been in white males, one study showed a substantial proportion (about 40 percent) to be in African Americans.[55] The substantial occurrence of HCM-related sudden death in young black male athletes contrasts sharply with the infrequent identification of black patients with HCM in hospital-based populations and may be explained by disproportionate access to subspecialty medical care, which makes it less likely for African American patients to achieve a cardiovascular diagnosis such as HCM.

Screening and Preparticipation Detection of Cardiovascular Abnormalities

Detection of preexisting cardiovascular abnormalities with the potential for significant morbidity or sudden death is an important objective of the widespread practice of preparticipation screening for high school- and college-aged athletes.[56] Athletic screening in the United States has customarily been performed in the context of a personal and family history and physical examination.[4] [28] [56] [56A] However, the utility of these routine evaluations for both U.S. high school- and college-aged student-athletes is limited by the complex nature of the responsible cardiovascular abnormalities and the infrequency with which they occur within the general population, as well as apparent inadequacies in the

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preparticipation cardiovascular screening process.[56A] For example, the approved history and physical examination questionnaires (which serve as guides to examiners) may be suboptimal for 25 percent or more of high school- and college-aged athletes.[56] [56A] Indeed, one retrospective study reported that potentially lethal cardiovascular abnormalities were suspected by preparticipation history and physical examination in only 3 percent of high school and collegiate athletes who ultimately died suddenly of these diseases (including only 2 percent of the HCM victims examined).[5]

Citing medical and ethical considerations, an American Heart Association consensus panel[28] recommended preparticipation cardiovascular screening, as well as a more systematic approach to implementation, to enhance the likelihood of suspecting or identifying important cardiovascular abnormalities. These recommendations included a personal and family history and physical examination targeted to detect those lesions known to predispose to sudden cardiac death.

Although the addition of noninvasive testing (e.g., echocardiography or ECG) to the screening process would undoubtedly enhance detection of many of the responsible lesions (particularly HCM),[51] this would be an unrealistic aspiration on a national scale in the United States owing to the prohibitive cost and other practical obstacles. It should be emphasized that no available screening design (even with diagnostic testing) is capable of detecting all important lesions and affected athletes, and medical clearance for participation in sports does not necessarily connote the absence of cardiovascular

disease.

Eligibility Considerations for Athletes with Known Cardiovascular Disease

When a cardiovascular abnormality is identified in a competitive athlete, the following considerations arise: (1) the magnitude of risk for sudden cardiac death (or disease progression) associated with continued participation in competitive sports and (2) criteria for discerning whether individual athletes should be withdrawn from sports competition. In this regard, the 26th Bethesda Conference[26] affords prospective consensus panel recommendations for athletic eligibility and disqualification, taking into account the severity of relevant cardiovascular abnormalities as well as the intensity of sports training and competition. These recommendations are predicated on the assumption that intense physical exertion in the context of competitive sports may act as a trigger in certain predisposed athletes with underlying structural heart disease. Although that risk cannot be quantified with precision, temporary or permanent withdrawal of selected athletes with cardiovascular disease from participation in certain competitive sports is regarded as a prudent strategy for diminishing the likelihood of sudden death.[5] [26] [30] The Bethesda Conference report[26] provides clear benchmarks for the expected standard of care that may be used to resolve future medicolegal disputes and has been cited by a U.S. Appellate Court as consensus expert guidelines that team physicians should rely on in formulating appropriate decisions regarding the eligibility of competitive athletes with cardiovascular disease.[57]

Cardiac Risks of Sports Unrelated to Structural Cardiovascular Disease

Although uncommon, virtually instantaneous cardiac arrest may result from a relatively modest and nonpenetrating blunt blow to the chest, in the *absence* of underlying cardiovascular disease or resultant structural injury to the chest wall or heart itself (i.e., commotio cordis) (see Chap. 51) .[16] [17] [17A] Such occurrences are produced either by a projectile (most commonly a baseball, softball, or hockey puck) or by bodily contact with another athlete. The blow to the chest is not perceived as unusual for the sporting event, nor of sufficient magnitude to result in a catastrophe. A common scenario is that of a young baseball player at bat struck in the chest by a pitched ball thrown from a standard distance. Of note, many of these catastrophes have occurred in purely recreational situations at home or on the playground, with the fatal injuries often inflicted by family members.

There appear to be three determinants of a commotio cordis event: (1) chest impact located directly over the heart, usually of relatively low energy[16] [17A] ; (2) precise timing of the blow to a narrow 15-msec segment of the cardiac cycle vulnerable to potentially lethal ventricular arrhythmias, just before the T wave peak,[17] apparently also involving activation of the potassium-ATP channel (K_{ATP})[58] ; and (3) a narrow, compliant chest wall, typical of young children.[16]

Certain measures aimed at prevention of commotio cordis events have been considered. Softer than standard (safety) baseballs reduced the risk for ventricular fibrillation in an experimental model of this syndrome, suggesting that sudden death prevention may be achieved through modification of athletic equipment.[17] [17A] Wider use

of padding designed to cover the precordium would theoretically protect against the occurrence of commotio cordis in youngsters competing in sports such as baseball, ice hockey, karate, lacrosse, and football. However, the infrequency of commotio cordis events represents an obstacle to documenting the effectiveness of any protective intervention.

Commotio cordis events are not uniformly fatal; about 10 percent of the reported victims are known to have survived, usually because of reasonably prompt cardiopulmonary resuscitation and defibrillation.[4] With enhanced public awareness of this syndrome, emergency measures are likely to be implemented more rapidly on the athletic field, possibly avoiding many future catastrophes.

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Chapter 60 - Medical Management of the Patient Undergoing Cardiac Surgery

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Several advances have occurred in cardiac surgery that make operative repair of a variety of cardiac lesions a viable therapeutic alternative for an increasing number of patients with cardiovascular disease. These advances include improvements in tools for assessment of perioperative risk, surgical and anesthesia techniques for myocardial revascularization, valve repair and replacement, and repair of complex congenital cardiac defects, as well as new approaches to management of patients with left ventricular dysfunction and cardiac arrhythmias.[1] [2] [3] [19A] [19B] [117A] [120A] [142A] Advances relating to minimally invasive cardiac surgical procedures have added additional options in the comprehensive care of patients with surgical cardiovascular disease.[4] [5] [6] [7] [8] [9] [40A] [60A] [60B] [60C] [65A] Perioperative medical and surgical supportive measures have progressed, including the proliferation of intraoperative transesophageal echocardiography,[9A] ventricular assist devices, pharmacological supportive strategies, and comprehensive blood conservation programs. Evidence suggests that translation of these improvements into routine surgical practice and institution of regular quality control surveillance measures have led to a reduction in risk-adjusted operative mortality for coronary artery bypass grafting (CABG) to less than 2 percent for the

general population and 3 to 4 percent for the Medicare population.[10] [11] [12] [117A] However, the profile of patients referred for surgery has also changed and is characterized by greater proportions of patients with advanced age, depressed left ventricular function, multiple comorbidities, prior revascularization operations, and failed acute interventional procedures, which has led to higher mortality rates in tertiary care referral centers that are called upon to operate on such patients with greater frequency.[13] [14] [15] [16] [17] [18] [19] [19A] [19B]

This chapter summarizes the information required by the cardiologist, whose important responsibilities include collaboration with the surgical team for both preoperative and postoperative care, especially care of the medical complications that may develop.

PREOPERATIVE EVALUATION

GENERAL MEDICAL CONDITION.

Except for life-threatening conditions (e.g., proximal aortic dissection,[20] cardiogenic shock caused by ruptured papillary muscle in acute myocardial infarction, penetrating wound of the heart), it behooves the consulting cardiologist to assess the overall medical condition of the patient and advise the surgical team if postponement of the operation seems warranted[21] [22] [23] [24] [25] [26] [27] [28] [29] (Table 60-1) . Particular attention should be paid to the patient's potential for development of one or more of the following complications: (1) bleeding during cardiopulmonary bypass while heparinized or while anticoagulated after

TABLE 60-1 -- PREOPERATIVE LABORATORY EVALUATION OF PATIENTS UNDERGOING CARDIAC SURGERY

PREOPERATIVE LABORATORY TEST	ABNORMAL FINDING	COMMENT
Complete blood count	1. Anemia, especially Hct <35%	1. Anticipate that hemodilution will occur on cardiopulmonary bypass and blood loss will occur intraoperatively. In stable patients, preoperative iron supplementation (weeks) or erythropoietin therapy (days) should be considered. Patients with unstable angina, congestive heart failure, aortic stenosis, and left main coronary artery disease should be advised against autologous donation of blood in the preoperative period.
	2. WBC >10,000	2. Search for possible infection

Coagulation screen	1. Prolonged bleeding time 2. Elevated PT and/or PTTlevated PT and/or PTT 3. Thrombocytopenia	All these laboratory abnormalities suggest that the patient is at risk for bleeding postoperatively and may have excessive chest tube drainage. Corrective measures (e.g., vitamin K, fresh frozen plasma, platelet transfusions) should be considered preoperatively, and surgery may need to be postponed. Hematological consultation may be required if an inherited defect in coagulation (e.g., von Willebrand factor deficiency) is suspected
Chemistry profile	1. Elevated BUN/creatinine	Abnormal renal function that may worsen in the perioperative period (caused by nonpulsatile flow on cardiopulmonary bypass and potential low flow postoperatively); may necessitate temporary or even permanent hemodialysis
	2. Potassium <4.0 mEq/liter and/or magnesium <2.0 mEq/liter	2. Electrolyte deficits may place the patient at risk of arrhythmias perioperatively and should be corrected before induction of anesthesia
	3. Abnormal liver function tests	3. Patient may clear anesthetic agents as well as other cardioactive drugs more slowly. Low albumin level may indicate a state of relative malnutrition that may need to be corrected with nutritional support perioperatively
Stool Hematest	Positive for occult blood	Because heparinization will take place while on the cardiopulmonary bypass apparatus, the patient may be at risk for GI bleeding perioperatively. The source of GI heme loss should be investigated preoperatively if clinical circumstances permit. The potential for bleeding in the future may influence the choice of prosthetic valve inserted.

Pulmonary function	Reduced VC or prolonged FEV_1	Anticipate longer than usual process of weaning from ventilator postoperatively if FEV_1 <65% of VC or FEV_1 <1.5-2.0 liters. Obtain baseline arterial blood gas analysis on room air to help guide respiratory management postoperatively
Thyroid function	These tests are not ordered routinely but should be performed in cases of suspected hypothyroidism or hyperthyroidism, known thyroid dysfunction during replacement therapy, and atrial fibrillation in patients who have not undergone evaluation of thyroid function	Hypothyroid patients require prolonged period of ventilatory support postoperatively because of slower clearance of anesthetic agents Hyperthyroid patients have a hypermetabolic state that places them at increased risk of myocardial ischemia, vasomotor instability, and poorly controlled ventricular rate in atrial fibrillation
Echocardiography	1. Decreased LV ejection fraction	1. Patients with decreased LV function are at higher perioperative risk for surgery. Selected patients should undergo viability assessment
	2. Decreased RV function	2. RV dysfunction increases perioperative risk and identification may lead to preoperative assessment of reversibility of pulmonary hypertension
	3. Aortic stenosis	3. Mild to moderate aortic stenosis (gradient <25 mm Hg) may be treated by prophylactic valve replacement in selected low-risk patients
	4. Aortic insufficiency	4. Ventricular dimension will help guide decisions to perform valve replacement in addition to revascularization in patients with combined aortic regurgitation and coronary disease.
	5. Mitral insufficiency	5. Moderate or severe mitral regurgitation may warrant valve exploration in patients undergoing coronary revascularization
	6. LV aneurysm	6. May alert surgeons to the need of aneurysmectomy in selected patients

	7. Ventricular septal defect	7. Identification will suggest the need for early surgical intervention
Cardiac catheterization	1. Elevated LV end-diastolic pressure and pulmonary capillary wedge pressure	1. May remain elevated in the early postoperative period and indicate a need for careful attention to maintenance of adequate preload postoperatively
	2. Elevated right atrial pressure	May reflect tricuspid regurgitation or RV dysfunction from prior infarction. Such patients require vigorous volume expansion postoperatively to maintain adequate cardiac output.
	3. Elevated pulmonary artery pressure (and pulmonary vascular resistance)	Fixed pulmonary vascular resistance should be suspected when the pulmonary artery diastolic pressure exceeds the mean pulmonary capillary wedge pressure. Vigorous oxygenation and pharmacological support with a pulmonary vasodilator (isoproterenol, prostaglandin E_1) are important in such cases. Patients with a pulmonary artery diastolic pressure equal to the pulmonary capillary wedge pressure usually have more rapid resolution of pulmonary hypertension postoperatively
	4. LV mural thrombus	4. Increased risk of stroke perioperatively
	5. Status of internal mammary arteries	5. Highly desirable arterial conduits for planned revascularization surgery. [40] [41] Particular care required during reoperation if patent internal mammary artery bypass is in place from previous surgery
	6. Status of saphenous vein grafts	"Pseudoextravasation" of dye outside the lumen in a patent graft with slow flow probably represents thrombus-filled atherosclerotic aneurysm of the graft

BUN=blood urea nitrogen; FEV_1 =volume of air expired at 1 second; GI=gastrointestinal; Hct=hematocrit; LV=left ventricular; PT=prothrombin time; PTT=partial thromboplastin time; RV=right ventricular; VC=vital capacity; WBC=white blood cell count.Dialysis or creatinine MORTALITY SCORE MEDIASTINITIS

insertion of a mechanical heart valve prosthesis [30] ; (2) deterioration in renal function; (3) arrhythmias secondary to electrolyte imbalance; (4) sepsis from incompletely treated pulmonary, urinary tract, or dental infection or dermatological infection over the sternum or saphenous vein harvest site; (5) need for prolonged ventilatory support postoperatively because of underlying pulmonary disease and preoperative malnutrition; and (6) exacerbation of a neurological deficit because of carotid artery disease or prior stroke.[22] When perioperative intraaortic balloon pump support may be needed, the status of the iliofemoral circulation should be assessed bilaterally. Of note, the risk of limb ischemia may be reduced by the use of sheathless, small-caliber balloon pump catheters.[31] Despite the increased risk of perioperative morbidity and mortality, recent data indicate that patients with combined coronary artery disease and peripheral vascular disease have a greater likelihood of long-term survival and freedom from myocardial infarction with CABG surgery versus medical therapy, particularly in the presence of two- and three-vessel coronary artery disease.[32]

The *protein-calorie malnutrition* associated with cardiac cachexia has been shown to compromise cardiac function and is associated with a greater risk of respiratory failure, sepsis, and prolonged hospitalization. If the clinical situation allows, patients in whom cardiac cachexia is diagnosed should receive a few weeks of preoperative nutritional support before undergoing elective cardiac surgery. The general principles of nutritional support in cardiac surgical patients are outlined in Figure 60-1 .

RISK FACTORS FOR CARDIAC MORBIDITY AND MORTALITY.

Risk factors for morbidity and mortality after coronary revascularization surgery have been analyzed extensively.[33] [34] [35] [36] [36A] [36B] A commonly used, simple clinical severity scoring system is shown in Table 60-2 . Although patients with low-risk scores may be considered candidates for "fast-track" cost-saving measures such as admission on the day of surgery or early extubation postoperatively, those with higher-risk scores are likely to experience increased morbidity, required longer intensive care unit (ICU) stays and more consultations by specialists, and consume a greater proportion of medical resources. Furthermore, clinical severity scoring is helpful in identifying patients at high risk for operative mortality (score >10). By assembling and reviewing the data necessary for accurate assessment of a patient's operative risk, cardiologists can help with the appropriate clinical triage of patients, contain hospital costs, and facilitate consultations with other medical specialists (e.g., dialysis team) as needed. Patients at increased risk of mediastinal infection include the elderly and those suffering from diabetes mellitus, malnutrition, severe pulmonary disease that is likely to lead to prolonged postoperative ventilatory support, and macromastia in women.[37] [38] [39]

VENTRICULAR DYSFUNCTION.

An especially important aspect of the preoperative evaluation of a cardiac surgical patient involves estimating the extent of underlying ventricular dysfunction. Evidence

exists that unrevascularized viable myocardium after myocardial infarction serves as a substrate for recurrent ischemic events.[39] [40] [40A] [41] [42] [43] Also, patients with severe multivessel disease and akinetic myocardial zones who suffer from chronic congestive heart failure as a result of hibernating myocardium (see Chap. 37) experience improved ventricular function after CABG.[39] Contemporary techniques that should be used for assessing myocardial viability in dysfunctional regions include imaging procedures that correlate perfusion with cell membrane integrity (thallium reperfusion), metabolic activity (positron-emission tomography), or contractile reserve (stress echocardiography).[39] [40] [40A] Clinicians should rely on imaging modalities with which they are most familiar and that are available at their institution.

Careful consideration should be given to the possibility of *right ventricular dysfunction* (see Table 60-1) , which

Figure 60-1 The nutritional status of cardiac patients has a significant impact on their postoperative outcome. Patients who are cachectic before elective cardiac surgery should be nutritionally bolstered for 2 to 3 weeks prior to surgery. Postoperative patients are in a hypermetabolic state and require increased nutrition to meet metabolic demands and facilitate wound healing. Oral diet is resumed 24 hours after uncomplicated surgery, and the diet is advanced as rapidly as tolerated. For patients who have perioperative complications such as stroke, a swallow evaluation is needed to assess the patient's ability to protect the airway during meals. If the patient fails the swallow evaluation or if the patient is intubated, nutritional requirements are met by early enteral feeding except in cases of gastrointestinal dysfunction. Oral feeding tubes are useful in the short term, while prolonged nutritional supportt is best handled by placement of an enteral tube.

should be suspected in patients with preoperatively elevated pulmonary artery systolic pressure (>60 mm Hg), a history of inferoposterior left ventricular infarction (which may be associated with right ventricular infarction), and longstanding tricuspid regurgitation. Patients with right ventricular dysfunction should receive an inotropic agent with vasodilating actions such as milrinone (5 mug/kg/min) or dobutamine (5 mug/kg/min) in addition to supplemental oxygen perioperatively in an attempt to lower pulmonary vascular resistance and improve right ventricular systolic performance. Intravenous nitrate infusions, in the perioperative period have also been shown to reduce pulmonary hypertension and ameliorate right ventricular failure. Inhaled agents, including aerosolized prostacyclin and nitric oxide, have also been shown to effectively lower pulmonary

TABLE 60-2 -- PREOPERATIVE RISK FACTORS FOR ADVERSE OUTCOMES IN PATIENTS UNDERGOING CABG SURGERY: A CLINICAL SEVERITY SCORING SYSTEM AND EVENT CURVES (NORTHERN NEW ENGLAND CARDIOVASCULAR DISEASE STUDY GROUP)

Preoperative Estimation of Risk of Mortality, Cerebrovascular Accident, and Mediastinitis

For use *only* in isolated CABG surgery

Directions: Locate outcome of interest, e.g., mortality. Use the score in that column for each relevant preoperative variable, and then sum these scores to get the total score. Take the total score and look up the approximate preoperative risk in the table below

PATIENT OR DISEASE CHARACTERISTICS	MORTALITY SCORE	CVA SCORE	MEDIASTINITIS SCORE
Age 60-69	2	3.5	
Age 70-79	3	5	
Age 80	5	6	
Female sex	1.5		
EF <40%	1.5	1.5	2
Urgent surgery	2	1.5	1.5
Emergency surgery	5	2	3.5
Prior CABG	5	1.5	
PVD	2	2	
Diabetes			1.5
Dialysis or creatinine 2	4	2	2.5
COPD	1.5		3.5
Obesity (BMI 31-36)			2.5
Severe obesity (BMI 37)			3.5
Total score			

PERIOPERATIVE RISK

TOTAL SCORE	MORTALITY (%)	CVA (%)	MEDIASTINITIS (%)
0	0.4	0.3	0.4
1	0.5	0.4	0.5
2	0.7	0.7	0.6
3	0.9	0.9	0.7
4	1.3	1.1	1.1
5	1.7	1.5	1.5

6	2.2	1.9	1.9
7	3.3	2.8	3.0
8	3.9	3.5	3.5
9	6.1	4.5	5.8
10	7.7	6.5	6.5
11	10.6		
12	13.7		
13	17.7		
14	28.3		

vascular resistance and improve perioperative right ventricular performance.[44]

Patients with mitral regurgitation and severe heart failure should undergo preoperative afterload reduction with such agents as oral angiotensin-converting enzyme (ACE) inhibitors and intravenous sodium nitroprusside to a systolic pressure of about 90 to 100 mm Hg. Potential contraindications to such preoperative afterload reduction include

TABLE 60-2 -- PREOPERATIVE RISK FACTORS FOR ADVERSE OUTCOMES IN PATIENTS UNDERGOING CABG SURGERY: A CLINICAL SEVERITY SCORING SYSTEM AND EVENT CURVES (NORTHERN NEW ENGLAND CARDIOVASCULAR DISEASE STUDY GROUP) *Continued*

Definitions

EF <40% (left ventricular ejection fraction): The patient's current EF is less than 40%

Urgent: Medical factors require patient to stay in hospital to have operation before discharge. The risk of immediate morbidity and death is believed to be low

Emergency: Patient's cardiac disease dictates that surgery be performed within hours to avoid unnecessary morbidity or death.

PVD (peripheral vascular disease): Cerebrovascular disease including prior CVA, prior TIA, prior carotid surgery, carotid stenosis by history or radiographic studies, or carotid bruit. Lower extremity disease including claudication, amputation, prior lower extremity bypass, absent pedal pulses, or lower extremity ulcers

Diabetes: Currently treated with oral medications or insulin.

Dialysis or creatinine
2: Peritoneal dialysis- or hemodialysis-dependent renal failure or creatinine
2 mg/dl

COPD (chronic obstructive pulmonary disease): Treated with bronchodilators or steroids

Obesity: Find the approximate height and weight in the table below to classify the person as obese or severely obese. Obesity: BMI 31-36. Severe obesity: BMI
37.

Example: A patient 5
7
and weighing 200 lb is classified as obese. If the patient weighed 236 lbs or more, that patient would be classified as severely obese

HEIGHT (FEET AND INCHES)	WEIGHT (LB)		HEIGHT (FEET AND INCHES)	WEIGHT (LB)	
	Obesity: BMI 31-36	Severe Obesity: BMI 37		Obesity: BMI 31-36	Severe Obesity: BMI 37
5 0	158-184	189	5 8	203-236	244
5 1	164-190	195	5 9	209-243	250
5 2	169-196	202	5 10	215-250	258

5	175-203		5	222-258	
3		208	11		265
5	180-209		6	228-265	
4		215	0		272
5	186-217		6	235-273	
5		222	1		280
5	191-222		6	241-280	
6		228	2		287
5	198-229		6	248-288	
7		236	3		296

BMI=body mass index; CABG=coronary artery bypass surgery; CVA=cardiovascular accident; TIA=transient ischemic attack.
From Eagle KA, Guyton RA, Davidoff R, et al.: ACC/AHA guidelines for coronary artery bypass surgery. J Am Coll Cardiol 34:1262-1347, 1999. Reprinted with permission from the American College of Cardiology.

concomitant severe aortic stenosis and hemodynamically significant cerebral or renal vascular disease. In these patients, early intervention with intraaortic balloon counterpulsation may be useful. Intraaortic balloon support is also commonly used in the setting of severe decompensation from acute mitral regurgitation secondary to conditions such as papillary muscle rupture. Infarct-related ventricular septal defect is another hemodynamically significant lesion that may require pharmacological and intraaortic balloon support in the perioperative period.

RISK OF MYOCARDIAL ISCHEMIA.

Acute thrombolytic and interventional catheterization treatment regimens for acute myocardial infarction may not successfully restore coronary perfusion because of inadequate thrombolysis, reocclusion of the infarct-related artery following initially successful thrombolysis, or dissection/acute thrombosis of the target vessel during angioplasty.[45] [46] Identification of patients for referral for emergency bypass surgery and decisions regarding the timing of such surgery remain a challenging clinical problem, particularly in view of the high perioperative mortality rate for patients who require surgery within 24 to 48 hours of thrombolysis.[46] [47]

Potential indications for emergency bypass surgery following failed attempts at reperfusion in acute myocardial infarction include significant left main stenosis and inability to maintain patency of the infarct-related artery, severe multivessel coronary artery disease with anatomy unsuitable for angioplasty and ischemic dysfunction of the noninfarct zones, and inability to maintain patency of an infarct-related artery that places a large amount of myocardium in jeopardy (proximal left anterior descending) in patients

with an infarct of less than 6 hours' duration.[45] [46] Although some clinical reports suggest that patients in cardiogenic shock who undergo urgent revascularization have improved survival in comparison to those who are not revascularized, these series suffer from potential selection bias, and definitive recommendations regarding the management of patients with cardiogenic shock and acute myocardial infarction must await the results of ongoing randomized trials.[45]

Patients who are referred for emergency revascularization surgery should be supported by an intraaortic balloon pump and, if technically feasible, an intracoronary perfusion catheter. Other methods for mechanical assistance of the failing circulation are described in Chapter 19 . Because patients who undergo emergency bypass surgery within 6 to 12 hours of administration of a thrombolytic agent are at greater risk for intraoperative and postoperative hemorrhage, they should receive a hemostatic agent such as aprotinin (2 million kallikrein-inhibiting units [KIU] over a 20-minute period, followed by a continuous infusion of 500,000 KIU/hr).[48]

Patients with other manifestations of an acute coronary syndrome such as active unstable angina may also be in tenuous hemodynamic balance as they proceed to the operating room, particularly if significant left main coronary artery stenosis or severe three-vessel coronary artery disease associated with left ventricular dysfunction and/or mitral regurgitation is present. Delays while awaiting surgery and the time between the induction of anesthesia and the institution of cardiopulmonary bypass are high-risk periods during which a vicious spiral of myocardial ischemia and low-output syndrome can rapidly develop. Such patients should be protected by an intraaortic balloon pump inserted preoperatively and infusion of nitroglycerin.

ANESTHESIA FOR CARDIAC SURGERY.

The details of the practice of cardiac anesthesia are beyond the scope of this chapter and are available in other sources.[49] High-dose synthetic narcotics that do not cause vasodilatation, such as fentanyl and sufentanil, have replaced morphine in many centers. Early extubation protocols are now followed in most cardiac units for patients with low or moderate risk. Advantages of early extubation include a decrease in respiratory complications, ventilatory support, and length of stay in the ICU. To achieve early extubation within 6 hours of surgery, anesthetic techniques have included combinations of inhalational anesthetics, such as enflurane and isoflurane, together with low to moderate amounts of intravenous opioids, such as fentanyl and sufentanil, along with the intravenous anesthetic propofol. The newer, inhaled anesthetics that have replaced nitrous oxide still have the potential to cause vasodilatation. Patients with critical aortic stenosis, critical mitral stenosis, and large right-to-left shunts may experience a dramatic reduction in cardiac output as ventricular stroke volume falls with a reduction in preload. Preoperative volume expansion and even administration of vasopressor agents may be necessary to avoid this problem.

Cardiac Rhythm

Although supraventricular arrhythmias after cardiac surgery are seldom life threatening, they frequently provoke disturbing symptoms, may jeopardize hemodynamic stability, and are associated with an increased incidence of postoperative stroke, increased length of stay in the ICU, and increased hospital costs.[50] [51] [52]

In the past it was a common preoperative practice in many institutions to administer digitalis prophylactically to all patients undergoing cardiac surgery, not only for inotropic support but also for "control" of the ventricular rate if atrial fibrillation (AF) occurred postoperatively.[52] There is little reason to believe that digoxin prevents the development of AF; indeed, clinical trails do not clearly substantiate either a lower incidence of AF or a slower ventricular rate in AF in patients treated prophylactically with digoxin.[53] Futhermore, hypoxia, hypokalemia, elevated catecholamine levels, and reduced clearance of digoxin are common postoperatively, and these conditions may predispose the patient to digoxin toxicity.

ATRIAL FIBRILLATION

Because of the hazards of postoperative AF, considerable effort has been devoted to identifying preoperative factors associated with an increased risk of postoperative arrhythmia.[52] Such factors include advanced age and male gender. It has been proposed that a prolonged P wave duration recorded on a signal-averaged electrocardiogram (ECG) and greater than 70 percent narrowing of the lumen of the right coronary artery are associated with an increased risk of postoperative AF.[54] [55] However, for a substantial number of patients with postoperative AF, no apparent preoperative risk factor can be identified. Cox has presented clinical data suggesting that about one-third of patients undergoing cardiac operations are vulnerable to postoperative AF because of mild nonuniformity in the distribution of their trial refractory periods.[56] Intraoperative atrial ischemia associated with rapid rewarming of the atria during prolonged periods of cold cardioplegic arrest may increase the dispersion of refractoriness in the atria of such patients and thereby increase the risk of postoperative AF.

Because of difficulties in reliably identifying patients at risk for AF preoperatively, it is common clinical practice to provide prophylactic therapy to the majority of patients undergoing CABG surgery. Beta-adrenoceptor blocking agents are most suitable for prophylaxis against AF.[52] [53] In the *absence* of an ejection fraction less than 30 percent, severe bronchospastic lung disease, or bradyarrythmias, we advocate the use of prophylactic beta blockers in patients undergoing CABG. Conclusive data regarding the use of prophylactic antiarrhythmic therapy to prevent postoperative AF are lacking, although prophylactic amiodarone in selected patients has appeared promising in several clinical trials.[57] [58]

BRADYARRHYTHMIAS AND ATRIOVENTRICULAR AND INTRAVENTRICULAR BLOCK.

Patients with high-grade (third-degree or type II second-degree) atrioventricular block and hemodynamic compromise (systolic pressure <90 mm Hg) are at high risk during general anesthesia unless a temporary transvenous pacemaker wire is inserted preoperatively.

In patients in whom a permanent pacemaker has been implanted, its specifications (model, mode, and settings) and, if possible, a statement regarding the pacemaker dependency of the patient should be noted in the medical record (see Chap. 24) . The possibility of postoperative malfunction in the permanent pacing system because of the effects of anesthesia, electrocautery, and surgical manipulation of the leads (e.g., during atrial cannulation) should be anticipated.[59] Clinicians should have the appropriate pacemaker programming equipment available postoperatively because many problems (secondary to electromagnetic interference from the electrocautery apparatus) can be quickly resolved by interrogation of the generator and reprogramming in the recovery area.

The risk of permanent, complete heart block postoperatively is increased with multiple valve replacements, particularly in patients who have had previous valve surgery. However, implantation of a permanent epicardial pacing lead is rarely needed at the time of surgery because of the ease of implantation of a transvenous endocardial system postoperatively. An exception would be patients who are undergoing tricuspid valve replacement with a mechanical prosthesis, especially if they are simultaneously undergoing an aortic or mitral valve operation. Because of the contraindication to passing a transvenous lead through the mechanical tricuspid prosthesis, the surgical team should be alerted to the need for placement of permanent epicardial leads intraoperatively.

Patients with previously implanted cardioverter-defibrillator devices should have their unit disabled prior to surgery to minimize the risk of inappropriate shocks from sensing of electrocautery signals intraoperatively. Until the device is reactivated in the postoperative period, equipment for rapid external defibrillation should be available.

Perioperative Drug Therapy

With the exception of oral anticoagulation with warfarin, most medications can and should be continued up to the time of surgery. Clinical trials of patients receiving saphenous vein bypass grafts demonstrated the importance of initiating antiplatelet therapy in the perioperative period.[60] Because of the increased risk of postoperative bleeding, some surgical groups discontinue aspirin use for several days preoperatively in elective cases. Many cardiologists are concerned about the risk of "breakthrough" episodes of ischemia if aspirin therapy is discontinued preoperatively and prefer to continue it up to the time of surgery and rely on preoperative donations of autologous red cells, cell saver techniques, autotransfusion of shed blood intraoperatively and postoperatively, and drugs such as aprotinin to minimize the need for and potential hazards of homologous blood transfusion. If aspirin is witheld preoperatively, it should be restarted within 24 to 48 hours after surgery to reduce the risk of vein graft occlusion.[60] Warfarin therapy should be stopped 2 to 3 days preoperatively and, if

necessary, treatment with heparin or low-molecular-weight dextran initiated.

Although definitive data are not available, it is our usual practice to continue both aspirin and clopidogrel up to the time of surgery in patients who have undergone implantation of a stent in the coronary circulation within the preceeding 2 weeks in order to minimize the risk of stent thrombosis preoperatively. For patients who have had a stent implanted more than 2 weeks prior to surgery, we discontinue clopidogrel administration but continue aspirin up to the time of surgery. For patients receiving long-term clopidogrel as secondary prevention for vascular disease, we discontinue use of the drug 5 to 7 days preoperatively.

To minimize the risk of intraoperative bleeding, if patients are undergoing interventional catheterization procedures and have normal renal function and if cardiac surgery is likely to take place within the ensuing 24 to 48 hours, we prefer to use a short-acting intravenous glycoprotein IIb/IIIa inhibitor such as eptifibatide or tirofiban rather than a long-acting agent such as abciximab. Treatment with the short-acting agent is usually discontinued 6 to 12 hours preoperatively to permit platelet function to return toward normal. We prefer to use abciximab in patients with renal dysfunction since the small, short-acting inhibitors are cleared predominantly through renal elimination. When abciximab is used, we discontinue the infusion at least 12 hours prior to surgery.

For patients who have received an intravenous glycoprotein IIb/IIIa inhibitor and must proceed urgently to cardiac surgery, the antiplatelet effects of abciximab may be reversed by platelet transfusions.[60A] In contrast, the high excess of free drug versus bound drug in the case of eptifibatide or tirofiban limits the ability of platelet transfusions to restore normal platelet function. In cases in which urgent removal of epifibatide or tirofiban from the circulation is desired, hemodialysis may be necessary.

Calcium antagonists previously prescribed for control of ischemic heart disease should be continued up to the time of surgery to reduce the chance of myocardial ischemia from withdrawal of the drug. In the case of diltiazem and verapamil, the dose may need to be reduced because these agents may provoke bradycardia and a low-output syndrome postoperatively, especially if a beta blocker or amiodarone is given concurrently or the patient is elderly. Profound atropine- and isoproterenol-resistant bradyarrhythmias may occur postoperatively in patients treated with these calcium antagonists, particularly when the patient has not yet recovered from the hypothermia that is imposed intraoperatively; temporary dual-chamber pacing support should be available to manage such patients.

CONTINUATION OF ANTIARRHYTHMICS.

With the exception of amiodarone, antiarrhythmic drugs that have been prescribed for hemodynamically compromising or life-threatening ventricular tachyarrhythmias should be continued up to the time of surgery because of the risk of "breakthrough" of a

potentially lethal ventricular arrhythmia in the preoperative period.

Patients with a documented history of resuscitation from sudden cardiac death who are receiving amiodarone should continue to receive this drug up to the time of surgery. However, in cases in which amiodarone was prescribed for a less overtly life-threatening arrhythmia (e.g., AF), the maintenance dosage has been greater than 200 mg/d, and the patient has a history of lung disease, we recommend at least a 3-month period of abstinence from the drug before subjecting the patient to elective cardiopulmonary bypass.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS.

Prophylactic implantation of cardioverter-defibrillators at the time of CABG in patients at high risk for ventricular arrhythmias (ejection fraction
35 percent, abnormal signal-averaged ECG) does not improve survival.[5]

INTRAOPERATIVE MANAGEMENT

Despite increased risks, particularly related to age and advanced disease, cardiac surgery patients today enjoy markedly improved outcomes when compared with patients operated on l0 years ago. Important intraoperative surgical advances that have contributed to this improval outcome include epiaortic echocardiographic scanning in patients with ascending aortic atherosclerosis, transesophageal echocardiography, retrograde blood cardioplegia, retrograde cerebral perfusion in patients requiring circulatory arrest, and performance of all vascular anastomoses with a single aortic cross-clamp under cardioplegic arrest. Emphasis on modern strategies to ensure blood conservation and minimize hemostatic complications has significantly decreased or eliminated homologous blood exposure for most patients undergoing cardiac surgery (Fig. 60-2) .

Until recently, nearly all cardiac surgical procedures were performed via a standard median sternotomy with the use of cardiopulmonary bypass and cardiac arrest to provide a bloodless, motionless field (Fig. 60-3). Cardiac surgeons have recently explored less invasive approaches to coronary and valvular heart disease. The impetus for this change has been to decrease overall surgical trauma associated with full sternotomy and cardiopulmonary bypass without compromising the efficacy and safety of procedures. In valvular heart disease, cardiopulmonary bypass is essential, and therefore the focus has been on reducing trauma through a variety of less invasive incisions (Fig. 60-4). In coronary surgery, smaller incisions have also been used with or without cardiopulmonary bypass, particulary to perform single-vessel bypass to the left anterior descending artery. Recent technical advances in myocardial stabilization (Fig. 60-5) have now focused attention on off-pump multivessel coronary bypass through a full sternotomy.[60B] This approach is particularly appealing in selected high-risk patients, including those with ascending aortic atherosclerosis, renal dysfunction, and severe pulmonary disease. Wider adoption of less invasive cardiac surgical techniques can be anticipated if ongoing clinical trials demonstrate short-term patient benefit and medium- and long-term results comparable to those obtained with standard

techniques.[60C]

Figure 60-2 Multimodality algorithm designed to optimize blood conservation in cardiac surgical patients. Preoperative, intraoperative, and postoperative strategies are all important to eliminate the requirement for homologous blood transfusion. ASA=aspirin; coag=coagulation; EPO=erythropoietin; Hct=hematocrit; Hx=history; IAD=intraoperative autologous donation; PLT=platelet; RAP=retrograde autologous priming; RCM=red cell mass. (From Rosengart TK: Open heart surgery without transfusion in high-risk patients. Am J Cardiol 83:31B-37B, 1999.)

Figure 60-3 Schematic diagram of a typical cardiopulmonary bypass circuit. Venous blood is drained by a cannula from the right atrium into a reservoir and then pumped through an oxygenator and heat exchanger and returned via an aortic cannula to the ascending aorta. Although cardiopulmonary bypass is extremely safe in the current era, morbidity may occur in selected patients. Cerebral emboli may result from aortic manipulation. End-organ perfusion may be reduced as a result of loss of pulsatile flow. Finally, the bypass circuit may cause hemodilution and trigger systemic activation.

POSTOPERATIVE MANAGEMENT

Fluid, Electrolyte, and Acid-Base Balance

Extracorporeal circulation is associated with an increase in extracellular fluid and total exchangeable sodium, along with a decrease in exchangeable potassium. The cumulative experience in many centers has led to the following basic principles of management:

1. For the first 48 hours after surgery, free water is limited to about 1000 ml/d and intravenous fluids are administered in the form of 5 percent glucose in water. Sodium replacement varies with volume needs.
2. Serum potassium levels can fluctuate dramatically; therefore, frequent measurement of serum potassium is indicated, especially in diabetics. We attempt to maintain serum potassium in the range of 4.5±0.5 mEq/liter and magnesium at 2.0 mEq/liter or greater to minimize the chance of cardiac arrhythmias.
3. Serum glucose levels are frequently elevated (250 to 400 mg/dl), as a result of glucose-containing intravenous solutions and surgically induced increases in cortisol and catecholamine levels. In nondiabetic patients, insulin therapy is not usually required, whereas it is routinely used in insulin-requiring diabetic patients to avoid uncontrolled hyperglycemia.
4. Mild metabolic acidosis or metabolic alkalosis may be present for the first 24 hours postoperatively, particularly during rewarming. These acid-base abnormalities usually do not require correction in the absence of preoperative renal dysfunction or development of acute renal failure postoperatively.[61] Significant metabolic acidosis (pH <7.35) should be avoided during the rewarming phase, particularly if

patients are dependent on an inotropic agent. Hyperventilation (P_{CO_2} <35 mm Hg) and treatment with sodium bicarbonate should be instituted.

5. Serum total calcium, phosphorus, and magnesium levels are frequently depressed for about 24 to 48 hours in normally convalescing patients, partly because of the effects of hemodilution. These electrolyte abnormalities are usually self-correcting, and replacement therapy is not generally required. A possible exception is hypomagnesemia, which may predispose to the development of cardiac arrhythmias.[52]

Respiratory Management

EFFECTS OF ANESTHESIA, STERNOTOMY, AND CARDIOPULMONARY BYPASS ON PULMONARY FUNCTION.

Four broad areas should be considered, as outlined in Table 60-3 .[62] [63] most all patients experience alveolar dysfunction after open-heart surgery because of right-to-left intrapulmonary shunting of blood from various intrinsic alveolar abnormalities (e.g., atelectasis, edema, infection) and pulmonary vascular events (e.g., extravasation of fluid, inhibition of hypoxia-induced vasoconstriction). Central respiratory drive and respiratory muscle function are depressed postoperatively because of a combination of pharmacological effects and mechanical derangements of thoracic function. Patients with preexisting pulmonary disease may experience more profound depression of respiratory function necessitating vigorous pulmonary toilette.

EARLY EXTUBATION.

Historically, most postoperative cardiac surgery patients received between 6 and 18 hours of ventilatory support (Table 60-4) . Early extubation protocols have now been widely adopted in cardiac ICUs, and stable patients are extubated within 4 hours. Advantages of early extubation include improved patient mobility with early transition to step-down units. Patient selection for early extubation is outlined in Table 60-4 .

SPECIAL PROBLEMS

Failure to meet early extubation criteria may result from a variety of factors. Careful assessment will usually identify one or more etiologies resulting in respiratory dysfunction.

INCREASED ALVEOLAR-ARTERIAL GRADIENT.

An increased alveolar-arterial gradient postoperatively is a serious problem that demands thorough evaluation. The ventilator settings should be checked and a chest radiograph obtained to ascertain the position of the tip of the endotracheal tube (to exclude, for example, intubation of the right main stem bronchus) and to rule out pneumothorax, lobar atelectasis or pneumonia, or a large pleural effusion. Hemodynamic monitoring by means of a pulmonary artery catheter can cause pulmonary hemorrhage from overinflation of the balloon, and bronchoscopy may need to be performed to diagnose and manage the problem (e.g., occlusion of the bronchus

draining the bleeding segment of the lung).

PULMONARY EDEMA (see also Chap. 17) .

The most common cause of pulmonary edema postoperatively is elevated pulmonary venous pressure arising from left ventricular dysfunction and/or a valvular lesion (e.g., mitral regurgitation). Such patients require aggressive diuresis, as well as vasodilator/inotropic and possibly Intraaortic balloon support. Mechanical ventilation with positive end-expiratory pressure (PEEP) is used until the patient's ventricular function improves. Repeat surgery may be needed if pulmonary edema persists despite attempts to control severe mitral regurgitation medically.

In a minority of patients, pulmonary edema after cardiac surgery is due to the adult respiratory distress syndrome. In its most extreme form, this disorder is associated with a generalized whole-body *postpump syndrome* characterized by increased capillary permeability, interstitial edema, fever, leukocytosis, renal dysfunction, and hemodynamic collapse.

UNDERLYING CHRONIC LUNG DISEASE.

General surgical preparation

Figure 60-4 Schematic representation of traditional incision and sternotomy (*A*) compared with a variety of less invasive incisions (dotted lines represent chest wall incisions). Limited skin incision/full sternotomy (*B*) is gaining in popularity because of improved cosmetics and reduced trauma from the limited chest wall retraction. Although once popular, the parasternal approach (*C*) is used less frequently because of the residual chest wall defect. Partial lower or upper sternotomy (*D* and *E*) has been used predominantly in valve procedures. Right anterior thoracotomy (*F*) is a useful approach, particularly in mitral valve reoperations. Left anterior thoracotomy has been described for coronary bypass procedures.

of patients with obstructive lung disease, including antibiotics, bronchodilators, and cessation of cigarette smoking, may help minimize the risk of respiratory failure from postoperative atelectasis and pneumonia.[62] [63] Inhaled bronchodilators should be continued postoperatively. Refractory patients may require a short course of corticosteroids (e.g., methylprednisolone 0.5 mg/kg every 6 hours for 3 days) to be weaned from the ventilator.[62] Previous enthusiasm for intravenous methylxanthines has waned because of evidence of limited efficacy and the risk of agitation, arrhythmias, and grand mal seizures.[64] Intravenous theophylline should therefore be reserved for extremely refractory cases and administered in a dose of 0.4 mg/kg/hr with careful monitoring of plasma levels to maintain them in the range of 10 to 15 mug/ml.

We have successfully operated on patients with severe respiratory compromise,

including those with a forced expiratory volume in 1 second (FEV_1) of less than 0.8 liters who require home oxygen therapy. All patients with severe pulmonary dysfunction are considered for early extubation. It is important to maintain the arterial carbon dioxide tension close to the patient's baseline level to ensure an adequate respiratory drive.

DIAPHRAGMATIC FAILURE.

Diaphragmatic dysfunction after cardiac surgical procedures usually occurs as a result of injury to the phrenic nerve(s). An elevated hemidiaphragm may be seen on postoperative radiographs in 25 percent of patients who undergo myocardial preservation including topical ice slush and harvesting of an internal mammary artery.[65] A simple bedside test of diaphragmatic function is to ask the patient to protrude the umbilicus, a movement that requires diaphragmatic functional integrity. Of note, an elevated hemidiaphragm is not usually associated with increased postoperative morbidity or mortality.

Recovery of the hemidiaphragm to normal position occurs in 80 percent of patients at 1 year and nearly all patients by 2 years postoperatively. Clinically important diaphragmatic dysfunction caused by unilateral or bilateral phrenic nerve injury develops in less than 1 percent of patients after cardiac surgery.

Evidence of diaphragmatic failure includes an inability to wean the patient from the ventilator, vital capacity less than 500 cc, and paradoxical movement of the diaphragm on fluoroscopy (abnormal "sniff" test)[62] or ultrasonography.

PROLONGED VENTILATORY INSUFFICIENCY.

Patients who fail to be weaned from the ventilator within 48 hours require special attention. Because of the risk of stress-induced gastritis, H_2 receptor blockers (e.g., ranitidine 50 mg intravenously every 8 to 12 hours) or a mucosal cytoprotective agent (sucralfate 1 gm orally two to four times per day) is administered. Nutritional support is critical to provide metabolic needs and prevent the catabolism of respiratory muscles (see Fig. 60-1) . Pressure support ventilation strategies are particularly useful for patients in need of prolonged ventilation. Barotrauma is minimized and patient comfort improved while permitting incremental weaning in small steps.

High-compliance, low-pressure cuff (<20 mm Hg) endotracheal tubes have reduced the risk of mechanical complications (e.g., tracheal stenosis) and permit patients to remain intubated for several weeks. Nonetheless, we believe that patients requiring prolonged ventilatory support beyond 10 to 14 days will generally benefit from a decision to

Figure 60-5 Off-pump coronary bypass surgery on the beating heart has been facilitated by the development of platform stabilization systems to provide isolated immobilization during the performance of distal anastomoses. The left anterior descending artery is most amenable to platform stabilization as opposed to the posterolateral circulation.

proceed with early tracheostomy.[65A] Tracheostomy provides improved patient comfort and greater pulmonary toilet and enhances weaning by minimizing pulmonary dead space. Percutaneous tracheostomy offers the advantage of bedside insertion with minimal surgical trauma and is particularly useful in patients with reasonable ventilatory mechanics but heavy secretions.

TABLE 60-3 -- ABNORMALITIES OF RESPIRATORY FUNCTION AFTER CARDIAC SURGERY

EFFECTS OF ANESTHESIA, THORACIC SURGERY, AND CARDIOPULMONARY BYPASS ON PULMONARY FUNCTION	POTENTIAL CAUSES
Alveolar dysfunction (e.g., widened alveolar-arterial oxygen gradient because of right-to-left intrapulmonary shunting)	Scattered regions of atelectasis with preserved perfusion Pulmonary edema (e.g., cardiogenic, noncardiogenic "postpump" alveolar capillary leak) Infection Inhibition of hypoxic pulmonary vasoconstriction by anesthetic agents Exacerbation of ventilation/perfusion mismatch by vasodilating agents used postoperatively (e.g., nitroprusside)
Decreased central respiratory drive	General anesthetics Narcotic analgesics Cerebral insult in perioperative period
Decreased respiratory muscle function	Thoracic pain (incision, chest tubes) Persistent effects of muscle relaxants Age Obesity Depressed cardiac function Primary diaphragmatic dysfunction (e.g., phrenic nerve injury)
Exacerbation of underlying chronic pulmonary disease	Increase in airway resistance Increased secretions and worsening bronchitis Pneumonia

TABLE 60-4 -- CARDIAC SURGERY EARLY EXTUBATION PROTOCOL

Definition	Extubation within 4 hr after surgery
Patient selection	

Inclusion criteria	All patients 80 yr old, LV ejection fraction >25%
Exclusion criteria	High inotropic requirement, postoperative bleeding or ischemia
Anesthetic management	
Intraoperative	Low-dose synthetic narcotics and inhalation agents
Postoperative	Muscle relaxant reversal Propofol 0.1 ml/kg/hr Minimize narcotic use
Ventilatory management	
Postoperative	SIMV mode Check ABGs and decrease ventilatory support every 20 min Always keep between pH 7.35 and 7.45 Always keep P_{O_2} >75 mm Hg
Extubation guidelines	
Oxygenation	P_{O_2} >75 mm Hg at an F_{IO_2} 0.50
Respiratory drive	P_{CO_2} <45 mm Hg and pH >7.35 Spontaneously breathing
Mechanics	Respiratory rate <25 breaths/min Negative inspiratory pressure >20 cm H_2O Tidal volume >8 cc/kg Vital capacity >10 cc/kg
Airway protection	Alert with gag reflex Absence of heavy secretions
Cardiovascular	Cardiac index >2.0 liters/min/m^2 MAP >80 and <120 mm Hg

ABG=arterial blood gas; LV=left ventricular; MAP=mean arterial pressure; SIMV=synchronized intermittent mandatory ventilation.

Hypertension

Postoperative hypertension has been defined variably in the literature,[66] but we consider it to be present if systolic pressure exceeds 140 mm Hg.[67] The incidence of postoperative hypertension ranges from 40 to 60 percent. It occurs more commonly in patients with a preoperative history of hypertension, prior maintenance therapy with a beta blocker, and well-preserved left ventricular function.[68] Postoperative hypertension

is especially frequent after CABG and surgical relief of left ventricular outflow tract obstruction (e.g., aortic valve replacement, correction of coarctation of the aorta).

The mechanism of postoperative hypertension probably varies from patient to patient but usually includes (1) a "rebound" effect from withdrawal of beta blockade administered preoperatively; (2) excessive sympathetic nervous system activity with elevated levels of circulating catecholamines (especially norepinephrine)[69] ; (3) pressor reflexes originating in the heart, great vessels, or coronary arteries[70] ; and (4) a drop in aortic pressure proximal to the site of the corrected coarctation with resultant stimulation of aortic and carotid baroreceptors by apparent "hypotension." The renin-angiotensin system is stimulated and peripheral resistance is increased. Sudden exposure of vascular beds downstream from the coarctation to "undamped" aortic pressure has also been reported to cause mesenteric arteritis.

The adverse consequences of elevated systemic pressure include an increased risk of postoperative bleeding, suture line disruption, and aortic dissection[61] ; elevated left ventricular afterload and a consequent reduction in left ventricular output; and injury to aortocoronary bypass grafts and postoperative stroke.

MANAGEMENT.

Although a variety of agents may be used for treating acute postoperative hypertension, we prefer those that are rapidly acting and titratable and have a short half-life. Nitroglycerin is our first-choice agent, beginning at a dose of 25 mug/min and titrating up to a dose of 300 mug/min. Sodium nitroprusside (0.5 to 2 mug/kg/min) may be required in hypertension refractory to nitroglycerin therapy. Because of its prominent vasodilatory effects, sodium nitroprusside should be administered with caution for the first 3 to 4 hours after surgery since volume shifts may occur during the rewarming phase. The ultrashort-acting beta blocker esmolol (50 to 250 mug/kg/min) may be useful in patients with a hyperdynamic circulation. It is initially preferred over longer-acting beta blockers when evaluating patient tolerance to beta blockade (e.g., moderately severe left ventricular dysfunction). The need for transition to oral antihypertensive therapy is assessed on an individual basis; chronic treatment is usually required in patients with a preoperative history of hypertension.

Perioperative Myocardial Infarction (See also Chap. 35)

Despite modern intraoperative myocardial protection and improvements in surgical technique, some degree of ischemia occurs nearly uniformly during CABG. Only a minority of patients (5 to 15 percent of patients undergoing CABG), however, actually experience a *perioperative myocardial infarction,* even in tertiary care centers currently operating on higher-risk patients, including those with failed interventional procedures.[71] [72] [73] Potential causes of myocardial ischemia and infarction in the perioperative period include incomplete revascularization; diffuse atherosclerotic disease of the distal coronary arteries; spasm, embolism, or thrombosis of the native coronary vessels or bypass grafts[74] [75] ; technical problems with graft anastomoses; inadequate myocardial preservation intraoperatively; increased myocardial oxygen needs, as in left ventricular hypertrophy; and hemodynamic derangements in the postoperative period (e.g.,

hypotension, hypertension, tachycardia). Although initially one might suspect that perioperative myocardial infarction results from occlusion of bypass grafts placed to circumvent diseased coronary arteries, autopsy studies have shown that bypass grafts are usually patent in patients dying of a perioperative myocardial infarction.[76] This observation lends support to the concept that poor myocardial protection or a mismatch between myocardial oxygen supply and demand postoperatively accounts for much of the infarction noted.

DIAGNOSIS.

The diagnosis of a myocardial infarction after cardiac surgery is more difficult than at other times because of the nonspecific ST-T wave abnormalities on ECG and nearly universal elevation of creatine kinase (CK) levels postoperatively. A number of diagnostic findings (Table 60-5) must be carefully interpreted and then integrated as shown in the algorithm displayed in Table 60-6 .

A 12-lead ECG should be obtained immediately on the patient's arrival in the ICU after surgery and no less frequently than once every 24 hours for the first few postoperative days. Measurements of total CK and CK-MB should be made every 8 hours for the first 24 to 36 hours if perioperative myocardial infarction is suspected.

TROPONIN.

Experience with newer, more sensitive serum markers of cardiac injury, such as troponin I and troponin T, is limited.[77] [78] However, initial reports suggest that cardiac-specific troponin I and

TABLE 60-5 -- DIAGNOSIS OF MYOCARDIAL INFARCTION AFTER CARDIAC SURGERY

DIAGNOSTIC FINDING	COMMENT
Symptoms	
Early (<24 hr postop)	Not reliable because of residual effects of anesthesia and postoperative analgesics
Late (>24 hr postop)	Potentially reliable but may be confused with incisional pain and pleuritic pain from chest tubes, pericarditis
Electrocardiogram	
New, persistent Q waves	Most reliable diagnostic finding, but only if the Q waves persist on serial ECGs over several days

Evolutionary ST-T changes	Supportive data favoring the diagnosis of MI only if a typical evolutionary pattern is observed. Because of the effects of cardiopulmonary bypass, hypothermia, postoperative pericarditis, mediastinal chest tubes, and medications (e.g., digitalis), a variety of nonspecific ST-T wave abnormalities may be seen and should not be relied on for diagnosing perioperative MI
Myocardial-specific enzymes	
Total CK	Elevated total CK levels postoperatively may arise from multiple sources, including skeletal muscle in the thorax and calf, as well as myocardium
CK-MB	Myocardial-specific CK may be released from ischemia occurring during cardiopulmonary bypass, as well as myocardial and aortic incisions made intraoperatively (e.g., right atrium for cannulation of the cavae). Because of the nearly universal release of CK-MB, a diagnosis of MI should not be made unless CK-MB is significantly elevated (e.g., >30 units/liter)
Echocardiogram	A regional wall motion abnormality is a helpful finding, particularly if it can be shown to be a new finding by comparison with a peroperative study. Paradoxical motion of the high anterior portion of the interventricular septum is a common finding postoperatively in the absence of MI and should not be taken as the sole evidence of new perioperative myocardial necrosis

CK=creatine kinase; MI=myocardial infarction.

TABLE 60-6 -- ALGORITHM FOR DIAGNOSIS OF PERIOPERATIVE MYOCARDIAL INFARCTION AFTER CARDIAC SURGERY

NEW Qs ON ECG	CK-MB >30 IU/LITER	NEW RWMA ON ECHO*	DIAGNOSIS	COMMENT
Yes	Yes	Yes	Definite MI	
Yes	Yes	No	Probable MI	New zone of necrosis not evident on ECHO. The persistence of new Q waves and abnormally elevated CK-MB suggests that Q waves are not a "benign" postoperative finding
Yes	No	Yes	Definite MI	CK-MB peak probably missed because of infrequent sampling

Yes	No	No	Possible MI	New Q waves may be false-positive finding
No	Yes	Yes	Probable MI	Non-Q-wave MI
No	Yes	No	MI unlikely	Small non-Q-wave MI cannot be entirely excluded
No	No	Yes	MI unlikely	Removal of "restraining" effect of pericardium may result in new RWMAs, especially in high anterior septal area
No	No	No	No MI	Although small patchy areas of necrosis may be seen histologically, these abnormalities are probably not of clinical significance

*Perioperative echocardiography is not *required* for the diagnosis of a perioperative MI but can provide useful supportive data or aid in the diagnosis in unclear cases, especially if obtained acutely.
ECHO=echocardiography; MI=myocardial infarction; RWMA=regional wall motion abnormality.

troponin T are elevated postoperatively in virtually all patients who undergo CABG surgery. Patients who experience a perioperative myocardial infarction release greater quanitities of troponin such that serum measurements may remain 10- to 20-fold higher than the upper limit of the reference interval for at least 4 to 5 days postoperatively. Even in patients not experiencing perioperative myocardial infarctions by conventional diagnostic criteria, the relative increase in proteins such as cardiac troponin I over preoperative baseline values is greater than that of CK-MB, which suggests that troponin measurements can detect small amounts of myocardial tissue damage that are not detected by CK-MB.

ELECTROCARDIOGRAPHY.

The ECG is the most reliable tool for diagnosing a perioperative myocardial infarction. New and persistent Q waves accompanied by new, persistent, and evolutionary ST-T wave abnormalities are the most helpful criteria. Pathological Q waves resulting from perioperative myocardial infarction may appear with an earlier time course (i.e., immediately on arrival from the operating room) than in a nonrevascularized patient.

ECHOCARDIOGRAPHY.

Bedside echocardiograms (transthoracic and if necessary transesophageal) play an important role in establishing the diagnosis of a perioperative myocardial infarction by detecting new regional wall motion abnormalities in cases in which the ECG or serum marker measurements are unclear. It is especially helpful to compare new echocardiograms with the preoperative studies that are almost always available.

RISKS AND CONSEQUENCES OF PERIOPERATIVE INFARCTION.

Variables that have been found to correlate with the development of perioperative myocardial infarction in patients undergoing CABG include emergency surgery, aortic cross-clamp time greater than 100 minutes, a recent myocardial infarction (within the prior week), and a history of previous revascularization (either percutaneous transluminal coronary angioplasty or CABG surgery).[73]

Patients with a perioperative myocardial infarction have increased hospital mortality (about 10 to 15 percent) when compared with patients undergoing CABG who have not sustained a perioperative myocardial infarction (about 1 percent).[73] [79]

Characteristics of patients who are especially at risk of increased short-term mortality after a perioperative myocardial infarction include age older than 65 years, unstable angina preoperatively, a myocardial infarction within 1 week before surgery, left ventricular aneurysm, intraventricular conduction disturbance (e.g., left bundle branch block), and the need for reoperation for bleeding. About two-thirds of the postoperative mortality is due to pump failure and one-third is due to malignant ventricular tachyarrhythmias.[79] Perioperative myocardial infarction also adversely affects the long-term prognosis, particularly if associated with inadequate revascularization and depressed left ventricular function.[80]

MANAGEMENT OF MYOCARDIAL ISCHEMIA AFTER CABG.

Patients with evidence of myocardial ischemia after coronary bypass surgery require an integrated assessment of clinical findings and laboratory tests on an individualized basis to define the appropriate management strategy. At the center of the decision pathway are the 12-lead ECG and hemodynamic observations (Fig. 60-6) . Patients with ST elevations and a low cardiac index require intraaortic balloon pump support. Two-dimensional echocardiography is useful to detect new wall motion abnormalities that may necessitate coronary angiography and a percutaneous revascularization procedure in selected patients.

Low-Output Syndrome and Shock States

RECOGNITION.

Sometimes, diagnosis of low-output syndrome and a shock state after cardiac surgery is difficult. Because cold extremities and mottled skin may result from hypothermia postoperatively, these observations lack sufficient specificity. Although reduced systolic pressure is the most striking manifestation of this disorder, low-output syndrome may be present even if the arterial systolic pressure exceeds 100 mm Hg because increased systemic vascular resistance (>1500 dyne-secccm^{-2}) may be supporting the peripheral perfusion pressure. It is important to recognize this syndrome because of the strong relationship between cardiac index in the early postoperative period and the probability of cardiac death after surgery. Common clinical features of the low-output syndrome and shock states after cardiac surgery include cold extremities, mottled skin, reduced systolic pressure (<90 mm Hg), decreased urine output (<30 ml/hr), low cardiac index

(<2.0 liter/min/m[2]), low mixed venous oxygen saturation (<50 percent), and acidosis.

One should make careful hemodynamic measurements and integrate them with bedside echocardiographic recordings to confirm the diagnosis of low-output syndrome and attempt to segregate the findings into one of the patterns (*reduced preload, cardiogenic shock,* or *sepsis*) in Table 60-7 . Although the hemodynamic findings among these patterns overlap and the coexistence of multiple disorders (e.g., bradycardia and hypovolemia) may blur the distinction between patterns, they offer a clinically useful approach to the evaluation of a patient with low-output syndrome. In addition to the specific treatment measures discussed below, a number of general measures are applicable to all patients who are in a shock-like condition after cardiac surgery, including prompt correction of any electrolyte and acid-base disturbances, transfusion to a hematocrit

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Figure 60-6 Myocardial ischemia after coronary bypass grafting is frequently observed. Hemodynamic assessment and ensurance of adequate coronary and systemic perfusion dictate early management strategies. Echocardiographic evaluation helps further tailor postoperative care. CABG = coronary artery bypass graft surgery; ECG = electrocardiogram; ECHO = echocardiography; IABP = intraaortic balloon pumping; MAP = mean arterial pressure.

over 30 percent for improved oxygen-carrying capacity of the blood, and a "low threshold" for mechanical ventilatory support to minimize the work of breathing and thereby reduce total-body oxygen needs.

REDUCED PRELOAD

Hypovolemia.

Low ventricular filling pressure, normal systemic vascular resistance, and a reduced cardiac index, coupled with echocardiographic demonstration of small ventricular volume with preserved systolic function, are indicative of *hypovolemia.* Possible causes include bleeding, excessive diuresis, the "leaky capillary state" associated with the postpump syndrome, and less frequently, inadequate vascular volume because of insufficient return of fluids at the conclusion of cardiopulmonary bypass. Rarely, adrenal cortical insufficiency as a result of perioperative hemorrhage into the adrenals has been reported as a cause of hypovolemic hypotension after cardiac surgery.

Therapeutic maneuvers include the administration of intravenous fluids (normal saline solution, lactated Ringer solution), transfusion with packed red blood cells if the hemoglobin is less than 8 gm/dl, and administration of colloid-type volume expanders. It is also important to discontinue any vasodilators or antihypertensives that may have been prescribed during a period when the patient was hypertensive. While waiting for the above measures to take effect, the patient may require transient infusion of a

vasoconstrictor (usually phenylephrine [Neo-Synephrine]) or an inotropic pressor (usually dopamine or epinephrine).

Vasodilatation.

Inhibition of sympathetic tone by the effects of anesthetic agents may cause peripheral vasodilatation. In combination with the increased venous capacitance that may occur during rewarming, a low-output syndrome may develop as a result of markedly reduced systemic vascular resistance (<1000 dyne-secccm^{-5}). This situation is best treated by infusion of a vasoconstrictor such as norepinephrine in a dose of 1 to 10 mug/min until the systemic vascular resistance returns to a normal level.

CARDIOGENIC SHOCK.

When right ventricular and left ventricular filling pressures are in the normal range and systemic vascular resistance is not reduced, a frequent cause of a cardiac index less than 2 liters/min/m[2] is *bradycardia.* Because the cardiac index is the product of stroke volume and heart rate, this abnormality is easily corrected by atrial or atrioventricular pacing at 85 to 100 beats/min.

Left Ventricular Failure.

The pattern of predominant *left ventricular failure* in the early postoperative state is characterized by a disproportionately elevated pulmonary capillary wedge pressure in comparison to right atrial pressure, a low cardiac index, and normal or elevated systemic vascular resistance. Echocardiography usually reveals a dilated, poorly contractile left ventricle, often exhibiting multiple regional wall motion abnormalities.

DIAGNOSIS.

The differential diagnosis of left ventricular failure after cardiac surgery includes the following conditions (which may coexist in the same patient): preoperative left ventricular dysfunction, inadequate surgical correction of the cardiac lesion (e.g., residual left ventricular outflow tract obstruction after repair of idiopathic hypertrophic subaortic stenosis, residual ventricular septal defect), complication of a surgical procedure (e.g., prosthetic valve leak or thrombosis, depression of stroke volume after correction of mitral regurgitation caused by elevation of afterload), dysrhythmia, depressant effect of a pharmacological agent (e.g., antiarrhythmic drug), acid-base or electrolyte disturbance, or myocardial ischemia and/or infarction. Bedside echocardiography can usually help identify mechanical disorders such as prosthetic valve dysfunction and dysrhythmias, and metabolic abnormalities and toxic drug levels can be readily recognized by ECG and laboratory measurements.[81]

Management.

The objectives of hemodynamic management of patients with *left ventricular failure*

postoperatively are to correct hypotension if present, increase forward left ventricular output, and return left and right ventricular filling

TABLE 60-7 -- HEMODYNAMIC DISTURBANCES FOLLOWING CARDIAC SUR

	REDUCED PRELOAD		CARDIOGENIC SHOCK		
	Hypovolemia	**Vasodilatation**	**Bradycardia (Inappropriately Slow HR Postoperatively)**	**LV Failure**	**RV Failure**
Hemodynamics					
RA	<8	<8	10	10	>10
PCW	<15	<15	>15	>20	15*
CI	<2.0	<2.0	<2.0	<2.0	<2.0
SVR	>1200	<1000	>1200	>1000	>1000
Other			HR <60		PCW >15 if LV failure is present

Echocardiogram	Small ventricular chambers with vigorous systolic contraction unless LV dysfunction was present preoperatively	Small ventricular chambers with normal systolic contraction unless LV dysfunction was present preoperatively	Normal-sized ventricular chambers with vigorous systolic contraction, albeit at a slow rate	Dilated LV with reduced systolic performance; regional wall motion abnormalities may reflect old or new myocardial ischemia and/or infarction	Dilated RA and RV with reduced RV systolic contraction. TR often present on Doppler study. LV contractile performance is variable
Management	IV fluids Transfusion if Hgb <10 Inotropes	Vasopressors	Cardiac pacing	Search for correctible lesion, offending agent, or laboratory abnormality Inotropes Vasopressors and vasodilators Mechanical assistance	Supplemental O_2 Pulmonary vasodilators Inotropes Mechanical assistance

CI=cardiac index; Hgb=hemoglobin; HR=heart rate; IV=intravenous; LV=left ventricular; PAd=pulmona
PCW=pulmonary capillary wedge; RA=right atrial; RV=right ventricular; SVR=systemic vascular resist
regurgitation.

pressures to the normal range. These parameters are intimately related, and treatment may require careful titration of several intravenous agents for pharmacological support of the failing circulation. Boluses of calcium chloride (0.5 to 1.0 gm) increase myocardial contractility, but the effect is modest and short-lived. A continuous infusion of dopamine (5 to 10 mug/kg/min) or epinepherine (1 to 4 mug/kg/min) is preferable if the primary goal is to increase systemic arterial pressure and cardiac output. Dobutamine (2 to 5 mug/kg/min), amrinone (bolus of 0.75 mg/kg and infusion of 5 to 10 mug/kg/min), or milrinone (bolus of 50 mug/kg/min and infusion of 0.375 to 0.75 mug/kg/min) also augment cardiac output and should be selected if a reduction in ventricular filling

pressure is desired; systemic arterial pressure is usually unchanged or may even drop slightly because of the peripheral vasodilatory effects of these drugs.[61] [82] [83] A commonly used combination is dopamine (2 mug/kg/min) to achieve greater renal perfusion in conjunction with dobutamine (2 to 5 mug/kg/min) for augmentation of cardiac output. If the mean arterial pressure is equal to or greater than 90 mm Hg, vasodilator therapy with nitroglycerin increases forward cardiac output and lowers pulmonary capillary wedge pressure further. When hypotension is profound (e.g., systolic pressure <70 mm Hg), norepinephrine or epinepherine 1 to 10 mug/min may be necessary to prevent coronary hypoperfusion.[61] [82]

We prefer to use an intraaortic balloon pump (see Chap. 19) for mechanical support of the circulation along with pharmacotherapy early in the course of management of postoperative left ventricular failure that does not respond to the initial pharmacological maneuvers already discussed. This protocol has the advantages of avoiding a continuous upward titration of the dose of sympathomimetic inotropic agents and vasoconstrictors associated with downregulation of beta-adrenoceptors and diminished perfusion of the renal, mesenteric, and coronary vascular beds. Also, intraaortic balloon counterpulsation does not increase myocardial oxygen demand. The intraaortic balloon pump is particularly helpful if significant mitral regurgitation is present but may be contraindicated in the presence of severe aortic regurgitation and if an abdominal aortic aneurysm is present. Delayed sternal closure is another important adjunct in the management of cardiogenic shock following surgery (Fig. 60-7) . If the patient fails to improve despite a combination of intraaortic balloon pumping, open-chest management, and pharmacotherapy, a ventricular assist device may be inserted for temporary support or as a "bridge" to cardiac transplantation until a donor is located.[84] [85] Serial evaluations of left ventricular function over time and under different loading conditions and supportive measures are best obtained with transesophageal echocardiograms.[86]

RIGHT VENTRICULAR FAILURE.

The pattern of predominant *right ventricular failure* is characterized by a disproportionate elevation in right atrial pressure in comparison to pulmonary capillary wedge pressure. In severe cases of postoperative right ventricular failure, right atrial pressure may exceed 20 mm Hg while pulmonary capillary wedge pressure remains equal to or less than 15 mm Hg. When left ventricular failure is present simultaneously, the difference between right atrial and pulmonary capillary wedge pressure lessens and differentiation from cardiac tamponade becomes difficult. Bedside echocardiography is useful for making a proper diagnosis (see Table 60-7) .

Postoperatively, predominant right ventricular failure may be seen as a result of one or more of the following conditions: elevated pulmonary vascular resistance (persistently elevated from preoperative elevations in pulmonary artery pressure; postoperative hypoxia, pulmonary embolus, or pneumothorax), primary right ventricular ischemia/infarction,[87] or a mechanical lesion (tricuspid regurgitation, residual shunt flow, right ventriculotomy).

Massive pulmonary embolism is a rare occurrence after cardiac surgery (see Chap. 52) . The diagnosis should be suspected when sudden deterioration in oxygenation occurs

in association with confusion, systemic hypotension, tachycardia, ECG abnormalities (unexplained right axis deviation, right bundle branch block, a right ventricular strain pattern), and elevation of right atrial pressure. Angiographic confirmation of the diagnosis is not usually necessary. Expeditious

Figure 60-7 Patients in a low output state may not tolerate immediate sternal closure, particularly in the setting of significant mediastinal and myocardial edema associated with prolonged cardiopulmonary bypass. A modified barrel syringe is inserted between the sternal tables and the wound is then covered with an Esmarch dressing. After resolution of edema and recovery of myocardial function, the patient is returned to the operating room for a standard sternal closure.

noninvasive confirmation by echocardiography is advisable in patients in whom the diagnosis remains uncertain.

MANAGEMENT.

Hemodynamic management of predominant right ventricular failure should focus on improvement in right ventricular output to allow adequate filling of the left ventricle. Supplemental oxygen and hyperventilation to decrease P_{CO_2} levels help lower pulmonary artery pressure. Bradycardia (>60 beats/min) is corrected by atrial or atrioventricular pacing, isoproterenol (1 to 2 mug/min in an average adult) increases right ventricular contractility and also causes pulmonary vasodilatation. Pulmonary hypertension may also be reduced by prostaglandin E_1 [88] and intravenous nitroglycerin.

Cardiac Tamponade (see Chap. 50) .

Postoperative echocardiography has shown that virtually all patients have pericardial effusion after cardiac surgery and that many

such effusions are asymmetrical and loculated.[89] Even with mediastinal drains in place, it is possible for cardiac tamponade to develop postoperatively; recognition of this condition requires a high index of suspicion and assessment of hemodynamics at the bedside.[90]

Recognition.

Important clinical features of tamponade, such as diminished heart sounds and pulsus paradoxus, may be obscured by mechanical ventilation. Asymmetrical, loculated accumulation of blood and clots in the mediastinum and pericardial space may cause isolated tamponade of one or two cardiac chambers and produce unusual elevations in diastolic pressure (e.g., right atrial tamponade with elevation of central venous pressure

without an increase in right ventricular end-diastolic pressure or pulmonary capillary wedge pressure).[91] Beside two-dimensional transthoracic and transesophageal echocardiography is usually helpful for diagnosing pericardial effusions and assessing the hemodynamic significance of fluid collections.[92] Diastolic collapse of the right atrium and right ventricle is an indication of a hemodynamically significant external compressive force and should prompt urgent treatment.

Treatment.

Although pericardiocentesis may be helpful in nonsurgical tamponade, it is unlikely to be successful in evacuating the organized pericardial and mediastinal material that develops after cardiac surgery; subxiphoid drainage and/or emergency sternotomy is preferred. Supportive measures that can be attempted in the interim include volume expansion with intravenous fluids (Plasmanate, whole blood) and inotropic agents (dobutamine).

SEPTIC SHOCK.

Low ventricular filling pressure, markedly reduced systemic vascular resistance, and a normal or unexpectedly high cardiac index in the setting of hypotension and a shocklike state should raise suspicion of the early stages of *sepsis.* With progression of septic shock, a capillary leak syndrome develops (hypovolemia) and myocardial depression may occur and result in a somewhat reduced contractile pattern of the ventricles on echocardiography. Combined therapy with intravenous fluids, antibiotics, and inotropic agents is required to interrupt the vicious cycle of hypotension, acidosis, and diminished coronary perfusion. Most patients in a septic state during the first several days after cardiac surgery are infected with a skin organism (e.g., indwelling catheters) or from seeding the bloodstream from a pulmonary or urinary source. Broad antibiotic coverage (e.g., vancomycin plus ceftazidine) should be instituted. Because the offending organism is likely to be resistant to the prophylactic antibiotic given preoperatively, it is wise to not include it as one of the empirical antibiotics selected to treat sepsis.

Perioperative Arrhythmias (See also Chap. 25)

EVALUATION AND TREATMENT.

There appear to be two peaks in the incidence of arrhythmias perioperatively: The first occurs in the operating room (most commonly during induction of anesthesia, weaning from cardiopulmonary bypass, rewarming), and the second occurs in the ICU between the second and fifth postoperative days. The electrophysiological mechanisms underlying perioperative arrhythmias are incompletely understood, but they can probably be ascribed to a combination of the effects of circulating catecholamines, alterations in autonomic nervous system tone, transient electrolyte imbalance, myocardial ischemia or infarction, and mechanical irritation of the heart.

APPROACH TO THE PATIENT.

Several factors may predispose to the development of arrhythmias, including ventilatory dysfunction, fever, electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia), anemia, myocardial ischemia or infarction, low cardiac output and reflex increase in sympathetic tone, hypertension, pericardial inflammation, and toxic effects of cardioactive medications (e.g., digitalis toxicity, bradycardia induced by diltiazem).[52] [93] *Every effort should be made to look for and eliminate any of the factors that may be provoking the arrhythmia.*

Although antiarrhythmic drug therapy and direct-current cardioversion are traditional methods for treating postoperative arrhythmias, cardiac pacing techniques have a number of advantages, including more rapid onset and offset of action, avoidance of potential drug toxicity (especially proarrhythmia), elimination of the need for anesthesia (required for cardioversion), reduced anxiety for the patient, greater safety in patients receiving digitalis, and perhaps most important, the ability to repeat the pacing protocol if the arrhythmia should recur, a not infrequent event. In addition to terminating arrhythmias, cardiac pacing can be used to suppress arrhythmias in many patients by atrial, atrioventricular sequential, or ventricular stimulation at a critical rate (e.g., 85 to 100 beats/min).

Surface Electrocardiogram.

The value of a 12-lead ECG and simultaneously recorded multiple standard ECG lead rhythm strips cannot be overemphasized if one is attempting to analyze a wide complex tachycardia. Unfortunately, a number of the criteria for differentiating supraventricular tachycardia with aberrant conduction from ventricular tachycardia (VT) (see Chap. 25) may not be applicable to postoperative patients because of previous or newly acquired infarction patterns, transient conduction defects (seen in 5 to 15 percent of patients in the early recovery period), and nonspecific repolarization patterns.

Epicardial Electrodes.

It is desirable to place two wires on the free wall of the right atrium and the right ventricle to allow for bipolar atrial recording and pacing or dual-chamber pacing. The advantages of bipolar pacing include a smaller stimulus artifact, the ability to record a bipolar atrial electrogram during ventricular pacing, and a reduced likelihood of precipitating undesired atrial arrhythmias if an atrial wire is used as the indifferent electrode during unipolar ventricular pacing. Schematic diagrams showing the typical intrathoracic positioning of the atrial and ventricular wires are shown in Figure 60-8 .

Supraventricular Arrhythmias

ATRIAL PREMATURE DEPOLARIZATIONS.

The hemodynamic consequences of atrial premature depolarizations are almost always minor, and one should resist the urge to suppress them with antiarrhythmic drugs. Instead, they should be considered a signal that the patient is possibly hypoxic or that

an electrolyte imbalance is present and a warning that the patient is at risk for more serious arrhythmia such as AF or atrial flutter. In the absence of such correctable abnormalities, one may want to administer a beta blocker to inhibit the effects of circulating catecholamines and also to slow the ventricular rate if AF should develop.

ATRIAL FLUTTER.

Control of the ventricular rate in atrial flutter is more difficult than in AF because of the limited number of ventricular responses to atrial activation (usually 2:1, 4:1, but rarely an odd-numbered multiple). Atrial flutter may be difficult to terminate with antiarrhythmic agents. Cardioversion with an energy of 25 to 50 watt-seconds delivered as a single discharge can be expected to terminate atrial flutter in more than 90 percent of patients.

Atrial flutter can also be terminated by rapid atrial pacing with the temporary epicardial atrial wires placed at the time of surgery (Fig. 60-9). The likelihood of success is increased if one uses sufficiently rapid rates of pacing (up to 140 percent of the spontaneous atrial rate), a sufficient duration of pacing (10 to 30 seconds) with adequate strength (5 to 20 mA), and pretreatment of the patient with procainamide.[94] To achieve the high drive rates required, a special stimulator is used.

ATRIAL FIBRILLATION.

Despite the fact that AF is an extremely common arrhythmia following cardiac surgery, the optimal management strategy has not been established. Even after prophylactic therapy with beta-adrenoceptor blockers, transient symptomatic AF occurs in at least 25 to 30 percent of patients after CABG and in 50 percent of patients following valvular surgery; AF appears with greatest incidence on the second or third postoperative day.[52]

Management.

Unless hemodynamic collapse is present, in which case direct-current cardioversion should be performed, the initial treatment of choice in a postoperative patient is to slow the ventricular rate. Provided that the patient's ventricular function is adequate, acute intravenous administration of beta blockers (e.g., metoprolol 5 mg every 5 minutes for up to three doses), verapamil (5-mg bolus every 5 to 10 minutes for three or four doses), or diltiazem (0.25- to 0.35-mg/kg bolus over a period of 2 minutes) is a more desirable option. Esmolol, an ultrashort-acting cardioselective beta blocker, when administered intravenously in a dose of 50 to 250 mug/kg/min, provides the option of rapid onset; in the event of hemodynamic deterioration, the effects of the drug are usually dissipated within 15 to 30 minutes after discontinuation of the infusion. In addition, the probability of conversion to sinus rhythm with esmolol appears to be better than with other agents such as verapamil.[95]

ANTICOAGULANTS.

Epidemiological observations suggest that the development of postoperative AF is associated with a marked increase in the risk of stroke (odds ratio 3.0) and prolonged

hospitalization.[50] [51] [52] No consensus has been reached regarding anticoagulation recommendations in patients with postoperative AF. The risk of hemorrhage in the early postoperative period must be weighed against the risk of systemic thromboembolism.[96] When AF develops beyond the second postoperative day, we generally advocate adherence to the guidelines established for nonsurgical patients and initiate anticoagulation (intravenous heparin followed by oral warfarin) in patients who have been in the arrhythmia for more than 48 hours, especially if the patient has a history of systemic embolism or if mitral valve disease or cardiomyopathy is present.[97]

Beyond control of the ventricular rate acutely, the two treatment strategies for management of postoperative AF are similar to those

Figure 60-8 Epicardial electrodes in patients undergoing cardiac surgery. The precise number and location of pacing wires may vary among institutions and also by the complexity of the operation (e.g., no atrial wires for routine coronary artery bypass surgery but both atrial and ventricular wires for valve surgery). In the example shown, the two atrial wires exit to the patient's right while the ventricular wires are the first two leads exiting to the patient's left; the subcutaneous ground wire is the one closest to the left anterior axillary line.

Figure 60-9 Recording of electrocardiographic leads II and III in a patient with atrial flutter. Panels *A* and *B* are not continuous tracings. The dots in *A* mark the onset of rapid atrial pacing at 350 beats/min with a pacing stimulator capable of high drive rates. The morphology of the atrial complexes changes dramatically such that by the end of the trace in *A,* the atrial complexes are positive in leads II and III. Panel *B* shows the termination of 30 seconds of atrial pacing at 350 beats/min. The circles represent the last paced atrial beat. With abrupt termination of the rapid atrial pacing, sinus rhythm appears. S = stimulus artifact. Time lines are at 1-second intervals. (From Waldo AL, MacLean WAH: Diagnosis and Treatment of Cardiac Arrhythmias Following Cardiac Surgery. Mt Kisco, NY, Futura, 1980.)

for nonsurgical patients: chronic anticoagulation while administering rate-controlling agents versus restoration of sinus rhythm and attempts at suppression of recurrence of AF. Because large-scale clinical trial data are not available to guide decision-making in this area, therapeutic approaches must be individualized.[96] Ibutilide, a class III antiarrhythmic agent, has been shown to be effective in the acute conversion of post-CABG AF when administered intravenously, albeit with a small risk (<2 percent) of torsades de pointes.[98] Procainamide is frequently used for the treatment of AF after open-heart surgery, although present evidence indicates that it has limited effectiveness in suppressing recurrence of AF.[99] Furthermore, any treatment decision formulated during hospitalization should be readdressed at the first postoperative visit (typically 4 to 6 weeks) to determine whether it is still a desirable course of action once the inflammation and metabolic alterations of the postoperative state have dissipated.

Patients with depressed left ventricular function or striking ventricular hypertrophy who

experience troublesome dyspnea and/or hypotension when in AF postoperatively are suitable candidates for a trial of restoration of sinus rhythm.

Permanent suppressive antiarrhythmic therapy is often necessary in patients with rheumatic heart disease and a preoperative history of AF despite successful aortic or mitral valve surgery even if sinus rhythm is present during the early postoperative period.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA.

The reentrant forms of paroxysmal supraventricular tachycardia (PSVT)--atrioventricular nodal reentry tachycardia and atrioventricular reentry tachycardia--occur less frequently in postoperative patients than does AF or atrial flutter but, fortunately, retain their responsiveness to vagal maneuvers and pharmacotherapy designed to inhibit atrioventricular nodal conduction. The antiarrhythmic agent adenosine, an endogenous nucleoside, has a number of features that make it the drug of choice for treating PSVT in postoperative patients.[100] A rapid (2 seconds) intravenous bolus of 6 mg terminates about 60 percent of episodes of PSVT within 20

seconds; a subsequent bolus of 12 mg administered 1 to 2 minutes later terminates PSVT in virtually all patients who failed to respond to the lower dose. Because adenosine is rapidly transported into the cell or degraded enzymatically to inosine, the physiological effects of adenosine are dissipated in less than 5 minutes. Untoward reactions such as flushing, chest pain, or dyspnea, although common, are mild and short-lived.

PSVT may also be diagnosed by atrial recordings and terminated by burst atrial pacing or randomly delivered ventricular or atrial premature depolarizations that invade the reentrant circuit and interrupt the arrhythmia.

Ventricular Arrhythmias

VENTRICULAR PREMATURE DEPOLARIZATIONS.

Isolated ventricular premature depolarizations (VPDs) commonly occur after cardiac surgery. An increase in the density of VPDs may be seen in patients with a preoperative history of VPDs, or they may appear de novo in patients with no history of ventricular arrhythmias. Although a fall in arterial pressure may be associated with isolated VPDs, this decreased pressure is usually extremely brief and of no significant hemodynamic consequence to the patient unless prolonged periods of bigeminy occur.

Management.

We advocate a conservative approach focusing on prompt detection and correction of provocative factors, liberal use of beta blockers in patients with an ejection fraction greater than 30 percent, overdrive atrial or atrioventricular sequential pacing between 85 and 100 beats/min, and restriction of suppressive antiarrhythmic therapy to patients with a preoperative history of serious ventricular tachyarrhythmias.[52] If the decision is made to suppress VPDs in a patient without a history of symptomatic ventricular arrhythmias, the treatment period should be brief (6 to 24 hours) and the patient should not be automatically converted to treatment with an oral antiarrhythmic drug regimen without careful reconsideration of the indications for treatment.

VENTRICULAR TACHYCARDIA.

Many of the same arguments cited above for isolated VPDs can be applied to paroxysms of nonsustained VT. No definitive guidelines are available, but we believe that symptomatic episodes of nonsustained VT in the absence of correctable factors and attempts at overdrive atrial or atrioventricular sequential pacing are indications for antiarrhythmic therapy, especially if the episodes are associated with hemodynamic compromise. *Sustained VT* is a serious emergency that should be handled in an orderly approach. If the clinical situation permits, a 12-lead ECG should be obtained for future reference and confirmation of the diagnosis; simultaneous recording of surface ECG leads with electrograms from the epicardial wires may be helpful in establishing the mechanism of a wide complex tachycardia.

Attempts at acute conversion of the tachycardia include the following maneuvers in the sequence listed: thumpversion, burst ventricular pacing, and boluses of antiarrhythmic agents (lidocaine 100 mg, procainamide up to 500 to 1000 mg over a period of 20 minutes, amiodarone 75 to 150 mg infused over a 10-minute period, or bretylium 500 to 1000 mg over a period of 5 to 10 minutes). In urgent circumstances, synchronized direct-current cardioversion with a low-energy shock (25 to 50 watt-seconds) may be used. Unsynchronized shocks of 100 to 200 watt-seconds should be administered if the tachycardia rate is greater than 160 beats/min and/or has a sinusoidal waveform on ECG. After conversion, a search for correctable disorders should be undertaken, and if none is found, a continuous infusion of lidocaine (2 mg/min), procainamide (2 mg/min), amiodarone (1.0 mg/min for 6 hours followed by a maintenance infusion of 0.5 mg/min), or bretylium (1 to 2 mg/min) is started.

VENTRICULAR FIBRILLATION.

As in nonsurgical patients, ventricular fibrillation (VF) must be promptly treated with an unsynchronized direct-current shock. VF can often be reverted with shocks of 200 watt-seconds, provided that the intervention is performed promptly. It should be possible to defibrillate postoperative patients in the ICU expeditiously; therefore, the higher energies (360 to 400 watt-seconds) used in the "field" are probably unnecessary--at least initially. Because of the small number of patients experiencing unexpected sustained, hemodynamically compromising VT or VF, epidemiological data on provocative factors and the prognosis of these arrhythmias are difficult to evaluate.[52] [101] [102] Unexplained VT or VF occurring within 24 hours after CABG surgery is

associated with very high in-hospital mortality, probably resulting from perioperative ischemia, infarction, and/or pump failure.[101] Episodes of VT or VF occurring more than 24 hours after bypass surgery have a slightly less ominous prognosis and may be due to reperfusion of previously ischemic zones, early postoperative occlusion of coronary bypass grafts, or transmembrane shift of electrolytes during the process of recovery.[103] [104]

Risk stratification of patients experiencing VT or VF postoperatively should include assessment of left ventricular function, coronary arteriography if ischemia/infarction is suspected, and consideration of an electrophysiological study to establish the most appropriate course of therapy.[105] Because of the numerous metabolic fluxes taking place in the early postoperative period, electrophysiological study should, if possible, be postponed until at least 5 to 7 days following surgery.[52] Serious consideration should be given to use of an implantable cardioverter-defibrillator in patients without an identifiable reversible cause of their arrhythmia, particularly those with a depressed ejection fraction.

ATRIOVENTRICULAR JUNCTIONAL RHYTHMS.

Nonparoxysmal atrioventricular junctional rhythms (rate >45 beats/min) can be seen after mitral or aortic valve surgery. Trauma and tissue swelling from surgical debridement and suture placement are believed to be the provocative mechanisms. Such rhythms are typically transient (
48 hours) and easily treated with atrial or atrioventricular sequential pacing at a rate above that of the intrinsic junctional mechanism.[106]

Bradyarrhythmias

Sinus bradycardia or sinus arrest with emergence of a slow atrioventricular junction escape rhythm may be seen postoperatively when one or more of the following factors are present: advanced age, hypothermia, drug effects (diltiazem, beta blocker, digitalis, procainamide), preoperative sinus node dysfunction, intraoperative trauma to the sinus node, and postoperative elevation in vagal tone.[107] In addition to modifying the dose or discontinuing the use of offending drugs (such as those noted above), atrial pacing at 85 to 100 beats/min should be initiated to maintain adequate cardiac output and urine flow.

Although a new conduction defect may develop in up to 45 percent of patients following cardiac surgery, the majority are usually transient and related to the extensive use of cold cardioplegia, hypothermia, perioperative electrolyte shifts, or surgical trauma during valve repair/replacement or closure of septal defects.[108] [109]

MANAGEMENT.

The decision to insert a permanent pacemaker (see Chap. 24) after cardiac surgery should be based on the hemodynamic consequences of bradycardia in the individual patient rather than on a specific heart rate. Most new conduction defects resolve in the early postoperative period, but some persist for as long as 2 weeks. Few data are

available to guide the decision about timing of implantation of a permanent pacemaker. We are willing to monitor a younger patient (<65 years) following CABG surgery with a temporary pacing system postoperatively to see whether a conduction defect resolves. However, we have a low threshold for implanting a permanent pacemaker following aortic or mitral valve surgery or if antiarrhythmic therapy or beta-blocker treatment is contemplated because these pharmacological measures might "stress" a diseased conduction system. We advocate early insertion of a permanent pacemaker in elderly patients with symptomatic

bradycardia because the recuperative process is facilitated, the period of relative immobilization and ECG monitoring is minimized, and hospital stay is shortened.[110] Finally, we are more aggressive about implantation of permanent pacemakers in patients with persistent advanced atrioventricular block than in to patients with isolated sinus bradycardia.

CARDIOVERSION.

Direct-current cardioversion should be used in postsurgical patients with the following additional considerations. The recent cardiotomy with resultant pericardial and mediastinal inflammation, the presence of chest tubes and/or pleural effusions, and elevated catecholamine levels after surgery may all contribute to higher energy requirements for reversion of arrhythmias such as AF than are commonly required in patients who have not recently undergone cardiac surgery. To achieve the maximum transcardiac spread of current after median sternotomy, the anterior paddle should be placed to the *right* of the sternum between the third and sixth intercostal space, and the other paddle should be positioned in the fourth to sixth intercostal space as far in the left axilla as possible or in a posterior location under the tip of the left scapula. Firm pressure is applied to the paddles to maintain contact with the chest wall as the discharge buttons are depressed.

Hemostatic Disturbances (See Chap. 62)

Multifactorial derangement of the hemostatic system develops in all patients who undergo cardiopulmonary bypass. These abnormalities are caused by exposure of the blood to artificial surfaces, hemodilution, and the effects of heparin[111] [112] [113] [114] [115] (Table 60-8) . Platelet dysfunction is the most significant hemostatic abnormality that occurs after cardiopulmonary bypass, although diminution of coagulation factor levels may assume greater significance in patients with preoperative deficiencies in hemostasis. Administration of the following drugs before surgery may predispose the patient to excessive bleeding: aspirin and other antiplatelet agents, nonsteroidal antiinflammatory agents, thrombolytic agents,[113] certain antibiotics (carbenicillin, ticarcillin, moxalactam, cefamandole, third-generation cephalosporins), dextran, amrinone, quinidine, cytotoxic agents, gold, phenylbutazone, and fish oils.[113]

MANAGEMENT.

The most obvious evidence of bleeding in a postoperative cardiac surgical patient is by means of chest tube drainage. "Acceptable" rates of bleeding are usually less than 100 ml/hr. In our institution, guidelines for returning to the operating room because of excessive bleeding include more than 500 ml/hr for 1 hour, more than 300 ml/hr for 3 hours, and 200 to 300 ml/hr for 5 hours. These guidelines may be tempered by correctable extenuating circumstances, such as uncontrolled hypertension postoperatively, failure to achieve normothermia, or an abnormal coagulation status that is being corrected. Emergency medical maneuvers that can be attempted after sending coagulation studies to the laboratory include the use of PEEP up to 10 cm H_2O for mediastinal tamponade, empirical "correction" of putative platelet dysfunction with desmopressin acetate (DDAVP, a synthetic analog of arginine vasopressin that increases plasma levels of von Willebrand factor) 0.3 mug/kg infused over a period of 15 to 30 minutes, and empirical administration of a small dose of protamine sulfate 25 to 50 mg because heparin may be liberated from the patient's fat stores as rewarming occurs.[116]

Once the coagulation profile returns, additional therapy in the form of platelet transfusions for a platelet count less than 100,000/mm[3] and fresh frozen plasma to correct an elevated prothrombin time can be prescribed. Aprotinin therapy (2×10^{5} KIU loading bolus followed by infusion of 0.5×10^{5} KIU/hr for 4 hours) is helpful in cases of excessive postoperative bleeding by virtue of its ability to inhibit fibrinolysis and replenish platelet glycoprotein Ib receptors and von Willebrand factor activity.[117] [117A] When monitoring bleeding from a chest tube, it is important to be alert to sudden cessation of hemorrhage, which may indicate that the chest tubes have clotted and the fluid is now draining into the mediastinum or the pleural spaces. Serial chest radiographs may be helpful while observing a patient during a bleeding episode. With correct medical management, less than 5 percent of patients need to return to the operating room for control of bleeding, preferaby within 3 to 4 hours of the original surgery, before hemodynamic destabilization occurs and large volumes of blood products are administered.

ANTITHROMBOTIC THERAPY IN CARDIAC SURGICAL PATIENTS.

A wide spectrum of patients recovering from cardiac surgery may require either short- or long-term antithrombotic therapy[118] (Table 60-9) . Furthermore the intensity of therapy will be dictated by the estimated risk of thromboembolism. Variables that may have an impact on the risk of thromboembolism include insertion of a prosthetic valve (mechanical more than bioprosthetic), valve location (mitral more than aortic), the presence of AF, size of the left atrium, history of thromboembolism, left atrial thrombi visualized at surgery, and ventricular wall motion abnormalities associated with mural thrombi.

TABLE 60-8 -- HEMOSTATIC DISTURBANCES FOLLOWING CARDIOPULMONARY BYPASS

ABNORMALITY	CAUSE
Exposure of blood to artificial surfaces	
1.Platelet dysfunction A. Prolonged bleeding time B. Decreased adhesiveness	1. Depletion of platelet alpha granules, reduced response to wounds, and increased plasma levels of platelet factor 4 and beta-thromboglobulin[111]
2. Inflammatory response	2. Activation of the complement, coagulation, fibrinolytic, and kallikrein cascades; activation of neutrophils with degranulation and protease enzyme release; oxygen free radical production; and synthesis of cytokines (tumor necrosis factor, interleukin-1, interleukin-6, interleukin-8)
Hemodilution	
1. Thrombocytopenia	1. Priming of extracorporeal bypass circuit with crystalloid solutions. Heparin-mediated immune thrombocytopenia may occur in about 5% of patients*
2. Coagulation factor depletion	2. Most coagulation factor levels are reduced by hemodilution by about 50%; factor V is reduced to 20-30% of normal and factor VIII is relatively unaffected. Factor levels usually return to normal within 12 hr after completion of cardiopulmonary bypass. Although plasminogen and fibrinogen levels are decreased by about 50%, fibrin degradation products usually do not appear in the plasma during bypass[113]
Heparinization	Thrombus formation is inhibited and excessive bleeding is avoided intraoperatively by maintaining the activated clotting time between 400 and 480 sec

*Note: reversal of heparin effects is accomplished with protamine sulfate. Vascular collapse has been reported in some patients during protamine treatment. To avoid the problem of heparin-induced thrombocytopenia and because heparin may not effectively inhibit all the thrombin generated during cardiopulmonary bypass ("heparin rebound"), novel antithrombins are being evaluated as alternatives to heparin during surgery.[114] [115]

TABLE 60-9 -- ANTICOAGULATION GUIDELINES FOR ANTITHROMBOTIC THERAPY IN CARDIAC SURGERY PATIENTS

SURGERY	ANTICOAGULANT	INR**
Mitral mechanical valve	Warfarin	2.5-3.5
Aortic mechanical valve	Warfarin	2.0-3.0
Tricuspid mechanical valve	Warfarin	2.5-3.0
Atrial fibrillation	Warfarin	2.0-2.5
Mitral tissue valve	Warfarin	2.0-3.0 for 6 wk
Mitral valve repair	Warfarin	2.0-2.0 for 6 wk
Tricuspid tissue valve	Warfarin	2.0-3.0 for 6 wk
Tricuspid repair	Warfarin	2.0-3.0 for 6 wk
LV thrombus	Warfarin	2.0-3.0 for 6 mo
LV aneurysm repair	Warfarin	2.0-3.0 for 6 wk
Aortic tissue valve	Aspirin (80 mg/d)	
Coronary artery bypass	ASA 325 mg/d, 81 mg/d if taking Coumadin	

ASA=acetylsalicylic acid (aspirin); LV=left ventricular.

*The target international normalized ratio is the midpoint of the range.

Infection

FEVER.

Despite its nonspecific nature, fever is the most common initial clinical sign of a postoperative infection.[119] It should be emphasized, however, that patients who experience a normal course of convalescence continue to show an elevated temperature for up to 6 days postoperatively.[120] In the absence of infection, such early fevers are believed to be caused by alterations in blood components after cardiopulmonary bypass. In addition to infectious causes, fevers that occur beyond 6 days may be due to drug reactions, phlebitis at the site of intravenous lines, atelectasis, pulmonary emboli, or the postpericardiotomy syndrome.

WOUND AND INCISION

Leg.

Infections of the leg wound are typically manifested by fever, induration, pain, erythema, local warmth, and drainage from the suture line. The usual infectious agents include *Staphylococcus, Streptococcus,* and aerobic gram-negative bacilli. Wound aspiration and Gram stain should be used to guide antibiotic treatment. More advanced cases

require wound debridement and open drainage. Techniques of minimally invasive saphenous vein harvesting now make it possible to avoid a long leg incision, which decreases the risk of postoperative leg infection[120A] (Fig. 60-10) .

Recurrent bacterial cellulitis in the leg used for saphenous vein harvest may be a recalcitrant problem that appears months to years after surgery. Antibiotic courses directed against staphylococcal and streptococcal species for each individual occurrence may be insufficient, and a long-term course of antibiotic therapy may be needed. It is important to search for evidence of superficial fungal infections in the affected leg because persistent tinea pedis infection has been reported to cause recurrent lower extremity cellulitis.[121] If a fungal infection is identified, treatment with topical miconazole or clotrimazole should be given in addition to antibacterial therapy.

Mediastinitis.

Mediastinitis and sternal osteomyelitis are among the most serious complications of median sternotomy.[37] [122] If one excludes operations that occur after thoracic trauma, it is estimated that mediastinitis occurs in about 2 percent of patients who undergo median sternotomy.

Most cases of mediastinitis occur within 2 weeks after sternotomy. Important diagnostic features of patients in whom mediastinitis

Figure 60-10 Minimally invasive approaches to saphenous vein harvesting have significantly reduced incisional morbidity. Traditional harvesting requires long leg incisions (*A*), as compared with the less invasive videoscopic harvesting (*B*). A dissection cannula is introduced through a small incision (*C*), and branches are later divided (*D*) under videoscopic guidance.

develops early after cardiac surgery include persistent fever in excess of 101°F beyond the fourth postoperative day, a systemic toxic condition, leukocytosis, bacteremia, and a purulent discharge from the sternal wound. Recognition of mediastinitis requires a high index of suspicion and a vigorous, repetitive search for evidence of sternal wound drainage in patients who are persistently febrile late into the first week after surgery and who have no other obvious focus of infection, such as pneumonia or urinary tract infection.[123] The diagnosis can be confirmed by needle aspiration from the subxiphoid approach followed by Gram's stain and culture.

Risk Factors and Diagnosis.

Risk factors for the development of mediastinitis include prolonged cardiopulmonary bypass time, excessive postoperative bleeding with reexploration for control of hemorrhage, and diminished cardiac output in the postoperative period. The incidence

of mediastinitis is increased when both internal mammary arteries are mobilized bilaterally for use as bypass conduits.[124] Therefore, many surgeons prefer to use only the left internal mammary artery, particularly in elderly diabetic patients, who may already be predisposed to delayed sternal wound healing.

The spectrum of microorganisms that cause mediastinitis includes *Staphylococcus* (*aureus* and *epidermidis*) in about 50 percent of patients and a variety of gram-negative bacilli in about 40 percent of cases.[123] [124] [125] Mixed infections and fungal infections are rare. The organism isolated frequently is resistant to the prophylactic antibiotic used preoperatively, especially if the isolate includes a gram-negative bacillus or a beta-lactamase-producing *S. aureus.*

DIAGNOSIS OF STERNAL WOUND INFECTION.

Definitive diagnosis requires exploration of the wound and culture of suspicious areas. In the past, closed (debridement, reclosure, and antibiotic irrigation) and open (debridement, packing, closure by secondary intent) approaches were commonly used. To facilitate functional recovery, we now favor early plastic surgical flap techniques to allow for immediate primary closure with vascularized tissue.[126] [127] Regardless of the sternal closure strategy used, bacterial-specific intravenous antibiotics are typically administered for 6 weeks.

INFECTIVE ENDOCARDITIS (see Chap. 47)

It has been convincingly shown that perioperative antibiotic prophylaxis is of benefit in patients undergoing cardiac surgery.[128] Although the antibiotic regimen varies, in part related to local differences in microbiological flora and personal preference, it is directed against gram-positive cocci (the most frequent causative pathogens in infections after cardiac surgery) and usually contains a cephalosporin. The regimen used in our institution consists of 1 gm of cefazolin intravenously 30 minutes before the skin incision and then repeated at 8-hour intervals for 48 hours after surgery.

PROSTHETIC VALVE ENDOCARDITIS (see Chaps. 46 and 47) .

Prosthetic valve endocarditis is a rare, but extremely serious complication of cardiac surgery, frequently arising from nosocomial bacteremias.[129] [130] It is estimated to occur in only 2 to 4 percent of patients; about half of the cases are classified as "early" (<60 days from the date of surgery) and half as "late" (>60 days from the date of surgery).[129] [130] [131] Pooled data from several series indicate that the organism responsible for early prosthetic valve endocarditis includes a *Staphylococcus* species in about 50 percent of cases.[131] The remainder of early cases of prosthetic valve endocarditis are caused by gram-negative bacilli, diphtheroids, and fungi.

Management.

Features of prosthetic valve endocarditis that have been associated with increased mortality include invasive infection (i.e., extension into the myocardium), congestive

heart failure resulting from dysfunction of the prosthesis, and the presence of antibiotic resistant, virulent microorganisms or a fungal organism.[131] Appropriate antibiotic therapy for prosthetic valve endocarditis is discussed in Chapter 47 .

VIRAL.

Viral infections that occur after cardiac surgery are almost exclusively the result of infectious complications of transfusion therapy and, with the exception of human immunodeficiency virus, primarily result in hepatitis. The incidence of viral infections after cardiac operations is decreasing as a result of a reduction in the number of transfusions of blood bank products (e.g., cell saver techniques and preoperative autologous blood donations) and improved screening techniques in contemporary blood bank practice. Cytomegalovirus infection is a febrile syndrome that typically occurs 1 month postoperatively. It is characterized by high-spiking fevers, abnormalities in liver function test results, and arthralgias. A self-limited illness, it is best treated with antipyretics and supportive fluid therapy.

FUNGAL.

Fungal infections that involve the heart are rare. They are typically seen in cases of fungemia and are usually fatal. Although the problem of fungemia is well described in immunocompromised hosts (e.g., heart transplant recipient), in an autopsy study of 60 patients with fungal infections of the heart, 25 percent of cases occurred in association with conventional valvular surgery.[132] About half of fungal infections of the heart are confined to the endocardium, and half involve both the endocardium and the myocardium. Extracardiac involvement is common, with spread of infection to the lungs, cerebrospinal fluid, urine, and skin. The most commonly encountered organisms, in descending order of frequency, are *Candida, Aspergillus,* and *Cryptococcus* species. Patients who appear to be at particular risk of fungal involvement of the heart are those who have received corticosteroids and long courses of antibiotic treatment postoperatively.

Peripheral Vascular Complications

Most adults who undergo cardiac surgery--especially coronary revascularization--have atherosclerosis of the peripheral vasculature (e.g., ileofemoral system) and may experience lower extremity ischemia after surgery because of low flow in the perioperative period with in situ thrombosis, embolism from the heart or aorta, or vascular compromise from an intraaortic balloon pump catheter. Management consists of anticoagulation and removal of indwelling catheters, if clinically feasible. Thrombectomy and even revascularization surgery of the lower extremities (e.g., femorofemoral, femoropopliteal, or axillofemoral bypass) may be required to salvage threatened limbs.

Asymptomatic deep venous thrombosis of the calf can develop before hospital discharge in about one-third to one-half of patients who receive saphenous vein bypass grafts. Occasionally, these thrombi propagate to the proximal leg veins; only rarely do

they cause massive pulmonary embolism.[30] [133] The best strategy is rigorous perioperative prophylaxis against venous thromboembolism in all such patients. Low-molecular-weight heparin (e.g., enoxaparin 30 to 40 mg subcutaneously every 12 hours) appears to be efficacious.

Other Complications

PERICARDITIS (see Chap. 50) .

Postoperative tamponade is discussed on p. 55 . Pericardial friction rubs are frequently audible in the early postoperative period and are probably the result of mechanical irritation from the mediastinal chest tubes. They usually disappear by the second or third postoperative day and are asymptomatic because of the narcotic analgesics prescribed at that stage of recovery. Although pericardial rubs develop in some patients toward the end of the first postoperative week, they are usually benign, do not indicate a need for prolongation of hospitalization, and do not require treatment. A separate clinical syndrome that appears late in the first postoperative month is the *postpericardiotomy syndrome.* [134] The relationship between postpericardotomy syndrome and chronic constrictive pericarditis is not firmly established, but a number of patients with *postoperative constrictive pericarditis* have a history of postpericardiotomy syndrome.

RENAL FAILURE (see Chap. 72) .

All patients who undergo cardiac surgery experience a reduction in renal blood flow and the glomerular filtration rate (GFR) as a consequence of both anesthesia and cardiopulmonary bypass. Risk factors for the development of persistent renal failure after cardiac surgery include a preoperative history of renal dysfunction or left ventricular dysfunction, prolonged bypass time (>180 minutes), prolonged aortic cross-clamping (>60 minutes), perioperative hypotension, advanced age (>70 years), and the development of medical complications postoperatively.[135]

Most cases of acute renal failure after cardiac surgery result from renal ischemia that lowers the GFR directly (prerenal disease) or, if severe or prolonged, can induce acute tubular necrosis. Possible additional contributory factors include sepsis, nephrotoxic drugs, radiocontrast material injection, cholesterol plaque embolization in the renal circulation, increased urine free hemoglobin levels from hemolysis while undergoing cardiopulmonary bypass, and the effects of ACE inhibitors on glomerular capillary pressure.[136] The detrimental effects of ACE inhibitors are most likely to occur when renal perfusion pressure is low because of renal artery stenosis or systemic hypotension caused by cardiac failure.

Urine output is variable in patients with postoperative acute renal failure. Anuria is uncommon and, if present, should raise the suspicion of urinary tract obstruction (e.g., occluded Foley catheter). More commonly, patients are either oliguric (<400 mg/d) or nonoliguric. Oliguric acute renal failure occurs less frequently than nonoliguric renal failure, usually reflects more severe renal injury, and is associated

with a greater probability of requiring dialysis during the acute phase.[136]

Differentiation Between Prerenal Azotemia and Acute Tubular Necrosis.

Important diagnostic studies in all patients with acute renal failure include urinalysis and estimation of pulmonary capillary wedge pressure and cardiac output by means of pulmonary artery catheterization. Prerenal azotemia should be suspected if the urine sodium level is less than 20 mEq/liter, the fractional excretion of sodium is less than 1 percent, and urine osmolality is greater than 500 mOsm/liter. Acute tubular necrosis should be suspected if the urine sodium level is greater than 40 mEq/liter, fractional excretion of sodium is greater than 2 percent, and urine osmolality is less than 350 mOsm/liter.[136]

Treatment.

Essential elements of therapy for both prerenal azotemia and acute tubular necrosis include optimization of intravascular fluid volume and cardiac output. The latter is best accomplished with vasodilators and inotropic agents rather than vasopressors to avoid further reductions in renal blood flow. Experimental studies suggest that several modalities may protect against the development of progressive renal failure in models of acute renal ischemic injury (e.g., renal artery clamping that simulates the effects of suprarenal aortic cross-clamping while undergoing cardiopulmonary bypass). Mannitol (which washes out obstructing casts), a loop diuretic (which decreases energy requirements in the thick ascending limb of the loop of Henle, thereby decreasing ischemic injury), and the combination of dopamine and atrial natriuretic peptide (but neither alone) have all been effective.[137]

It is prudent to undertake a trial of furosemide and mannitol (only if the patient can tolerate the volume load of the latter) within the first 12 to 24 hours after the development of oliguria. The aim of such therapy is to increase urine output. Because of the renal vasodilating effects of dopamine (2 to 3 mug/kg/min), patients with both oliguric and nonoliguric renal failure may experience an increase in urine output.[138]

If oliguria persists beyond 12 hours, a number of supportive measures must be initiated, including careful attention to electrolyte balance, specifically avoiding hyperkalemia; avoidance of excessive free water administration, which might lead to hyponatremia; correction of acidosis (adding bicarbonate to daily fluids); and adjustment of medication dosages for delayed excretion if the drug is cleared by renal mechanisms. Analysis should be carried out for pericarditis, refractory hyperkalemia, uremic encephalopathy, or colitis. Continuous arteriovenous hemofiltration can be used to remove excess fluid.

Cardiac Surgery in Patients with Chronic Renal Failure.

Patients with chronic renal failure who undergo surgery have an increased risk of exacerbation of renal dysfunction perioperatively. Deterioration in renal function may require temporary or even permanent hemodialysis, and these eventualities should be addressed with the patient and the cardiac surgical team preoperatively. Surgery can be safely performed in patients who are already maintained by hemodialysis, but careful coordination of the surgical and dialysis schedules is essential to minimize postoperative problems with fluid and electrolyte management.

GASTROINTESTINAL COMPLICATIONS.

Serious gastrointestinal complications after cardiac surgery [139] , [140] are rare (occurring in about 1 percent of patients) and can usually be handled by a conservative approach. Only about 0.5 percent of patients who undergo cardiac surgery require a general surgical operation for a gastrointestinal complication.[140] [141] Patients with circulatory compromise and those who require intraaortic balloon pump support are more likely to have gastrointestinal complications. Despite their relative rarity, gastrointestinal complications are associated with significant mortality (approaching 40 percent in some series), thus highlighting the need for careful monitoring and repeated physical examination in high-risk patients.[139] [140] Most complications occur within 7 days of surgery.

NEUROLOGICAL COMPLICATIONS.

Neurological complications after cardiac surgery are quite common, particularly in the elderly, if one is attentive to the subtle cognitive (short-term memory loss, lack of concentration) and psychological (depression, increased sense of dependency) changes seen early after surgery.[22] [142] [142A] A positive and supportive attitude on the part of the staff and enlistment of the aid of family members help minimize these problems. Although many patients return to their postoperative state by 4 to 6 weeks after surgery, about 10 percent continue to show deterioration in neuropsychological functioning over the next 6 months, especially if they are older than 65.[22] [142] More serious neurological complications such as stroke occur in 1 to 5 percent of patients but may be seen in as many as 10 percent of patients older than 65.[22]

Symptomatic visual defects may be seen after cardiac surgery and result from retinal emboli, occipital lobe infarction, or anterior ischemic optic neuropathy. Risk factors for cerebrovascular accident (CVA) or transient ischemic attack (TIA) after cardiac surgery include preoperative carotid bruit, previous CVA or TIA, postoperative AF, prolonged cardiopulmonary bypass (>2 hours), and preoperative left ventricular mural thrombus.[22] [143]

Neuropathies in the upper extremities have been reported after cardiac operations. A pattern of injury involving predominantly the ulnar nerve and medial antebrachial cutaneous nerve suggests that the lesion involves brachial plexus compression or a traction injury.[144] The average duration of symptoms after such an injury is 2 months, but some patients show a slower time course of improvement extending over 6 to 12

months.

REHABILITATION AND PREPARATION FOR DISCHARGE (see Chap. 39)

A coordinated, multidisciplinary cardiac exercise program is essential to overcome the physical deconditioning and psychosocial upheaval associated with cardiac surgery. Emphasis should be placed on early mobilization and progressively more patient self-care, including initiation of these measures in the ICU during the first 24 hours postoperatively. After transfer out of the ICU, the patient should be encouraged to engage in low-density (2 to 3 METS) isotonic activities such as walking and range-of-motion exercises.[145] The nursing staff should monitor the patient's progress while being alert to any undue accelaration in heart rate (>120 beats/min) or hemodynamically compromising arrhythmias.

Patients should also participate in an education program focusing on instructions regarding postoperative medications and initiation of secondary measures targeted at preventing graft occlusion and progression of atherosclerosis.[60] [146] [147] Because of the overwhelming evidence indicating that platelet inhibition is critical to prevention of graft occlusion, all patients undergoing bypass surgery should receive long-term therapy with aspirin unless contraindicated. Ticlopidine may be useful in aspirin-intolerant patients, but there is no evidence of significant benefit from the routine use of either dipyridamole or sulfinpyrazone. Fast-track discharge protocols are now standard, and uncomplicated patients are typically discharged on the fifth postoperative day.[148]

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Chapter 61 - General Anesthesia and Noncardiac Surgery in Patients with Heart Disease

LEE GOLDMAN
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The cardiovascular system of patients undergoing general anesthesia and noncardiac surgical procedures is subject to numerous stresses owing to depression of myocardial contractility and respiration as well as fluctuations in temperature, arterial pressure, ventricular filling pressures, blood volume, and activity of the autonomic nervous system. Complications of anesthesia and operation, such as hemorrhage, infection, fever, pulmonary embolism, and myocardial infarction, impose additional burdens on the cardiovascular system. Patients who have cardiac disease and who are compensated preoperatively may be unable to meet these increased demands during the perioperative period, in which case arrhythmias, myocardial ischemia, and/or heart failure may develop.[1] [2] [3] As a consequence, a substantial proportion of all deaths in most series of noncardiac operations results from cardiovascular complications.

Because both the frequency and the seriousness of cardiovascular complications of general anesthesia and operation are considerably increased in patients with known cardiovascular disease, the magnitude of these risks must be appreciated to decide on the advisability of noncardiac surgery in cardiac patients. In addition, both the life

expectancy and the quality of life of patients must be taken into account. For instance, a noncardiac surgical procedure with a high risk, directed to correct a disorder that is not life threatening, may be difficult to justify if the patient's cardiac condition precludes a survival period sufficient to allow the patient to reap the benefits of the operation. Obviously, the dangers and disability of the disease for which an operation is being proposed must also be balanced against the risk of the operation itself.

ANESTHESIA

Changes in cardiovascular function during general anesthesia are due to many factors, including direct effects of the anesthetic agent(s) and indirect effects mediated primarily through the autonomic nervous system. In addition, if respiration is inadequately maintained, the resulting hypoxemia, hypercarbia, and acidosis may further depress myocardial contractility and increase cardiac irritability. The interplay of these several variables may produce changes in arterial and central venous pressures, cardiac output, and rate and rhythm. To minimize the risk of operation in patients with a compromised cardiovascular system, it is essential to minimize these changes.[3]

The choice of the anesthetic approach and the specific anesthetic agents to be used should be made by a qualified anesthesiologist, commonly after careful evaluation of the patient's medical and cardiac condition and often after consultation with the surgeon and the internist or cardiologist. Different anesthesiologists may prefer different anesthetic techniques, and the anesthesiological literature clearly indicates that there is little, if any, correlation between the anesthetic route or agents and the likelihood of major clinical complications. Thus, the skill and experience of the anesthesiologist, including the ability to monitor hemodynamics and respond quickly, are far more important than the specific agent or technique that is used. Although the cardiological consultant should not expect to dictate the anesthetic approach, the quality of the consultation will be improved if the consultant appreciates the clinical pharmacology of the anesthetic agent.

General Anesthesia

The induction of general anesthesia is usually accomplished with intravenous anesthetics. The common agents used for the induction of anesthesia, barbiturates and benzodiazepines, lower systemic arterial pressure by about 20 to 30 percent in healthy patients but sometimes by a greater amount in hypertensive patients.[3] Barbiturates reduce blood pressure through depression of myocardial contractility and sympathetic tone. Benzodiazepines act primarily by venodilation and have a more modest effect on blood pressure. Ketamine, a phencyclidine derivative, stimulates the sympathetic nervous system and thus does not lower blood pressure but can increase myocardial oxygen demand. It is most often used in severely hypovolemic patients. During laryngoscopy and tracheal intubation, blood pressure can increase by 20 to 30 mm Hg.[3] Such increases can be avoided by adequate topical anesthesia because the hypertension appears to be caused by the laryngoscopy rather than by the passage of a tube into the trachea. Maintenance of general anesthesia can be achieved with inhalational or intravenous agents. In most cases, a combination of agents is used, so-called balanced anesthesia.

INHALATION AGENTS.

These agents enter the bloodstream by way of the alveoli and are excreted across the

alveoli essentially unchanged. The predominant hemodynamic effects of the commonly used inhalational agents (halothane, enflurane, and isoflurane) are depression of myocardial contractility and reduction in arterial blood pressure.[4] Nitrous oxide also decreases myocardial contractility but does not result in significant hypotension because of reflex vasoconstriction. Although the physiological and pharmacological properties of the inhalational agents differ slightly, no single agent has been shown to be appreciably safer in patients with cardiac disease.[5] [6] [7] [65A]

INTRAVENOUS ANESTHETICS.

Narcotics are the principal intravenous agents used for maintenance of general anesthesia. Most narcotics cause some degree of hypotension through venodilation, with little effect on myocardial contractility. The short-acting agents fentanyl, sufentanyl, and alfentanyl are less likely to cause hypotension than morphine.[4] Propofol is an attractive agent because of its very rapid onset and, particularly, offset of action. It may, however, cause moderate to severe hypotension principally due to venodilation. It is often used as a sedative agent in intensive care settings as well as a general anesthetic agent.

MUSCLE RELAXANTS.

Drugs used for muscle relaxation also may have cardiovascular effects. *Succinylcholine* can cause bradycardia, which can be reversed or prevented by administration of atropine. In patients anesthetized with halothane, *pancuronium* and *gallamine* cause an increase in heart rate, arterial pressure, and cardiac output, whereas *tubocurarine* and *metocurine* result in a fall in mean arterial pressure with mild elevations in heart rate and little, if any, change in cardiac output. *Vecuronium* has essentially no cardiovascular side effects.

Spinal and Epidural Anesthesia

Spinal and epidural anesthesia cause sympathetic denervation, which produces peripheral arteriodilation and venodilation. Systemic vascular resistance may be reduced by 10 to 15 percent. Venodilation may cause a marked reduction in right ventricular preload as a consequence of sympathetic denervation. Under these circumstances, right ventricular preload depends critically on the effects of gravity on the patient's position, as well as on the total blood volume.

In four randomized trials comparing general anesthesia with either spinal/epidural anesthesia or combined general plus spinal/epidural anesthesia, no differences in cardiac outcomes have been found.[8] [9] [10] [11] Furthermore, in an informal meta-analysis combining the data from these trials, still no difference was noted.[12] The choice of anesthetic technique should ultimately be left to the anesthesiologist.

REGIONAL AND LOCAL ANESTHESIA.

Cardiovascular effects from peripheral nerve blocks with local anesthetic agents are uncommon but can occasionally result from absorption of local anesthetic agents into the bloodstream. A major concern with local or regional anesthesia is whether the technique provides adequate anesthesia and analgesia for the planned procedure; the cardiological consultant should not underestimate the cardiovascular consequences of inadequate anesthesia.

Intraoperative Hemodynamics and Arrhythmias

During the operative procedure, it is not uncommon for systolic blood pressure to fall into the range of 95 to 105 mm Hg. Such blood pressure reductions are often brief and may respond to a lightening of the anesthesia, to a brisk fluid challenge, or to the use of intravenous sympathomimetic agents. Such blood pressure reductions are equally likely with general versus spinal/epidural anesthesia.[13] Any severe reduction in arterial pressure in patients with ischemic heart disease can reduce coronary flow and precipitate myocardial ischemia. In general, transient reductions in blood pressure are not associated with major cardiac complications. Marked or sustained reductions in blood pressure, such as a 33 percent reduction below the preoperative blood pressure lasting more than 10 minutes, have been associated with increased cardiac complication rates.[14] [15]

Positive-pressure ventilation during general anesthesia reduces the return of blood to the right side of the heart and tends to reduce ventricular preload. Fluid that is administered during positive-pressure ventilation does not increase preload to the extent that it would in patients who are ventilating spontaneously. When the positive-pressure ventilation of general anesthesia ceases, ventricular preload increases, often abruptly, and hypertension or pulmonary congestion may result. Analogous physiological changes can occur with the cessation of spinal or epidural anesthesia because the venodilation caused by these agents also reduces right ventricular preload.

Transient bradycardias, such as sinus bradycardia and junctional rhythm, can occur during periods of vagal stimulation. These bradyarrhythmias commonly respond to a lightening of the anesthesia or to the administration of atropine or $beta_1$ -adrenoceptor agonists such as isoproterenol or epinephrine. Tachyarrhythmias can result from hypovolemia or vasodilation as well as from sensitization of the myocardium to catecholamines that are circulating and/or released by sympathetic nerve endings in the heart.[16] Tachycardia is poorly tolerated by patients with mitral stenosis (see Chap. 46) and can cause myocardial ischemia in patients with coronary artery disease. Therapy

with specific antiarrhythmic medications is usually indicated only when the arrhythmia causes circulatory compromise and does not respond to changes in the depth of anesthesia or to attention to problems such as hypoxemia, hypovolemia, hypotension, or potentially precipitating surgical manipulation.

Mild hypothermia frequently occurs during the intraoperative period. For most patients, there are few if any consequences from a transient decline in body temperature. In a study of patients undergoing vascular surgery, however, intraoperative hypothermia was associated with an increased risk of myocardial ischemia.[17] Furthermore, in a randomized trial comparing routine thermal care with supplemental warming during the intraoperative and early postoperative period in patients undergoing vascular surgery, postoperative cardiac morbidity was reduced in the warmed group.[18]

MONITORING.

In patients who have severe underlying heart disease and who are undergoing noncardiac surgery, it is mandatory to monitor cardiac function during anesthesia,[19] including cardiac rate and rhythm and directly recorded arterial blood pressure. A radial artery line permits not only monitoring of intraarterial pressure but also frequent sampling for determination of blood gas values. In the presence of peripheral vasoconstriction, indirect (cuff) blood pressure measurements may greatly underestimate true arterial pressure.

Multiple lead monitoring of cardiac rhythm and ST segments has become the standard of care in high-risk patients with coronary artery disease. Although intraoperative ischemia is less predictive of adverse cardiac outcomes than either preoperative or postoperative ischemia, prolonged episodes of intraoperative ischemia are associated with adverse cardiac events.[20]

The use of pulmonary artery (PA) catheters to measure pulmonary artery capillary wedge pressure and cardiac output is controversial. Many small studies have shown no reduction in adverse cardiac outcomes with the use of an intraoperative PA catheter in unselected high-risk patients undergoing vascular surgery.[21] [22] Nevertheless, in certain situations, a PA catheter may be helpful, such as in patients with severe left ventricular dysfunction, in patients who have severe aortic stenosis or unstable angina and who are undergoing high-risk surgery, and to monitor intracardiac fluid status closely.[23] [24] The decision to use an introperative PA catheter should be left to the anesthesiologist, but it is

appropriate for the cardiological consultant to recommend consideration of its use in very high-risk patients.

THE OPERATION

Just as consultant cardiologists must understand the pharmacological effects of anesthesia, they must also recognize the physiological effects of surgery, including the direct consequences of the operation and the expected responses to postoperative recuperation.

NATURE OF THE OPERATION.

A key element in perioperative risk assessment is an estimation of the baseline risk. This is the average risk of a particular procedure at a particular institution. This baseline risk may then be modified by the clinical characteristics of an individual patient. Among noncardiac surgical procedures, the highest cardiovascular complication rates are commonly associated with abdominal aortic aneurysm surgery,[25] which causes substantial myocardial stress because of aortic cross-clamping and major shifts in fluid and electrolytes. The risk of cardiac complications is also higher in other major abdominal and thoracic procedures than in procedures on the extremities, in large part because of the more difficult postoperative course.[26] Patients who undergo operation for aortic aneurysm, carotid arterial disease, or peripheral vascular disease often have substantial coronary artery disease as well, and the extent of the latter may be underestimated because of the limitations caused by the peripheral arterial disease. At the other end of the spectrum, ophthalmalogical surgery, upper endoscopy, and transurethral prostate resection can be safely performed even in patients with heart disease.[27] [28] The estimated risk of myocardial infarction or cardiac death due to various surgical procedures is shown in Table 61-1 .

DURATION.

The risk of cardiovascular mortality and morbidity is generally correlated with the duration of anesthesia, but this is principally because the longest operations are more often on the aorta or in the abdomen or chest than on the extremities. The risk of major cardiovascular complications does not appear to correlate with the duration of surgery after controlling for the type of surgery, unless the operation is prolonged because of intraoperative complications.

EMERGENCY OPERATION.

When an operation is carried out under emergency conditions, it is associated with greatly increased mortality in patients with cardiovascular disease. The risk of postoperative cardiac complications, including postoperative myocardial infarction or cardiac death, is increased anywhere from 2.5- to 4-fold in emergency compared with elective surgery.[13] [25] [29] [30] Part of this increased risk is because patients undergoing emergency operations may often have poorly controlled or unappreciated general medical problems, such as fluid and electrolyte imbalance or hepatic dysfunction.[13] [25] However, emergency surgery appears to be an important correlate of postoperative

complications, even after controlling for the underlying medical disease.[25] [29] [30]

ESTIMATION OF RISK.

A few patients have such compelling reasons for operation (e.g., leaking abdominal aortic aneurysm or perforated viscus) that estimation of operative risk is an academic exercise, because failure to operate almost certainly will result in the patient's death. The timing or even the performance of an operation is often elective, however, and under these circumstances estimation of operative risk is an important aspect of the medical consultant's role.

One convenient method to estimate surgical risk is to use multifactorial indices. The original index of Goldman and colleagues[29] and its modification[31] weighted several clinical factors based on their relative significance as predictors of adverse cardiac outcomes (Table 61-2) . Both indices have been validated in prospective series of general surgical patients[25] and in other studies.[32] [33] [34] [35] Because these indices were developed on general surgical patients, they tend to underestimate risk in patients undergoing vascular surgery and in patients with stable coronary artery disease.[36] Moreover, these indices were based on data from the 1970s and early 1980s; most patients undergoing surgery in 1999 had a low risk score, thus limiting the indices' ability to discriminate among patients.[31] [32]

A revised cardiac risk index has been developed using data from the 1990s.[37] In this study, Lee and colleagues identified six independent and relatively equally important predictors of postoperative adverse cardiac outcomes (see Table 61-2) . In this simple index, the number of predictors correlated with the risk of cardiac morbidity and mortality. When compared with the older indices and with the American Society of Anesthesiologists (ASA) class, the revised index was found to be superior.[37] Moreover, the revised index appears to predict risk accurately in vascular surgery,

TABLE 61-1 -- RISK OF MYOCARDIAL INFARCTION OR CARDIAC DEATH FOR NONCARDIAC PROCEDURES*

High risk (often >5%)	Aortic surgery
	Peripheral vascular surgery
	Emergent major operations, particularly in the elderly
	Anticipated prolonged surgical procedures associated with larger fluid shifts or blood loss
Intermediate risk (1-5%)	Intrathoracic and intraperitoneal surgery
	Carotid endarterectomy
	Head and neck surgery
	Orthopedic surgery
	Open prostate surgery

Low risk (generally <1%)	Endoscopic procedures
	Cataract surgery
	Superficial procedures and biopsies
	Transurethral prostate surgery

**Adapted from ACC/AHA Task Force Report: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. J Am Coll Cardiol 93:1278, 1996.*

with the exception of abdominal aortic aneurysm surgery. The optimal use of cardiac risk indices may be to modify a baseline risk such as that shown in Table 61-1 rather than to predict an absolute risk of complications.[38] [39] Furthermore, indices should generally serve as an adjunct to a thorough evaluation of specific cardiac conditions.

INFLUENCE OF SPECIFIC CARDIOVASCULAR DISORDERS

Ischemic Heart Disease

Assessment of Risk

CLINICAL.

Ischemic heart disease is a major determinant of perioperative morbidity and mortality. The incidence of perioperative myocardial infarction is increased 5- to 50-fold in patients who have previously suffered infarcts compared with patients who do not have a clinical history of coronary disease.

During the 1970s, several studies reported about a 30 percent risk of reinfarction or cardiac death when patients were operated on within 3 months of the previous myocardial infarction, about a 15 percent risk when the operation was performed 3 to 6 months after a prior infarction, and about a 5 percent risk when the operation was performed more than 6 months after the infarction.[13] Complication rates were subsequently reduced during the 1980s.[36] [40] [41] For example, Rao and colleagues[40] reported only a 6 percent reinfarction rate within 3 months after preoperative myocardial infarction and only a 2 percent reinfarction rate between 3 and 6 months after a myocardial infarction, and they then confirmed these low risks in a subsequent report.[41] The reduction in cardiac morbidity and mortality has been attributed to the use of perioperative monitoring and careful regulation of hemodynamic status, cardiac rhythm, oxygenation, electrolytes, and hematocrit.

Obviously, truly life-saving procedures must be performed almost regardless of the cardiac risk, and purely elective surgery should commonly be delayed for 6 months after infarction, when the cardiovascular risks will have returned to a stable, long-term baseline risk. The more difficult issue is in patients in whom the operation is not truly

emergent but is also not purely elective--for example, a patient with severe symptomatic peripheral vascular disease

TABLE 61-2 -- MULTIFACTORIAL CARDIAC RISK INDICES

RISK FACTOR	POINTS	INTERPRETATION
Goldman et al*		
Age >70 yr	5	
MI in previous 6 mo	10	Class I 0-5 points } low risk
S_3 gallop or jugular venous distention	11	
Important aortic stenosis	3	Class II 6-12 points } intermediate risk
Rhythm other than sinus or PACs on last preoperative ECG	7	
>5 PVCs/min documented at any time before operation	7	Class III 13-25 points high risk
		Class IV >26 points
P_{O_2} <60 or P_{CO_2} >50 mm Hg; K <3.0 or HCO_3 <20 mEq/L; BUN >50 or Cr >3.0 mg/dl; abnormal AST, signs of chronic liver disease, or bedridden from noncardiac causes	3	
Intraperitoneal, intrathoracic, or aortic operation	3	
Emergency operation	4	
Detsky et al		
MI in previous 6 mo	10	
MI >6 mo previously	5	
Canadian Cardiovascular Society Angina		
Class III	10	
Class IV	20	
Unstable angina in previous 6 mo	10	<15 points=low risk
Alveolar pulmonary edema		
Within 1 wk	10	
Ever	5	>15 points=high risk

Suspected critical aortic stenosis	20	
Rhythm other than sinus or sinus plus PACs on last preoperative ECG	5	
>5 PVCs/min at any time before surgery	5	
Poor general medical status	5	
Age >70 yr	5	
Emergency operation	10	
Lee et al		
Intrathoracic, intraperitoneal, or infrainguinal vascular surgery	1	
History of ischemic heart disease	1	0-1 point=low risk
History of congestive heart failure	1	2 points=intermediate risk
Insulin treatment for diabetes mellitus	1	3 or more points=high risk
Serum creatinine level >2.0 mg/dl	1	
History of cerebrovascular disease	1	
PAC=premature atrial complexes; ECG=electrocardiogram; PVC=premature ventricular complexes; BUN=blood urea nitrogen; Cr=creatinine; AST=aspartate aminotransferase; K=potassium; HCO_3 =bicarbonate.		

**Adapted from Goldman L, Caldera DL, Nussbaum SR, et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.*

Adapted from Detsky AS, Abrams HB, McLaughlin JR, et al: Predicting cardiac complications in patients undergoing noncardiac surgery. J Gen Intern Med 1:211, 1986.

Adapted from Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100:1043, 1999.

or a patient with a potentially resectable malignant tumor. In such situations, one would like to delay operation sufficiently long for cardiac risk to be reduced but not wait a full 6 months. Because full healing of a myocardial infarction usually takes about 4 to 6 weeks, one rational approach is to evaluate the patient with post-myocardial infarction prognostic studies, such as a submaximal exercise tolerance test, and to use the patient's clinical and cardiological conditions as the guide for surgery sometime between 4 weeks and 3 months after the infarction.

A recent preoperative myocardial infarction increases a patient's relative risk of reinfarction with operation, but the absolute risk depends on various factors in addition to the timing of the infarction. Patients who have good exercise tolerance and left

ventricular function after infarction and who can resume normal activity levels within 4 to 6 weeks after infarction should be able to undergo operation with relatively small absolute risks, even if their relative risk might be slightly lower if one could wait the full 6 months. By comparison, risks are likely to be substantially higher in patients who have postinfarction angina or who have evidence of ischemia on exercise electrocardiography, thallium scintigraphy, or dobutamine stress echocardiography.

When a patient with angina pectoris is evaluated, the patient's current (preoperative) exercise tolerance should be ascertained and an assessment made about whether the anginal pattern is stable or unstable (see Chap. 36) . In patients who can carry objects such as two grocery bags or a young child up a flight of stairs without stopping and without appreciable symptoms, most surgical procedures are generally well tolerated.[42] Physicians should avoid relying on the *frequency* of angina because patients who voluntarily reduce their activity level may also greatly reduce their symptoms. This phenomenon is especially true in patients whose surgical conditions, such as orthopedic disorders or peripheral vascular disease, limit ambulation.

NONINVASIVE TESTING FOR ISCHEMIA.

Exercise treadmill testing is an objective means for assessing exercise tolerance and is especially beneficial if the history is unreliable. Unfortunately, the limited sensitivity and specificity of standard electrocardiographic exercise tolerance testing limit the use of this test for diagnosing coronary artery disease (see Chap. 6) . In studies of patients undergoing vascular surgery, postoperative cardiac complications were significantly less common in patients who exercised to higher heart rates and cardiac workloads.[27] The prognostic value

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of limited exercise tolerance has also been reported in persons older than 65[35] [43] in whom the inability to perform 2 minutes of bicycle exercise in a supine position and to raise the heart rate above 99 beats/min was an independent important predictor of cardiac complications in noncardiac surgery. Of note was that poor exercise capacity was an independent predictor of cardiac complications but that electrocardiographic changes with exercise were not.

In patients who are unable to exercise because of noncardiac disability (e.g., intermittent claudication or orthopedic abnormalities), dipyridamole thallium imaging, ambulatory ischemia monitoring, or stress echocardiography can be used to assess perioperative risk. Dipyridamole thallium imaging (see Chap. 9) has been successful in identifying high-risk patients among selected subgroups of patients who are referred for the test before undergoing vascular surgery, and it is especially appealing for patients who have abnormal resting electrocardiograms or are taking medications such as digoxin that make electrocardiographic monitoring unreliable for the detection of ischemia.

Among 1410 patients in the five largest series of such patients,[44] [45] [46] [47] [48] a reversible defect on thallium scintigraphy had a sensitivity of 85 percent for predicting postoperative cardiac complications and a specificity of 60 percent; the relative risk of cardiac complications in a patient with a reversible defect was 9.0. When dipyridamole thallium scintigraphy was used in *unselected* consecutive patients having abdominal aneurysm or major vascular surgery, it was *not* proved useful for predicting perioperative myocardial infarction, myocardial ischemia, or cardiac death.[49] [50] In the largest single series of 451 *consecutive* unselected patients, the presence of a reversible thallium defect had a sensitivity of just 36 percent, a specificity of 65 percent, and a relative risk of 1.0 (i.e., it was of no value whatsoever) for predicting major perioperative cardiac events.

Ambulatory electrocardiographic (Holter) recording can identify up to 90 percent of patients who will develop major postoperative ischemic complications.[51] Patients with asymptomatic preoperative ischemia or asymptomatic postoperative ischemia have as high as a 30 percent risk of developing a clinical event, including myocardial infarction, unstable angina, ischemic pulmonary edema, or cardiac death.[20] [51] [52] In contrast, asymptomatic intraoperative ischemia is less predictive.[20] [53] Asymptomatic postoperative ischemia, which is found in a substantial minority of patients with or at risk for atherosclerotic disease,[54] [55] commonly precedes a clinical event by an hour or more[52] [56] ; longer episodes of postoperative ischemia are associated with a higher risk of a major clinical event.[56] Patients with perioperative ischemia also have more late cardiac events well after surgery.[53] [57] The requirement for a near-normal resting electrocardiogram and a 24-hour testing period generally makes this test less practical than either dipyridamole thallium scintigraphy or stress echocardiography.

Although some investigators have used radionuclide ventriculography to predict risk,[58] in other studies data from resting and/or exercise radionuclide ventriculography did not add important independent information for predicting overall perioperative cardiac risk.[35] [49] [59] [60] Similarly, routine transthoracic echocardiography adds little for the prediction of postoperative complications.[61]

Stress echocardiography after exercise or agents such as dipyridamole or dobutamine can be used to identify patients at markedly increased risk on the basis of the provocation of left ventricular wall motion abnormalities with stress.[62] [63] [64] [65] [65A] [66] [67] [68] [69] Poldermans and colleagues studied 300 consecutive unselected patients undergoing major vascular surgery with dobutamine stress echocardiography. Of 72 patients with a stress-induced new regional wall motion abnormality, 17 suffered a perioperative myocardial infarction or cardiac death. None of the 228 patients without a stress-induced wall motion abnormality suffered a cardiac complication.[65] Stress echocardiography appears to be at least as good as dipyridamole thallium scintigraphy or ambulatory ischemia monitoring for predicting complications.

Many studies have evaluated the extent to which specific clinical variables can be used to select patients for preoperative noninvasive ischemia testing. In patients undergoing vascular surgery, Eagle and colleagues found that age greater than 70 years, a history of ventricular arrythmias requiring treatment, angina, diabetes mellitus, and abnormal Q

waves on the electrocardiogram were independent predictors of cardiac complications.[44] Patients with none of these variables were at low risk for complications, and those with three or more were at high risk regardless of the results of dipyridamole thallium scintigraphy. In the group with one or two of these variables, dipyridamole thallium scintigraphy accurately identified patients as either high or low risk. In a similar study, L'Italien and colleagues added a history of congestive heart failure as an independent predictor of adverse cardiac outcomes and found coronary revascularization within 5 years to have a protective effect.[70] Thallium scintigraphy added useful predictive information only to the group of patients found to be at intermediate risk on the basis of assessment using clinical variables.

Fewer data are available on dobutamine stress echocardiography. However, in patients with low-risk clinical variables, it appears that dobutamine echocardiography does not add appreciably to the clinical risk assessment. Unlike thallium scintigraphy, however, a normal dobutamine stress echocardiogram result in a patient with high-risk clinical variables may predict a low risk of perioperative complications.[65] Hypotension during dobutamine echocardiography predicts perioperative cardiac events.[65A] In conclusion, most data support the use of noninvasive ischemia testing in preoperative evaluation of patients found to be at intermediate risk on clinical assessment.

PRIOR CORONARY REVASCULARIZATION.

Patients who have undergone successful coronary revascularization can undergo major noncardiac surgical procedures with a low mortality rate,[71] except perhaps in the first 30 days postoperatively.[71A] An analysis of patients in the Coronary Artery Surgery Study registry[71] showed that total operative mortality was 2.4 percent in 458 patients who had significant coronary artery disease and underwent noncardiac operations without prior coronary artery bypass grafting (CABG). By comparison, operative mortality was 0.9 percent among 399 patients who had had a CABG procedure performed before noncardiac surgery. The mortality was higher in patients who had more severe left ventricular dysfunction or dyspnea on exertion and in patients who used nitrates, were older, and had diabetes. The risk of myocardial infarction, however, was not significantly different between the patients with and without preoperative CABG, and the cardiac death rates were only 0.4 percent and 1.3 percent, respectively, in the two groups. Subsequent studies have confirmed that prior CABG, particularly if within 5 years of subsequent noncardiac surgery, is associated with a decreased risk of perioperative cardiac death.[70]

Fewer data are available to evaluate the effects of preoperative percutaneous transluminal coronary angioplasty (PTCA). In three different series of high-risk patients who underwent PTCA before vascular surgery, the mortality with noncardiac surgery was less than 3 percent.[72] [73] [74]

APPROACH TO RISK ASSESSMENT.

A practical approach to patients with known ischemic heart disease or with specified high-risk characteristics[44] should use information from the history as well as diagnostic tests.[38] [39] [75] [76] [77] If the history reliably indicates that the patient has Canadian

Cardiovascular Society class I or class II angina, the patient is able to raise the double product (the heart rate multiplied by the systolic blood pressure) above the range to be expected with general anesthesia and surgery and hence

Figure 61-1 Risk assessment in patients with ischemic heart disease.

should be able to withstand the stress of the procedure.[71] If the history is unreliable, exercise testing to assess physical function[35] [44] will aid in risk assessment. If the patient is unable to exercise because of noncardiac conditions, dipyridamole thallium imaging or stress echocardiography should be considered, particularly for patients believed to be at intermediate risk on clinical assessment. An approach to risk assessment in patients with ischemic heart disease is shown in Figure 61-1 .

Patients who have angina or who have had a myocardial infarction but who can exercise to class I or II level or have normal dipyridamole thallium imaging or stress echocardiography results can undergo most operations with acceptable risk, roughly a 4 to 5 percent risk of myocardial infarction and a 1 percent mortality. Patients who cannot perform class I or II activities or who have positive dipyridamole thallium or stress echocardiography results are likely to have a 5 to 25 percent risk of myocardial infarction and a 5 to 25 percent mortality. For any patient with an appropriate indication for noninvasive ischemia testing or coronary angiography independent of planned noncardiac surgery, such testing should generally precede surgery, particularly if the results may lead to a coronary revascularization procedure.

RISK REDUCTION STRATEGIES.

Medications.

All baseline preoperative cardiac medications should be continued up to and including the day of surgery and resumed promptly once the patient is eating. In three small studies, the institution of prophylactic beta-blocking agents immediately before surgery was associated with decreased intraoperative ischemia and, in one of these studies, a decreased risk of postoperative myocardial infarction.[78] [79] [80] A randomized controlled trial of prophylactic atenolol in patients with known coronary artery disease or at high risk for it demonstrated a significant reduction in both 6-month and 12-month mortality but no reduction in perioperative mortality or cardiac morbidity.[81] In a more recent study of prophylactic beta-adrenergic blockade, 112 high-risk patients were randomized to either preoperative bisoprolol or placebo before undergoing major vascular surgery. Oral bisoprolol, at a dose of 5 mg or 10 mg daily, was begun at least 7 days before surgery and continued until the 30th postoperative day. The combined incidence of perioperative cardiac death or nonfatal myocardial infarction was 34 percent in the placebo group compared with 3.4 percent in the bisoprolol group.[82] This difference was

highly statistically significant. There is now sufficient evidence to recommend the routine use of prophylactic bisoprolol or atenolol in high-risk patients who are undergoing major surgery and are not already taking beta-blocking agents.[82A]

Nitrates have been shown in multiple studies to reduce intraoperative ischemia but have never demonstrated a reduction in adverse cardiac outcomes.[83] Prophylactic nitrates, most commonly intravenous nitroglycerin, should therefore be considered only for high-risk patients. Few data are available on the use of prophylactic calcium channel blocking agents during the perioperative period; thus, no firm recommendations can be made.

The alpha-adrenergic blockers may also be useful to reduce perioperative risk. Clonidine has been shown to reduce perioperative ischemia but has not demonstrated a reduction in cardiac morbidity.[84] [85] A newer agent, mivazerol, also appears to reduce ischemia and in a single study was associated with a decreased risk of myocardial infarction in patients undergoing vascular surgery.[86] [87] At the present time, however, beta-blocking agents are the preferred method to reduce risk in patients with ischemic heart disease.

Preoperative Cardiac Optimization.

In patients found to be at high risk because of poor cardiac functional status

or a positive result of a noninvasive ischemia test, one approach is to optimize the cardiac medications and then reevaluate cardiac status in a few weeks. Although not proved in clinical trials, an improvement in cardiac functional status or in the results of ischemia testing may be associated with a reduction in the risk of cardiac complications.

Intensive preoperative hemodynamic optimization has been advocated by some to reduce perioperative morbidity in high-risk patients. Three randomized controlled trials have demonstrated a reduction in perioperative morbidity,[23] [88] [89] and a fourth shows no difference,[90] with the use of immediate preoperative optimization of hemodynamic parameters. In these studies, patients were admitted to an intensive care setting where a PA catheter was placed. Intravenous fluid infusions, inotropic agents, and afterload-reducing agents were used to achieve goal values for the pulmonary capillary wedge pressure (usually 8 to 15 mm Hg) and oxygen delivery (usually 600 ml/min/m^2). Although goal values were achieved for most patients, the reduction in complication risk was independent of achieving the goal values. On the other hand, in other studies, when hemodynamics were optimized in medical and postoperative patients in an intensive care unit, there was no reduction in mortality or morbidity.[91] [92] Preoperative hemodynamic optimization of this type can be considered for high-risk patients undergoing high-risk operations.

CORONARY REVASCULARIZATION.

In patients who have an indication for coronary angiography and/or revascularization independent of planned noncardiac surgery, it is advisable to perform the cardiac procedures first. This is particularly important in high-risk patients. The use of prophylactic coronary revascularization, however, is controversial. No randomized controlled trials have evaluated the use of prophylactic coronary revascularization before noncardiac surgery. Two decision analyses attempted to define the precise role of prophylactic revascularization.[93] [94] Both concluded that routine revascularization is not warranted and that the subgroups most likely to benefit remain undefined. Patients found to be at low risk have roughly a 1 percent cardiac mortality with noncardiac surgery.[95] The mortality from CABG or PTCA ranges from 0.5 to 2 percent.[96] Therefore, prophylactic revascularization is not likely to reduce *total* mortality in low-risk patients.

In high-risk patients, prophylactic revascularization may be a reasonable strategy because such patients face a 5 to 25 percent mortality with noncardiac surgery.[44] Furthermore, if one considers potential long-term mortality reduction, prophylactic revascularization seems reasonable in certain groups. For example, high-risk patients undergoing vascular surgery, particularly those with diabetes mellitus, have significantly reduced long-term survival largely because of premature cardiac death and thus may be the most likely to benefit from prophylactic revascularization[97] , particularly surgical revascularization.[97A]

The risk of thrombosis is significant in patients soon after percutaneous coronary stent placement, particularly if anticoagulation is stopped too soon. Thus, noncardiac surgery should not immediately follow a stent procedure.

PREOPERATIVE TRANSFUSION.

No large randomized clinical trials have determined the optimal hemoglobin level before surgery or the appropriate threshold for transfusion. Most data suggest that perioperative morbidity and mortality increase as the preoperative hemoglobin level decreases.[98] [99] This relationship appears to be more pronounced in patients with cardiovascular disease.[98] At preoperative hemoglobin levels below 9.0 g/dl, the risk of mortality appears to increase sharply. Thus, in patients with cardiac disease, particularly ischemic heart disease, it is reasonable to consider preoperative blood transfusion when the hemoglobin level is less than 9 gm/dl. In general, however, the risks and benefits of transfusion should be individualized on the basis of the patient's comorbidities and the anticipated surgical blood loss. It is important to consider that the combined risk of transmission of human immunodeficiency virus, hepatitis C, or hepatitis B through transfusion of one unit of allogeneic blood is estimated to be 1 in 34,000.[100]

Hypertension (see Chap. 28)

Several studies have documented that patients with hypertension have higher risks of

suffering major cardiac complications during or shortly after noncardiac operation than do patients who have always been normotensive. However, most of this increased risk is because of the ischemic heart disease, left ventricular dysfunction, renal failure, or other abnormalities that often occur in patients with hypertension. In patients with mild to moderate hypertension, diastolic pressures less than 110 mm Hg, and systolic blood pressure less than 200 mm Hg, and no evidence of serious end-organ damage, general anesthesia and major noncardiac surgery are generally well tolerated.[15] Hypertensive patients are, however, at higher risk for labile blood pressures and for hypertensive episodes during surgery and especially just after extubation. Thus, it is neither mandatory nor desirable to delay noncardiac operation for the weeks or months that may be required to achieve ideal blood pressure control in stable patients who have mild to moderate hypertension but who have no hypertensive end-organ damage.

Patients with severe hypertension in the immediate preoperative period are at increased risk for perioperative myocardial infarction and congestive heart failure.[15] In such patients, blood pressure should be controlled before surgery. Commonly used agents for this purpose include intravenous sodium nitroprusside and labetalol because they may be easily titrated. Although uncontrolled early studies suggested that the continuation of any hypertensive agents might increase the risk of perioperative hypotension, substantial subsequent data from more careful studies indicate that patients whose hypertension is well controlled do at least as well, if not better, if their medications are, in fact, continued up to the time of operation.[15]

Thiazide and other diuretics cause some degree of chronic volume depletion, and patients receiving these drugs may require more fluid administration early during the operative procedure.

Valvular Heart Disease (see Chap. 46)

Patients who have valvular heart disease and who are undergoing anesthesia and noncardiac operation are subject to many potential hazards: heart failure, infection, tachycardia, and embolization. As might be expected, patients with no or only mild limitation of activity (i.e., those in Class I or II) tolerate operation well and probably require little more than careful perioperative care and prophylaxis for infective endocarditis. Those with more serious impairment of cardiac reserve (i.e., those in Class III or IV) tolerate major noncardiac operations poorly, and their prognosis for surviving major surgery is distinctly worse.[13] [26]

Patients with symptomatic critical aortic stenosis[29] are at increased risk for sudden death or acute pulmonary edema during the perioperative period, if demands on cardiac output are suddenly increased or if atrial fibrillation and a rapid ventricular rate are precipitated by anesthesia or operation.

The risk associated with severe aortic stenosis may be most prominent when the valvular disease is not known to the surgical or anesthesia team before surgery.[101] It is therefore crucial to make the diagnosis of severe aortic stenosis before surgery to allow for appropriate preoperative and intraoperative treatment. In general, patients with symptomatic severe aortic stenosis should undergo corrective valve surgery or, when

appropriate, valvuloplasty, before noncardiac surgery.[102] [103] On the other hand, in two series of patients with severe aortic stenosis, defined as an aortic valve area less than 1.0 cm^2 , and normal left ventricular function who underwent major noncardiac surgery, only 2 of 36 patients died during the perioperative period.[101] [104] This suggests that when preoperative correction of the valvular lesion is not feasible, surgery may be performed with an acceptable risk. In such cases, appropriate anesthetic care may involve invasive hemodynamic monitoring and anesthetic agents or techniques that minimize reductions in preload.

In patients with mitral stenosis, control of heart rate and, particularly, avoidance of atrial fibrillation with a rapid ventricular response are important to prevent perioperative congestive heart failure.[27] In patients with severe mitral stenosis, corrective valve surgery or valvuloplasty should precede noncardiac surgery.

Perioperative cardiac morbidity in patients with aortic or mitral regurgitation appears to be largely related to the associated congestive

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heart failure. Therefore, preoperative control of heart failure is crucial. This should include the use of diuretic agents and afterload-reducing agents.

HYPERTROPHIC CARDIOMYOPATHY (see Chap. 48) .

Patients with hypertrophic cardiomyopathy are intolerant of hypovolemia, which may lead to both a reduction in the elevated preload necessary to maintain cardiac output and an increase in the obstruction to left ventricular outflow. Similarly, decreases in afterload may also increase dynamic outflow obstruction. With careful perioperative, intraoperative, and postoperative care, however, the risk of major cardiac complications in such patients is small. In the two largest series of noncardiac operations in patients with hypertrophic cardiomyopathy, no deaths and only two myocardial infarctions ensued after a total of 133 operations. Reversible cardiac complications were common, however. Arrhythmias occured in more than 20 percent of patients, congestive heart failure in 16 percent, and hypotension requiring vasopressor therapy in 14 percent.[105] [106] It has previously been suggested that spinal anesthesia may be relatively contraindicated in patients with hypertrophic obstructive cardiomyopathy because of its tendency to reduce systemic vascular resistance and increase venous pooling and thereby increase the severity of obstruction to outflow.[105] However, Haering and colleagues[106] did not find spinal anesthesia to be associated with an increase in cardiac complications. Hemodynamic monitoring is not routinely required but may be helpful when these patients undergo major aortic, abdominal, or thoracic procedures.

PROSTHETIC HEART VALVES.

Most patients with mechanical prosthetic heart valves receive anticoagulants on a long-term basis to prevent thromboembolic complications (see Chap. 46) . If these

medications are continued through the period of noncardiac operation, hematoma formation and persistent postoperative bleeding can ensue. Anticoagulants can be temporarily discontinued during the perioperative period with minimal risk of thrombosis. In one study,[107] no thromboembolic complications occurred in 159 patients who had prosthetic valves and were undergoing 180 noncardiac operations when warfarin was discontinued an average of 2.9 days preoperatively and resumed 2.7 days postoperatively.[107] Using a similar approach. Katholi and associates did not observe thromboembolic complications in 25 noncardiac operations on patients with prosthetic aortic valves[108] ; however, two such complications occurred in the 10 patients with mitral valve prostheses when anticoagulants were discontinued for noncardiac operations, although these patients had Kay-Shiley caged-disc valves, which are associated with a somewhat higher risk of thromboembolic complications. Using a decision analytical approach, Kearon and Hirsh concluded that perioperative heparinization with either intravenous standard heparin or subcutaneous low-molecular-weight heparin in patients with mechanical heart valves leads to a substantial increase in major bleeding risk and only a modest reduction in thromboembolic risk.[109] They recommended discontinuation of warfarin 4 days before surgery and resumption as soon as possible after surgery. Because it takes 4 days on average for the International Normalized Ratio (INR) to drop below 1.5 in patients with a baseline INR of 2.0 to 3.0, the number of days with normal anticoagulation is usually only 2 or 3 using this approach.[109] In certain patients, the risk of perioperative thromboembolism may be particularly high, such as in those with a caged-disc valve or those who have had a recent embolic event. In such patients, perioperative heparinization may be justified. Warfarin should be discontinued 4 days before surgery and heparin (intravenous standard heparin or subcutaneous low-molecular-weight heparin) begun once the INR has dropped below 1.5. Heparin is then stopped 6 hours before surgery and resumed at least 12 hours after surgery if considered safe by the surgeon. Analyses indicate that these various anticoagulation regimens are cost-effective, provided that they do not result in lengthening the hospitalization.[110] Even 1 day of additional hospitalization is relatively costly, and the daily risk of thromboembolic complications is low. Thus, perioperative anticoagulation management should focus on regimens that provide reasonable protection from thromboembolic disease but that permit patients to be discharged when the surgical condition itself permits.[110]

Endocarditis Prophylaxis (see Chap. 47)

Numerous surgical procedures are associated with the development of transient bacteremia with organisms that may cause endocarditis.[111] However, the risk of developing endocarditis after surgery is low,[111] [112] and a reduction in risk with the use of prophylactic antibiotics has not been demonstrated in controlled clinical trials. Nevertheless, because the risks associated with prophylactic antibiotics are low and the potential morbidity of endocarditis is high, antibiotic prophylaxis is recommended for patients with moderate- or high-risk structural cardiac lesions undergoing procedures with a high risk of bacteremia.

Congenital Heart Disease (see Chap. 44)

Depending on the nature of the malformation, patients with congenital heart disease may be subject to one or more potentially serious complications, such as infection, bleeding, hypoxemia, hypotension, and paradoxical embolization during general anesthesia and operation. As is the case for patients with valvular heart disease, patients who have congenital heart disease and who are to undergo a surgical procedure require prophylaxis to prevent infective endocarditis.

Patients with cyanotic congenital heart disease tolerate systemic hypotension poorly because this increases the right-to-left shunt and the severity of hypoxemia. In one large series, induction was commonly accomplished using ketamine or fentanyl to avoid hypotension, and anesthesia was maintained with morphine and nitrous oxide or with large doses of fentanyl with or without nitrous oxide. With use of careful anesthetic techniques, the risk of major anesthetic complications is extremely low even in very ill and cyanotic patients.[113] However, spinal anesthesia, which causes peripheral arterial vasodilation and reduces venous return, can have deleterious hemodynamic effects in patients with cyanotic congenital heart disease. Infusion of a vasoconstrictor such as phenylephrine may occasionally be required to raise systemic vascular resistance and thereby decrease the magnitude of the right-to-left shunt. Because patients with right-to-left shunts are subject to the risk of paradoxical emboli, including air emboli, meticulous techniques with regard to intravenous solutions and injections are mandatory to prevent such complications.

Congestive Heart Failure (see Chaps. 17 and 18)

Congestive heart failure is a major determinant of perioperative risk, irrespective of the nature of the underlying cardiac disorder. Mortality with noncardiac surgery increases with worsening cardiac class[13] [42] and with the presence of pulmonary congestion,[13] [25] especially when a third heart sound is noted. [29] The perioperative mortality rate appears to depend more on a patient's condition at the time of operation than on the most severe depression of cardiovascular status the patient has ever experienced. Patients with well-controlled congestive heart failure have an increased risk of developing postoperative pulmonary edema but little excess mortality.[49] When heart failure is not well controlled, as evidenced by the presence of an S_3 gallop, rales on lung examination, or pulmonary edema on chest radiograph, the risk of death may be as high as 15 percent.[13] It is therefore advisable to control heart failure preoperatively with the use of diuretics and afterload-reducing agents. In such patients, it is important to avoid overdiuresis in the immediate preoperative period because the risk of severe intraoperative hypotension is increased in intravascularly volume-depleted patients. It is therefore desirable, if possible, to stabilize a patient's condition by treating heart failure for approximately 1 week rather than for only 1 or 2 days before the contemplated operation. Perioperative cardiogenic pulmonary edema develops in about 2 percent of patients who are older than 40 years and are undergoing

major noncardiac surgery without prior congestive heart failure, in about 6 percent of patients whose heart failure is well controlled, and in about 16 percent of patients whose heart failure persists on physical examination or chest radiograph before surgery.[13]

Digitalis is one of the most common causes of iatrogenic complications in hospitalized patients, and it may be associated with a higher risk of intraoperative bradyarrhythmias.[13] Therefore, preoperative digitalization is *not* recommended except in patients whose congestive heart failure is sufficiently severe that they would normally meet the criteria for long-term digitalization.

Arrhythmias (see Chap. 25)

Arrhythmias may be a manifestation of the severity of underlying left ventricular dysfunction and of coronary artery disease and hence are frequently markers for the likelihood of perioperative cardiac complications. Because patients who have ventricular premature complexes but no evidence of underlying heart disease on detailed examination have an apparently normal cardiac prognosis, ventricular premature complexes in the *absence* of underlying heart disease should not be considered a risk factor for cardiac complications with noncardiac surgery.

Although it would be ideal for arrhythmias to be well controlled preoperatively, the risks associated with arrhythmias appear to be related more to the underlying cardiac disease than to the arrhythmias per se. Furthermore, the frequency of preoperative ventricular premature complexes or nonsustained ventricular tachycardia in patients with known structural heart disease does not appear to correlate with adverse cardiac outcomes.[114] Therefore, no current evidence shows that asymptomatic ventricular premature complexes or episodes of nonsustained ventricular tachycardia require aggressive preoperative control or prophylactic intraoperative suppression. Similarly, in patients with well-controlled atrial fibrillation, cardioversion need not be carried out specifically because of planned noncardiac surgery if such a management option would not otherwise be appropriate. Careful rhythm monitoring during surgery and in the immediate postoperative period would be prudent.

Patients who are most at risk for the development of postoperative supraventricular tachyarrhythmias include elderly patients undergoing pulmonary surgery, patients with subcritical valvular stenoses, and patients with prior histories of supraventricular tachyarrhythmias. Although previous data suggested that digitalis may reduce the risk of development of postoperative supraventricular tachycardia and decrease the ventricular rate when it does occur,[13] the use of prophylactic digitalis has not been formally studied. Given the effectiveness of beta-adrenergic blocking agents, calcium channel antagonists, and adenosine for the treatment of supraventricular arrhythmias, it may be most prudent simply to treat the arrhythmia when it occurs rather than use prophylactic digitalis.

Several studies have shown that pretreatment with amiodarone or sotalol reduces the incidence of postoperative atrial fibrillation after CABG or cardiac valve surgery.[115] [116] [117] [118] In a randomized controlled trial of 85 patients, the use of prophylactic sotalol begun 24 to 48 hours before cardiac surgery and continued for 4 days was associated

with a 12 percent incidence of postoperative atrial fibrillation, compared with 38 percent in the placebo group.[118] Similarly, intravenous amiodarone administered immediately after cardiac surgery was associated with a 35 percent incidence of atrial fibrillation, compared with 47 percent for placebo.[115] Such results are promising and justify consideration of prophylactic therapy in patients at risk for developing atrial fibrillation after cardiac surgery. It is not known whether prophylactic therapy with amiodarone or sotalol is effective for noncardiac surgery; therefore, it is not currently recommended for routine use.

CONDUCTION DEFECTS.

Patients with *complete heart block* must respond to the demands for an increased cardiac output by augmenting stroke volume, but this compensatory response is prevented in many patients by a concurrent impairment of cardiac contractility. In addition, most anesthetic agents depress myocardial contractility and/or produce peripheral vasodilatation. Furthermore, anesthesia can cause further depression of the automaticity, and therefore the ventricular rate, of patients with heart block. Thus, patients with untreated complete heart block may be unable to meet the increased demands placed on the cardiovascular system by anesthesia and operation, and a permanent or temporary pacemaker should be inserted before the use of general anesthesia, even in asymptomatic patients (see Chaps. 24 and 25) .

Another problem is presented by patients with *chronic bifascicular block* (see Chap. 25) . A significant fraction of patients developing this abnormality in the course of an acute myocardial infarction progress to complete heart block, often accompanied by sudden severe hemodynamic compromise. Progression from bifascicular to complete heart block has not been documented during the perioperative period in patients without a previous history of third-degree heart block. Prophylactic pacemaker placement for such patients or for patients with first-degree atrioventricular (AV) block or type I second-degree AV block (Wenckebach) is not recommended, although a pacemaker should always be available in the operating room for emergency placement.[27] However, in patients who have bifascicular block and type II second-degree AV block and who have a history of unexplained syncope or transient third-degree AV block, the risk of development of complete heart block is much higher, and a temporary pacemaker should be inserted preoperatively.

In general, a prophylactic *temporary pacemaker* should be inserted before noncardiac operations only if the patient meets the indications for permanent pacemaker insertion and the operation should not be delayed for the time required for a permanent pacemaker insertion, or if the operative course is likely to be complicated by transient bacteremia. In such situations, a temporary pacemaker should be placed initially, and the permanent pacemaker can be inserted after the operation.

PATIENTS WITH A PERMANENT PACEMAKER OR DEFIBRILLATOR (seeChap. 24) .

When a patient with a permanent pacemaker or defibrillator in situ is about to undergo operation, the device should be carefully evaluated to ensure that it is functioning properly preoperatively. Demand pacemakers and defibrillators are sensitive to

electromagnetic interference, such as that produced by the electrocautery, which may result in failure to pace or provoke defibrillator discharge. The danger of this potentially hazardous interaction can be reduced by placing the indifferent plate of the cautery unit as far as possible from the lead and pacemaker pulse generator, and the electrocautery should be used in brief bursts rather than continuously. Also, a magnet should be available in the operating room to convert the pacemaker from the demand to the fixed-rate mode. Defibrillators should have sensing inactivated preoperatively to prevent the device from sensing electrocautery as ventricular fibrillation and delivering a shock. Because the cautery may also interfere with the electrocardiographic monitor and render results temporarily uninterpretable, arterial pressure should be monitored directly when the cautery is being used.

GENERAL MEDICAL PROBLEMS.

Patients with heart disease and with a general medical status complicated by diabetes, renal insufficiency, hepatic abnormalities, hypoxemia, or electrolyte abnormalities have a higher risk of cardiac complications, presumably because these nonmedical conditions exacerbate the stress placed on the heart by the operation.[13] [25] [29] Morbidity is also higher in markedly obese patients[118A] because obesity is often associated with abnormal cardiorespiratory function, metabolic function, and hemostasis. Every effort should be made to correct any of these noncardiac problems before

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operation, and the potential long-term benefits of surgery must also be interpreted in light of the patient's general prognosis.

POSTOPERATIVE COMPLICATIONS

MYOCARDIAL INFARCTION.

Transient intraoperative ischemia does not appear to be a major correlate of postoperative ischemic events in patients undergoing noncardiac surgery,[20] [53] but most clinical postoperative ischemic events are preceded by asymptomatic episodes of postoperative ischemia that can be detected by ambulatory ischemic monitoring.[20] [52] [53] [54] [56] Although series from before 1980 showed a peak in the risk of myocardial infarction on about the third postoperative day, more recent series show that a combination of frequent electrocardiograms and cardiac enzymes detects many non-Q-wave infarctions in the first 24 hours postoperatively.[34] [51] [119] [120] [121] Although care must be taken in interpreting cardiac enzymes in the perioperative period,[120] it may be that supply-demand imbalances cause an early peak in non-Q-wave postoperative infarctions, whereas the hypercoagulable postoperative state leads to a later (3 to 5 days postoperatively) peak in Q wave infarctions. For both types of infarction, postoperative stresses include general surgical complications, hypoxia and other pulmonary complications, fluid and electrolyte abnormalities, and the stresses of modern postoperative ambulation protocols. Substantial data indicate that prophylactic

anticoagulation with low-dose heparin reduces the risk of postoperative venous thromboembolic complications,[122] and such therapy is routinely indicated in most cardiac patients who undergo noncardiac operations. In fact, such anticoagulation regimens may permit a more gradual postoperative ambulation protocol in cardiac patients and hence possibly lower the incidence of postoperative myocardial infarction.

The diagnosis of postoperative myocardial infarction can be difficult. Roughly 50 percent of patients who have postoperative myocardial infarctions are pain free.[13] [95] Other signs such as hypotension, hypertension, arrhythmias, or altered mental status may often be the only clue to the presence of myocardial ischemia or infarction. In patients with signs or symptoms of myocardial ischemia or infarction, measurement of serum cardiac enzyme levels may be helpful. Elevated troponin I levels (>1.0 ng/ml) may be somewhat more specific for myocardial ischemia or infarctions than are elevations in CK-MB isoenzymes.[121] [123]

HYPERTENSION.

Postoperative hypertension is most likely to occur soon after the cessation of positive-pressure ventilation or in the recovery room, and it is more common after carotid endarterectomy and major abdominal vascular procedures.[15]

Common precipitants include fluid overload after cessation of positive-pressure ventilation, hypoxemia, anxiety, and pain. The principal therapeutic approaches should therefore concentrate on ensuring adequate oxygenation, pain control, and fluid control. In general, supplemental oxygen, morphine, and diuretics are the mainstays of the treatment of postoperative hypertension. Nitroprusside and labetalol (see Chap. 29) are the preferred medications for more severe hypertension. Intravenous hydralazine in small doses is effective for treating postoperative hypertension, but it has the potential of precipitating supraventricular tachyarrhythmias.

CONGESTIVE HEART FAILURE.

Although postoperative heart failure can be precipitated by myocardial infarction or ischemia, a substantial proportion of the cases are directly caused by excess fluid administration. Heart failure tends to occur soon after cessation of positive-pressure ventilation and again at about 24 to 48 hours after operation, when the fluid that was given in the perioperative period is mobilized from the extravascular sites. Diuretics, often given intravenously and occasionally supplemented with afterload-reducing agents, are usually sufficient therapy for postoperative congestive heart failure.

POSTOPERATIVE ARRHYTHMIAS.

Arrhythmias are common after operation and are often a manifestation of a noncardiac complication, such as bleeding, infection, or an acid-base or electrolyte imbalance occurring in a patient with heart disease. Management of such arrhythmias often requires recognition and correction of extracardiac factors.

A new postoperative supraventricular tachyarrhythmia should prompt a search for remediable medical problems. Direct antiarrhythmic therapy is often unnecessary and is usually secondary in importance to correction of the underlying cause of the arrhythmia.

Sinus tachycardia is the most common rhythm disturbance in postoperative patients. Many noncardiac etiological factors have been identified, including pain, hypovolemia, hypervolemia, fever, anemia, hypoxemia, pulmonary emboli, anxiety, infection, hypotension, and electrolyte abnormalities (especially hypokalemia). These noncardiac factors are much more common causes of sinus tachycardia in postoperative cardiac patients than is either myocardial infarction or heart failure. Sinus tachycardia not caused by congestive heart failure does not slow with cardiac glycosides.

Atrial fibrillation is also a common postoperative arrhythmia. Atrial dilatation, which lowers the threshold for development of this arrhythmia, can result from heart failure, mitral valve disease, and/or hypervolemia. Noncardiac precipitants include pneumonia, atelectasis, and pulmonary emboli. Initially, postoperative patients with atrial fibrillation should be treated with a beta-blocking agent, calcium channel antagonist, or digitalis. Cardioversion is usually delayed until the precipitating factors have been eliminated, because patients who undergo cardioversion before clearing of the atelectasis or pneumonia frequently have reversion to atrial fibrillation, whereas patients whose pulmonary problem or congestive heart failure is adequately treated often have spontaneous reversion to sinus rhythm.

In the case of coronary artery or cardiac valve surgery, postoperative atrial fibrillation is very common, occurring in up to 40 percent of patients,[124] and is associated with thromboembolic complications and prolonged hospital stays. Unlike the noncardiac surgery setting, most cases of postoperative atrial fibrillation do not appear to be associated with reversible noncardiac conditions. Therefore, early cardioversion can be beneficial. In one study, intravenous ibutilide was shown to be effective and safe for the treatment of postoperative atrial fibrillation following cardiac surgery.[125] It is not known whether ibutilide is as useful in the noncardiac surgery setting; however, these data suggest that when urgent cardioversion is indicated after noncardiac surgery, ibutilide should be considered.

Atrial flutter is often poorly tolerated because of the rapid ventricular rate and the difficult pharmacological management. Cardioversion is the treatment of choice.

IMPLICATIONS OF POSTOPERATIVE COMPLICATIONS FOR LONG-TERM MANAGEMENT.

When a patient develops a perioperative myocardial infarction, the evaluation and the recuperative process generally should be analogous to when a myocardial infarction occurs in other patients (see Chap. 35) . Because postoperative congestive heart failure is commonly precipitated by iatrogenic fluid overload, the patient commonly does not need long-term therapy for congestive heart failure. Similarly, perioperative arrhythmias are often precipitated by specific stimuli, and patients with a postoperative arrhythmia should not automatically be consigned to long-term antiarrhythmic therapy. In patients who develop either postoperative congestive heart failure or arrhythmias, it is often

appropriate to discontinue new cardiac

therapies several days before discharge and to observe patients to see whether long-term therapy is indicated.

THE ROLE OF THE MEDICAL CONSULTANT

The physician called on to evaluate the status of a patient with suspected or overt cardiac disease before elective or emergency noncardiac surgery first must determine whether cardiovascular disease is present and, if it is, must identify those factors that can increase the risk of operation. It may be necessary to invest considerable time and effort to prepare patients for operation. In addition, patients must be carefully monitored after operation to detect and manage the cardiac problems that frequently complicate the postoperative period.

PREPARATION OF PATIENTS FOR ANESTHESIA AND OPERATION.

Careful preparation of cardiac patients for operation may diminish the frequency and seriousness of intraoperative and postoperative complications. The medical consultant should, after appropriate discussion with the surgeon, be prepared to urge postponement or cancellation of an elective operation or to insist on sufficient time to institute any measures that are necessary to minimize risk. The consultant should attempt to be brief and to the point and to provide a limited number of explicit, relevant suggestions. The cardiological consultant should work closely with the anesthesiologist and the surgeon so that their talents may be combined to maximize the likelihood of a favorable outcome.

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GUIDELINES
SUMMARY OF GUIDELINES FOR REDUCING CARDIAC RISK WITH NONCARDIAC SURGERY

Thomas M. Lee

Guidelines on the assessment and management of perioperative risk of coronary artery disease in noncardiac surgery were published by the American College of Physicians (ACP) in 1997[1] and an American College of Cardiology/American Heart Association (ACC/AHA) task force in 1996.[2] These guidelines preceded research demonstrating the beneficial impact of beta blockers on high-risk patients undergoing noncardiac surgery,[3] [4] as well as the publication of the Revised Cardiac Risk Index.[5]

Both the ACP and the ACC/AHA guidelines emphasize the importance of using clinical data to stratify patients according to their risk of major cardiac complications. The ACP guidelines recommend use of a modification[6] of the Cardiac Risk Index of Goldman and colleagues.[7] Compared with this modification and other algorithms available when these guidelines were developed, the revised cardiac risk index[5] is more accurate and identifies a larger percentage of patients as having intermediate or high risk. Thus, this new index may be incorporated into future guidelines.

Low-risk patients may proceed directly to surgery, whereas special risk-reducing strategies (e.g., coronary angiography and revascularization) may be appropriate for very high-risk patients (Table 61-G-1) . Among patients undergoing vascular surgery, both guidelines also recommend focusing use of noninvasive testing for further risk stratification on those with intermediate clinical risk. The ACP guidelines differ from the ACC/AHA guidelines by recommending against noninvasive testing in nonvascular

patients with an intermediate risk determined by clinical evaluation.

These recommendations may be influenced in future revisions by randomized trial data demonstrating marked reductions in perioperative risk associated with treatment with bisoprolol in a population of patients who had abnormal results of stress echocardiography examinations and who underwent major vascular surgery.[3] These findings raise the possibility that an appropriate strategy may be to use beta blockers for intermediate- and high-risk patients rather than use noninvasive testing or coronary angiography to identify patients for revascularization. No prospective data show that testing or revascularization strategies can improve overall outcomes for patients undergoing noncardiac surgery.

TABLE 61--G-1 -- ACC/AHA GUIDELINES FOR MANAGEMENT OF CARDIAC RISK IN NONCARDIAC SURGERY

Issue	Class I	Class II	Class III
Recommendations for preoperative noninvasive evaluation of left ventricular function	Patients with current or poorly controlled CHF	Patients with prior CHF and patients with dyspnea of unknown cause	As a routine test of left ventricular function in patients without prior CHF
Perioperative therapy with beta blockers[*]	Beta blockers required in the recent past to control symptoms of angina or patients with symptomatic arrhythmias or hypertension	Preoperative assessment identifies untreated hypertension, known coronary disease, or major factors for coronary disease	Contraindication to beta blockade
Recommendations for intraoperative nitroglycerin	High-risk patients previously on nitroglycerin who have active signs of myocardial ischemia without hypotension	As a prophylactic agent for high-risk patients to prevent myocardial ischemia and cardiac morbidity, particularly in those who have required nitrate therapy to control angina	Patients with signs of hypovolemia or hypotension

Intraoperative use of pulmonary artery catheters	Patients at risk for major hemodynamic disturbances that are most easily detected by a pulmonary artery catheter who are undergoing a procedure that is likely to cause these hemodynamic changes in a setting with experience in interpreting the results (e.g., suprarenal aortic aneurysm repair in a patient with angina)	Either the patient's condition or the surgical procedure (but not both) places the patient at risk for hemodynamic disturbances (e.g., total hip replacement in a patient with chronic renal insufficiency)	No risk of hemodynamic disturbances

CHF=congestive heart failure; Class I=Appropriate indication; Class II=equivocal indication; Class III=contraindicated. For definitions, see p. 1714.

From Guidelines for perioperative evaluation for noncardiac surgery: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 93:1278-1317, 1996.

*Recommendations precede prospective randomized trials demonstrating beneficial impact of beta blockade on outcomes.[3] [4]

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Part VIII - CARDIOVASCULAR DISEASE AND DISORDERS OF OTHER ORGAN SYSTEMS

Chapter 62 - Hemostasis, Thrombosis, Fibrinolysis, and Cardiovascular Disease

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BASIC MECHANISMS OF HEMOSTASIS AND THROMBOSIS

The human hemostatic system has evolved as a remarkably orchestrated scheme of linked activities designed to preserve the integrity of blood circulation. Hemostasis is regulated to promote blood fluidity under normal circumstances. It is also prepared to clot blood with speed and precision at sites of vascular damage to arrest blood flow and

prevent exsanguination whenever and wherever the integrity of the circulation is disrupted. Finally, hemostasis has the capability to restore blood flow and perfusion upon subsequent healing of a damaged vessel. The major components of the hemostatic system include (1) the vessel wall itself, (2) plasma proteins (the coagulation and fibrinolytic factors), and (3) platelets (and probably other formed elements of blood, such as monocytes and red cells). These constituents function virtually inseparably (Fig. 62-1) . Although they are discussed in this chapter individually, it is important to recognize the interdependence of the actions of the vessel wall, plasma clotting factors, and platelets.

Figure 62-1 Interactions between the major components of the hemostatic system: the vessel wall, plasma proteins (clotting and fibrinolytic factors), and platelets.

Vascular Endothelium

A monolayer of endothelial cells lines the intimal surface of the entire circulatory tree, thereby representing the only stationary cell type that components of blood ever come in contact with under normal circumstances. The endothelial surface of the adult human is enormous: It is composed of about 1 to 6×10^{13} cells, weighs approximately 1 kg, and covers a surface area equivalent to about six tennis courts.[1] [2] Yet, as recently as the first half of the 20th century, endothelial cells were viewed simply as barriers of blood flow, acting "merely in a negative manner," "similarly to a layer of paraffin or oil."[3] Today, we recognize that endothelium is a dynamic organ with complex metabolic capabilities, including the ability to control vascular permeability, the flow of biologically active molecules and nutrients, cell-cell and cell-matrix interactions within the vessel wall, blood flow and vascular tone, interactions of blood cells, the inflammatory response, and angiogenesis.

Endothelium is also an ideal regulator of hemostasis.[4] [5] It is endowed with a remarkable repertoire of activities that permit it to rapidly transform from a potent antithrombotic to a prothrombotic surface wherever the need arises. Indeed, attempts to reproduce these properties in clinical settings such as cardiovascular prostheses, extracorporeal circuits, and bypass grafts by pharmacological or even gene transfer methods have proven suboptimal, leading to more recent approaches to tissue engineering of vessels.[6]

Normal, quiescent endothelium constitutively displays a potent antithrombotic (thromboresistant) surface to blood (Fig. 62-2) . It expresses anticoagulant, profibrinolytic, and platelet inhibitory properties. Whenever endothelium is activated or perturbed, however, it is rapidly transformed to a prothrombotic surface that actually promotes coagulation, inhibits fibrinolysis, and activates platelets. These are not entirely

uniform phenomena, however. Throughout the circulatory

Figure 62-2 Balance of antithrombotic and prothrombotic properties of vascular endothelium. In general, antithrombotic properties dominate in quiescent endothelium under normal physiological conditions. In contrast, prothrombotic properties are expressed whenever endothelium is perturbed or activated. GAGs=glycosaminoglycans; AT III=antithrombin III; TFPI=tissue factor pathway inhibitor; t-PA=tissue-type plasminogen activator; u-PA=urokinase-type plasminogen activator; PAI=plasminogen activator inhibitor; TAFI=thrombin-activatable fibrinolysis inhibitor; vWF=von Willebrand factor; PAF=platelet-activating factor.

Figure 62-3 Regulation of vascular tone by the balance of endothelium-derived vasodilators and vasoconstrictors. ADPase=adenosine diphosphatase; EDHF=endothelium-derived hyperpolarizing factor; PAF=platelet-activating factor; TXA_2 =thromboxane A_2 .

tree, even within a single organ, there is marked heterogeneity in the phenotype of endothelial cells.[7] [8] [9] [10] [11] With respect to hemostasis, for example, endothelial cells from different tissues are heterogeneous in their expression of von Willebrand factor, plasminogen activators, and tissue factor.[1] [12] [13] This endothelial heterogeneity is determined by both genetic and environmental factors. Exposure to different microenvironmental stimuli, including variable hemodynamic forces and cellular and humoral mediators, contributes significantly to the heterogeneity of endothelial phenotypes that develops throughout the circulation.[14]

The specific antithrombotic and prothrombotic properties of endothelial cells that are shown in Figure 62-2 are described in more detail in the following sections. The hemostatic conversion of the vessel wall is triggered by mechanical damage or by perturbation and activation of the vascular cells by agents such as cytokines, endotoxin, hypoxia, and hemodynamic forces.

Similarly, as illustrated in Figure 62-3 , a delicate balance exists in the capability of endothelial cells to modulate vascular tone. An important physiological vasodilator released by endothelial cells is nitric oxide (NO), a simple diatomic gas synthesized from the terminal guanidino nitrogen atoms of L-arginine by the action of a group of enzymes known as nitric oxide synthases (NOSs).[15] [16] [17] [18] [159A] [173A] The major isoform of NOS present in endothelial cells, eNOS, is constitutively active and is further activated by stimuli that increase intracellular calcium, including several receptor-dependent agonists (e.g., thrombin) and hemodynamic forces (shear stress and cyclic stretch).[19] NO acts as a potent vasodilator as well as an inhibitor of platelet adhesion and platelet aggregation by stimulating soluble guanylate cyclase and thereby elevating intracellular levels of cyclic guanosine monophosphate in vascular smooth muscle cells and platelets. Prostaglandin I_2 (PGI_2 , prostacyclin) is a major endothelium-derived oxygenation product of arachidonic acid, synthesized by the sequential actions of cyclooxygenase (COX) and prostacyclin synthase.[4] [20] [21] Prostacyclin, like NO, is both a vasodilator and inhibitor of platelet aggregation (but not adhesion), exerting these actions by stimulating adenylate cyclase and thereby

elevating intracellular cyclic adenosine monophosphate (AMP) in target vascular smooth muscle and platelets. Endothelium-derived hyperpolarizing factor (EDHF)[21] [22] [23] and carbon monoxide (CO), a byproduct of heme metabolism to biliverdin by heme oxygenases,[24] are also direct vasodilators elaborated by endothelial cells. Endothelial ecto-adenosine diphosphatase (ADPase), recently identified as CD39,[25] is a membrane-associated platelet inhibitor but may also indirectly promote vasodilation by generating adenosine.[5] These vasodilator properties of endothelium are counterbalanced by endothelium-derived vasoconstrictors, including platelet-activating

factor,[26] [27] endothelin-1,[28] [29] [30] and thromboxane A_2 (TXA_2).[31]

In many cases, endothelium-derived vasodilators are also platelet inhibitors and, conversely, endothelium-derived vasoconstrictors can also be platelet activators. The net effect of vasodilation and inhibition of platelet function is to promote blood fluidity, whereas the net effect of vasoconstriction and platelet activation is to promote hemostasis. Thus, as indicated in Figures 62-2 and 62-3 , blood fluidity and hemostasis can be exquisitely regulated by the balance of antithrombotic/prothrombotic and vasodilatory/vasoconstrictor properties of endothelial cells, which are often coordinately modulated by their relative states of quiescence and activation.[5]

Coagulation

Plasma coagulation proteins ("clotting factors") normally circulate in plasma in their biologically inactive zymogen (or proenzyme) forms. When the thromboresistant nature of the vascular system is altered, by either mechanical injury or inflammatory and other systemic stimuli, (e.g., coronary plaque rupture in patients who develop unstable angina), the coagulation system is activated. If the physiological antithrombotic defenses can be overwhelmed, the result will be the formation of hemostatic thrombi composed of platelets and fibrin. In cases where activation of the coagulation system is triggered by focal vascular injury, the occlusive hemostatic thrombus will be precisely localized at and limited to the site of damage.

The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a "waterfall" or a "cascade" (Fig. 62-4) . The coagulation cascade is a highly coordinated and regulated series of linked enzymatic reactions that involves the sequential activation of plasma zymogens to serine proteases. Each protease then catalyzes the subsequent zymogen-protease transition by cleavage of peptide bonds. This creates a biochemical amplifier in which a small initiating stimulus rapidly generates high levels of the end product fibrin.[32] [33] [34] Our understanding of the coagulation cascade has been refined with the recognition that it actually involves a series of linked enzymatic multiprotein complexes, each consisting of a serine protease, one or more cofactor proteins, divalent cations, and a cellular surface (e.g., platelet membranes) on which these components can be assembled.[34]

Two pathways of blood coagulation have been recognized: the so-called intrinsic or contact activation pathway and the so-called extrinsic or tissue factor pathway. These two pathways of activation of the coagulation cascade converge to form a "common" pathway, which leads to the generation of the pivotal coagulation enzyme thrombin. As illustrated in Figure 62-4 , thrombin not only catalyzes the conversion of fibrinogen to fibrin but also serves an important role in sustaining the cascade by feedback activation of coagulation factors at several strategic sites.

INTRINSIC PATHWAY.

This pathway of coagulation is triggered by the autoactivation of factor XII to its active serine protease form (factor XIIa) on "negatively charged" surfaces, optimally in the presence of two other contact activation proteins, prekallikrein and high-molecular-weight kininogen.[35] The physiological negatively charged surface for contact activation of factor XII and the intrinsic pathway of coagulation is really the cell membrane, which serves as a foundation for the assembly and activation of these proteins.[36] Factor XIIa converts the zymogen factor XI to its corresponding serine protease, factor XIa. Factor XIa, in turn, then serves as an activator of factor IX to IXa. The final step in the intrinsic pathway is the activation of the plasma zymogen factor X to factor Xa by factor IXa, a reaction that requires the activated form of the plasma cofactor, factor VIIIa. Factor VIIIa is generated by thrombin-induced limited proteolysis of factor VIII.

In vivo, however, coagulation is probably not initiated primarily by this intrinsic pathway. The most compelling support of this is the

Figure 62-4 The coagulation cascade. This scheme emphasizes recent understanding of the importance of the tissue factor pathway in initiating clotting in vivo, the interactions between pathways, and the pivotal role of thrombin in sustaining the cascade by feedback activation of coagulation factors. TF=tissue factor; PK=prekallikrein; HMWK=high-molecular-weight kininogen; PL=phospholipid; PT=prothrombin; Th=thrombin. (Modified from Schafer AI: The primary and secondary hypercoagulable states. *In* Schafer AI [ed]: Molecular Mechanisms of Hypercoagulable States. Austin, TX, Landes Bioscience, 1997, pp 1-48.)

clinical observation that individuals with inherited deficiencies of any of the contact activation factors (factor XII, prekallikrein, high-molecular-weight kininogen) do not have a bleeding tendency. Thus, it has been argued that this system has little to do with the initiation of hemostasis.[36] In fact, these proteins may play important roles in other physiological systems, such as vasoregulation and as antithrombotic and profibrinolytic agents.[37] In contrast, individuals with deficiencies of factors XI, IX, or VIII do have clinical bleeding tendencies; and, therefore, these proteins in the intrinsic pathway do appear to play important roles in hemostasis. The participation of factor XI in hemostasis is therefore probably not dependent on its activation by factor XIIa but rather on its positive feedback activation by thrombin. Thus, this positive feedback loop (see Fig. 62-4) would permit factor XIa to function in the propagation and amplification, rather than in the initiation, of the coagulation cascade.

EXTRINSIC PATHWAY.

Coagulation in vivo is probably initiated predominantly through the extrinsic pathway. The immediate trigger is the injury-induced expression of the integral membrane glycoprotein tissue factor[38] [39] [40] on the surfaces of activated endothelial cells and circulating blood cells (particularly leukocytes), cells that normally do not express tissue factor activity on their surfaces.[41] Alternatively, vascular damage can expose blood to tissue factor that is constitutively expressed on the surfaces of subendothelial cellular components of the vessel wall, such as smooth muscle cells and fibroblasts. The serine protease

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factor VIIa (activated factor VII) circulates in blood at trace levels[42] but possesses very poor enzymatic activity in its free form. Exposure of blood to cell surface tissue factor activates coagulation by binding this free factor VIIa. The tissue factor/factor VIIa complex then acts as a bimolecular enzyme to rapidly autocatalyze the conversion of factor VII to VIIa, thereby generating more tissue factor/factor VIIa complexes and amplifying this initial hemostatic response.[43] Factor Xa and thrombin can also induce factor VII activation (see Fig. 62-4) ; in fact, these two enzymes may be kinetically preferred over the tissue factor/factor VIIa complex as physiological activators of factor VII.[44] The final reaction in the extrinsic pathway is the activation of factor X to factor Xa. This can be catalyzed directly by the tissue factor/factor VIIa bimolecular enzyme complex. Alternatively, the complex can indirectly activate factor X by initially converting factor IX to factor IXa (providing communication between the extrinsic and intrinsic pathways of coagulation), which then activates factor X. This indirect route of factor X activation is probably the one that is favored kinetically.

COMMON PATHWAY.

Factor Xa, which can be formed through the actions of either the tissue factor/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor), initiates the common pathway of coagulation by converting the inactive plasma zymogen prothrombin to thrombin, the pivotal protease of the coagulation system. The essential cofactor for this reaction is factor Va, a plasma protein that shares about 30 percent sequence identity to the other plasma coagulation cofactor, factor VIIIa. Like the homologous factor VIIIa, factor Va is produced by thrombininduced limited proteolysis of factor V. As noted earlier and further described later, thrombin is a multifunctional enzyme, but its major role in the common pathway is to convert soluble plasma fibrinogen to an insoluble fibrin matrix.[45] Fibrin polymerization involves an orderly process of intermolecular associations.[46] Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor XIIIa, a transglutaminase that covalently cross-links and thereby stabilizes the fibrin clot.[46] [47]

The coagulation cascade that culminates in fibrin formation would occur extremely inefficiently and slowly in fluid phase plasma. However, the assembly of these clotting

factors on activated cell membrane surfaces greatly accelerates their reaction rates and also serves to localize blood clotting to sites of vascular injury.[32] [34] [38] In addition, proteases in the coagulation factor complexes assembled on cell surfaces are sequestered from inactivation by their physiological antithrombotic regulators described later, further enhancing the efficiency of membrane-dependent reactions. The critical cell membrane components on which these coagulation reactions proceed are acidic phospholipids. These phospholipid species are not normally exposed on resting cell membrane surfaces. However, when platelets, monocytes, and endothelial cells are activated by vascular injury or inflammatory stimuli, the procoagulant head groups of the membrane anionic phospholipids become translocated to the surfaces of these cells, making them available to support and promote the plasma coagulation reactions.[48] [49]

PROTHROMBINASE COMPLEXES.

Major membrane phospholipid-associated enzyme complexes in the coagulation cascade include the "Xase" (or tenase) and "prothrombinase" complexes (Fig. 62-5) . Each complex consists of a serine protease enzyme, its zymogen substrate, and its cofactor assembled in association with each other on the membrane surface. The "extrinsic Xase" complex consists of the tissue factor/factor VIIa enzyme complex and its zymogen substrates, factor IX and factor X. The "intrinsic Xase" complex consists of factor IXa as the enzyme, factor X as its substrate, and factor VIIIa as the cofactor. The "prothrombinase complex" consists of factor Xa as the enzyme, prothrombin (factor II) as its substrate, and factor Va as the cofactor. Factor IXa generated by the "extrinsic Xase" complex becomes the enzyme of the "intrinsic Xase" com

Figure 62-5 Schematic representation of the phospholipid membrane-associated enzyme complexes of coagulation. Each vitamin K-dependent serine protease (factors VIIa, IXa, and Xa and alpha-thrombin [IIa]) is shown in association with its cofactor protein (tissue factor [TF], factors VIIIa and Va, and thrombomodulin [TM]) and zymogen substrate(s) (factors IX and X, prothrombin [II] and protein C [C]) on the membrane surface. The cofactor proteins, factor VIIIa and factor Va, are characterized by a two-domain structure and consist of heavy (H) and light (L) chains that are bridged together by Ca^{2+} ions. Both domains are required for cofactor-membrane association and cofactor-protease binding. (Modified from Jenny NS, Mann KG: Coagulation cascade: An overview. *In* Loscalzo J, Schafer AI [eds]: Thrombosis and Hemorrhage. 2nd ed. Baltimore, Williams & Wilkins, 1998, pp 3-27.)

plex. Factor Xa generated by either the "extrinsic Xase" or the "intrinsic Xase" complex becomes the enzyme of the "prothrombinase" complex. These successive reaction complexes of coagulation most likely occur by diffusion of products along the same cell membrane surface.[34]

The final enzyme product, thrombin, is detached from cell membranes and out into the blood to serve its multiple purposes. A major terminating reaction, also shown in Figure 62-5 , involves membrane assembly of the "protein Case" complex in which free

thrombin (factor IIa) binds to the integral membrane protein, thrombomodulin, which serves as the site for activation of protein C, a major antithrombotic protein discussed later in the chapter.

Anticoagulant (Antithrombotic) Mechanisms

Several physiological antithrombotic mechanisms act in concert to prevent clotting under normal circumstances. Optimal activity of each of the anticoagulant systems depends on the integrity of vascular endothelium. Thus, these physiological mechanisms operate to preserve blood fluidity in the intact circulation and also to limit blood clotting to specific focal sites of vascular injury.[50]

Endothelial PGI_2 , nitric oxide, ADPase, and carbon monoxide are physiological platelet inhibitory mediators (see Fig. 62-2). Other anticoagulant systems are designed to limit fibrin accumulation. Several of these mechanisms, including antithrombin, the protein C/protein S/thrombomodulin system and tissue factor pathway inhibitor (TFPI), act at different sites in the coagulation cascade to dampen fibrin accumulation. Fibrin that forms despite these anticoagulant defenses is then degraded by the fibrinolytic system. The sites of action of the major physiological antithrombotic pathways are shown in Figure 62-6.

ANTITHROMBIN.

Antithrombin (or antithrombin III) is the major plasma protease inhibitor of thrombin and the other clotting factors in the intrinsic and common pathways of coagulation. It is a single-chain glycoprotein that is synthesized primarily in the liver and belongs to the serine protease inhibitor ("serpin") family of proteins.[51] [52] Antithrombin neutralizes thrombin and other activated coagulation factors by forming a complex between the active site of the enzyme and the reactive center (Arg393 and Ser394) of antithrombin. The rate of formation of these inactivating complexes increases by a factor of several thousand in the presence of heparin. This is the major anticoagulant mechanism of action of heparin (see later). Heparin and heparan sulfate proteoglycans are actually present as endogenous components of the vessel wall. Thus, antithrombin inactivation of thrombin and other activated clotting factors probably occurs physiologically on vascular surfaces, where heparins are present to catalyze these reactions, rather than in fluid phase plasma. Inherited quantitative or qualitative deficiencies of antithrombin lead to a lifelong predisposition to venous thromboembolism.[11] , [32] , [50] , [53]

PROTEIN C/PROTEIN S/THROMBOMODULIN.

Protein C is another plasma glycoprotein synthesized by the liver, which becomes an anticoagulant when it is activated by thrombin through cleavage of an Arg169-Leu170 bond in its heavy chain.[54] [55] The thrombin-induced activation of protein C occurs physiologically on thrombomodulin, a transmembrane proteoglycan binding site for thrombin on endothelial cell surfaces.[56] [57] Thrombomodulin thus serves an antithrombotic function both by binding and thereby removing thrombin from the circulation and also by promoting generation by thrombus of anticoagulantly active

protein C. Activated protein C acts as an anticoagulant by cleaving multiple bonds and thereby destroying the membrane-bound activated forms of coagulation factors V (Va)

Figure 62-6 Sites of action of the four major physiological antithrombotic pathways: antithrombin (AT); protein C/protein S (PC/PS); tissue factor pathway inhibitor (TFPI); and the fibrinolytic system, consisting of plasminogen, plasminogen activator (PA), and plasmin (Pl). (From Schafer AI: The primary and secondary hypercoagulable states. *In* Schafer AI [ed]: Molecular Mechanisms of Hypercoagulable States. Austin, TX, Landes Bioscience, 1997, pp 1-48.)

and VIII (VIIIa). This reaction is accelerated by a cofactor, protein S. Like protein C, protein S is a glycoprotein that undergoes vitamin K-dependent posttranslational carboxylations to form gamma-carboxyglutamic acid ("Gla") residues that allow it to bind to negatively charged phospholipid surfaces. Protein S acts as a cofactor by increasing the affinity of activated protein C for phospholipids in the formation of the membrane-bound protein Case complex (see Fig. 62-5) . Quantitative or qualitative deficiencies of protein C or protein S, or resistance to the action of activated protein C by a specific mutation at its target cleavage site in factor Va (factor V Leiden), lead to hypercoagulable states.[11] [32] [50] [53]

TISSUE FACTOR PATHWAY INHIBITOR.

TFPI is a plasma protease inhibitor that regulates the tissue factor-induced extrinsic pathway of coagulation.[58] Unlike other coagulation inhibitors, which are members of the serpin family, TFPI is a multivalent Kunitz-type serine protease inhibitor. This structure permits TFPI to exert dual inhibitory actions against both tissue factor/factor VIIa (mediated by its Kunitz-1 domain binding to factor VIIa), as shown in Figure 62-6, as well as factor Xa (mediated by its Kunitz-2 binding to factor Xa). Circulating plasma TFPI is bound to lipoproteins. TFPI can also be released by heparin from endothelial cells, where it is bound to glycosaminoglycans, and from platelets.

THE FIBRINOLYTIC SYSTEM.

Any thrombin that escapes the inhibitory effects of the physiological anticoagulant systems described earlier is available to convert fibrinogen to

fibrin. In response, the endogenous fibrinolytic system is then activated to dispose of intravascular fibrin and thereby maintain or reestablish the patency of the circulation. Just as thrombin is the key protease enzyme of the coagulation system, plasmin is the major protease enzyme of the fibrinolytic system, acting to digest fibrin to fibrin degradation products. The general scheme of fibrinolysis and its control is shown in Figure 62-7 .

Plasminogen, the inactive zymogen form of plasmin, is synthesized primarily in the liver and circulates in plasma in high (micromolar) concentrations. It is a single-chain glycoprotein, which has significant sequence homology with apolipoprotein (a). Elevated plasma levels of lipoprotein (a) are associated with atherosclerotic cardiovascular risk.[59] Indeed, one possible atherogenic mechanism for lipoprotein (a) might be to inhibit fibrinolysis by competing with plasminogen for plasmin generation.

Plasminogen Activators.

These cleave the Arg560-Val561 bond of plasminogen to generate the active enzyme plasmin, a two-chain molecule that derives its heavy chain (or A chain) from the amino-terminal region and its light chain (or B chain) from the carboxy-terminal region of plasminogen. The enzyme-active site of plasmin is localized in the B chain, whereas the A chain contains lysine-binding sites. The lysine-binding sites of plasmin (and plasminogen) permit it to bind to fibrin, so that physiological fibrinolysis is "fibrin specific." Plasmin is a serine protease the actions of which are not limited to fibrinolysis; plasmin also plays important roles in tissue remodeling, wound healing, angiogenesis, and cell migration.[60]

The major physiological plasminogen activators that convert plasminogen to plasmin are tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Both are serine proteases that are released by endothelial cells into plasma in trace concentrations. Plasmin can convert t-PA from its single-chain form to a two-chain molecule, in which the heavy and light chains are disulfide bonded. Both the single-chain and two-chain forms of t-PA are catalytically active to convert plasminogen to plasmin. In contrast, single-chain u-PA (scu-PA) has little enzyme activity and must be converted to its disulfide bonded, two-chain active form by hydrolysis of a Lys158-Ile159 bond. t-PA and u-PA are released from endothelial cells by a variety of humoral factors (e.g., growth factors, hormones, and cytokines), as well as hemodynamic forces, but many of these stimuli also induce the release of plasminogen activator inhibitors.

Both plasminogen (through its lysine-binding sites) and t-PA possess specific affinity for fibrin and thereby bind selectively to clots. In the absence of fibrin, t-PA activates

Figure 62-7 Scheme of the fibrinolytic system and its control.

plasminogen to plasmin relatively slowly. Fibrin provides a surface for the sequential binding of t-PA and plasminogen. The assembly of a ternary complex, consisting of fibrin, plasminogen, and t-PA, promotes the localized interaction between plasminogen and t-PA and thereby greatly accelerates the rate of plasminogen activation to plasmin. Moreover, partial degradation of fibrin by plasmin exposes new plasminogen and t-PA binding sites in carboxy-terminus lysine residues of fibrin fragments to enhance further these reactions. Thus, early fibrin digestion by plasmin further accelerates fibrinolysis, thereby amplifying the process. This creates a highly efficient mechanism to generate

plasmin focally on the fibrin clot, which then becomes plasmin's substrate for digestion to fibrin degradation products. Thus, the fibrin surface itself is an important regulator of its own degradation by providing binding sites for fibrinolytic proteins.

In addition to its interactions with fibrin, components of the fibrinolytic system are also efficiently assembled on cell surfaces, similar to the coagulation system, to localize and kinetically optimize the generation of plasmin.[61] [62] Specific binding sites for plasminogen and t-PA are present on the surfaces of endothelial cells, identified with annexin II, and other cell surfaces[63] to catalyze plasminogen activation. The presence of u-PA receptors (u-PAR) has also been identified on endothelial cells and other cell types.

The capacity of endothelial cells to synthesize and release plasminogen activators and then to bind these and other components of the fibrinolytic system provides a powerful paracrine mechanism to concentrate and activate fibrinolysis in proximity to intravascular thrombi contiguous to sites of endothelial damage. At the same time, receptors for the fibrinolytic proteins are also present on the surfaces of other cell types, including platelets and leukocytes that accumulate within thrombi.[64]

Plasmin cleaves fibrin at different rates at different sites of the fibrin molecule. This orderly process leads to the generation of characteristic fibrin fragments during the process of fibrinolysis. At the end of this sequential proteolysis, the D and E domains of fibrin are liberated. The sites of plasmin cleavage of fibrin are the same as those in fibrinogen. However, when plasmin acts on covalently cross-linked fibrin, D-dimers are released; hence, D-dimers can be measured in plasma as a relatively specific test of fibrin (rather than fibrinogen) degradation. Fibrin(ogen) degradation products may have potent anticoagulant and antiplatelet actions, thereby further contributing to the net antithrombotic effects of fibrinolysis.

Fibrinolytic Inhibitors.

As shown in Figure 62-7 , physiological regulation of fibrinolysis occurs primarily at two levels: (1) Plasminogen activator inhibitors (PAIs), specifically PAI-1 and PAI-2, inhibit the physiological plasminogen activators, and (2) $alpha_2$ -antiplasmin inhibits plasmin. PAI-1 is the primary inhibitor of t-PA and u-PA in plasma.[65] [66] This serine protease inhibitor is a single-chain glycoprotein derived from endothelial cells and other cell types. PAI-1 inhibits t-PA by the formation of a complex between the active site of t-PA and the "bait" residues (Arg346-Met347) of PAI-1.[67]

PAI-2, which also belongs to the serpin superfamily, was originally identified in trophoblastic epithelium and hence is referred to as placental-type PAI.[68] Particularly elevated plasma levels of PAI-2 are found in pregnant women. $Alpha_2$ -antiplasmin is a single-chain glycoprotein serpin that is synthesized predominantly by the liver. It is the main inhibitor of plasmin in human plasma, forming a 1:1 stoichiometric complex with plasmin that inactivates the enzyme.[67] $Alpha_2$ -macroglobulin also inhibits plasmin, but at a much slower rate than $alpha_2$ -antiplasmin; therefore, $alpha_2$ -macroglobulin is of

questionable importance in the physiological regulation of fibrinolysis.

Platelets

Platelets are cytoplasmic fragments that are released into blood from bone marrow megakaryocytes and circulate with an average life span of 7 to 10 days.[69] These terminal cell fragments are anucleate and therefore possess minimal capacity to synthesize new protein.

Figure 62-8 Sequence of events in platelet activation. *A,* Under normal conditions, a monolayer of endothelial cells lines the intimal surface of the circulatory tree, releasing platelet-inhibitory mediators such as PGI_2 (prostacyclin) and nitric oxide (NO). *B,* At a site of vascular injury, endothelium is lost and platelets undergo "adhesion" (platelet-vessel wall interactions) to subendothelial structures that are now exposed (e.g., collagen). *C,* Adherent platelets are activated, and release granule constituents (e.g., ADP, fibrinogen, von Willebrand factor) and thromboxane A_2 (TXA_2). *D,* Substances released from activated platelets recruit additional platelets from the circulation to the site of injury and mediate the process of platelet "aggregation" (platelet-platelet interactions), resulting in the formation of an occlusive platelet plug.

The antithrombotic properties of intact vascular endothelium include potent platelet inhibitors (see Fig. 62-2 and Fig. 62-8 *A*). These inhibitors include PGI_2 , NO, and CO, which are labile molecules that are released by endothelial cells and act locally as autocoids, and ADPase, an ectonucleotidase of endothelial membranes that breaks down platelet-activating ADP.

ADHESION.

On vascular intimal injury, the antiplatelet properties of endothelium are diminished locally, while previously cryptic, thrombogenic subendothelial substances (e.g., collagen) become exposed to flowing blood. Circulating platelets recognize sites of vascular disruption and undergo the process of adhesion to the site of injury (see Fig. 62-8 *B*). Adhesion results in the formation of a monolayer of platelets that are attached to the denuded vascular intimal surface. Platelet adhesion (i.e., platelet-vessel wall interaction) is mediated primarily by von Willebrand factor (vWF), a multimeric protein consisting of a wide spectrum of polymerized subunits that create a mature protein with a molecular mass that ranges from about 550 to more than 10,000 kDa, one of the largest soluble proteins in plasma.[70] [71] vWF is synthesized by both endothelial cells and megakaryocytes, where it is stored in Weibel-Palade bodies and alpha granules, respectively, before its regulated secretion. Released vWF is present in both plasma and in the extracellular matrix of the subendothelial vessel wall, to which the platelets are anchored. The large vWF multimers serve as the primary "molecular glue" to attach platelets to a damaged vessel wall with sufficient strength to withstand the high levels of shear stress that would tend to detach them with the flow of blood. The receptor for vWF

on the platelet surface is localized in membrane glycoprotein (Gp) Ib, part of the platelet membrane Gp Ib/IX-V complex.[72] [73] Higher levels of shear stress on the arterial side of the circulation promote the interaction between vWF and platelet membrane Gp Ib, probably through subtle shear-induced changes in the vWF molecule and/or its platelet receptor.[74] Platelet adhesion is also facilitated by direct binding to subendothelial collagen by means of specific platelet membrane collagen receptors.[75] [76] [77]

ACTIVATION.

Adherent platelets then become activated[78] (Fig. 62-8 *C*). The platelet activation process results from the combined actions of several agonists that bind to their respective membrane receptors on adherent platelets and transmit platelet-activating intracellular signals. These platelet stimuli include humoral mediators in plasma (e.g., epinephrine, thrombin), mediators released from activated cells (e.g., ADP, serotonin), and vessel wall extracellular matrix constituents that come in contact with adherent platelets (e.g., collagen, vWF). Several of these stimuli can synergistically activate platelets[79] [80] and may also act in concert with shear forces to which platelets are simultaneously exposed.[81] Activated platelets undergo the release reaction, during which they secrete prepackaged constituents of their cytoplasmic granules: ADP, adenosine triphosphate, and serotonin from the dense granules; soluble adhesive proteins (fibrinogen, vWF, thrombospondin, fibronectin); growth factors (including platelet-derived growth factor, transforming growth factor-alpha and transforming growth factor-beta); and procoagulants (platelet factor 4, factor V) from the alpha granules.[82] Simultaneously, activated platelets synthesize *de novo* and release the potent platelet activator and vasoconstrictor TXA_2 . TXA_2 is the major cyclooxygenase product of arachidonic acid metabolism in platelets. As described later in the section on antiplatelet agents, aspirin inhibits cyclooxygenase and thereby blocks TXA_2 synthesis in platelets.

TXA_2 acts in concert with several of the substances released from granules to induce the activation of additional platelets in the microenvironment of the developing thrombus.[83] [84]

AGGREGATION.

The products of the platelet release reaction, including secreted granule constituents and TXA_2 , mediate the final phase of platelet activation, the process of aggregation (see Fig. 62-8 *D*). During platelet aggregation (platelet-platelet interaction) additional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. As discussed earlier, the platelet plug is anchored and stabilized by the fibrin mesh that develops simultaneously as the product of the coagulation cascade. At lower shear levels (e.g., in the venous circulation), the "molecular glue" that mediates aggregation is fibrinogen, which can be derived either from plasma or from the alpha-granule releasate of activated platelets. At higher shear

levels (e.g., in arteries), vWF itself, which is also the ligand that mediates platelet adhesion, can substitute for fibrinogen as the ligand of aggregation.[74] Fibrinogen or vWF binds to specific platelet membrane receptors that are located in the Gp IIb/IIIa integrin complex.[85] [86] Integrins are widely distributed on the surfaces of adherent eukaryotic cells. All receptors in the integrin superfamily contain an alpha and a beta subunit. Individual integrins can often bind to more than one ligand; thus, platelet Gp IIb/IIIa can recognize both fibrinogen and vWF, as well as some other adhesive proteins.

The Gp IIb/IIIa complex is the most abundant receptor on the platelet surface. Its alpha subunit (Gp IIb) is expressed specifically on platelets, but its $beta_3$ subunit (Gp IIIa) is shared by other integrins, including receptors on vascular cells. The heterodimeric, ligand-binding Gp IIb/IIIa complexes are not normally exposed in their active forms on the surfaces of quiescent circulating platelets. However, platelet activation converts Gp IIb/IIIa into competent receptors by means of specific signal transduction pathways,[86] [87] enabling Gp IIb/IIIa to bind to fibrinogen and vWF. The binding of these adhesive proteins requires that they contain the specific tripeptide sequence Arg-Gly-Asp (RGD). Recognition of fibrinogen and other ligands by the active Gp IIb/IIIa complex involves the RGD tripeptide sequence (located at positions 95-97 and 572-574 of each of the two A-alpha chains of fibrinogen). When two activated platelets with functional Gp IIb/IIIa receptors each bind the same fibrinogen molecule, a fibrinogen bridge is created between the two platelets (Fig. 62-9). Because the surface of each platelet has about 50,000 Gp IIb/IIIa fibrinogen binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges.[88] In addition to its RGD sequences, the gamma chains of fibrinogen also contain a 12-amino acid residue (dodecapeptide HHLGGAKQAGDV) that also has the ability to bind to the platelet Gp IIb/IIIa receptor. These events of ligand binding to activated platelet membrane Gp IIb/IIIa receptors, which mediate the process of platelet aggregation, have served as targets for antiplatelet therapy with Gp IIb/IIIa antagonists.

Central Role of Thrombin

Thrombin plays a pivotal role in coordinating, integrating, and regulating hemostasis. Depending on the circumstances, it can either promote or prevent blood clotting. This multifaceted effect of thrombin has been referred to as the "thrombin paradox."[89] The balance of prothrombotic and antithrombotic activities of thrombin is determined by at least two variables: (1) the concentration of free thrombin in blood and (2) the presence or absence of endothelial cells at thrombin's site of action.

When free thrombin is available in blood at high concentrations, particularly at a site of vascular injury where

Figure 62-9 Linkage of two activated platelets by fibrinogen, which binds to its receptors in the platelet Gp IIb/IIIa complex by means of tripeptide RGD (arginine-glycine-aspartic acid) sequences located on the alpha chains of dimeric fibrinogen. The high density of Gp IIb/IIIa complexes on the surfaces of activated

platelets permits the rapid formation of a network of fibrinogen bridges, leading to platelet aggregation at the site of vascular injury. (In regions of high shear stress, such as in diseased coronary arteries, von Willebrand factor may replace fibrinogen as the primary aggregating ligand. Like fibrinogen, the von Willebrand factor molecule has RGD sequences that mediate this process.) The result of platelet aggregation is the formation of an occlusive platelet thrombus. (From Schafer AI: Antiplatelet therapy with glycoprotein IIb/IIIa receptor inhibitors and other novel agents. Tex Heart Inst J 24:90-96, 1997.)

the antithrombotic influence of endothelium is lost, thrombin is a potent inducer of clotting (Fig. 62-10) . This enzyme catalyzes several coagulation factor activation reactions that lead to fibrin formation, factor XIII activation to promote fibrin cross-linking, and activation and aggregation of platelets. In fact, under these procoagulant conditions, reciprocal, interdependent, and mutually self-amplifying interaction occurs between thrombin generation and platelet activation. Membranes of activated platelets facilitate thrombin generation by providing a surface for the assembly of coagulation factors and cofactors (Fig. 62-11 and described earlier). Conversely, thrombin is a potent activator of platelets, stimulating the availability of additional activated platelet surface for further thrombin generation. Thus, this reciprocal interaction between thrombin and platelets promotes and amplifies the formation of a tightly focused hemostatic plug composed of platelets and fibrin.

At lower concentrations of thrombin and in the presence of intact endothelium, the antithrombotic effects of thrombin predominate (see Fig. 62-10) . Low levels of thrombin stimulate increased levels of the endogenous circulating anticoagulant, activated protein C.[90] Accordingly, as shown in Figure 62-12 , a J curve describes the relationship between the thrombotic potential of blood and free thrombin concentration.[89] Furthermore, in the presence of normal endothelial cells in the intact circulation (see Fig. 62-10) , endothelial thrombomodulin removes free thrombin from blood and low concentrations of thrombin stimulate t-PA release and the release of antiplatelet PGI_2 and NO from endothelial cells. Thus, thrombin plays a central role in modulating the state of blood coagulability, depending on its free concentration in blood and the presence or absence of intact endothelial cells at its site of action.

Figure 62-10 Central role of thrombin in modulating the state of blood coagulability, depending on the presence or absence of intact endothelial cells (EC) at its site of action. In the presence of intact EC *(lower part of figure),* free thrombin is removed from the circulation by EC thrombomodulin and the antithrombotic effects of thrombin predominate: activation of protein C, release of tissue-type plasminogen activator (t-PA), and release of platelet-inhibitory nitric oxide (NO) and prostaglandin I_2 (PGI_2) by intact EC. In the absence of intact EC *(upper part of figure),* free thrombin is available in blood at higher concentrations and its prothrombotic effects predominate: activation of coagulation factors, fibrin formation and cross-linking, and activation of platelets (PLTS). PAI-1=plasminogen activator inhibitor-1.

Figure 62-11 Reciprocal interaction between thrombin generation and platelet activation. Membranes of

activated platelets facilitate thrombin generation by providing a surface for assembly of coagulation factors. Conversely, thrombin is a potent activator of platelets, thus acting to promote and amplify activation of the coagulation system. This reciprocal interaction results in the accelerated and tightly focused formation of a hemostatic plug composed of platelets and fibrin. (From Schafer AI: The primary and secondary hypercoagulable states. *In* Schafer AI [ed]: Molecular Mechanisms of Hypercoagulable States. Austin, TX, Landes Bioscience, 1997, pp 1-48.)

Figure 62-12 The thrombin paradox. At low concentrations of thrombin, protein C is activated and elevated activated protein C exhibits antithrombotic activity. At increasingly higher levels of thrombin, the procoagulant properties of thrombin become dominant and prothrombotic potential is markedly increased. (Adapted from Griffin JH: The thrombin paradox. Nature 378:337-338, 1995.)

ANTITHROMBOTIC DRUGS

Heparin

Because its onset of action is practically immediate when administered parenterally, heparin is the anticoagulant of choice when rapid anticoagulation is required.[91] Commercial preparations of unfractionated heparin consist of a heterogenous mixture of glycosaminoglycans, with molecular weights ranging from 3000 to 30,000.[91] [92] However, only about one third of the molecules in these products are anticoagulantly active. Heparin exerts its anticoagulant effect by interacting with antithrombin III (AT), as shown in Figure 62-13 (Figure Not Available) . A specific pentasaccharide sequence in heparin accounts for its ability to bind with high affinity to lysine sites on AT. In the absence of heparin, AT binds to and neutralizes thrombin and other activated clotting factors (see earlier) slowly; however, heparin-bound AT undergoes a conformational change that dramatically accelerates its ability to bind to and neutralize these factors. In these reactions, arginine reactive centers in AT bind to the enzyme active center serines of thrombin and other serine protease coagulation factors, thereby inhibiting their activities. Heparin then dissociates from these complexes and can be reused to bind to other AT molecules. Heparin thus acts as a true catalyst in accelerating the neutralization of thrombin and other activated clotting factors by AT.[93] Fibrin-bound thrombin is relatively protected from inactivation by the heparin/AT complex.

Heparin is poorly absorbed from the gastrointestinal tract and therefore must be administered parenterally. The complex pharmacokinetics of unfractionated heparin are due to its nonspecific binding to many plasma proteins (including some acute-phase reactants) and to vascular and blood cells. Provided that the doses used are adequate, the efficacy and safety of heparin are comparable when administered by continuous intravenous infusion or by subcutaneous injection.[94] Intermittent intravenous injections of heparin are associated with more bleeding complications than is continuous intravenous infusion.

HEPARIN MONITORING.

Because of unfractionated heparin's often unpredictable pharmacokinetics and its narrow therapeutic range, therapy with this agent requires laboratory monitoring for proper dosing.[95] This is conventionally performed with the activated partial thromboplastin time (aPTT), a test that is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. For the treatment of deep venous thrombosis or pulmonary embolism, heparin is usually initiated with an intravenous bolus of 5000 U, followed by continuous intravenous infusion of 30,000 to 35,000 U/24 hours that is subsequently adjusted to maintain the aPTT at one and one-half to two and one-half times the control value. To standardize and optimize management with intravenous heparin, dosage-adjustment nomograms (which can be adapted into preprinted order sheets) and computer algorithms have been used. Weight-adjusted nomograms for heparin treatment of unstable angina have been published.[96] Heparin can also be monitored by heparin levels using protamine titration (therapeutic range: 0.2 to 0.4 U/ml), or by antifactor Xa levels (therapeutic range: 0.3 to 0.6 U/ml), but these assays are more expensive and not available in all hospital laboratories. The aPTT is sensitive over a heparin range of 0.1 to 1.0 U/ml. Because the aPTT becomes immeasurably prolonged at heparin concentrations of more than 1.0 U/ml, this test is unsuitable for monitoring heparin dosage during percutaneous coronary interventions (angioplasty and stenting) and during cardiac bypass surgery, in which patients require higher levels of anticoagulation with heparin. In these procedures, heparin can be monitored by the activated clotting time, because this test provides a graded response to heparin concentrations in the range of 1 to 5 U/ml.[91]

Low-dose subcutaneous unfractionated heparin has also been used to prevent (rather than treat) venous thromboembolism in high risk patients. Doses of 5000 U every 8 or 12 hours generally do not prolong the aPTT and therefore do not require monitoring in this setting.

COMPLICATIONS.

The major complication of heparin is bleeding. Factors that predispose to increased bleeding risk include advanced age, serious concurrent illness, heavy consumption of alcohol, concomitant use of aspirin, and renal failure.[92] Due to its relatively short half-life, simple discontinuation of heparin is usually adequate to control bleeding complications. Protamine sulfate can be used in emergency situations with serious bleeding. Protamine, a strongly basic protein, practically instantaneously neutralizes heparin, which is highly negatively charged.

Two distinct types of thrombocytopenia are associated with heparin therapy. The more common form, which may occur in up to 15 percent of patients receiving therapeutic doses of heparin, is a benign and self-limited side effect. This dose-dependent, non-immune-mediated type of thrombocytopenia rarely causes severe reductions in the platelet count or clinical complications and usually does not require discontinuation of heparin. In contrast, the rarer, immune form of heparin-induced thrombocytopenia (HIT) can, paradoxically, cause serious, limb- and life-threatening arterial as well as venous

thrombosis. The mechanism in these cases is the interaction of antibody (usually IgG) with a complex of heparin and platelet factor 4 (PF4) on the surfaces of platelets from which PF4 is released upon activation.[97] [98] This complex results in the activation of platelets through their FcgammaIIa receptors and their intravascular aggregation, which may cause apparently paradoxical thrombosis in the presence of thrombocytopenia. In HIT, the platelet count decreases, often precipitously, characteristically 5 to 10 days after starting heparin.

Figure 62-13 (Figure Not Available) Mechanism of heparin action. (Modified from Rosenberg RD: Hemorrhagic disorders: I. Protein interactions in the clotting mechanism. *In* Beck WS [ed]: Hematology. 5th ed. Cambridge, MIT Press, 1991, pp 507-542.)

The decline in platelet count in HIT is usually moderate, with a typical nadir of 50,000 to 60,000/mm[3] . However, HIT can cause severe thrombocytopenia even in the absence of thrombosis; and, conversely, heparin-induced thrombosis can actually occur with a normal platelet count. Immune-mediated HIT is not heparin dose dependent and can develop with low-dose heparin or even with heparin flushes or the use of heparin-bonded catheters. There is no single, definitive laboratory test to ascertain the diagnosis of HIT. Laboratory testing for HIT can involve functional assays in which the heparin-induced activation of platelets in vitro is tested by aggregation, serotonin release, or platelet activation markers.[98] Alternatively, enzyme immunoassays of antibody-heparin-PF4 complexes can be used to test for HIT.[99]

When HIT is suspected, any source or route of heparin being administered to the patient must be discontinued immediately. Because many such patients need continued anticoagulation for the underlying problem that required heparin, alternative treatment may include danaparoid, a mixture of low-molecular-weight anticoagulant glycosaminoglycans with relatively weak cross-reactivity with HIT sera,[100] or a direct thrombin inhibitor such as hirudin[101] or argatroban, a small-molecule synthetic antithrombin.[102] Low-molecular-weight heparins (LMWH) should not be substituted for heparin because they have stronger cross-reactivity with HIT sera.[98] [103]

Other side effects of heparin include cumulative dose-dependent osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, and hypoaldosteronism.[92] Heparin is the anticoagulant of choice during pregnancy; unlike warfarin, it does not cross the placenta and is not teratogenic.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins are manufactured from standard, unfractionated heparin by chemical or enzymatic depolymerization that yields fragments about one-third the size of unfractionated heparin.[104] [105] [106] An important mechanism of action of LMWH that presumably provides them with therapeutic and safety advantages over unfractionated heparin is their ability to inhibit and neutralize factor Xa relatively selectively. Inhibition of thrombin requires that heparin bind to both AT and thrombin,

thereby forming a ternary complex (Fig. 62-14) .[104] Ternary complex formation requires that heparin contain at least 18 saccharide residues, including the high-affinity pentasaccharide sequence that binds to AT. In contrast, inhibition of factor Xa requires that heparin bind only to AT; hence, only the pentasaccharide sequence of heparin is needed for this simpler reaction. Most heparin chains in LMWH preparations have less than 18 saccharide units and therefore are of insufficient length to bind to both AT and thrombin. However, the shorter heparin fragments in LMWH are able to catalyze the inhibition of factor Xa by AT, provided that they contain the essential pentasaccharide sequence. Thus, the effects of LMWH in the coagulation cascade are restricted to relatively selective inactivation of factor Xa, while standard (unfractionated) heparin has equivalent inhibitory activity against factor Xa and thrombin.

LMWH has been considered theoretically superior to standard heparin in several additional ways.[106] [106A] First, unlike unfractionated heparin, it can inhibit platelet-bound factor Xa and therefore should be a more effective anticoagulant. Second, LMWH binds less readily to plasma proteins (including acute phase reactants) and vascular and blood cells, and LMWH is more resistant to neutralization by platelet factor 4; this produces a longer plasma half-life, more predictable bioavailability, and more favorable pharmacokinetics than standard heparin. Third, LMWH has less pronounced effects on platelet function and vascular integrity, properties that presumably contribute to its lower risk of bleeding complications than standard heparin. The longer plasma half-life and more predictable anticoagulant response of LMWH preparations allow their administration as fixed-dose, once-daily or twice-daily subcutaneous injections, without need for laboratory monitoring. The convenience of use of LMWH has been extended to outpatient management of patients with uncomplicated acute venous thromboembolism, a situation that previously required continuous intravenous heparin infusion in the hospital.[105] Although several LMWH preparations have been approved for use in North America and Europe, they are prepared by different depolymerization methods and have somewhat different molecular compositions, pharmacological properties, and anticoagulant profiles.[107] Therefore, caution should be exercised in the interchangeability of these LMWH products.

Many (though not all) studies have shown that LMWH

Figure 62-14 Mechanisms of inhibitory action of unfractionated heparin (heparin) and low-molecular-weight heparin (LMWH) on thrombin and factor Xa. Both unfractionated heparin and LMWH bind to antithrombin (AT) through a high-affinity pentasaccharide sequence (5) that both types of heparin contain. Inhibition of thrombin *(left side of figure)* requires formation of a ternary complex of heparin with both antithrombin (AT) and thrombin. Unfractionated heparins have sufficient length (18 saccharide residues, including the pentasaccharide sequence) to accomplish this, but LMWHs do not. In contrast, inhibition of factor Xa *(right side of figure)* requires that heparin bind only to AT, which unfractionated heparin and LMWH can catalyze equally effectively through their common pentasaccharide sequences. Thus, LMWH (but not unfractionated heparin) inactivates factor Xa selectively relative to thrombin.

Figure 62-15 Activation and inhibitors of coagulation. New anticoagulants act by inhibiting the tissue factor pathway (initiation), thrombin generation, and thrombin activity. (Modified from Hirsh J, Weitz JI: New antithrombotic agents. Lancet 353:1431-1436, 1999.)

are associated with a lower incidence of major bleeding complications than standard, unfractionated heparin. Furthermore, the frequency of immune-mediated HIT is much lower with LMWH.[108] Osteoporosis also occurs less often with long-term administration of LMWH than with standard heparin.[109]

OTHER GLYCOSAMINOGLYCAN-DERIVED DRUGS (NEW HEPARINS)

Heparan sulfate, dermatan sulfate, and proteoglycans are endogenous heparin-like molecules with antithrombotic activity.[110] Several of these endogenous glycosaminoglycans have been developed as clinical anticoagulants.[111] , [112]

Danaparoid (Orgaran, formerly ORG 10172) is a mixture of low-molecular-weight anticoagulant glycosaminoglycans, predominantly heparan sulfate (84 percent) and dermatan sulfate (12 percent).[98] , [113] It preferentially inhibits factor Xa and has a lesser degree of antithrombin activity. Bioavailability of danaparoid is essentially 100 percent by subcutaneous dosing, and twice-daily administration is required when using this route. Rapid full anticoagulation is better achieved by an initial intravenous bolus.[114] Danaparoid is a weak anticoagulant as measured by the prothrombin time (PT) and aPTT tests. Therefore, laboratory monitoring of danaparoid can only be performed using anti-factor Xa levels. However, in view of the predictable dose-dependent anticoagulant response to danaparoid, laboratory monitoring is not required in most patients. Because danaparoid is excreted largely unchanged into the urine, dose reduction and laboratory monitoring are required in patients with renal failure. A disadvantage of danaparoid is the inability of protamine sulfate to neutralize its activity.

Dermatan sulfate, a naturally occurring glycosaminoglycan, catalyzes the inactivation of thrombin by heparin cofactor II. Like direct thrombin inhibitors (see later), and unlike standard and low-molecular-weight heparins, dermatan sulfate can inactivate fibrin-bound thrombin.[115]

Pentasaccharide, representing the high-affinity heparin binding site for antithrombin, and its synthetic analogs (SR90107A/ORG31540, SANORG 32701) selectively catalyze the inactivation of factor Xa by antithrombin without inhibiting thrombin (Fig. 62-15) .[116] Definitive clinical trials will be required to demonstrate the superiority of these and other heparin mimetics obtained by chemical synthesis.[117]

Warfarin

Warfarin (Coumadin) is the most frequently used oral anticoagulant.[118] Oral anticoagulants, which are derivatives of coumarins, exert their anticoagulant actions as vitamin K antagonists. As shown in Figure 62-16 , [119] the reduced form of vitamin K, vitamin KH_2 , is normally required as a cofactor for the gamma-carboxylation of glutamic acid residues in coagulation factors II (prothrombin), VII, IX, and X. This posttranslational modification of these clotting factors is necessary for them to function physiologically in the coagulation cascade by allowing them to bind to and form calcium-dependent complexes on cellular phospholipid surfaces. Oral anticoagulants block the reductase enzymes that are required to recycle vitamin K epoxide to vitamin KH_2 after the gamma-carboxylation reaction, thereby depleting the active vitamin K cofactor.

Warfarin is rapidly and almost completely absorbed from the gastrointestinal tract and circulates bound to albumin with a mean plasma half-life of approximately 40 hours.[104] [120] Numerous drugs alter the anticoagulant response to warfarin by pharmacokinetic or pharmacodynamic interactions. Drugs such as phenylbutazone, erythromycin, fluconazole, cimetidine, amiodarone, clofibrate, isoniazid, and propranolol increase warfarin levels, whereas drugs such as cholestyramine, barbiturates, rifampin, and sucralfate decrease warfarin levels. Dietary variations in vitamin K likewise alter warfarin's anticoagulant effects; high vitamin K intake in the diet (including nutritional supplements and vitamin preparations) reduces the anticoagulant response to warfarin. Conversely, liver disease, malabsorption, and hypermetabolic states enhance the anticoagulant effect of warfarin.

MONITORING.

Oral anticoagulant therapy requires laboratory monitoring with the PT test. Commercially available thromboplastin reagents that are used in the PT assay vary considerably in their clotting ability. This problem previously created major variability in the PT values reported by different laboratories. To standardize PT reporting, the international normalized ratio (INR) is now used. The INR corrects for differences in the thromboplastin reagents used by different laboratories. The optimal therapeutic range of warfarin dose for the prevention of venous thromboembolism and for the prevention of systemic embolism from atrial fibrillation and tissue heart valves targets an INR of 2.0 to 3.0. Higher intensity anticoagulation (INR 2.5 to 3.5) is required in patients with mechanical prosthetic heart valves.

Figure 62-16 Vitamin K cycle and its inhibition by warfarin. Warfarin inhibits vitamin K epoxide reductase and vitamin K quinone reductase and so blocks the conversion of vitamin K epoxide to vitamin KH_2 . Vitamin KH_2 is a cofactor for the carboxylation of inactive proenzymes (factors II, VII, IX, and X) to their active forms. (From Furie B, Furie BC: Molecular basis of vitamin K-dependent gamma-carboxylation.

Blood 75:1753-1762, 1990.)

"Loading doses" of warfarin should not be employed in initiating oral anticoagulation. Although warfarin has a rapid onset of action, its optimal antithrombotic effect requires several days. The activity of all four of the vitamin K-dependent clotting factors must be inhibited to achieve clinically effective anticoagulation. The effects of warfarin require depletion of circulating clotting factors that are already gamma-carboxylated and hence biologically active when warfarin is started. The vitamin K-dependent clotting factors have different half-lives, with factor VII having the shortest. Therefore, the initial increase in the INR is predominantly due to a decrease in functional factor VII. A large "loading dose" of warfarin (i.e., 10 mg or more per day) will thus create a selective, severe factor VII deficiency state, with its attendant bleeding risk, while still failing to provide antithrombotic effect. In addition, a precipitous reduction in the plasma level of protein C, a vitamin K-dependent anticoagulant (rather than clotting) factor, which has the shortest half-life of all vitamin K-dependent proteins, can lead to a transient paradoxical hypercoagulable state during the first 36 hours of warfarin therapy (see later).[121] [122] Therefore, the initial dose of warfarin should approximate the chronic maintenance dose that is anticipated, generally in the range of 4 to 6 mg/d in most adults.[120]

COMPLICATIONS.

Skin necrosis is a very rare complication that occurs within the first few days of starting warfarin therapy and tends to occur in patients with underlying inherited protein C or protein S deficiency. As noted earlier, it is likely to be related to the initial precipitous decrease in protein C levels (especially in individuals who may already have a congenitally low level of protein C). This leads to a transient prothrombotic imbalance, particularly with the use of large loading doses of warfarin. Warfarin should be avoided in pregnancy because of its potential to cause embryopathy and peripartum neonatal and maternal bleeding complications.

As with heparin, bleeding complications are the most frequent adverse effects of warfarin. For an individual patient, the cumulative risk of bleeding complications is directly related to the intensity and duration of anticoagulant therapy.[123] Major bleeding on warfarin occurs at a rate of 5 to 7 percent per year.[124] As noted earlier, the INR can vary despite a stable, chronic dose of warfarin as a function of changes in other medications or diet. When the INR exceeds the therapeutic range, discontinuing or reducing the dose of warfarin is usually sufficient; stopping warfarin generally normalizes the INR within about 3 days. If more rapid reversal of warfarin effect is required because of extreme elevations of the INR or clinical bleeding, vitamin K can be administered orally or parenterally. However, particularly when vitamin K is given at higher doses, a transient resistance to re-anticoagulation with warfarin may be encountered subsequently. Emergency reversal of warfarin effect can be rapidly achieved by infusion of fresh frozen plasma (usually starting with 2 to 4 units). Algorithms for the management of elevated INR with or without bleeding have been proposed.[120] [125]

Thrombin Inhibitors and Other Specific Coagulation Inhibitors

New anticoagulants have been developed that specifically target inactivation of thrombin, factor Xa, factor IXa, and the factor VIIa/tissue factor complex, as well as inactivation of factors VIIIa and Va by enhancement of the protein C anticoagulant pathway.[116] The sites of action of these anticoagulants are shown in Figure 62-15. Except for the direct thrombin inhibitors, most of these agents have yet to be evaluated in phase 3 trials.

THROMBIN INHIBITORS

Direct thrombin inhibitors inactivate both free (fluid-phase) thrombin and fibrin-bound thrombin. In this respect, these agents differ from heparin and its low-molecular-weight derivatives, which require complex formation with antithrombin III and are thus weak inhibitors of clot-bound thrombin.[126] [127] [128] The thrombin molecule has distinct functional domains. The "active site" of thrombin is the catalytic site that possesses serine protease activity. "Exosite 1" of thrombin serves to dock substrates in the proper orientation and is the binding site for fibrin(ogen).[129] Direct thrombin inhibitors interact with one or both of these sites. Hirudin and bivalirudin are more specific for thrombin than active-site inhibitors because they are bivalent, binding to thrombin at both the active site and exosite 1. In contrast, low-molecular-weight thrombin inhibitors such as argatroban and efegatran bind to only the active site of thrombin. Because the active site of thrombin is structurally similar to other serine proteases, these active-site inhibitors are less selective for thrombin than the bivalent inhibitors.[116] [128]

Hirudin (desirudin) is the prototype of the direct thrombin inhibitors. It is a 65-amino acid polypeptide that was originally isolated from the saliva of *Hirudo medicinalis*, the medicinal leech. Hirudin is now produced by recombinant DNA technology. It binds tightly to thrombin, forming a slowly reversible, 1:1 stoichiometric complex. In this complex, the amino-terminal of hirudin binds to the active site and its carboxy-terminal binds to exosite 1 of thrombin.

Bivalirudin (formerly Hirulog) is a synthetic 20-amino acid polypeptide. It is composed of a peptide sequence (D-Phe-Pro-Arg-Pro) that is directed at the active site of thrombin, linked to a dodecapeptide analog of the exosite 1-binding carboxy-terminal of hirudin.[130] Thus, like hirudin, bivalirudin interacts bivalently with both the active site and exosite 1 of thrombin, forming a 1:1 stoichiometric complex. However, once bound, thrombin cleaves the Arg-Pro bond and thereby removes the active site binding part of bivalirudin, leaving only a low-affinity, weaker inhibitory interaction with thrombin. Consequently, the potent thrombin inhibitory effect of bivalirudin is short lived, conferring on it a potential safety advantage.

Hirudin, bivalirudin, and other direct thrombin inhibitors have theoretical advantages

over heparin. First, as noted earlier, they can inactivate clot-bound thrombin. Second, unlike heparin, they do not bind to plasma proteins. Therefore, they have the pharmacokinetic advantage of a more predictable anticoagulant response. This should permit their administration without laboratory monitoring. However, the narrow therapeutic window for hirudin makes its monitoring necessary and may prove to be a significant limitation. In clinical trials of hirudin, used in conjunction with thrombolytic therapy in patients with acute myocardial infarction, concentrations of hirudin were selected that produced a prolongation of the aPTT similar to that achieved with heparin. The excessive bleeding observed with hirudin in these trials suggests that hirudin causes more bleeding than heparin when these agents are used in doses that prolong the aPTT to the same extent,[131] and it points out the potential pitfalls of extrapolating from the experience of heparin when choosing a laboratory test to monitor a new antithrombotic agent.[126] The better benefit-to-risk profile of bivalirudin appears to permit its administration in weight-adjusted doses without laboratory monitoring.[130]

Several low-molecular-weight direct thrombin inhibitors have been developed. These less-specific agents target only the active site of thrombin. Argatroban is the prototype of the noncovalent class of these active site inhibitors, which also includes napsagatran, inogatran, and melagatran. Efegatran and boroarginine derivatives are reversible-covalent active site inhibitors of thrombin. They serve as pseudosubstrates for thrombin, which are cleaved by thrombin to form a covalent enzyme-inhibitor adduct.[130]

OTHER SPECIFIC COAGULATION INHIBITORS

Inhibitors of factor Xa (see Fig. 62-15) [128] [132] include tick anticoagulant peptide (TAP) and antistatin. Both are potent and specific factor Xa inhibitors that are available in recombinant forms. DX-9065[133] is a synthetic, low-molecular-weight, reversible factor Xa inhibitor that has oral bioavailability. Experimental agents that are inhibitors of factor IXa include a monoclonal antibody and an active site-blocked factor IXa.[134] Specific inhibitors of the tissue factor pathway under study include a soluble mutant form of tissue factor that has decreased cofactor function for factor VIIa-induced activation of factor X[135] ; active-site-blocked factor VIIa (VIIai), which competes with factor VII for tissue factor binding; NAPc2, a small, nematode-derived anticoagulant protein that binds to factor X and inhibits factor VIIa within the factor VII/tissue factor complex[136] ; and recombinant TFPI.[137] Protein C activators that have been studied as therapeutic anticoagulants include plasma and recombinant forms of protein C and recombinant soluble thrombomodulin.[116]

Thrombolytic (Fibrinolytic) Drugs

The fibrinolytic system has been described previously and is illustrated in Figure 62-7 (see p. 2104). The common mechanism of action of currently available thrombolytic (fibrinolytic) agents, including streptokinase, urokinase, alteplase (recombinant tissue-type plasminogen activator [rt-PA]), and anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]), involves the conversion of the inactive plasma zymogen, plasminogen, to the active fibrinolytic enzyme, plasmin.[138] Plasmin has relatively weak substrate specificity and can degrade not only fibrin but any protein

that has an arginyl-lysyl bond available for enzymatic attack, including fibrinogen. Because indiscriminate plasmin lysis of both fibrin and fibrinogen can produce a systemic state of fibrin(ogen)olysis (or "systemic lytic state"), which might cause a serious systemic bleeding tendency, attempts have been made to develop thrombolytic agents that generate plasmin preferentially at the fibrin surface in a preformed thrombus ("fibrin specific agents"). Plasmin associated with fibrin is protected from rapid inhibition by $alpha_2$ -antiplasmin (see earlier) and can thereby effectively degrade the fibrin of a clot.[139] Thus, the biochemical strategy was to develop fibrinolytic agents that bind to fibrin and thereby produce only fibrin-bound plasmin from fibrin-bound plasminogen.

Streptokinase and urokinase induce a systemic lytic state, with extensive systemic activation of the fibrinolytic system, deplete $alpha_2$ -antiplasmin, and degrade circulating fibrinogen. In contrast, the physiological plasminogen activators t-PA and scu-PA, as well as staphylokinase, activate plasminogen preferentially at the fibrin surface.[140] The promise of a marked reduction in the risk of hemorrhage with "second generation" fibrin-specific agents has not been fulfilled in large clinical trials, however. This may be due to the inability of plasmin to discriminate between fibrin in pathological thrombi, which is the desired target, and fibrin in physiological hemostatic plugs, the lysis of which will induce bleeding.

Streptokinase

Streptokinase is isolated from hemolytic streptococci and is produced from bacterial cultures. The mechanism of activation of plasminogen by streptokinase is unique among plasminogen activators in that streptokinase itself possesses no enzymatic activity.[141] Streptokinase forms a complex with plasminogen, and it is the streptokinase-plasminogen complex that actually possesses enzymatic activity toward plasminogen. The streptokinase-plasminogen complexes are thereby converted to streptokinase-plasmin complexes, and the enzyme active sites in the streptokinase-plasmin complexes are the same as those in plasmin. The streptokinase-plasmin(ogen) complexes activate circulating and fibrin-bound plasminogen relatively indiscriminately, producing a systemic lytic state.

Because of its bacterial source, streptokinase is antigenic. Most individuals have preexisting antibodies resulting from previous streptococcal infection. The administration of streptokinase stimulates the rapid formation of high titers of neutralizing antistreptokinase antibodies, which are sufficient to neutralize standard doses of streptokinase. Although antibody titers may return to near-baseline levels as early as 2 years after a single dose,[142] once streptokinase has been used then subsequent thrombolytic treatment should be with an immunologically unrelated agent because of the uncertain efficacy of repeated treatment.[140] Streptokinase causes transient hypotension in many patients and significant allergic reactions in some, including a serum sickness-type syndrome, fever, rash, and bronchospasm.[143]

Anisoylated Plasminogen/Streptokinase Activator Complex

Although the streptokinase/plasmin complex possesses high plasmin-generating

efficiency, it is rapidly inactivated in

plasma by protease inhibitors. This limitation led to the synthesis of anisoylated plasminogen-streptokinase activator complex (APSAC; anistreplase), in which streptokinase is noncovalently associated with plasminogen and the enzyme active site of plasminogen is protected by the covalent addition of a *p*-anisoyl group. APSAC retains the fibrin-binding properties of the streptokinase-plasminogen complex, but it is enzymatically inert. Therefore, when injected intravenously, APSAC circulates to the site of fibrin deposition. APSAC cannot be inactivated by plasma alpha$_2$ -antiplasmin because its enzyme active site is inaccessible. Deacylation of fibrin-bound APSAC then uncovers the catalytic center, which converts plasminogen to plasmin. APSAC thereby permits fibrin-targeted thrombolysis.

Compared with streptokinase, APSAC has greater stability in plasma (fibrinolytic half-life of 12 to 18 minutes vs. 40 to 60 minutes), and can be administered rapidly as a single intravenous bolus without hypotension. Like streptokinase, the bacterial origin of APSAC causes immunological complications. Some individuals with preexisting antistreptococcal antibodies demonstrate a blunted fibrinolytic response to APSAC, and high titers of neutralizing antibodies following a single treatment persist for months.[144] As with streptokinase, APSAC can also cause allergic reactions in a small percentage of patients.

Urokinase

Urokinase, or two-chain urokinase-type plasminogen activator (tcu-PA), is a trypsin-like serine protease composed of two polypeptide chains with molecular masses of 20 and 34 kDa, respectively, linked by a disulfide bridge. Urokinase is produced from cultures of human fetal kidney cells. It directly activates plasminogen to plasmin, leading to relatively nonspecific degradation of fibrin, fibrinogen and other plasma proteins, depletion of circulating alpha$_2$ -antiplasmin, and a systemic lytic state. Urokinase is not antigenic and does not cause allergic reactions.[138]

Single-Chain Urokinase-Type Plasminogen Activator

Single-chain urokinase-type plasminogen activator (scu-PA; prourokinase) is a naturally occurring 54 kDa protein that is the zymogenic precursor of urokinase; scu-PA is converted to proteolytically active urokinase (two-chain u-PA) by means of limited hydrolysis by plasmin and kallikrein. In plasma, scu-PA is mostly inactive. Although scu-PA does not directly bind to fibrin, it induces plasminogen activation in the presence of fibrin, leading to relative fibrin-specific plasminogen activation. Urokinase-type plasminogen activator receptors (u-PAR) on endothelial cells and leukocytes may also modulate scu-PA fibrinolytic activity. Plasmin generation is enhanced by binding of

scu-PA to u-PAR.[141] [145]

Tissue-Type Plasminogen Activator

Tissue-type plasminogen activator (t-PA) is a naturally occurring molecule released from vascular endothelial cells. For therapeutic thrombolysis, it is produced commercially by recombinant DNA technology (rt-PA; alteplase) and, as a "second-generation" agent, it is relatively fibrin specific.

t-PA is a single-chain serine protease composed of 527 amino acids with a molecular mass of 68 kDa. It activates plasminogen directly and follows Michaelis-Menten kinetics.[141] The efficiency of plasminogen activation by t-PA is significantly enhanced in the presence of fibrin. The basis for the relative fibrin specificity of t-PA action is described previously in the section on the fibrinolytic system. Briefly, fibrin provides a surface for the sequential binding of enzyme (t-PA) and substrate (plasminogen). The assembly of this ternary complex thereby promotes the activation of plasminogen to plasmin that is efficiently localized to the fibrin clot; fibrin then becomes the substrate for lysis by the plasmin that is generated on its surface.

t-PA is converted by plasmin to a disulfide-linked two-chain form by hydrolysis of the Arg 275--Ile276 bond; alteplase consists mainly of the single-chain form of t-PA. Both the single-chain and two-chain forms of t-PA are cleared from plasma according to a two-compartment model, with initial half-lives of 3 to 6 minutes and terminal half-lives of 40 to 50 minutes. The currently preferred dosage regimen of fibrin-selective alteplase for coronary thrombolysis consists of weight-adjusted, accelerated ("front-loaded") administration. The front-loaded administration of alteplase achieves a mean steady-state plasma concentration during the initial 30 minutes that is 45 percent higher than that achieved with standard infusion, although it does not alter the plasma half-life.[141] [146]

VARIANTS, CHIMERAS, AND CONJUGATES OF PLASMINOGEN ACTIVATORS

These thrombolytic agents have been engineered to favorably alter the pharmacokinetic and functional properties of currently used drugs. They are designed to have prolonged half-lives, improved enzymatic efficiency, enhanced local concentrations in the clot by altered binding to fibrin and stimulation by fibrin, and resistance to plasma protease inhibitors.[140] [141] [147] Several of these agents have begun to undergo clinical trial.[148]

Reteplase (r-PA) is a single-chain nonglycosylated deletion variant of t-PA, containing only the kringle-2 and serine protease domains. This deletion mutant has a prolonged half-life and, therefore, can be administered by bolus injection.[149] A mutant of rt-PA, TNK-rt-PA, contains amino acid substitutions at three sites: threonine (T) at position 103 is replaced by asparagine; asparagine (N) at position 117 is replaced by glutamine; and four amino acids, lysine (K), histidine, arginine, and arginine, are replaced by alanine-alanine-alanine-alanine at positions 296 through 299. TNK-rt-PA is characterized by a prolonged half-life, improved fibrin specificity, and increased resistance to inhibition by PAI-1.[150] Another third-generation agent that is a modification

of wild-type t-PA is lanoteplase (n-PA), which has an even longer half-life than TNK-rt-PA and can be administered by single-bolus, weight-adjusted injection.[151] Prolonged half-lives have also been obtained by substitution or deletion of one or more selected amino acids in the finger or epidermal growth factor domains of t-PA.[140] [147] One of these t-PA variants is E6010, in which Cys is replaced by Ser at position 84; it possesses a half-life of 23 minutes or more after a single intravenous bolus. The t-PA of saliva from the vampire bat *Desmodus rotundus* (bat-PA) has potent and relatively fibrin-specific thrombolytic properties.[152] [153] Different molecular forms of bat-PA have been purified, characterized, cloned, and expressed.

Antibody targeting of thrombolytic agents is a potentially powerful approach to localizing the actions of these drugs to specific components of different types of thrombi (e.g., directed at platelet antigens in arterial thrombi, or thrombin in recently formed thrombi). This can be achieved by conjugating plasminogen activators with monoclonal antibodies that are specific, for example, for fibrin but do not cross react with fibrinogen.[154] These bifunctional molecules are engineered to contain both a highly specific antigen-binding site that concentrates the drug at the clot and an effector site that promotes thrombolysis.

STAPHYLOKINASE

Staphylokinase [155] [156] [157] is isolated from *Staphylococcus* species. Like streptokinase, it forms a 1:1 stoichiometric complex with plasminogen. Unlike the streptokinase-plasminogen complex, however, the staphylokinase-plasminogen complex is enzymatically inactive; it must be converted to staphylokinase-plasmin to become a potent plasminogen activator. Also unlike streptokinase-plasmin(ogen), the staphylokinase-plasmin complex is rapidly neutralized in the circulation by $alpha_2$ -antiplasmin. After inhibition by $alpha_2$ -antiplasmin, staphylokinase is released from the complex and is recycled to bind other plasminogen molecules. The relative fibrin selectivity of staphylokinase resides in the ability of fibrin to largely (> 100-fold) protect it from inhibition by $alpha_2$ -antiplasmin. As a bacterial plasminogen activator, staphylokinase is an antigenic thrombolytic agent that induces antibody formation and resistance to repeated administration.

Antiplatelet Agents

The sequence of events involved in the process of platelet activation is described in detail in the previous section on platelets and is summarized in Figures 62-8 (p. 2105) and 62-17 . Inhibition of platelet function can be targeted at any

Figure 62-17 Sequence of events in platelet activation, with potential targets for antiplatelet therapy. *A,*

Platelet adhesion to the injured vascular intimal surface is mediated by von Willebrand factor (vWF) binding to its receptor on platelet membrane Gp Ib. *B,* Adherent platelets are also anchored to the damaged vessel wall by binding of subendothelial collagen (COL) to its platelet surface COL receptors. Other platelet stimuli in blood, including thrombin (THR) and epinephrine (EPI), bind to their respective receptors. *C,* In response to these different stimuli, adherent platelets are activated and release thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP), which bind to their own respective platelet receptors and amplify the activation process. AA=arachidonic acid; PGG_2 and PGH_2 =labile prostaglandin endoperoxides. *D,* Platelet aggregation is mediated by fibrinogen (FIB) binding to its receptors on adjoining platelets, forming fibrinogen bridges. The FIB receptor is formed by the complexing of Gp IIb/IIIa in the membrane of activated platelets. (Modified from Schafer AI: Antiplatelet therapy with glycoprotein IIb/IIIa receptor inhibitors and other novel agents. Tex Heart Inst J 24:90-96, 1997.)

one of these activation steps. Platelet blockade would be expected to be most effective if it is directed at either the initial (adhesion) (see Fig. 62-17 *A*) or final (aggregation) (see Fig. 62-17 *D*) points in the sequence. Antiplatelet agents targeted at any one of the intermediate events should be less potent, because platelet adhesion is followed by the binding of several specific agonists to their respective receptors and the activation of several simultaneous intracellular pathways (e.g., ADP release, TXA_2 synthesis) that act in concert to induce the final step of platelet aggregation. Therefore, pharmacological interruption of only one of these intermediate steps (e.g., with aspirin, antithrombins, ticlopidine, clopidogrel) may permit platelet activation through alternative, uninhibited pathways. Agents that block the interaction of vWF with its platelet membrane Gp Ib receptor should inhibit adhesion (see Fig. 62-17 *A*) as well as the subsequent downstream cascade of platelet activation events, including secretion of mitogens into the vessel wall and platelet aggregation.[158] Therapeutic approaches to inhibit adhesion could involve anti-vWF or anti-Gp Ib monoclonal antibodies or agents that interfere with vWF-platelet Gp-Ib binding. These strategies have yet to be translated to clinical practice, however. In contrast, considerable clinical evidence has now validated various powerful therapeutic strategies to block the final step of platelet aggregation that is mediated by the interaction of fibrinogen (or vWF) with its platelet Gp IIb/IIIa receptors (see Fig. 62-17 *D*).

Aspirin

Aspirin (acetylsalicylic acid), which has been used medicinally since antiquity and has been demonstrated to have antithrombotic efficacy for almost 50 years, has stood the test of time as an effective, inexpensive, and relatively safe drug for the prevention of various thrombotic and vascular disorders, particularly in the arterial circulation where platelets are the predominant participants in the thrombotic process.[159] [159A] Until recently, aspirin has been essentially the only available, clinically effective antiplatelet drug. However, there are several clinical settings in which aspirin

Figure 62-18 Aspirin (acetylsalicylic acid) inhibition of cyclooxygenase (prostaglandin-G/H synthase). Aspirin acetylates serine at position 529 of cyclooxygenase, rendering the enzyme inactive. Acetylated

cyclooxygenase does not function to catalyze the oxygenation of arachidonic acid to prostaglandin G_2 . Aspirin thereby blocks the formation of thromboxane A_2 (in platelets) and prostacyclin (in vascular cells). (From Loscalzo J, Schafer AI: Anticoagulants, antiplatelet agents, and fibrinolytics. *In* Loscalzo J, Creager MA, Dzau MV [eds]: Vascular Medicine: A Textbook of Vascular Biology and Diseases. Philadelphia: Lippincott Williams & Wilkins, 1996.)

fails to provide full (or even partial) antithrombotic benefit.[160]

Aspirin is readily absorbed from the stomach and upper small intestine and is then hydrolyzed to release free acetyl groups. As shown in Figure 62-18, this moiety acetylate serine residues at position 529 of cyclooxygenase (COX; prostaglandin G/H synthase), which leads to irreversible inactivation of the enzyme.[161] [162] Inactive, acetylated COX is unable to function to catalyze the oxygenation of arachidonic acid to prostaglandin G_2 . Aspirin thereby blocks the formation of TXA_2 , a potent mediator of platelet aggregation and vasoconstrictor. Because anucleate platelets are essentially unable to synthesize new, unacetylated COX, aspirin blocks the function of platelets exposed to it for their remaining lifetime (normally 7 to 10 days) in the circulation. This accounts for the lengthy therapeutic effect of aspirin despite its plasma half-life of only 20 minutes.

The inhibitory effects of aspirin on platelet TXA_2 production and ex vivo aggregation are rapid, with maximal effects achieved within 15 to 30 minutes of oral administration of a dose as low as 81 mg.[163] A single oral dose of 100 mg of aspirin almost completely suppresses platelet TXA_2 synthesis in both normal individuals and in patients with cardiovascular disease. Daily administration of only 30 to 50 mg of aspirin exerts a cumulative effect and likewise results in almost complete inhibition of platelet TXA_2 production within 7 to 10 days.[159] These aspirin effects on platelet TXA_2 formation generally correlate well with inhibition of ex vivo platelet aggregability and prolongation of the skin bleeding time. Although platelet function remains impaired for 4 to 7 days after a single dose of aspirin, reflecting the life span of irreversibly inhibited platelets, the prolonged bleeding time generally returns to normal within 24 to 48 hours of aspirin ingestion: This discrepancy is due to the release from bone marrow into the circulation of a sufficient cohort of uninhibited platelets after the elimination of aspirin from blood to restore normal in vivo hemostasis (bleeding time) even before complete normalization of ex vivo platelet function.

Aspirin also inhibits COX in vascular endothelial cells, leading to suppression of platelet inhibitory and vasodilatory endothelium-derived PGI_2 ; this would be expected to offset the antiplatelet effects of aspirin. Attempts to design "platelet selective" aspirin regimens have not translated to clinical feasibility. Nevertheless, there is ample evidence that the antithrombotic effects of aspirin predominate in vivo, possibly due to mechanisms in addition to platelet TXA_2 inhibition.[161]

NON-ASPIRIN NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

Non-aspirin NSAIDs likewise inhibit COX. Unlike aspirin, however, these other NSAIDs

are reversible inhibitors of the enzyme; and, therefore, their durations of TXA_2 and platelet inhibitory action are dependent on the clearance of the drugs from the circulation.[164] Thus, there is considerable variability in the extent and duration of the effects of various NSAIDs on ex vivo platelet aggregation and bleeding time prolongation.[164] Non-aspirin NSAIDs reversibly inhibit COX by preventing its arachidonic acid substrate from gaining access to the active site of the enzyme.[165] Interaction of NSAIDs with COX may prevent acetylation of the enzyme by aspirin. This suggests that the concomitant administration of non-aspirin NSAIDs may actually antagonize the

effects of aspirin on COX by competitive interaction, and consequently blunt aspirin's antiplatelet efficacy.[166]

The constitutive isoform of COX, COX-1, is the one that is present in platelets and produces TXA_2 . Aspirin and the traditional NSAIDs are nonselective inhibitors of both COX-1 and COX-2. The newer COX-2-specific inhibitors are designed to maximize the antiinflammatory effects that are mediated by the COX-2 isoform, while minimizing the common side effects (e.g., bleeding) that are attributed to the COX-1 isoform. Therefore, the antiplatelet potency of the new COX-2 inhibitors is several orders of magnitude lower than that of aspirin and the standard NSAIDs[167] [168] and generally cannot be assumed to afford antithrombotic protection.[169]

OTHER THROMBOXANE INHIBITORS

Figure 62-17 *C* illustrates other opportunities to interrupt platelet TXA_2 synthesis and/or action in addition to COX blockade. The reduced incidence of atherosclerotic cardiovascular disease in Greenland Eskimos has been attributed, at least in part, to their diets rich in fish oils containing omega-3 polyunsaturated fatty acids. A major omega-3 fatty acid in fish oils is eicosapentaenoic acid (EPA), which incorporates into cell membrane phospholipids and competes with arachidonic acid as substrate for COX. The product of EPA oxygenation is TXA_3 , an eicosanoid that is devoid of the potent platelet activating and vasoconstrictor actions of arachidonic acid-derived TXA_2 . Large and often unpalatable doses (> 10 gm EPA daily) of medicinal fish oils are required to simulate changes in platelet membrane fatty acid content attained with Eskimo diets and thereby produce antiplatelet actions.[158] Thromboxane synthase inhibitors (e.g., dazoxiben) and TXA_2 receptors antagonists, as well as dual thromboxane synthase/TXA_2 receptor inhibitors (e.g. ridogrel), have been developed but have generally not been found to be superior to aspirin in limited clinical trials.[158] [170]

Ticlopidine and Clopidogrel

Ticlopidine (Ticlid) and clopidogrel (Plavix) are structurally related thienopyridine

derivatives. They produce their antiplatelet effects by inhibiting the ADP-dependent pathway of platelet activation.[171] After oral administration, both drugs apparently require modification to active forms. They exert a permanent effect on a platelet protein(s),[162] which is the ADP receptor itself or a platelet membrane component closely related to the ADP receptor. As ADP receptor blockers, these drugs inhibit ADP-induced platelet aggregation (see Fig. 62-17 *C*).

Presumably because they must be converted to an active form in vivo, ticlopidine and clopidogrel have a relatively slow onset of antiplatelet action, which may make them less than optimal agents in clinical settings where rapid effect is desired (e.g., unstable angina). Full platelet inhibitory effect is achieved only 3 to 5 days after oral administration of ticlopidine, and the bleeding time does not become maximally prolonged until 5 to 6 days after starting treatment. Regimens involving bolus administration of these thienopyridines may accelerate their antiplatelet effects. The effect of ticlopidine on platelets persists for 4 to 8 days after discontinuation of the drug, reflecting the circulating lifetime of platelets and consistent with an irreversible antiplatelet effect.

Severe neutropenia, which is usually reversible with discontinuation of the drug, has been noted in up to 1 percent of patients on ticlopidine. The risk of this adverse effect is much lower (about 0.1 percent) with clopidogrel. (See also Chapter 67.) In addition, thrombotic thrombocytopenic purpura (TTP), a serious and sometimes fatal disorder, is a rare complication of therapy with ticlopidine. TTP typically occurs within 2 to 8 weeks of initiation of ticlopidine[172] and has been noted in 0.02 percent of patients receiving ticlopidine after coronary stenting.[173] [173A] More recently, TTP has also been reported after the initiation of clopidogrel therapy, often within the first two weeks of treatment.[173A] Other side effects, including gastrointestinal symptoms, pruritus, urticaria, and bleeding, also appear to occur less often with clopidogrel than with ticlopidine.[171]

Dipyridamole

The mechanism of antiplatelet action of dipyridamole is unclear. Although this drug has been previously demonstrated to stimulate PGI_2 synthesis, potentiate the platelet inhibitory effects of PGI_2 , raise platelet cyclic AMP levels by inhibiting phosphodiesterase, and block uptake of adenosine into vascular and blood cells, these potential antiplatelet actions generally do not occur at therapeutically achievable drug concentrations.[158] Unlike aspirin, dipyridamole does not prolong the bleeding time or inhibit ex vivo platelet aggregation at therapeutic doses. Although numerous clinical trials have failed to demonstrate antithrombotic efficacy of dipyridamole when it is used alone in any clinical setting, it may enhance the effect of warfarin in preventing systemic embolization from mechanical heart valve prostheses and add to the beneficial effect of aspirin in preventing the progression of peripheral occlusive arterial disease or, when used in a sustained release preparation, in the secondary prevention of ischemic stroke.[174]

Glycoprotein IIb/IIIa Antagonists

Regardless of the stimulus for their activation, the aggregation of platelets is finally regulated through their membrane binding sites for fibrinogen in the Gp IIb/IIIa receptor complex (see Fig. 62-17 *D*). This provides the rationale for pharmacological intervention directed against the platelet Gp IIb/IIIa complex.[175] [176] The role of the platelet Gp IIb/IIIa complex in platelet activation is discussed in more detail earlier in the section on platelets. Because Gp IIb/IIIa antagonists do not block TXA_2 production by activated platelets, [177] concomitant use of aspirin may enhance their antithrombotic efficacy.

Platelet Gp IIb/IIIa antagonists generally belong to one of the following classes: (1) monoclonal antibody against Gp IIb/IIIa; (2) peptide (peptidomimetic) antagonists, many of which contain the RGD sequence that can compete with fibrinogen for its Gp IIb/IIIa binding site; and (3) nonpeptide (nonpeptide-mimetic) antagonists of Gp IIb/IIIa. Three drugs currently available for coronary intervention or acute coronary syndromes represent the prototypes for these groups: Abciximab (c7E3 Fab, ReoPro) is a monoclonal antibody, eptifibatide (Integrilin) is a peptide antagonist, and tirofiban (Aggrastat) is a nonpeptide mimetic. These agents are approved for intravenous administration, but numerous oral Gp IIb/IIIa antagonists are currently under development and in phase II trials for chronic antiplatelet therapy.[175] [178] [179] Although the mechanism of action of these agents (i.e., inhibition of ligand binding to the receptor) is similar, it should not be assumed that they react at the same site within the receptor or that the consequences of their binding to Gp IIb/IIIa are identical.[179] Monoclonal antibody has a relatively extended duration of antiplatelet action, whereas the peptides and nonpeptide mimetics have a shorter elimination half-life.

Abciximab is the Fab fragment of a monoclonal antibody to Gp IIb/IIIa that has been humanized (mouse/human chimera) to reduce immunogenicity.[180] Abciximab is not specific to platelet Gp IIb/IIIa: It cross reacts with the related integrin, $alpha_v$ -$beta_3$, the vitronectin receptor that is present on vascular cells. This cross reactivity was originally considered to be of potential therapeutic benefit in the prevention of coronary restenosis and inhibition of thrombin generation.[181] [182] Abciximab is presently administered as an intravenous bolus followed by infusion for 12 to 24 hours for coronary interventions.[175] Because abciximab is derived from an antibody, concern has been raised about repeat administration. However, initial data indicate that readministration is safe and efficacious and that the same indications for first-time use can apply to subsequent readministration.[183]

Eptifibatide is a synthetic cyclic heptapeptide that contains a modified lysine-glycine-aspartic acid (KGD), rather than RGD, sequence that recognizes the binding site of platelet Gp IIb/IIIa[184] (see Fig. 62-9) . The rationale for eptifibatide is that the substitution of a single lysine (K) for

arginine (R) makes this agent specific for the platelet Gp IIb/IIIa integrin. Whether this is an advantageous or disadvantageous property (see earlier) has yet to be definitely

determined. Eptifibatide is administered by bolus intravenous injection followed by infusion for up to 72 hours in acute coronary syndromes.[175] Patients who undergo coronary interventions are usually continued on eptifibatide infusion for 18 to 24 hours after intervention. Eptifibatide is not immunogenic and is safe for repeated administration.[185]

Tirofiban (Aggrastat) is a nonpeptide mimetic. In contrast to the RGD (or KGD) peptidomimetics, which inhibit platelet aggregation by binding competitively to the RGD recognition site of Gp IIb/IIIa, the nonpeptides mimic the geometric, stereotactic, and charge characteristics of the RGD sequence.[88]

The clinical development of oral Gp IIb/IIIa antagonists has proven to be challenging.[88A] A major problem has been the question of optimal inhibition and monitoring of platelet function. Although 80 percent Gp IIb/IIIa blockade has been found to be effective and relatively safe with brief intravenous administration of the currently available agents in a controlled hospital environment, appropriate dosing of oral agents for chronic therapy remains problematic. Interindividual variability of response to chronic inhibition may be caused by genetic polymorphism of the Gp IIb/IIIa complex. Rapid, simple laboratory monitoring of Gp IIb/IIIa antagonist therapy will be required,[186] [187] and "therapeutic range" of inhibition of platelet function may have to be established for long-term administration. Chronic oral Gp IIb/IIIa blockade with certain agents may also be complicated by a paradoxical prothrombotic effect due to partial agonist effects at certain doses.[188]

COMPLICATIONS.

Bleeding complications with currently approved intravenous platelet Gp IIb/IIIa antagonists have primarily involved vascular access puncture sites in patients undergoing percutaneous intervention. Reduction and weight-adjustment in adjunctive heparin dosing in patients undergoing coronary interventions have reduced the incidence of these bleeding problems. No increase in intracerebral hemorrhage has been observed with the Gp IIb/IIIa antagonists. Therefore, the need for platelet transfusion to treat life-threatening bleeding is extremely rare, particularly with the short-acting agents eptifibatide and tirofiban.[175] Severe thrombocytopenia (platelet count <20,000/mul) occurs in 0.1 to 0.5 percent of patients treated with the intravenous agents, and the incidence appears to be slightly higher with abciximab.[175] [179] There may be more than one mechanism for thrombocytopenia: A precipitous decrease in platelet count may occur within 1 to 2 hours of initial exposure, or there may be a significant decline several days after initiation of therapy.

ANTITHROMBOTIC AND THROMBOLYTIC THERAPY IN CARDIOVASCULAR DISEASE

Primary Prevention of Ischemic Heart Disease

Three major trials have now evaluated the potential benefits of aspirin and/or warfarin in the primary prevention of ischemic heart disease. Two trials, the United States

Physicians' Health Study[189] and the British Doctors' Trial,[190] compared aspirin therapy with placebo. The ultimate design of the Thrombosis Prevention Trial was a 2×2 factorial design comparing warfarin with placebo and comparing aspirin with placebo.[191]

ASPIRIN.

In the Physicians Health Study, over 22,000 healthy male physicians were treated with either aspirin (325 mg every other day) or placebo for 5 years. Although treatment with aspirin reduced the risk of a first myocardial infarction by 44 percent, the absolute risks of myocardial infarction in both aspirin and placebo groups were low (0.2 percent/year and 0.4 percent/year, respectively). This reduction in myocardial infarction risk was manifest only in those 50 years of age or older, and hemorrhagic stroke and gastrointestinal bleeding tended to occur more frequently in those treated with aspirin. There was no difference in the incidence of cardiovascular mortality, the primary study endpoint.

In the British Doctors' Trial,[190] 5139 male physicians were randomized to take either aspirin (500 mg daily in most cases) or to avoid aspirin. After 6 years of therapy, there was no difference in the rates of myocardial infarction or cardiovascular death. Disabling strokes were more common in those treated with aspirin. When the Physicians' Health Study and the British Doctors' Trial are considered together, aspirin therapy resulted in a 32 percent reduction in nonfatal myocardial infarction and a 13 percent reduction in any vascular event, although there was no difference in total cardiovascular death and there was a trend toward increased risk of nonfatal stroke.[192]

In one arm of the Thrombosis Prevention Trial,[191] approximately 4000 men aged 45 to 69 years at high risk for the development of ischemic heart disease were randomized to either aspirin (75 mg daily of controlled-release formulation) or placebo. Aspirin therapy reduced the incidence of nonfatal myocardial infarction by 32 percent, corresponding to an absolute reduction of 2.3 events/1000 person-years. There was no reduction in fatal myocardial infarction. Overall stroke rates were similar, although there tended to be more hemorrhagic strokes in those treated with aspirin.

The previous three trials enrolled only men, and as of yet there are no randomized data examining aspirin therapy in women for primary prevention. The results of three prospective observational studies and one case-control study of aspirin in women have yielded conflicting results.[193] Two studies showed a reduced incidence of myocardial infarction, one showed no effect on ischemic heart disease, and one showed no effect on acute myocardial infarction but an increased risk of overall ischemic heart disease. The ongoing Women's Health Study, in which 40,000 women are randomized to either aspirin (100 mg every other day) or placebo, should yield important information on the role of aspirin for primary prevention of ischemic cardiac events in women.

WARFARIN.

In the other arm of the Thrombosis Prevention Trial design, patients were treated with either warfarin (target INR 1.5) or placebo. Warfarin therapy reduced the incidence of

nonfatal myocardial infarction by 10 percent, fatal myocardial infarction by 39 percent, and the combined endpoint of ischemic cardiac events by 21 percent. There tended to be more hemorrhagic and all-cause strokes, as well as a greater incidence of aortic aneurysm rupture, in those treated with warfarin. The all-cause mortality rate was reduced by warfarin therapy by a statistically significant 17 percent.

In patients who received both warfarin and aspirin therapy, nonfatal and fatal myocardial infarctions were reduced 35 percent and 29 percent, respectively, when compared with placebo therapy. This reduction was, however, accompanied by an increase in hemorrhagic and fatal strokes. Of note, approximately half of all patients in the Thrombosis Prevention Trial had withdrawn from treatment by the time the study was completed. Figure 62-19 displays the results of the Thrombosis Prevention Trial for the four treatment groups (placebo, aspirin alone, warfarin alone, aspirin plus warfarin).

RECOMMENDATIONS.

Although aspirin therapy does appear to reduce the incidence of nonfatal myocardial infarction in men, the absolute reduction is extremely modest (two to five events per 1000 subjects per year), has only been shown to be of benefit in those at least 45 to 50 years old, and may be accompanied by a small increased risk of hemorrhagic stroke. Therefore, it is difficult to recommend the widespread use of aspirin for the primary prevention of myocardial infarction. Aspirin therapy may have some modest benefit in selected higher risk patients older than 45 to 50 years. The utility of aspirin in the primary prevention of myocardial infarction in women is at present unresolved, and recommendations regarding its use must await the results of the Women's Health Initiative.

Figure 62-19 Cumulative proportion of men in the four treatment groups (WA=warfarin+aspirin; W=warfarin; A=aspirin; P=placebo) with fatal or nonfatal myocardial infarction (All IHD), fatal myocardial infarction (Fatal IHD), or nonfatal myocardial infarction (Nonfatal IHD). (From Medical Research Council's General Practice Research Framework: Thrombosis prevention trial: Randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. Lancet 351:238, 1998.)

Warfarin therapy in high-risk male subjects does lead to a reduction in the risk of myocardial infarction and overall mortality. However, as with aspirin therapy, the absolute reductions are modest (three ischemic cardiac events and one death per 1000 men per year) and this benefit appears to be accompanied by a small risk of serious adverse events. Combination warfarin and aspirin therapy may lead to the greatest reduction in ischemic cardiac events, but it may also be accompanied by an increased risk of hemorrhagic and fatal stroke. Furthermore, as suggested by the results of the Thrombosis Prevention Trial, many patients will discontinue treatment over time, owing to bleeding or other factors. The modest benefits in absolute terms of warfarin or

combination therapy must therefore be balanced by physicians and patients against the small but real risks of bleeding and the inconveniences of anticoagulation monitoring.

Secondary Prevention of Ischemic Heart Disease (See also Chap. 37)

ANTIPLATELET AGENTS FOR SECONDARY PREVENTION.

The fissuring of atherosclerotic plaque with subsequent platelet deposition and activation of the coagulation cascade are key events in the pathogenesis of acute coronary syndromes. Thus, antiplatelet agents and anticoagulants are useful therapeutic strategies for prevention of vascular events in patients with stable or unstable angina as well as post-myocardial infarction.[194] [195] [196] [197] [198] [199] [200]

The 1994 Antiplatelet Trialists' Collaboration is a meta-analysis of the effect of prolonged antiplatelet therapy on prevention of vascular events including myocardial infarction, stroke, and cardiovascular death.[201] This overview included over 70,000 high-risk patients with known atherosclerotic disease. Among these categories, about 20,000 patients were post-myocardial infarction, 10,000 were post stroke or transient ischemic attack (TIA), 4000 had unstable angina, and 16,000 were in the other vascular disease categories (e.g., stable angina, percutaneous transluminal coronary angioplasty). The absolute reduction of vascular events for every 1000 patients treated was 40 events in patients with myocardial infarction treated for 2 years, 40 events in patients with previous strokes treated for 3 years, 50 events in patients with unstable angina treated for 6 months, and 20 events in patients belonging to the other vascular disease categories treated for 1 year (Fig. 62-20). This benefit was separately statistically significant in middle-aged and older patients, men and women, hypertensive and normotensive patients, and diabetic and nondiabetic patients. Doses of aspirin in the range of 75 to 325 mg/d were as effective as higher doses of aspirin or other antiplatelet regimens in this meta-analysis. The reader is directed to a review of individual randomized trials of antiplatelet therapy for secondary prevention of vascular events in patients post-myocardial infarction.[202]

Since publication of the 1994 Antiplatelet Trialists' Collaboration overview, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial has addressed secondary prevention in patients with vascular disease.[203] This trial enrolled 19,185 patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease to a regimen of clopidogrel (75 mg once daily) or aspirin (325 mg once daily). The study had initially planned to enroll 15,000 patients with 5000 patients in each of the major subgroups of vascular disease. However, the sample size had to be increased partly because of a lower than expected incidence of the composite endpoints in the active control or aspirin group. The primary endpoint of reduction in vascular events defined as ischemic stroke, myocardial infarction, or cardiovascular death occurred in 5.32 percent of patients assigned to clopidogrel and 5.83 percent of patients assigned to aspirin after a mean follow-up of 1.91 years (p=0.043, relative risk reduction of 8.7 percent). Although the overall endpoint was slightly in favor of clopidogrel, the subgroup of patients enrolled with previous myocardial infarction did not have a reduction in the composite endpoint, which occurred in 5.03 percent of patients on clopidogrel and 4.84

percent of patients on aspirin. There were no major differences in adverse effects between the two agents. The incidence of neutropenia was only 0.1 percent, unlike in previous large trials with ticlopidine, a congener of clopidogrel. However, the rather modest benefit of clopidogrel for prevention of vascular events when compared with aspirin presently makes its major indication for patients who are intolerant to or have true aspirin allergy. The mechanism for inhibition of platelet aggregation is different for the two agents, with clopidogrel working through the ADP pathway and aspirin working through the thromboxane pathway. Thus, combination therapy may have the potential for synergistic clinical benefit. This strategy is being explored in ongoing clinical trials.

ANTICOAGULANTS FOR SECONDARY PREVENTION.

The value of long-term oral anticoagulation with warfarin in survivors of acute myocardial infarction remains unresolved after more than five decades of clinical research. The early trials such as the Working Party on Anticoagulant Therapy in Coronary Thrombosis (MRC) and the Veterans Administration Cooperative long-term therapy study (VA Coop) performed in the 1950s to 1970s suggested relative reduction in mortality of 10 to 30 percent as well as significant reduction in reinfarction, venous thrombosis, and embolic events.[204] [205] This efficacy was at the cost of an increase in both total and serious bleeding complications (an absolute increase in total bleeding events by 8 to 15 percent over 5 years). These trials were the basis for long-term

Figure 62-20 Prevention of death, myocardial infarction (MI), and stroke by prolonged antiplatelet therapy. SD=standard deviation; TIA=transient ischemic attack. (From Antiplatelet Triallists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--1: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 308:81-106, 1994.)

anticoagulant therapy after myocardial infarction as standard of care (Fig. 62-21 and Table 62-1) . The decline in the use of oral anticoagulants in the late 1970s and 1980s was related to the results of the German-Austrian Aspirin (GAMIS) and the Enquete de Prevention Secondaire de L'Infarctus du Myocarde (EPSIM) trials, suggesting that benefits of a magnitude similar to those derived from oral anticoagulants can be realized by chronic treatment with aspirin.[194] [206]

The GAMIS trial randomized 946 patients who had survived a myocardial infarction for 30 to 42 days to aspirin (1.5 gm/d), phenprocoumon, or placebo. Total mortality after 2 years of follow-up was lower but not statistically significant in the aspirin group (8.5 percent) than in the placebo (10.3 percent) and phenprocoumon (12.1 percent) groups. Similar reductions in cardiovascular death and myocardial infarction were observed in the aspirin group compared with either oral anticoagulation or placebo groups but failed to reach statistical significance. The EPSIM trial enrolled 1303 patients to a treatment of either aspirin or oral anticoagulants for secondary prevention after myocardial infarction.

After a mean follow-up of 29 months there was identical mortality between the two groups. The incidences of total and severe bleeding were increased in the anticoagulant arm, with rates of 16 percent versus 5 percent and 3 percent versus 1 percent, respectively. The aspirin group was associated with a higher incidence of gastritis and peptic ulceration. These two trials shifted the pendulum in favor of aspirin for secondary prevention of vascular events in survivors of myocardial infarction at least in North America.

The Warfarin-Aspirin Reinfarction Study (WARIS) trial revived the debate of the benefits of long-term oral anticoagulation after myocardial infarction.[207] The trial randomized 1214 patients to a regimen of warfarin (target INR of 2.8 to 4.8) versus placebo for an average treatment period of 37 months. The total mortality based on intention-to-treat was reduced from 20 to 15 percent, a relative risk reduction of 24 percent with warfarin therapy. When the analysis was

Figure 62-21 Long-term therapy with warfarin (Coumadin) in survivors of MI. The figure shows the odds ratio with 95 percent confidence interval for mortality comparing warfarin versus placebo in the major randomized trials spanning over four decades. Pooling of data from all trials shows a significant but modest overall treatment benefit. (From Loscalzo J, Schafer AI [eds]: Thrombosis and Hemorrhage. 2nd ed. Baltimore, Williams & Wilkins, 1998, p 1320.)

TABLE 62-1 -- LONG-TERM COUMADIN THERAPY IN SURVIVORS OF MYOCARDIAL INFARCTION (MI): RESULTS OF MAJOR RANDOMIZED TRIALS

STUDY	YEAR	NO. RANDOMIZED	TARGET INR	WEEKS AFTER MI*	YR OF FOLLOW-UP	INR IN TARGET RANGE (%)
MRC[204]	1955-60	383	2.0-2.5	4-6	4	60
VA Coop[205]	1957-60	739	2.0-2.5	3	5	82
GAMIS[194]	1970-77	626	2.5-5.0	4-7	2	62-75
WARIS[207]	1983-86	1214	2.8-4.8	4	5	75
ASPECT[208]	1986-91	3404	2.8-4.8	2	3	74

INR=International normalized ratio.*From Loscalzo J, Schafer AI (eds): Thrombosis and Hemorrhage. 2nd ed. Baltimore, Williams & Wilkins, 1998, p 1320.*

*Enrollment time=weeks after MI.

based on patients actually receiving treatment, striking reductions in mortality (35 percent), reinfarction (43 percent), and cerebrovascular accident (61 percent) were observed. The magnitude of survival benefit afforded by warfarin in this trial was larger than that possible with the use of aspirin alone after myocardial infarction. The investigators attributed the lower mortality to the greater degree of anticoagulation achieved (higher target INRs) and to maintaining a higher proportion of patients in the therapeutic range compared with earlier trials of oral anticoagulation.

The Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial was initiated before the publication of the WARIS trial.[208] The results of this trial were thus crucial to confirm the magnitude of benefits of oral anticoagulants suggested by the WARIS trial. The ASPECT trial randomized 3404 hospital survivors of myocardial infarction to anticoagulant (target INR 2.8 to 4.8) or placebo treatment within 6 weeks of discharge. During a mean follow-up of 37 months, total mortality was reduced by 10 percent, a difference that was not statistically significant. However, significant reductions of recurrent myocardial infarction by 53 percent, cerebrovascular events by 40 percent, and all vascular events by 35 percent were observed. This efficacy on secondary endpoints was at the cost of 3.87-fold increase in bleeding events with anticoagulation.

Because aspirin and oral anticoagulants mediate their antithrombotic effect through different pathways, the potential for additive or synergistic clinical benefit when the two agents are combined was explored in the Coumadin Aspirin Reinfarction Study (CARS) and in the Combination Hemotherapy and Mortality Prevention (CHAMP) trial.[209] [210] The CARS trial was designed to evaluate whether a combination of low-dose warfarin and low-dose aspirin would reduce vascular events compared with aspirin monotherapy without excessive bleeding risk in patients with previous myocardial infarction. The trial randomized 8803 patients to daily therapy with (1) aspirin (160 mg), (2) warfarin (3 mg) with aspirin (80 mg), or (3) warfarin (1 mg) with aspirin (80 mg). The design reflects the observational data that high doses of aspirin in combination with standard anticoagulation (target INR of 2.5 to 4.5) predisposes patients to an unacceptably high rate of bleeding complications, predominantly gastrointestinal. There were no significant reductions in the incidence of vascular events defined as reinfarction, nonfatal ischemic stroke, or cardiovascular death at 1 year between the groups (8.6 percent, 8.4 percent, and 8.8 percent, respectively). This lack of difference in benefit was associated with a significant increase in spontaneous bleeding complications in the 3 mg warfarin plus 80 mg aspirin group (1.4 vs. 0.7 percent, p=0.014). The CARS trial provides compelling evidence that a combination of low fixed-dose warfarin with 80 mg of aspirin does not provide clinical benefit beyond that achievable with 160-mg aspirin monotherapy. The results of the CHAMP trial also have not demonstrated any benefit of the combination of warfarin and aspirin in comparison with aspirin alone. In summary, the meta-analysis of both antiplatelet and oral anticoagulant trials as well as the more recent combination hemotherapy study demonstrate reductions in all-cause mortality and recurrent myocardial infarctions and cerebrovascular accidents with these agents.

RECOMMENDATIONS.

All survivors of myocardial infarction should be treated with aspirin, 160 to 325 mg daily

The magnitude of benefit in most survivors of myocardial infarction with oral anticoagulant alone or in combination with aspirin over and above aspirin monotherapy does not appear large enough to justify the increased rate of nonfatal major hemorrhage and the greater cost and complexity associated with their use. However, patients who develop atrial fibrillation, congestive heart failure, mobile mural thrombus, or systemic/pulmonary embolism after myocardial infarction may benefit from oral anticoagulant therapy.

Acute Coronary Syndromes and ST Segment Elevation Myocardial Infarction

Antiplatelet, anticoagulant, and fibrinolytic therapy have become a mainstay of the modern management of acute myocardial infarction. These important therapies are discussed in the chapter on acute myocardial infarction (see Chap. 35) .

Prevention of Cardiac Chamber and Prosthetic Valvular Thromboembolism

PREVENTION OF LEFT VENTRICULAR THROMBOEMBOLISM AFTER MYOCARDIAL INFARCTION (See alsoChap. 35) .

The underlying substrate for ventricular mural thrombus formation is multifactorial and probably related to a combination of regional myocardial akinesis/dyskinesis, abnormal endocardial surface, aberrant blood flow dynamics associated with low cardiac output, and concomitant atrial fibrillation. The early short-term anticoagulation studies such as the MRC, Bronx Municipal Hospital study, and VA Cooperative study in aggregate demonstrated an absolute reduction in mortality (4.2 percent) and thromboembolism (7.9 percent) with early heparinization soon after the diagnosis of acute myocardial infarction followed by oral anticoagulation.[202] [212] [213] [214] However, changing practices of the care of patients with acute myocardial infarction, such as the advent of coronary care units, thrombolytic therapy, aspirin use, and early mobilization of patients, have challenged the applicability of these early trials to contemporary practice.

The earlier observations that anterior myocardial infarctions are associated with a higher incidence of mural thrombi have been validated by the predischarge echocardiographic observations of the 8326-patient Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico-3 (GISSI-3) trial.[215] Although the overall incidence of thrombi in patients at low to medium risk for left ventricular (LV) thrombus formation (patients with severe pump failure and Killip class IV were excluded) was 5.1 percent, the incidence in patients with anterior myocardial infarction was 11.5 percent compared with 2.3 percent for patients with myocardial infarction at other sites (p<0.0001). In addition, patients with LV ejection fraction (LVEF) less than 40 percent had a higher incidence of ventricular thrombi (10.5 percent) compared with those with an EF greater than 40 percent (4 percent).

In a serial echocardiographic study of 99 consecutive patients with anterior wall infarction, Mooe and coworkers observed a 44 percent incidence of LV thrombi during hospitalization and a 30 percent incidence at discharge.[216] Repeat echocardiogram at 1 month, 3 months, and 12 months after hospital discharge showed that the thrombi had resolved in 81 percent, 84 percent, and 90 percent of the patients, respectively. Oral anticoagulants were used in 24 percent of patients and did not enhance the resolution of

thrombi at 1 month. Patients with LV thrombi during the hospital stay had more extensive myocardial dysfunction and significantly higher mortality during the follow-up period of over 3 years than those without thrombi (23 vs. 7 percent, $p<0.01$).

In an observational analysis of 2231 patients post-myocardial infarction enrolled in the Survival and Ventricular Enlargement (SAVE) trial the rate of stroke was 1.5 percent per year of follow-up.[217] The independent risk factors for cerebral thromboembolic event included a lower EF (for every decrease of 5 percentage points in the EF there was an 18 percent increase in the risk of stroke), older age, and the absence of aspirin or anticoagulant therapy (administered on a nonrandomized basis). There was an 81 percent reduction in risk of stroke with anticoagulation in this trial. (This was not a specified endpoint of this trial of angiotensin-converting enzyme inhibitor administration on mortality post-myocardial infarction.) This reduction was of greater magnitude than the reduction in stroke observed in either the ASPECT (39 percent) or the WARIS (55 percent) trials. The use of aspirin was associated with a 56 percent risk reduction for cerebrovascular accidents in the SAVE trial. The limitations of this study include the lack of data on the intensity of anticoagulation and the fact that therapy with aspirin and anticoagulant agents was not randomly assigned.

Randomized trials of high-dose subcutaneous heparin versus placebo during the hospital stay in patients with acute myocardial infarction have shown that this therapy is effective at reducing the formation of LV thrombi by 50 to 66 percent.[218] [219] [220] However, these trials had an adequate sample size only to evaluate the surrogate endpoint of resolution of LV thrombi with active treatment and should not be taken as evidence of benefit in preventing thromboembolic or vascular events.

RECOMMENDATIONS.

Oral anticoagulation with warfarin should be used in patients with large anterior myocardial infarction for 3 to 6 months at a target INR of 2 to 3. Although it is prudent to use oral anticoagulant in patients with protruding or mobile LV thrombi, the routine administration in all patients after acute myocardial infarction must await further clarification. [220]

DILATED CARDIOMYOPATHY (See also Chap. 48) .

Patients with LV systolic dysfunction due to either ischemic or nonischemic dilated cardiomyopathy are at risk of developing both arterial and venous thromboembolic events.[221] The presence of regional wall motion abnormality, of poor contractility creating areas of relative stasis, of concomitant atrial fibrillation, and of chronic hypercoagulable state are factors that predispose to thromboembolism in these patients.[222] The incidence of thromboembolic events has ranged from 37 to 50 percent in older autopsy studies.[223] However, when clinically apparent events are evaluated, the incidence has been much lower. Fuster and coworkers observed 3.5 clinically apparent

embolic events per 100 patient-years in a retrospective analysis of 104 patients with nonischemic dilated cardiomyopathy.[224] In a prospective follow-up of 264 patients with dilated cardiomyopathy, Katz and coworkers observed that the incidence of stroke was 1.7 per 100 patient-years.[225] In a more recent retrospective analysis by Natterson and coworkers of 224 patients awaiting cardiac transplantation, an arterial embolization rate of 3.2 per 100 patient-years was observed.[226]

The observational analysis of the factors predisposing to mortality and cerebral thromboembolism in the large prospective heart failure trials evaluating the use of angiotensin converting enzyme inhibitors (V-HEFT, SOLVD, and SAVE) has been published.[217] [227] [228] [229] Although these trials are not directly comparable to those of patients with dilated cardiomyopathy, the factors predisposing to thromboembolic events for patients with chronically depressed LV systolic function are relevant. These studies, which are elaborated here, have the following limitations: (1) The oral anticoagulant or antiplatelet regimens were not randomly allocated, (2) the intensity or the duration of anticoagulation is unknown, and (3) the number of patients on aspirin alone or warfarin alone is not available from the data base.

The observational analysis of the Veterans Affairs Vasodilator-Heart Failure Trials (V-HEFT I and II) included 642 men with heart failure who were followed for an average of 2.28 years (V-HEFT I) and 804 men were followed for an average of 2.56 years (V-HEFT II).[229] The incidence of all thromboembolic events in V-HEFT I was 2.7 per 100 patient-years, and in V-HEFT II was 2.1 per 100 patient-years; and it was not reduced in patients treated with warfarin. Patients with lower peak oxygen consumption (MV_{O_2}) and lower EF had a higher risk of thromboembolic events, but only the difference in MV_{O_2} was significant. The use of oral anticoagulants was associated with a small but statistically insignificant increase in thromboembolic events in this analysis. There was no significant difference in the rate of thromboembolism between patients with ischemic and non-ischemic cardiomyopathy in this trial.

The retrospective analysis of Studies of Left Ventricular Dysfunction (SOLVD) was limited to the 6378 patients who were in sinus rhythm because of the confounding influence of atrial fibrillation on thromboembolic events.[228] The annual incidence of thromboembolic events was higher in women (2.4 percent) than in men (1.8 percent). Multivariate analysis revealed a 53 percent increased risk of thromboembolism for every 10 percent reduction in EF in women (p=0.02), but no increased risk was observed in men. The use of anticoagulants alone or the combination of anticoagulants plus antiplatelet agents was not associated with significant risk reduction on the incidence of thromboembolism in either men or women. However, aspirin monotherapy resulted in 23 percent risk reduction in men (p=0.06) and 53 percent risk reduction in women (p=0.03).

A separate analysis focusing on warfarin anticoagulation and mortality in the 6797 patients enrolled in the SOLVD prevention and treatment trials has also been reported.[227] This cohort was divided into 861 patients on warfarin and 5652 patients on no oral anticoagulants. The patients on warfarin were sicker, as evidenced by lower mean EF, higher prevalence of atrial fibrillation, and cerebrovascular disease. When all-cause mortality was evaluated without adjusting for differences in baseline

characteristics, there was no benefit of warfarin. However, after adjusting for baseline differences, warfarin use was a highly significant predictor of favorable outcome with a hazard ratio of 0.76 (95 percent confidence interval 0.65 to 0.89, *p*=0.0006). A similar analysis after adjusting for differences in baseline characteristics has not been reported for the V-HEFT. These differences in baseline variables may explain the higher thromboembolic event rate (although not statistically significant) in patients on anticoagulants in the V-HEFT study. The reduction in the relative risk of stroke with anticoagulation (81 percent) and antiplatelet agents (56 percent) in the SAVE trial has been elaborated in the section on prevention of LV thrombi post-myocardial infarction.[217]

RECOMMENDATIONS.

A placebo-controlled randomized trial of long-term anticoagulation in patients with dilated cardiomyopathy has not yet been performed. Thus, the routine use of oral anticoagulants cannot be universally recommended, especially in view of the observed benefits of aspirin monotherapy from CARS and several nonrandomized trials.[209] [220] Oral anticoagulation should thus be individualized to patients with high-risk characteristics such as large, protruding, or mobile ventricular thrombi and in patients with concomitant atrial fibrillation.

Prosthetic Heart Valves (See also Chap. 46)

Risks associated with implantation of prosthetic heart valves include thromboembolism, particularly stroke, and valve thrombosis. Although patients with bioprosthetic valves are at risk for thromboembolic events primarily during the first 90 days after surgery, those with mechanical valves remain at significant risk indefinitely.[230] [231] In one analysis, the incidence of major embolism in the absence of antithrombotic therapy was calculated to be 4 per 100 patient-years.[232] Factors that are associated with an increased risk of thromboembolism include the presence of older "first generation" mechanical valves (e.g., Starr-Edwards "ball and cage" valve), valves in the mitral position, the presence of more than one prosthetic valve, prior embolism, atrial fibrillation, enlarged left atrium, low LVEF, and advanced age.[232] [233] [234] [235] [236]

ANTIPLATELET THERAPY ALONE.

There have been no randomized placebo-controlled trials assessing antiplatelet therapy alone as an antithrombotic regimen in patients with mechanical heart valves. Nonrandomized studies of aspirin, dipyridamole, or both in patients with mechanical heart valves have shown only modest or no significant protective effect.[232] [237] In one open prospective randomized trial of patients with mitral or aortic Starr-Edwards valves, combination antiplatelet therapy (aspirin plus dipyridamole or aspirin plus pentoxifylline) was associated with a higher incidence of thromboembolism when compared with treatment with warfarin.[238] Based on the previous reports, antiplatelet therapy alone is

not considered to provide adequate antithrombotic protection in patients with mechanical prostheses.[239]

There have likewise been no randomized nor placebo-controlled trials of antiplatelet therapy alone in patients with bioprosthetic valves. One series of 185 patients with bioprosthetic valves in the mitral or mitral and aortic positions who were in sinus rhythm reported no thromboembolic events with a mean follow-up of 32 months in patients treated with aspirin (500 mg every other day to 1 gm/d).[240]

WARFARIN THERAPY.

Studies of patients with bileaflet mechanical valves (such as the commonly used St. Jude valve) have shown that oral anticoagulation to achieve lower INRs is not associated with a clinically significant increase in thromboembolic complications compared with those with higher INRs. In one prospective study, subset analysis of patients in sinus rhythm with nonenlarged left atria showed little difference in thromboembolic events when INR values of 1.8 to 2.7 were compared with those of 2.5 to 3.2.[241] In a large series of patients from the Netherlands, patients with bileaflet valves had no more complications at INRs of 2.0 to 2.9 than INRs of 3.0 to 3.9 or 4.0 to 4.9, although those with tilting disc or caged ball or disc valves had less overall adverse outcomes at higher INRs. In the AREVA study, patients at low risk for embolic events randomized to anticoagulation at an INR of 2.0 to 3.0 had similar thromboembolic events and less hemorrhagic events than those randomized to anticoagulation at an INR of 3.0 to 4.5.[242]

Patients treated with bioprosthetic valves, especially in the mitral position, are at significant risk of thromboembolism during the first 90 days after surgery; and this risk is decreased with anticoagulation therapy.[230] In one study of patients who received bioprosthetic valves, those randomized to anticoagulation with an INR of 2.0 to 2.25 had thromboembolic rates comparable to those treated with a target INR of 2.5 to 4.0.[243]

These and other studies have led to lower recommended INR ranges for the prevention of thromboembolic events in patients with mechanical valves (particularly those with St. Jude valves) and with bioprosthetic valves.[231] [239] [244] [245]

WARFARIN PLUS ANTIPLATELET THERAPY.

Several trials have evaluated the utility of combined warfarin and antiplatelet therapy compared with warfarin therapy alone. Turpie and colleagues randomized a group of patients consisting of those with either mechanical heart valves or high-risk characteristics and bioprosthetic valves to treatment with warfarin (target INR 3.0 to 4.5) and either aspirin (100 mg daily) or placebo. Major systemic embolism of vascular death occurred at a rate of 1.9 percent/year in those treated with aspirin and 8.5 percent/year in those treated with placebo. All-cause death occurred in 2.8 percent and 7.4 percent of patients, respectively. Although bleeding was more common in the combined therapy group, most of the increased incidence of bleeding was due to minor bleeding.[246] A meta-analysis of five randomized trials comparing warfarin therapy alone with warfarin

therapy combined with antiplatelet therapy (aspirin or dipyridamole) found that combination therapy reduced embolism by 67 percent and overall mortality by 40 percent. Although the risk of bleeding was increased with combination therapy, the benefits of combination therapy appeared to outweigh this increased bleeding risk.[247]

In a trial comparing the combination of lower-intensity anticoagulation with warfarin (INR 2.5 to 3.5) and aspirin (100 mg/d) with higher-intensity anticoagulation alone (INR 3.5 to 4.5), the incidence of thromboembolic events was similar; bleeding tended to be more common in patients treated with higher-intensity anticoagulation therapy.[248] Altman and coworkers found no difference in systemic embolization or vascular death in patients treated with combination therapy between those who received relatively low-dose aspirin (100 mg/d) and those treated with high-dose aspirin (650 mg/d).[249] Thus, combination warfarin and antiplatelet therapy in many patients appears to reduce the risk of thromboembolic events without unacceptably increasing bleeding complications. Antiplatelet therapy with as low as 100 mg/d of aspirin in this setting appears adequate.

RECOMMENDATIONS.

Recommendations regarding antithrombotic therapy in patients with prosthetic heart valves have been published from a consensus conference of the American College of Chest Physicians (ACCP)[239] and others[231] [244] [245] based on the above and other data. The following summarizes in simplified form the latest (as of this writing) ACCP guidelines.

All patients with mechanical prosthetic heart valves should be treated with oral anticoagulants. The intensity of anticoagulation recommended in specific situations can be thought of as a three-tier system, based on the presence or absence of certain factors associated with increased risk of thromboembolism and on the just discussed studies. For patients with a bileaflet valve (e.g., "St. Jude") in the aortic position, without other factors that have been correlated with increased risk of thromboembolism (enlarged left atrium, atrial fibrillation, low LVEF), treatment should be with warfarin with a target INR of 2.5 (range 2.0 to 3.0). For patients with a bileaflet or tilting disc valve in the aortic position with atrial fibrillation or with bileaflet or tilting disc valve in the mitral position, treatment should be with either (1) warfarin alone with a target INR of 3.0 (range 2.5 to 3.5) or with (2) warfarin with a target INR of 2.5 (range 2.0 to 3.0) plus aspirin (80 to 100 mg/d). For patients with caged ball (e.g., "Starr Edwards") or caged disc valves or those with any mechanical valves and other factors associated with increased risk of thromboembolism, combined therapy with warfarin with a target INR of 3.0 (range 2.5-3.5) and aspirin (80-100 mg/d) is recommended.

Patients with bioprosthetic heart valves should be treated with warfarin with a target INR of 2.5 (range 2.0-3.0) for 3 months. After this period, those not at risk of systemic embolism from other factors (e.g., atrial fibrillation) can be treated with aspirin (162 mg/d).

Percutaneous Coronary Interventions

Antiplatelet and anticoagulant therapy has made modern percutaneous arterial

interventions practical.[250] The strategies for using these therapies in patients undergoing coronary interventions are discussed in detail in Chapter 38 . A summary of the key findings follows.

ANTIPLATELET AGENTS IN PERCUTANEOUS CORONARY INTERVENTIONS.

In the era of balloon angioplasty alone, before the advent of stents, the utility of aspirin for prevention of periprocedural myocardial infarction and/or recurrent ischemia requiring urgent revascularization was established. The quest to reduce further ischemic complications of percutaneous coronary intervention in the 1990s was aided by the introduction of potent new antiplatelet agents such as the Gp IIb/IIIa receptor inhibitors.[251] [252] [253] [254] [255] [256] The Gp IIb/IIIa receptor antagonists have been evaluated in five major prospective, randomized, double-blind, placebocontrolled trials in patients undergoing balloon angioplasty.[251] [252] [253] [257]

Figure 62-22 The reduction in acute ischemic complications after percutaneous transluminary coronary angioplasty defined as death, myocardial infarction, or urgent target vessel revascularization (triple composite) in trials of GP IIb/IIIa inhibitors versus placebo at 30 days. The odds ratio with 95 percent confidence intervals for each trial is shown. The odds ratio circle for each trial is relatively proportional to its sample size, which is also shown as a number. The embedded table shows the event rate in the treated and control groups. (Adapted from Lincoff AM, Tcheng JE, Califf RM, et al: Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa blockade with abciximab: One-year outcome in the EPILOG trial. Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade. Circulation 99:1951-1958, 1999. Copyright 1999, American Heart Association.)

Although there are some differences between studies, the overall direction has been one of marked reduction in ischemic complications of balloon angioplasty with the use of these agents (Fig. 62-22) .

The success of these early Gp IIb/IIIa inhibitor trials, along with the potential drawbacks of monoclonal Fab fragments such as immunogenicity, a finite incidence of thrombocytopenia (
5 percent), and the extended duration of antiplatelet effect, created an impetus to evaluate other Gp IIb/IIIa receptor antagonists.[258] [259] [260] [261] Two phase III clinical trials using cyclic RGD peptides (eptifibatide) or nonpeptide RGD mimetics (tirofiban) that compete for ligand binding to the Gp IIb/IIIa receptor have been reported. Their results show a similar reduction in triple composite endpoint in the first 24 to 72 hours after percutaneous transluminal coronary angioplasty. However, clinical efficacy with these shorter-acting agents was not sustained at 30 days and 6 months.[252] [253]

ANTICOAGULANTS IN PERCUTANEOUS CORONARY INTERVENTIONS.

Coronary interventions before the Gp IIb/IIIa inhibitor era were often performed by using approximately 150 U/kg of heparin (with a 10,000- to 15,000-unit initial bolus), targeted to an activated clotting time (ACT) between 300 and 350 seconds.[262] [263] The rationale for this level of anticoagulation during angioplasty was the observation of an inverse relationship between ACT and the risk of ischemic complications. Periprocedural ischemic events increase the synthesis of heparin-binding proteins and potentiate the local release of platelet factor 4 (PF4) by platelets.[264] This leads to heparin resistance and/or inactivation with consequent reduction in ACT and aPTT values. These shortcomings of heparin along with the biochemical advantages afforded by the direct thrombin inhibitors hirudin and its congener bivalirudin provided an impetus to test these agents for prevention of ischemic complications and restenosis after angioplasty.[265] After encouraging preliminary studies, two large prospective randomized trials evaluated the two direct thrombin inhibitors in patients undergoing percutaneous coronary intervention (Fig. 62-23) .[266] [267] The failure of the direct thrombin inhibitor to substantially alter the long-term outcome in patients undergoing percutaneous coronary intervention or in acute coronary syndromes may be multifactorial, possibly related to continued thrombin generation during, as well as rebound increase in thrombin activity upon cessation of, infusion.[268]

ANTITHROMBOTIC THERAPY AFTER DEPLOYMENT OF CORONARY STENTS.

Coronary stenting has outpaced balloon angioplasty as the most frequently performed percutaneous revascularization procedure.[250] The early experience with coronary stenting was associated with a 5 to 20 percent incidence of stent thrombosis that frequently resulted in clinical events such as death, myocardial infarction, or urgent target lesion revascularization.[269] [270] [271] The tendency for ischemic complications after stenting occurred despite intense anticoagulation during the procedure with high-dose heparin, dextran, and postprocedure warfarin administration to an INR of 3.0 to 4.5.[271] The need to optimize oral anticoagulation during heparin infusion as well as bleeding complications as a result of intense anticoagulation led to prolonged hospitalizations. The introduction of thienopyridine ADP antagonists (ticlopidine and clopidogrel) and the optimization of stent deployment techniques have eliminated the need to treat patients with warfarin after coronary stenting. Trials have now shown the superiority of the combination antiplatelet regimen of aspirin and ticlopidine over aspirin alone, or aspirin plus oral anticoagulation with warfarin, not only in patients with optimal stent deployment but also in patients who are at high risk of stent thrombosis[272] [273] [274] [275] [276] (Fig. 62-24) .

Although ticlopidine has proven to be effective in preventing stent thrombosis in multiple trials, the enthusiasm

Figure 62-23 The reduction in acute ischemic complications after PTCA defined as death in the hospital, myocardial infarction (MI), abrupt vessel closure, or rapid clinical deterioration of cardiac origin in the HELVETICA and Hirulog in Angioplasty trials. The odds ratio with 95 percent confidence intervals for each trial is shown. The odds ratio of the intravenous (IV) and subcutaneous (SC) arms of HELVETICA, the overall group as well as the postinfarction angina subgroup in the Hirulog in Angioplasty trial, are shown. The odds ratio circle for each trial is relatively proportional to its sample size, which is also shown as a number. The embedded table shows the event rate in the treated and control groups.

Figure 62-24 The reduction in clinical sequelae of stent thrombosis defined as death, myocardial infarction, revascularization of the target lesion, or angiographically evident thrombosis within 30 days in the stent trials. The odds ratio with 95 percent confidence intervals for each trial is shown. The event rate in the control groups is either for aspirin treatment alone (STARS vs. A and Hall and coworkers) or aspirin plus oral anticoagulation with warfarin (STARS vs. OA, ISAR, ISAR H [denoting high-risk group] and MATTIS). The ISAR (H) and the MATTIS trial enrolled patients who were at high risk of stent thrombosis. The odds ratio circle for each trial is relatively proportional to its sample size, which is also shown as a number. The embedded table shows the event rate in the treated and control groups.

Figure 62-25 The incidence and type of each myocardial infarction for each treatment group in the EPISTENT trial. The predominant effect of abciximab was in the reduction of large non-Q wave myocardial infarction which comprised 86 percent of the benefit. (From EPISTENT Investigators: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Lancet 352:87-92, 1998.)

for this agent was tempered by a small but finite incidence of hematological side effects such as neutropenia and thrombotic thrombocytopenic purpura.[277] [278] [279] [280] [281] [282] [283] [284] [285] [286] [287] [288] This provided the impetus to evaluate clopidogrel, a congener of ticlopidine.[289] The preliminary results of the CLASSICS (Clopidogrel plus ASA vs. Ticlopidine plus ASA in patients with stents) study suggest that clopidogrel provides comparable efficacy and fewer side effects than ticlopidine.[211] Recently, TTP has been described in association with clopidogrel as well as with ticlopidine, albeit at lower frequency.[173A]

ROLE OF GP IIB/IIIA INHIBITORS IN CORONARY STENTING.

The EPISTENT trial was designed to evaluate the synergism between optimization of luminal rheology with coronary stenting and potent platelet blockade with Gp IIb/IIIa inhibitors.[254] In this trial, 2399 patients were randomized to a strategy of balloon angioplasty with abciximab, stent deployment with abciximab, and stent deployment with routine anticoagulation with weight-based heparin (100 U/kg). There was a dramatic reduction in the triple composite endpoint of death, myocardial infarction, and urgent target vessel revascularization at 30 days in the two abciximab groups (6.9 and 5.3 percent) compared with stent deployment on the background of routine heparin

therapy (10.8, $p<0.007$, and 0.001, respectively). The predominant effect of abciximab was in the reduction of large non-Q wave myocardial infarction that comprised 86 percent of the benefit (Fig. 62-25). The best outcome was in the stent plus abciximab group, indicating that there is synergism between optimization of luminal rheology and potent platelet inhibition. Preliminary data regarding the durability of benefit for the combined abciximab/stent strategy versus stenting alone for reduction of death rates (0.8 percent vs. 2.4 percent) at 1 year are now available. The ESPRIT study is evaluating the potential benefit of treatment with eptifibatide in patients primarily without traditional high-risk clinical or angiographic features who are undergoing coronary stent implantation. Results of this study should be forthcoming.

ANTITHROMBOTIC THERAPY FOR PREVENTION OF CORONARY RESTENOSIS.

The paradigm that coronary restenosis is predominantly a result of mural thrombosis that provides a scaffold for the subsequent migration and proliferation of neointimal smooth muscle cells has recently been challenged by serial intravascular ultrasound studies in patients undergoing percutaneous transluminal coronary angioplasty.[290] These observations have highlighted the importance of both acute vessel recoil and late vascular remodeling as the major factors contributing to luminal narrowing after this procedure.[291] Thus, it is not surprising that a decade of animal and clinical studies with both conventional antiplatelet agents and antithrombins has yielded negative results for the prevention of coronary restenosis.[250]

RECOMMENDATIONS.

All patients undergoing percutaneous coronary intervention should be pretreated with aspirin (160-325 mg/d) in the absence of specific contraindications such as true aspirin allergy. Whereas Gp IIb/IIIa inhibitors should be considered in most patients undergoing percutaneous coronary intervention, their use is strongly recommended for patients at high risk of ischemic complications such as intracoronary thrombus, post-myocardial infarction, and unfavorable lesion morphology. Combination antiplatelet therapy with aspirin and a thienopyridine (ticlopidine or clopidogrel) should be used in all patients undergoing intracoronary stenting for 2 to 4 weeks after stent implantation (and aspirin alone should then be continued indefinitely).

Antithrombotic Therapy after Coronary Artery Bypass Surgery (See also Chap. 37)

The disease process in the vein grafts is initiated at the time of explantation from the leg and progresses through an early thrombotic phase in the first month after surgery, followed by intimal hyperplasia over the next 12 months, which creates a substrate for accelerated atherosclerosis.[292] [293] [294] [295] [296] Saphenous vein graft occlusion in the first month is therefore a result of thrombotic occlusion and is reported to occur in 3 to 12 percent of grafts. The predisposition to thrombosis is initiated at the time of harvesting when high pressure distention is required to overcome venous spasm.[297] [298] [299] [300] This results in prominent endothelial cell loss and medial damage, with consequent deposition of fibrin, platelets, and neutrophils on the denuded luminal surface. In addition, the disruption of endothelial integrity results in reduction of tissue plasminogen activator production, impairment of thrombomodulin mediated inhibition of the

coagulation cascade, and exposure of tissue factor.[301] The thrombotic tendency in the first several weeks after aortocoronary bypass led to the use of antiplatelet agents in an effort to prevent graft occlusion (Fig. 62-26) . [292] [293] [296] [302] [303] [304] [305]

Landmark clinical trials conducted in the 1980s by Chesebro and coworkers as well as Goldman and coworkers have shown that (1) aspirin (100 to 975 mg daily) when initiated either before, on the day of, or 1 day after bypass surgery is effective at reducing thrombotic graft occlusion; (2) the combination of dipyridamole and aspirin is no more effective than aspirin alone; (3) initiation of aspirin before bypass surgery is associated with an increase in perioperative bleeding events without an increase in graft patency when compared with aspirin therapy started within the first 24 hours after surgery; (4) aspirin therapy after the first 48 hours is not effective in preventing graft occlusion; and (5) there are no benefits on vein bypass graft patency of aspirin therapy for longer than 1 year.[306]

For patients who are intolerant of or allergic to aspirin, ticlopidine started within the first 2 days after grafting is a viable alternative based on the study by Limet and coworkers.[302] There are no studies of combination therapy with aspirin and ticlopidine or clopidogrel, which is a potentially useful regimen because these agents mediate their

Figure 62-26 The effect of antithrombotic therapy with aspirin alone (100-975 mg), aspirin plus dipyridamole, or ticlopidine compared with placebo on saphenous vein graft patency in different trials is depicted as odds ratio with 95 percent confidence intervals for each trial. The odds ratio circle for each trial is relatively proportional to number of vein grafts evaluated, which is also shown as a number. The embedded table shows the duration of follow-up and the rate of graft patency in the treated versus the control groups.

antiplatelet effect by different pathways. On the basis of the efficacy of combined therapy with aspirin plus ticlopidine or aspirin plus clopidogrel in reducing subacute stent thrombosis, it is reasonable to evaluate the potential synergy of these regimens for prevention of vein graft thrombosis.[289] [307]

The use of oral anticoagulants initiated before or immediately after surgery provides no additional improvement in graft patency when compared with aspirin therapy.[308] [309] [310] In addition, bleeding complications occurred more frequently in the oral anticoagulant group.[308] [309] The Post CABG study evaluated whether aggressive lowering of low-density lipoprotein cholesterol levels or low-dose anticoagulation would delay the progression of atherosclerosis in vein grafts.[311] The study enrolled 1351 patients 1 to 11 years after bypass surgery with at least one patent vein graft in a 2×2 factorial design to aggressive or moderate treatment to lower low-density lipoprotein cholesterol and to treatment with warfarin or placebo. The warfarin group achieved a mean INR of only 1.4. The primary outcome in this trial was angiographic progression of disease that was lowered by aggressive lipid-lowering therapy. However, warfarin was not superior to

placebo in influencing rates of disease progression (34 vs. 32 percent; *p*=0.48) or graft occlusion. These angiographic outcomes were accompanied by no differences in the rates of myocardial infarction (5.0 vs. 5.0 percent) or the need for revascularization (7.8 vs. 7.9 percent) between the warfarin-treated and placebo-treated patients.

The improved understanding of the pathogenesis of early

thrombotic occlusion of vein grafts has led to experimental studies using innovative strategies.[294] [312] [313] The saphenous vein grafts are ideal targets for gene therapy because the explanted veins are available for ex vivo transfer of exogenous genetic material before grafting. The replication-defective adenoviral vectors have been successfully used to transfer genes in experimental porcine vein graft models.[314] In addition, cultured human saphenous veins have been successfully transfected with an adenoviral vector encoding bovine endothelial NOS, yielding a marked increase in venous endothelial NO production.[313] This strategy, if clinically feasible, has the potential to provide a potent local antithrombotic milieu in the early vulnerable period of thrombosis after graft implantation. The administration of platelet selective NO donors and the modulation of tissue factor with anti-tissue factor antibody are some of the other approaches undergoing investigation in experimental animal models.[312] [315]

RECOMMENDATIONS.

Early antiplatelet therapy with aspirin should be used in all patients after coronary artery bypass surgery to prevent vein graft occlusion. Preoperative aspirin may increase intraoperative bleeding and is not more beneficial than aspirin started within the first 24 to 48 hours after surgery. Therefore, for elective surgery and if the clinical situation permits, aspirin should be withheld until after the operation. Aspirin at doses of 100 to 325 mg/d should be started immediately after surgery. A delay in the initiation of aspirin beyond 48 hours is associated with reduced efficacy. The addition of dipyridamole to aspirin has not been shown to enhance vein graft patency.

The appropriate duration of antiplatelet therapy after surgery is controversial. Studies suggest that aspirin therapy for at least 1 year reduces vein graft occlusion. Although studies do not show an improvement in vein graft patency with antiplatelet therapy beyond the first year, the beneficial effects of aspirin for secondary prevention of coronary artery disease argue that it be continued indefinitely in these patients. For patients allergic to aspirin, ticlopidine, 250 mg twice daily, beginning 48 hours after surgery has been reported to be effective and may be considered as an alternative.

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Chapter 63 - Diabetes Mellitus and the Cardiovascular System

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SCOPE OF THE PROBLEM

In the coming decades, the burden of cardiovascular diseases (CVDs) related to diabetes will increase substantially. Diabetes, formerly thought of as a problem of glucose metabolism, actually produces most of its harm by effects on the cardiovascular system.[1] [2] [2A] Microvascular disease underlies the pathogenesis of diabetic retinopathy, a common cause of blindness. Microvascular disease also causes diabetic renal disease, a major contributor to need for dialysis therapy.

Most diabetics die of CVD, and atherosclerosis accounts for some 80 percent of all diabetic mortality. About three-quarters of the cardiovascular deaths from diabetes result from coronary artery disease (CAD). The remaining quarter results from cerebral or peripheral vascular disease. Atherosclerotic disease causes some three-quarters of all hospitalizations for diabetic complications. Tight control of glycemia consistently reduces the risk of microvascular complications of diabetes in large clinical trials.

However, the benefits of glycemic control on the macrovascular complications of diabetes are less firmly established. With the success of currently available hypoglycemic agents in mitigating microvascular disease, a shift toward a preponderance of macrovascular complications may well occur.

The burden of diabetic disease in the population will increase markedly in the coming years. In the United States, the prevalence of diabetes has increased from approximately 2 million cases in the early 1960s to some 15 million in the year 2000. Current estimates project 22 million cases by the year 2025. This increase goes hand in hand with an epidemic of obesity, which affected approximately 18 percent of the U.S. population in 1998.[3] During the 7 years from 1991 to 1998, the body weight of American men increased over 3 percent and that of women almost 5 percent. The significant clustering of atherogenic risk factors, including glucose levels and body weight, links the current epidemic of obesity and diabetes mellitus.[4]

The coming wave of CVD related to diabetes will take a particularly heavy toll in certain minority populations. Hispanics, blacks, Native Americans, and Asian Indians will bear a disproportionate burden of diabetic CVD.[5] The predilection of these ethnic groups to the development of obesity and glucose intolerance on a Western diet may have a genetic basis. The ability to store fat may have conferred a survival advantage in populations subject to famine. This selective pressure could enrich the population in genes that facilitate fat storage, the so-called thrifty gene hypothesis.[6] [7] As discussed below, diabetics with CVD fare worse than their nondiabetic counterparts. Hence, physicians caring for patients with CVD have a compelling need to have a working knowledge of the effects of diabetes mellitus on the heart and blood vessels.

NEW DIAGNOSTIC CRITERIA.

In 1997, the American Diabetes Association promulgated new criteria for the diagnosis of diabetes mellitus. These criteria use a single blood glucose determination after an 8-hour fast (fasting plasma glucose [FPG]) as the major diagnostic criterion (Table 63-1) . An FPG of less than 110 mg/dl is considered normal. A new diagnostic category known as impaired fasting glucose

TABLE 63-1 -- CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

NORMAL	IMPAIRED FASTING GLUCOSE AND IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLITUS
FPG <110 mg/dl	FPG ;110 mg/dl and <126 mg/dl (IFG)	FPG ;126 mg/dl
2-hr PG* <140 mg/dl	2-hr PG* ;140 mg/dl and <200 mg/dl (IGT)	2-hr PG* ;200 mg/dl
2-hr PG*		Symptoms of DM and random plasma glucose concentration ;200 mg/dl

IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

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*Rather than using the classic glucose tolerance curve with multiple time points sampled, the new criteria use, in parallel with fasting plasma glucose (FPG) measurements, a 2-hour post-glucose load (PG) set of criteria. The plasma sample is obtained 2 hours following an oral administration of 75 gm of anhydrous glucose in aqueous solution.

encompasses FPGs greater than 110 but less than 126 mg/dl. An FPG greater than 126 mg/dl establishes the diagnosis of diabetes mellitus.

Type II diabetics, previously known as noninsulin-dependent diabetics, represent about 90 percent of the diabetic population. However, those with type I diabetes (previously known as insulin-dependent or juvenile diabetes) also have an independently higher risk of cardiovascular events, and their disease generally develops at a much younger age than in the type II diabetic population.

PATHOPHYSIOLOGY OF THE CARDIOVASCULAR COMPLICATIONS OF DIABETES

A number of metabolic, cellular, and molecular mechanisms underlie diabetic CVD (Table 63-2) . A brief discussion of the most important pathophysiological concepts follows:

DYSLIPIDEMIA AND ASSOCIATED METABOLIC ABNORMALITIES (see alsoChap. 31).

The longest studied, best understood, and most substantiated mechanism for enhanced atherogenesis in type II diabetes is the dyslipidemia and associated cluster of risk factors known as the "metabolic syndrome" (Table 63-3) . Increased hepatic production of very low-density lipoproteins (VLDLs) by the liver lies at the center of the pathogenesis of diabetic dyslipidemia (Fig. 63-1) . The liver increases its production of VLDL in response to increased delivery of fatty acid from several sources. Uptake of free fatty acids by striated muscle depends on insulin. Under conditions of insulin resistance, striated muscle takes up less free fatty acids, which increases the presentation of free fatty acids to the liver. In addition, central obesity increases the delivery of free fatty acids to the liver. Abdominal obesity, particularly in men, consists primarily of increased visceral adipose tissue that is drained by the portal vein and delivers an excessive load of free fatty acid to the liver, where it furnishes the substrate for increased VLDL synthesis. The accumulation of triglyceride-rich lipoproteins in

plasma depends not only on increased production of VLDL by the liver but also on decreased catabolism of triglyceride-rich lipoproteins, including dietary chylomicrons. Lipoprotein lipase activity decreases in uncontrolled type II diabetes. This enzyme

TABLE 63-2 -- MECHANISMS OF VASCULAR ABNORMALITIES IN DIABETES MELLITUS

Hyperglycemia
Increased diacylglycerol, protein kinase C activation
Increased sorbitol
Hyperinsulinemia
Oxidative stress
Reactive oxygen species
Carbonyl overload
Advanced glycation end products (AGEs)
Activation of nuclear factor kappa B (NF-kappaB)
Overproduction of inflammatory cytokines
Dyslipidemia
Small dense LDL
Low HDL
Hypertriglyceridemia
Procoagulant, antifibrinolytic state
Elevated fibrinogen
Increased plasminogen activator inhibitor (PAI)
Heightened platelet function
Genetic abnormalities
Peroxisomal proliferation-activating receptor-gamma (PPAR-gamma) mutations

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE 63-3 -- COMPONENTS OF THE CARDIOVASCULAR DYSMETABOLIC SYNDROME

Insulin resistance
Hyperglycemia
Dyslipidemia
Hypercoagulability
Obesity

plays a key role in clearing postprandial lipemia, which largely consists of triglyceride-rich particles.

The increase in triglyceride-rich lipoprotein partially accounts for the low levels of high-density lipoprotein (HDL) characteristic of diabetic dyslipidemia. The high concentration of triglyceride-rich lipoproteins provides an increase in substrate for cholesterol ester transfer protein, which promotes the flux of cholesterol from HDL particles and decreases the level of HDL cholesterol. Part of HDL's protective effect against atherosclerosis may result from its ability to reduce the oxidation of low-density lipoprotein (LDL). In addition to a quantitative decrease in HDL cholesterol levels in uncontrolled diabetes, recent evidence suggests qualitative differences in HDL particles from poorly controlled type II diabetic patients. In particular, HDL isolated from such patients protects LDL from oxidation less effectively than does HDL from nondiabetic subjects.[8]

Curiously, diabetics tend to not have markedly elevated plasma LDL concentrations. However, LDL particles in uncontrolled type II diabetic patients characteristically have qualitative alterations as well. In particular, LDL from such diabetic subjects tends to be smaller and denser than typical LDL particles. These small, dense LDL particles show greater susceptibility to oxidative modification in vitro. Moreover, LDL from poorly controlled type II diabetics has increased susceptibility to oxidation because of decreased antioxidant defense mechanisms in the plasma of diabetics.[9]

Alterations in the traditional variables of the lipoprotein profile go hand in hand with other risk factors in diabetic patients. In addition to the triad of increased triglycerides, decreased HDL, and small dense LDL, insulin-resistant patients tend to have hypertension and obesity, as well as hyperglycemia (see Table 63-3). Abnormalities in coagulation and fibrinolysis in type II diabetes are considered below. The mechanistic link between visceral adiposity and diabetic dyslipidemia has already been discussed. Many life style or hygienic issues contribute to insulin resistance. For example, the visceral adiposity at the root of diabetic dyslipidemia commonly results from excessive caloric intake in the face of limited physical activity.

Genetic Predisposition.

Increasing evidence, however, supports the concept that genetic predisposition may contribute to the development of type II diabetes. Recent work has defined a specific mutation that leads to severe insulin resistance, diabetes mellitus, and hypertension. In two kindreds, dominant negative mutations in a transcription factor known as peroxisomal proliferation-activating receptor-gamma (PPAR-gamma) caused this insulin resistance constellation in members of two affected kindreds at a relatively young age.[10] Interestingly, the thiazolidinedione family of insulin-sensitizing agents acts by binding and activating the nuclear receptor/transcription factor PPAR-gamma. While this single-gene mutation probably accounts for the insulin resistance syndrome in a small number of individuals, it illustrates how a genetic abnormality can cause this condition. With completion of the human genome project and study of single-nucleotide

polymorphisms increasingly practicable, other genetic predisposing factors for type II diabetes will probably emerge. These factors may well involve

Figure 63-1 Pathogenesis of diabetic dyslipidemia. Increased production of very low-density lipoprotein by the liver results from increased delivery of fatty acids because of decreased utilization by muscle and increased delivery of fatty acids from visceral abdominal fat to the liver via the portal circulation. Decreased catabolism of postprandial triglyceride-rich lipoprotein particles because of reduced lipoprotein lipase activity accentuates diabetic dyslipidemia (not shown here; see Fig. 31-4).

haplotypes or polygenic conditions, as well as single-gene mutations, as illustrated by the PPAR-gamma mutation.

OXIDATIVE STRESS IN DIABETES MELLITUS.

Numerous basic science and clinical studies indicate an increased level of oxidative stress in diabetes.[11] Hyperglycemia leads to increased production of reactive oxygen species by several cell types. The reactive oxygen species can, in turn, augment the formation of reactive carbonyl species. Nonoxidative reactions can also increase the concentrations of reactive carbonyl compounds under hyperglycemic conditions. The reactive carbonyl species can derivatize proteins and lipids. The products of reactions of proteins with reactive oxygen and carbonyl species include the advanced glycation end products (AGEs) discussed below. There is little doubt that products of glycation accumulate in diabetic patients. However, they accumulate in nondiabetic elderly individuals as well.[11] Recent evidence suggests that inundation of the detoxification mechanisms for reactive carbonyl groups may account for the increase in oxidant and carbonyl stress in diabetics.

From a practical standpoint, the issue of whether oxidant stress causes diabetic complications or merely serves as a marker of deranged metabolism is crucial. In several recent clinical trials that included diabetic subjects, the lack of a protective effect of antioxidant compounds suggests the importance of emphasizing measures known to improve cardiovascular outcomes in diabetic subjects, such as lipid management and angiotensin-converting enzyme (ACE) inhibitor administration, while awaiting further information regarding the potential benefits of antioxidant strategies.

ADVANCED GLYCATION END PRODUCTS AND THEIR RECEPTORS.

The hyperglycemia characteristic of diabetes leads to nonenzymatic glycation of macromolecules. Use of hemoglobin A_{1c} allows the clinician to gauge the extent of hyperglycemia in a patient by measurement of this glycated form of hemoglobin. In hyperglycemic states, many other proteins and even lipids can become glycated. The chemistry of nonenzymatic glycation involves the formation of a labile covalent link

between the aldehyde function on the glucose molecule and amino side chains on sugars and lipids, which results in the formation of an aldimine or Schiff base. The aldimine slowly undergoes a chemical reaction to form a ketoamine by the Amadori rearrangement. The glycated hemoglobin commonly used to monitor diabetic patients is one such Amadori product.

However, more complex chemical reactions can ensue and allow condensation into larger heterocyclic derivatives of sugars linked to macromolecules. These structures, known as AGEs, are fluorescent and actually cause the macromolecule to take on a brown hue. Numerous chemical studies have characterized the structure of AGEs. A great deal of information is emerging regarding the potential significance of AGEs in the pathobiology of the complications of diabetes, notably, the accelerated vascular disease characteristic of this condition.[11] [12] [13] [14] Recent studies have shown accumulation of AGE-modified proteins, aside from hemoglobin, in diabetic subjects. The presence of glycated forms of LDL can engender an immune response and otherwise contribute to macrovascular disease.[15] Phospholipids and apolipoproteins can form AGEs.[16] AGE-modified LDL apoprotein and LDL lipid increase in diabetic subjects in comparison to nondiabetics.[16]

Cells contain several receptors for AGEs that mediate their biological effects. Exposure to AGE-modified proteins can elicit the production of inflammatory cytokines from vascular cells, cause impaired endothelial-dependent vasodilator function, and augment the endothelial expression of various leukocyte adhesion molecules implicated in atherogenesis in vivo.[17] [18] One extensively characterized receptor for AGEs is known as the receptor for advanced glycation end products, or RAGE.[19] Recent experiments support a functional role for RAGEs in the development of experimental atherosclerosis. Mice lacking the apolipoprotein E gene are susceptible to atherosclerosis. Administration of an antibody fragment that neutralizes RAGEs attenuated the atherosclerosis in these mutant mice. This beneficial effect on atherosclerotic lesion development did not depend on a change in blood sugar or lipoprotein profile.[20] These data support a role for AGEs in atherogenesis. However, they do not explain why the link between glycemic control and macrovascular disease in diabetes has proved so elusive.

EFFECTS OF THE DIABETIC STATE ON THROMBOSIS AND FIBRINOLYSIS.

Type II diabetes and its associated metabolic abnormalities favor an imbalance in the coagulation/fibrinolytic systems that support clot formation and stability.[21] Diabetic patients have increased levels of fibrinogen[22] and plasminogen activator inhibitor type 1 (PAI-1) in the plasma and in lesions.[23] [24] They also appear to have abnormal platelet function.[25] These various abnormalities may contribute to heightened susceptibility to the thrombotic complications of atherosclerosis.

ACTIVATION OF PROTEIN KINASE C IN DIABETES.

In diabetes, hyperglycemia can lead to an increased concentration of the metabolite diacylglycerol in the cell. Diacylglycerol, in turn, is a classic activator of a family of enzymes that perform key regulatory functions by phosphorylating proteins important in metabolic control. This family of enzymes, known as protein kinase C (PKC), has some dozen members. A great deal of recent work has implicated activation of the PKC family in the cardiovascular complications of diabetes.[26] [27]

Activation of PKC can inhibit expression of the endothelial form of nitric oxide synthase and thus promote impaired endothelial vasodilator function, as discussed below.[28] PKC can also augment cytokine-induced tissue factor gene expression and procoagulant activity in human endothelial cells.[29] Glucose-induced activation of PKC can augment the production of extracellular matrix macromolecules that accumulate during atherosclerotic lesion formation.[27] PKC activation can also increase the production of proinflammatory cytokines and the proliferation of vascular wall cells.[27] In vivo evidence supports a role of PKC activation in the pathogenesis of various aspects of vascular dysfunction in vivo. Administration of a selective inhibitor of PKC-beta to diabetic rats improves retinal blood flow.[30]

As discussed below, considerable evidence supports the existence of a diabetic form of cardiomyopathy distinct from ischemia. PKC activation may contribute not only to vascular dysfunction but also to cardiomyopathy in diabetes. Indeed, PKC-beta activity increases in the hearts of diabetic rats. Cardiac hypertrophy and fibrosis develop in transgenic mice overexpressing a PKC-beta isoform in the heart.[31] Early thickening of the interventricular septum, left ventricular hypertrophy, and a decrease in left ventricular dP/dt in concert with increased activity of PKC develop in diabetic rats.[32] These various studies provide evidence in vitro and in diabetic animals of a role of the PKC system in diabetic cardiovascular complications. Studies currently in progress will evaluate the relevance of this intriguing laboratory work to the clinical situation.

ABNORMAL VASODILATOR FUNCTION IN DIABETES.

The ability to measure vasodilator function in intact humans has furnished a new window into mechanisms of vascular dysfunction. Numerous studies have documented impaired endothelial-dependent vasodilator function in human arteries. Type I diabetics without hypertension or dyslipidemia had impaired endothelial-dependent vasodilator function when compared with age-matched nondiabetic subjects. The diabetic and nondiabetic groups had similar responses to endothelial-independent vasodilators.[33] Type II diabetic patients appear to have defects in both endothelial-dependent vasodilation and smooth muscle function.[34] [35] Experimental studies have indicated that overproduction of oxygen-derived free radicals in response to elevated glucose contributes to endothelial cell dysfunction.[36] Indeed, high doses of the antioxidant vitamin C can improve endothelial-dependent vasodilation in both type II[37] and type I[38] diabetic subjects. Further mechanistic studies have shown a significant correlation between insulin sensitivity and endothelial nitric oxide production.[39] Insulin's well-known vasodilator response depends in part on endothelial nitric oxide production. Type II

diabetic subjects do not show improvement in endothelial-dependent vasodilation in comparison to lean nondiabetic controls when infused with insulin in glucose clamp experiments.[40] Acute hyperglycemia impairs endothelial-dependent vasodilation in both microvessels and macrovessels in normal subjects.[41] In type II diabetics, treatment of the dyslipidemia with a fibric acid derivative improves both fasting and postprandial endothelial function.[42] This finding shows that dyslipidemia, as well as hyperglycemia, can contribute to impaired endothelial vasodilator responses in diabetic humans. It further demonstrates the ability of therapy to improve endothelial-dependent vasodilation in humans.

As noted above, firm evidence now supports a link between genetics and the insulin-resistant syndrome. In this regard, first-degree relatives of type II diabetic patients who are normotensive and without overt diabetes show impaired endothelial-dependent vasodilation and insulin resistance, as determined by clamp studies.[43] This impaired endothelial vasodilatory function in the young first-degree relatives of type II diabetics did not depend on traditional risk factors.

Recent work has identified a novel potential mechanism for mediating impaired endothelial-dependent vasodilator function.[43A] An endogenous competitive inhibitor of nitric oxide synthase known as asymmetrical dimethylarginine (ADMA) is augmented in hypercholesterolemics.[44] Accumulation of ADMA may result from inhibition of its catabolism because of a reduction in activity of the enzyme dimethylarginine dimethylaminohydrolase.[45] Recent evidence suggests that dysregulation of this enzyme may raise levels of ADMA in diabetics.[45] [45A] These new findings provide yet another potential molecular pathway of impaired vascular function in diabetes.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

The prevalence of both diabetes and impaired fasting glucose is increasing within the U.S. population (see Fig. 63-1).[46] Approximately 6 percent of the U.S. population has diabetes, and only half of those cases have been diagnosed. Moreover, impaired glucose tolerance occurs twice as frequently as overt diabetes. This disease places a major demand on resources of the health care system. Data from a managed care organization on the 1-year cost of treating more than 85,000 patients with diabetes as compared with age- and sex-matched nondiabetic counterparts confirm the impact of CVD in diabetes.[47] The largest proportion (17 percent) of the excess cost associated with diabetes was attributable to CAD. In contrast, end-stage renal disease accounted for 11 percent of the excess costs of treatment. The general population in the United States has enjoyed impressive declines in the mortality associated with heart disease in the last decades. However, the drop in cardiovascular mortality in diabetic men and women has lagged well behind that of the general population.[48] Two other important factors--aging of the U.S. population overall and the increasing prevalence of diabetes--suggest that the relationship between diabetes and coronary heart disease (CHD) morbidity and mortality will become even more important in the future.

CHD MORBIDITY AND MORTALITY IN TYPE II DIABETES MELLITUS

The clinical association between diabetes, elevated glucose, and CVD has been intensively studied for many years.[49] The excess morbidity and mortality remain even after adjustment for traditional CHD risk factors. In the Framingham Study, 20-year follow-up of individuals aged 45 to 74 years at the initial screening showed a twofold to threefold elevation in the risk of clinically evident atherosclerotic disease in those with diabetes as compared with the nondiabetic cohort.[50] These data also showed loss of the protection against CHD in women with diabetes, who had a rate of CHD mortality as high as that in diabetic men. In the Multiple Risk Factor Intervention Trial (MRFIT), more than 5000 men (out of approximately 350,000 screened) who reported taking medications for diabetes were monitored for an average of 12 years.[51] For every age stratum, ethnic background, and risk factor level, men with diabetes had an absolute risk of CHD death more than three times higher than that in the nondiabetic cohort, even after adjustment for established risk factors. Similar findings were seen in a large cohort of 11,554 white men and 666 black men between the ages of 35 and 64 screened from 1967 to 1973 and monitored prospectively for 22 years.[52] A recent Finnish study showed that diabetics without a prior myocardial infarction had the same risk of a first myocardial infarction as did nondiabetic survivors of myocardial infarction (Fig. 63-2) .[53] Data from the Rancho Bernardo Study and the Nurses' Health Study show that women with diabetes experience a disproportionately greater impact from diabetes than do men with diabetes.[54] [55]

CHD MORTALITY IN TYPE I DIABETES MELLITUS

Type II diabetes accounts for more than 90 percent of all cases of diabetes, and most studies of CHD risk have evaluated middle-aged or

Figure 63-2 Marked increase in the risk of coronary artery disease in type II diabetics. These data show a striking increase in the risk of a first or recurrent myocardial infarction in diabetics as compared with nondiabetic subjects in a population-based study in Finland over a 7-year follow-up period. These data also show that a diabetic without a history of previous myocardial infarction has an approximately equal risk for a first myocardial infarction as a nondiabetic subject who has already sustained myocardial infarction. These data support recent recommendations from the American Diabetes Association to treat diabetic subjects as though they already have established coronary artery disease. *(From Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998.)*

elderly populations consisting of mostly type II diabetics. However, a smaller collection of data also identifies an increased risk of CHD in patients with type I diabetes. In the Framingham Study, 292 patients with type I diabetes monitored for 20 to 40 years had a cumulative CAD mortality that was approximately 4 times that seen in nondiabetics (35 vs. 8 percent by age 55).[56] Regardless of the age of onset, the first deaths related to CAD occurred by the fourth decade of life, and the cumulative mortality rate increased at a similar rate in the subsequent 20 years. The increase in CAD mortality after age 30

appeared particularly striking in patients with renal complications, who had an estimated risk of CAD that was 15 times higher than that in patients without persistent proteinuria. Observational studies in other populations have made similar findings.[57] [58] [59] These data identify persistent proteinuria as a strong predictor of the development of CAD in this population. Proteinuria serves as a marker of generalized vascular damage that on a wider scale emerges as a predisposition to cardiovascular disease.

Aggregation of Traditional CHD Risk Factors in Diabetes

The high prevalence of "established" risk factors for CHD in diabetics complicates the epidemiological assessment of CHD in this patient population.[60] [61] [62] CHD risk factors such as hypertension, dyslipidemia, and obesity cluster in patients with diabetes.[4] In type II diabetics at time of diagnosis, over 50 percent have hypertension and over 30 percent have hypercholesterolemia. In MRFIT, the "classic" risk factors known to predict CVD mortality in nondiabetics--serum cholesterol (
;200 mg/dl), systolic blood pressure (
;120 mm Hg), and cigarette smoking--independently predict CVD mortality in diabetic subjects.[51] Most men in either the diabetic or nondiabetic group had one or more of these risk factors, with the majority having two or more. Within each stratum of risk (no risk factors, one only, two only, all three), CVD mortality was substantially higher for men with diabetes (Fig. 63-3) . Notably, there was a synergistic effect of diabetes and other risk factors such that the presence of any single risk factor or the combination of any two or all three was associated with a steeper increase in CVD mortality in men with diabetes than in those without it.

Figure 63-3 Age-adjusted cardiovascular disease death rates according to the presence of a number of risk factors for men with and without diabetes at baseline who were screened for the MRFIT. The presence of diabetes confers a steep increase in the cardiovascular death rate at any level of concomitant risk factors. *(From Stamler J, Vaccaro O, Neaton JD, et al: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434-444, 1993. Reproduced with permission of the American Diabetes Association, Inc.)*

The United Kingdom Prospective Diabetes Study (UKPDS) has provided perhaps the most compelling data to support the importance of risk factor aggregation in enhancing the CHD risk profile of patients with newly diagnosed diabetes.[63] This study evaluated a large number of middle-aged subjects with newly detected type II diabetes (n=3055), in 335 of whom CAD developed during a median follow-up of 8 years. CAD was significantly associated with increased concentrations of LDL cholesterol, decreased concentrations of HDL cholesterol, increased levels of hemoglobin A_{1c} and systolic blood pressure, and a history of smoking as measured at baseline.

Plasma Glucose as an Independent Risk Factor for Atherosclerosis

Although diabetes clusters with the admixture of traditional risk factors for CHD mentioned above, the rate of CHD morbidity and mortality in diabetics exceeds the rate expected from the interaction of these multiple risk factors by approximately 50 percent.

Hyperglycemia itself has emerged as a leading candidate responsible for this excess CHD risk in diabetes.

Compelling data in this regard have emerged from prospective observations of patients with type II diabetes in which patients were stratified by fasting glucose levels.[64] [65] In one such study, the average fasting blood glucose level independently related to all-cause (p=0.0002), cardiovascular (p=0.0006), and ischemic heart disease (p=0.03) mortality (Fig. 63-4) . No obvious threshold level for this association was noted; rather, the lower the fasting blood glucose level, the better the outcome. Comparable results in the San Antonio Heart Study substantiate a dose-response relationship between hyperglycemia and CVD mortality.[65] In this study, diabetic subjects in the top quartile of FPG had a risk of CVD mortality 4.7 times greater than did diabetic subjects in quartiles 1 and 2 combined (p=0.01). This increase in risk remained after adjustment for other potential risk factors. The graded, continuous pattern linking hyperglycemia and CVD risk in type II diabetes also applies to subjects with type I diabetes. Ten-year follow-up in the Wisconsin Epidemiological Study of type I diabetics showed that for each 1 percent increase in glycated hemoglobin, the hazard ratio for CHD mortality nearly doubled.[66] Indeed, even in individuals without frank diabetes, evidence points to a continuum of CHD risk that is dependent on glucose levels across the spectrum from normal glucose tolerance through impaired glucose tolerance to diabetes.[67] Data from a cohort study performed in Rancho Bernardo showed that in both men and women, the incidence of myocardial infarction and stroke correlated positively with glucose tolerance status. Other studies in diverse populations have also generally

Figure 63-4 All-cause mortality, cardiovascular mortality, and ischemic heart disease mortality in patients with type II diabetes by quintiles of average fasting blood glucose. Cardiovascular mortality and all-cause mortality increase throughout the range of fasting plasma glucose levels in a graded fashion. *(From Andersson DK, Svardsudd K: Long-term glycemic control relates to mortality in type II diabetes. Diabetes Care 18:1534-1543, 1995. Reproduced with permission of the American Diabetes Association, Inc.)*

shown a graded relationship between glucose tolerance and the rate of CHD events.[52] [68] [69]

Investigations into the relationship between glucose and CHD risk in the studies noted above focused on CHD or ischemic mortality as the endpoint. Although powerful indicators of the graded, continuous effect of glucose, these studies do not provide any evidence of glucose's effect on the vessel wall itself. Several studies have evaluated intima-media thickness (IMT) of the carotid artery by ultrasound.[70] [71] [72] [73] Carotid IMT correlates well with cardiovascular risk factors and the occurrence of CHD.[74] In the Atherosclerosis Risk in Communities (ARIC) Study, carotid wall thickness correlated with fasting glucose tolerance in all gender and race subgroups in a large and diverse sample of 15,800 subjects aged 45 to 64 without symptomatic CVD (Fig. 63-5) .[70]

It is still unclear whether CVD risk is distributed across a continuum of glucose values in diabetic subjects or whether a critical value exists above which CVD rates increase. Also, whether evidence of an association is altered by the method of evaluating plasma glucose (postchallenge vs. fasting) requires further investigation. In a study from Japan in a population cohort of men, postchallenge glucose was a better predictor of CVD death than wave fasting glucose levels.[75] In general, the results of studies examining this relationship are difficult to compare because of differences in study design (e.g., longitudinal vs. cross-sectional), endpoints (e.g., CVD event rates vs. changes in carotid IMT), and patient populations.

Insulin Resistance as an Independent Risk Factor

As stated previously, diabetes clusters with other CVD risk factors, among them hypertension, obesity, and dyslipidemia. Almost all subjects with a combination of these metabolic disorders also have insulin resistance.[76] Hyperinsulinemia may provide the crucial link between hyperglycemia and CVD (see Table 63-3).[77] This collective occurrence of multiple metabolic abnormalities in an individual patient has been variously termed syndrome X, the insulin resistance syndrome, and cardiovascular dysmetabolic syndrome. Data from a number of studies indicate that hyperinsulinemia independently predicts CVD risk. For example, in a large (n=1625) triethnic population consisting of equal numbers of subjects with diabetes, hyperglycemia, and normal glucose tolerance, insulin resistance correlated positively with atherosclerosis as assessed by carotid IMT.[78] Since insulin resistance typically precedes the development of hyperglycemia, these findings may explain, in part, the elevated risk of CHD that is found in individuals with newly diagnosed type II diabetes.

Figure 63-5 Sex- and race-specific associations between average carotid artery intima-media thickness (IMT) by fasting glucose status and the presence of diabetes mellitus in participants free of cardiovascular disease at baseline in the Atherosclerosis Risk in Communities (ARIC) Study from 1987 to 1989. The average carotid IMT increases across the entire range of fasting glucose levels. *(From Folsom AR, Eckfeldt JH, Weitzman S, et al: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities [ARIC] Study Investigators. Stroke 25:66-73, 1994. By permission of the American Heart Association.)*

Other data suggest that endogenous insulin itself, rather than insulin resistance, may have direct adverse effects on the cardiovascular system. One case-control study monitored over 2000 nondiabetic men without apparent ischemic heart disease at baseline for 5 years.[79] Individuals who had experienced a CHD event had fasting insulin concentrations at baseline that were 18 percent higher than in controls ($p<0.001$), an association that remained valid after adjusting for the potentially confounding effects of systolic blood pressure, plasma triglycerides, apolipoprotein B, and LDL and HDL cholesterol.

RISK FACTOR INTERVENTION TO REDUCE CHD IN PATIENTS WITH DIABETES

MELLITUS (see also Chap. 32)

Intensive Glycemic Control

Numerous studies have shown a positive correlation between CHD endpoints and increasing glucose levels in patients with diabetes. In the UKPDS, hemoglobin A_{1c} levels above 6.2 percent were associated with an increased risk of macrovascular disease.[63] For each 1 percent elevation in hemoglobin A_{1c} , CHD risk increased by 11 percent. However, it also appeared that the relative risk of CHD did not increase in association with hemoglobin A_{1c} levels below 7 percent, thus suggesting a threshold. Therefore, several clinical trials have sought to determine whether intensive treatment of blood glucose levels can reduce the risk of CHD associated with diabetes.

In the Diabetes Control and Complications Trial (DCCT), 1441 patients with type I diabetes (mean age of 27 years) and no significant retinopathy at baseline were randomized to intensive glycemic control (external insulin pump or three or more insulin injections per day) or conventional therapy (one to two insulin injections per day).[80] Patients were monitored prospectively for a mean of 6.5 years, with regular assessment of microvascular and macrovascular outcomes. After 5 years, the cumulative incidence of retinopathy was approximately 50 percent less in the intensive-treatment group than in the

conventional-treatment group ($p < 0.001$). Intensive therapy also reduced the risk of macrovascular disease (cardiovascular and peripheral vascular disease) by 41 percent, although the difference between groups lacked statistical significance. A second, smaller Veterans Affairs (VA) Study that tested the feasibility of intensive blood glucose control in type II diabetics also showed no significant differences in cardiovascular endpoints between treatment arms.[81] These two trials had a number of important limitations. Both lacked adequate power to detect a difference in macrovascular events between treatment groups given the small number of events in each group. In the DCCT, the low event rate probably resulted from the relative youth of the study population, and in the VA Study, it probably resulted from the small patient population and a short follow-up period.

Larger, adequately powered studies such as UKPDS showed a nonsignificant trend in favor of intensive blood glucose control in terms of reduction of myocardial infarction.[82] This trial randomized 3867 patients with newly diagnosed type II diabetes to intensive therapy (diet plus oral therapy or insulin) or conventional therapy. Patients entered into the study had a low background prevalence of CHD and a low rate of CHD risk factors. Patients were monitored for approximately 10 years. As in the DCCT, microvascular endpoints were improved in the intensive-therapy arm. A trend toward a reduced rate of myocardial infarction was also noted in the group receiving intensive blood glucose

control (*p*=0.052). [82]

Treatment of Hypertension in Diabetics (see also Chaps. 28 and 29)

Hypertension and diabetes frequently occur together as part of the dysmetabolic syndrome. The addition of hypertension to the clinical picture of diabetes amplifies the already high risk of CVD in these patients. In addition, hypertension significantly contributes to the development of microalbuminuria and retinopathy in diabetes. The role of antihypertensive therapy in reducing cardiovascular morbidity and mortality in patients with diabetes has engendered controversy, as in patients without diabetes. In nondiabetics, older trials of diuretic and beta blocker antihypertensive therapy did not show a reduction in cardiovascular mortality. The deleterious effects of these agents on metabolic indices (triglycerides, HDL, and blood sugar) may have accounted for these findings. Contemporary antihypertensive agents, including calcium channel blockers (CCBs) and ACE inhibitors, do not adversely affect metabolic factors that might counteract the benefits of blood pressure lowering.

Two recent trials compared the effects of CCBs and ACE inhibitors in patients with type II diabetes.[83] [84] They showed a greater reduction in CHD endpoints with an ACE inhibitor than with a dihydropyridine CCB. The results of these two studies suggested that CCBs did not benefit and might even harm diabetic patients at high risk for cardiovascular events. Although the results of these trials imply that ACE inhibitors would be the preferred agents for treating diabetic patients, interpretation of these relatively small studies in which cardiovascular endpoints were not the primary outcome measure requires caution.[85] More rigorously designed studies, such as the UKPDS and the Systolic Hypertension in Europe Trial (Syst-Eur), have not supported the findings of the two smaller trials noted above and have shown beneficial effects for both ACE inhibitors and CCBs in patients with diabetes (Table 63-4) .[85A] For example, in the UKPDS,[86] 1148 hypertensive patients with type II diabetes responded equally well to captopril or atenolol in terms of achieving blood pressure control and had similar reductions in the risk of macrovascular disease. Myocardial infarction declined 21 percent in the group randomized to tight blood pressure control (*p*=NS). This group also had a 44 percent reduction in the risk of fatal and nonfatal stroke when compared with the group assigned to less tight blood pressure control. Although the blood pressure achieved in the UKPDS subgroup assigned to tight blood pressure control was good (144/82), data from the Syst-Eur Trial[87] [89] and the Hypertension Optimal Treatment (HOT) Trial[88] indicate that achieving even lower blood pressure goals is associated with low rates of cardiovascular complications during CCB-based therapy. A recent analysis of initially nondiabetic subjects in the Atherosclerosis Risk in Communities (ARIC) Study showed no increased risk of developing diabetes when treated with ACE inhibitors, CCB, or thiazides.[89A] However, there was a 28% increased risk of developing diabetes in those who received beta blockers in this study.

Treatment of Dyslipidemia in Diabetics(see also Chaps. 31 and 33)

The central role of diabetic dyslipidemia in accelerating atherosclerosis in type II diabetics has major therapeutic implications. While strict glycemic control in and of itself does not appear to consistently reduce macrovascular disease, tight glycemic control

can ameliorate features of the lipoprotein profile associated with increased risk. Thus, as in all individuals with or at risk for atherosclerosis, individuals with impaired glucose intolerance or frank diabetes or those with a strong family history of type II diabetes should have intense counseling regarding life style modification. In particular, achieving and maintaining an ideal body weight and performing regular aerobic exercise can improve insulin sensitivity. Even though LDL levels often lie within the average range in type II diabetic subjects, treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors reduces coronary risk.[90] [91] Furthermore, treatment with fibric acid derivatives targets in particular the low HDL and high triglycerides characteristic of diabetic dyslipidemia. The results of the recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) suggest that a population of individuals, many of whom have a lipoprotein profile of insulin resistance, show a reduction in coronary events and stroke when treated with a fibric acid derivative.[92] The recent Diabetes Atherosclerosis Intervention Study (DAIS) showed delayed angiographic progression of coronary atherosclerosis in diabetic patients treated with fenofibrate.[92A] The thiazolidinedione agents improve insulin sensitivity by activating PPAR-gamma. Future work should define the role of the thiazolidinediones in preventing the cardiovascular complications of type II diabetes inasmuch as the rationale for a beneficial effect appears strong.

TREATMENT OF ACUTE CORONARY SYNDROMES IN DIABETES MELLITUS

PROGNOSIS.

Diabetic patients have higher mortality than nondiabetics do during the acute phase of myocardial infarction, as well as in short- and long-term follow-up. The diabetic population will comprise a greater proportion of patients with myocardial infarction in the future. Numerous mechanisms in diabetic patients conspire to increase the risk of myocardial infarction. This section will review the state of knowledge regarding optimizing treatments for this important population with acute coronary syndromes

FIBRINOLYTIC THERAPY IN DIABETICS (see also Chap. 35).

Fibrinolytic therapy has reduced early and late mortality from acute myocardial infarction in patients with and without diabetes. Despite some concern that the elevated levels of PAI-1, fibrinogen, coagulation factors, and reactive platelets commonly encountered in diabetes might reduce the likelihood of successful reperfusion,[93] both the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) thrombolysis trials demonstrated similar infarct-related artery patency rates in diabetic and nondiabetic subgroups.[94] [95] [96] Indeed, diabetic patients experience the same or greater benefit from thrombolysis as nondiabetics do. In the Second International Study of Infarct Survival (ISIS-II), diabetic patients receiving streptokinase had a 31 percent improvement in survival in comparison to placebo, greater than the 23 percent improvement seen in the nondiabetic group. Pooled data from five recent major thrombolysis trials show that 30-day mortality has been substantially reduced to 11 percent in diabetics and 6 percent in nondiabetics--an odds ratio similar to that observed in the earlier literature. Formerly, concern about hemorrhage from diabetic retinopathy

made diabetes a contraindication to thrombolysis. However, only 1 of 6011 (0.02 percent) diabetic patients receiving thrombolytic therapy experienced intraocular hemorrhage.[97]

TABLE 63-4 -- LARGE STUDIES EVALUATING ANTIHYPERTENSIVE THERAPY IN PATIENTS MELLITUS

SOURCE, YEAR	NO. OF PATIENTS (% WITH DIABETES)	STUDY ENTRY CRITERIA	TYPE OF DRUGS	FOLLOW-UP, YEARS	BLOOD PRESSURE EFFECTS
Placebo-Controlled Studies					
SHEP,[5] 1996	583 (12.3)	Systolic hypertension defined as 160-219 mm Hg; diastolic, <90 mm Hg	Placebo vs. diuretic-based (chlorthalidone)	4.5	Difference between diuretic and placebo group was 9.8 mm Hg systolic and 2.2 mm Hg diastolic
Syst-EUR,[6] 1999	492 (10.5)	Systolic hypertension defined as 160-219 mm Hg; double-blind; diastolic, <95 mm Hg	Placebo vs. nitrendipine	2§	Difference between nitrendipine and placebo group was 8.6 mm Hg systolic and 3.9 mm Hg diastolic
HOPE,[7] 2000	3578 (38.5)*	Diabetes and 1 other cardiovascular risk factor or	Ramipril and vitamin E vs. placebo	4.5¶	Difference between ramipril and placebo group was <2 mm Hg systolic and 1 mm Hg diastolic

		No diabetes and history of cardiovascular disease			
Treat to Blood Pressure Target Studies					
HOT,[8] 1998	1501 (8)	Diastolic hypertension defined as 100-115 mm Hg; randomized into 3 target blood pressure groups of approximately 500	Felodipine-based and angiotensin-converting enzyme inhibitor, beta-blocker, or diuretic	3.8[§]	Difference among the 3 groups at end point was approximately 4 mm Hg
UKPDS,[4] [9] 1998	1148 (100)	Open randomization	Less tight blood pressure control vs. tight control; further randomization to captopril or atenolol	8.4[§]	Less tight blood pressure control, 154/87 mm Hg; tight control, 144/82 mm Hg; similar reduction in blood pressure with both drugs
Angiotensin-Converting Enzyme Inhibition vs Other Agents Studies					
CAPPP,[10] 1999	572 (5.2)	Diastolic hypertension defined as >100 mm Hg	Captopril vs. diuretic or beta-blocker	>6[§]	Baseline blood pressure greater in captopril group; similar reduction with both drugs

ABCD,[11] 1998	470 (100)	Diabetes and diastolic hypertension defined as 90 mm Hg	Nisoldipine vs. enalapril	5¶	Similar reduction in blood pressure with both drugs
FACET,[12] 1998	380 (100)	Systolic hypertension defined as >140 mm Hg or diastolic hypertension defined as >90 mm Hg	Amlodipine vs. fosinopril	<3§	Similar reduction in blood pressure with both drugs

SHEP = Systolic Hypertension in the Elderly Program; Syst-EUR = Systolic Hypertension in Europe; H
Outcomes Prevention Evaluation; HOT = Hypertension Optimal Treatment; UKPDS = United Kingdom
Diabetes Study; CAPPP = Captopril Prevention Project; ABCD = Appropriate Blood Pressure Control
trial; FACET = Fosinopril versus Amlodipine Cardiovascular Events randomized Trial.

From Cooper ME. Johnston CI: Optimizing treatment of hypertension in patients with diabetes. JAMA 283:3178-3179,2000.

§Values are expressed as medians.
* Of the 3578, 1808 received placebo and 1770 received ramipril.
¶Values are expressed as means.

Of the 1148, 390 had less tight blood pressure control. The 758 who had tight blood pressure control were randomized, and 400 received captopril and 358 received atenolol.

Of the 572, 309 received captopril vs. 263 who received a diuretic or beta-blocker.

MECHANISMS OF AGGRAVATION OF OUTCOMES.

Mortality after acute myocardial infarction correlates with the severity of left ventricular dysfunction. The nature and time course of left ventricular remodeling are major determinants of this risk. Numerous factors related to diabetes may adversely affect remodeling. Previous silent infarction, diabetic cardiomyopathy, hypertension,[98] and autonomic dysfunction[99] are conditions that either alone or in combination can affect non-infarct zone function and predispose to ventricular remodeling.[85] [100] [101] Endothelial cell dysfunction may result in impaired coronary perfusion and lead to ischemia.[102] Diabetes also retards coronary collateral development.[103]

Metabolic changes in diabetes may also contribute to the worsened prognosis of this group of patients with acute coronary syndromes. Insulin resistance impairs the ability of the heart to metabolize free fatty acids. Ordinarily, ischemia increases levels of the glucose transporter protein GLUT-4 (the predominant insulin-sensitive glucose

transporter) in human myocardium, which augments glycolysis and adenosine triphosphate (ATP) production. In diabetes, elevated free fatty acid levels depress GLUT-4 activity and, hence, glucose entry and glycolysis in myocardial cells. This shift in substrate supply results in less efficient ATP production and the generation of oxygen free radicals, both of which impair left ventricular contractile performance.[104]

Autonomic nervous system (ANS) dysfunction in diabetes can also contribute to excess mortality (see below for an extended discussion of a cardiovascular autonomic neuropathy in diabetes). Approximately 50 percent of people with diabetes for 10 or more years have impaired heart rate variability because of parasympathetic denervation, which results in a relative increase in sympathetic tone. Sympathovagal imbalance may alter hemostasis in favor of thrombosis, lower the threshold for coronary plaque disruption, alter the circadian pattern of ischemia, and increase the risk for reinfarction and ventricular arrhythmia.[105] [106] [107] Elevated levels of PAI-1, fibrinogen, and coagulation factors (factors VII, IX, X, and XII), combined with hyperaggregable platelets, also contribute to an increased risk for early and late reinfarction in diabetic patients.[93] [108] [109]

Such factors may also account for the twofold higher risk of death conferred by diabetes that was observed in the control treatment arms of trials that evaluated the efficacy of platelet glycoprotein IIb/IIIa inhibitors in unstable angina/non-Q-wave infarction, such as the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) Trial or the PRISM PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) Study. At 7 and 30 days, diabetics with unstable coronary syndromes experienced a mortality rate similar to that of nondiabetics with Q wave infarction.[110] [111]

Medical Therapy

ASPIRIN

Studies have consistently shown that patients with either type I or type II diabetes have enhanced platelet aggregation in response to a variety of agonists.[112] Platelets from diabetic patients exhibit increased production of thromboxane, a potent vasoconstrictor and platelet agonist.[113] In the Early Treatment of Diabetic Retinopathy Study (ETDRS), patients with type I or type II diabetes randomized to aspirin 650 mg/d had a significantly lowered risk of myocardial infarction without incurring an increase in the risk of vitreous or retinal bleeding, even in patients with retinopathy.[114] In the Bezafibrate Infarction Prevention Study (BIPS), an observational analysis of aspirin use by individuals with a history of CAD, the absolute benefit per 100 patients treated with aspirin in diabetic patients exceeded that in nondiabetic patients (cardiac mortality reduction, 5 vs. 2.1 percent; total mortality, 7.8 vs. 4.1 percent).[115] The American Diabetes Association currently recommends enteric-coated aspirin in a dose of 81 to 325 mg/d (1) as secondary prevention in men and women with diabetes and evidence of macrovascular disease and (2) as primary prevention in persons with type I or II diabetes and additional coronary risk factors.[116]

BETA-ADRENERGIC BLOCKING AGENTS

Despite overwhelming evidence that beta-adrenergic blocking agents (beta blockers) reduce mortality and reinfarction in patients with myocardial infarction, their use in diabetic patients has only recently become accepted. Beta blockers produced an early and late post-myocardial

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infarction survival benefit in comparison to placebo in patients with diabetes that exceeded the degree of benefit seen in their nondiabetic counterparts in several studies.[117] Although these data derive from retrospective subgroup analyses of trials in the prethrombolytic era, they concur with more recent results. The National Cooperative Cardiovascular Project reviewed over 45,000 patients, 26 percent of whom had diabetes. After adjusting for confounding variables, beta blocker use was associated with a lower 1-year mortality rate in diabetic patients without an increase in diabetes-related complications.[118] Furthermore, a recent post hoc analysis of the BIPS Study demonstrated that the use of beta blockers was associated with improved long-term survival in a large group of type II diabetic subjects, 30 percent of whom had never experienced a prior myocardial infarction.[119]

The greater relative benefit of beta blockers in the presence of diabetes may derive from several factors. Beta blockers can help restore sympathovagal balance in diabetic patients with autonomic neuropathy. These drugs may also decrease free fatty acid utilization within the myocardium and hence reduce oxygen need. Beta blockers can, however, mask the warning signs of hypoglycemia, inhibit the glycemic response to hypoglycemia by suppressing glycogenolysis, interfere with insulin release, and further impair glucose tolerance in patients with diabetes. In addition, some clinicians have concerns that beta blockers may elevate serum triglycerides, reduce HDL, and increase LDL and thereby potentially counteract some of the widely accepted cardioprotective benefits of these drugs. However, recent data indicate that the currently used beta blockers may not adversely affect the lipid profile.[120] Much of the concern surrounding the use of these drugs in diabetes stems from earlier experience with noncardioselective agents in higher dosage. The risk of hypoglycemia in diabetic hypertensive patients taking cardioselective beta blockers was no different from that of patients taking placebo.[121] Cardioselective agents have less tendency to worsen glycemic control than nonselective agents do, although diabetes may develop in over 20 percent of nondiabetic hypertensive patients given beta blockers.[89A]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors reduce infarct size, limit ventricular remodeling, improve survival after myocardial infarction, and may be of particular benefit in patients with diabetes.[85] A post hoc analysis of one thrombolytic trial (Grupo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico-3 [GISSI-3]) revealed that early administration of

lisinopril in the setting of acute myocardial infarction reduced 6-week and 6-month mortality comparatively more in diabetic versus nondiabetic patients (30 vs. 5 percent reduction at 6 weeks and 20 vs. 0 percent at 6 months, respectively). Lisinopril administration resulted in 37 lives saved per 1000 treated diabetic patients. Another retrospective analysis, the Trandolapril in Patients with Reduced Left Ventricular Function after AMI (TRACE) Study, compared the effect of oral trandolapril versus placebo in anterior myocardial infarction in patients with and without diabetes.[122] Patients with diabetes experienced a greater relative improvement in survival over 5 years of follow-up than did the nondiabetic cohort. Furthermore, ACE inhibitor treatment reduced by nearly 50 percent the risk of sudden death, reinfarction, and progression of congestive heart failure (CHF) in patients with diabetes, whereas subjects without diabetes experienced only trends in protection against these secondary outcomes.

Many factors may explain the particular benefits of ACE inhibitors in diabetic patients with acute myocardial infarction. These agents can prevent or limit remodeling of the ventricle, particularly when administered early in the course of acute myocardial infarction,[123] reduce recurrent ischemic events,[124] and restore sympathovagal imbalance.[125] ACE inhibitors may also improve endothelial function in diabetes,[126] counteract reduced fibrinolysis by suppression of PAI-1 expression,[127] and decrease insulin resistance.[128] In one recent study (Heart Outcomes Prevention Evaluation [HOPE]), ramipril significantly reduced the rates of myocardial infarction, stroke, and cardiovascular death in diabetic subjects with or without a prior history of CAD or CHF over a 5-year period when compared with placebo.[129] The ACE inhibitor's efficacy in the absence of a clinical history of CHF and hypertension in the majority of patients in the HOPE Study points to the importance of these nonhemodynamic benefits of ACE inhibitors.

GLYCOPROTEIN IIb/IIIa BLOCKERS (see also Chaps. 36 and 62)

These potent antiplatelet agents have improved outcomes in patients with unstable angina and non-Q-wave infarction. Overall, glycoprotein IIb/IIIa antagonists have equal or better efficacy in diabetic than nondiabetic patients. Adverse effects (mostly bleeding) also appear equivalent in diabetics.

The PRISM PLUS Study compared heparin with heparin plus tirofiban

in 362 patients with diabetes and 1208 without diabetes.[111] At 7 days, the cumulative endpoint of death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina in diabetic patients was reduced from 21.8 percent with heparin alone to 14.8 percent with heparin plus tirofiban. In nondiabetic subjects, the cumulative endpoint was reduced from 16.7 to 12.4 percent when tirofiban was added to heparin. Despite the increased aggregability of platelets in patients with diabetes, no significant difference was observed in the ability of standard dosing of abciximab to achieve 80 percent or greater platelet inhibition during a 12-hour infusion in patients with and

without diabetes.[130]

In the EPILOG (Evaluation of PTCA to Improve Long-Term Outcomes by c7E3 Glycoprotein IIb/IIIa Receptor Blockade) Trial, abciximab treatment resulted in fewer acute adverse events after percutaneous transluminal coronary angioplasty (PTCA) in both the diabetic and nondiabetic groups, although longer-term follow-up revealed a higher rate of target vessel revascularization if diabetes were present.[131] In the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition in Stenting) Trial, however, a highly significant 51 percent decrease (8.1 vs. 16.6 percent; p=0.02) in target vessel revascularization at 6 months was experienced by stented diabetic patients randomized to abciximab versus stented diabetic patients receiving placebo.[132]

INSULIN

Recent studies have evaluated the role of strict glycemic control in diabetic patients during the acute phase of myocardial infarction. The blood glucose level may increase in proportion to infarct size and hemodynamic stress in nondiabetic patients with myocardial infarction as catecholamines, cortisol, and growth hormone are released. These hormones may create "transient" insulin resistance, with serum glucose returning to normal at discharge. In some cases, a very high admission glucose level out of proportion to infarct size indicates previously undiagnosed diabetes. Nevertheless, substantial evidence points to the admission glucose level as an independent predictor of early and late mortality after myocardial infarction in patients with and without diabetes mellitus.[133] [134] [135] [136]

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study randomized 620 diabetic patients with acute myocardial infarction to either intensive insulin therapy (insulin-glucose infusion for 24 hours, followed by subcutaneous insulin injection for 3 months) or a standard glycemic control strategy.[137] Those receiving the intensive insulin regimen had a lower blood glucose level during the first hour (9.6 vs. 11.7 mmol/liter; $p < 0.01$) and at discharge (8.2 vs. 9.0 mmol/liter; $p < 0.01$) than the control group did. The infusion group had a significant reduction in 1-year mortality when compared with the control group (19 vs. 26 percent; $p < 0.027$). The two groups were similar in baseline characteristics and in other treatments received. After 3.4 years, mortality remained lower in the insulin infusion group than the group receiving conventional care (33 percent in the infusion group and 44 percent in the control group; p=0.011). Predictors of mortality were age, history of CHF, diabetes duration, admission glucose, and admission hemoglobin A_{1c} level.[138] The greatest survival benefit was seen in the subgroup whose diabetes had been managed with diet or oral hypoglycemic drugs before infarction.

Several mechanisms may explain the findings of the DIGAMI Trial. Insulin-glucose infusion may (1) increase the availability of glucose as a substrate for ATP generation in cardiac muscle; (2) reduce lipolysis and decrease the generation of free fatty acids, which can impair myocardial contractility and trigger ventricular arrhythmia; and (3) shift cardiac metabolism from free fatty acid oxidation to glycolysis. In addition, tight glycemic control can reverse hyperglycemia-induced platelet reactivity and reduce the typically elevated PAI-1 activity in patients with diabetes. Part of the benefit derived from the use

of insulin in the tight control arm may have resulted from the removal of any potential cardiac risk associated with the use of sulfonylureas (see below).

SULFONYLUREAS

In the 1970s, the University Group Diabetes Program (UGDP), a prospective trial evaluating the efficacy of tolbutamide versus insulin in patients with type II diabetes, reported an increase in cardiovascular mortality and CAD in the group assigned to tolbutamide.[139] A smaller study reported similar results.[140] Despite controversy at the time, the sulfonylurea class of hypoglycemic agents have become widely used as the benefits of improved glycemic control in preventing diabetes-related microvascular complications have become established.

The UKPDS investigated the impact of tight glycemic control with a variety of treatment strategies on the incidence and severity of microvascular and macrovascular complications in newly diagnosed diabetes. A higher incidence of sudden death or myocardial infarction was not seen in patients assigned to sulfonylureas over a 10-year follow-up.[82] A retrospective study recently identified sulfonylurea use as a risk factor for in-hospital mortality among diabetic patients undergoing PTCA for acute myocardial infarction.[141]

Concern over the use of sulfonylureas, particularly in the setting of myocardial injury, stems from their blockade of ATP-sensitive potassium channels (K^+ -ATP). [142] [143] In the pancreas, such inhibition results in the secretion of insulin, thus accounting for the hypoglycemic effect of these drugs. In the myocardium, however, blockade of K^+ -ATP channels may limit ischemic preconditioning, a cardioprotective mechanism, and attenuate coronary vasodilation.[144] [145] [146] In patients undergoing PTCA 90 minutes after receiving either glibenclamide or placebo, intracoronary electrocardiograms (ECGs) were recorded at the end of the first and second balloon inflations. The group pretreated with glibenclamide experienced no difference in the degree of ST segment shift from the first to the second inflation. The placebo group, however, demonstrated less ST segment shift and had less pain with the second balloon inflation, which is an indication of induction of ischemic preconditioning not present in the sulfonylurea-treated patients.[147] Another study using treadmill-induced ischemia showed no abolition of ischemic preconditioning with glibenclamide versus placebo.[148] The number of sulfonylurea drugs has grown since the initial concerns raised by the UGDP Study. Glibenclamide but not glimepiride significantly inhibited the forearm vasodilator response to the activation of K^+ -ATP channels by diazoxide, which suggests that different sulfonylureas have different specificities for vascular and/or myocardial K^+ -ATP channels.[149] Sulfonylureas may be either proarrhythmic or antiarrhythmic, depending on the presence or absence of ischemia, as a result of the role of the K^+ -ATP channel in regulating the duration of the cardiac action potential.[150] [151] The choice of specific sulfonylureas for patients with diabetes on the basis of the presence or absence of coronary disease remains unclear at this time.

Coronary Revascularization (see also Chaps. 37 and 38)

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

Large-scale trials have generally not shown a benefit of aggressive revascularization after thrombolytic therapy for acute myocardial infarction. Similar considerations apply to diabetic patients.[152] Although diabetic and nondiabetic patients have similar rates of initial angioplasty success,[153] diabetics have higher restenosis rates after PTCA[154] [155] and worse longer-term outcomes.[156] [157]

Diabetics also have a higher risk of in-hospital mortality, restenosis, and long-term mortality after coronary artery stenting and atherectomy.[155] [158] Although stenting has reduced restenosis rates in both diabetics and nondiabetics overall, smaller lumina in the stented vessels and a significantly higher restenosis rate (55 vs. 20 percent; p=0.001) were seen in diabetics within 4 months of the procedure despite similar baseline and procedural characteristics.[158] The mechanisms underlying the increased restenosis rate in diabetes after coronary intervention is unclear. Serial intravascular ultrasonography has suggested that exaggerated intimal hyperplasia develops in diabetics after intervention.[159] Histological study found increased collagen-rich fibrous tissue in atherectomy specimens from diabetics.[160]

CORONARY ARTERY BYPASS GRAFT SURGERY.

Most studies comparing outcomes in diabetic and nondiabetic patients undergoing coronary artery bypass graft surgery (CABG) show an increased risk of postoperative death, 30-day and long-term mortality, and need for subsequent reoperation. Diabetic patients have a worse risk profile, tend to be older, and have more extensive CAD and poorer left ventricular function than nondiabetic patients do.[161] However, their higher long-term mortality is in part independent of these factors and continues to diverge from that in nondiabetic patients during long-term follow-up. This difference probably reflects accelerated disease progression in both the nonbypassed and the bypassed native coronary vessels.

The Bypass Angioplasty Revascularization Investigation (BARI) Trial, which included 641 patients with and 2962 patients without diabetes, evaluated the role of CABG in diabetic patients.[162] Five-year mortality was higher in diabetic patients. After 5 years of follow-up, Q wave myocardial infarction occurred more frequently in diabetic patients (8 vs. 4 percent). CABG significantly reduced the mortality after a myocardial infarction when compared with angioplasty, whereas no such protective effect of surgery was noted in nondiabetic patients experiencing myocardial infarction.

TABLE 63-5 -- INDICATIONS FOR CARDIAC TESTING IN DIABETIC PATIENTS

Testing for CAD is warranted in patients with the following:

Typical or atypical cardiac symptoms

Resting electrocardiogram suggestive of ischemia or infarction

Peripheral or carotid occlusive arterial disease

Sedentary life style, age
;35 yr, and plans to begin a vigorous exercise program

Two or more of the following risk factors in addition to diabetes

Total cholesterol
;240 mg/dl, LDL cholesterol
;160 mg/dl, or HDL cholesterol <35 mg/dl

Blood pressure >140/90 mm Hg

Smoking

Family history of premature CAD

Positive microalbuminuria/macroalbuminuria test

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Taken from Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People With Diabetes. Diabetes Care 21:1551-1568, 1998.

CABG VERSUS PTCA.

In general, randomized trials comparing PTCA with CABG have reported similar outcomes. Diabetes, however, may alter the outcomes of these different revascularization treatments.[163] The BARI Trial, which randomized patients with multivessel disease to CABG or PTCA, found that bypass surgery in treated diabetic patients was associated with a higher survival rate at 5 years than was PTCA (80.6 vs. 65.5 percent; p=0.003).[164] The benefit of CABG accrued primarily in patients receiving internal mammary artery conduits. Cardiac mortality was 2.9 percent when an internal mammary artery graft was used as compared with 18.2 percent when only saphenous vein grafts were used, a mortality similar to that observed with PTCA.[165]

Screening for Coronary Artery Disease

Because diabetics have blunted anginal symptoms and a poor outcome following coronary events, the issue of screening for CAD in patients with diabetes mellitus has particular importance.[166] A recent American College of Cardiology/American Diabetes Association Consensus Development Conference established guidelines for screening diabetic individuals for CAD (Table 63-5) .[167] Screening in asymptomatic diabetic individuals will establish a diagnosis of significant CAD in 5 to 15 percent of those without diabetic complications, in 20 to 60 percent of patients with peripheral or carotid arterial disease, and in the majority of those with chronic renal failure.[168] A number of factors specific to diabetic patients may interfere with the sensitivity and specificity of noninvasive diagnostic tests for myocardial ischemia.[168] However, most agree on the

need to perform screening in diabetic patients before major noncardiac or vascular surgery or before initiation of an exercise program.[169] These subgroups face definable periods of excess cardiac risk, and discovery of significant CAD can have a major impact on management.

DIABETIC CARDIOMYOPATHY

Over the years, substantial evidence has accumulated that a specific, "true" diabetic cardiomyopathy distinct from ischemic injury does indeed exist.[170] [171] [172] The exact prevalence, nature, and cause of cardiac dysfunction directly attributable to diabetes have given rise to considerable debate inasmuch as other factors common in diabetes, such as hypertension, coronary atherosclerosis, and microvascular dysfunction, can independently impair myocardial performance.

EPIDEMIOLOGICAL EVIDENCE.

Data from the Framingham Heart Study corroborated early observations suggesting the existence of a diabetic cardiomyopathy. In the Framingham cohort, after adjustment for age, blood pressure, cholesterol level, obesity, and history of CAD, the presence of diabetes quadrupled the risk for CHF in men 35 to 64 years old and doubled it in men 65 years or older. In women 35 to 64 years of age, diabetes entailed an eightfold increase in CHF and a fourfold increase in risk in older women.[173]

More recent epidemiological studies using case-control analyses have confirmed the association between diabetes and idiopathic cardiomyopathy in men[174] and in women[175] and have emphasized a possible interaction between diabetes and a history of hypertension. In men screened for the MRFIT Study who had cardiomyopathy, diabetes was a risk factor for mortality.[176] By combining the original Framingham Study Cohort and the Framingham Offspring Study, gender-specific linear regression analysis probed the contribution of diabetes and glucose intolerance to age-adjusted echocardiographic parameters in more than 4500 men and women. Diabetic individuals, particularly women, had higher heart rates and greater left ventricular wall thickness and cardiac mass than unaffected subjects did.[177]

PATHOLOGY.

Early postmortem studies in diabetic subjects revealed myocyte hypertrophy, myofibril depletion with replacement fibrosis, interstitial deposition of periodic acid-Schiff-positive material, and perivascular fibrosis. Coronary arterioles demonstrate increased thickening of basement membranes and microaneurysms in autopsy specimens, as well as in tissue obtained at the time of coronary bypass surgery.[178] [179] More recently, endomyocardial biopsies from patients with diabetes have demonstrated a range of ultrastructural changes, including capillary basement membrane thickening and interstitial fibrosis, that are accentuated by coexisting hypertension.[180] Coexisting hypertension and diabetes accentuate myocardial fibrosis and collagen content.[98]

Noninvasive methods have confirmed fibrosis as a key feature of the heart in diabetic

patients without evident cardiac disease. Ultrasound tissue characterization with backscatter analysis has been used to evaluate the myocardium of type I diabetic individuals with normal systolic function but with a variety of diabetes-related complications. When compared with an age-matched population, the diabetic group exhibited cardiac acoustic abnormalities suggesting increased collagen content of the myocardium.[181] Another study compared 26 type I diabetic subjects without hypertension or CAD with an age- and sex-matched control group by using a similar technique to assess myocardial acoustic properties. This study documented increased myocardial echodensity suggestive of increased collagen deposition despite normal septal and posterior wall thickness.[182]

MECHANISMS OF DIABETIC CARDIOMYOPATHY (Table 63-6) .

AGEs accumulate in tissue exposed to hyperglycemia and may contribute to the vascular complications of diabetes mellitus, as discussed above.[12] [13] Accumulation of AGE-modified extracellular matrix results in inelasticity of the vessel wall and could interfere with myocardial function as well. Serum levels of AGEs correlate with microvascular and renal complications in type I diabetes. In 52 patients with type I diabetes, prolongation of the isovolumic relaxation time as assessed by Doppler echocardiography correlated with serum levels of AGEs after adjustment for age, diabetes duration, renal function, blood pressure, and autonomic function parameters.[183] Experimental studies in diabetic dogs have also shown decreased left ventricular compliance associated with intramyocardial deposition of collagen in the absence of hypertrophy.[184] These data help explain the clinical observation that diabetic patients can have CHF as a result of diastolic dysfunction in the absence of hypertension and/or increased wall thickness.

Abnormalities in myocardial calcium handling may also contribute to abnormal cardiac mechanics in the diabetic heart.[185] Insulin-dependent diabetes impairs sarcoplasmic reticular Ca^{2+} pump activities, which reduces the rate of calcium removal from the cytoplasm in

TABLE 63-6 -- POSSIBLE CONTRIBUTORS TO DIABETIC CARDIOMYOPATHY

Collagen accumulation decreasing myocardial compliance, accumulation of advanced glycosylation end product-modified extracellular matrix proteins leading to diastolic dysfunction[183] [184]
Abnormalities in myocardial calcium handling may also contribute to abnormal cardiac mechanics in the diabetic heart[185] [186] [187] [188]
Activation of protein kinase C triggered by increased intracellular diacylglycerol[27]
Cardiac autonomic neuropathy[189]
Genetic abnormalities[190] [191] [192]

diastole. Such alterations may contribute to the increased diastolic stiffness that characterizes diabetic cardiomyopathy.[186] [187] Diabetes-related changes in troponin T, the contractile regulatory protein of the thin myofilament, may also contribute to both diastolic and systolic dysfunction.[188] In addition, activation of PKC may contribute to cardiac hypertrophy and failure, as discussed above.[27] In addition, a possible major cause of or contributor to chronic left ventricular dysfunction (cardiomyopathy) may be the direct effects of hyperglycemia and insulin resistance on myocardial cellular metabolism. The unavailability of glucose as an energy substrate and the shift in intracellular metabolism from glycolysis to free fatty acid oxidation can result in inadequate ATP generation and increased production of oxygen free radicals, both of which lead to depressed contractile function.[188A]

A recent study showed that a subset of type I diabetics without overt cardiac disease had abnormal left ventricular function with exercise despite normal contractile indices at rest. This decrement in left ventricular reserve correlated with evidence of reduced sympathetic innervation (see below), thus implicating dysautonomia in the pathogenesis of diabetic cardiac dysfunction.[189]

Genetic abnormalities may predispose to the development of cardiomyopathy in diabetics. Mitochondrial DNA mutations and deletions associated with diabetes mellitus may increase the risk for cardiac disease.[190] [191] A recent cross-sectional analysis evaluated the relationship between the ACE I/D genotypes and left ventricular mass in 289 type II diabetic subjects.[192] Presence of the ACE D/D genotype was independently associated with an increase in left ventricular mass.

CLINICAL FEATURES.

In diabetic patients, the range of pathological and cellular abnormalities in the diabetic myocardium discussed above can reduce left ventricular compliance and cause shortness of breath out of proportion to the degree of systolic dysfunction. The natural history of diabetic cardiomyopathy is poorly understood. Many diabetic patients have diastolic dysfunction recognized on clinical grounds, but subsequent systolic dysfunction does not appear to develop. In others, left ventricular systolic dysfunction does intervene to produce a typical "congestive" cardiomyopathy.

Even young, asymptomatic type I diabetics frequently have echocardiographic evidence of diastolic dysfunction.[193] [194] It is more difficult to isolate diabetes-specific abnormalities in left ventricular function in type II diabetics because many of these individuals also have hypertension and/or CAD, which alone or together can cause diastolic and/or systolic dysfunction. However, considerable evidence suggests more decline in both systolic and diastolic function in diabetics than nondiabetics.[195] [196]

As noted above in the Framingham Study (without separation into type I and type II), women with diabetes had increased wall thickness, end-diastolic dimensions, and cardiac mass when compared with their nondiabetic counterparts.[177] Women with glucose intolerance showed similar, but less significant trends in these echocardiographic parameters, thus supporting the concept that changes in cardiac

structure and function may occur in the setting of insulin resistance before the onset of hyperglycemia and a diagnosis of diabetes. In addition, the increased relative risk for cardiac death in diabetic women as opposed to diabetic men may result in part from these sex-specific effects on cardiac mass, an important independent predictor of outcome in the Framingham Study. Increased cardiac mass in the normotensive nondiabetic obese population is strongly associated with the degree of insulin resistance measured by the insulin and glucose response to an intravenous glucose tolerance test.[197] This relationship was independent of body weight, age, and blood pressure. A hemodynamic study comparing diastolic function in lean and obese nonhypertensive and hypertensive adults without CAD showed that left ventricular chamber stiffness was highest in the obese hypertensive individuals.[198] These subjects had the highest fasting glucose levels (within the normal range), which implicates insulin resistance as an important cofactor for the development of decreased left ventricular compliance even in the absence of diabetes. Elevated plasma insulin levels may induce myocardial hypertrophy by a direct growth-stimulating effect on myocardial cells.[199] Hyperinsulinemia increases salt reabsorption by the kidney. The expanded extracellular fluid compartment and blood volume could also lead to an increase in cardiac mass over time. When combined with hypertension, itself a cause of increased cardiac mass, these factors may result in proportionately more left ventricular hypertrophy than when hypertension is not associated with insulin resistance.

CARDIOVASCULAR AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN DIABETES MELLITUS

Cardiovascular autonomic neuropathy (CAN) probably contributes to the poor prognosis of CVD in both type I and type II diabetes mellitus. The majority of patients with CAN come to clinical attention with complaints of postural hypotension, resting tachycardia, exercise intolerance, or painless myocardial ischemia or infarction. The risk for CAN depends on the duration of diabetes and the degree of glycemic control and tends to parallel the development of other end-organ diseases related to diabetes such as retinopathy, nephropathy, and vasculopathy. Symptoms and signs of CAN often occur relatively late in the natural history of this complication. Because reliable and quantitative noninvasive methods to assess ANS function have now become available, the diagnosis of CAN may now precede the development of symptoms. Most clinicians regard CAN as a major complication of type I diabetes because the challenge of managing this complication often dominates the care of these patients. CAN tends to be less fully expressed in a patient with type II diabetes, who is typically older and has a wider variety of comorbid conditions.

DIAGNOSIS.

A variety of tests can assess parasympathetic and sympathetic function in diabetics. A series of bedside maneuvers can aid in the diagnosis of CAN and differentiate the relative contribution of parasympathetic and sympathetic dysfunction in CAN. These tests use the ECG to measure beat-to-beat heart rate variation during deep breathing, at assumption of an upright posture, and during the Valsalva maneuver.[200] Recently, tests have emerged that can detect the presence of CAN before symptoms develop. A number of methods assess heart rate variability during 24-hour recordings and thereby

permit detection of subtle disorders in autonomic balance. Cardiac radionuclide imaging with the norepinephrine analog metaiodobenzylguanidine (MIBG) can directly image the sympathetic nerve activity of the myocardium. Diabetic individuals generally have less myocardial MIBG uptake with more pronounced regional differences from base to apex than do patients without diabetes. In addition, positron-emission tomographic (PET) scanning with the sympathetic neurotransmitter analog ^{11} C-labeled hydyoxyephedrine can evaluate myocardial sympathetic innervation. These noninvasive methods, alone or in combination with the standard bedside examination, can establish the presence and severity of CAN and be used to evaluate the effects of interventions.[201]

PREVALENCE.

The prevalence of CAN varies with the method used and the population studied, but CAN appears to be quite common. In a large group of type I and II diabetic subjects, heart rate variability on 24-hour ambulatory ECG showed abnormalities in nearly 50 percent of diabetics, far more than in controls.[202] MIBG scintigraphy in patients with type I diabetes for at least 10 years who had CAD excluded by thallium single-photon emission computed tomography (SPECT) revealed regional adrenergic denervation

in 18 of 24 subjects.[203] In newly diagnosed type I diabetic individuals examined by a battery of tests, 8 percent had definite CAN.[200]

PROGNOSIS.

Numerous studies have documented increased mortality in diabetic patients with CAN.[204] [205] [206] In type I diabetics, 5-year mortality in patients with CAN exceeded the 5-year mortality in those without CAN by fivefold.[205] Another study involving both type I and type II patients examined the relationship between ANS function and retinopathy, nephropathy, glycemic control, and cardiovascular risk factors. CAN conferred excess mortality beyond that attributable to other risk factors.[207] The relationship of ANS dysfunction to outcome in type II diabetic patients is less well characterized. In a Finnish study, 70 men with newly diagnosed type II diabetes and baseline, 5-year, and 10-year assessment of heart rate variability were compared with a control group. Sympathetic ANS dysfunction at the 5-year examination predicted the 10-year cardiovascular mortality.[99]

EFFECTS OF TREATMENT.

Institution of strict glycemic control in type I diabetic patients can reverse abnormalities in heart rate variability in diabetic patients with early CAN[208] and reduce the degree of left ventricular sympathetic denervation on PET scanning with labeled hydroxyephedrine.[209] Pancreatic-kidney transplantation in type I patients can result in an improvement in cardiovascular reflexes.[210] Other treatment modalities found to

improve autonomic function include the antioxidant alpha-lipoic acid,[211] an ACE inhibitor,[212] [213] and aldose reductase inhibition.[214] [215]

Mechanisms Responsible for Increased Morbidity and Mortality

Numerous mechanisms may underlie the increased cardiovascular morbidity and mortality associated with CAN in diabetes mellitus (Table 63-7) .

IMPAIRED ANGINA PERCEPTION.

Clinicians have recognized for some time that myocardial ischemia or infarction may be associated with less severe angina in a diabetic versus a nondiabetic patient. CAN may explain the blunted appreciation of cardiac ischemic pain in diabetic patients. Instead of typical angina, patients may have shortness of breath, diaphoresis, gastrointestinal complaints, profound fatigue, or abrupt changes in glycemic control. When compared with nondiabetic patients with exercise-induced ischemia, diabetic individuals are less apt to be limited by angina at the time of ST segment depression than nondiabetics are.[216] In one study that used ambulatory ST segment monitoring to examine diabetic patients with documented

TABLE 63-7 -- CARDIOVASCULAR AUTONOMIC NEUROPATHY AND INCREASED CARDIOVASCULAR MORBIDITY AND MORTALITY IN DIABETES MELLITUS

EFFECTS OF SYMPATHOVAGAL IMBALANCE
Impairs angina recognition
Silent ischemia and infarction
Alters threshold for ischemia
Increased resting heart rate and blunted chronotropic response to exercise
Impaired coronary vasomotor regulation
Causes abnormal diastolic and systolic function
Factor in cardiac cardiomyopathy
Increases risk for ventricular arrhythmia
In presence or absence of myocardial ischemia
Alters circadian pattern of triggering of acute cardiac events
Loss of nocturnal protection against myocardial infarction
Alters circadian blood pressure regulation
Increased cardiac mass
Risk factor for microalbuminuria and diabetic nephropathy
Adversely affects the natural history of congestive heart failure
Causes hemodynamic instability in the perioperative period

CAD, over 90 percent of ischemic episodes were asymptomatic.[106] Shortness of breath reflecting ischemia-induced heart failure may precede the perception of angina during treadmill testing and correlates with the degree of CAN on cardiovascular reflex testing[217] [218] and MIBG scanning,[219] thus suggesting a direct link between autonomic neuropathy and defective angina recognition. Histological damage to cardiac afferent nerve fibers has been demonstrated in diabetic patients with silent myocardial infarction.[220] The blunted recognition of ischemia because of CAN may delay treatment and worsen the outcome.[96] [221] Blunted perception also makes it difficult to monitor antiischemic treatment or determine whether restenosis has occurred after coronary intervention.

CAN AND MYOCARDIAL INFARCTION TRIGGERING.

Diabetic patients with CAN show a homogeneous distribution of myocardial infarction throughout the full 24-hour period,[106] while diabetics without CAN have a circadian pattern of ischemia like that seen in nondiabetic patients, with a typical prominence in the early morning.[105] [222] [223]

CAN AND THE THRESHOLD FOR MYOCARDIAL ISCHEMIA.

Myocardial ischemia occurs when there is an imbalance between myocardial oxygen supply and demand, both of which can be affected by CAN. Resting tachycardia caused by parasympathetic denervation, an early manifestation of CAN, increases myocardial oxygen demand and can place diabetic patients with CAD closer to their ischemic threshold. Even transient sympathovagal imbalance can trigger ischemia-mediated sudden death. In a small group of patients with CAD who had sudden cardiac death during Holter monitoring, transient decreases in heart rate variability preceded onset of the ST segment shift and precipitated life-threatening arrhythmias in all eight cases.[224]

EFFECT OF CAN ON CORONARY BLOOD FLOW REGULATION.

The status of the ANS can affect coronary blood flow regulation independent of mechanisms mediated by endothelial cell function.[225] Diabetic patients with sympathetic nervous system dysfunction have impaired dilation of coronary resistance vessels in response to cold pressor testing when compared with diabetics without defects in cardiac adrenergic nerve density.[226] In another study, global myocardial blood flow and coronary flow reserve in response to adenosine were subnormal in diabetics with CAN as defined by similar PET criteria.[227] The aspects of CAN described above may well provoke ischemic episodes by upsetting the balance between myocardial supply and demand.

CAN AND SUDDEN CARDIOVASCULAR DEATH IN DIABETICS.

It has been recognized for some time that sudden death can occur in the absence of CAD in patients with diabetes mellitus. The association of abnormal cardiovascular reflex testing and sudden cardiac death in early case studies pointed to a direct link between autonomic balance and arrhythmogenesis. The relationship of sudden death

(defined as unexpected death within 1 or 24 hours of symptoms) to glucose intolerance was examined in 8006 Japanese-American men after 23 years' follow-up in the Honolulu Heart Program.[228] After adjustment for recognized cardiac risk factors, the relative risks for sudden death within 24 hours in subjects with high normal glucose (151 to 224 mg/dl), asymptomatic high glucose values (>225 mg/dl), and diabetes versus those with lower glucose values (<151 mg/dl) were 1.59, 2.22, and 2.76, respectively ($p < 0.05$).

The recognition that sympathetic imbalance relates to the pathophysiology of sudden death in the familial long QT syndrome has supported CAN as a risk factor for premature cardiac death in individuals with diabetes. Prolongation of the corrected QT interval in diabetic patients correlates with the degree of autonomic neuropathy.[229] Newer methods to assess arrhythmogenic potential have firmly established CAN as a risk factor for sudden death in diabetes. The presence of QT dispersion on the 12-lead ECG reflects dispersion of ventricular refractoriness and increased risk for arrhythmia. When compared with a nondiabetic control

group and a diabetic group without CAN, QT dispersion was greatest in diabetic patients with CAN.[230] Diabetic patients with the most advanced cardiovascular sympathetic denervation have the highest mortality rate. This apparent paradox may be explained by recent data demonstrating that diabetic patients with severe autonomic neuropathy can have marked heterogeneity in left ventricular sympathetic neuronal uptake on PET scanning with the neurotransmitter analog ^{11} C-hydroxyephedrine.[231]

PERIOPERATIVE HEMODYNAMIC INSTABILITY.

Perioperative hemodynamic instability in the setting of CAN may contribute to the twofold to threefold greater risk of cardiac morbidity and mortality in diabetics undergoing noncardiac surgery. During induction of general anesthesia, heart rate and blood pressure may decline to a greater degree than in patients without diabetes. In rare cases, cardiovascular collapse has occurred after brachial plexus block.[232] Diabetics with autonomic neuropathy require perioperative pharmacological support with pressors to stabilize blood pressure more often than do diabetics without CAN.[233] Despite the preponderance of data linking diabetes and perioperative cardiac risk, no relationship was seen between autonomic function and hemodynamic behavior in a recent study comparing diabetic and nondiabetic patients undergoing CABG surgery.[234]

FUTURE PERSPECTIVES

Cardiovascular complications have emerged over the last decade as the key target to reduce morbidity and mortality in diabetics. The focus in treatment of diabetes is shifting from blood sugar to the blood vessel. Future studies will doubtless more often specify cardiovascular events as major endpoints rather than merely specifying surrogates such as glycemia. Evaluation of the possible cardiovascular protective effects of new classes

of agents such as the insulin sensitizers (thiazolidinediones) is under way, for example. The role of fibrates in place of or in addition to statins for the treatment of diabetic dyslipidemia needs careful evaluation. The benefits of initiating treatment of individuals with impaired glucose tolerance to slow the progression to overt diabetes also merits study. Inevitably, this challenging group of patients will become more and more an integral part of the daily practice of cardiology in the years to come.

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Chapter 64 - The Heart in Endocrine Disorders

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In 1835, Robert Graves described "three cases of violent and long-continued palpitation in females" with thyrotoxicosis.[1] Twenty years later, Thomas Addison reported that patients with disease of the "suprarenal capsules" had a "pulse, small and feeble . . . excessively soft and compressible." As the disease progressed, "the body wastes . . . the pulse becomes smaller and weaker, and . . . the patient at length gradually sinks and expires."[2] Thus, since the mid-19th century, it has been known that deranged hormonal secretion can significantly alter cardiovascular function. The purpose of this chapter is to summarize the more important cardiovascular manifestations of endocrine and nutritional diseases.

ACROMEGALY

The anterior pituitary gland secretes at least seven polypeptide hormones. Four (adrenocorticotropic hormone [ACTH] and related peptides, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone [TSH]) primarily produce their biological effect indirectly by altering hormonal secretion from a specific target gland (adrenal cortex, gonad, or thyroid). Thus, the pathophysiological manifestations of a

derangement in their secretion are the same as those of their target organs and will be discussed later. No cardiovascular manifestations of altered prolactin secretion are known, but acromegaly (growth hormone [GH] excess) is associated with a number of clinical signs and symptoms related to the cardiovascular system.

ACTIONS OF GROWTH HORMONE.

GH is only one of a family of peptides whose overall function is to regulate growth of the organism.[3] [4] Two hormones secreted by the hypothalamus (somatotropin-releasing hormone and somatostatin) regulate the release of GH from the anterior pituitary, with the former stimulating and the latter suppressing its release.[5] [6] A variety of other factors also modify GH release, many of which work through a GH secretagogue receptor.[7] An orally active agonist of this receptor, MK-677, can stimulate GH release in normal and elderly individuals.[8] [9] Whether it can do so in pathophysiological states in which GH is suppressed is uncertain.

After GH is released into the circulation, it binds to a plasma protein that is identical in amino acid composition to the extracellular domain of the GH receptor. The purpose of the binding protein is unclear. It may prolong the plasma half-life of GH and thereby its biological effect. Contrariwise, GH-binding protein can compete with the GH receptor and thereby reduce GH's biological effect. The GH receptor consists of nearly equal extracellular and intracellular domains with two GH-binding sites per receptor.[10] It is a member of the cytokine receptor superfamily and mediates its effects via activation of the JAK (Janus Kinase) family of intracellular tyrosine kinases and the STAT (signal transducer and activator of transcription) family of transcription factors.[11] GH mediates its effects in two ways: directly and by increasing the production of somatomedins (insulin-like growth factors [IGFs] I and II).[3] [4] [11] GH's predominant effect is on modifying IGF-I's synthesis as suggested by the following: GH-deficient individuals are deficient in IGF-I but not IGF-II, and IGF-I reduces GH release from the pituitary.

In humans, the gene for IGF-I is located on chromosome 12 and that for IGF-II on chromosome 11 near the insulin gene. Expression of mRNA from these genes occurs in many tissues, particularly in the fetus. They are homologs of the proinsulin molecule and exert biological effects that are qualitatively similar to those of insulin.[3] [12] Postpartum, mRNA levels are highest in the liver but are also found in a number of other tissues. IGF is synthesized in the liver in response to GH and, for the most part, is bound to one of six specific binding proteins. Because production of these binding proteins can be regulated by growth factors, they may play a functional role by producing a readily available circulating reservoir of growth factors.[13] While many of the actions attributed to GH are actually produced by IGFs, GH does have direct effects, some of them the opposite those of IGFs. For example, GH antagonizes the action of insulin while the IGFs mimic it. GH's other direct effects include increasing amino acid transport and incorporation in the heart and stimulating outgrowth of vascular smooth muscle cells in culture. However, in this chapter, by convention the term *growth hormone effects* is used, although most of these effects are probably mediated by the IGFs, particularly IGF-I.

Much of our knowledge of GH's action comes from animal and/or in vitro studies with all

their limitations, and relatively little information is available in humans because of the scarcity of human GH until recently. Thus, the following description needs to be interpreted with caution until more human data are available. GH's effects influence many metabolic processes, but the net effect is anabolic. Thus, when GH is administered to a GH-deficient individual, positive nitrogen balance with retention of calcium, sodium, potassium, magnesium, and chloride is manifested within days.[3] [4]

GH also induces changes in both fat and carbohydrate metabolism.[3] [4] When administered for a short time, it increases the uptake and utilization of glucose by fat cells, thus increasing lipogenesis. However, when administered over a long period, it promotes lipolysis, thus increasing plasma free fatty acid levels and their oxidation and promoting ketogenesis, particularly in diabetic patients or animals. GH reduces glucose uptake by fat and muscle cells, increases gluconeogenesis, and increases peripheral resistance to insulin; as a consequence, plasma glucose levels rise. Because of this reduced tissue uptake of glucose and the increased blood levels of free fatty acids and ketones, tissues, such as the myocardium, that are able to use these latter compounds as energy substrates do so. In contrast, if IGF-I is administered to patients with noninsulin-dependent diabetes mellitus, glycemic control improves and insulin sensitivity increases.[14]

EFFECT OF GROWTH HORMONE AND SOMATOSTATIN ON THE HEART.

Specific receptors for GH and IGF-I in the heart promote cardiac remodeling and inotropism. Activation of these receptors induces the expression of genes for specific contractile proteins and also those responsible for myocyte hypertrophy. GH also increases the force of contraction and shifts the myosin form to the low-adenosine triphosphatase (ATPase) activity V_3 isoform[15] (see Chap. 14) . Short-term administration of GH to normal subjects, which produces changes in GH levels similar to those observed in patients with mild acromegaly, increases the heart rate and myocardial contractility, the latter reflected

in fractional shortening of the left ventricle and mean circumferential shortening of velocity as determined by echocardiography.[16] GH has no effect on mean arterial blood pressure. In adults with GH deficiency, replacement therapy also modifies cardiac function, but the changes differ from those observed in normal subjects given GH. Left ventricular mass, stroke volume, and cardiac output increase significantly, whereas total peripheral resistance and arterial pressure decrease. However, systolic blood pressure does not change either at rest or during exercise.[17]

Somatostatin has an effect on the heart beyond that induced by its effect on GH secretion. Infusion of somatostatin causes bradycardia and a fall in cardiac output. Furthermore, in some cases of supraventricular arrhythmias, somatostatin administration restores sinus rhythm.[18] Finally, cardiac nerves have been shown to contain somatostatin, which suggests that this hormone may be an important

physiological regulator of cardiac conduction.

CLINICAL AND BIOCHEMICAL MANIFESTATIONS.

Acromegaly is almost invariably the result of a GH producing chromophobic or eosinophilic pituitary adenoma, although it may rarely be secondary to ectopic production of GH or somatotropin-releasing hormone.[19]

A derangement in carbohydrate metabolism is the most common metabolic consequence of chronic overproduction of GH. Impaired glucose tolerance is found in half the patients, and hyperinsulinemia is present in nearly all; thus, a state of insulin resistance exists. However, clinical diabetes mellitus is present in only 20 to 30 percent of patients, which suggests that only in those who are predisposed and have limited insulin reserve does overt disease actually develop.[3] [19] The insulin-resistant state may also contribute to other features of the disease, e.g., the hypertension. Nearly three-quarters of subjects are overweight. Thus, it might be anticipated that hyperlipidemia would be common in acromegaly. Yet, it is in fact infrequently observed except in patients with clinical diabetes mellitus.[3] [4] [17] Even in these patients it is probably secondary to the decreased secretion of insulin rather than the increased secretion of GH.

Cardiovascular Manifestations

The cardiac manifestations of acromegaly include cardiac enlargement that is greater than would be anticipated for the generalized organomegaly. In addition, the frequency of a number of other cardiovascular disorders is increased in patients with acromegaly: hypertension, premature coronary artery disease, congestive heart failure, and cardiac arrhythmias, particularly frequent ventricular premature beats and intraventricular conduction defects.[16] [20] Indeed, because of the frequent occurrence of congestive heart failure and cardiac arrhythmias in patients who otherwise have no predisposing factors (e.g., no hypertension or arteriosclerosis), it has been suggested that a specific acromegalic cardiomyopathy exists (see below).

CARDIOMEGALY.

Nearly all patients with acromegaly have cardiomegaly (Fig. 64-1) (Figure Not Available) , particularly after the fifth decade.[16] [20] [21] Echocardiographic assessment suggests that cardiac mass is frequently increased, particularly asymmetrical septal hypertrophy, with a sizable minority having left ventricular dilatation and a reduced ejection fraction.[20] [21] [22] [201A] Although the cardiomegaly may be related to the generalized effect of GH on protein synthesis, some data suggest that other factors may also be important. For example, enlargement of the heart is often greater than that of other organs. Furthermore, no direct relationship can be found between the degree of cardiomegaly and the level of circulating GH.[20] [21] However, the duration of acromegaly correlates with the severity of cardiac hypertrophy. Other factors that may be important in the genesis of cardiomegaly include the hypertension and atherosclerosis that occur with increased frequency in acromegaly. Focal cardiac interstitial fibrosis and myocarditis

with a lymphocytic infiltrate have also been reported in the majority of cases.[16] The former is probably due to the effect of GH on collagen synthesis. Additionally, small-vessel disease of the myocardium may occasionally be present. The resultant dysfunction in cardiac contraction secondary to any of these pathological changes could also contribute to the cardiac enlargement. Finally, the cardiomyopathy characteristic of acromegaly may also contribute to the cardiomegaly.

HYPERTENSION.

The most common cardiovascular manifestation of acromegaly, hypertension, occurs in 25 to 50 percent of patients in most studies if individuals with hypopituitarism are excluded. However, the frequency of hypertension may be overestimated if hypertension is defined by 24-hour blood pressure monitoring. Minniti and colleagues found that 60 percent of patients with acromegaly reported to be hypertensive by traditional criteria were normotensive by 24-hour ambulatory blood pressure data.[23] Hypertensive acromegalic patients tend to be older and to have had their acromegaly longer than nonhypertensive acromegalic patients. The underlying pathophysiology is uncertain. However, the hypertension is usually mild, uncomplicated, and readily responsive to drugs.[19] Most investigators either have searched for factors other than GH that could cause hypertension or have attempted to determine how GH itself may produce hypertension. In many respects, patients with acromegaly appear to have an expanded plasma volume; the presence of an increase in the glomerular filtration rate, renal plasma flow, extracellular fluid volume, and sodium space and a reduction in plasma renin activity all support this hypothesis.[3] [4] [24] Indeed, the striking increase in plasma volume in active acromegaly is reduced following treatment.

A number of studies have suggested that GH itself may be responsible for the hypertension. Thus, pituitary irradiation

Figure 64-1 (Figure Not Available) Opened left ventricle of the heart of an acromegalic patient showing marked dilatation and hypertrophy, with fibrosis in the left septal endocardium. (From Rossi L, Thiene G, Caragaro L, et al: Dysrhythmias and sudden death in acromegalic heart disease. A clinicopathologic study. Chest 72:496, 1977.)

or hypophysectomy significantly reduces arterial pressure in hypertensive acromegalic patients, even with full glucocorticoid replacement, unless GH levels are not normalized.[21] Indeed, the apparent volume expansion may relate directly to the elevated GH levels because administration of GH can produce retention of sodium, expansion of extracellular fluid volume, and abnormalities in white blood cell sodium transport. It has been proposed that the pathophysiology of the hypertension in acromegaly may be similar to that in essential hypertension. In both conditions, cardiac output may be initially elevated secondary to expansion of the extracellular fluid volume (see Chap. 28) . This response could elevate arterial pressure and ultimately lead to changes in the peripheral vasculature that produce fixed hypertension.

ATHEROSCLEROSIS.

In view of the alterations in carbohydrate and lipid metabolism caused by GH (see above), as well as the high incidence of hypertension, it is not surprising that premature atherosclerosis occurs in patients with acromegaly. What is uncertain is its frequency.[19]

Acromegalic Cardiomyopathy

Some patients with acromegaly but no evidence of hypertension or atherosclerosis have significant cardiac dysfunction.[20] [25] They primarily have cardiomegaly, congestive heart failure, and/or cardiac arrhythmias[10] [20] [25] [26] [27] ; the congestive heart failure is particularly resistant to conventional therapy. It has been suggested that these manifestations of acromegalic cardiomyopathy are related to the higher collagen content per gram of heart than found in normal myocardium. Histological observations show cellular hypertrophy, patchy fibrosis, and myofibrillar degeneration (Fig. 64-2) . Sudden death has been associated with inflammatory and degenerative damage to the sinoatrial perinodal nerve plexus and degeneration of the atrioventricular (AV) node.

It is not clear whether acromegalic cardiomyopathy is a specific entity. The evidence favoring this view, although indirect, comes from five types of observations: (1) Nearly 50 percent of acromegalic patients have electrocardiographic abnormalities.[26] The most common findings are ST segment depression with or without T wave abnormalities, patterns consistent with left ventricular hypertrophy, intraventricular conduction disturbances--specifically, bundle branch block--and supraventricular or ventricular ectopic rhythms. Indeed, in one controlled study, 48 percent of acromegalic patients had complex ventricular arrhythmias as compared with 12 percent of normal subjects. Although no correlation has been found between the severity of ventricular arrhythmias and GH levels, the frequency of premature ventricular contractions increases with the duration of acromegaly.[26] Although hypertension or signs of atherosclerosis are present in many, 10 to 20 percent of patients with acromegaly and electrocardiographic changes have no evidence of these conditions. (2) Ten to 20 percent of acromegalics have overt congestive heart failure. Perhaps a fourth of such individuals have no known predisposing cause.[27] (3) The majority of patients with acromegaly but without hypertension or atherosclerosis have subclinical evidence of cardiac, particularly diastolic, dysfunction.[20] (4) Approximately half of all patients with acromegaly, including patients without hypertension, have echocardiographic evidence of left and right ventricular hypertrophy.[20] [27] [28] [29] These patients have GH levels that are significantly higher than those of patients without left ventricular hypertrophy. Half of the patients with left ventricular hypertrophy exhibit asymmetrical septal hypertrophy, and these patients have a significantly greater percentage of internal dimensional shortening during systole than do either patients with concentric hypertrophy or those without left ventricular hypertrophy. (5) The most compelling evidence for a specific effect of GH hypersecretion inducing cardiac abnormalities comes from the impact of administration of the somatostatin analogs octreotide and lanreotide, which inhibit secretion of GH. In one study, 7 patients with acromegaly, 3 of whom had refractory congestive heart failure, were given octreotide subcutaneously three times daily. Right-heart catheterization performed before and after 3 months of therapy showed an 18 percent

increase in stroke volume and a return of the cardiac index to normal. Within 40 days of treatment, the 3 patients with congestive heart

Figure 64-2 Histopathological features of acromegalic heart disease. *A,* Nonspecific myocardial hypertrophy and interstitial fibrosis (F). *B,* Myocarditis with predominantly lymphomononuclear cell infiltrate. *C,* Small-vessel disease (proliferative fibrous wall thickening) or intramural coronary artery branches. (From Lie JT: Acromegaly and heart disease. Prim Cardiol 7:53, 1981.)

failure had dramatic clinical improvement that was sustained for up to 3 years.[30] In a second study, within 1 week of initiating octreotide therapy, left ventricular mass was reduced, as assessed by echocardiography.[31] In a third study in 11 normotensive patients with active acromegaly, 6 months of octreotide therapy produced a significant reduction in left ventricular mass index, mean wall thickness, and isovolumic relaxation time, as well as a significant increase in the ratio of early to late peak velocity of right ventricular filling. This improvement in diastolic function was not accompanied by significant differences in systolic function indices.[32] Finally, 1 patient treated for 1 year with octreotide had substantial improvement in the histopathological appearance of myocardial biopsy specimens.[33] However, improvement in left ventricular function does not universally occur following correction of the excess GH production. In some patients who have had longstanding active acromegaly, left ventricular filling abnormalities may be only partly reversible. In these patients, presumably nonreversible interstitial fibrosis prevents correction of the GH-induced cardiomyopathy.[34]

DIAGNOSIS AND TREATMENT

The *diagnosis* of acromegaly is established by documenting the nonsuppressibility of serum GH levels following glucose loading.[5] [4] In most laboratories, GH concentrations in normal subjects are less than 2 ng/ml 120 minutes after the oral administration of 100 gm of glucose. IGF-I levels may be more useful than GH levels to diagnose and monitor the course of the disease after treatment because of IGF-I's greater stability and longer serum half-life. It is also important to evaluate the integrity of the other pituitary hormones and, in hypertensive patients, to rule out an associated pheochromocytoma or aldosteronoma. The presence of sinus tachycardia or atrial fibrillation in a patient with acromegaly warrants a careful search for coexisting hyperthyroidism.

Surgery and irradiation remain the mainstays of treatment. The surgical approach is more often transsphenoidal rather than transfrontal; heavy-particle (proton beam) instead of conventional irradiation is often used.[3] Because of the delayed reduction in GH levels with the latter method, progression of cardiovascular disease in acromegalics continues even though GH levels are falling if they are not normal.[21] Secretion of GH can be suppressed in some acromegalics with somatostatin analogs.[30] [31] [32] [33] Whether these agents have any effect on tumor growth, however, is unclear.

Acromegalic patients with cardiovascular abnormalities usually respond to conventional therapeutic measures for hypertension, heart failure, and arrhythmias. Two caveats should be taken into consideration: (1) Those with hypertension appear particularly responsive to volume-depleting maneuvers, i.e., diuretics and sodium restriction, perhaps even more so than patients with essential hypertension; (2) on the other hand, some patients with congestive heart failure, primarily those *without* underlying hypertensive heart disease (i.e., those who are considered to have acromegalic cardiomyopathy), appear particularly resistant to therapy.

THYROID DISEASE

Thyroid hormone has a profound effect on a number of metabolic processes in virtually all tissues, with the heart being particularly sensitive to its effects. Therefore, it is not surprising that thyroid dysfunction can produce dramatic cardiovascular effects, often mimicking primary cardiac disease. Thyroid's actions on the heart can be grouped into three broad categories: (1) direct cardiac effects, (2) effects mediated by thyroid hormone's action on the sympathetic nervous system, and (3) effects secondary to hemodynamic changes.

ACTION OF THYROID HORMONE.

Two biologically active hormones are secreted by the thyroid: thyroxine (T_4) and triiodothyronine (T_3). Most studies support the hypothesis that T_3 is the final mediator and T_4 is a prohormone, primarily because of the universal presence of T_3 but not T_4 nuclear receptors in tissues responsive to thyroid hormone, specifically the heart.[35] [36] [37] [38]

Nuclear-Mediated Effects of Thyroid Hormone.

The majority of thyroid hormone's effects are mediated via a change in the expression of responsive genes. This process begins with diffusion of T_4 and T_3 across the plasma membrane because of their lipid solubility. In the cytosol, T_4 is converted into T_3 by the action of 5
-monodelodinase, the concentration of which varies from tissue to tissue in direct relation to the tissue's responsiveness to thyroid hormone. Then, the circulating and newly synthesized T_3 passes through the nuclear membrane to bind to specific thyroid hormone receptors (THRs). The THR is part of the nuclear receptor superfamily of proteins, which also includes proteins that act as receptors for steroids, vitamin D, and retinoic acid.

There are two THR genes--THRalpha located on chromosome 17 and THRbeta located on chromosome 3. The predominant THR form in the heart is $alpha_1$, whereas the predominant receptor form in the pituitary and liver is the beta isoform. Several other isoforms have also been reported, the functions of which are unclear.[39] The THR is

located almost exclusively within the nucleus. After interacting with T_3 and other protein transcription factors, the entire complex binds to thyroid response elements (TREs) located on the promoter region on specific genes (for additional details, the reader is referred to a review by Tsai and O'Malley[40]).

Thyroid hormone's effect on the synthesis of specific proteins can be either direct or indirect. Indirect effects include a change in production of an intermediate factor necessary for the function or activity of a more distant targeted protein. Thyroid hormone can have a positive or negative effect on regulating gene transcription. Positive effects have been documented for the following genes: myosin heavy-chain alpha,[41] Ca^{2+} -ATPase,[42] Na+, K+-ATPase, [43] $beta_1$ -adrenergic receptor,[44] glucose transporter (Glut-4),[45] cardiac troponin, [46] [47] and atrial natriuretic protein.[48] Thyroid hormone also can negatively regulate genes, e.g., myosin heavy-chain beta and the glucose transporter Glut-1, at least neonatally.[45]

Thyroid Extranuclear Actions.

Whereas the predominant effects of thyroid hormone are via its effect in regulating gene expression as noted above, thyroid hormone has also been clearly documented to have extranuclear effects. For example, T_3 increases both glucose and calcium uptake by the heart. Although some of these effects could be nuclear-mediated events, some studies suggest that thyroid hormone must also have a membrane effect. Evidence supporting a membrane effect includes rapid onset (for calcium uptake, maximum effect is achieved within 30 seconds), independence from new protein synthesis, and thyroid hormone specificity in that analogs of thyroid hormone that have no biological effect do not produce similar changes.[37] [49] [50]

In summary, thyroid hormone's nuclear and extranuclear effects on the heart lead to changes in the proportion of myosin heavy-chain protein from beta to alpha, thereby increasing myosin V_1 and decreasing myosin V_3 isoenzyme levels and thus leading to an increased velocity of contraction and diastolic relaxation. It also increases transcription of the calcium-ATPase gene. Extranuclear effects include thyroid hormone's direct effect on calcium current and cytosolic calcium changes induced by inotropic factors, including isoproterenol and the external calcium concentration.[51] [52]

As a secondary event, thyroid hormone also increases ATP consumption. However, because less of the chemical energy is used in the contractile process and more is dissipated as heat, myocardial metabolism is less efficient.[35] [51] [52]

RELATIONSHIP BETWEEN THE THYROID AND THE SYMPATHETIC NERVOUS SYSTEM

It has been proposed that some of the effects of thyroid hormone on the heart are indirect and secondary to changes in activity of the sympathetic nervous system (Table 64-1) . Many of the cardiovascular effects of hyperthyroidism, i.e., tachycardia, systolic hypertension, increased cardiac output, and myocardial contractility, can be abolished or reduced by blocking the activity of the sympathetic nervous system.[53] Thyroid

hormone may alter the relationship between the sympathetic nervous and cardiovascular systems either by increasing the activity of the sympathoadrenal system or by enhancing the response of cardiac tissue to normal sympathetic stimulation. Also, it has been suggested that sympathetic stimuli merely exert a direct additive effect on cardiovascular function above that produced by thyroid hormone. On the other hand, evidence has also been presented that hyperthyroidism reduces the sensitivity of cardiac tissue to sympathetic stimuli.[49]

Thus, the results of experiments on the relationship between the sympathoadrenal system and hyperthyroidism have evoked considerable controversy. Thyroid hormone's effect in three areas has been explored: adrenergic output, adrenergic receptors, and adrenergic transduction mechanisms. Plasma and urine levels of norepinephrine, epinephrine, dopamine, and beta-hydroxylase are either low or normal in hyperthyroidism and either normal or elevated in hypothyroidism. Therefore, the sympathomimetic features of hyperthyroidism cannot be due simply to an overall increase in adrenergic activity but are rather due to a change in the affinity of catecholamines for their receptors or a change in receptor number or to modification of a postreceptor mechanism. In the rat heart, which has been the organ most extensively studied, administration of thyroid hormone causes an increase in both the number of receptors and their affinity for their ligand, while hypothyroidism induces the opposite effect.[49] Thyroid hormone also increases mRNA levels for the $beta_1$ -adrenergic receptor.[44] [49]

TABLE 64-1 -- CLINICAL FEATURES OF HYPERTHYROIDISM

DIRECT THYROID HORMONE EFFECT*	BETA-ADRENERGIC-LIKE EFFECT*

Resting heart rate >90/min (90%)	Resting heart rate >90/min (90%)
	Palpitations (85%)
Palpitations (85%)	Exertional dyspnea (80%)
Atrial fibrillation (10%)	Increased pulse pressure (systolic
Pedal edema (30%)	hypertension)
Increased oxygen consumption (basal	Active apical impulse
metabolism)	Loud first heart sound and pulmonic
Weight loss	component of the second heart sound
Skeletal muscle myopathy	Midsystolic murmur, usually basal
Increased bone turnover (occasional	Third heart sound (occasional)
osteoporosis or hypercalcemia)	Means-Lerman scratch (rare)
Fair skin	
Fine brittle hair	Tremor
Brittle nails	Brisk reflexes
Oligomenorrhea or amenorrhea	Increased perspiration
Increased bowel frequency	Heat intolerance
	Insomnia
	Anxiety
	Stare, lid lag§

*Both types of effects contribute to the tachycardia and palpitations.

Numbers in parentheses are approximate prevalence of the findings compiled from several large series. Goiter is almost always present, although in elderly patients thyroid enlargement may be minimal or absent.

A systolic scratch or click in the 2nd left intercostal space that is probably generated by the pleura and pericardium rubbing together.
§These effects reflect upper lid retraction. Infiltrative ophthalmyopathy with exophthalmos is found only when Graves disease is the cause of the hyperthyroidism and is not related to the hyperthyroid state per se.*From Kaplan MM: The thyroid and the heart: How do they interact? J Cardiovasc Med 7:893, 1982.*

These changes in receptor number and affinity then lead to changes in sensitivity of the myocardium to beta adrenoceptor agonists. For example, stimulation of adenylate cyclase activity by isoproterenol is increased in hyperthyroidism and reduced in hypothyroidism. Changes are also seen in the force of contraction, with increased sensitivity of ventricular muscle to isoproterenol-induced contraction in hyperthyroidism and reduced sensitivity in hypothyroidism.[49] These effects were also observed in vivo in dogs, in which propranolol-induced reductions in heart rate and myocardial contractility were greater in hyperthyroid than euthyroid animals.[54]

Circulating blood elements have also provided additional evidence in support of the concept that thyroid hormone "upregulates" beta adrenoceptors. When patients are used as their own control, both the number of beta adrenoceptors and the sensitivity of adenylate cyclase to isoproterenol stimulation in mononuclear cells are increased by thyroid hormone.[55] [56] Additionally, in circulating reticulocytes of hypothyroid animals,

the number of receptors is decreased.[49]

Evidence supporting an effect of thyroid hormone in modifying the transduction mechanisms mediating adrenergic effects is less clear. In cultured developing rat myocardial cells, the addition of T_3 increased the level of G_{salpha} protein while reducing G_{salpha} and the beta subunits of G proteins. These results suggest that thyroid hormone elevates G protein subunits that activate adenylate cyclase and suppresses those that inhibit it. However, Levine and colleagues could not document an effect of thyroid hormone on G_{salpha} subunits in adult rat ventricles, although an apparent inhibitory effect of thyroid hormone on G_{salpha} 2 and 3 protein, G_{beta} 1 and 2 protein, polypeptide, and mRNA levels was confirmed.[57] Similar effects have been reported for adipose tissue,[58] which probably explains the reduced lipolytic response to catecholamines in hypothyroidism. Thus, thyroid hormone has a complex interaction with the adrenergic nervous system. Hyperthyroidism increases the number and potentially the affinity of beta-adrenergic receptors and also modifies the intracellular G protein milleu to enhance the transduction potential of agonists binding to the adrenergic receptor.

Effect of Thyroid Hormone on the Heart

Abundant evidence indicates that thyroid hormone may alter cardiac function directly, as noted above. additionally, the increased heart rate and myocardial contractility observed in experimental hyperthyroidism are not completely reversed by either sympathetic or parasympathetic blockade.[54] Finally, T_4 enhances the rate of contraction of cardiac muscle, even in the presence of adrenergic blockade. Right ventricular papillary muscles isolated from cats rendered hyperthyroid exhibited augmented myocardial contractility, as reflected in an upward shift of the myocardial force-velocity curve, along with greatly increased velocity of myocardial fiber shortening, reduced time to peak tension during isometric contraction, and development of augmented peak tension. Single ventricular myocytes isolated from hyperthyroid rats exhibited marked augmentation in twitch velocity and abbreviated contraction and relaxation times. Prior catecholamine depletion by pretreatment with reserpine did not alter this inotropic effect of hyperthyroidism, thus providing further evidence for a direct cardiac effect. This hypothesis has been assessed in intact conscious animals. The results suggest that the major actions of T_4 on the left ventricle are (1) a direct positive inotropic effect and (2) an increase in the size of the ventricular cavity without a change in end-diastolic pressure or length of the sarcomere in diastole, although hypothyroidism does not necessarily impair pump function.[49]

The available data suggest that the direct effect of thyroid hormone on the heart is primarily mediated via a change in protein synthesis, as described above. Specifically, synthesis of myosin heavy chains is changed from the beta to the alpha form, thereby increasing the level of the more mobile myosin isoenzyme (V_1). With the reduction in mRNA levels for beta-myosin heavy chain, the slower V_3 myosin isoform is substantially reduced. Goto and associates demonstrated in the hyperthyroid rabbit heart that an increase in the myosin isoform V_1 /V_3 ratio is associated with decreased contractile efficiency and increased energy cost of excitation-contraction coupling.[59] This change

produces a less efficient system, thereby leading to more heat production per contractile response. In contrast to thyroid hormone's marked effect on myosin isoenzyme composition in rats and rabbits, in humans there appears to be much less of an effect. The myosin heavy-chain beta form is the isoenzyme overwhelmingly present in human hearts and is little affected by thyroid status. Even the alpha form increases very little when thyroid hormone is given to severely hypothyroid subjects.[60]

Thyroid hormone's effect on cardiac contractility also appears to be mediated in part by changes in intracellular calcium handling. Thyroid hormone increases expression of sodium-calcium-ATPase, which augments transsarcolemmal calcium influx in cultured ventricular cells.[61]

In ferret ventricular muscle, hypothyroidism reduces peak tension and prolongs the duration of contraction in association with changes in cytosolic calcium that are decreased and prolonged in relation to ventricular muscle obtained from euthyroid animals (Fig. 64-3) . Hyperthyroidism produces the opposite changes. Thus, alteration in intracellular calcium handling, specifically that related to recycling of calcium by the sarcoplasmic reticulum, may account for the thyroid-induced changes in myocardial contractile function.[62] Finally, the effect of T_4 on myosin isoenzyme appears to be localized primarily to the ventricles, with atrial isoenzymes relatively unaltered by changes in thyroid hormone. Thus, while thyroid hormone itself has a major direct effect on modifying protein synthesis, changes in cardiac workload may also contribute. Studies using heterotrophic cardiac isografts suggest that the changes in myosin enzyme levels may in part be secondary to changes in workload.[63] Again, how much the changes described in rodents apply to humans is uncertain.

Thyroid hormone modifies the electrical activity of the heart by several mechanisms. It increases recruitment of slower inactivating sodium channels.[64] It also modifies the expression and/or composition and thereby the activity of

Figure 64-3 The thyroid state influences the time course of the isometric contraction and the Ca^{2+} transient. The isometric tension (T) and the aequorin light signal, reflecting intracytoplasmic $[Ca]^{2+}$ (L), were recorded from myocardium obtained from a hypothyroid (*A*), euthyroid (*B*), and hyperthyroid (*C*) ferret at 30°C, 0.33 Hz stimulation. I is expressed in millinewtons per square meter muscle cross-sectional area. The Ca^{2+} transients (aqueorin signals) are scaled to equal amplitudes and superimposed in *D.* In *E,* the tensions have been scaled to equal amplitudes and superimposed. The time from the beginning of the stimulus sweep (S) to the stimulus represents 100 milliseconds. (From MacKinnon R, Gwathmey JK, Allen PD, et al: Modulation by the thyroid state of intracellular calcium and contractility in ferret ventricular muscle. Circ Res 63:1080, 1988. By permission of the American Heart Association.)

one or more potassium channels and several calcium channels.[52] [65] [66] [67] These effects probably result from altered gene transcription because of thyroid hormone. In

general, these channel effects lead to a reduction in early repolarization in the absence of thyroid hormone and an accelerated decline in the action potential when thyroid hormone is present in excess. The tachycardia observed in hyperthyroidism appears to be due to a combination of an increased rate of diastolic depolarization and a decreased duration of the action potential in the sinoatrial node cells. The propensity for the development of atrial fibrillation may be due to the shortened refractory period of atrial cells.

Hyperthyroidism

Hyperthyroidism is the clinical state resulting from excess production of T_4 , T_3 or both. The most common cause is a diffuse toxic goiter (Graves disease). Although the etiology of this condition is still unknown, the hyperproduction of T_4 and T_3 is thought to result from circulating IgG autoantibodies that bind to the thyrotropin receptor on the thyroid gland. The second most common form of hyperthyroidism is nodular toxic goiter, a condition in which localized areas of the gland function excessively and autonomously.[68]

Hyperthyroidism is a relatively common disease that occurs four to eight times more often in women than men, with a peak incidence in the third and fourth decades. Commonly associated signs and symptoms (see Table 64-1) include fatigue, hyperactivity, insomnia, heat intolerance, palpitations, dyspnea, increased appetite with weight loss, nocturia, diarrhea, oligomenorrhea, muscle weakness, tremor, emotional lability, increased heart rate, systolic hypertension, hyperthermia, warm moist skin, lid lag, stare, and brisk reflexes. Serum T_4 levels are increased and serum TSH is suppressed.

CARDIOVASCULAR MANIFESTATIONS.

The heart is among the most responsive organs to thyroid hormone. Cardiovascular signs and symptoms are therefore important clinical features of hyperthyroidism.[68] [69] Palpitations, dyspnea, tachycardia, and systolic hypertension are common findings. Diastolic hypertension can also occur. Typically noted are a hyperactive precordium with a loud first heart sound, an accentuated pulmonic component of the second heart sound, and a third heart sound; occasionally, a systolic ejection click is heard. Midsystolic murmurs along the left sternal border are common, and a systolic scratch, the so-called Means-Lerman scratch, is occasionally heard in the 2nd left intercostal space during expiration. It may represent a pulmonic flow murmur related to cardiac output.

As would be anticipated, the cardiac and stroke volume index, mean systolic ejection rate, velocity and extent of wall shortening (Fig. 64-4) , and coronary blood flow are all increased, the systolic ejection period and preejection period are abbreviated, the pulse pressure is widened, and systemic vascular resistance is reduced in hyperthyroidism. The changes in left ventricular performance induced by thyroid hormone appear to be secondary to augmented contractility rather than alterations in loading conditions or a change in heart rate. If the hyperthyroidism is relatively mild, many of the indices of left

ventricular function are normal, with exercise needed to bring out abnormalities.[69] It has been suggested that many of the changes in cardiac function are secondary to the increased metabolic demands of peripheral tissue. However, the increase in cardiac output is greater than would be predicted on the basis of the increased total-body oxygen consumption, thus supporting the view that thyroid hormone exerts a direct cardiac stimulant action independent of its effect on general tissue metabolism, as noted above. Furthermore, normalization of the myocardial contractile response to exercise may not occur until several months after normalization of thyroid function. However, it is likely that the overall pathological consequences associated with thyrotoxicosis result from an interaction between the effect of thyroid hormone on the heart and its effect on the peripheral circulation (Fig. 64-5) .

Roentgenographic and electrographic changes are common, but nonspecific in hyperthyroidism.[69] Thus, on chest x-ray the left ventricle, aorta, and pulmonary artery are

Figure 64-4 Rate-corrected velocity of shortening in SD units from the normal mean regression line obtained from 11 patients at varying levels of the free thyroxine index. A strong positive correlation can be seen between the level of thyroid hormone and the change in contractile state. The shaded area represents the normal range for the serum free thyroxine index. (From Feldman T, Borow KM, Sarne DH, et al: Myocardial mechanics in hyperthyroidism: Importance of left ventricular loading conditions, heart rate and contractile state. J Am Coll Cardiol 7:967, 1986. Reprinted with permission from the American College of Cardiology.)

prominent, and in some cases, generalized cardiac enlargement can be noted. In patients with sinus rhythm, the magnitude of the tachycardia in general parallels the severity of the disease. Sinus tachycardia is present in 40 percent of patients with hyperthyroidism and occurs most frequently in the younger age groups and often at night.[70] Ten to 15 percent of patients with hyperthyroidism have persistent atrial fibrillation, which is often heralded by one or more transient episodes of this arrhythmia.[69] Shortening of the AV conduction time and functional refractory period results in an increased frequency at which the AV conduction system transmits rapid atrial impulses. Intraatrial conduction disturbances, manifested by prolongation or notching of the P wave and prolongation of the PR interval in the absence of treatment with digitalis, occur in 15 and 5

Figure 64-5 Cardiovascular effects of hyperthyroidism. Cardiac output is increased as a result of thyroid hormone augmentation of the hemodynamic parameters indicated in the figure. LVEDV = Left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume. (Modified from Woeber KA: Thyrotoxicosis and the heart. N Engl J Med 327:94, 1992.)

percent of patients with hyperthyroidism, respectively. Occasionally, second- or

third-degree heart block may result. The cause of the AV conduction disturbance is not clear because animal experiments have shown that the functional refractory period of the AV conduction system and the conduction time were shortened in dogs with hyperthyroidism and prolonged in dogs with hypothyroidism.[71] Intraventricular conduction disturbances, most commonly right bundle branch block, occur in about 15 percent of patients with hyperthyroidism without associated heart disease of other etiology. Paroxysmal supraventricular tachycardia and flutter are rare in hyperthyroidism. Finally, occult thyrotoxicosis may underlie either chronic or paroxysmal isolated atrial fibrillation.[72]

Both angina pectoris and heart failure occur in patients with hyperthyroidism. For many years it was assumed that these conditions were seen only in the presence of underlying cardiovascular disease. More recently, however, five lines of evidence have suggested otherwise: (1) Congestive heart failure has been produced in experimental animals by simply administering T_4 . (2) Congestive heart failure may develop in children with thyrotoxicosis and no underlying cardiac disease.[73] (3) Angina has been reported in a hyperthyroid patient with normal coronary arteries, presumably secondary to thyroid-induced coronary artery spasm. (4) The abnormal left ventricular function observed during exercise in hyperthyroid subjects is not reversed by beta blockade but is reversed by treating the hyperthyroidism.[49] [68] [69] (5) Finally, Ebisawa and coauthors reported that the cardiomyopathy in patients with thyrotoxicosis may be irreversible. Four patients with this condition had increased left ventricular end-diastolic volumes and reduced ejection fractions, even 13 to 15 years following treatment of their hyperthyroidism. Myocardial biopsies, performed in two patients, showed no specific light microscopic abnormalities.[74]

Thus, when it is severe and persistent, thyrotoxicosis can overtax even a normal heart, although in most instances the development of clinical manifestations of heart failure and myocardial ischemia in patients with hyperthyroidism signifies the presence of underlying cardiac or coronary vascular disease. The frequency of hyperthyroidism is also increased in patients with familial hypertrophic cardiomyopathy. In one kindred, 3 of 17 members with hypertrophic cardiomyopathy also had hyperthyroidism.[75] Finally, hyperthyroidism is associated with mitral value prolapse in more than a third of cases.[49] [68] [69]

TREATMENT OF CARDIOVASCULAR DISEASE IN HYPERTHYROIDISM.

Hyperthyroid patients with cardiovascular disease are particularly resistant to therapy. It has been well documented that both heart failure and arrhythmias are resistant to conventional doses of cardiac glycosides. Although the specific mechanisms underlying these altered responses remain obscure, they may be related to both systemic and local effects.[76] First, serum levels of cardiac glycosides are diminished in hyperthyroidism, not primarily because its metabolism is increased but because its volume of distribution is greater. Second, experimental hyperthyroidism reduces the enhancement in myocardial contractile force and the prolongation in the AV nodal refractory period produced by these agents.[76] Because of this decreased sensitivity to cardiac glycosides, toxicity may develop at a dose that has relatively little therapeutic effect.

DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM

The mainstay of treatment is beta-adrenergic blocking agents pending initiation of more definite treatment of the hyperthyroidism. Hyperthyroidism in most patients is clinically manifested as described above. The diagnosis is confirmed with a low TSH level, which reflects an elevated level of thyroid hormone in the blood. In elderly patients with apathetic hyperthyroidism, cardiovascular manifestations predominate, specifically, atrial fibrillation and/or congestive heart failure, and therefore evaluation of thyroid function in such patients is particularly important.

Definitive treatment of hyperthyroidism is surgical removal of the gland or irradiation with radioactive iodide. In severely ill patients, particularly those with thyroid storm, significant cardiovascular symptoms, or both, neither of these therapies is appropriate. Thus, medical therapy is directed at reducing both the production and the biological effect of thyroid hormone with thionamides and beta blockers.[76] [77] [78] Tachycardia, palpitations, tremor, restlessness, muscle weakness, and heat intolerance are reversed by these agents, which offer the additional benefit of inhibiting the conversion of T_4 to the biologically active T_3 in peripheral tissues.

TREATMENT OF CARDIOVASCULAR MANIFESTATIONS OF HYPERTHYROIDISM.

Prompt treatment of hyperthyroidism can significantly reduce, if not eliminate the associated cardiovascular symptoms. About half of patients with concurrent onset of hyperthyroidism and angina pectoris experience complete remission of this symptom after treatment of hyperthyroidism.[78] Furthermore, in 30 to 40 percent of thyrotoxic patients with atrial fibrillation sustained for 1 week or longer, spontaneous reversion to sinus rhythm occurs when they become euthyroid.[49] [68] [69]

Beta blockers can be administered orally or intravenously, but because these drugs interfere with the effects of sympathetic stimulation on the heart, they must be used with caution in patients with congestive heart failure. However, if the heart failure is in part related to the tachycardia, beta blockade may be beneficial.[77] Beta-blocking drugs also slow the ventricular rate in atrial fibrillation. The most useful agents for correcting the fundamental defect are thionamides such as propylthiouracil,[76] which inhibits thyroid hormone synthesis. Iodine inhibits the release of thyroid hormones from the thyrotoxic gland, and its beneficial effects occur more rapidly than those of thionamides. It is therefore useful for rapid amelioration of the hyperthyroid state in patients with thyroid heart disease. Ipodate may be particularly useful for this purpose. Iodine may also be used along with antithyroid agents to control thyrotoxicosis following ^{131}I treatment until the radioactive iodide has had time to take effect. Most hyperthyroid patients, however, escape from the effects of iodide after 10 to 14 days.

Hypothyroidism

Hypothyroidism results from reduced secretion of both T_4 and T_3 , which occurs in most cases as a consequence of destruction of the thyroid gland itself, usually by an inflammatory process. The most common cause in the United States is Hashimoto's thyroiditis. Less commonly, it is secondary to decreased secretion of TSH because of either pituitary or hypothalamic disease. In secondary hypothyroidism, the signs and symptoms associated with deficiency of other pituitary hormones are also usually present. The incidence of hypothyroidism peaks between the ages of 30 and 60 years, and it is twice as common in women as men. The following signs and symptoms are common: cold intolerance, dryness of the skin, weakness, impairment in memory, personality changes, shortness of breath, constipation, hoarseness, menorrhagia and other forms of menstrual dysfunction, and occasionally, heart failure.

CARDIOVASCULAR MANIFESTATIONS (Fig. 64-6) .

The heart in overt myxedema is often pale, flabby, and grossly dilated. Histological examination discloses myofibrillar swelling, loss of striations, and interstitial fibrosis. With early detection and treatment of hypothyroidism, the classic findings of cardiac enlargement, cardiac dilatation, significant bradycardia, weak arterial pulses, hypotension, distant heart sounds, low electrocardiographic voltage, nonpitting facial and peripheral edema, and evidence of congestive heart failure, such as ascites, orthopnea, and paroxysmal dyspnea, are now seen only infrequently. However, exertional dyspnea and easy fatigability continue to be common complaints.

Myxedema is associated with increased capillary permeability and subsequent leakage of protein into the interstitial space; these abnormalities result in pericardial effusion, a common clinical finding in overt myxedema that occurs in about one-third of all patients. Rarely, it is complicated

Figure 64-6 Cardiovascular effects of hypothyroidism. Cardiac output is decreased because of diminished total blood volume, impaired left ventricular contractility, and bradycardia. Hypertension results from increased systemic vascular resistance. Pericardial effusion results from increased capillary permeability and interstitial protein leak.

by cardiac tamponade. [49] [68] Echocardiography is the most useful method of establishing the diagnosis. The effusions disappear with thyroid replacement therapy. Myxedema-associated cardiogenic shock has also rarely been reported, and it, too, responds to thyroid replacement therapy.[79]

Electrocardiographic changes include sinus bradycardia and prolongation of the QT interval. The P wave amplitude is usually very low. It is possible that hypothyroidism may contribute to reentrant ventricular arrhythmias,[80] which may be due to prolonged action potential duration.[80A] The incidence of AV and intraventricular conduction disturbances is about three times greater in patients with myxedema than in the general

population. Incomplete or complete right bundle branch block has been observed, and a primary myocardial abnormality suggestive of cardiomyopathy has been reported.[81] Other electrocardiographic changes are those associated with pericardial effusion.

The frequency of hypertension is increased in patients with hypothyroidism, although not in patients with severe myxedema.[49] [68] In one study of 477 patients, 15 percent of the hypothyroid subjects had a blood pressure greater than 160/95 as compared with 5.5 percent in age-matched euthyroid subjects. Replacement of thyroid hormone resulted in a substantial reduction in blood pressure in the hypertensive patients.[82] In a study of 688 consecutive hypertensive patients, hypothyroidism was found in 25 (3.6 percent). In nearly one-third of this subgroup, treatment of the hypothyroidism lowered the blood pressure to within the normal range.[83] Thus, individuals with mild to moderate hypothyroidism have an increased possibility of the development of hypertension, particularly diastolic hypertension, whereas individuals with severe hypothyroidism are more likely to have normal or slightly low blood pressure.[82] [83]

MYOCARDIAL EFFECTS.

Hypothyroid patients have reduced cardiac output, stroke volume, and blood and plasma volume.[49] [68] [84] Right- and left-heart filling pressures are usually within normal limits unless they are elevated by pericardial effusion. Blood flow is redistributed, with mild reductions in cerebral and renal flow and significant reductions in cutaneous flow. The ventricular isovolumetric relaxation time is prolonged but is normalized during T_4 replacement.[85] The impact of hypothyroidism on cardiac function can occur quickly in patients rendered hypothyroid for assessment of thyroid status in the treatment of thyroid cancer. Two weeks after discontinuing thyroid medication, the left ventricular end-diastolic diameter and

peak velocity of early diastolic filling, as well as the heart rate, were reduced. No changes were observed in systolic or diastolic blood pressure.[86]

Cardiac muscle isolated from cats with experimentally produced hypothyroidism exhibited reduced contractility characterized by depression of the myocardial force-velocity curve, a reduction in the rate of tension development, and prolongation of the contractile response.

Congestive heart failure is not common in myxedema, nor does it occur in the absence of other cardiac disease. Presumably, the depressed myocardial contractility is sufficient to sustain the reduced workload placed on the heart in hypothyroidism. However, it may be difficult to distinguish between symptoms of myxedema and heart failure. Dyspnea, edema, effusions, cardiomegaly, and T wave changes occur in both conditions. In left-sided heart failure, pulmonary arterial pressure is usually elevated during exercise, cardiac output fails to rise normally, and the Valsalva response is normal, whereas the opposite occurs in myxedema. Also, the hemodynamic changes in myxedema respond

to thyroid hormone administration.

Cardiac catecholamine levels are not reduced in hypothyroidism. Neither the sensitivity of the mechanical performance of the heart to sympathetic nerve stimulation nor the response of cardiac adenylate cyclase to norepinephrine is altered in hypothyroidism. However, the total number of myocardial beta receptors is reduced.[62] [56] Both isoproterenol-stimulated contractility and the accumulation of cyclic adenosine monophosphate are reduced in hearts obtained from hypothyroid rats. In experimental hypothyroidism, calcium in isolated myocardial sarcoplasmic reticulum particles is reduced, which may explain the altered contractile state.[59]

Finally, while the clinical and morphological cardiac features of hypothyroidism resemble those associated with dilated cardiomyopathy few clinical data are available to support a connection between these conditions. Fruhwald and colleagues examined the prevalence of thyroid abnormalities in 61 patients with idiopathic dilated cardiomyopathy. By ultrasonography, 8 percent had morphological abnormalities of the thyroid. Yet none had clinical or biochemical evidence of hyperthyroidism or hypothyroidism. In the 10 patients who were taking amiodarone, the frequency of morphological thyroid abnormalities was similar to the frequency of abnormalities with the rest of the patients.[87]

ATHEROSCLEROSIS.

It has been suggested that patients with hypothyroidism have an increased risk of atherosclerosis because of significant changes in lipid metabolism. Hypercholesterolemia and hypertriglyceridemia, which are associated with the development of premature coronary artery disease, are commonly found in patients with hypothyroidism.[88] Treatment of the hypothyroidism corrects the abnormal lipid pattern. For example, Arem and Patsch noted a 22 percent reduction in the mean low-density lipoprotein (LDL) cholesterol concentration after 4 months of thyroid replacement therapy.[89] High-density lipoprotein (HDL) cholesterol levels did not change appreciably. Support for a connection between hypothyroidism and atherosclerosis has come from several sources, including the documentation that the latter occurs with twice the frequency in patients with myxedema than in age- and sex-matched controls and that the development of atherosclerosis in cholesterol-fed animals is enhanced by the presence of hypothyroidism and reduced when thyroid hormone is administered. Yet myocardial infarction and angina pectoris are relatively uncommon in hypothyroidism. This low frequency of cardiac complications from atherosclerosis may simply reflect the decreased metabolic demand on the myocardium in hypothyroidism. However, the known effects of hypothyroidism on serum enzyme concentrations do complicate the assessment of chest pain in patients with myxedema.

DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM

Diagnosis is made by documentation of an elevated serum TSH level. Caution must be exercised in treating hypothyroid patients who are elderly and who may have underlying heart disease to avoid precipitating myocardial infarction or severe congestive heart

failure; a slow replacement program is indicated in these individuals.

Treatment of congestive heart failure is particularly difficult in patients with myxedema, both because of the effect of thyroid hormone on the heart and because the heart's response to cardiac glycosides is altered. Patients with severe angina pectoris and untreated myxedema pose a difficult clinical dilemma because angina may be exacerbated by thyroid hormone replacement and the usual medical management of angina with beta blockers may induce severe bradycardia. Coronary arteriography often shows severe coronary artery disease in these patients, and an excellent surgical team can perform successful coronary revascularization with minimal thyroid replacement. Full thyroid replacement can then be safely achieved during the postoperative period, without the recurrence of angina.[90]

Amiodarone and the Thyroid

The widespread use of amiodarone for cardiac arrhythmias is now one of the most common causes of thyroid abnormalities in patients with cardiovascular disease[91] [92] (see also Chap. 23) . Amiodarone has structural similarity to T_4 and T_3 and is also rich in iodine. Amiodarone decreases the peripheral conversion of T_4 to T_3 , which leads to elevated levels of circulating T_4 and lower levels of circulating T_3 . Since this inhibition occurs in the pituitary gland as well, a transient increase in TSH is seen early in treatment but usually resolves over the next 3 months.[93] [94] These laboratory test changes are common and not usually associated with any clinical manifestations of thyroid dysfunction.

HYPOTHYROIDISM.

Hypothyroidism, the most common clinical manifestation of amiodarone-induced thyroid dysfunction in the United States and United Kingdom, occurs in as many as 13 percent of patients.[91] [92] The mechanism of this dysfunction is not clearly defined but may be related to the effect of the large iodine load on inhibition of thyroid hormone release and synthesis superimposed on underlying autoimmune thyroid disease.[95] It has also been suggested that amiodarone itself may cause autoimmune thyroid dysfunction by altering T-cell function.

Symptoms are the same as those seen in other forms of hypothyroidism, and the diagnosis is confirmed with the demonstration of an elevated TSH level. Some patients will regain normal thyroid function several months after stopping amiodarone therapy, although others will have permanent hypothyroidism. If thyroid function does not return to normal with discontinuation of therapy or if amiodarone administration is continued, thyroid hormone replacement at a dose that normalizes the TSH level will treat the condition.

HYPERTHYROIDISM.

Amiodarone-induced hyperthyroidism most commonly occurs in areas of the world with

iodine deficiency but can be seen in iodine-replete individuals as well.[91] [92] Patients may demonstrate typical symptoms of hyperthyroidism such as weight loss, heat intolerance, and tremor, but at times the initial symptom may be the onset or recurrence of cardiac arrhythmias. Diagnosis is made by the patient's history, clinical examination, and thyroid function testing, which shows low TSH and elevated T_4 . Since low TSH and elevated T_4 levels can also be commonly seen in the early phase of amiodarone therapy without symptoms, measurement of total T_3 may be helpful in distinguishing these conditions. In the early phase of treatment with amiodarone, T_3 levels are decreased, whereas in hyperthyroidism, the T_3 level is increased.[96]

Two mechanisms have been proposed for amiodarone-induced hyperthyroidism. Type I occurs in abnormal thyroid glands and is caused by iodine-induced increased thyroid hormone synthesis in subjects with nodular goiters or latent Graves disease. Type II occurs in what is a normal gland. It is presumably secondary to a thyroid-destructive process caused by iodine or amiodarone per se.[97] In the latter case, amiodarone may induce thyrotropin receptor

antibodies, which then cause the hyperthyroid state.[98] Some investigators have suggested that type I (hypervascular state) and type II (hypovascular state) thyrotoxicosis can be distinguished by color flow Doppler sonography. Another sometimes useful distinguishing feature is an increased serum interleukin-6 level in type II but not type I. It has been reported to be important to distinguish these two types since their treatments differ. Patients with type II but not type I sometimes respond very well to glucocorticoids.[99]

Cessation of amiodarone therapy will lead to eventual resolution of the hyperthyroidism, although normalization can sometimes take several months. However, amiodarone therapy often cannot be stopped, in which case other treatment modalities must be instituted. The two primary modalities are thionamides and surgery. Propylthiouracil or methimazole may be successful, but not in all cases. When medical management fails, thyroidectomy may be the procedure of choice to allow continuation of amiodarone therapy. Radioactive iodine therapy is most commonly not an option because of the high iodine content of amiodarone and the resultant increased thyroidal stores leading to very low radioactive iodine uptake by the thyroid.

THYROID MONITORING.

Because of the frequency of thyroid dysfunction with amiodarone therapy, routine monitoring of thyroid function tests is recommended. Several algorithms for monitoring have been published. One such algorithm is depicted in Figure 64-7 .

DISEASES OF THE ADRENAL CORTEX

Since Addison's description in 1855 of adrenal insufficiency,[2] it has been appreciated that steroids secreted by the adrenal cortex exert a significant effect on the cardiovascular system. For many years, the primary influence was assumed to be mediated by the adrenal steroids' effect in modifying blood pressure. Recently, it has been proposed that these steroids, particularly aldosterone, have a much broader impact on cardiovascular function. Yet diseases of the adrenal cortex are often associated with changes in blood pressure. Adrenal insufficiency is characterized by hypotension, whereas hypertension often accompanies excessive production of adrenal steroids.

Three classes of steroids are secreted by the adrenal cortex: glucocorticoids, e.g., cortisol; mineralocorticoids, e.g., aldosterone; and androgens, e.g., dehydroeplandrosterone. In this section, the physiology and pathophysiology of glucocorticoid and mineralocorticoid secretion are addressed.

Figure 64-7 Algorithm for evaluating thyroid status in patients taking amiodarone. Amiodarone withdrawal may also be appropriate in some cases. TPO = thyroid peroxidase. (Adapted from Newman CM, Price A, Davies DW, et al: Amiodarone and the thyroid: A practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart 79:121, 1998.)

HORMONE ACTIONS

CORTISOL.

The primary glucocorticoid, cortisol, is synthesized from cholesterol in the inner layers of the adrenal cortex. Its average plasma concentration is 15 mug/dl in the morning, which falls to 5 mug/dl by early evening.[100] The fundamental mechanism of action of the glucocorticoids is similar to that of other steroid hormones. They enter a target tissue by diffusion and combine with a specific high-affinity intracellular receptor protein. The receptor-cortisol complex can then bind to promoters of target genes and regulate their transcription. The major action of glucocorticoids is to promote gluconeogenesis, and in that respect, they have both catabolic and antiinsulin properties.

Glucocorticoids also have antiinflammatory effects. They maintain normal vascular responsiveness to circulating vasoconstrictors such as norepinephrine and have a major effect on both the distribution and excretion of body water.

ALDOSTERONE.

The major mineralocorticoid produced by the human adrenal gland is aldosterone. It is also synthesized from cholesterol, but almost exclusively in the outer layer

(glomerulosa) of the adrenal cortex. Aldosterone has two important functions: (1) It is a major regulator of extracellular fluid volume by its effect on sodium retention, and (2) It is a major determinant of potassium metabolism. Aldosterone acts predominantly on the distal convoluted tubule and/or collecting duct of the kidney, where it promotes the reabsorption of sodium. Potassium then diffuses into the lumen of the tubules because of the change in electrochemical gradient produced by active reabsorption of the positively charged sodium ion. Hydrogen ion may also be more freely excreted because of this change in the electrochemical gradient. Although aldosterone also acts on salivary and sweat glands and on epithelial cells of the gastrointestinal tract, these actions have little impact on total-body sodium and potassium homeostasis.

Three well-defined mechanisms control aldosterone release.[100] [101]

1. The renin-angiotensin system is the major system for control of extracellular fluid volume by regulating aldosterone secretion. Aldosterone is linked in a negative feedback loop with the renin-angiotensin system. Thus, during periods registered as volume deficiency, release of the enzyme renin from the juxtaglomerular cells of the kidney is increased. Renin then increases the production of angiotensin I from its substrate. Angiotensin I is rapidly converted into the biologically active angiotensin II, which increases aldosterone secretion. Angiotensin II also produces vasoconstriction, thereby raising blood pressure and reducing blood flow to a variety of tissues, especially the kidney.
2. Potassium ion also regulates aldosterone secretion independent of the renin-angiotensin system; an elevated potassium concentration increases aldosterone secretion and vice versa. The adrenal cortex is very sensitive to changes in potassium concentration, with as little as a 0.1-mEq/liter increment producing significant changes in plasma aldosterone levels.
3. ACTH also affects aldosterone secretion profoundly. However, because control of aldosterone release is not appreciably altered in patients who have been on a long-term regimen of steroid therapy, ACTH probably has a smaller role than the other two factors do in maintaining normal aldosterone secretion.

In addition to these major stimuli controlling aldosterone secretion, salt-losing hormones such as atrial natriuretic peptide and dopamine inhibit aldosterone secretion, particularly in response to angiotensin II.[101] Finally, poor dietary intake of both sodium and potassium alters the magnitude of the aldosterone response to acute stimulation, sodium restriction, and potassium loading, both of which enhance the response of the adrenal, perhaps by modifying the local (adrenal) renin-angiotensin system.[100] [101]

ALDOSTERONE: A CARDIOVASCULAR RISK FACTOR.

While diseases of the adrenal cortex primarily affect the cardiovascular system via changes in blood pressure or volume homeostasis, even at physiological levels aldosterone may enhance the risk of cardiovascular damage. This increased risk is mediated, in part, by aldosterone's classic action on epithelial cells (e.g., renal tubular cells) whereby sodium, volume, and potassium homeostasis is modified and in part, by several nonclassic effects on nonepithelial cells (e.g., myocytes and fibroblasts) in which a variety of functions are modified. For example, aldosterone has a direct effect on

collagen metabolism in cardiac fibroblasts. In rats treated with a high-salt diet and aldosterone, cardiac fibrosis develops within 6 weeks.[102] [103] [104] [105] A clinical correlate of this effect is a reactive perivascular and interstitial cardiac fibrosis in patients with primary aldosteronism that does not seem to be due to pressure overload alone. In the stroke-prone, spontaneously hypertensive rat, administering an angiotensin-converting enzyme (ACE) inhibitor markedly attenuates the early death rate.[106] Since this manipulation will reduce both angiotensin II and aldosterone levels, either could be involved in mediating this damage. When Rocha and colleagues returned angiotensin II levels to normal with an infusion of angiotensin II, the damage recurred unless the animals were adrenalectomized or the mineralocorticoid receptor blocked biochemically before the infusion began. By this technique, not only the cardiac damage but also the renal and cerebral damage was prevented even in the face of an increased angiotensin II level and persistently elevated blood pressure.[107] [108] [109] [109A] [109B] These data strongly support the hypothesis that it is aldosterone and not angiotensin II that is the principal mediator of this damage. Finally, aldosterone also may increase plasminogen activator inhibitor type 1 (PAI-1) expression and secretion and contribute to the inflammatory response accompanying microvascular disease.[109A] [109B]

Support for these experimentally derived data comes from clinical studies. Increased plasma aldosterone levels in patients with essential hypertension are associated with decreased systemic arterial compliance.[110] Plasma aldosterone levels more closely correlate with left ventricular mass than does plasma renin activity.[111] Finally, results of the Randomized Aldosterone Evaluation Study (RALES) provide strong support for a role of aldosterone independent of effects on electrolytes[112] (see also Chap. 18) . Over 1600 patients with New York Heart Association (NYHA) Class III or IV heart failure were randomized to treatment with a low-dose mineralocorticoid receptor antagonist (spironolactone) or placebo on top of standard therapy (ACE inhibitors, loop diuretics, and in the majority, digoxin). A highly significant (30 percent) reduction was noted in all-cause mortality in the treatment group. The magnitude of this effect, observed despite concomitant therapy with an ACE inhibitor, is comparable in magnitude to the benefit of an ACE inhibitor alone in this population. The applicability of these findings to other cardiovascular diseases and milder forms of hypertension awaits the results of future studies.

Cushing Syndrome (see also Chap. 28)

In 1932, Harvey Cushing reported a syndrome characterized by truncal obesity, hypertension, fatigue, weakness, amenorrhea, hirsutism, purple abdominal striae, glucosuria, edema, and osteoporosis.[113] The majority of cases are secondary to bilateral adrenal hyperplasia, with the predominant feature being excess production of glucocorticoids and androgens.[100] Some cases are due to ACTH-producing tumors of either the pituitary gland (Cushing disease) or nonendocrine tissue (ectopic ACTH production). Fifteen to 20 percent of cases are due to primary adrenal neoplasia, either adenoma or carcinoma. Most patients have a typical body habitus: central obesity and slender extremities with proximal muscle weakness. Hypertension is present in 80 to 90 percent of patients, and diabetes occurs in 20 percent, probably in individuals with a predisposition.[100] Evidence of androgen excess may also be present, including

hirsutism, amenorrhea, and clitorimegaly.

Laboratory tests disclose evidence of excess production of both glucocorticoids and androgens in the majority of cases. Thus, urinary metabolites of these steroids, 17-ketosteroids and 17-hydroxysteroids, are characteristically increased. Most patients show some evidence of glycosuria or hyperglycemia.

CARDIOVASCULAR MANIFESTATIONS.

Before the development of effective therapy for Cushing syndrome, accelerated atherosclerosis was a common finding. Early death usually occurred from myocardial infarction, congestive heart failure, or stroke. Even with more effective treatment, the mortality of patients with Cushing syndrome is still significantly higher than that in the general population, primarily because of an increased risk of cardiovascular disease.[114] Although the pathophysiology of the accelerated atherosclerosis is not clear, the hypertensive process probably contributes. Chronic excess production of cortisol leads

to hyperlipidemia and hypercholesterolemia, both of which may promote the development of atherosclerosis.[100]

The pathophysiology of the hypertension in Cushing syndrome has been much debated. Early studies suggested that it was secondary to volume expansion as a result of cortisol's mineralocorticoid properties. Support for this mechanism comes from the demonstration of increased levels of atrial natriuretic hormone in patients with Cushing syndrome, which suggests a volume-expanded state.[115] However, recent studies have not supported this hypothesis. Alternative hypotheses include glucocorticoid potentiation of the response of vascular smooth muscle to vasoconstrictive agents and ACTH- or cortisol-induced increases in renin substrate.[100] The latter thesis suggests that the increased blood pressure is secondary to increased generation of angiotensin II. Support for the potentiation hypothesis comes from a documented increased vascular response to both angiotensin II and catecholamines in patients with Cushing syndrome as compared with normal subjects.[116] [117] A final possibility is increased vasoconstrictor sensitivity to cortisol itself, which has been suggested to occur in essential hypertension, probably by modifying renal vascular resistance.[118] [119] Thus, the pathophysiology of the hypertension may be multifactorial and related to volume expansion, increased production of vasoactive agents, e.g., angiotensin II, and increased sensitivity of vascular smooth muscle to vasoactive agents.

Hemodynamic, electrocardiographic, and roentgenographic studies of patients with Cushing syndrome have revealed no specific abnormalities except those that are in general associated with either hypertension or hypokalemia. PR intervals tend to be shorter than normal. Echocardiograms have shown ventricular hypertrophy with asymmetrical septal thickening. The frequency of these abnormalities is greater than that seen in patients with essential hypertension and equivalent levels of blood

pressure.[120]

Rarely, Cushing syndrome and cardiac myxoma occur in the same individual. In addition to having these two conditions, 80 percent of patients have a cutaneous abnormality. In most, it is a pigmented lesion; in some, it is a subcutaneous myxoma. Histologically, the adrenal glands show nodular hyperplasia.[121]

DIAGNOSIS AND TREATMENT.

The diagnosis of Cushing syndrome is established by the lack of appropriate suppression of cortisol secretion by dexamethasone. The best screening test is the administration of 1 mg of dexamethasone at bedtime with measurement of plasma cortisol between 7 and 10 the next morning.[100] In normal subjects, cortisol levels are less than 5 mug/dl. Some patients, particularly the obese, may have false-positive responses, but false-negative responses occur only rarely. Definitive diagnosis of Cushing syndrome is made by the administration of 0.5 mg of dexamethasone every 6 hours for 2 days, with measurement of either plasma cortisol levels at the end of the second day (normal, <5 mug/dl) or the 24-hour cortisol excretory rate on the second day of dexamethasone suppression (normal, <10 mug/24 hr).[100]

Therapy for Cushing syndrome is usually directed at the specific cause. Thus, patients with adrenal carcinoma or adenoma or an ACTH-producing pituitary tumor are treated surgically. In some cases, patients with adrenal carcinoma have nonresectable lesions, and therefore surgery is combined with chemotherapy. Treatment of patients with bilateral hyperplasia but no evidence of an ACTH-producing tumor is controversial because the cause is often unknown. In some centers, bilateral adrenalectomy is the treatment of choice, while more commonly, therapy directed at the pituitary (either surgery or irradiation) is used.[100]

Treatment of the *cardiovascular abnormalities* associated with Cushing syndrome is directed at lowering blood pressure and correcting the hypokalemia if present. Caution should be exercised in treating the hypertension with potassium-losing diuretics because of the tendency for hypokalemia to develop in these patients. Thus, potassium-sparing diuretics or potassium supplements are often required. As in all clinical conditions in which hypokalemia may be present, cardiac glycosides should be used with caution in patients with Cushing syndrome.

The hypertension is often resistant to conventional antihypertensive programs. Fallo and coworkers reported that only 15 percent of their hypertensive patients with Cushing syndrome had control of blood pressure with conventional medications: diuretics, calcium antagonists, and ACE inhibitors either as single agents or in combination. In 12 patients who failed conventional therapy, treatment with ketoconazole, an adrenal enzyme inhibitor, normalized blood pressure in all but 1 subject. In that 1 subject cortisol levels were not decreased. Thus, specific therapy directed at lowering cortisol production appears to be more effective than conventional antihypertensive therapy is in controlling hypertension in patients with Cushing syndrome.[122]

Hyperaldosteronism (see also Chap. 28)

CLINICAL AND BIOCHEMICAL MANIFESTATIONS.

Aldosteronism is a syndrome associated with hypersecretion of aldosterone. Primary aldosteronism signifies that the stimulus for the excess aldosterone production resides within the adrenal. In secondary aldosteronism, the stimulus is of extraadrenal origin.

In patients with primary aldosteronism, which is most commonly due to an aldosterone-producing adrenal adenoma, hypertension, hypokalemia, and metabolic alkalosis are common.[100] [123] Polyuria may exist because of the hypokalemia, and glucose intolerance is increased in frequency. Muscle cramps secondary to the hypokalemia may be present, but little else distinguishes this type from other forms of hypertension. Laboratory studies confirm the presence of hypokalemic alkalosis with a low specific gravity of urine and normal levels of adrenal glucocorticoids. The incidence of primary aldosteronism is between 0.5 and 2 percent of the hypertensive population, and it occurs twice as frequently in females as in males, with the initial manifestation usually occurring between the ages of 30 and 50 years.[100]

CARDIOVASCULAR MANIFESTATIONS.

Many of the cardiovascular effects of aldosteronism are nonspecific and are related to aldosterone's effect on atrial pressure and potassium balance. Thus, T wave flattening or U wave prominence on the electrocardiogram and the presence of premature ventricular contractions and other arrhythmias as a result of hypokalemia are observed. Traditionally, it has been assumed that primary aldosteronism is not associated with significant cardiovascular complications. However, recent studies do not support this conclusion.[124] [125] [126] [127] [128] [129] Nishimura and colleagues identified cardiovascular complications in 34 percent of their patients, with 16 percent having strokes and 7 percent having renal insufficiency.[128] Halimi and Mimram reported that albuminuria was greater and more frequent in patients with primary aldosteronism than in those with essential hypertension matched for age, gender, and severity and duration of hypertension.[126] Finally, strokes occur in 11 to 16 percent of patients with glucocorticoid-remediable aldosteronism (see below) before the age of 30.[129] Thus, these data support the hypothesis that in hypertensive patients, the presence of hyperaldosteronism represents an independent cardiovascular risk factor.

DIAGNOSIS AND TREATMENT.

The diagnosis of primary aldosteronism is made by the presence of diastolic hypertension without edema, hypersecretion of aldosterone that fails to be appropriately suppressed during volume expansion, hyposecretion of renin, and hypokalemia with inappropriate urinary potassium loss during salt loading. The state of the renin-angiotensin system is often used to distinguish primary aldosteronism from other conditions that produce hypertension and hypokalemia. For example, hypertension

and hypokalemia may be part of the clinical picture of secondary aldosteronism that accompanies malignant or accelerated hypertension or is associated with renal artery stenosis. Secondary aldosteronism can be readily distinguished from primary aldosteronism by plasma renin activity, which is increased in the former and reduced in the latter. However, the combination of hypertension and low plasma renin activity does not necessarily mean primary aldosteronism. Between 15 and 30 percent of patients with essential hypertension have low renin levels, so-called low-renin essential hypertension.[123] The possibility of excess mineralocorticoid secretion has been extensively evaluated in these patients; however, no definitive evidence for such exists (see Chap. 28) .

Another entity that mimics primary aldosteronism is glucocorticoid-remediable aldosteronism (see also Chaps. 28 and 56) . This condition is an inherited hypertensive disorder with dysregulation of aldosterone secretion secondary to a gene mutation. The mutation is a fusion gene product between two genes coding for the enzymes responsible for the last step in the biosynthesis of aldosterone and cortisol, i.e., 11-beta-hydroxylase/aldosterone synthase. This chimeric enzyme is expressed in fasciculata cells, thereby leading to ACTH control of aldosterone synthase--a condition that normally does not occur. These patients can be distinguished by either genetic assessment or measurement of unique 18-hydroxycortisol steroids in the urine.[130]

The principal therapy for primary aldosteronism is surgical removal of the aldosterone-producing adenoma. In some cases, removal is not possible because of the excessive risk imposed by the general physical status of the patient, in which case spironolactone, which pharmacologically blocks the effects of aldosterone, is used long-term. This form of therapy may be of limited benefit in men because compliance is reduced by the undesirable side effects of gynecomastia and impotence, particularly when doses greater than 200 mg/d are required.[100]

In some patients, primary aldosteronism is due not to a solitary adenoma but to bilateral hyperplasia.[123] Although the clinical characteristics of these two conditions are similar, their responses to surgery are different. In both cases, hypokalemia is corrected, but patients with bilateral hyperplasia often do not exhibit a reduction in arterial pressure. Patients with bilateral hyperplasia are best treated with aldosterone receptor antagonists (e.g., spironolactone) and other antihypertensive agents. Thus, preoperative distinction between bilateral hyperplasia and an adrenal adenoma by adrenal venography or adrenal scanning is important.

Adrenal Insufficiency

Clinically, patients with adrenal insufficiency can be divided into four types[100] : (1) the most common, primary insufficiency (Addison disease); (2) secondary insufficiency caused by a lack of ACTH; (3) selective hypoaldosteronism; and (4) enzyme deficiency

(congenital adrenal hyperplasia).

Addison disease may occur at any age and affects both genders equally. It is commonly due to a destructive process involving both adrenal glands; this process is sometimes infectious, but most often it is autoimmune.[100] Nearly all patients with primary adrenal insufficiency have weakness, increased skin pigmentation, significant weight loss, anorexia, nausea, vomiting, and hypotension, particularly postural. As the disease progresses, serum levels of sodium, chloride, and bicarbonate are gradually reduced, and potassium levels are increased.

CARDIOVASCULAR MANIFESTATIONS.

The most common cardiovascular finding in adrenal insufficiency is arterial hypotension. In severe cases, blood pressure may be in the range of 80/50 mm Hg, with postural accentuation. Indeed, syncope occurs in a significant percentage of patients. In severe cases, heart size and peripheral pulses decrease. The most common electrocardiographic abnormalities are low or inverted T waves, sinus bradycardia, a prolonged QT_c interval, and low voltage. Conduction defects also occur, with first-degree block present in 20 percent of patients. Changes secondary to the hyperkalemia are not common, and cardiac failure is unusual.[131]

DIAGNOSIS AND TREATMENT.

Decreased response of the adrenal cortex to ACTH establishes the diagnosis of Addison disease. The best screening test is the administration of synthetic ACTH (cosyntropin) 0.25 mg intramuscularly or intravenously, with measurement of plasma cortisol levels 30 to 60 minutes later. Cortisol levels double or increase by 10 mug/dl in normal subjects. Definitive evaluation is by prolonged (usually 24-hour) infusion of ACTH with assessment of either plasma cortisol excretion of cortisol or both.[100]

It is possible to differentiate primary adrenal insufficiency from secondary adrenal insufficiency, isolated hypoaldosteronism, or congenital adrenal hyperplasia because one of the adrenal hormonal functions is normal in each of the latter three conditions.

An increasingly common form of hypoaldosteronism is that associated with *hyporeninism.* Most commonly, this syndrome is observed in older diabetic patients with a mild degree of renal impairment and hypertension; acidosis is also common. Usually, these patients have unexplained hyperkalemia. The cause is unknown but may be secondary to damage to the juxtaglomerular apparatus and/or reduced conversion of a renin precursor into the active enzyme. This clinical syndrome is particularly important in the presence of cardiovascular disease. Furthermore, commonly used drugs (beta blockers and calcium antagonists) can exacerbate this condition by further compromising aldosterone release.[132]

Treatment of adrenal insufficiency is accomplished by replacement of the deficient steroid. In adults with primary or secondary insufficiency, hydrocortisone 20 to 30 mg daily is administered in divided doses, usually two-thirds in the morning and one-third in

midafternoon. In patients with associated aldosterone deficiency, 9-alpha-fluorohydrocortisone 0.05 to 0.10 mg daily is given. During periods of significant stress (surgery, infection, or trauma), the glucocorticoid dose should be increased.

PHEOCHROMOCYTOMA (see also Chap. 28)

Effects of Catecholamines on the Cardiovascular System

The adrenal medulla and sympathetic nervous system are linked morphologically, biochemically, and physiologically and are often referred to as the sympathoadrenal system.[133] [134] In addition to their important effects on the cardiovascular system, cathecholamines also have significant metabolic effects consisting of stimulation of glycogenolysis and gluconeogenesis, that is, increasing the production of glucose from glycogen and amino acid precursors and stimulating lipolysis.

CLINICAL AND BIOCHEMICAL MANIFESTATIONS.

A pheochromocytoma is a catecholamine-producing tumor derived from chromaffin cells. Those arising from extraadrenal chromaffin cells are called nonadrenal pheochromocytomas or paraganglionomas. Rarely, these tumors occur in the heart or pericardium.[135] [136] Probably less than 0.1 percent of patients with hypertension have a pheochromocytoma. Although it is an uncommon disease, pheochromocytomas generate a great deal of interest, largely because of the significant morbidity and mortality associated with these tumors, with detection often resulting in cure. Pheochromocytomas are highly vascular tumors; less than 10 percent are malignant as indicated by local invasion or metastasis, but as with other endocrine tumors, malignancy cannot always be determined by microscopic appearance alone.

Although the vast majority of tumors occur sporadically, approximately 5 percent are inherited as an autosomal trait, by which they are often part of a pluriglandular neoplastic syndrome,[133] [134] which in addition to pheochromocytoma may consist of medullary carcinoma of the thyroid, parathyroidadenoma, and retinal or cerebellar hemangioblastomas. Most pheochromocytomas are solitary adrenal tumors, with 10 percent being bilateral and 10 percent nonadrenal. However, in the familial form of pheochromocytoma, nearly half of patients have bilateral adrenal tumors.

CARDIOVASCULAR MANIFESTATIONS.

Hypertension is the major cardiovascular manifestation of pheochromocytoma. The features that suggest pheochromocytoma in hypertensive patients are (1) paroxysmal attacks of any kind, (2) headaches, (3) excessive sweating, (4) signs of hypermetabolism, (5) orthostatic hypotension, and (6) unusual blood pressure elevation as a result of trauma or surgery.[133] [134] Many of the features are similar to those of hyperthyroidism. Although paroxysmal attacks are the hallmark of pheochromocytoma,

more than half the patients have fixed hypertension and nearly 10 percent are normotensive.

The lability of blood pressure in patients with pheochromocytoma has been suggested to be due not only to episodic discharge of catecholamines but also to a reduction in plasma volume, as well as impaired sympathetic reflexes. A number of observations suggest that chronic volume depletion is present.[137] For example, alpha adrenoceptor blockade or removal of the tumor produces severe hypotension, which is correctable by volume expansion.[133] Cardiac output has been reported to be normal, whereas the heart rate is increased and orthostatic hypotension is accompanied by decreased stroke volume and inadequate adjustments in peripheral resistance indicative of impaired peripheral vascular reflexes.[133] An occasional patient has markedly elevated central aortic pressure and severe systemic hypotension resulting from severe arterial vasoconstriction. Patients with pheochromocytoma may also have acute pulmonary edema.[138] Some patients with pheochromocytoma have hemodynamic features indistinguishable from those of essential hypertension. These results suggest that long-term exposure to high circulating levels of catecholamines may produce a different clinical picture than that observed after acute administration. These differences may be due to desensitization induced by chronic exposure to catecholamines.[137]

The electrocardiogram is abnormal in as many as 75 percent of patients with pheochromocytoma. Changes consist of T wave inversion, left ventricular hypertrophy, sinus tachycardia, and in some cases, other alterations in rhythm, such as frequent supraventricular ectopic beats or paroxysmal supraventricular tachycardia.[139] [140] An occasional patient has a short PR interval and a narrow QRS complex, which suggests that catecholamines are modifying the AV conduction system. When arterial pressure increases markedly, changes suggestive of myocardial damage are present, including transient ST segment elevations, marked diffuse T wave inversions, and depression of ST segments. These changes are usually transient, and the electrocardiographic pattern reverts to normal after removal of the tumor or pharmacological blockade.[134] However, the acute rise in blood pressure does not seem to be related to the development of complex arrhythmias. These hypertensive events are associated with a significant reduction in vagal tone. However, this finding is similar to what is observed in essential hypertension.[139] Some of the electrocardiographic abnormalities are presumably due to hypertensive heart disease or myocardial ischemia. However, a specific catecholamine-induced myocarditis and/or cardiomyopathy has also been suggested.[138] [141] [142] Interestingly, a patient with catecholamine-induced cardiomyopathy was treated with captopril, with resolution of the cardiomyopathy within 2 weeks.[143] In rats with pheochromocytoma, treatment with captopril also markedly attenuated the cardiomyopathy but did not modify contraction of isolated rings of the thoracic aorta in response to either epinephrine or angiotensin II.[144] The mechanism by which captopril produced these beneficial effects is unclear but could be related to inhibiting angiotensin II-induced cardiac fibrosis.[103]

The echocardiogram often shows left ventricular hypertrophy with normal left ventricular

systolic function but occasionally mimics hypertrophic obstructive cardiomyopathy.[140] During a hypertensive crisis the electrocardiogram may show systolic anterior involvement of the anterior mitral leaflet, paradoxical septal motion, and proximal excursion of the posterior wall.

Myocarditis.

Pathologically, the myocarditis consists of focal necrosis with infiltration of inflammatory cells, perivascular inflammation, and contraction band necrosis[133] [145] [146] (Fig. 64-8), finally resulting in fibrosis. In some studies, 50 percent of patients who died of pheochromocytoma had myocarditis, usually accompanied by left ventricular failure and pulmonary edema. Although coronary atherosclerosis is usually present, medial thickening is the most characteristic lesion of the coronary arteries. When norepinephrine is infused into the rabbit, sustained coronary

Figure 64-8 Left ventricular myocardium with acute myocarditis and contraction band necrosis in a patient with pheochromocytoma dying of catecholamine crisis. *A,* Diffuse infiltration by inflammatory cells through myocardium. *B,* Perivascular inflammation. *C,* Close-up of the inflammatory infiltrate. *D,* Contraction band necrosis of myocytes. Hematoxylin-eosin; original magnification ×20 (*A*), ×45 (*B*), ×540 (*C*), ×330 (*D*). (From McManus, BM, Fleury TA, Roberts WC: Fatal catecholamine crisis in pheochromocytoma: Curable cause of cardiac arrest. Am Heart J 102:930, 1981.)

Figure 64-9 Pheochromocytoma-induced cardiomyopathy. *Left,* Chest x-ray on admission. Cardiomegaly, right pleural effusion, and signs of congestive heart failure are present. *Right,* One month after removal of the tumor, no signs of congestion and a significant decrease in heart size are noted. (From Velasquez G, D'Souza VJ, Hackshaw BT, et al: Phaeochromocytoma and cardiomyopathy. Br J Radiol 57:89, 1984.)

vasoconstriction occurs and within 48 hours leads to histologically documented myocardial damage.[147] Occasionally, patients with pheochromocytoma have manifestations of cardiomyopathy that may be reversed when the tumor is removed (Fig. 64-9) . The myositis is not necessarily limited to the myocardium; it may also occur in skeletal muscle.[148]

DIAGNOSIS AND TREATMENT.

The diagnosis of pheochromocytoma is established by documenting increased urinary or plasma levels of catecholamines or one of their metabolites.[133] Three tests are commonly used: (1) total catecholamines, (2) vanillylmandelic acid, and (3) metanephrine. The last two are metabolites of catecholamine and were first used to screen for pheochromocytoma because they are present in greater quantities. When

reliably performed, these tests are probably equivalent in accuracy. The probability of pheochromocytoma being present in a hypertensive patient with a single normal urine level is less than 5 percent. It is most desirable to measure both the catecholamines and one of the two metabolites, preferably metanephrine, when screening for pheochromocytoma. If the blood pressure fluctuates, it is particularly important to collect the urine at a time when the pressure is elevated. Chromogranin A blood levels are another potential screening test for pheochromocytoma. Chromogranin A is a cosecretory product from neuroendocrine tumors and does not have a known biological effect. Reliability, sensitivity, and precision estimates in comparison to urine hormonal measurements have not yet been reported, however.[149] Specific pharmacological tests to screen for pheochromocytoma are of limited benefit, usually hazardous, and therefore warranted only in unusual circumstances. Clonidine has been proposed as a useful definitive test for pheochromocytoma, although it is necessary only in unusual cases. Catecholamine levels are suppressed in normal subjects via stimulation of central alpha adrenoceptors; after clonidine administration in patients with pheochromocytoma, however, catecholamine levels are not suppressed.[150] Unfortunately, profound and prolonged hypotension has been reported in some patients during the course of this test.

Once the diagnosis of pheochromocytoma is established, specific pharmacological blockade should be initiated.[133] Administration of phenoxybenzamine hydrochloride should be begun, with the initial dosage being 10 mg every 12 hours; the dose is then gradually increased every 2 to 3 days until arterial pressure is restored to normal. Alternatively, prazosin may be used. However, it should be noted that alpha adrenoceptor blockade may induce a decline in arterial pressure accompanied by serious postural hypotension, presumably because of the vasodilation occurring in the presence of hypovolemia. This hypotensive response can be prevented by adequate sodium intake; if the response is very striking, infusion of saline may be required. Adequate control of arterial pressure is essential before any arteriographic procedure, before initiating beta adrenoceptor blockade, and before surgery. Calcium antagonists may be useful both in treating the hypertension associated with pheochromocytoma and in reducing catecholamine production.

Beta adrenoceptor blockade is useful in patients with pheochromocytoma who have significant tachycardia, palpitations, and catecholamine-induced arrhythmias. However, beta blockade with a drug affecting $beta_2$ receptors must not be initiated prior to inadequate alpha blockade since severe *hypertension* may occur as a result of unopposed alpha-stimulating activity of the circulating catecholamines.

Definitive treatment is surgical removal of the tumor, usually after localization with computed tomography, arteriography, or scanning with a radioactive iodide derivative of guanethidine as the scanning agent.[151] [152] Scanning may be particularly important in localizing extraadrenal, e.g., thoracic, pheochromocytomas. Precise definition of the anatomical boundaries of this tumor is important preoperatively if surgery is to be successful.[153] In patients with inoperable lesions, long-term use of a combination of alpha and beta adrenoceptor blockers has been helpful. Drugs that inhibit the biosynthesis of catecholamines, such as alpha-methyltyrosine, and generalized chemotherapeutic agents have also been used in patients with malignant

pheochromocytoma.[154] Although rare, of particular importance to the cardiologist is the presence of a cardiac pheochromocytoma.[135] [136] [153]

PARATHYROID DISEASE

Disordered parathyroid secretion is associated with two cardiovascular disturbances: cardiac arrhythmias and hypertension. Changes in calcium metabolism, as well as a direct effect of parathyroid hormone (PTH) on the cardiovascular system, appear to be responsible.

CLINICAL AND BIOCHEMICAL MANIFESTATIONS.

PTH is a single-chain polypeptide of 84 amino acids. Its major biological effect is to increase mobilization of calcium into the extracellular fluid from a variety of tissues; this action is linked in a negative feedback loop with the serum unbound calcium concentration. Thus, an increase in serum calcium concentration reduces PTH release and vice versa.[155] PTH also increases urinary excretion of phosphate, augments bone resorption, and reduces the urinary excretion of calcium.

Primary hyperparathyroidism, the excess production of PTH, is usually secondary to a solitary parathyroid adenoma. Occasionally, generalized parathyroid hyperplasia exists, and infrequently, carcinoma of the parathyroid gland is found. The signs and symptoms of primary hyperparathyroidism are related to the direct effects of PTH on kidney or bone or those associated with the hypercalcemia. Nearly half the patients have signs and symptoms of renal dysfunction, such as polyuria, nocturia, renal stones, and in severe cases, nephrocalcinosis and renal failure.

Cardiac hypertrophy is found with increased frequency in patients with hyperparathyroidism, even in the absence of hypertension. In one study, 5 of 18 patients with hypertrophic cardiomyopathy had raised serum PTH levels but normal serum calcium levels. In contrast, left ventricular hypertrophy did not occur in 6 patients with hypercalcemia alone.[155]

Cardiovascular Manifestations of Parathyroid Diseases

CARDIAC EFFECTS.

Although most of the effects of PTH on the heart are probably secondary to a change in extracellular calcium, PTH also has direct effects on the heart that result in an increased beating rate of isolated heart cells and positive inotropic action.[156] [157] [158] [159] [160] These effects are probably mediated by PTH binding to specific receptors, which leads to increased entry of calcium into cardiac cells, and by PTH increasing the release of endogenous myocardial norepinephrine. The direct effect of PTH may be deleterious

Figure 64-10 Heart showing the distribution of calcific deposits in the tricuspid and mitral valve annuli and at the bases of both pulmonic and aortic valve cusps in a 43-year-old woman with hypercalcemia secondary to primary hyperparathyroidism. (From Roberts WC, Waller BF: Effect of chronic hypercalcemia on the heart: An analysis of 18 necropsy patients. Am J Med 71:371, 1981.)

because it causes necrosis of rat myocytes and may be directly responsible for the increased accumulation of calcium in dystrophic muscles and for the heart damage found in uremia. On the other hand, hypoparathyroidism may cause a dilated cardiomyopathy, presumably secondary to the hypocalcemia.[161] [162] However, because longstanding hypocalcemia does not necessarily produce left ventricular dysfunction,[163] hypomagnesemia and reduced circulating PTH may also be involved. PTH also has a direct effect on vascular smooth muscle and causes vasodilation.

Chronic hypercalcemia from a variety of causes is associated with increased deposition of calcium in the fibrous skeleton of the heart and valvular cusps, as well as in coronary arteries and myocardial fibers[164] (Fig. 64-10) . Chronic hypercalcemia may also be a risk factor for accelerated coronary atherosclerosis.[162]

The plateau of the action potential of cardiac fibers is prolonged by low and shortened by high extracellular calcium concentrations (see Chap. 22) . The changes in duration of the action potential are accompanied by corresponding changes in duration of the refractory period, the ST segment, and the QT interval. Thus, the major electrocardiographic change in hypercalcemia is shortening of the QT interval. Less frequently, disorders of intraventricular conduction have been reported with shortening of the PR interval. Complete heart block occurs only rarely.

Hypocalcemia produces the opposite effect on the electrocardiogram: prolongation of the QT interval and nonspecific ST and T wave changes. Normal contractile function of cardiac muscle requires calcium, and heart failure has been reported in patients with chronic hypocalcemia secondary to hypoparathyroidism.[165]

HYPERTENSION.

Hypercalcemic patients detected by routine serum calcium screening techniques have higher arterial pressure than do matched normocalcemic subjects.[162] Yet in patients with hyperparathyroidism, the level of serum calcium is similar in those who are normotensive and those who have hypertension, which suggests that hypercalcemia per se is not the dominant cause of the hypertension. Thus, the pathophysiology of the hypertension is uncertain and may be multifactorial.[166] [167] [168] Hypercalcemia produces nephrocalcinosis, which may lead to renal failure and hypertension. Thus, reversal of hypertension after successful parathyroid surgery is more likely to occur when renal function is normal. Increased serum calcium also increases myocardial contractility, peripheral resistance, and release of or vascular sensitivity to vasoconstrictor agents

such as angiotensin II and norepinephrine. Although hypercalcemia can increase cardiac contractility and arterial pressure acutely, it is unlikely that this action produces a significant alteration in cardiac output or performance on a long-term basis in the absence of PTH. Thus, elevated peripheral resistance is the most likely cause of the hypertension associated with hyperparathyroidism. Although PTH itself is a vasodilator, except subacutely,[166] characteristic changes in other hormones that occur in hyperparathyroidism may contribute to the hypertension. For example, PTH increases 1-alpha-hydroxylation of 25(OH) vitamin D, thereby leading to higher levels of $1,25(OH)_2$ vitamin D. $1,25(OH)_2$ vitamin D enhances vascular reactivity,[169] and the higher levels in hyperparathyroidism could contribute to hypertension. Finally, a circulating hypertensive factor produced in the parathyroid gland has been identified and termed "parathyroid hypertensive factor" (PHF).[170] [171] PHF is distinct from PTH and has the ability to increase the intracellular calcium concentration in vascular smooth muscle cells primarily via opening L-type calcium channels.[172] PHF was first found in the parathyroid glands of spontaneously hypertensive rats,[171] but it has since been found in the circulation of essential hypertensives, especially those who are salt sensitive and have low renin levels.[173] Elevated levels have been reported to predict a beneficial response to calcium channel blockers.[174] However, further support for the existence and physiological role of PHF is required.

DIAGNOSIS AND TREATMENT

An elevated or even a normal concentration of PTH in the presence of hypercalcemia establishes the diagnosis of hyperparathyroidism; many patients with this condition manifest hypercalcemia for the first time after starting thiazide therapy for the associated hypertension. Treatment consists of surgical removal of the parathyroid tumor or hyperplastic glands.

Patients with hypertension should have a determination of serum calcium levels before therapy is begun. If thiazide diuretics are used in treatment, serum calcium levels should be determined every 6 months. If thiazide-induced hypercalcemia occurs, serum calcium should be determined for 2 to 3 months after discontinuation of thiazide treatment. Persistence of the hypercalcemia suggests that the patient has primary hyperparathyroidism.[165]

Patients with hypoparathyroidism and hypocalcemia are usually treated with calcium supplementation and vitamin D or one of its metabolites such as calcitriol (1,25-dihydroxyvitamin D).

GONADAL HORMONES AND THE CARDIOVASCULAR SYSTEM

Estrogen (see also Chap. 58)

The past several years have witnessed an explosion in the investigation of estrogen's effects on the cardiovascular system. It has long been observed that premenopausal women enjoy protection against cardiovascular disease and that this protection is lost at menopause. Based on this observation, it has been hypothesized that it is the loss of

estradiol with menopause that is responsible for the loss of cardiovascular protection. It has therefore been postulated that giving postmenopausal women estrogen as hormone replacement therapy would reduce cardiovascular risk. The role of estrogen in cardiovascular protection remains controversial.

Several mechanisms that involve different systems have been proposed to explain the cardiovascular benefit induced by estrogen.[175] Some of these mechanisms include alterations in lipid metabolism and coagulation, as well as direct vascular effects. Oral estrogen increases HDL and lowers LDL cholesterol. This potential benefit appears to account for only 30 percent of the benefit seen. More recently, the effect of estrogen on coagulation has been investigated, and it has been shown that estrogen lowers levels of plasminogen activator inhibitor type I, thereby leading to more fibrinolysis. Estrogen causes vasodilation of both peripheral vessels and coronary arteries. Most of this effect appears to be mediated by the vascular endothelium and release of nitric oxide.

Observational studies have demonstrated a decrease in cardiac risk factors in postmenopausal women taking estrogen. The Rancho Bernado study of 1057 postmenopausal women showed that estrogen users were more likely than nonusers to have lower weight, diastolic blood pressure, fasting insulin, and total cholesterol, with higher HDL cholesterol.[176] A similar benefit in altering cardiovascular risk factors was seen in the Atherosclerosis Risk in Community study of 4958 postmenopausal women.[177]

Furthermore, observational studies have demonstrated a reduction in coronary heart disease in postmenopausal women who use estrogen. The Nurses Health Study of 48,470 postmenopausal women monitored for up to 10 years demonstrated that the use of estrogen was associated with a relative risk of 0.56 for major coronary disease and 0.72 for death from cardiovascular disease.[178]

Despite the mechanistic and epidemiological data supporting a cardiovascular benefit of estrogen, the only published randomized prospective study showed no benefit on coronary heart disease prevention. The Heart and Estrogen/Progestin Replacement Study (HERS) studied 2763 postmenopausal women with a prior history of coronary heart disease in a prospective secondary prevention trial. With an average follow-up of 4 years, no reduction in cardiovascular events was seen in the group of women receiving estrogen (0.625 mg conjugated equine estrogen) given in combination with medroxyprogesterone (2.5 mg).[179] Whether estrogen is beneficial as primary prevention should be answered by the ongoing Women's Health Initiative.[180] In addition, whether other estrogens or combinations with other progestins will provide a benefit remains to be determined.

Selective Estrogen Receptor Modulators

Because concern about an increased risk for breast cancer is a major deterrent to

estrogen use, the class of drugs termed selective estrogen receptor modulators (SERMs) has been developed. These drugs do not bind well to the breast or uterine estrogen receptor. The effects that they will have on cardiovascular disease are not known as yet. The first drug of this class in common use was tamoxifen, which has been used primarily in the treatment of breast cancer. Several studies of tamoxifen in the treatment of breast cancer have shown a decrease in either fatal myocardial infarction or hospital admissions for cardiac disease.[181] [182] Caution must be used in viewing these results since the studies were not designed to look at heart disease as a primary endpoint. Tamoxifen has been shown to lower LDL cholesterol as a potential mechanism for its cardiovascular benefit.[183] The only other SERM now approved for use is raloxifene, which is indicated for the prevention and treatment for osteoporosis. Raloxifene lowers LDL cholesterol without increasing HDL cholesterol.[184] Whether raloxifene will have any benefit on cardiovascular morbidity or mortality is currently under investigation.

Oral Contraceptives

The literature on the association between oral contraceptive use and coronary heart disease is controversial. The controversy is due in large part to the decreasing estrogen content in oral contraceptives over the past 40 years, as well as the incorporation of varying progestins with different androgenic potencies. The changing spectrum of oral contraceptive composition also makes it difficult to extend data based on earlier agents to today's preparations. Several studies have shown an increased risk of myocardial infarction in oral contraceptive users.[185] However, prior oral contraceptive use does not confer an increased risk for cardiovascular disease. Studies of the effect of newer contraceptive agents are not available.[186]

BLOOD PRESSURE EFFECTS OF ORAL CONTRACEPTIVES AND HORMONAL REPLACEMENT THERAPY

Oral contraceptive use has been associated with a rise in blood pressure since their widespread use in the 1960s. When blood pressure rises, it usually remains within the normotensive range; rarely, it increases into the hypertensive (140/90 mm Hg) range. Even with the earlier-generation oral contraceptives, which used a higher estrogen dose and varied progestins, data were conflicting regarding whether whether blood pressure rises.[187] [188] [189] Differences in responses to oral contraceptives may depend on the quantity of estrogen, the type of progestin, and the race and genetic background of the user. Studies of the new generation of oral contraceptives, which contain no greater than 35 mug ethinyl estradiol and less androgenic progestins, are more limited. Available data on desogestrel-containing oral contraceptives include a multicenter trial of more than 1600 women monitored over 23,000 cycles. No significant change in mean blood pressure over a 2-year period of use was observed, and only a 0.3 percent incidence of hypertension was noted.[190] Other studies of this agent have revealed similar results.[191] [192] Although activation of the renin-angiotensin-aldosterone axis occurs in oral contraceptive users, the degree of activation may be greater in those who remain normotensive than those who became hypertensive. Thus, the etiology of oral contraceptive-induced hypertension remains unclear.

The belief that estrogens used for hormone replacement therapy induce hypertension is

largely based on the older oral contraceptive literature. In fact, the use of estrogen in many trials is associated with no change in blood pressure. It is likely that estrogens differ in their effect on blood pressure. Estrone and estradiol, natural estrogens, may actually lead to a fall in blood pressure.

ANDROGENS AND THE HEART.

Similar to the view that women are protected against cardiovascular disease because of estrogen, it has been assumed that the increased incidence of cardiovascular disease in men is in part related to testosterone levels. However, studies designed to examine this link, although limited in number and size, have instead suggested that testosterone has a neutral or perhaps even beneficial effect on cardiovascular risk in men.

Observational studies have failed to show a positive relationship between testosterone levels and cardiovascular disease in men. Several studies of over 3000 men in different countries have shown no relationship between baseline testosterone levels and the future development of cardiovascular disease in men.[193] [194] Since these studies are cross-sectional, it is possible that the lower testosterone levels are a consequence of the coronary heart disease, not a cause.

Unfortunately, at this time, few intervention studies are available to help determine the cause-and-effect relationship. In a study of 62 men with a history of angina, men were randomized to receive placebo or oral testosterone. Of note, the serum testosterone levels of these men were normal, but significantly lower than controls at baseline. The group that received testosterone had a significant reduction in anginal symptoms and improvement in ST segment changes on electrocardiographic and Holter monitoring. [195] A more recent study evaluated the effect of acute intravenous testosterone on 14 men with a history of angina and angiographically proven coronary artery disease and low serum testosterone levels. In this study, the time to ST segment depression on exercise tolerance tests was prolonged by 20 percent in men receiving testosterone versus placebo.[196]

CARDIOVASCULAR CONSEQUENCES OF OBESITY

The prevalence of obesity is increasing in many developing countries and in the United States. Estimates based on the

National Health and Nutritional Examination Survey III study indicate that as of 1994, 33 percent of the U.S. population was obese,[197] and this percentage is predicted to steadily increase. Obesity is associated with higher levels of blood pressure, dyslipidemia, and type II diabetes mellitus, all contributors to cardiovascular disease. However, in addition, obesity appears to be an independent predictor of coronary artery disease in both men and women.[198] [199] Recent studies indicate that it is not just obesity that is associated with increased cardiovascular disease, but that upper body obesity

further increases the risk.[200]

Evidence of circulatory dysfunction in the massively obese, in association with cardiac enlargement during life and at autopsy, was first described by Smith and Willius in 1933.[201] Cardiac changes in obesity may often be related to concomitant hypertension. The elevated leptin levels seen in obesity may be mediators of the hypertensive process.[201A] Left ventricular hypertrophy also may be present in the absence of systemic hypertension.[202] Right ventricular hypertrophy may also be seen, most commonly as a result of obesity-related obstructive sleep apnea and pulmonary hypertension. Much of the cardiovascular risk associated with obesity is probably associated with the concomitant insulin resistance (see Chap. 63) .

TREATMENT OF THE CARDIOVASCULAR MANIFESTATIONS OF OBESITY.

Although weight reduction would seem to be the most beneficial treatment of cardiovascular disease in obesity, conclusive longitudinal studies are lacking. However, with weight reduction often comes improvement in the hypertension, dyslipidemia, and insulin resistance seen in obesity. Weight reduction is also associated with regression of left ventricular hypertrophy independent of blood pressure changes,[203] as well as shortening of the prolonged QT_c seen in obese patients.[204]

CARDIAC COMPLICATIONS OF WEIGHT LOSS.

Rapid weight loss has been associated with cardiac arrhythmias and sudden death.[205] In some cases, these complications are probably secondary to inadequate electrolyte supplementation. In others, they may be related to a reduction in myocardial protein and cardiac atrophy. Although initially associated with a liquid protein diet, sudden death may occur under any circumstance associated with rapid weight loss.[206]

MALNUTRITION

Malnutrition, particularly protein-calorie deficiency, is prevalent in many underdeveloped areas of the world. However, in recent years, it has also become a concern in developed countries in individuals who have chronic diseases, in whom it exists as a result of both anorexia and hypermetabolism, and in otherwise healthy individuals with anorexia nervosa.

CARDIAC CHANGES IN MALNUTRITION.

The circulatory status of patients with severe nutritional depletion and electrolyte imbalance is precarious: Cardiac output, systolic pressure, and pulse pressure are abnormally low, and massive, generalized edema may be present; the PR interval may be shortened. Loss of subcutaneous fat may be observed, as well as general wasting and atrophy of most organs, including the heart, which is thin walled, pale, and flabby on gross examination. Histological study reveals atrophy of muscle fibers. Treatment of a dehydrated or severely anemic patient with protein-calorie malnutrition involves

correction of hematological, fluid, and electrolyte imbalance. Congestive heart failure can be avoided if care is taken to avoid overloading with sodium, water, or blood.

ANOREXIA NERVOSA.

This common psychiatric condition, seen particularly in young women, is associated with significant cardiac morbidity and mortality. Many of the cardiac changes relate to protein-calorie malnutrition, including destruction of cardiac myofibrils.[207] Echocardiographic findings include small ventricular chamber size and mass, even when corrected for weight, reduced cardiac index, and abnormalities in mitral valve function.[208] Hypocalcemia and hypomagnesemia may contribute to arrhythmias, heart failure, and sudden death since bradycardia thought to be secondary to increased vagal tone is common. QT_c prolongation can also be seen and may indicate a predisposition to arrhythmias and sudden death. Predictors of QT_c prolongation are weight, body mass index, and rapidity of weight loss even in the absence of electrolyte disturbances.[209]

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Chapter 65 - Pregnancy and Cardiovascular Disease

URI ELKAYAM

CARDIOVASCULAR PHYSIOLOGY DURING PREGNANCY AND THE PUERPERIUM

PREVALENCE.

Although heart disease is limited to only 0.5 to 1.0 percent of pregnant women, it remains an important cause of maternal morbidity and even mortality and has a significant effect on fetal outcome.[1] [2] [3] Pregnancy and the peripartum period are associated with important cardiocirculatory changes[4] that can lead to marked clinical deterioration in the woman with heart disease. Hemodynamic changes occurring during pregnancy are summarized in Table 65-1 .

BLOOD VOLUME.

Blood volume increases substantially during pregnancy, starting as early as the sixth week and rising rapidly until midpregnancy, when the rise continues but at a much slower rate[4] (Fig. 65-1) . The degree of maximum volume expansion varies considerably in the individual patient (20 to 100 percent) and averages 50 percent. This

increase is reported to correlate with fetal weight, placental mass, weight of the products of conception, and maternal and neonatal weight.[4] A higher increment in blood volume is reported in multigravidas and in women with multiple pregnancies.[3]

Because increase in plasma volume is more rapid than increase in red blood cell mass (see Fig. 65-1) , hemoglobin concentration falls during pregnancy gradually until week 30, causing the "physiological anemia of pregnancy" with hematocrit levels that can be as low as 33 to 38 percent, a condition that can be partially corrected with iron therapy.[4] Changes in blood volume during pregnancy are attributable to estrogen-mediated stimulation of the renin-aldosterone system,[5] [6] which results in sodium and water retention. Changes in other hormones, including deoxycorticosterone, prostaglandins, estrogen, prolactin, placental lactogen, growth hormone, adrenocorticotropic hormone, and atrial natriuretic peptides, may also be involved in water retention during pregnancy.[4] [7]

CARDIAC OUTPUT, STROKE VOLUME, AND HEART RATE.

Cardiac output during pregnancy is estimated to increase by approximately 50 percent.[4] It begins to rise around the fifth week and increases rapidly until the 24th week, when it plateaus or continues to rise slightly[4] [8] [9] (Fig. 65-2 , Table 65-1) . During the third trimester, body position can substantially influence cardiac output, which increases in the lateral position and declines in the supine position, owing to caval compression by the gravid uterus and decreased venous return to the heart. The increase in cardiac output early in pregnancy is predominantly due to augmentation in stroke volume, whereas in the third trimester it is largely due to an accelerated heart rate and stroke volume does not change or even declines as a result of caval compression (see Fig. 65-2) . Increase in cardiac output seems to be enhanced in subsequent pregnancies.[9]

Heart rate peaks during the third trimester with an average increase of 10 to 20 beats/min[4] [9] (see Fig. 65-2) , although on occasion it may be markedly faster. Pregnancy with multiple fetuses is associated with an even higher heart rate.

BLOOD PRESSURE AND SYSTEMIC VASCULAR RESISTANCE.

Systemic arterial pressure begins to fall during the first trimester, reaches a nadir in mid pregnancy, and returns toward pregestational levels before term[4] [9] (see Table 65-1) . Because diastolic blood pressure decreases substantially more than systolic pressure, the pulse pressure widens.[4] Reduction in blood pressure is caused by a decline in systemic vascular resistance due to reduced vascular tone,[10] probably mediated by (1) gestational hormonal activity, increased levels of circulating prostaglandins, and atrial natriuretic peptides,[4] [11] as well as endothelial nitric oxide[12] ; (2) increased heat production by the developing fetus; and (3) the creation of low-resistance circulation in the pregnant uterus.

SUPINE HYPOTENSIVE SYNDROME OF PREGNANCY.

The supine hypotensive or the uterocaval syndrome of

TABLE 65-1 -- CARDIOCIRCULATORY CHANGES DURING NORMAL PREGNANCY

PARAMETER	CHANGES AT VARIOUS TIMES (WEEKS)					
	5	12	20	24	32	38
Heart rate						
Systolic blood pressure						
Diastolic blood pressure						
Stroke volume						
Cardiac output						
Systemic vascular resistance						
Left ventricular ejection fraction						

,
5%;

, 6-10%;

, 11-15%;

, 16-20%;

, 21-30%;

, >30%;

>40%.

Figure 65-1 Changes in plasma volume, erythrocyte volume, and hematocrit during pregnancy. Increase in plasma volume is more rapid than increase in erythrocyte volume, causing the "physiological anemia of pregnancy," which can be partially corrected with iron supplements. *(From Pitkin RM: Nutritional support in obstetrics and gynecology. Clin Obstet Gynecol 19:489, 1976.)*

pregnancy occurs with significant decreases in heart rate and blood pressure in up to 11 percent of pregnant women.[4] These hemodynamic changes are associated with weakness, lightheadedness, nausea, dizziness, and even syncope and are explained by acute occlusion of the inferior vena cava by the enlarged uterus (Fig. 65-3) (Figure Not Available) . When the supine position is abandoned, these hemodynamic effects and symptoms usually are promptly relieved.

HEMODYNAMIC CHANGES DURING LABOR AND DELIVERY.

Hemodynamics are altered substantially during labor and delivery secondary to anxiety, pain, and uterine contractions.[4] Oxygen consumption increases threefold; and cardiac output rises progressively during labor owing to increase in both stroke volume and heart rate, and it is higher in the lateral position. Both systolic and diastolic blood pressures increase markedly during contractions, with greater augmentation during the second stage.[4] [13] Hemodynamic changes during labor and delivery are greatly influenced by the form of anesthesia and analgesia.[4] [13] Reduction of pain and apprehension by local, caudal, and epidural anesthesia may limit hemodynamic changes and rise in oxygen consumption.[4] [13]

HEMODYNAMIC EFFECTS OF CESAREAN SECTION.

To avoid the hemodynamic changes associated with vaginal

Figure 65-2 Percent changes of heart rate, stroke volume, and cardiac output measured in the lateral position throughout pregnancy compared with prepregnancy values. *(Modified from Robson SC, Hunter S, Boys RJ, Dunlop W: Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol 256:H1060-H1065, 1989.)*

delivery, cesarean section is frequently recommended for women with cardiovascular disease. However, this form of delivery can also be associated with considerable hemodynamic fluctuations related largely to intubation, drugs used for anesthesia and analgesia,[14] larger extent of blood loss, the relief of caval compression, extubation, and postoperative awakening.[3]

HEMODYNAMIC CHANGES POST PARTUM.

A temporary increase in venous return may occur immediately after delivery due to relief of caval compression and, in addition, blood shifting from the contracting uterus into the systemic circulation (autotransfusion).[14] This change in effective blood volume occurs despite blood loss during delivery and can result in a substantial rise in ventricular filling pressure, stroke volume, and cardiac output and may lead to clinical deterioration. Both heart rate and cardiac output return to prelabor values by 1 hour after delivery and mean blood pressure and stroke volume by 24 hours after delivery.[4] [13] Hemodynamic adaptation to pregnancy persists post partum and gradually returns to prepregnancy values within 12 to 24 weeks after delivery.[4]

Figure 65-3 (Figure Not Available) Venocaval compression of the inferior vena cava and abdominal aorta by the gravid uterus can lead to reduced venous return and thus to decreased cardiac output. *(From Lee W, Shah PK, Amin DK, et al: Hemodynamic monitoring of cardiac patients during pregnancy. In Elkayam U, Gleicher N: Cardiac Problems in Pregnancy. 2nd ed. New York, Alan R. Liss, 1990, p 61.)*

CARDIOVASCULAR EVALUATION DURING PREGNANCY

History and Physical Examination

Normal pregnancy is often accompanied by symptoms of fatigue, decreased exercise capacity, hyperventilation, dyspnea, palpitations, lightheadedness, and even syncope (Table 65-2) .[15] [16] In addition, augmentation of jugular venous pulsation due to increased blood volume, and leg edema (often observed in late pregnancy), could lead to an erroneous diagnosis of heart failure or overestimation of its severity. Systemic arterial pulses are full and collapsing and are similar to those palpated in patients with aortic regurgitation or hyperthyroidism. A left ventricular impulse is easily detected in most women in late pregnancy and is hyperactive and brisk. Right ventricular heave is usually present during the second and third trimester, and the pulmonary trunk and pulmonic valve closure are often palpable. This group of findings may result in difficulty in assessing the presence and/or severity of pulmonary hypertension.

CARDIAC AUSCULTATION (see Chap. 4) .

Especially after the first trimester, auscultation often reveals an increased first heart sound (S_1) with exaggerated splitting that may be misinterpreted as a fourth heart sound (S_4) or as a systolic click.[15] The second heart sound (S_2) is often increased in late pregnancy and may exhibit persistent splitting when the patient is examined in the lateral position. These changes in S_2 may be interpreted as signs of pulmonary hypertension (loud P_2) or atrial septal defect (systolic murmur and splitting of S_2). Auscultation of the third heart sound (S_3) and S_4 is uncommon in normal pregnancy.

Innocent Systolic Murmurs.

These can be heard in most pregnant women and are the result of the hyperkinetic circulation of pregnancy. Murmurs are usually midsystolic and soft, are heard best at the lower left sternal edge and over the pulmonic area, and radiate to the suprasternal notch and more to the left than to the right side of the neck.[15] Not uncommonly the benign murmur of pregnancy

TABLE 65-2 -- CARDIAC SYMPTOMS AND FINDINGS DURING NORMAL PREGNANCY

SYMPTOMS
Decreased exercise capacity
Tiredness
Dyspnea

Orthopnea
Palpitations
Lightheadedness
Syncope
PHYSICAL FINDINGS
Inspection
Hyperventilation
Peripheral edema
Distended neck veins with prominent a and v waves and brisk x and y descents
Capillary pulsation
Precordial Palpation
Brisk, diffuse, and displaced left ventricular impulse
Palpable right ventricular impulse
Palpable pulmonary trunk impulse
Auscultation
Pulmonary basilary rales
Increased first heart sound with exaggerated splitting
Exaggerated splitting of second heart sound
Midsystolic ejection-type murmurs at the lower left sternal edge and over the pulmonary area radiating to suprasternal notch and more to the left than right side of neck
Continuous murmurs (cervical venous hum, mammary souffle)
Diastolic murmurs (rare)

TABLE 65-3 -- ELECTROCARDIOGRAPHIC FINDINGS DURING NORMAL PREGNANCY

QRS axis deviation
Small Q wave and inverted P wave in lead III (abolished by inspiration)
ST segment and T wave changes (ritodrine tocolysis, cesarean section)
Frequent sinus tachycardia
Higher incidence of arrhythmias
Increase R/S ratio in leads V_2 and V_1

may be louder or longer and may sound like those associated with atrial septal defect or stenosis of one of the semilunar valves. In such cases an echocardiographic and

Doppler evaluation is warranted to rule out an abnormal cardiac condition. Two benign continuous murmurs that may be heard during gestation are the cervical venous hum and mammary souffle. The venous hum is usually heard maximally over the right supraclavicular fossa but can radiate to the contralateral area and sometimes to the area below the clavicle. The mammary souffle may be either systolic or continuous, is heard over the breast late in gestation or in the lactating woman, and is caused by increased flow in the mammary vessels. Characteristically, the murmur decreases or vanishes when pressure is applied to the stethoscope or when the patient moves to the upright position.[15] Diastolic murmurs may be heard in normal pregnant women due to increased blood flow through the atrioventricular valve.[15] Such a finding, however, is infrequent in the healthy pregnant woman and therefore requires careful diagnostic work-up to rule out organic disease.

Laboratory Examinations

ELECTROCARDIOGRAPHY (see Chap. 5) .

In normal pregnancy, the QRS axis may shift to either the left or the right, but it usually stays within normal limits[15] (Table 65-3) . A small Q wave and an inverted P wave in lead III that vary with respiration as well as a greater r wave amplitude in lead V_2 may be present. A high incidence of ST segment depression mimicking myocardial ischemia but not associated with wall motion abnormalities has been described between induction of anesthesia and the end of surgery in patients undergoing cesarean section.[17] [18] Increased susceptibility to arrhythmias during pregnancy is manifested by the frequent finding of sinus tachycardia and atrial and/or ventricular premature beats.[16] There is an increased incidence of paroxysmal supraventricular tachycardia during normal pregnancy,[19] and several cases of ventricular tachycardia have been reported in healthy women.[20]

CHEST RADIOGRAPHY (see Chap. 8) .

Although the radiation dose associated with a routine chest radiograph is minimal, because of the potential for adverse biological effects from any amount of radiation the pelvic area should be shielded by protective lead material[21] (Table 65-4) .

Changes seen on chest films in normal pregnancy may simulate cardiac disease and should be interpreted with caution.[22] Straightening of the left upper cardiac border because of prominence of the pulmonary conus is often seen. The heart may seem enlarged because of its horizontal positioning secondary to the elevated diaphragm. In addition, an increase in lung markings may simulate a pattern of flow redistribution seen with increased pulmonary venous pressure. Pleural effusion is often found early post partum. It is usually small and resorbs 1 to 2 weeks after delivery.[15]

DOPPLER ECHOCARDIOGRAPHY (see Chap. 7) .

Gestational use of both maternal and fetal cardiac ultrasound is considered safe.[23] [23A] Transesophageal echocardiography has been increasingly used in pregnancy and

seems to be well tolerated by both mother and fetus[24] (Table 65-5) .

TABLE 65-4 -- CHEST RADIOGRAPHIC FINDINGS DURING NORMAL PREGNANCY

Straightening of the left upper cardiac border
Horizontal position of the heart
Increased lung marking
Small plural effusion in early postpartum period

TABLE 65-5 -- DOPPLER AND ECHOCARDIOGRAPHIC FINDINGS DURING NORMAL PREGNANCY

Slightly increased systolic and diastolic left ventricular dimensions (when patient examined in the lateral position)
Unchanged or slightly improved left ventricular systolic function
Moderate increase in size of right atrium, right ventricle, and left atrium
Progressive dilation of pulmonary, tricuspid, and mitral valve annuli
Functional pulmonary, tricuspid, and mitral regurgitation
Small pericardial effusion

Pericardial effusion, usually small or minimal, has been noted in normal pregnant women late in pregnancy.[25] There is a progressive increase in all cardiac chamber dimensions with an approximately 20 percent increase in the size of the right atrium and the right ventricle, 12 percent in left atrial size, and 6 percent in left ventricular size.[26] [27] Post parturm these changes gradually return toward baseline but may remain different from prepregnancy values for several months.[9] In addition, there is early and progressive dilatation of mitral, tricuspid, and pulmonary annuli, which is associated with increase in valvular regurgitation.[28]

STRESS TESTING (see Chap. 6) .

An exercise test using bicycle ergometry or a treadmill can be carried out during pregnancy to help establish the diagnosis of ischemic heart disease and to assess functional capacity and cardiac reserve.[29] The safety of such testing in pregnancy has not been fully established. Because fetal bradycardia has been reported with maximal but not with submaximal exercise,[29] [30] a low-level exercise protocol allowing heart rate increase to 70 percent of maximal predicted heart rate with fetal monitoring is recommended when stress testing is indicated.[15]

RADIATION.

Exposure of the embryo to irradiation during the first 10 days post conception would most likely have either no effect or lead to resorption.[31] Irradiation during organ formation (days 10-50) may cause a teratogenic effect, whereas after completion of organogenesis, it may cause intrauterine growth retardation, central nervous system abnormalities, and possible increased incidence of childhood cancer or leukemia. Current recommendations related to intrauterine radiation exposure are

Less than 5 rads--patient can be reassured of very low likelihood of risk.

Five to 10 rads--patient should be counseled regarding low risk of problems.

Ten to 15 rads during first 6 weeks--individual considerations for termination of pregnancy should be made.

More than 15 rads--termination of pregnancy recommended.

Routine chest radiography is associated with radiation of 20 mrad to the chest. Standard fluoroscopy could deliver 1 to 2 rads/min to the chest and high level fluoroscopy or cine as much as 5 to 10 rads/min. The amount of radiation scattered to the uterus and absorbed by the embryo is less than 5 percent of radiation absorbed by the directly radiated tissue. Direct irradiation to the fetus should be avoided and can be prevented by covering the patient with a lead apron during radiographic procedures. The use of a lead apron, however, is of little help in reducing fetal irradiation due to Compton-scattered photons.[31]

Radiation to the fetus from nuclear medicine procedures is mainly due to distribution of radiopharmaceuticals to the bladder or the placenta or directly across the placental barrier. The expected radiation with thallium-201 or technetium-99m-labeled sestamibi diagnostic procedures is less than 1 rad per examination. Cardiac function studies with technetium-99m-labeled red blood cells is associated with fetal radiation of 1 to 2 rads, peripheral contrast radiographic venography of 0.5 rad or less, and pulmonary scintigraphy with technetium-macroaggregated albumin of 0.05 rad or less.[31]

MAGNETIC RESONANCE IMAGING (see Chap. 10) .

Although magnetic resonance imaging poses no known risks to the fetus, experience with this technique is limited and its safety has not been fully established.[32] Currently, the U.S. Food and Drug Administration recommends prudence in using magnetic resonance imaging during pregnancy.[32] This technique should therefore be used only when evaluation cannot be delayed until after pregnancy, and if possible after the first trimester.

PULMONARY ARTERY CATHETERIZATION.

Hemodynamic monitoring with the aid of a pulmonary artery catheter can be of great help in managing patients at high risk during pregnancy, labor, delivery, and the postpartum period.[33] The ability to insert and position the flotation catheter with pressure monitoring without the need for fluoroscopy makes it particularly attractive for use during pregnancy. Hemodynamic monitoring is recommended throughout labor and delivery for any patient with symptomatic cardiac disease during pregnancy or with the potential for deterioration due to valvular, myocardial, or ischemic heart disease. Because significant circulatory changes that may lead to hemodynamic deterioration occur in the early postpartum period,[4] hemodynamic monitoring should be continued for at least several hours after delivery to ensure stability.

CARDIAC CATHETERIZATION (see Chap. 11) .

Cardiac catheterization may be indicated in rare instances of cardiac decompensation when sufficient information cannot be obtained by noninvasive techniques, especially if cardiac surgery, coronary angioplasty, or balloon valvuloplasty is being considered. Although this technique provides high-quality images, it is associated with a relatively high dose of radiation. To minimize radiation to the pelvic and abdominal areas, the brachial rather than the femoral approach is preferred, fluoroscopy and cine time should be reduced to the minimum required, and direct irradiation to the fetus should be avoided.

PREGNANCY IN WOMEN WITH CONGENITAL HEART DISEASE (See Chap. 44)

Because of increased survival in children with congenital heart disease, pregnancy has become more common in this patient population.[34] [35] Preconception management should include careful history and assessment of risk for both the mother and the fetus.[35] [36] [37]

The patient should be counseled regarding contraceptive alternatives,[38] potential maternal and fetal risks of pregnancy,[39] [40] and, when appropriate, expected long-term maternal morbidity and survival as well as the risk of congenital malformations in the offspring.[41] In addition, guidance concerning anticoagulation and prophylactic antibiotics, if needed, should be provided.[42]

MATERNAL AND FETAL OUTCOME.

In general, a good maternal outcome can be expected in most cases with noncyanotic congenital heart disease. Maternal outcome is determined by the nature of the disease, surgical repair, presence and severity of cyanosis, increased pulmonary vascular resistance, maternal functional capacity, myocardial dysfunction, left ventricular obstruction, and history of arrhythmias[42A] [42B] or other prior cardiac events.[40] Unfavorable outcome, including development of congestive heart failure, arrhythmias, and hypertension, is commonly seen in patients with impaired functional status and

those with cyanosis.[40] [41] [42] Other reported complications include angina, infective endocarditis, and thromboembolic phenomena.

Maternal functional capacity and cyanosis also determine fetal outcome.[43] [44] Fetal wastage was reported in 45 percent of cyanotic mothers compared with 20 percent in acyanotic mothers with congenital heart disease.[44] Low birth weight for gestational age and prematurity are common in cyanotic mothers and correlate with maternal hemoglobin and hematocrit values.[43] [44] Risk of congenital heart disease is increased for the offspring of mothers with congenital heart disease with a reported incidence of 4 to 8 percent.[45] [46] In addition, there are a greater number of noncardiac congenital malformations, as well as mental and physical impairments in children born to mothers with congenital heart disease.

LABOR AND DELIVERY.

Elective induction of labor when fetal maturity is confirmed may be used in high-risk patients for better planning of hemodynamic monitoring and availability of expert personnel[34] during labor and delivery. Vaginal delivery is preferred for most patients, and cesarean section is indicated in the stable patients only for obstetric reasons. Oxygen should be given to hypoxemic mothers, and hemodynamic as well as blood gas monitoring is recommended in most patients with impaired functional capacity, cardiac dysfunction, pulmonary hypertension, and cyanotic malformations. Blood volume loss must be anticipated and treated promptly.

ANTIBIOTIC PROPHYLAXIS.

Official recommendations by the American Heart Association suggest that antibiotic prophylaxis for an uncomplicated delivery is unnecessary except for cases with a prosthetic heart valve or a surgically constructed systemic-to-pulmonary shunt.[47] Because of difficulties in predicting complicated deliveries and potential devastating consequences of endocarditis,[48] antibiotic prophylaxis

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for vaginal delivery in all patients with congenital heart disease (except those with an isolated secundum type of atrial septal defect and those 6 months or more after repair of septal defects or surgical ligation and division of patent ductus arteriosus) seems reasonable.

Specific Malformations

ATRIAL SEPTAL DEFECT (see also Chap. 44) .

Atrial septal defect is usually well tolerated in pregnancy even in patients with large left-to-right shunts. The development of pulmonary hypertension and atrial arrhythmias

rarely occurs in the childbearing age. Because endocarditis is rare, antibiotic prophylaxis is not indicated in patients with secundum-type atrial septal defect. Recommendations concerning pregnancy in patients with atrial septal defect should be made on an individual basis, considering accompanying lesions, functional status, and the level of pulmonary vascular resistance.[34]

VENTRICULAR SEPTAL DEFECT (see also Chap. 44) .

Women with isolated ventricular septal defect usually tolerate pregnancy well, although congestive heart failure and arrhythmias have been reported.[34] The risk posed by pregnancy after closure of an uncomplicated ventricular septal defect should not differ from that in patients without heart disease. The incidence of ventricular septal defect in offspring has been reported to be 4 to 11 percent.[34] Marked reduction in blood pressure during or after delivery as a result of blood loss or anesthesia can lead to shunt reversal in patients with pulmonary hypertension. The use of vasopressors and volume replacement to stabilize blood pressure should prevent further complications.

PATENT DUCTUS ARTERIOSUS (see also Chap. 44) .

Maternal outcome in patients with patent ductus arteriosus with left-to-right shunt is usually favorable[34] [42] ; however, clinical deterioration and congestive heart failure can occur in some patients. There were no maternal deaths among a large number of patients with patent ductus arteriosus.[40] [48] The need for surgical intervention during pregnancy is rare. A fall in systemic vascular resistance during gestation and hypotension early post partum can lead to shunt reversal in women with pulmonary hypertension. Peripartum decrease in systemic blood pressure should be corrected by means of vasopressor agents.

CONGENITAL AORTIC VALVE DISEASE (see also Chap. 44) .

Most patients with mild aortic stenosis have favorable outcome of pregnancy provided that they receive early diagnosis and appropriate care, including hemodynamic monitoring during labor and delivery and appropriate anesthesia.[3] [34] [49] At the same time, however, moderate and severe aortic stenosis is likely to be associated with symptomatic deterioration during pregnancy and may lead to maternal morbidity and even mortality.[3]

Symptoms usually develop in the second or third trimester and may include exertional dyspnea, chest pain, lightheadedness, and syncope. Increased incidence of cardiac defects has been reported in liveborn infants of mothers with left ventricular outflow obstruction.[43] Because of the risk involved, patients with severe aortic stenosis (aortic valve area <1.0 cm^2) should consider undergoing valve replacement before becoming pregnant. Optional management strategies of a pregnant patient with severe aortic stenosis include (1) early abortion followed by valve replacement and repeat pregnancy and (2) continuation of pregnancy and plan for percutaneous balloon valvuloplasty or surgical intervention in patients who show clinical deterioration not controlled by medical

therapy.[50] [51]

Both replacement of aortic valve and percutaneous balloon valvuloplasty have been performed successfully in pregnant women with aortic stenosis.[50] [51] [52] [53] These procedures, however, are not free of complications. Although valvuloplasty obviates the general anesthesia and cardiopulmonary bypass required for surgery, it can be associated with prolonged radiation exposure and hemodynamic fluctuations that can lead to immediate and late fetal complications. Surgical replacement of the aortic valve during pregnancy can be associated with increased incidence of maternal complications and fetal loss.[53] These procedures should therefore be considered only in symptomatic patients with severe disease not manageable by medical therapy and should be avoided when possible during the first trimester.

COARCTATION OF THE AORTA (see also Chap. 44) .

Both maternal and fetal outcome is usually favorable in cases with aortic coarctation.[54] [55] [56] At the same time, however, cases of severe hypertension, congestive heart failure, and aortic dissection have been reported.[42] [56] A recent study reported congenital heart disease in 3 percent of newborns born to patients with corrected coarctation.[57] Because a higher incidence of infective endocarditis in the mother and of congenital heart disease in the fetus have been shown in cases with surgically uncorrected compared with corrected coarctation,[43] it seems advisable to correct aortic coarctation before pregnancy.[57]

Measures to reduce the incidence of aortic dissection and rupture of cerebral aneurysms during pregnancy consist of limiting physical activity and controlling blood pressure. Excessive blood pressure reduction, however, may compromise uteroplacental blood flow and should be avoided. Surgical correction of coarctation has been performed successfully during pregnancy[57] and may be indicated in patients with severe, uncontrollable systolic hypertension or heart failure.

PULMONIC STENOSIS (see also Chap. 44) .

Isolated pulmonic stenosis is usually well tolerated during pregnancy.[3] [34] [34A] When possible, however, severe stenosis should be corrected before conception. In the rare instance of progressive right ventricular failure or symptoms clearly related to the stenotic valve, or in a patient with intracardiac shunt at either the atrial or ventricular level with cyanosis, percutaneous balloon valvotomy should be considered during pregnancy.

TETRALOGY OF FALLOT (see also Chap. 44) .

Hemodynamic changes associated with pregnancy may become severe and cause clinical deterioration in women with surgically uncorrected or only partially corrected tetralogy of Fallot. Increase in blood volume and venous return to the right atrium raises right ventricular pressure, which combined with a fall in systemic vascular resistance can produce or exacerbate right-to-left shunt and cyanosis. Labor and delivery are

particularly important because a fall in blood pressure can also increase right-to-left shunt and the degree of cyanosis. Maternal hematocrit above 60 percent, arterial oxygen saturation below 80 percent, right ventricular hypertension, and syncopal episodes are poor prognostic signs. Pregnancies in women with cyanosis are associated with high rate of spontaneous abortion, premature deliveries, and fetal growth retardation.[43] [44] [45] [58] [59]

Close monitoring of systemic blood pressure and blood gases during labor and delivery is recommended for cyanotic or symptomatic patients. Incidence of cardiac defects reported in born infants ranges between 3 and 17 percent.[40]

Patients who have undergone only palliative procedures or who have significant residual defects after repair, such as residual ventricular septal defect, pulmonic stenosis or regurgitation, and ventricular dysfunction, are still at higher risk during pregnancy. Patients who had undergone shunt procedures to improve cyanosis may develop pulmonary hypertension, which increases the risk of pregnancy. Because maternal and fetal outcomes seem to be markedly improved after surgical repair, this procedure should be performed before conception. Because revision of an incompletely repaired defect is recommended in patients with residual ventricular septal defect when the pulmonary/systemic flow ratio is greater than 1.5:1.0, in those

with right ventricular outflow obstruction (right ventricular systolic pressure >60 mm Hg), and in those with right ventricular failure due to pulmonic regurgitation, such revision should be performed before conception in a woman who plans to conceive.

EISENMENGER SYNDROME (see also Chap. 44) .

This condition continues to be associated with a high risk of maternal morbidity and mortality. A recent review of 55 women who had at least one pregnancy showed maternal mortality of 39 percent.[34] Similarly, a recent analysis of 65 published cases with Eisenmenger syndrome from more than 20 countries showed 43 percent maternal mortality.[60] Cause of maternal death is often unclear; it usually occurs in the first few days after delivery and is preceded by desaturation and hemodynamic deterioration. Eisenmenger syndrome is also associated with a poor fetal outcome, with a high incidence of fetal loss, prematurity, intrauterine growth retardation, and perinatal death.[34] [34A]

Because of the high risk of maternal mortality, patients with Eisenmenger syndrome should be advised against pregnancy and early abortion should be recommended for patients who are already pregnant. Management of a patient who decides to proceed to term must include close follow-up for early detection of clinical deterioration. Because of increased incidence of peripartum thromboembolism, anticoagulant therapy seems indicated in the third trimester of gestation and for 4 weeks post partum. Because premature delivery is common, women with Eisenmenger syndrome should be

hospitalized for any sign of premature uterine activity. For this reason and to ensure restriction of activity and close follow-up, early elective hospitalization is recommended. Spontaneous labor is preferred to induction and should lower the chance of prematurity or the need for cesarean section. Blood pressure, electrocardiographic, and blood gas monitoring are essential during labor and delivery to ensure early detection and correction of problems; high concentrations of oxygen may be helpful. Most patients in stable condition will tolerate vaginal delivery; however, an attempt should be made to shorten the second stage of labor by the use of forceps or vacuum extraction. Because of the higher risk of fetal distress during vaginal delivery and potential need for emergency cesarean section, a planned cesarean section is often preferred. Insertion of a Swan-Ganz catheter may be difficult and associated with the development of arrhythmias, and its routine use is not recommended.[61] Inhaled nitric oxide has been used successfully to reduce pulmonary pressure and improve oxygenation during labor and the early postpartum period in two patients with Eisenmenger syndrome.[62] [63] Both patients gave birth to live infants but died 2 and 21 days post partum.

EBSTEIN ANOMALY.

Pregnancy in women with noncyanotic Ebstein anomaly is well tolerated. In cyanotic cases pregnancy is associated with increased risk of maternal heart failure, prematurity, and fetal loss.[64] [65] The approach to labor and delivery in symptomatic or cyanotic patients with Ebstein anomaly includes antibiotic prophylaxis, oxygen administration, hemodynamic and blood gas monitoring, and efforts to prevent a drop in systemic blood pressure in response to peripheral vasodilation or blood loss.

COMPLEX CYANOTIC CONGENITAL HEART DISEASE.

The more widespread use of palliative and corrective surgical procedures for complex cyanotic congenital cardiac anomalies has allowed more women who are so affected to reach childbearing age.[34] Although successful pregnancies have been reported in patients with partially corrected and uncorrected cyanotic heart disease, including pulmonary and tricuspid atresia,[44] [66] transposition of the great vessels,[64] [65] [66] [67] [68] [69] [70] truncus arteriosus,[71] single ventricle,[72] [73] [74] double-outlet right ventricle,[75] and double-inlet left ventricle, [76] pregnancy is associated with increased risk in these patients. A report[44] of 96 pregnancies in 44 patients with cyanotic heart disease without Eisenmenger reaction demonstrated cardiovascular complications in 32 percent of the patients. These complications included heart failure, thromboembolic events, supraventricular tachycardia, and peripartum bacterial endocarditis resulting in postpartum maternal death in one patient. In addition, a high incidence of fetal wastage (57 percent), premature deliveries, small-for-gestational-age newborns, and both cardiac and noncardiac congenital malformations have been reported.[34]

RHEUMATIC HEART DISEASE

Although the incidence of rheumatic heart disease is declining in the United States, the disease continues to be prevalent in many developing countries and may be associated

with significant morbidity and even mortality.[3] [77]

ACUTE RHEUMATIC FEVER (see Chap. 66) .

This disease occurs most often in children, before puberty, and only rarely during pregnancy.[77] The management of acute rheumatic fever during pregnancy is similar to that of nonpregnant patients. Because heart failure is usually due to an incompetence of the mitral or aortic valve, diuretics and vasodilators should be the therapy of choice. Surgical repair of valvular incompetence should be performed in patients not responding to medical therapy. The results of mitral valve repair in patients with acute rheumatic disease, however, are inferior to those seen in patients with other forms of valvular regurgitation. Mild cases of heart failure require only bed rest and treatment of streptococcal pharyngitis and comorbidity, including anemia and nutritional difficulty.[77]

CHRONIC RHEUMATIC VALVULAR DISEASE (see Chap. 46) .

Patients with chronic rheumatic valvular disease should be managed individually according to the site and severity of the lesion. However, certain general guidelines apply to the care of all patients. These include (1) restriction of physical activity in symptomatic patients to reduce cardiovascular load and prevent hemodynamic and symptomatic worsening and (2) prophylactic antibiotic treatment to prevent streptococcal infection and recurrence. Although antibiotic prophylaxis during labor and delivery has not been uniformly recommended,[47] it is commonly used for vaginal and abdominal deliveries. Hemodynamic monitoring is strongly recommended from the onset of labor to approximately 24 hours post partum in any patient who experiences symptoms of heart failure during pregnancy and for those with severe valvular disease, left ventricular dysfunction, or pulmonary hypertension.

MITRAL STENOSIS (see also Chap. 46) .

This condition is the most common rheumatic valvular lesion in pregnancy.[77] The majority of patients with moderate to severe mitral stenosis demonstrate a worsening of one or two classes in the New York Heart Association functional status during gestation.[3] [77] Although mitral stenosis is often accompanied by some degree of mitral regurgitation, hemodynamic problems are related predominantly to flow obstruction. The pressure gradient across the narrowed mitral valve may increase greatly secondary to the physiological increase in heart rate and blood volume of pregnancy.[3] Increased left atrial pressure can result in atrial flutter or fibrillation, substantially accelerating the ventricular rate and further elevating left atrial pressure. In addition, decreased serum colloid osmotic pressure during pregnancy and excessive peripartum intravenous fluid administration can both predispose to pulmonary edema. A recent study has demonstrated a high incidence of worsening of functional class and the development of heart failure, which led to the need for hospitalizations and either starting or increasing the dose of cardiac medications in patients with moderate to severe mitral stenosis. In addition, there was a marked increase in the rate of prematurity and fetal growth retardation in these cases. Despite marked increase in maternal morbidity, there was no

mortality.[3]

Treatment.

The therapeutic approach to patients with significant mitral stenosis should aim to reduce the heart rate and decrease blood volume. Both heart rate and symptoms can be controlled effectively by restricting physical activity and administering beta-adrenergic receptor blockers.[77] [78] [79] In patients with atrial fibrillation, digoxin may also be useful for control of ventricular rate. Blood volume can be decreased through restriction of salt intake and the use of oral diuretics; aggressive use of diuretic agents should,

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however, be avoided to prevent hypovolemia and reduction of uteroplacental perfusion.

Although careful medical therapy allows successful completion of pregnancy in the great majority of women,[77] repair or replacement of the valve during pregnancy may be indicated in some patients with severe symptoms in spite of adequate medical therapy.[80] [81] [82] In both mitral valve commissurotomy (open or closed) and replacement, the risk in pregnant patients is comparable to that in nonpregnant patients.[81] In contrast, however, open commissurotomy and valve replacement are likely to result in increased fetal loss.[81] [82] Closed mitral commissurotomy is associated with only minimal risk to the fetus; it is, therefore, preferable to the open technique.[83] However, it should be recommended only in centers where it is performed routinely.

Balloon Valvuloplasty (see also Chap. 46) .

The use of percutaneous mitral balloon valvuloplasty during pregnancy has been reported in an increasing number of pregnant patients with mitral stenosis.[84] [85] [86] [87] [88] [89] In the majority of cases, hemodynamic and symptomatic improvement has been achieved without apparent untoward maternal and fetal effects. At the same time, however, serious complications have occasionally been reported, including initiation of uterine contraction,[86] maternal arrhythmia leading to fetal distress,[87] cardiac tamponade requiring surgical intervention, and systemic embolization.[88] In addition, this procedure is associated with some risk to the fetus secondary to unavoidable ionizing radiation. This information suggests that percutaneous mitral balloon valvuloplasty is an attractive alternative to surgery during pregnancy, but it is limited by the exposure to radiation and possible complications that may result in fetal distress or require surgical intervention during pregnancy. The procedure should be avoided if possible during the first trimester[77] and should be performed by experienced operators with adequate abdominal and pelvic shielding with minimum radiation exposure or under echocardiographic guidance, if possible.

Mitral Valve Repair or Replacement (see also Chap. 46) .

For all of the aforementioned reasons, mitral valve repair or replacement during pregnancy should be considered only in cases with severe mitral stenosis (mitral valve area < 1.0 cm^2) refractory to optimal medical therapy or when close follow-up during pregnancy, labor, and delivery is not possible. When valve replacement is indicated, selection of the type of prosthesis should be based on its hemodynamic profile and durability and the need for anticoagulation.

Vaginal delivery can be permitted in most patients with mitral stenosis. In symptomatic patienvs, those with moderate or severe stenosis (mitral valve area <1.5 cm^2), hemodynamic monitoring is recommended during labor and delivery. Initiation of monitoring at onset of labor allows hemodynamic optimization by means of intravenous diuretics, digoxin (in case of atrial fibrillation), beta blockers, or nitroglycerin and prevention of a rise in left atrial pressure during labor and delivery. With delivery and thus relief of venocaval obstruction due to the gravid uterus, there is an immediate increase in venous return, which may lead to a substantial increase in pulmonary artery wedge pressure. For this reason, hemodynamic monitoring should be continued for at least several hours post partum.

Epidural anesthesia is the most appropriate form of analgesia in patients with mitral stenosis for both vaginal and abdominal delivery. This form of anesthesia is often associated with a significant fall in pulmonary arterial and left atrial pressures due to systemic vasodilation. With this approach, the great majority of patients with mitral stenosis, even if it is severe, can be delivered with few complications.

MITRAL REGURGITATION (see also Chap. 46) .

This condition is usually well tolerated in pregnancy, presumably because of left ventricular unloading secondary to the physiological fall in systemic vascular resistance. In symptomatic patients, drug therapy with diuretics is indicated, and digoxin may be useful in those with impaired left ventricular systolic function. Because hydralazine has been shown to be safe for use during pregnancy,[90] it may be used for further reduction of left ventricular afterload and prevention of hemodynamic worsening associated with isometric exercise during labor.[91]

AORTIC STENOSIS (see also Chap. 46) .

Rheumatic aortic stenosis is rare during pregnancy and occurs in conjunction with mitral valve disease in approximately 5 percent of pregnant patients with rheumatic valvular disease.[77] Although most patients with aortic stenosis and valve area greater than 1.0 cm^2 tolerate pregnancy well, patients with more severe stenosis may demonstrate clinical deterioration with exertional dyspnea, near-syncope, or syncope and pulmonary edema.[3] [92] Development of serious symptoms during pregnancy, especially if resistant to medical therapy, may require termination of pregnancy or repair of the valve either

surgically (valve replacement) or by percutaneous balloon valvuloplasty.[81] [93]

AORTIC REGURGITATION (see also Chap. 46) .

Similar to mitral regurgitation, aortic regurgitation is also well tolerated during pregnancy, probably because of reduced systemic vascular resistance and increased heart rate, which results in shortening of diastole. In symptomatic patients, diuretics, digoxin, and hydralazine for left ventricular afterload reduction can be safely used.

Other Conditions Affecting the Valves, Aorta, and Myocardium

Mitral Valve Prolapse (see also Chap. 46)

The prevalence of mitral valve prolapse in the general population has been recently found to be 2.4 percent and was reported in approximately 1.2 percent of pregnant women. Because of high incidence of systolic functional murmurs and wide splitting of the first heart sound during pregnancy, mitral valve prolapse may be falsely diagnosed and needs to be confirmed by echocardiographic criteria.[94] At the same time, the incidence of prolapse-related auscultatory and echocardiographic findings may decrease during gestation as a result of an increase in left ventricular end-diastolic volume.[95]

For the few patients with mitral valve prolapse with chest pain or cardiac arrhythmias, the emphasis should be on reassurance and attempts to avoid the use of medications during pregnancy. Beta-adrenergic blocking agents are recommended when therapy is indicated. Patients with mitral valve prolapse, especially those with a thickened mitral valve and mitral regurgitation, are at increased risk for infective endocarditis. Although antibiotic prophylaxis for uncomplicated vaginal delivery has not been uniformly recommended, the development of bacteremia during vaginal delivery and cesarean section cannot always be predicted. For this reason, prophylaxis for labor and delivery in patients with mitral valve prolapse accompanied by valve thickening and/or regurgitation seems warranted.

Marfan Syndrome (See also Chap. 40)

Pregnancy in women with Marfan syndrome poses a twofold problem: (1) cardiovascular complications and (2) a high risk of having a child who will inherit the condition.[96] [97] Cardiovascular complications during pregnancy include dilatation of the ascending aorta, which may lead to the development of aortic regurgitation and congestive heart failure, and proximal and distal dissections of the aorta with occasional involvement of the iliac and coronary arteries (see Fig. 65-3) (Figure Not Available) . The risk of aortic dissection is significantly higher in patients with a dilated aorta or a history of previous dissection. Patients with Marfan syndrome who have only minor involvement of the cardiovascular system and aortic diameter less than 40 mm usually

Figure 65-4 Chest radiograph demonstrating severe dilatation of the thoracic aorta in a 23-year-old woman with Marfan syndrome who presented with sharp chest pain radiating to the back during her 16th week of gestation. The patient was found to have thoracoabdominal aortic aneurysm and descending aortic dissection and had an elective abortion at 19 weeks.

tolerate pregnancy well without subsequent worsening of their cardiovascular status attributable to pregnancy.[98] The majority of complications are developed in the later phase of pregnancy. Marfan syndrome may also be responsible for cervical incompetence, abnormal placental site, and postpartum hemorrhagic complications.[99]

The management of pregnancy in women with Marfan syndrome should include preconception counseling to discuss potential maternal and fetal risks.[96] Women with significant cardiac involvement--in particular, dilatation of the aorta and previous history of aortic dissection--are at high risk for complications during gestation and should be advised against conception or, if they are already pregnant, to have an early abortion (Fig. 65-4) . In contrast, the risk in patients without cardiac complications and with a normal aortic diameter is significantly lower. Still, a favorable outcome is not guaranteed, and aortic dissection can occur, albeit infrequently, in patients with a normal-sized aorta.[96] Preconception echocardiographic assessment of the aorta and periodic follow-up during pregnancy are highly recommended.[98] Because aneurysms and dissections of the aorta can occasionally involve the descending aorta, the use of transesophageal echocardiography seems preferred to transthoracic examination.[100] During pregnancy, vigorous physical activity should be avoided. Beta blockers, which have been shown to reduce the rate of aortic dilatation and the risk of complications in patients with Marfan syndrome, should be administered.[101] In case of substantial dilatation of the aorta during pregnancy, therapeutic abortion or surgical intervention should be considered.[96] In women with aortic dilatation, aortic dissection, or other cardiac complications, abdominal delivery by cesarean section should be the preferred mode of delivery to minimize hemodynamic changes associated with vaginal delivery.[96] [98]

Cardiomyopathies (See Chap. 48)

HYPERTROPHIC CARDIOMYOPATHY.

Reported experience in over 100 pregnancies in patients with hypertrophic cardiomyopathy reveals a favorable outcome in most cases but at the same time a potential for increased morbidity and even mortality.[102] [103] New onset or worsening of congestive heart failure has been reported in approximately 20 percent of cases, and a few patients experienced chest pain, palpitations, dizzy spells, and syncope. Poorly tolerated resistant supraventricular tachycardia with fetal distress[104] has also been reported as well as new-onset atrial fibrillation leading to hemodynamic deterioration and direct-current cardioversion.[105] Few patients had ventricular arrhythmias, which

proved fatal in one,[102] and in one patient sudden death occurred at 28 weeks during moderate exertion.[106] Fetal outcome in most cases does not seem to be affected by maternal hypertropic cardiomyopathy. The risk of inheriting the disease may be as high as 50 percent in familial cases and less in sporadic cases.[102]

The therapeutic approach to the pregnant patient with hypertrophic cardiomyopathy depends on the presence of symptoms and left ventricular outflow obstruction. In the symptomatic patient with obstructive hypertrophic cardiomyopathy, an attempt should be made to avoid blood loss and use of drugs that can lead to vasodilation or sympathetic stimulation during labor and delivery. Indications for drug therapy during gestation include arrhythmias and symptoms other than those caused by normal pregnancy. Symptoms associated with elevated left ventricular filling pressure should be treated with beta-adrenergic blocking agents, with diuretics and calcium antagonists added if beta blockers alone are not sufficient.[102] Dual-chamber pacing may be considered before pregnancy in symptomatic patients.[107] Because of the potential arrhythmogenic effect of pregnancy, implantation of an automatic defibrillator before pregnancy should be considered in patients with hypertrophic cardiomyopathy with aborted syncope, or life-threatening arrhythmias.

Vaginal delivery has been shown to be safe in women with hypertrophic cardiomyopathy.[88] In those with symptoms or outflow obstruction, the second stage of labor may be shortened by the use of forceps. The use of prostaglandins to induce uterine contractions may be risky in a patient with obstructive hypertrophic cardiomyopathy, owing to their vasodilatory effect, whereas oxytocin should be well tolerated. Because tocolytic agents with beta-adrenergic receptor activity may aggravate left ventricular outflow tract obstruction, other medications such as magnesium sulfate are preferred. Similarly, spinal and epidural anesthetics should be used with caution in obstructive hypertrophic cardiomyopathy because of their vasodilatory effect, and excessive blood loss should be avoided or replaced promptly with intravenous fluid or blood.[102] [103]

Because the risk for infective endocarditis is increased in hypertrophic cardiomyopathy, especially the obstructive form, and in patients with mitral valve abnormalities, antibiotic prophylaxis should be considered for labor and delivery.

PERIPARTUM CARDIOMYOPATHY.

Peripartum cardiomyopathy is a form of dilated cardiomyopathy with left ventricular systolic dysfunction that results in signs and symptoms of heart failure. Symptoms usually occur during the last trimester of gestation, and diagnosis is usually made in the early peripartum period.[108] [108A] Because there is no specific test available for the diagnosis of peripartum cardiomyopathy, it is established by exclusion of other causes of left ventricular dilatation and systolic dysfunction (Table 65-6) . The reported incidence of the disease in the United States is approximately 1 in 15,000 with a higher incidence (up to 1 in 1,000) in certain parts of Africa.[108]

Common symptoms and signs are shortness of breath, fatigue, chest pain, palpitations, weight gain, peripheral edema, peripheral or pulmonary embolization, and arrhythmias.

Physical examination often reveals an enlarged heart, S_3 , and murmurs of mitral and tricuspid regurgitation. The electrocardiogram may show tachycardia, ST-T wave

TABLE 65-6 -- MODIFIED CRITERIA FOR DIAGNOSIS OF PERIPARTUM CARDIOMYOPATHY

Development of cardiac failure during pregnancy or within 6 months of delivery
Absence of a determinable cause for cardiac failure
Demonstrable impairment in left ventricular systolic function

changes, conduction abnormalities, and arrhythmias. Chest radiography usually shows cardiomegaly, pulmonary venous congestion with interstitial or alveolar edema, and occasionally pleural effusion. Doppler echocardiography commonly shows enlargement of all four cardiac chambers, with marked reduction in left ventricular systolic function. Small-to-moderate pericardial effusion and mitral, tricuspid, and pulmonic regurgitation may be evident. The clinical presentation and hemodynamic changes are indistinguishable from those found in other forms of dilated cardiomyopathy. [109] A few patients with high-output heart failure have been reported.[110]

The incidence of peripartum cardiomyopathy is greater in multiparous women and in those with preeclampsia and twin pregnancies, as well as in women older than 30 years of age.[111] Although the etiology of peripartum cardiomyopathy is still unknown, the unique nature of this syndrome is suggested by its relation to pregnancy, its occurrence at a relatively young age when compared with other forms of dilated cardiomyopathy, the relatively rapid recovery of cardiac size and function in a large number of patients, and the recurrence of left ventricular depression with subsequent pregnancies.[108] Association between myocarditis and peripartum cardiomyopathy was suggested by some investigators who reported a high incidence of myocarditis documented by endomyocardial biopsy.[112] Later reports, however, have indicated a low incidence of myocarditis in patients with peripartum cardiomyopathy that was comparable to that found in an age- and sex-matched nonpregnant, control population with idiopathic dilated cardiomyopathy.[108] [113]

The clinical course of peripartum cardiomyopathy varies, with 50 to 60 percent of patients showing complete or near-complete recovery of clinical status and cardiac function, usually within the first 6 months postpartum[111] ; the rest of the patients demonstrate either further clinical deterioration, leading to cardiac transplantation or early death, or persistent left ventricular dysfunction and chronic heart failure.

Management.

Acute heart failure should be treated vigorously with oxygen, diuretics, digitalis, and

vasodilator agents. The use of hydralazine as an afterload-reducing agent is safe during pregnancy.[90] The use of organic nitrates, dopamine, dobutamine, or milrinone has been reported in pregnancy in a limited number of cases. Nitroprusside has been used successfully during pregnancy, but experiments in animals have shown the potential for fetal toxicity.[90] Angiotensin-converting enzyme inhibitors have a teratogenic effect, may cause fetal renal dysfunction, and should therefore not be used during pregnancy.[114] Because of the increased incidence of thromboembolic events in peripartum cardiomyopathy, anticoagulant therapy is recommended. Because the disease may be reversible, the temporary use of an intraaortic balloon pump or left ventricular assist device may help stabilize the patient's condition pending improvement.[115] [116] A small retrospective study of intravenous immune globulin showed a favorable effect on recovery of left ventricular dysfunction in patients with peripartum cardiomyopathy.[117] Further evaluation of this therapy seems warranted. The presence of preeclampsia may be associated with greater improvement in left ventricular dysfunction post partum.[111] Because of the high risk of mortality, patients with severe heart failure, who do not recover early, should be considered for cardiac transplantation. Two reports comparing results of cardiac transplantation in age-matched females with peripartum cardiomyopathy and idiopathic cardiomyopathy showed favorable and comparable long-term survival in both groups.[118] [119] Although mortality from peripartum cardiomyopathy was reported to be over 40 percent in early studies,[108] two recent studies reported incidence of death or cardiac transplantation to be in the range of 12 to 18 percent.[111] [112]

Subsequent pregnancies in women with peripartum cardiomyopathy are often associated with relapse, leading to left ventricular dysfunction, symptomatic deterioration, and even to death. Although the likelihood of such relapse is greater in patients with persistently abnormal cardiac function, it has also been reported in women in whom left ventricular function is restored after the first episode.[120] Two recent surveys on the risk of subsequent pregnancy in women with history of peripartum cardiomyopathy reported mortality of 0 to 2 percent in patients with normal left ventricular ejection fraction before the subsequent pregnancy and 8 to 17 percent in patients with depressed left ventricular ejection fraction (Table 65-7) .[120] [121] For these reasons, subsequent pregnancies should be discouraged in patients with peripartum cardiomyopathy who have persistent cardiac dysfunction; women with recovered cardiac function cannot be guaranteed an event-free pregnancy, and recurrence of the disease is possible. The risk of mortality in such cases, however, seems to be small.

Hypertension in Pregnancy (See Chap. 28)

Hypertensive disorders are the most common medical complications of pregnancy and are a major cause of maternal and perinatal morbidity and mortality.[2] [122] In general, hypertension in pregnancy is defined as blood pressure greater than 140 mm Hg systolic and 90 mm Hg diastolic on at least two occasions 6 hours apart.[123] Hypertension complicates 8 to 10 percent of all pregnancies and is an important cause of maternal mortality and morbidity, including abruptio placentae, pulmonary edema, respiratory failure, disseminated intravascular coagulation, cerebral hemorrhage,

TABLE 65-7 -- MATERNAL AND FETAL OUTCOME IN 67 SUBSEQUENT PREGNANCIES IN 60 PATIENTS WITH A HISTORY OF PERIPARTUM CARDIOMYOPATHY

GROUPS	MATERNAL OUTCOMES			FETAL OUTCOME		
	Normal (%)	Left Ventricular Dysfunction (%)	Death (%)	Live birth (%)	Abortions (%)	Still birth (%)
A	74	23	2	93	5	2
B	37	54	8	83	17	0

Group A--43 pregnancies in 40 patients with history peripartum cardiomyopathy who had recovery of left ventricular function.

Group B--24 pregnancies in 23 patients with history of peripartum cardiomyopathy and persistent left ventricular dysfunction

TABLE 65-8 -- MODIFIED CLASSIFICATION OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

Pregnancy-Induced Hypertension
Hypertension that develops as a consequence of pregnancy and regresses post partum
Hypertension without proteinuria or pathological edema
Preeclampsia: with proteinuria or pathological edema
Mild
Severe
Eclampsia: with proteinuria or pathological edema
Pregnancy-Aggravated Hypertension
Underlying hypertension worsened by:
Superimposed preeclampsia
Superimposed eclampsia
Coincidental Hypertension
Chronic hypertension that antecedes pregnancy or persists post partum

hepatic failure, and acute renal failure.[123] Fetal complications include prematurity, intrauterine growth retardation, stillbirth, and neonatal death. Hypertensive disorders in pregnancy can be divided into three broad categories: chronic hypertension, gestational hypertension,[124] and preeclampsia (Table 65-8) .

CHRONIC HYPERTENSION.

Chronic hypertension is defined as hypertension that precedes pregnancy, hypertension that occurs before the 20th gestational week, and hypertension that persists beyond the 6th postpartum week.[123] It occurs in 1 to 5 percent of pregnancies and is associated with increased complications (15 percent), such as fetal growth retardation, premature delivery, abruptio placentae, acute renal failure, and hypertensive crisis; most of these complications occur in patients older than age 30 years with a longer duration of hypertension or those who develop superimposed preeclampsia. Drug therapy is recommended for patients with high-risk characteristics. Therapy options for patients with high-risk chronic hypertension are shown in Table 65-9 .

GESTATIONAL HYPERTENSION.

This is defined as hypertension induced by pregnancy beginning after 20 weeks of gestation and resolving by the sixth postpartum week.[123] Gestational hypertension is further classified as transient hypertension (hypertension without proteinuria) and preeclampsia (hypertension with proteinuria). Transient hypertension usually presents in the late third trimester with return of blood pressure to normal by the 10th postpartum day. It should be noted that the presence of proteinuria can occur late in the course of preeclampsia and the distinction between transient hypertension and preeclampsia can be difficult and made retrospectively. For this reason, in uncertain situations, preeclampsia should be considered and seizure prophylaxis should be instituted empirically in patients with blood pressure greater than 160/110 mm Hg. Pregnancy outcome is usually favorable, and use of antihypertensive therapy should be reserved for patients with blood pressure greater than 160/110 mm Hg. Recommended drugs include parenteral hydralazine, parenteral labetolol, and oral nifedipine.[124]

PREECLAMPSIA-ECLAMPSIA.

Preeclampsia usually occurs after 20 weeks' gestation in the first pregnancy and near term in multiparous women. Preeclampsia can be subclassified into mild and severe.[123] In mild preeclampsia, systolic blood pressure is greater than 140 mm Hg but less than 160 mm Hg, and diastolic blood pressure is greater than 90 mm Hg but less than 110 mm Hg, and mild proteinuria (<5.0 g/24 hr) is the only laboratory abnormality. In severe preeclampsia, blood pressure is greater than 160 mm Hg systolic or more than 110 mm Hg diastolic, proteinuria is greater than 5.0 g/24 hr, platelet count is less than 100.000/ml, and there is evidence for microangiopathic hemolytic anemia or elevated levels of hepatic enzymes. Other symptoms consistent with severe disease are persistent headache, visual disturbance, pulmonary edema, and epigastric pain. Preeclampsia is always associated with increased risk to both mother and fetus and can progress to eclampsia, a life-threatening convulsive phase. Preeclampsia usually regresses within 24 to 48 hours post partum. In the minority of cases, postpartum eclampsia with hypertension, proteinuria, and convulsions occurs within 10 days after delivery.[123]

Patients with stable, mild preeclampsia may be followed until fetal pulmonary maturity is verified or until after 37 weeks of gestation with cervical ripening.[124] There is no evidence for need or benefit of antihypertensive drug therapy in this subgroup of patients. Severe preeclampsia can be rapidly progressive, leading to sudden deterioration of the status of both mother and fetus. Patients with severe preeclampsia who are at or past 34 weeks' gestation should be delivered promptly. Patients with severe preeclampsia who are at 24 to 34 weeks' gestation may receive expectant management that includes admission, bed rest, 24 hours of intravenous magnesium sulfate for seizure prophylaxis, blood pressure control, fetal assessment, and corticosteroids for acceleration of fetal lung maturity. Indicators for delivery

TABLE 65-9 -- ANTIHYPERTENSIVE DRUGS IN PREGNANCY

CLASS	DRUG	STARTING DOSE	MAXIMUM DOSE
Drugs for Long-Term Treatment of Hypertension			
Central alpha$_2$ - agonist	Methyldopa	250 mg tid	4 g/d
	Clonidine	0.1-0.3 mg bid	1.2 mg/d
Alpha$_1$ -adrenergic blocker	Prazosin	1 mg bid	20 mg/d
Calcium channel blocker	Nifedipine	10 mg qid	120 mg/d
Beta-adrenergic blocker	Atenolol	100 mg qd	100 mg/bid
Alpha/beta-adrenergic blocker	Labetalol	100 mg tid	2400 mg/d
Diuretics	Hydrochlorothiazide	25 mg qd	50 mg/d

CLASS	DRUG	DOSE
Drugs for Acute Treatment of Severe Hypertension		
Arterial dilator	Hydralazine	5-10 mg IV q 15-30 min
	Diazoxide	30-60 mg IV q 10-15 min
Calcium channel blocker	Nifedipine	10-20 mg PO q 30 min
Alpha/beta-adrenergic blocker	Labetalol	20-40-80 mg IV q 10-20 min (up to 300 mg)
Arterial/venous dilator	Sodium nitroprusside	(50 mg/250 mL saline): 0.5-5.0 mug/kg/min

include eclampsia, resistant, severe hypertension (refractory to maximum doses of three antihypertensive drugs), completion of 34 weeks of gestation, HELLP syndrome

(hemolysis, elevated liver enzymes, low platelet count), and fetal testing suggesting a problem is present.[123] Because of potential risks to the mother and fetus, conservative management of severe preeclampsia has been recommended only at tertiary perinatal centers under a very close maternal and fetal monitoring. The primary goal of treatment is to prevent cerebral complications. Recommended goal of therapy is reduction of mean blood pressure below 126 mm Hg but not less than 105 mm Hg and diastolic blood pressure between 90 and 105 mm Hg. Use of intravenous hydralazine is recommended as initial therapy, given intravenously in 5-mg bolus doses at intervals of 20 minutes up to cumulative dose of 20 mg. If not effective or associated with maternal side effect (tachycardia, headache, nausea), labetalol (20 mg intravenously) or nifedipine (10 mg orally) should be given.

PREGNANCY AFTER CARDIAC TRANSPLANTATION (SeeChap. 20)

A recent study conducted to determine the outcome of pregnancy in cardiac allograft recipients identified 47 pregnancies in 35 heart transplant recipients, which resulted in 35 (74 percent) live births.[125] Therapeutic abortion was performed in five cases owing to a short interval between transplantation and conception. Maternal hemodynamic changes during gestation seemed well tolerated, and rejection episodes were rare. At the same time, however, a higher incidence of maternal complications was reported, including chronic hypertension, preeclampsia, worsening kidney failure, premature rupture of membranes, and infections.[126] Although fetal loss does not seem to be increased, an increased incidence of preterm deliveries and fetal growth retardation and cesarean sections were reported. No maternal deaths were reported during pregnancy. The incidence of late death, however, was high compared with age-matched healthy women. None of the newborns was found to have congenital malformations, supporting a lack of teratogenic effect of immunosuppressive agents.[126] This limited information suggests, therefore, that pregnancy in women after cardiac transplantation is not associated with increased maternal mortality; however, it results in increased maternal morbidity, preterm deliveries, and fetal growth retardation. In addition, the patients and their families should be informed regarding risk of shorter life span after delivery in patients after heart transplantation.

CORONARY ARTERY DISEASE (See Chaps. 35 , 36 , and 37)

PATHOGENESIS.

Although coronary artery disease is encountered during pregnancy with increasing frequency because of increasing maternal age and fertility,[127] it is still rare among women of childbearing age; and the occurrence of peripartum acute myocardial infarction is anecdotal.[128]

Risk factors for coronary artery disease in women younger than the age of 50 years include cigarette smoking, high levels of total plasma cholesterol, low levels of high-density lipoproteins, diabetes mellitus, hypertension, a family history of coronary artery disease, toxemia of pregnancy, and the use of oral contraceptives.[127] [128] [129] [130] The combination of heavy smoking or hypertension and concurrent use of oral contraceptives has been shown to be a powerful predictor of acute myocardial

infarction.[130]

In the assessment of risk factors for coronary artery disease during pregnancy it should be noted that total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels are significantly increased during pregnancy.[131]

ACUTE MYOCARDIAL INFARCTION (see also Chap. 35) .

Peripartum acute myocardial infarction has been reported at any stage of pregnancy and at ages between 16 and 45. The highest incidence, however, occurs in the third trimester and in women older than age 33 years. In addition, acute myocardial infarction has been noted to occur more commonly in multigravidas and its location to be more commonly in the anterolateral wall. Most maternal death occurred either at the time of infarction or within 2 weeks.[128] To reduce the risk for acute myocardial infarction, oral contraceptives should be avoided or formulations with lower effective doses of estrogen should be used in cigarette smokers and in women with hypertension.

Although atherosclerotic disease seems to be the primary cause of acute myocardial infarction[128] [132] [133] [134] peripartum acute myocardial infarction is often associated with normal coronary angiograms and has been suggested as being due to a decrease in coronary perfusion caused by spasm or in situ thrombosis. Although the presence of spasm has not been documented and its cause is not clear, it has been suggested as a cause of myocardial infarction in some instances with pregnancy-induced hypertension and with the administration of ergot derivatives, bromocriptine,[135] oxytocin, and prostaglandin[136] used to suppress lactation or uterine bleeding and in patients with pheochromocytoma.[137] Coronary arterial dissection mostly in the immediate postpartum period has been commonly associated with peripartum acute myocardial infarction.[128] [135] [138] [139] The dissection involves the left anterior descending artery in approximately 80 percent of cases and the right coronary artery in most other cases. Other potential causes of acute myocardial infarction during pregnancy have been collagen vascular disease, Kawasaki disease, sickle cell anemia, and hemostatic abnormalities.[128] [135] [140]

DIAGNOSIS.

The diagnostic approach to ischemic myocardial disease in pregnancy is influenced to some extent by whether a diagnostic procedure could harm the fetus and by normal changes seen during pregnancy that may mimic pathological changes. T wave inversion, Q wave in lead III, and increased R/S ratio in leads V_1 and V_2 are commonly seen in normal pregnancy. ST segment depression, not associated with chest pain or echocardiographic wall motion abnormalities, has been described during elective cesarean section and can mimic myocardial ischemia. Because fetal bradycardia has been reported during maximal exercise in normal women, a submaximal exercise protocol with fetal monitoring is recommended for the evaluation of ischemic myocardial disease during pregnancy.

Radionuclide myocardial perfusion scans and radionuclide ventriculography expose the fetus to some radiation and should be used only when the potential benefits seem to

outweigh fetal risk. For similar reasons, cardiac catheterization involving fluoroscopy and cineangiography should be used only when relevant information cannot be obtained by other, noninvasive methods. The diagnosis of myocardial ischemia and infarction has been reported to be delayed during pregnancy because of the low level of suspicion.[128] Concentrations of myoglobin, creatine kinase, and creatine kinase MB were found to be increased twofold 30 minutes after delivery, whereas level of troponin I remained below the cutoff value for discriminating myocardial infarction. For this reason, troponin should be used to diagnose myocardial infarction after delivery.[141]

MANAGEMENT.

Both maternal and fetal considerations should influence the therapeutic approach to ischemic heart disease during pregnancy. Morphine sulfate does not cause congenital defects. Because it crosses the placenta, it can cause neonatal respiratory depression when given shortly before delivery.[128] Available reports on the use of thrombolytic therapy during pregnancy do not support a teratogenic effect, and the majority of reported cases resulted in favorable maternal and fetal outcome.[128] [133] [142] This therapy, however, is associated with risk of maternal hemorrhage, especially when given at the time of delivery. Because of their safety in pregnancy, beta blockers appear to be the drugs of choice. The use of organic nitrates and calcium antagonists in patients with acute myocardial ischemia or infarction has been described in a limited number of patients. These drugs should be given cautiously to prevent maternal hypotension and potential fetal distress. Use of high-dose aspirin during pregnancy is debatable, because it has been reported to cause fetal growth retardation and bleeding in the neonate and in the mother.[143] Use of low-dose aspirin, however, is safe during pregnancy.[143] [144]

Coronary reperfusion by means of percutaneous transluminal coronary angioplasty[133] [145] [146] or coronary artery bypass graft surgery[134] [139] [147] has been reported to be successful during pregnancy although experience is still limited. Such procedures should be avoided during the first trimester, if possible, owing to the potential deleterious fetal effects due to ionizing radiation as well as cardiopulmonary bypass.

Risk stratification after acute myocardial infarction during pregnancy should be determined by noninvasive methods. Total cholesterol, low density lipoprotein cholesterol, and triglyceride levels are significantly increased during pregnancy.[131] Coronary angiography should be done only in cases in which coronary angioplasty or bypass surgery seems indicated during pregnancy.

Management of the Pregnancy.

Management should focus on reducing cardiovascular stress during pregnancy and the peripartum period. Termination of pregnancy may be required in patients with intractable ischemia or heart failure in the early phase of gestation. During labor, adequate

analgesia and supplemental oxygen should be given; and, if desired, cardiac output can be increased by placing the patient in the left lateral decubitus position. Labor in the supine position, however, may decrease venous return and thus reduce right and left ventricular filling pressures. Low forceps can be used to shorten the second stage of labor. Pulmonary artery catheterization with hemodynamic monitoring can help in the early detection and correction of hemodynamic abnormalities during labor and delivery.[148] Although elective cesarean section is not indicated in every case, it should be used in patients with active ischemia or hemodynamic instability despite adequate medical therapy.[149] Continued hemodynamic monitoring is advisable for several hours post partum to detect hemodynamic worsening associated with postpartum hemodynamic changes described earlier.

ARRHYTHMIAS (See Chap. 25)

Pregnancy is associated with an increased incidence of arrhythmias in women both with and without structural heart disease.[16] [150] [151] [152] [153] In healthy women, multiple and even frequent atrial and ventricular premature complexes may occur, usually without effect on either the mother or the fetus.[16] There is also a strong suggestion for an increased frequency of paroxysmal supraventricular tachycardia during pregnancy.[152] [153]

ATRIAL FLUTTER AND ATRIAL FIBRILLATION.

Atrial flutter and fibrillation are rare during normal pregnancy and are usually associated with rheumatic mitral valve disease.[3] Recent reports have described atrial fibrillation during gestation accompanied by treatment with magnesium sulfate[154] and in a patient with preexcitation.[155] Ventricular tachycardia is a rare occurrence in pregnancy. It has been reported in women without structural disease,[156] [157] but it is usually associated with structural heart disease, drugs,[158] [159] [160] electrolyte abnormalities,[161] or eclampsia. [162]

Although palpitations, dizziness, and even syncope are relatively common symptoms in normal pregnancy, these are rarely associated with cardiac arrhythmias.[16] Cardiac arrhythmias, however, when they occur, can be hemodynamically significant even in patients with a normal heart during gestation.[19] Reduction in blood pressure occasionally associated with such arrhythmias can result in fetal bradycardia and the need for immediate treatment with antiarrhythmic drugs, electric cardioversion, or urgent cesarean section. The effect of pregnancy on women with the hereditary long QT syndrome has been reported.[163] The postpartum interval was associated with a significant increase in the risk for cardiac events, including death, aborted cardiac arrest, and syncope. Treatment with beta-adrenergic blockers was independently associated with a decrease in the risk for cardiac events.

Synchronized electrical cardioversion has been performed safely during all stages of pregnancy[157] [164] [165] and can be used in patients with tachyarrhythmias unresponsive to drug therapy that are associated with hemodynamic decompensation. Insertion of an implantable cardioverter-defibrillator has not been reported during pregnancy; however, pregnancies in women with an implantable cardioverter-defibrillator have been reported

to be uneventful.[166]

COMPLETE HEART BLOCK.

This condition has been described during pregnancy and is usually congenital.[167] [168] [169] Patients with complete heart block may remain asymptomatic during pregnancy and have an uncomplicated labor and delivery without treatment.[167] Improvement of atrioventricular nodal conduction during two successive uncomplicated pregnancies in a patient with congenital heart block has been reported.[170] Symptomatic patients with conduction abnormalities, including bifascicular block,[171] second-degree atrioventricular block,[172] and complete heart block,[173] have been treated during pregnancy with either temporary or permanent pacemakers; and numerous pregnancies have been reported in patients after pacemaker implantation. In an attempt to reduce exposure to ionizing radiation, placement of a pacemaker during pregnancy has been done with electrocardiographic and echocardiographic guidance in some cases.[172] [174] Skin irritation and ulceration at the implant site due to enlargement of the breast and abdomen during pregnancy have been reported.

MANAGEMENT OF ARRHYTHMIAS.

A complete evaluation is indicated in patients with arrhythmias during pregnancy to rule out a treatable cause such as electrolyte imbalance, thyroid disease, and arrhythmogenic effects of drugs, alcohol, caffeine, and cigarette smoking. An identified cause should be treated and antiarrhythmic drug therapy initiated only if the arrhythmia persists and is symptomatic, hemodynamically important, or life threatening. When drug therapy seems necessary, the smallest therapeutic dose of drugs known to be safe for the fetus should be used (Table 65-10) . Therapeutic blood levels and the indication for continuous drug therapy should be reevaluated periodically. Electrophysiological evaluation is usually postponed until the postpartum period but can be performed under echocardiographic guidance if indicated during pregnancy.[174] Because of the unpredictable exposure to ionizing radiation, catheter ablation procedures should be performed, if possible, after delivery.

OTHER CARDIOVASCULAR DISORDERS

Aortic Dissection (See also Chap. 40)

A predisposition to aortic dissection during gestation has been suggested.[175] [176] Over the past 50 years, approximately 200 cases of aortic dissection in association with pregnancy have been reported. The incidence is increased among multiparous women older than age 30 years with coarctation of the aorta and Marfan syndrome. Pregnancy-related aortic dissection may be due to alterations in the structure of the vascular wall[175] [177] and seems to occur most often during the third trimester and peripartum period.

Transesophageal echocardiography provides a powerful and safe tool for establishing the diagnosis of aortic dissection during pregnancy.[178] This method is preferable to

computed tomography, which involves radiation exposure, and to magnetic resonance imaging, the safety of which during gestation has not been fully established.[32]

The combination of intravenous nitroprusside and beta-adrenergic blocking agents is currently recommended to control hypertension in nonpregnant patients with aortic dissection. Because nitroprusside can result in fetal toxicity, it should be used only post partum or in patients refractory to other drugs during pregnancy and can be substituted by hydralazine or nitroglycerin.[90] To avoid blood pressure elevation associated with labor and vaginal delivery in women with aortic dissection, cesarean section using epidural anesthesia is recommended.[179] [180]

Takayasu Arteritis (See Chap. 67)

Because Takayasu arteritis often occurs in young women, there is a high likelihood of pregnancy in patients with this condition.[181] Review of the literature revealed information on pregnancies in over 50 women with Takayasu disease.[182] The majority of more recently published cases have reported favorable maternal outcome, although increase in blood pressure during pregnancy and the development of heart failure have been described.[183] [184] Although fetal growth retardation and premature labor and delivery are common,[185] [186] [187] favorable fetal outcome has been reported in most cases. Mode of delivery in the majority of cases was vaginal, and forceps were often used to expedite the second stage of labor. Cesarean section delivery has been performed mainly for obstetrical indications or maternal hypertension and vascular disorders. In the great majority of patients, abdominal delivery has been performed under epidural anesthesia with

TABLE 65-10 -- CARDIOVASCULAR DRUGS IN PREGNANCY

DRUG	USE IN PREGNANCY	POTENTIAL SIDE EFFECTS	SAFETY	BREASTFEEDING[213]
Adenosine[19]	Maternal and fetal arrhythmias	No side effects reported in >30 cases treated for maternal arrhythmia; data on use during first trimester, however, are limited to few patients.	Safe	NA

Amiodarone[215]	Maternal and fetal arrhythmias	IUGR, prematurity, hypothyroidism	Unsafe	Not recommended
Angiotensin-converting enzyme inhibitors[216]	Hypertension	Oligohydramnios, IUGR, prematurity, neonatal hypotension, renal failure, anemia, and death. Skull ossification defect, limb contractures, patent ductus arteriosus	Unsafe	Compatible
Beta-adrenergic blocking agents[217]	Hypertension, maternal arrhythmias, myocardial ischemia, mitral stenosis, hypertrophic cardiomyopathy, hyperthyroidism, Marfan syndrome	Fetal bradycardia, low placental weight, prolonged labor, low birth weight, hypoglycemia, respiratory dysfunction	Safe	Compatible; monitoring of infant's heart rate recommended
Digoxin[218]	Maternal and fetal arrhythmias, heart failure	Low birth weight, prematurity	Safe	Compatible
Disopyramide[215]	Maternal arrhythmias	May induce uterine contraction and delivery	Limited data	Compatible
Diuretics[219]	Hypertension, congestive heart failure	Reduced uteroplacental perfusion	Potentially unsafe	Compatible

Flecainide[215]	Maternal and fetal arrhythmias	Two cases of fetal death after successful maternal treatment for fetal supraventricular tachycardia reported. Neither death could be attributed with certainty to flecainide.	Limited data	Compatible
Lidocaine[215]	Local anesthesia, maternal arrhythmias	May cause infants central nervous depression at birth with high dose	Safe	Compatible
Mexiletine[215]	Maternal arrhythmias	Fetal bradycardia, IUGR, low Apgar score, and neonatal hypoglycemia have been reported	Limited data	Compatible
Nifedipine[90]	Hypertension	Fetal distress due to maternal hypotension reported	Safe	Compatible
Organic nitrates[90]	Myocardial infarction and ischemia, hypertension, pulmonary edema, tocolysis	Fetal heart rate deceleration and bradycardia	Limited data	NA
Procainamide[215]	Maternal and fetal arrhythmias	None reported	Probably safe	Compatible

Propafenone[215]	Maternal and fetal arrhythmias	Fetal death reported after direct intrauterine administration in fetuses with nonimmune fetal hydrops	Limited data	NA
Quinidine[215]	Maternal and fetal arrhythmias	Minimal oxytoxic activity, high doses may cause premature labor and abortion. Transient neonatal thrombocytopenia and damage to eighth nerve reported	Safe	Compatible
Sodium nitroprusside[90]	Hypertension, aortic dissection	Potential thiocyanate toxicity with high-dose, fetal mortality reported in animals	Potentially unsafe	NA
Sotalol[217]	Maternal arrhythmias, hypertension, fetal tachycardia	Fetal bradycardia, IUGR	Limited data	Compatible; significant quantities in breast milk, careful monitoring of infants recommended

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (a
is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Catetory B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no co
studies in pregnant women or animal-reproduction studies have shown an adverse effect (other th
decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and th
evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or emb
or other) and there are no controlled studies in women or studies in women and animals are not ava
Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant wom
be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious
for which safer drugs cannot be used or are ineffective).

IUGR=intrauterine growth retardation; NA=no data available.

*Risk factors have been assigned based on level of risk to the fetus[214] :

favorable results. A study of C-reactive protein scores and digital plethysmography showed improvement rather than deterioration of Takayasu arteritis with pregnancy.

Primary Pulmonary Hypertension (See Chap. 53)

Primary pulmonary hypertension is one of the few cardiovascular conditions in which pregnancy can be associated with a high maternal mortality. Review of the literature has revealed maternal mortality of 30 to 40 percent.[188] [189] Clinical deterioration during pregnancy or death cannot be predicted on the basis of the patient's preconceptual clinical status. Symptomatic deterioration usually occurs in the second trimester and is manifested by fatigue, exertional dyspnea, syncope, chest pain, palpitations, nonproductive cough, hemoptysis, and leg edema. Worsening of symptoms during pregnancy led to early hospitalization in many reported cases. Death has occurred a few hours to several days post partum, usually due to sudden death or progressive right ventricular failure. Although the exact cause of death in patients with primary pulmonary hypertension is not clear, right ventricular ischemia and failure, cardiac arrhythmias, and pulmonary embolism are likely mechanisms. In addition to high maternal risk, primary pulmonary hypertension is associated with poor fetal outcome with high incidence of fetal loss, prematurity, and fetal growth retardation.[188]

Because of the potential deleterious effect of pregnancy on both mothers with primary pulmonary hypertension and their fetuses, pregnancy should be avoided in these patients and tubal ligation should be recommended. Because an etiological link between pulmonary hypertension and estrogen-containing oral contraceptives has been suggested, this form of birth control is not recommended for women with primary pulmonary hypertension. Early abortion is indicated in patients with primary pulmonary hypertension who become pregnant. If the patient elects to continue the pregnancy, physical exertion should be restricted to reduce the circulatory load. The incidence of premature deliveries is increased in patients with primary pulmonary hypertension and should be anticipated. Because of the beneficial effect of anticoagulation in patients with primary pulmonary hypertension[190] [191] and the increased incidence of thromboembolism during pregnancy, such therapy is recommended throughout gestation or at least during the third trimester and early postpartum phase. Hemodynamic monitoring and blood gas measurements should be performed continuously during labor and delivery. Oxygen should be provided to prevent hypoxemia, and every effort should be made to prevent or immediately correct blood loss during delivery.[188]

Most patients can tolerate vaginal delivery, and spontaneous labor is preferable to induction. Because of the high rate of early postpartum maternal death, close monitoring is recommended for several days post partum. Successful short-term use of calcium antagonists has been reported in patients with primary pulmonary hypertension during pregnancy.[192] Prostaglandins have also been used to lower pulmonary pressure for a

short period during pregnancy.[192] The safety of these drugs, when used chronically, however, is not known.

Cardiac Surgery During Pregnancy

Because heart disease that requires surgery is usually diagnosed and treated before pregnancy, cardiac surgery during gestation is uncommon; and the experience continues to be anecdotal.[193] [194] The effects of anesthesia and the surgical procedure, especially cardiopulmonary bypass, on the uteroplacental circulation and fetal outcome are still not well understood. Recent review of the literature published between 1984 and 1996[194] identified 161 cases of various cardiovascular operations, 137 with and 24 without cardiopulmonary bypass.[195] Surgery during pregnancy resulted in high fetal-neonatal mortality of 30 percent. Week of gestation at time of surgery, surgery with cardiopulmonary bypass, longer duration, and temperature of cardiopulmonary bypass did not influence fetal-neonatal outcome. Operations performed during pregnancy resulted in a moderately high maternal mortality at 6 percent, and surgery performed immediately after delivery was associated with even higher mortality at 12 percent. Hospitalization after the 27th gestational week and emergency surgery were associated with poor maternal outcome. Nine percent maternal mortality was reported in cases that involved valvular surgery and 22 percent in cases of aortic or arterial dissection repairs and pulmonary embolectomies. Maternal risk associated with peripartum cardiovascular surgery seems therefore higher than risk of similar surgery in nonpregnant patients.

Because of high incidence of fetal wastage and moderate increase in maternal risk, surgery should be recommended only for patients who do not respond to medical therapy. To minimize the risk of teratogenicity, surgery should be avoided during the first trimester. Because heart surgery is indicated after failure of medical therapy, many of these patients will be hemodynamically unstable and will require hemodynamic evaluation and optimization before operation and monitoring during surgery. Anesthetic agents should be selected on the basis of their hemodynamic effects and fetal safety. When the patient is at or near term, abdominal delivery by cesarean section can be performed before cardiac surgery, once fetal maturity has been confirmed. Fetal heart monitoring should be performed continuously during surgery by experienced personnel.

Pregnancy in Patients with Prosthetic Heart Valves (See Chap. 46)

VALVE SELECTION.

The selection of a prosthetic heart valve for women of childbearing age remains difficult.[195] [196] New-generation mechanical valves offer excellent durability, low risk of reoperation, and superior hemodynamic profile. However, the need for anticoagulation is associated with an increased risk of maternal bleeding and fetal loss. Tissue valves have a high incidence of deterioration in young patients, which is further accelerated during pregnancy,[197] [198] [199] [200] with a 30 percent expected rate of valve replacement within 10 years, and an inferior hemodynamic profile, especially with small valve sizes in the aortic position.[201] Although homograft valves and new pericardial valves appear to have better hemodynamics, information regarding pregnancy in women with these valves is limited.[202] [203] Because of their durability and hemodynamic advantage, and,

with careful anticoagulation, only a small risk of thromboembolic as well as bleeding complications, second-generation mechanical prostheses seem to be the preferred choice in all women of childbearing age who need valve replacement and who can be closely monitored.

Risks associated with pregnancy in women with prosthetic valves are related mainly to the increased hemodynamic burden and incidence of thromboembolic events as well as to fetal untoward effects caused by cardiovascular drugs and anticoagulation. Experience in more than 1000 pregnancies indicates that most asymptomatic or mildly symptomatic patients before gestation tolerate the hemodynamic burden of pregnancy, although decreased functional capacity and need to start or increase drug therapy are not uncommon.[197] [198] [199] [200] [201] [202] [203] [204]

Increased thromboembolic events have been reported, with an incidence as high as 10 to 15 percent. Approximately two thirds of these patients present with valve thrombosis, leading to death in 40 percent of them.[197] [198] [199] [200] Thromboembolism, however, has been reported mostly with older-generation mechanical prostheses in the mitral position.[197] [198] [199] [200] [204] Heparin has been considered the anticoagulant of choice during pregnancy because of its proven safety for both the patient and the fetus.[205] Oral anticoagulant

Figure 65-5 Suggested algorithm for the management of anticoagulation in patients with mechanical prosthetic heart valves during pregnancy.

agents have been considered contraindicated in pregnancy because of their teratogenic effect, increased fetal bleeding complications, and risk of central nervous system damage during gestation. Reports of increased incidence of mechanical valve thrombosis during use of subcutaneous heparin during pregnancy[198] [199] [204] have raised concern regarding the effectiveness of heparin in pregnant women with mechanical heart valves.[206] This has led to recommendations for the use of warfarin as an anticoagulant of choice for the first 35 weeks of pregnancy in patients with a mechanical prosthetic valves.[198] [204] [207] [208] These recommendations have been problematic and have not been adopted by both patients and physicians, especially in the United States.[209] [210] The concern regarding use of warfarin during pregnancy is related to the risk of warfarin-induced embryopathy (depressed nasal bridge, nasal hypoplasia, small nasal bones, hypoplastic alae nasi, telacanthus, upper airway obstruction due to choanal stenosis, and punctate epiphyseal dysplasia of the long bones and the cervical and lumbar vertebral plates) and increased risk of intracranial bleeding.[205] The incidence of warfarin-induced embryopathy is 5 to 9 percent and is dose related.[206] [211] Limited information indicates that in patients with new-generation mechanical prosthetic valves the use of adjusted-dose heparin either throughout pregnancy or during the first trimester and after the 35th to 36th week of gestation is safe.[195]

ANTICOAGULATION (see also Chap. 46) .

Our recommendations for anticoagulation during pregnancy in patients with mechanical valve prosthesis are shown in Figure 65-5 . Thromboembolic prophylaxis of women seems to be best achieved with oral anticoagulation with first-generation prosthetic valves in the mitral position, especially in those patients who can achieve therapeutic anticoagulation with less than 5 mg/d of warfarin (international normalized ratio of 3.0-4.5) for the first 35 weeks. An alternative therapy for patients electing to avoid warfarin in the first gestational trimester is intravenous or subcutaneous heparin with aggressive monitoring and appropriate dose adjustment[206] for the first trimester, followed by warfarin between 13 and 36 weeks and then intravenous or subcutaneous heparin until delivery. High heparin intensity should be used in patients at high risk, aiming at antifactor Xa levels of 0.55 to 0.8 U/ml or an activated partial thromboplastin time of 2.5 to 3.5.

Because of a high incidence of premature labor in patients with prosthetic heart valves,[204] [209] warfarin should be substituted for heparin at the 35th or 36th week to avoid onset of labor during warfarin therapy. The switch from warfarin to heparin should be performed in the hospital. In lower-risk patients, including those with an aortic prosthetic valve and second-generation prosthesis in the mitral position, subcutaneous heparin therapy is advocated throughout pregnancy (activated partial thromboplastin time of 2.0-3.0).[195] [196] [205] Use of warfarin during weeks 13 to 35 or 36 is an alternative regimen in cases in which self-injection of heparin is not desirable by the patient or is associated with side effects. A higher level of anticoagulation seems justified in patients with mechanical prostheses in the mitral position, in patients with more than one mechanical prosthesis, in patients with atrial fibrillation, and/or in patients with a history of systemic embolization. The intensity of anticoagulation should be frequently monitored and immediately corrected if needed. Because a small dose of aspirin is safe during pregnancy[143] and can reduce the incidence of systemic embolization or death when added to oral anticoagulation,[212] 80 mg of aspirin may be added to maximize the antithrombolic effect.

Safe use of low-molecular-weight heparin has been reported in few patients with prosthetic heart valve.[195] Low-molecular-weight heparin provides a better effect, owing to its superior bioavailability and longer half-life, and may reduce the risk of bleeding and osteoporosis. This drug, however, is less readily reversible by protamine sulfate and may be more difficult to handle during labor and delivery. More information is therefore required before low-molecular-weight heparin can be routinely recommended for anticoagulation in a patient with a prosthetic valve during gestation. For more information on cardiovascular drugs, see Table 65-10 . [213] [214] [215] [216] [217] [218] [219]

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GUIDELINES
MANAGEMENT OF VALVULAR DISEASE IN PREGNANCY

Thomas H. Lee

Recommendations for management of valvular heart disease in pregnancy are included in the 1998 ACC/AHA guidelines on valvular disease.[1] These guidelines do not recommend routine antibiotic prophylaxis in patients with valvular heart disease undergoing uncomplicated vaginal delivery or cesarean section unless infection is suggested. For high-risk patients, such as those with prosthetic heart valves or prior histories of endocarditis, antibiotics are considered optional.

Complex guidelines are offered on anticoagulation for patients with mechanical prosthetic heart valves (Table 65-G-1) . These guidelines reflect high complication rates in pregnant women managed with subcutaneous heparin and support the use of intravenous heparin during the first trimester. After the 36th week of pregnancy, transition from warfarin to heparin is recommended in anticipation of labor. Data on low-molecular-weight heparin in this setting were too sparse for the development of recommendations.

TABLE 65--G-1 -- GUIDELINES FOR ANTICOAGULATION DURING PREGNANCY IN PATIENTS WITH MECHANICAL PROSTHETIC VALVES

Indication	Class I	Class IIa	Class IIb	Class III

Anticoagulation during pregnancy in patients with mechanical prosthetic valves: weeks 1 through 35	The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.[2] High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose *not* to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the midinterval (6 hours after dosing) aPTT to two to three times control. Transition to warfarin can occur thereafter.	In patients receiving warfarin, INR should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.	Women at low risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted-dose subcutaneous heparin (17,500 to 20,000 U b.i.d.) to prolong the mid-interval (6 hours after dosing) aPTT to two to three times control.

Anticoagulation during pregnancy in patients with mechanical prosthetic valves: after the 36th week		Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor. If labor begins during treatment with warfarin, a cesarean section should be performed. In the absence of significant bleeding, heparin can be resumed 4 to 6 hours after delivery and warfarin begun orally.		

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

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Chapter 66 - Rheumatic Fever

ADNAN S. DAJANI

Rheumatic fever (RF) is generally classified as a connective tissue disease or collagen-vascular disease. Its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissue. The rheumatic process is expressed as an inflammatory reaction that involves many organs, primarily the heart, the joints, and the central nervous system. The clinical manifestations of acute RF follow a group A streptococcal (GAS) infection of the tonsillopharynx after a latent period of approximately 3 weeks. The major importance of acute RF is its ability to cause fibrosis of heart valves, leading to crippling hemodynamics of chronic heart disease.

RF is the most common cause of acquired heart disease in children and young adults worldwide. Although the incidence of RF declined sharply in many developed countries, the disease remains a major problem in many developing countries. The precise reasons for the fluctuations in the incidence of the disease remain only partly understood. Although RF has been studied extensively, the pathogenesis of the disease is not well defined.

Epidemiology

The incidence of RF and prevalence of rheumatic heart disease are markedly variable in different countries.[1] [2] At the beginning of the 20th century, the incidence of RF in the United States exceeded 100 per 100,000 population, ranged between 40 and 65 per 100,000 between 1935 and 1960, and is currently estimated at less than 2 per 100,000. Beginning in 1984, several outbreaks of acute RF were reported from a number of geographically distinct areas in the United States.[2] These focal outbreaks were not associated with a national increase in the incidence of RF.[3] The decline in the incidence of RF in industrialized countries is in sharp contrast to the persistent high incidence of the disease in nonindustrialized countries.

In many developing countries, the incidence of acute RF approaches or exceeds 100 per 100,000.[1] In keeping with the falling incidence of RF in industrialized countries, the prevalence of rheumatic heart disease has declined. Table 66-1 compares the prevalence of rheumatic heart disease in school-age children in different regions of the world.

The decline in incidence of RF and prevalence of rheumatic heart disease has been attributed to several factors. Although the decline preceded the introduction of antimicrobial agents for the treatment of streptococcal pharyngitis, some reports suggest that the use of these agents may have enhanced the rate of this decline.[4] Improved economic standards, better housing conditions, decreased crowding in homes and schools, and access to medical care are often credited, at least in part, for the marked decline in RF.[1] Epidemiological observations in the United States[5] and the United Kingdom[6] show periodic shifts in the appearance and disappearance of specific M types in a particular geographical location. Such shifts may be another explanation for the decline and resurgence of RF in some parts of the world.

Because of the causal relationship between RF and GAS pharyngitis, the epidemiologies of the two illnesses are very similar. Initial attacks of RF occur most commonly between the ages of 6 and 15 years, and RF rarely occurs before the age of 5 years.[7] The risk of RF is increased in populations at high risk for streptococcal pharyngitis, such as military recruits, persons living in crowded conditions, and those in close contact with school-age children. The incidence of RF is equal in male and female patients. The seasonal incidence of RF also parallels that of streptococcal pharyngitis. The peak incidence of RF in Europe and the United States is in spring. Although RF used to be considered a disease of temperate climates, it is now more common in warm tropical climates, particularly in developing countries.

Pathogenesis

The evidence that GAS is the agent causing initial and recurrent attacks of RF is strong but indirect. It is based on clinical, epidemiological, and immunological observations. Factors that contribute to the pathogenesis of RF are related to both the putative causative agent and the host (Table 66-2) .

THE ETIOLOGICAL AGENT.

An untreated GAS tonsillopharyngitis is the antecedent event that precipitates RF.[8] RF does not follow streptococcal skin infection (impetigo). Proper antimicrobial treatment of streptococcal pharyngitis with eradication of the organism virtually eliminates the risk of RF.[8] In situations conducive to epidemic streptococcal pharyngitis (such as the military population, crowding), as many as 3 percent of untreated acute streptococcal sore throats may be followed by RF.[9] Endemic infections result in much lower attack rates. It has been well documented that about one-third of all cases of acute RF follow mild, almost asymptomatic pharyngitis. The lack of symptomatic pharyngitis was particularly striking in most of the recent outbreaks of acute RF in which the majority of patients (58 percent) had no history of pharyngitis. [2] This is an alarming observation, because primary prevention of acute RF relies on identification and proper treatment of streptococcal pharyngitis.

The major factors that are related to the risk of RF are the magnitude of the immune response to the antecedent streptococcal pharyngitis and persistence of the organism during convalescence.[9] Variations in the rheumatogenicity of GAS strains are a factor influencing the attack rate of RF.[10] The concept that RF is associated with infections due to virulent encapsulated (mucoid) strains capable of inducing strong type-specific immune responses to M protein and other streptococcal antigens[11] has been strengthened by observations made during the outbreaks of acute RF in the

TABLE 66-1 -- RHEUMATIC HEART DISEASE IN SCHOOL-AGE CHILDREN

LOCATION	PREVALENCE PER 1000
United States	0.6
Japan	0.7
Asia (other)	0.4-21.0
Africa	0.3-15.0
South America	1.0-17.0

TABLE 66-2 -- PATHOGENESIS OF RHEUMATIC FEVER GROUP A STREPTOCOCCUS

Tonsillopharyngeal infection, no other sites
Intensity of the infection
Brisk antibody response

Persistence of the organism

Rheumatogenic strains

M types 1, 3, 5, 6, 14, 18, 19, 27, and 29

Distinct structural characteristics of M proteins

Long terminal antigenic domain

Epitopes shared with human heart tissue

Heavily encapsulated, forming mucoid colonies

Resistance to phagocytosis

Does not produce opacity factor

SUSCEPTIBLE HOST

Genetic predisposition

Presence of specific B-cell alloantigen

High incidence of class II HLA antigens

mid-1980's. The streptococci isolated from patients with RF and their sibling contacts during these outbreaks were primarily strains belonging to M types 1, 3, 5, 6, and 18.[12] M proteins of rheumatogenic streptococci show distinct structural characteristics: They share a long terminal antigenic domain[13] and contain epitopes that are shared with human heart tissue, particularly sarcolemmal membrane proteins and cardiac myosin.[14] [15]

THE HOST.

Although only a small proportion of individuals with untreated streptococcal pharyngitis may develop RF (3 percent), the incidence of the disease after streptococcal pharyngitis in patients who have had a previous episode of RF is substantially greater (about 50 percent). Numerous epidemiological studies also indicate familial predisposition to the disease. These observations and more recent studies strongly suggest a genetic basis for susceptibility to RF. A specific B-cell alloantigen, identified by monoclonal antibodies, has been described in almost all patients (99 percent) with RF but in only a small number (14 percent) of controls.[16] Furthermore, susceptibility to RF has been linked with HLA-DR 1, 2, 3, and 4 haplotypes in various ethnic groups.[17]

Pathology

The acute phase of RF is characterized by exudative and proliferative inflammatory reactions involving connective or collagen tissue. Although the disease process is diffuse, it affects primarily the heart, joints, brain, and cutaneous and subcutaneous tissues. A generalized vasculitis affecting small blood vessels is commonly noted, but unlike the vasculitis of some other connective tissue disorders, thrombotic lesions are not seen in RF.

The basic structural change in collagen is fibrinoid degeneration. The interstitial connective tissue becomes edematous and eosinophilic, with fraying, fragmentation, and disintegration of collagen fibers. This is associated with infiltration of mononuclear cells including large modified fibrohistiocytic cells (Aschoff's cells). Some of the histiocytes are multinucleated and form Aschoff's giant cells.

The Aschoff's nodule in the proliferative stage is considered pathognomonic of rheumatic carditis. These nodules have been found almost invariably in the autopsies of patients who died of rheumatic carditis; however, more recent observations indicate that Aschoff's nodules are observed in only 30 to 40 percent of biopsy specimens from patients with primary or recurrent episodes of RF.[18] Aschoff's bodies may be seen in any area of the myocardium but not in other affected organs such as joints or brain. They are most often noted in the interventricular septum, the wall of the left ventricle, or the left atrial appendage. Aschoff's nodules persist for many years after a rheumatic attack, even in patients with no evidence of recent or active inflammation.

Inflammation of valvular tissue accounts for the more commonly recognized clinical manifestations of rheumatic carditis. Initial inflammation leads to valvular insufficiency. The histological findings in endocarditis consist of edema and cellular infiltration of the valvular tissue and the chordae tendineae. Hyaline degeneration of the affected valve leads to the formation of verrucae at its edge, preventing total approximation of the leaflets. Fibrosis and calcification of the valve occur if inflammation persists. This process may eventually lead to valvular stenosis.

DIAGNOSIS

No specific clinical, laboratory, or other test establishes the diagnosis of RF.[18A] In 1944, T. Duckett Jones formulated his criteria for the diagnosis of RF[19] ; these criteria are still valuable. They have been modified, revised, edited, and updated by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young (American Heart Association).[20] The most recent guidelines (Table 66-3) emphasize the diagnosis of *initial attacks* of RF. Dividing clinical and laboratory findings into major and minor manifestations is based on the diagnostic importance of a particular finding. If supported by evidence of preceding GAS infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute RF.

Major Clinical Manifestations

CARDITIS.

Rheumatic carditis is a pancarditis affecting the endocardium, myocardium, and pericardium to various degrees. Clinically, rheumatic carditis is almost always associated with a murmur of valvulitis. The severity of carditis is variable. In its most severe form, death due to cardiac failure may occur. More commonly, carditis is less intense, and the predominant effect is subsequent scarring of the heart valves.

Evidence of carditis may be very subtle; signs of valvular involvement may be mild and transient and may be easily missed on auscultation. Baseline studies, including electrocardiographs and echocardiographs, should be obtained in patients in whom RF is suspected. Patients who show no clear evidence of carditis on initial examination should be closely monitored for a few weeks to assess cardiac involvement.

Carditis is often regarded as the most specific manifestation

TABLE 66-3 -- GUIDELINES FOR THE DIAGNOSIS OF INITIAL ATTACKS OF RHEUMATIC FEVER (JONES CRITERIA, UPDATED 1992)

MAJOR MANIFESTATIONS	**MINOR MANIFESTATIONS**
Carditis	Clinical findings
Polyarthritis	Arthralgia
Chorea	Fever
Erythema marginatum	Laboratory findings
Subcutaneous nodules	Elevated acute phase reactants
	Erythrocyte sedimentation rate
	C-reactive protein
	Prolonged PR interval

SUPPORTING EVIDENCE OF ANTECEDENT A STREPTOCOCCAL INFECTION

Positive throat culture or rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer

From Dajani AS, Ayoub EM, Bierman FZ, et al: Guidelines for the diagnosis of rheumatic fever: Jones Criteria, updated 1992. JAMA 268:2069, 1992. Copyright 1992 American Medical Association.

Figure 66-1 Relative frequency of major manifestations of rheumatic fever in earlier (dark bars) and more recent (light bars) reports in the 1980s

of RF. It is noted in at least 50 percent of patients with acute RF (Fig. 66-1) . Recent outbreaks in the United States suggested that the frequency of carditis was somewhat higher than traditionally reported and may be in part due to more sophisticated diagnostic methods.[2] In one report, carditis was diagnosed in 72 percent of cases by auscultation and in 91 percent of cases by Doppler ultrasonography. The risk of overdiagnosing valvular incompetence by echocardiography should be emphasized, and overreliance on this tool in diagnosing rheumatic carditis should be avoided.

Valvulitis (endocarditis) involving mitral and aortic valves and the chordae of the mitral valve is the most characteristic component of rheumatic carditis. Mitral regurgitation is the hallmark of rheumatic carditis. Aortic regurgitation is less common and usually associated with mitral regurgitation. The pulmonic and tricuspid valves are rarely involved. Residual valvular damage is a major concern in patients with RF and may lead to intractable cardiac failure requiring surgical intervention.

Myocarditis or pericarditis in the *absence* of valvulitis is *not* likely to be due to RF. Tachycardia is an early sign of myocarditis but may also be due to fever or cardiac failure. Transient arrhythmias may occur in patients with myocarditis. Severe myocarditis or valvular regurgitation may lead to cardiac failure. Cardiac enlargement occurs when severe hemodynamic changes result from valvular, myocardial, or pericardial disease. Inflammation of the visceral and parietal surfaces of the pericardium occurs, resulting in pericarditis and the accumulation of pericardial fluid.

ARTHRITIS.

Polyarthritis is the most common major manifestation of RF (see Fig. 66-1) but the least specific. It is almost always asymmetric and migratory and involves larger joints (knees, ankles, elbows, and wrists). Swelling, redness, heat, severe pain, limitation of motion, and tenderness to touch are characteristic. The arthritis of RF is benign and does not result in permanent joint deformity. Joint fluid shows findings characteristic of inflammation (not infection). In untreated cases, arthritis usually lasts 2 to 3 weeks. A striking feature of rheumatic arthritis is its dramatic response to salicylates. Indeed, if a patient does not improve substantially after 48 hours of adequate salicylate treatment, the diagnosis of RF should be in doubt.

Some patients may develop arthritis and other multisystem manifestations after acute streptococcal pharyngitis that do not fulfill the Jones criteria for the diagnosis of acute RF. This "syndrome" has been referred to as poststreptococcal reactive arthritis (PSRA). The arthritis of PSRA does not respond dramatically to antiinflammatory agents. Some patients with PSRA may have silent or delayed-onset carditis[21] ; therefore, these patients should be carefully observed for several months for the subsequent development of carditis.

CHOREA.

Sydenham's chorea, St. Vitus' dance, or chorea minor occurs in about 20 percent of patients with RF (see Fig. 66-1) . The rheumatic inflammatory process in the central nervous system specifically involves the basal ganglia and caudate nuclei. Chorea is a *delayed* manifestation of RF, usually appearing 3 months or longer after the onset of the precipitating streptococcal infection. This is in sharp contrast to the latent period of carditis or arthritis, which is usually 3 weeks. As such, chorea is frequently the only manifestation of RF. Furthermore, evidence of a recent GAS infection may be difficult to document, and other supporting historical, clinical, or laboratory findings to fulfill the Jones criteria may be lacking. The diagnosis of RF can be made in a patient with chorea

without strictly adhering to the Jones criteria.

Sydenham's chorea is characterized clinically by purposeless and involuntary movements, muscle incoordination and weakness, and emotional lability. The manifestations are more evident when a patient is awake and under stress and may disappear during sleep. All muscles may be involved, but primarily muscles of the face and extremities. Speech may be affected, being explosive and halting. Handwriting deteriorates, and patients become uncoordinated and easily frustrated. The symptoms of Sydenham's chorea must be distinguished from tics, athetosis, conversion reactions, hyperkinesis, and behavior problems. Symptoms usually resolve in 1 to 2 weeks, even without treatment.

ERYTHEMA MARGINATUM.

This distinctive rash is a rare manifestation of RF, occurring in less than 5 percent of patients. It is an evanescent, erythematous, macular, nonpruritic rash with pale centers and rounded or serpiginous margins. Lesions vary greatly in size and occur mainly on the trunk and proximal extremities, not on the face. The rash may be induced by application of heat.

SUBCUTANEOUS NODULES.

These are firm, painless, freely movable nodules that measure 0.5 to 2 cm. They are rarely seen in patients with RF (about 3 percent); when present, they are most often seen in patients with carditis. They are usually located over extensor surfaces of the joints (particularly elbows, knees, and wrists), in the occipital portion of the scalp, or over spinous processes. The overlying skin is freely movable, shows no discoloration, and is not inflamed.

Minor Manifestations

CLINICAL FINDINGS.

Fever and arthralgia are nonspecific, common findings in patients with acute RF. Their diagnostic value is limited because they are encountered commonly in various other diseases. They are used to support the diagnosis of RF when only a single major manifestation is present. Fever is noted during the acute stages of the disease and has no characteristic pattern. Arthralgia is pain in one or more large joints without objective findings on examination and must not be considered a minor manifestation if arthritis is present. Epistaxis and abdominal pain may also occur but are not included as minor diagnostic criteria for RF.

LABORATORY FINDINGS.

Elevated acute phase reactants offer objective but nonspecific indications of tissue inflammation. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

level are almost always elevated during the acute stages of the disease in patients with carditis or polyarthritis but are usually normal in patients with chorea. The ESR is useful in monitoring the course of the disease; it usually returns to normal as the rheumatic activity subsides. The ESR may be elevated in patients with anemia and may be suppressed to normal levels in patients with congestive cardiac failure. Unlike the ESR, the CRP level is unaffected by anemia or cardiac failure.

A common finding in patients with acute RF is a prolonged PR interval for age and rate on electrocardiography. This finding alone is not diagnostic of carditis and does not

correlate with the ultimate development of chronic rheumatic cardiac disease. Other findings on electrocardiography include tachycardia, atrioventricular block, and QRS-T changes suggestive of myocarditis; these changes are not considered minor manifestations.

Leukocytosis may be observed in the acute stages of RF, but the leukocyte count is variable and not dependable. Anemia is usually mild or moderate and normocytic normochromatic in morphology (anemia of chronic inflammation). Chest roentgenograms are useful in assessing cardiac size; however, normal findings on a chest roentgenogram do not preclude the presence of carditis. Pericarditis, pulmonary edema, and increased pulmonary vascularity are also detected by this examination. Echocardiography may be helpful in detecting endocardial, myocardial, and pericardial involvement. Antimyosin antibody imaging has been reported to be useful in the detection of rheumatic carditis.[21A]

Antecedent Group A Streptococcal Infection

A number of illnesses mimic acute RF, and no laboratory test or tests establish a specific diagnosis of RF. It is therefore important to establish an antecedent streptococcal infection by demonstrating GAS in the tonsillopharynx or an elevated or rising streptococcal antibody titer. *Evidence of an antecedent streptococcal infection is required for confirmation of the initial diagnosis of acute RF.*

At the time of diagnosis of acute RF, only about 11 percent of patients have throat cultures positive for GAS.[2] The paucity of positive cultures is due, in part, to elimination of the organism by host defense mechanisms during the latent period between the onset of the infection and the subsequent development of RF. Several rapid GAS antigen detection tests are commercially available. These tests vary in method. Most have a high degree of specificity but a low sensitivity in a clinical setting. A negative test result does not preclude the presence of GAS in the pharynx. A positive throat culture result or rapid antigen test does not distinguish between a recent infection that can be associated with acute RF and chronic pharyngeal carriage of the organism.

Because the presence of GAS in the pharynx may not represent active infection,

elevated or rising antistreptococcal antibody titers provide more reliable evidence of a recent streptococcal infection than does a positive culture or a positive rapid antigen test result. The most commonly used antibody tests are the antistreptolysin O (ASO) and antideoxyribonuclease B (anti-DNase B). The ASO test is usually performed first, and if results are not elevated, the anti-DNase B test is done. Elevated titers for both tests may persist for several weeks or months. ASO titers rise and fall more rapidly than anti-DNase B. A commercially available slide agglutination test measures antibodies to several streptococcal antigens. It is simple to perform, rapid, and widely available; however, the test is not well standardized and not very reproducible and is not recommended as a definitive test for evidence of a preceding GAS infection.

TREATMENT

GENERAL.

Whenever possible, patients should be admitted to a hospital for close observation and appropriate work-up. Bed rest is generally considered important because it lessens joint pain. The duration of bed rest may be variable and individually determined. Ambulation may be attempted once fever abates and acute phase reactants return to normal. Patients should be allowed to return to a reasonably active life with normal physical activity. Strenuous physical exercise should be avoided, however, particularly if carditis was present. Although throat cultures are rarely positive for GAS at the time of onset of RF, patients should receive a 10-day course of penicillin therapy. Patients allergic to penicillin should be treated with erythromycin.

If heart failure intervenes, patients should receive diuretics, oxygen, and digitalis and be on a restricted sodium diet. Digitalis preparations should be used cautiously because cardiac toxicity may occur with conventional dosages.

ANTIRHEUMATIC THERAPY.

There is no specific treatment for the inflammatory reactions initiated by RF. Supportive therapy is aimed at reducing constitutional symptoms, controlling toxic manifestations, and improving cardiac function.

Patients with mild or no carditis usually respond well to salicylates. Salicylates are particularly effective in relieving joint pain; such pain usually abates within 24 hours of starting salicylates. Indeed, if joint pain persists after salicylate treatment, the diagnosis of RF may be questionable and patients should be reevaluated. Because no specific diagnostic tests for RF exist, antiinflammatory therapy should be withheld until the clinical picture has become sufficiently clear to allow for a diagnosis. Early administration of antiinflammatory agents may suppress clinical manifestations and prevent appropriate diagnosis. For optimal antiinflammatory effect, serum salicylate levels around 20 mg percent are required. Aspirin, at doses of 100 mg/kg/d, given four to five times daily, usually results in adequate serum levels to achieve a clinical response. Optimal salicylate therapy must be individualized, however, to ensure adequate response and avoid toxicity. Tinnitus, nausea, vomiting, and anorexia are

common dose-related toxicities associated with salicylism. Side effects may subside after a few days of treatment despite continuation of the medication.

Patients with significant cardiac involvement--particularly those with pericarditis or congestive heart failure--respond more promptly to corticosteroids than to salicylates. Indeed, steroids may be life saving in very ill patients. Patients who do not respond to adequate doses of salicylates may occasionally benefit from a trial course of corticosteroids. Prednisone, 1 to 2 mg/kg/d, is the usual dose.

There is no evidence that salicylate or corticosteroid therapy affects the course of carditis or diminishes the incidence of residual heart disease. Therefore, the duration of therapy with antiinflammatory agents is arbitrarily based on an estimate of the severity of the episode and the promptness of the clinical response.

Mild attacks with little or no cardiac involvement may be treated with salicylates for about 1 month or until there is sufficient clinical and laboratory evidence of inflammatory inactivity. In more severe cases, therapy with corticosteroids may be continued for 2 to 3 months. The medication is then gradually reduced over the next 2 weeks. Even with prolonged therapy, some patients (approximately 5 percent) continue to demonstrate evidence of rheumatic activity for 6 months or more. A "rebound," manifested by reappearance of mild symptoms or of acute phase reactants, may occur in some patients after antiinflammatory medications have been discontinued, usually within 2 weeks. Modest symptoms usually subside without treatment; more severe symptoms may require treatment with salicylates. Some physicians recommend the use of salicylates (aspirin, 75 mg/kg/d) during the period when corticosteroids are being tapered and believe that such an approach may reduce the likelihood of a rebound.

Information about the use of salicylates other than aspirin is very limited. No evidence shows that other nonsteroidal antiinflammatory agents are more effective than aspirin. In patients who cannot tolerate aspirin or who are allergic to it, a trial of other nonsteroidal agents may be warranted. Aspirin preparations that are coated or that contain alkali or buffers may also be tried; however, little evidence shows that such preparations are better tolerated, and some may have undesirable side effects.

PREVENTION

Primary Prevention

Prevention of primary attacks of RF depends on prompt recognition and proper treatment of GAS tonsillopharyngitis. Eradication of GAS from the throat is essential. Although appropriate antimicrobial therapy started up to 9 days after the onset of acute streptococcal pharyngitis is effective in preventing primary attacks of rheumatic fever,[8] early therapy is advisable because it reduces both morbidity and the period of infectivity. In selecting a regimen for the treatment of GAS pharyngitis, various factors should be

considered, including bacteriological and clinical efficacy; ease of adherence to the recommended regimen (frequency of daily administration, duration of therapy, palatability); cost; spectrum of activity of the selected agent; and potential side effects.[22]

Penicillin is the antimicrobial agent of choice for the treatment of GAS, except in patients with history of allergy to penicillin.[23] [24] Penicillin has a narrow spectrum of activity, has a longstanding proven efficacy, and is the least expensive regimen. GAS resistant to penicillin has not been documented.[25] Penicillin may be administered intramuscularly or orally (Table 66-4) , depending on the patient's likely adherence to an oral regimen.

Intramuscular benzathine penicillin G is preferred, particularly for patients who are unlikely to complete a 10-day course of oral therapy and for patients with a personal or family history of RF or rheumatic heart disease. Benzathine penicillin G injections should be given as a single dose in a large muscle mass. This formulation is painful; injections that contain procaine penicillin in addition to benzathine penicillin G are less painful. Less discomfort is associated with intramuscular benzathine penicillin G if the medication is warmed to room temperature before administration.

The oral antibiotic of choice is penicillin V (phenoxymethyl penicillin). Patients should take oral penicillin regularly for an entire 10-day period, although they are likely to be asymptomatic after the first few days. Although the broader-spectrum amoxicillin is often used for treatment of GAS pharyngitis, it offers no microbiological advantage over penicillin.

Oral erythromycin is acceptable for patients allergic to penicillin. Treatment should also be prescribed for 10 days. Erythromycin estolate (20 to 40 mg/kg/d in two to four divided doses), or erythromycin ethyl succinate (40 mg/kg/d in two to four divided doses) is effective in treating streptococcal pharyngitis; however, efficacy of a twice-daily regimen in adults requires further study. The maximal dose of erythromycin is 1 gm/d. Although strains of GAS resistant to erythromycin are prevalent in some areas of the world and have resulted in treatment failures,[26] they are uncommon in most parts of the United States.[25]

The macrolide azithromycin has similar susceptibility to that of erythromycin against GAS but may cause fewer gastrointestinal side effects. Azithromycin can be administered once daily and produces high tonsillar tissue concentrations. A 5-day course of azithromycin is approved by the Food and Drug Administration as a second-line therapy for the treatment of patients 16 years of age or older with GAS pharyngitis. The recommended dosage is 500 mg as a single dose on the first day followed by 250 mg once daily for 4 days.[27]

A 10-day course of an oral cephalosporin is an acceptable alternative, particularly for penicillin-allergic patients. Narrower-spectrum cephalosporins, such as cefadroxil or

TABLE 66-4 -- PREVENTION OF RHEUMATIC FEVER

AGENT	DOSE	ROUTE	DURATION
Primary Prevention			

Benzathine penicillin G	600,000 units for patients kg 1,200,000 units for patients >27 kg	IM	Once
	or		
Pencillin V	Children: 250 mg 2-3 times daily Adolescents and adults: 500 mg 2-3 times daily	PO	10 days
For patients allergic to penicillin:			
Erythromycin	40 mg/kg/d 2-4 times daily (maximum 1 gm/d)	PO	10 days
	Secondary Prevention		
Benzathine penicillin G	1,200,00 units every 3-4 wk	IM	See Table 66-5
	or		
Penicillin V	250 mg b.i.d.	PO	See Table 66-5
	or		
Sulfadiazine	0.5 gm once daily for patients 10104;27 kg (60 lb) 1.0 gm once daily for patients >27 kg (60 lb)	PO	See Table 66-5
For patients allergic to penicillin and sulfadiazine:			
Erythromycin	250 mg b.i.d.	PO	See Table 66-5

IM=intramuscularly; PO=orally.*Modified from Dajani AS, Taubert K, Ferrieri P, et al: Treatment of streptococcal pharyngitis and prevention of rheumatic fever. Pediatrics 96:758, 1995. Reproducted by permission of Pediatrics.*

cephalexin, are probably preferable to the broader-spectrum cephalosporins such as cefaclor, cefuroxime, cefixime, and cefpodoxime. Some penicillin-allergic persons (<15 percent) are also allergic to cephalosporins, and these agents should not be used by patients with immediate (anaphylactic-type) hypersensitivity to penicillin.

Several reports indicate that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx.[28] [29] [30] [31] Reports suggest that a 5-day course with selected oral cephalosporins is comparable to a 10-day course of oral penicillin in eradicating GAS from the pharynx.[32] [33] [34]

Certain antimicrobials are not recommended for treatment of streptococcal upper respiratory tract infections.[24] Tetracyclines should not be used because of the high prevalence of resistant strains. Sulfonamides and trimethoprimsulfamethoxazole will not eradicate GAS in patients with pharyngitis and should not be used to treat active

infections. Chloramphenicol is not recommended because of unpredictable efficacy and potential serious toxicity.

Secondary Prevention

Patients who have suffered a previous attack of RF and who develop streptococcal pharyngitis are at high risk for a recurrent attack of RF. A GAS infection need not be symptomatic to trigger a recurrence. Furthermore, RF can recur even when a symptomatic infection is optimally treated. For these reasons, prevention of recurrent RF requires continuous antimicrobial prophylaxis rather than recognition and treatment of acute episodes of streptococcal pharyngitis.

Continuous prophylaxis is recommended for patients with a well-documented history of RF (including cases manifested solely by Sydenham's chorea) end those with definite evidence of rheumatic heart disease. Such prophylaxis should be initiated as soon as acute RF or rheumatic heart disease is diagnosed. A full therapeutic course of penicillin (as outlined in Table 66-4) should first be given to patients with acute RF to eradicate residual GAS even if a throat culture is negative at that time. Streptococcal infections occurring in family members of rheumatic patients should be treated promptly.

CONTINUOUS ANTIMICROBIAL PROPHYLAXIS.

This provides the most effective protection from RF recurrences. Risk of recurrence depends on several factors. Risk increases with several previous attacks, whereas the risk decreases as the interval since the most recent attack lengthens. The likelihood of acquiring a streptococcal upper respiratory tract infection is an important consideration. Patients with increased exposure to streptococcal infections include children and adolescents; parents of young children; teachers, physicians, nurses, and allied health personnel in contact with children; military recruits; and others in crowded housing. A higher risk of recurrences in economically disadvantaged populations has been demonstrated.

Physicians must consider each individual situation when determining appropriate duration of prophylaxis. Patients who have had rheumatic carditis are at a relatively high risk for recurrences of carditis and are likely to sustain increasingly severe cardiac involvement with each recurrence. Therefore, patients who have had rheumatic carditis should receive long-term antibiotic prophylaxis, perhaps for life. Duration of prophylaxis depends on whether residual valvular disease is present or absent (Table 66-5) . Prophylaxis should continue even after valve surgery, including prosthetic valve replacement. Patients who have had RF without carditis are at considerably less risk of cardiac involvement with a recurrence. Therefore, prophylaxis may be discontinued in these individuals after several years.[35] In general, prophylaxis should continue until 5 years have elapsed since the last RF attack or age 21 years, whichever is longer. The decision to discontinue prophylaxis or reinstate it should be made after discussion with

the patient of potential risks and benefits and careful consideration of the epidemiological risk factors enumerated earlier.

An injection of 1,200,000 units of long-acting penicillin preparation every 4 weeks is the recommended regimen for secondary prevention in most circumstances in the United States (see Table 66-4) . In countries where the incidence of RF is particularly high, in special circumstances, or in certain high-risk individuals, such as patients with residual rheumatic carditis, the administration of benzathine penicillin G every 3 weeks is recommended.[36] Long-acting penicillin is of particular value in patients with a high risk of

TABLE 66-5 -- DURATION OF SECONDARY PROPHYLAXIS IN PATIENTS WITH RHEUMATIC FEVER

CATEGORY	DURATION
Rheumatic fever with carditis and residual valvular disease	At least 10 yr after last episode and at least until age 40 Sometimes lifelong prophylaxis
Rheumatic fever with carditis but no residual valvular disease	10 yr or well into adulthood, whichever is longer
Rheumatic fever without carditis	5 yr or until age 21, whichever is longer

From Dajani AS, Taubert K, Ferrieri P, et al: Treatment of streptococcal pharyngitis and prevention of rheumatic fever. Pediatrics 96:758, 1995; with permission.

recurrence of RF. The advantages of benzathine penicillin G must be weighed against inconvenience to patients and pain of injection, which cause some patients to discontinue prophylaxis.

Successful oral prophylaxis depends primarily on patients' adherence to prescribed regimens. Patients need careful and repeated instructions about the importance of continuing prophylaxis. Most failures of prophylaxis occur in nonadherent patients. Even with optimal patient adherence, risk or recurrence is higher in individuals receiving oral prophylaxis compared with those receiving intramuscular benzathine penicillin G.[22] Oral agents are more appropriate for patients at lower risk for rheumatic recurrence. Accordingly, some physicians switch patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of rheumatic attacks for at least 5 years.

Penicillin V is the preferred oral agent (see Table 66-4) . There are no published data about the use of other penicillins, macrolides, or cephalosporins for secondary prevention of RF. Although sulfonamides are not effective in eradication of GAS, they do prevent infection. Sulfadiazine and sulfisoxazole appear to be equivalent; the use of sulfisoxazole is acceptable on the basis of extrapolation from data demonstrating that sufladiazine has proven effectiveness in secondary prophylaxis. The recommended dose of sulfisoxazole is the same as that for sulfadiazine. Sulfonamide prophylaxis is contraindicated in late pregnancy because of transplacental passage of the drugs and potential competition with bilirubin for albumin-binding sites. Erythromycin is

recommended for patients who are allergic to penicillin and sulfisoxazole.

Infective Endocarditis Prophylaxis (See also Chap. 47)

Patients with rheumatic valvular heart disease also require additional short-term antibiotic prophylaxis before certain surgical and dental procedures to prevent possible development of infective endocarditis. Patients with prosthetic valves or previous endocarditis are at particularly high risk. *Antibiotic regimens used to prevent recurrences of acute RF are inadequate for prevention of bacterial endocarditis.* The current recommendations of the American Heart Association concerning prevention of bacterial endocarditis should be followed.[37] Because alpha-hemolytic streptococci in the oropharynx may have developed resistance to oral penicillin being used for secondary prevention of RF, the agent selected to prevent endocarditis should not be a penicillin. Patients who have had RF but who do not have evidence of rheumatic heart disease do not need endocarditis prophylaxis.

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Chapter 67 - Rheumatic Diseases and the Cardiovascular System

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Systemic rheumatologic conditions are pleomorphic and often involve the cardiovascular system. Patients may present because of musculoskeletal disease, fever of uncertain origin, regional or visceral ischemia, organ failure (e.g., uremia, hypoxemia, dementia, congestive heart failure), or inflammation (e.g., pericarditis, pleurisy). The cardiologist is usually not the initial source of care but becomes involved through the consultative process. However, in certain circumstances, cardiologists or cardiothoracic surgeons may be the first to recognize clinical "outliers" for which systemic autoimmune disease should be part of the differential diagnosis. Several examples include young patients with ischemic heart disease, aortic aneurysms and valvular regurgitation, claudication, or multifocal thrombi or any patient in whom cardiovascular abnormalities occur in the setting of systemic illness. The varied presentations and treatments of rheumatic illnesses and their cardiovascular manifestations are the subjects of this chapter.

Vasculitis

Vasculitis is the common denominator of rheumatic diseases that affect the cardiovascular system, although each of the many forms of systemic vasculitis is uncommon. This fact alone makes it a challenge for the clinician. Additionally, all forms of vasculitis are readily confused with other systemic illnesses for which immunosuppressive therapy may have adverse or lethal consequences. Processes that may be confused with vasculitis include sepsis (particularly bacterial endocarditis), drug toxicities and poisonings (especially with agents that are likely to produce vasospasm, e.g., cocaine, amphetamines), coagulopathies, malignancies, cardiac myxomas, and multifocal emboli from large vessel aneurysms[1] (Table 67-1) . The most certain diagnosis of vasculitis lies in the identification of compatible clinical features and pathologic proof of vasculitis. In some instances, vasculitis may present as a characteristic constellation of findings within systemic illness. For example, the presence of upper and lower airway inflammation and red blood cell casts in the urine sediment, with or without renal insufficiency, would suggest Wegener granulomatosis. Hypertension and upper extremity claudication in a young individual, especially if female, should suggest Takayasu arteritis. Unfortunately, many patients with vasculitis do not present with such readily recognizable features. Instead, one may have to rely on combinations of less typical clues. A patient with fever, active urinary sediment, and peripheral neuropathy is likely to have vasculitis, especially if the previously noted competing diagnoses have already been ruled out. The presence of a purpuric rash, particularly if it is palpable, furthers the probability of this diagnosis, which can be confirmed by a simple skin biopsy. When such features occur in a patient with an already established autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, or relapsing polychondritis), the likelihood of vasculitis being present increases.

The incidence of vasculitis appears to be on the rise, with aging of the population.[1A] [1B] [1C] The considerable social and economic costs of the vasculitides may have been underestimated in the past.[1D] A recent bibliography provides an update on the literature of the vasculitic syndromes.[1E]

PROOF OF DIAGNOSIS.

Definitive proof depends on visualizing vasculitic lesions in affected tissue, and the greatest success in achieving a tissue diagnosis comes from biopsy of abnormal or symptomatic sites. In patients with proven vasculitis, the yield from biopsies of clinically normal sites is considerably less than 20 percent. Therefore, a biopsy of apparently normal tissue is not recommended.[2] [3] Biopsies of abnormal organs provide diagnostically useful information in over 65 percent of cases. Yield is less than 100 percent because uniform involvement of vessels in vasculitis is uncommon.

A biopsy may not be practical in an illness with symptoms of visceral ischemia, carotidynia, or findings of unequal pulses or blood pressures. Biopsies of large vessels and diagnostic laparotomy, in the absence of an acute abdomen, are usually impractical. In this setting, angiography may be helpful. Evidence of vascular injury may

be apparent from areas of vascular stenosis and/or aneurysm formation that cannot be explained on the basis of atherosclerosis. Angiography is particularly useful for patients with diseases that involve large (Takayasu arteritis, giant cell

TABLE 67-1 -- DIAGNOSIS OF VASCULITIS: DISEASES THAT CAN MIMIC PRIMARY SYSTEMIC VASCULITIS

Sepsis, especially endocarditis
Drug toxicity/poisoning
Coagulopathy
Malignancy
Cardiac myxoma
Multifocal emboli from large vessel aneurysms (cholesterol, mycotic)

(From Hoffman GS: Textbook of Rheumatology, Systemic Vasculitis. Update 28. Philadelphia, WB Saunders, 1998.)

arteritis of the elderly [GIA]) and medium-sized vessels (e.g., polyarteritis nodosa). Serological tests may provide additional information.[3A] [3B]

Once the diagnosis of vasculitis is clearly established and based on the strongest of circumstantial evidence or biopsy proof of vascular inflammatory injury, one must still consider whether such lesions are due to *secondary vasculitis* from bacterial, fungal, and viral infections (e.g., hepatitis B or C and, in immunologically compromised patients, human immunodeficiency virus or cytomegalovirus) or malignancies. Paraneoplastic vasculitis should be considered on the basis of a suspicious history or laboratory finding, or in patients who fail to respond to usually effective aggressive immunosuppressive therapy.

Takayasu Arteritis

Takayasu arteritis (TA), an idiopathic large-vessel vasculitis in young individuals, affects the aorta and its major branches (Fig. 67-1 *A* and *B*). Histologically, TA is characterized by intense mononuclear leukocyte infiltration and the presence of giant cells (see Fig. 67-1 *C*). Women are affected about 10 times more often than men. Morbidity results from arterial stenosis and organ ischemia, as well as aneurysm formation, especially of the aortic root, where it may produce aortic regurgitation. Hypertensive or primary cardiac, renal, and central nervous system vascular disease account for most deaths. Estimates of mortality range from 3 percent at 8 years[4] to 35 percent at 5 years follow-up.[5]

Symptoms of large-vessel abnormalities or the finding of hypertension, especially in young patients, necessitate careful examination of extremity pulses and blood pressures

for asymmetry as well as a search for vascular bruits. Other indications of active disease include increasing extremity or visceral ischemia, malaise, myalgias, arthralgias, night sweats, and fever. Occurrence of such symptoms that take place in the presence of an elevated erythrocyte sedimentation rate suggests active disease. However, a significant number of patients may not have any constitutional or new vascular symptoms, and as many as 50 percent may have normal sedimentation rates and still experience progressive disease.[6] [7] [8] The occurrence of active TA in this setting has been documented by the finding of (1) new vascular abnormalities on sequential angiographic studies in patients who were thought to be in remission and (2) inflammatory changes in bypass specimens from patients in whom surgery was performed because of critical flow abnormalities, in the setting of clinically "quiescent" disease.[7] [8] [9] Until we are able to judge more accurately the degree of disease activity in TA, outcomes will be compromised. Studies using refinements in magnetic resonance imaging techniques may enable the clinician to detect qualitative abnormalities in the vessel wall that imply inflammatory change.[10] These abnormalities may then be followed sequentially to determine response to therapy.

The cardiac sequelae of TA are far more commonly due to aortic regurgitation and inadequately treated hypertension than arteritis affecting the coronary vessels.[6] [11] When coronary artery vasculitis occurs, it is most frequent in the ostial regions. However, more distal involvement can also occur and both types of lesions may coexist in the same patient. These observations underscore the importance of considering vasculitis in the differential diagnosis of young patients with ischemic syndromes.[12]

TREATMENT.

Approximately 60 percent of patients with TA respond to corticosteroid therapy (e.g., prednisone, 1 mg/kg/d), with subsequent resolution of symptoms and stabilization of arteriographically demonstrable abnormalities. However, progressive tapering of corticosteroid therapy has been associated with disease relapse in over 40 percent of patients. Corticosteroid-resistant or relapsing patients may

Figure 67-1 Takayasu arteritis. *A,* The arrows in this aortic arch angiogram show the characteristic narrowing that occurs in the brachiocephalic, carotid, and subclavian arteries. *B,* Gross photography of the same patient at autopsy shows two cross sections of the right carotid artery with pronounced intimal thickening and minimal residual lumen. *C,* This histologic section illustrates arterial media destruction by mononuclear inflammation with giant cells that takes place in active Takayasu aortitis. (From Schoen FJ, Cotran RS: Blood vessels. *In* Cotran RS, Kuman V, Collins T [eds]: Robbins Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, pp 493-541.)

respond to the addition of daily therapy with cyclophosphamide (~2 mg/kg) or weekly therapy with methotrexate (~20 mg).[7] [9] [13] About 40 percent of patients who are treated with a cytotoxic agent and a corticosteroid will achieve remission, but over time about half of these patients will also experience relapse, leading to the requirement for chronic immunosuppressive therapy in approximately 25 percent of all patients with TA.

A discussion of pharmacological therapy for TA addresses only one important aspect of

care. Other important

Figure 67-2 Takayasu arteritis. Standard Takayasu arteritis diagram used by the Cleveland Clinic Center for Vasculitis Care and Research. In this young man, occlusion of both subclavian arteries has led to leg pressures being the only reliable measure of central aortic pressure. He has also had a left renal artery bypass for a stenotic lesion, which was responsible for severe hypertension. Also note bilateral common carotid stenosis.

issues include treatment of the anatomic effects of vascular lesions. Patients with TA may have signs of clinical deterioration caused by fixed critical stenoses or aneurysms. Hypertension affects 21 to 90 percent of patients.[7] [9] [14] [15] [16] In Asia and Mexico, TA is one of the most common causes of hypertension in the adolescent and young adult population. Inadequately treated hypertension may lead to cerebral, cardiac, and renal injury. One of the most common errors in clinical management occurs when the physician does not know whether blood pressure recordings in an extremity are representative of aortic root pressure. Because over 90 percent of patients have stenotic lesions and the most common site of stenosis is the subclavian artery(s), blood pressure in one or both arms may underestimate pressure in the aorta. Elevated aortic root pressure, unrecognized and untreated, enhances the risks of hypertensive complications. This potential pitfall can best be avoided by recording arterial pressures when performing angiography (Fig. 67-2) . These observations emphasize the importance of knowing the distribution and severity of all vascular lesions. In the setting of renal insufficiency, the potential contrast agents to cause further renal impairment may limit exploration of the extent of all potential vascular lesions. However, in the absence of contraindications, the entire aorta and its primary branches should be included in vascular imaging studies. Magnetic resonance angiography lacks the ability to measure intravascular pressures. If the clinical examination does not suggest the presence of extremity lesions or show unequal extremity pressures, a magnetic resonance study may be sufficient to delineate other vascular lesions without resorting to invasive contrast angiography. Whenever feasible, anatomic correction of clinically significant lesions should be considered, especially when renal artery stenosis and hypertension are present.

Aortic root involvement may lead to valvular insufficiency, angina, and congestive heart failure in about 20 percent of patients.[7] [16] Severe or progressive changes may require aortic surgery, with or without valve replacement. Because determining disease activity based solely on clinical and laboratory parameters may be difficult, *all* such surgeries should include histopathological evaluation of vascular specimens.[7] [8] [9] It is always preferable to operate on patients with TA when their disease is in apparent remission. Pathology findings from surgical specimens should guide the need for postoperative immunosuppressive treatment.

The care of patients with TA requires a team approach that includes clinicians familiar

with the proper use of immunosuppressive therapies, vascular imaging/intervention specialists, and, in the setting of critical stenoses or aneurysms, cardiovascular physicians and surgeons. For most patients, medical and surgical therapies are palliative.

Giant Cell Arteritis of the Elderly

Giant cell arteritis (GCA) and Takayasu arteritis are the principal diseases associated with sterile granulomatous inflammation

Figure 67-3 Temporal (giant cell) arteritis: Active aortitis with perivascular lymphoplasmacytic infiltrate in the adventitia, unorganized periadventitial fibrin and secondary infarcts and patchy scarring involving approximately 50 per cent of the media in giant cell arteritis. (Courtesy of F. J. Schoen.)

of large and medium-sized vessels (Fig. 67-3). GCA affects people 50 years of age and older (mean=70 years). Although women are more often affected (2-3:1), this gender difference is not as striking as in TA (6-10:1). The demographic characteristics of GCA are the same as for patients with polymyalgia rheumatica and, in fact, 30 to 50 percent of patients with GCA may concurrently present features of polymyalgia rheumatica. The most characteristic features of GCA include new onset of atypical and often severe headaches, scalp and temporal artery tenderness, acute visual loss, and pain within the muscles of mastication (Table 67-2) .[17] When such abnormalities occur in conjunction with an elevated erythrocyte sedimentation rate, a clinical diagnosis of GCA can be presumed and treatment initiated even without the benefit of a temporal artery biopsy.

TABLE 67-2 -- GIANT CELL ARTERITIS: CLINICAL PROFILE

ABNORMALITY	FREQUENCY (%)
Atypical headache	60-90
Tender temporal artery	40-70
Systemic symptoms not attributable to other diseases	20-50
Fever	20-50
Polymyalgia rheumatica	30-50
Acute visual abnormalities	12-40
Transient ischemic attacks or stroke	5-10
Claudication	
"Jaw"	30-70
Extremities	5-15
Aortic aneurysm	15-20

Dramatic response to corticosteroid	~100
Positive temporal artery biopsy	~50+

(From Hoffman GS: Textbook of Rheumatology, Systemic Vasculitis. Update 28. Philadelphia, WB Saunders, 1998.)

The diagnosis is doubtful if dramatic improvement does not occur within 24 to 72 hours. The specific findings of a positive biopsy would be helpful in guiding treatment when typical features are not present, but the diagnosis is suggested because of vague systemic symptoms, atypical headache in the setting of normal or elevated sedimentation rate, and exclusion of all other reasonable diagnoses have been ruled out. The yield of positive temporal artery biopsies in patients clinically diagnosed with GCA has been estimated to be 50 to 80 percent, depending in part on the size of the biopsy and whether bilateral samples have been obtained.

GCA may produce aortitis in at least 15 percent of cases and involve the primary branches of the aorta in a similar number of individuals.[1A] [1B] [1C] [1D] [1E] [18] [19] [20] [21] Consequently, some patients with GCA may present with features that resemble those of TA. The same considerations and precautions must be applied in GCA among the elderly with large vessel inflammatory diseases in patients with TA (e.g., the need to identify an extremity that provides a reliable blood pressure equivalent to aortic root pressure; follow-up should include careful observation for new bruits, pulse and blood pressure asymmetry, and the possible development of aortic aneurysms). Recent studies have demonstrated that patients with GCA were more than 17 times more likely than age-matched controls to have thoracic aortic aneurysms and about two times more likely than aged-matched controls to have abdominal aortic aneurysms.[19] [20] Fifty-five percent of patients with thoracic aortic aneurysms died as a result of those lesions. Because aneurysms were found either in the course of routine care or at postmortem, these may be conservative estimates. The finding of large vessel disease, including aortic aneurysms, in elderly persons with GCA should not merely be assumed to be secondary to atheromatous disease.

It is not surprising that objective features of cardiac disease would be present in about half of all patients with GCA.[22] However, it appears that myocardial infarction due to GCA is rare[23] or rarely appreciated because histopathological findings in coronary arteries are infrequently sought in patients with a mean age of 70 years.

Corticosteroids continue to be the most effective therapy for GCA. Prednisone (~0.7-1 mg/kg/d) will reduce symptoms within 1 to 2 days and often eliminates symptoms within a week. Tapering of corticosteroids can begin about 1 month after clinical and laboratory parameters (particularly the erythrocyte sedimentation rate) have normalized. Unfortunately, the erythrocyte sedimentation rate does not always normalize even with disease control, so it should not be relied on as the only measure of disease activity. Occasional patients may either not achieve complete remission or not respond to tapered-off corticosteroids. Some authors have recommended cytotoxic or immunosuppressive agents for such individuals, but the utility of these agents has not been proven, as demonstrated in controlled comparative trials.

Idiopathic Aortitis

Aortitis, a recognized feature of TA and GCA, may also occur in uncommon diseases such as Behcet disease and Cogan syndrome and as a complication of Kawasaki disease in children. Occasionally, it is an unanticipated finding in patients undergoing surgery for aortic valve regurgitation, aneurysm resection, or coarctation. Little is known about the frequency and clinical characteristics of idiopathic aortitis.

A recent 20-year review of pathological specimens from consecutive aortic surgeries at the Cleveland Clinic Foundation revealed that 52 of 1204 specimens (4.3 percent) were classified as idiopathic aortitis, a designation that required

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exclusion of vasculitis associated with postoperative infections, atherosclerosis, or inflammation occurring around surgical materials from prior operations. Sixty-seven percent of patients with idiopathic aortitis were women. In 96 percent of cases, aortitis was present in the thoracic aorta. If one considered only thoracic aortic aneurysms, 12 percent of 386 thoracic specimens had idiopathic inflammatory features. In 96 percent of cases, symptoms of systemic illness had not been present at the time of surgery. In 69 percent of cases, idiopathic aortitis was not related to a current or past history of systemic disease. In 31 percent (16/52), aortitis was associated with a past history of giant cell arteritis, Takayasu arteritis, systemic lupus, Wegener granulomatosis, and a variety of other disorders. Over a mean follow-up period of 42 months, new aneurysms were identified among 6 of 25 patients who were not treated with glucocorticosteroids and none of 11 patients who were treated with glucocorticosteroids. Although the observations on nonrandomized patients could indicate a benefit of such therapy in this setting, marked variation of dose and duration of therapy raises uncertainty about the efficacy of therapy. Because 17 percent of patients subsequently developed new aneurysms, it is prudent for patients with idiopathic aortitis, identified at the time of surgery, to be periodically evaluated for recurrent or persistent disease. If proof of recurrent disease is present, treatment should be pursued, as recommended for Takayasu arteritis and GCA.

The broad spectrum of aortitis includes patients who may have systemic illnesses known to affect large vessels. However, in the setting of a cardiovascular surgery practice, aortitis may first become apparent only after pathological evaluation of excised specimens.

KAWASAKI DISEASE (See also Chap. 45)

Kawasaki disease (KD) is an acute febrile illness that primarily affects children younger than 4 years of age and almost never affects children older than 8 years (mean age in Japan is 12 months, and in the United States it is 2.8 years).[24] The most prominent features are included in the Centers for Disease Control and Prevention case definition

guidelines (Table 67-3) . KD is usually self-limiting within 4 to 8 weeks; its mortality rate is 2 percent. Deaths usually result from acute thrombosis of coronary artery aneurysms, the result of prior vasculitis. Case studies using noninvasive techniques find coronary artery aneurysms in 20 percent of patients, compared with 60 percent discovered by angiography. Data from postmortem studies have also demonstrated vasculitis of the aorta and celiac, carotid, subclavian, and pulmonary arteries. Rare case reports of gut vasculitis in KD exist.[25] [26] Gastrointestinal morbidity may depend more on small-vessel than large-vessel disease. Treatment with high doses of aspirin (30 mg/kg/d) or intravenous gamma globulin may prevent aneurysms or hasten their regression.

VASCULITIS OF SMALL/MEDIUM-SIZED VESSELS THAT MAY AFFECT THE CARDIOVASCULAR SYSTEM

Hypersensitivity vasculitis, Henoch-Schonlein purpura, Wegener granulomatosis, microscopic polyangiitis, polyarteritis nodosa, and Churg-Strauss syndrome (CSS) may all have cardiac consequences.[26A] Surveys of the literature and the original observations of Churg and Strauss indicate that CSS (asthma, eosinophilia, and vasculitis) may be complicated by congestive heart failure (25-50 percent), acute or constrictive

TABLE 67-3 -- CDC CASE DEFINITION OF KAWASAKI DISEASE

Fever 5 days, without other explanation, plus at least four of the following:
1. Bilateral conjunctival injection
2. Mucous membrane changes: injected or fissured lips; injected pharynx or "strawberry" tongue
3. Extremity abnormality: erythema of palms/soles, edema of hands/feet or generalized or peripheral desquamation
4. Rash
5. Cervical lymphadenopathy
Note: 80% of cases occur in children younger than 4 years old; it is rare in children older than 8 years old.

pericarditis (10-30 percent), hypertension (30-75 percent), myocarditis, and, rarely, myocardial infarction. The majority of deaths in CSS relate to cardiovascular disease.[27] [28] [29] [30] Cardiac involvement is associated with an increased relative risk of death in CSS, polyarteritis nodosa, and related vasculitides of small and medium-sized vessels.[31] [32] Patients with cardiac involvement almost always have an established diagnosis based on prior recognition of more specific disease manifestations. Treatment of active inflammatory lesions of the heart is the same as would be applied to other sites of vasculitis. Because vasculitis usually involves small vessels, opportunities for invasive therapeutic measures are limited.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory

polyarthritis. Present in approximately 70 percent of patients, rheumatoid factor does not confirm the diagnosis of RA, and it is frequently present in other diseases, including chronic viral hepatitis and bacterial endocarditis. Systemic complications of RA include pericarditis, pleuritis, systemic necrotizing arteritis, compressive neuropathies, interstitial lung disease, and Sjogren and Felty syndromes.

PERICARDIAL DISEASE (see also Chap. 50) .

RA affects the pericardium in approximately 50 percent of patients, as indicated by echocardiographic and necropsy studies (see Chap. 50) . Chronic, asymptomatic effusive pericardial disease is more common than acute pericarditis.[33] [34] [35] Although the frequency of symptomatic pericarditis among outpatients with RA has been estimated as less than 0.5 percent, in a series of 41 selected patients with severe RA, 75 percent had symptoms compatible with acute pericarditis.[33] Patients with rheumatoid pericardial disease are generally older and have long-standing RA. Although it may show characteristic changes in acute pericarditis, the electrocardiogram is usually normal in patients with chronic pericardial disease. Coexistent small pleural effusions are common and may reflect rheumatoid serositis or hemodynamic effects of the pericarditis. Pericardial calcification has been reported,[36] mimicking tuberculous pericarditis. Limited data have been published on the nature of pericardial fluid in RA. Fluid is frequently blood tinged, and leukocyte counts range from scant to more than 30,000/mm[3] , generally with a neutrophil predominance. The glucose level may be quite low when compared with serum glucose values, similar to markedly depressed glucose levels reported in rheumatoid pleural effusions. The presence of rheumatoid factor in the fluid does not confirm the diagnosis of RA pericarditis. Infection must be excluded. Constrictive pericarditis has been reported, and it must be distinguished from restrictive cardiomyopathy, a rare complication of secondary amyloidosis in patients with long-standing RA. Treatment of clinical pericarditis includes the use of nonsteroidal antiinflammatory drugs, intensified systemic immunosuppressive therapy, pericardial steroid injections, and surgical decompression. A pericardial window may be required if systemic therapy is ineffective or already at an intense level. The pressure of pericardial constriction usually requires surgical treatment. Chest pain due to costochondritis is far more common than pericarditis. The use of aggressive medical therapy early in the course of rheumatoid disease may decrease the frequency of pericardial involvement.

OTHER CARDIOVASCULAR INVOLVEMENT.

Patients with RA have a decreased life expectancy, and their leading cause of death is cardiovascular disease.[37] Potential risk factors for coronary artery disease (CAD) in patients with RA include the systemic inflammatory state, the use of corticosteroids, which may accelerate atherosclerosis, and possibly the use of methotrexate, which can elevate levels of circulating homocysteine, although the relative contributions of these factors to acceleration of CAD are not clear.[38] [39] Significant ischemic disease may be clinically silent owing to the relative physical inactivity of patients

Figure 67-4 Aortic valve in a patient with rheumatoid arthritis with florid chronic active inflammation including numerous plasma cells, lymphocytes, and polymorphonuclear leukocytes. (Courtesy of F. J. Schoen.)

with severe rheumatoid disease. Coronary arteritis is a rarely reported complication of RA.[40] Treatment of CAD does not differ from that of patients without RA. Coronary arteritis, occurring along with systemic arteritis, is treated with combination immunosuppressive therapy, including corticosteroids plus cyclophosphamide or other agents.

RA is not usually associated with clinically significant myocarditis or congestive heart failure. Secondary amyloidosis is rare in rheumatoid disease, but it can cause cardiomyopathy and atrioventricular conduction abnormalities. Tachyarrhythmias can occur as a result of rheumatoid pericarditis. Focal myocardial involvement with rheumatoid disease has been well described and may result in conduction system abnormalities. Rheumatoid nodules involving the conduction system have been reported.[41] All levels of conduction block have been described and, once established, do not generally respond to antiinflammatory therapy.

Autopsy studies have indicated frequent involvement of the cardiac valves (Fig. 67-4) and aorta, but these abnormalities are rarely of clinical significance. Slowly progressive granulomatous valvulitis may be difficult, if not impossible, to distinguish from disease unrelated to RA. A rapidly progressive inflammatory aortic valvulitis of the aortic valve, advancing to need for valve replacement over less than 5 years has been described previously. [42] Rheumatoid aortitis, with involvement of the aortic valve, has been reported,[43] but aortitis is not frequently recognized ante mortem. RA does not cause primary pulmonary hypertension, but secondary pulmonary hypertension may result from rheumatoid lung disease.

HLA-B27-Associated Spondyloarthropathies

The rheumatoid factor-negative spondyloarthropathies share several features that distinguish them from rheumatoid arthritis. Unlike rheumatoid arthritis, the entire spine, not just the cervical region, may be involved. Involvement of the sacroiliac joint occurs frequently, and it may be the only musculoskeletal manifestation. Large peripheral joints are commonly involved. Inflammation of the tendon sheaths and bone insertions (enthesitis) occurs frequently. Diffuse tendon sheath involvement may produce "sausage digits." There is an increased frequency of the HLA-B27 gene in these disorders. Although approximately 10 percent of healthy American whites have the HLA-B27 gene, it is present in 90 percent of American whites with ankylosing spondylitis and approximately 60 percent of patients with inflammatory bowel-related spondylitis. These percentages are much lower in African Americans and Asians. Presence of the gene predisposes to anterior uveitis, cardiac conduction disease, and proximal aortitis.

Thus, some patients with psoriatic arthritis, enteropathic arthritis, reactive arthritis including Reiter syndrome, and ankylosing spondylitis are predisposed to these complications. Patients may express extraskeletal HLA-B27-related complications without overt rheumatic disease.

Pericarditis, although reported,[44] is not characteristic of these diseases (see also Chap. 50) . CAD does not occur at an increased rate, and arteritis is not expected. Diastolic dysfunction has been reported[45] in patients who have the HLA-B27 gene but is rarely of clinical significance. Cardiac conduction disease has been well described in patients with ankylosing spondylitis as well as Reiter syndrome. It has been estimated that up to one third of patients with ankylosing spondylitis develop conduction disease.[46] Initially, the atrioventricular conduction block may be intermittent, but it tends to progress. Conduction disease occurs more commonly in males, and as many as 20 percent of males with permanent pacemakers carry the HLA-B27 gene.[47] Conduction disease may be the only abnormality associated with the HLA-B27 gene. Electrophysiological studies indicate that the level of block is usually at the atrioventricular node, not fascicular.[48] [49] It has been suggested that atrial fibrillation occurs more commonly than expected in patients who carry the HLA-B27 gene.

AORTIC ROOT DISEASE (see also Chap. 40) .

This condition, with involvement of the aortic valve, has been reported in up to 100 percent of patients in autopsy series and 30 percent in echocardiographic studies. Characteristic findings have included thickening of the aortic root with subsequent dilatation. Aortic cusp nodularity with proximal thickening comprises the "subaortic bump."[50] Transesophageal echocardiography located the subaortic bump in 74 percent of 44 patients with ankylosing spondylitis.[51] In this study, aortic regurgitation developed in 50 percent of patients and 20 percent of patients developed congestive heart failure, underwent valve replacement, suffered a stroke, or died as compared with only 3 percent of age- and sex-matched volunteers. The aortic lesions progressed in 24 percent of patients and resolved in an additional 20 percent of patients over approximately a 2-year follow-up. The severity of aortic root disease was associated with the patients' age and duration of spondylitis. Because dilatation and stiffening of the aortic root contributes to the aortic regurgitation, the regurgitant murmur may be best heard along the right sternal border. Inflammatory aortic disease can occasionally extend to the mitral valve, causing mitral regurgitation.

Systemic Lupus Erythematosus (See also Chap. 51)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of immune complexes and a constellation of clinical features that may include serositis, arthritis, glomerulonephritis, central nervous system dysfunction, hemolytic anemia, thrombocytopenia, leukopenia, and autoantibodies. Histologically, the arteritis of SLE can include fibrinoid necrosis as well as intense perivascular

Figure 67-5 Systemic lupus erythematosus. Vasculitis with fibrinoid necrosis. (From Schoen FJ, Cotran RS: Blood vessels. *In* Cotran RS, Kuman V, Collins T [eds]: Robbins Pathologic Basis of Disease. 6th ed. Philadelphia, WB Saunders, 1999, pp 493-541.)

cuffing by leukocytes (Fig. 67-5). Antiphospholipid antibodies (APLAs) are present in more than 20 percent of lupus patients. The disease is more common in women, and it can occur at any age. Idiopathic and drug-induced lupus have cardiac manifestations. Drug-induced lupus is well recognized after treatment with various cardiac medications, including procainamide, quinidine, and hydralazine. Over 90 percent of patients with SLE have antinuclear antibodies, although the presence of even high titers of antinuclear antibodies is *not* diagnostic of SLE. Anti-double-stranded DNA is present in 50 to 70 percent of patients with idiopathic SLE and is most common in those with glomerulonephritis.

PERICARDIAL DISEASE (see also Chap. 50) .

Imaging and autopsy series demonstrate pericardial involvement in more than 60 percent of patients, and clinically significant pericarditis occurs in less than 30 percent,[52] making pericarditis the most common cardiac problem among patients with SLE.[53] Although unexplained chest pain is common in these patients, it is more likely caused by causes other than pericarditis. Pericarditis may occur as the initial manifestation of SLE, but it may also appear at any point during the disease course or as a complication of chronic renal disease. Pericardial fluid, when obtained, has generally demonstrated a high neutrophil predominance,[53] an elevated protein level, and a low or normal glucose level. Complement levels in the fluid tend to be low, but this is not a characteristic unique to SLE. Indeed, the fluid is indistinguishable from that obtained from patients with bacterial pericarditis. Pericardial tamponade may occur at any point in the course of SLE, including the initial presentation.[54] When effusions occur in the setting of chronic renal failure, it is difficult to distinguish uremic from lupus pericarditis. Patients with mild pericarditis without hemodynamic compromise are generally treated with NSAID therapy, unless there is a contraindication to such therapy, such as renal insufficiency. If corticosteroid therapy does not engender a prompt response, large sterile pericardial effusions, particularly those accompanied by fever and/or hemodynamic compromise, are best treated with drainage and consideration of a pericardial window. Pericarditis, as well as tamponade, can occur with drug-induced lupus. Constrictive pericarditis, presumably as a sequela of lupus pericarditis, has been reported. Pericardial thickening has been described in approximately 30 percent of patients with SLE.

CORONARY ARTERY DISEASE.

Coronary arteritis that results in ischemic syndromes occurs in patients with SLE. The distinction between CAD and coronary arteritis may require sequential angiographic

studies, with documentation of more rapid change in luminal images than is usually seen with CAD. Despite the young age of many patients with lupus, atherosclerosis remains the most common cause of ischemic cardiac disease. The prevalence of subclinical CAD is quite high, as measured by thallium exercise testing and autopsy studies, and angina or myocardial infarction occurs in less than 20 percent of patients. As patients live longer with their disease, the prevalence of clinical events will increase.

Cardiovascular disease is the most common cause of death in patients with long-standing SLE. There are reports of young patients with SLE who suffer myocardial infarction as the initial manifestation of their CAD. Middle-aged women with lupus are more than 50 times more likely to experience myocardial infarction[55] than other women of similar age. Risk factors include disease duration, period of time treated with corticosteroids, postmenopausal status, and hypercholesterolemia. Additional causes of acute coronary syndromes include thrombosis, often related to the presence of APLAs, and embolism from nonbacterial vegetative endocarditis (Libman-Sacks). The presence of APLAs predisposes to thrombosis in some patients and has been associated with valvular thickening and nonbacterial endocarditis. Antiendothelial antibodies may accelerate atherogenesis. In this regard, APLAs were an independent predictor of CAD in a subset analysis of the Helsinki heart study.[56] Treatment of ischemic disease in patients with SLE is similar to those patients with "routine" atherosclerotic disease. Exceptions include the rare patients with coronary arteritis, who should be treated aggressively with high doses of corticosteroids, and those patients with thrombotic disease related to APLAs. These latter patients should be treated with long-term high-dose anticoagulation. Aspirin is *not* sufficient. Thrombocytopenia is common in patients with APLAs and may complicate therapy.

MYOCARDIAL DISEASE.

Myocardial dysfunction in lupus is usually multifactorial and may result from immunologic injury, ischemia, valvular disease, or coexistent problems such as hypertension. Acute myocarditis is infrequent, but it can be the initial presentation of SLE. Patients with peripheral skeletal myositis are reportedly at increased risk for myocarditis.[57] Measurement of cardiotroponin-I may be of value in documenting cardiac involvement, but the MB fraction of CPK may be elevated in the presence of skeletal myositis, even in the absence of myocarditis. Echocardiographic and systolic time interval studies have demonstrated abnormal cardiac function in patients with active SLE. These changes usually reverse with control of disease

activity. In the absence of other contributing factors,[58] acute or chronic congestive heart failure due to SLE is not common. Findings on endomyocardial biopsy specimens are not specific, generally revealing patches of myocardial fibrosis, sparse interstitial mononuclear cell infiltrates, and occasional myocyte necrosis.[59] If acute left ventricular failure occurs in patients with active SLE in the absence of CAD or valve disease, a trial of corticosteroid therapy is indicated.

ARRHYTHMIAS.

Tachyarrhythmias can occur in patients with SLE secondary to pericarditis or ischemia. Sinus tachycardia may be the earliest manifestation of myocarditis. A gallium scan may be abnormal in lupus myocarditis.[60] Abnormal heart rate variability has been described and may be due to autonomic dysfunction or to occult myocarditis. Abnormal heart rate variability and abnormal myocardial single-photon emission computed tomography have been described, including some patients with normal resting echocardiograms.[61] Unexplained sinus tachycardia that resolves with treatment of SLE can occur in the presence of active SLE even without demonstrable cardiac dysfunction. Occult pulmonary embolism should always be considered as a cause of tachycardia in patients with SLE, especially in the presence of antiphospholipid antibodies.

Infants born to mothers with SLE and other systemic autoimmune diseases have an increased incidence of congenital complete heart block. The pathogenic mechanism is the transmission of maternal anti-Ro and anti-La antibodies in utero, which causes myocardial inflammation and fibrosis of the conduction system.[62] [63] The risk for development of third-degree atrioventricular block in infants born to mothers carrying this antibody is quite low. However, women with systemic autoimmune diseases should be screened for antibody presence before pregnancy. If they are present, the patients should be examined with fetal ultrasound studies throughout pregnancy to detect complete heart block or hydrops. Heart block usually appears after the first trimester of pregnancy; it is almost always irreversible. If recognized early, dexamethasone in utero may be successful in reversing myocarditis.[64] Plasmapheresis and intravenous gamma-globulin therapy may also be tried. It is frequently necessary to place a pacemaker in the infant shortly after delivery.[65]

VALVULAR DISEASE.

Valvular involvement in SLE is common. Recognized 50 years ago as noninfectious vegetations (Libman-Sacks endocarditis), transesophageal studies have shown valvular abnormalities in over 50 percent of patients with SLE.[66] Valvular thickening is the most striking finding, followed by vegetations and valvular insufficiency. The vegetations are generally located on the atrial side of the mitral valve and the arterial side of the aortic valve; they are usually immobile. Over time, the lesions may either resolve or worsen, and fibrosis may cause retraction of the valve, causing insufficiency. Less commonly, the vegetations on the valve may occlude the orifice causing stenosis.[67] Valvulitis, with valve fenestrations and rapidly progressing dysfunction, may occur. There are descriptions of mitral and aortic valve replacement in patients with SLE.[68] Valve repair has also been described.[69] Recurrence of valve disease, particularly thrombosis, may affect prosthetic valves. The nonbacterial vegetations rarely embolize and cause stroke syndromes. Several studies have demonstrated an increased prevalence of cardiac valve dysfunction in the presence of APLA, with or without SLE.[70] Because vegetations may occur in APLA-negative patients with SLE,[71] there appear to be multiple mechanisms that affect heart valves in lupus patients. Because of the high prevalence of valvular abnormalities in SLE patients, these patients should receive consideration for antibiotic prophylaxis for endocarditis. However, at present no adequate studies to

evaluate this intervention have been performed.

Pulmonary artery hypertension is common in patients with SLE as assessed noninvasively.[72] Clinically significant pulmonary hypertension is less common. Causes for development of pulmonary hypertension include thromboembolic disease due to APLA, intimal proliferation of the pulmonary artery, chronic vasospastic disease associated with peripheral Raynaud disease, and, very rarely, arteritis of the pulmonary vessels. Successful heart-lung transplantation has been reported in a patient with SLE and progressive pulmonary hypertension.[73] Aortitis rarely occurs in patients with SLE.[74]

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APLAS) is defined as the presence of either APLA or a lupus anticoagulant *and* a history of otherwise unexplained recurrent venous or arterial thrombosis, or frequent second- or third-trimester miscarriages. Mild thrombocytopenia and livedo reticularis are also common. APLAs are quite common in patients with SLE, although not all of these patients will exhibit the clinical syndrome. Low to moderate levels of APLA can also be found in association with a number of infectious and other autoimmune diseases, usually without clinical consequence. In the absence of another systemic disease, APLAS is termed *primary.*

Primary APLAS is not associated with pericarditis, myocarditis, or conduction disease. Cardiac manifestations include thrombotic CAD, intracardiac thrombi,[75] and nonbacterial endocarditis.[76] Heart valve abnormalities can be found in approximately 30 percent of patients with primary APLAS. Valvular involvement can include thrombotic masses extending from the valve ring or leaflets, vegetations, or thickening. The mitral valve is affected more frequently than aortic valve; regurgitation is far more common than stenosis. Most valvular involvement is clinically silent. The first manifestation of valvular involvement with APLAS may be a thromboembolic event such as stroke. The incidence of superimposed bacterial endocarditis is not known.

Thrombosis in the setting of APLAs is treated with full-dose anticoagulation with warfarin (Coumadin) using a target international normalized ratio of 3.0. Treatment of clinically significant valvular or intracardiac masses is high-dose anticoagulation with warfarin,[77] with or without the addition of aspirin. Patients likely can also be treated with full therapeutic doses of heparin. Management of heparin dosing, in the setting of a lupus anticoagulant that prolongs the baseline PTT, may require consultation with the coagulation laboratory.[78] The lack of prospective controlled trials with matched patients precludes making any firm recommendations about the long- and short-term utility of adding acetylsalicylic acid to either anticoagulation regimen, although this is often done in patients with recurrent thrombosis despite anticoagulation. Treatment needs to be tailored to the unique clinical circumstances that are present in each patient. There are no data to direct decisions regarding anticoagulation in the setting of APLAS and valvular disease, without thrombosis. Vegetations may resolve with anticoagulation therapy over several months.[79] Patients with APLAS are at risk for myocardial infarction and reocclusion after angioplasty or bypass grafting. Aggressive prophylactic anticoagulation should be employed perioperatively in patients with APLAS and previous thrombosis.[80] Pulmonary hypertension can occur in patients with APLAS

secondary to chronic thromboembolic disease. It has also been proposed that APLAs can directly stimulate pulmonary artery intimal proliferation.

Scleroderma

Scleroderma (progressive systemic sclerosis [PSS]/CREST syndrome) and its variants are characterized by the presence

of microvascular disease and various patterns of cutaneous and parenchymal fibrosis; antinuclear antibodies are present in more than 90 percent of patients. Generalized scleroderma (PSS) includes proximal cutaneous fibrosis; Raynaud phenomenon, which occurs in 90 percent of patients and is often severe; gastrointestinal dysmotility; pulmonary fibrosis; and cardiac disease. These patients are at risk to develop scleroderma renal crisis.[81] Most of the manifestations of scleroderma are due to fibrosis, not to acute inflammation. Corticosteroids are not the mainstay of treatment.

The more limited CREST variant includes calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Patients with CREST syndrome may develop isolated pulmonary hypertension and cardiac conduction disease, but they are not prone to pulmonary fibrosis or renal crisis.

Pericardial involvement is common in scleroderma and includes fibrinous pericarditis in up to 70 percent of patients at autopsy (see also Chap. 50) .[82] Small pericardial effusions are demonstrated at echocardiography in 40 percent or less of patients. Acute pericarditis syndromes, including significant effusions, also occur.[83] The presence of moderate or large pericardial effusions is an independent risk factor for mortality.[84] Pericarditis with effusions may require corticosteroid therapy, but there is concern over the risk of inducing scleroderma renal crisis with the use of corticosteroids.

Necropsy and endomyocardial biopsy demonstrate the presence of patchy myocardial fibrosis, occasionally with contraction band necrosis. The latter finding has been attributed to intermittent and intense ischemia produced by microvascular occlusion, perhaps due to vasospasm.[85] Extramural coronary arteries are generally normal. However, approximately 80 percent of PSS and 65 percent of CREST patients have fixed perfusion defects on thallium imaging.[86] Myocardial infarctions have been documented in PSS patients with angiographically normal coronary arteries.[85] Ventricular conduction abnormalities are common and, along with a septal pseudoinfarct pattern, correlate with reduced myocardial function with exercise.[87] Electrical abnormalities can be found throughout the conduction system, and ventricular ectopy is present in more than 60 percent of patients. Patients with scleroderma, especially those with a history of palpitations or syncope, are prone to sudden death, a risk that is further increased in patients with coexistent skeletal myositis.[88] Primary valvular disease is not common. Renal crisis may be associated with variable degree of hypertension, rapidly rising creatinine levels, microangiopathy, and left ventricular failure. Treatment is with

angiotensin-converting enzyme inhibitors, not corticosteroids.

Pulmonary hypertension is a major clinical problem that occurs in both limited scleroderma and PSS. In PSS, it may be due to intrinsic pulmonary artery disease or be secondary to interstitial fibrosis.[89] Patients with CREST and PSS should have periodic echocardiograms to screen for asymptomatic pulmonary hypertension, [90] which may respond to vasodilator therapy.[91]

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are characterized by inflammation and resultant weakness of proximal greater than distal skeletal muscles; both can be associated with fever and interstitial lung disease. Respiratory muscles may be involved in severe cases. Other visceral organ involvement is uncommon in adults. Dermatomyositis has characteristic skin lesions that include extensor tendon erythema; Gottron papules overlying knuckles, elbows, and knees; edema of the eyelids; and a photosensitive diffuse papular eruption with scale. In a minority of cases, dermatomyositis may be a paraneoplastic syndrome. Both polymyositis and dermatomyositis are associated with progressive proximal muscle weakness. Acute disease may be associated with intense myalgia as well as weakness.

Although pericarditis is uncommon, it can be seen when polymyositis occurs as part of an overlap syndrome with other autoimmune diseases such as SLE or PSS (see also Chap. 50) . Coronary arteritis and ischemic CAD would be rare as part of these syndromes. Localized or generalized myocardial dysfunction is common by echocardiographic assessment but infrequently causes clinical failure.[92] The cardiomyopathy may be corticosteroid responsive. Corticosteroid myopathy generally affects skeletal, but not respiratory or cardiac, muscle.

Polymyositis and dermatomyositis frequently affect the conduction system. In an electrocardiographic study of 77 patients, 23 percent had conduction block,[93] which can occur in the absence of cardiomyopathy and may be progressive. Pulmonary hypertension can occur but is usually secondary to interstitial lung disease.

Sarcoidosis (See also Chap. 48)

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology that primarily affects the lung parenchyma. It can also cause significant adenopathy, arthropathy, myositis, fever, and renal, liver, skin, and cardiac disease.

Pericarditis has been frequently described, and necropsy studies have documented cardiac involvement in 27 percent of patients.[94] This granulomatous, infiltrative disease of the myocardium is often

Figure 67-6 Sarcoid vasculitis. Aortogram from a 20-year-old African-American male who presented with

chronic polyarthritis, uveitis, Bell palsy, and upper extremity claudication. He has had occlusion of both the subclavian and innominate vessels, which led to claudication, and also has aneurysmal dilatation of the entire aorta.

TABLE 67-4 -- RELATIVE FREQUENCIES OF CARDIAC INVOLVEMENT IN SELECTED SYST DISORDERS

	PERICARDIAL	ISCHEMIC ARTERITIS/THROMB.	MYOPATHY	CONDUCTION	VALVULAR
RA	++++	+/++++	+	++	+
B27 Spondylo.	+		+	++++	+++ (aortic)
SLE	++++	++/++++	+++	++++*	++++
APLA		-/++++			++++
Scleroderma	++++	-/+	++	++++	
Polymyositis	+		+++	+++	
Sarcoidosis	+++		+	++	

RA=Rheumatoid arthritis; B27 Spondylo.=HLA-B27-associated spondyloarthropathies; SLE=systemic APLA=antiphospholipid antibody syndrome; ARTERITIS/THROMB.=coronary arteritis/thrombotic or a coronary artery disease.

+=reported; ++=rare; +++=well described; ++++=frequently reported.

*Congenital complete heart block.

asymptomatic, but it can cause arrhythmias, conduction disease, and, rarely, otherwise unexplained congestive heart failure.[95] Granulomatous infiltration may be patchy, and there is a predilection toward involvement of the left ventricle, particularly the upper septal area. This distribution may influence the results of diagnostic right-sided endomyocardial biopsy. Use of gallium imaging may be helpful in determining the need and duration of immunosuppressive therapy.[96] Sarcoid dilated cardiomyopathy may be difficult to distinguish from idiopathic cardiomyopathy or giant cell myocarditis. Conduction disease is more common in patients with sarcoidosis,[97] and thallium perfusion defects tend to preferentially affect the anterior septal and apical regions. Biopsy may help to distinguish sarcoidosis from giant cell myocarditis,[98] but the diagnostic yield of endomyocardial biopsy is low.[99] Sarcoidosis is at least somewhat steroid responsive. Pulmonary artery hypertension can occur in sarcoidosis, generally as a result of pulmonary fibrosis.

Systemic vasculitis is an uncommon complication of sarcoidosis. Its precise frequency

remains unknown. Sarcoid vasculitis can affect small- to large-caliber vessels, including the aorta. The latter presentation can be easily confused with Takayasu arteritis (Figure 67-6) . African-American patients appear predisposed to the development of large vessel involvement. Although corticosteroid therapy may be palliative for all forms of sarcoid vasculitis, relapses of the disease are common and often preclude withdrawal of treatment. Morbidity from disease and treatment is common. Deaths from sarcoid vasculitis occur in a minority of reported cases.[100]

Summary

The different rheumatic diseases can affect the heart in distinct patterns (Table 67-4) . Occasionally, cardiac involvement represents the initial manifestation of a systemic autoimmune disease. The clinical pattern of involvement may provide a clue as to the underlying diagnosis. Cardiologists will encounter patients with these diseases and their cardiac and extracardiac complications and should remain vigilant to recognize these patterns when they occur.

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Chapter 68 - Cardiovascular Abnormalities in HIV-Infected Individuals

STACY D. FISHER
STEVEN E. LIPSHULTZ

Infection with the human immunodeficiency virus (HIV) is one of the leading causes of acquired heart disease and specifically of symptomatic heart failure (Table 68-1) . The cardiac complications of HIV infection tend to occur late in the disease and are therefore becoming more prevalent in our society as therapy and longevity improve. Mean annual incidence is estimated at 15.9 cases of cardiac disease per 1000 HIV-infected patients.[1]

The Joint United Nations Program on HIV/AIDS estimated that, worldwide, 33.4 million people were living with HIV infection or acquired immunodeficiency syndrome (AIDS) in 1998.[2] The incidence of new HIV infection in the United States has decreased substantially over the past 5 years. Deaths related to HIV infection decreased 42 percent in 1996-1997 and 20 percent in 1997-1998 because of improved antiretroviral therapies and better identification and treatment of opportunistic infections. By the end of 1998, about 300,000 people in the United States were living with AIDS and the number of long-term survivors was increasing.[3] Early in the epidemic, HIV infections were chiefly found in homosexual males; however, now most new cases occur in

injection drug users and heterosexual partners of infected persons. Minority groups are overrepresented.[3]

The range of cardiac abnormalities caused by HIV infection is suggested in one recent autopsy study of 440 patients. Eighty-two had cardiac involvement: the conditions, in order of frequency, were pericardial effusion, lymphocytic interstitial myocarditis, dilated cardiomyopathy (frequently with myocarditis), infective endocarditis, and malignancy (myocardial Kaposi's sarcoma and B-cell immunoblastic lymphoma).[4]

Left Ventricular Systolic Dysfunction

CLINICAL PRESENTATION.

In HIV-infected patients, concurrent pulmonary infections, pulmonary hypertension, anemia, portal hypertension, malnutrition, or malignancy may alter or confuse the characteristic signs that define heart failure in other populations. Thus, patients with left ventricular systolic dysfunction may be asymptomatic or may present with New York Heart Association Class III or IV heart failure.

Echocardiography is a useful test to assess left ventricular systolic function in this population and, in addition to left ventricular dysfunction, often reveals either low-tonormal wall thickness or left ventricular hypertrophy and a dilated left ventricular chamber. Electrocardiography (ECG) may reveal nonspecific conduction defects or repolarization changes. In one multicenter trial, 57 percent of asymptomatic HIV-infected individuals had baseline ECG abnormalities, including supraventricular and ventricular ectopic beats.[5] The chest radiograph has low sensitivity and specificity for congestive heart failure in patients with HIV infection.

Encephalopathy is associated with symptomatic heart failure in HIV-infected individuals, suggesting that it may be comorbid with cardiac dysfunction in late-stage HIV infection.[6]

INCIDENCE.

One prospective study of asymptomatic HIV-infected adults with initial CD4 counts of more than 400 cells/ml found that 76 of 952 (8 percent) had significant left ventricular dysfunction (diffuse left ventricular hypokinesis with an ejection fraction less than 45 percent and left ventricular end-diastolic volume index greater than 80 ml/m[2]) over 60 months follow-up.[1] Almost all had fewer than 400 CD4-positive cells/ml at the time of diagnosis of cardiomyopathy. The mean annual incidence for asymptomatic patients was calculated at 15.9 cases of dilated cardiomyopathy per 1000 patients. Cardiomyopathy was diagnosed 28 ± 10 (mean standard deviation) months after enrollment.[1]

A 4-year observational study of 296 patients with a spectrum of HIV-related disease found 44 (15 percent) with dilated cardiomyopathy (fractional shortening less than 28 percent, with global left ventricular hypokinesis), 13 (4 percent) patients with isolated right ventricular dysfunction (right ventricle larger than left ventricle on standard

two-dimensional views), and 12 (4 percent) patients with borderline left ventricular dysfunction (left ventricular end-systolic diameter greater than 58 mm, but fractional shortening greater than 28 percent, or global dysfunction reported by one or two, but not all three observers) (Fig. 68-1) .[7] Dilated cardiomyopathy was strongly associated with a CD4 count of less than 100 cells/ml.[7]

Left ventricular dysfunction is a common consequence of HIV infection in children. In a study of 205 vertically (mother to child) HIV-infected children (enrolled at a median age of 22 months and followed with echocardiography every 4 to 6 months and ECG, Holter monitoring, and chest radiography every year), the prevalence of decreased left ventricular function (fractional shortening <28 percent)

TABLE 68-1 -- CARDIOVASCULAR ABNORMALITIES IN HIV-INFECTED PATIENTS

TYPE	POSSIBLE ETIOLOGIES AND ASSOCIATIONS	INCIDENCE
Dilated cardiomyopathy	Infectious	Estimated 15.9 patients/1000 asymptomatic HIV-infected persons[1]
	HIV documented in mycocytes	
	Toxoplasma gondii	
	Coxsackievirus group B	
	Epstein-Barr virus	
	Cytomegalovirus	
	Adenovirus	
	Autoimmune response to infection	
	Drug-related	
	Cocaine	
	Possibly nucleoside analogues	
	Interleukin-2, doxorubicin, interferon	
	Metabolic/Endocrine	
	Nutritional deficiency/wasting	
	Selenium, vitamin B_{12} , carnitine	
	Thyroid hormone	
	Growth hormone	

	Adrenal insufficiency	
	Hyperinsulinemia	
	Cytokines	
	Tumor necrosis factor-alpha, nitric oxide, tumor growth factor-beta, endothelin-1	
	Hypothermia	
	Hyperthermia	
	Autonomic Insufficiency	
	Encephalopathy	
	Acquired Immunodeficiency	
	HIV viral load	
	Length of infection	
Pericardial effusion	Bacteria	11%/year [26]
	Staphylococcus aureus	Spontaneous resolution in up to 42% of affected patients[16] [26]
	Streptococcus pneumoniae	
	Proteus mirabilis	
	Nocardia asteroides	
	Staphylococcus epidermidis	
	Pseudomonas aeruginosa	
	Klebsiella pneumoniae	
	Enterococcus species	
	Listeria species	
	Mycobacteria	
	Mycobacterium tuberculosis	
	Mycobacterium avium-intracellulare	
	Mycobacterium kansaii	
	Viral Pathogens	
	HIV	
	Herpes simplex virus	
	Herpes simplex virus type 2	
	Cytomegalovirus	

	Other Pathogens	
	Cryptococcus neoformans	
	Toxoplasma gondii	
	Histoplasma capsulatum	
	Malignancy	
	Kaposi's sarcoma	
	Malignant lymphoma	
	Capillary leak/wasting/malnutrition	
	Hypothyroidism	
	Low CD4 count	
	Prolonged acquired immunodeficiency	
Infective endocarditis	Autoimmune response to infection	Up to 6% incidence[29]
	Bacterial	
	Staphylococcus aureus	
	Salmonella species	
	Streptococcus species	
	Enterococcus	
	Hemophilus parainfluenzae	
	Staphylococcus epidermidis	
	Pseudalleschira boydii	
	Fungal/Yeast	
	Aspergillus fumigatus	
	Candida species	
	Cryptococcus neoformans	

TABLE 68-1 -- CARDIOVASCULAR ABNORMALITIES IN HIV-INFECTED PATIENTS
Continued

TYPE	POSSIBLE ETIOLOGIES AND ASSOCIATIONS	INCIDENCE

Nonbacterial thrombotic endocarditis (generally tricuspid valve)	Underlying valvular endothelial damage, vitamin C deficiency, valvular injury secondary to catheters or injected impurities (intravenous drug use), disseminated intravascular coagulation, hypercoagulable state, malnutrition, wasting, prolonged acquired immunodeficiency	Rare (<3-5%) incidence[29] [32]
Malignancy	Prolonged immunodeficiency, low CD4 count	1% incidence (3/440) [33]
(Kaposi's sarcoma, non-Hodgkin's lymphoma, leiomyosarcoma)	Viral Associations	
	Human herpesvirus-8	
	Epstein-Barr virus	
Isolated right ventricular and pulmonary disease	Recurrent bronchopulmonary infections, pulmonary arteritis, microvascular pulmonary emboli due to thrombus or drug injection	
Primary pulmonary hypertension	Plexogenic pulmonary arteriopathy Mediator release from endothelium	0.5% incidence[38]
Vasculitis		
Systemic necrotizing	Drug therapy (antibiotic and antiretroviral)	Case reports becoming more common
Hypersensitivity		
Henoch-Schonlein purpura		
Lymphomatoid granulomatosis		
Primary central nervous system angiitis		
Accelerated atherosclerosis		
Coronary artery disease	Protease inhibitor therapy, atherogenesis by virus-infected macrophages, chronic inflammation	Up to 8% prevalence by autopsy and case reports[42] [44]
Cerebrovascular disease		

Autonomic dysfunction	Associated nervous system disease	Common in late-stage disease[47]
	Drug therapy side effects Prolonged immunodeficiency Malnutrition	
Arrhythmias	Drug therapy	Unknown
	Pentamidine Autonomic dysfunction	

was 5.7 percent. The 2-year cumulative incidence was 15.3 percent.[8] The cumulative incidence of symptomatic congestive heart failure and/or the use of cardiac medications was 10 percent over 2 years.[8]

Global estimates of HIV-infected people range from 33.4 to 120 million people worldwide between the years 1998 and 2000.[2] If there is a 10 percent incidence of symptomatic congestive heart failure over the 2 years,[8] then there would be 3.34 to 12 million cases of congestive heart failure during a 2-year interval.

PATHOGENESIS.

A wide variety of possible etiological agents have been postulated in HIV-related cardiomyopathy (see Table 68-1) , including myocardial infection with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, cardiotoxicity from therapeutic or illicit drugs, nutritional deficiencies, cytokine overexpression, and many others.[9]

Myocarditis (see Chap. 48) .

Myocarditis is perhaps the best studied of the possible causes. Dilated cardiomyopathy may be related to a direct action of HIV on the myocardial tissue or to an autoimmune process induced by HIV alone or in conjunction with co-infecting viruses.[1] , [9A] *Toxoplasma gondii,* coxsackievirus group B, Epstein-Barr virus, cytomegalovirus, adenovirus, and HIV in myocytes have been found in biopsy specimens.[10] Postmortem biopsy samples of children with HIV revealed histological evidence of myocarditis in 11 of 32 and borderline myocarditis in another 13 cases, possibly relating to the development of cardiomyopathy and to rapid progression of HIV disease.[10A]

Right ventricular biopsy performed on 76 patients within 1 month of the diagnosis of cardiomyopathy revealed evidence of myocarditis in 63, HIV nucleic acid sequences in cardiac myocytes in 58, and active myocarditis in 36.[1] In the 36 patients with active myocarditis, 9 had coexisting viral infections (coxsackievirus group B [n=6], cytomegalovirus [n=2], or Epstein-Barr virus [n=1]).[1]

Autopsy and biopsy results have revealed only scant and patchy inflammatory cell infiltrates in the myocardium.[11] HIV virions appear to infect myocardiocytes in patchy

distributions. The infected cells are not surrounded by an inflammatory response, and no clear association has been made between the infection and functional disability. Nevertheless, myocardial biopsy may be clinically helpful, because it may reveal lymphocytic infiltrates suggesting myocarditis or treatable opportunistic infections (by special stains), permitting aggressive therapy for an underlying pathogen.

Notably, HIV-related cardiomyopathy is often not associated with any specific opportunistic infection, and approximately 40 percent of patients have not experienced any opportunistic infection before the onset of cardiac symptoms.[12]

Cytokine Alterations.

HIV infection increases the production of tumor necrosis factor-alpha, which alters intracellular calcium homeostasis and increases nitric oxide (NO) production, tumor growth factor-beta, and endothelin-1 upregulation.[12] [13] NO induced in high levels has been shown experimentally to have a negative inotropic effect and to be cytotoxic to myocytes.

In one study, HIV-infected individuals with dilated cardiomyopathy were much more likely to have myocarditis, and had a broader spectrum of viral infections, than did HIV-negative patients with idiopathic dilated cardiomyopathy.[14] Also, levels of tumor necrosis factor-alpha and induced NO synthase were higher in myocytes from the HIV-infected patients with dilated cardiomyopathy (particularly those with viral co-infections) and levels varied inversely with the CD4 count. Barbaro and associates postulate that immunodeficiency may favor the selection of viral variants of increased pathogenicity or enhance the cardiovirulence of viral strains.[14]

Nutritional Deficiencies.

Nutritional deficiencies are

Figure 68-1 *Top,* Survival curves for 296 HIV-infected patients with structurally normal hearts, dilated cardiomyopathy (DCM), left ventricular dysfunction (LVD), or right ventricular dysfunction (RVD). *Bottom,* Time to death related to AIDS in 81 patients with CD4+ cell counts less than 20×10^{6} cells per liter. (From Currie PF, Jacob AJ, Foreman AR, et al: Heart muscle disease related to HIV infection: Prognostic implications. BMJ 309:1605, 1994.)

common in HIV infection, particularly in late-stage disease. Poor absorption and diarrhea both lead to electrolyte imbalances and deficiencies in elemental nutrients. Deficiencies of trace elements have been associated with cardiomyopathy. For example, selenium deficiency increases the virulence of coxsackievirus to cardiac tissue.[15] Selenium replacement reverses cardiomyopathy and restores left ventricular

function in nutritionally deplete patients. Levels of vitamin B_{12} , carnitine, and growth and thyroid hormone may also be altered in HIV disease; all have been associated with left ventricular dysfunction.

Pathogenesis in Children.

In children with vertically transmitted HIV infection, two mechanisms of pathogenesis have been described. One is the dilation of the left ventricle with a reduction in thickness-to-end-systolic dimension ratio of the ventricle. The other is concentric hypertrophy of the muscle; with dilation, the thickness-to-end-systolic dimension ratio remains normal or is increased.[6]

COURSE OF DISEASE.

Patients with asymptomatic left ventricular dysfunction (fractional shortening less than 28 percent, with global left ventricular hypokinesis) may have transient disease by echocardiographic criteria. In one serial echocardiographic study, three of six patients with abnormal fractional shortening had normal readings after a mean of 9 months. The three with persistently depressed left ventricular function died within 1 year of baseline.[16]

Prognosis.

Mortality in HIV-infected patients with cardiomyopathy is increased independent of CD4 count, age, sex, and risk group. The median survival to AIDS-related death was 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart, at similar infection stage (see Fig. 68-1) . [7] Isolated right ventricular dysfunction or borderline left ventricular dysfunction did not place patients at risk. Compared with idiopathic cardiomyopathy, patients with HIV-related cardiomyopathy had a hazard ratio of 4.0 (95% confidence interval 2.80-5.74) for death over a mean follow-up period of 4.4 years.[16A]

In the P[2] C[2] HIV study of children with vertically transmitted HIV infection (median age, 2.1 years), 5-year cumulative survival was 64 percent.[17] Mortality was higher in children with baseline depressed left ventricular fractional shortening or increased left ventricular dimension, thickness, mass, wall stress, heart rate, or blood pressure (Fig. 68-2). Decreased left ventricular fractional shortening and increased wall thickness were also predictive of survival after adjustment for age, height, CD4 count, HIV RNA copy number, clinical center, and encephalopathy.[6] [17] Fractional shortening was abnormal for up to 3 years before death, whereas wall thickness identified a population at risk only 18 to 24 months before death. Thus, in children, fractional shortening may be a useful long-term predictor and wall thickness a useful short-term predictor of mortality.[18]

Rapid-onset congestive heart failure has a grim prognosis

Figure 68-2 Kaplan-Meier cumulative survival curves for 193 HIV-infected children according to baseline echocardiographic measurements after prospective follow-up. Patients are stratified by Z scores adjusted for age or body surface area for each measurement. *Left,* Fractional shortening. *Right,* Left ventricular mass. (Based on data from Lipshultz SE, Easley KA, Orav EJ, et al: Cardiac dysfunction and mortality in HIV-infected children: The prospective P[2] C[2] HIV multicenter study. Circulation, in press.)

in HIV-infected adults and children, with over half of patients dying of primary cardiac failure within 6 to 12 months of presentation.[6] [12] Chronic-onset heart failure may respond better to medical therapy in this patient population.[12]

Therapy

Therapy for dilated cardiomyopathy associated with HIV infection is generally similar to therapy for nonischemic cardiomyopathy and includes diuretics, digoxin, and angiotensin-converting enzyme inhibitors as tolerated. No studies have investigated the efficacy of specific cardiac therapeutic regimens other than intravenous immunoglobulin.[19] [20]

Opportunistic or other infections should be sought aggressively and treated, with potential to improve or resolve the cardiomyopathy.[21] Right ventricular biopsy may be useful in identifying infectious causes of heart failure to institute targeted therapy.[21] However, right ventricular biopsy is probably underused.

After medical therapy is begun, serial echocardiographic studies should be performed at 4-month intervals.[21] Monitoring recommendations for testing and timing of follow-up are based on studies relating impairment of fractional shortening to a worse prognosis.[21] If function continues to worsen or the clinical course deteriorates, a biopsy should be considered.

Intravenous immunoglobulins have had some success in acute congestive cardiomyopathy and nonspecific myocarditis in HIV-uninfected patients.[20] Immunoglobulin therapy is beneficial in Kawasaki disease, an immunologically mediated illness with cardiac dysfunction resembling that seen with HIV disease.[22] [23] Monthly immunoglobulin infusions in HIV-infected pediatric patients have been associated with minimized left ventricular dysfunction, an increase in left ventricular wall thickness, and a reduction in peak left ventricular wall stress (Fig. 68-3) , suggesting that both impaired myocardial growth and left ventricular dysfunction may be immunologically mediated.[18]

The apparent efficacy of immunoglobulin therapy may be the result of immunoglobulins removing cardiac autoantibodies

Figure 68-3 Mean echocardiographically measured cardiac dimensions in patients taking intravenous immunoglobulin (IVIG) and patients not taking it. All measurements are presented as age- or body surface area-adjusted Z scores. ED=end diastolic; ES=end systolic. (From Lipshultz SE, Orav EJ, Sanders SP, et al: Immunoglobulins and left ventricular structure and function in pediatric HIV infection. Circulation 92:2220, 1995. Copyright 1995, American Heart Association.)

or dampening the secretion or effects of cytokines and cellular growth factors. Immunomodulatory therapy may be helpful in special circumstances or in children with declining left ventricular function. A randomized, multicenter trial is warranted to evaluate the efficacy of this therapy.

Patients should be evaluated for nutritional status, and any with deficiencies should receive supplements. Supplementation with selenium, carnitine, multivitamins, or all three may be helpful, especially in anorexic patients or in those with wasting or diarrheal syndromes.

Animal Models

Chronic pathogenic simian immunodeficiency virus (SIV) infection in rhesus macaques resulted in significant depression of left ventricular ejection fraction and extensive coronary arteriopathy suggestive of a cell-mediated immune response.[24] Notably, two thirds of chronically infected macaques that died of SIV had myocardial pathology with lymphocytic myocarditis in 9 of 15 and coronary arteriopathy in 9 of 15 (6 alone and 3 in combination with myocarditis). Coronary arteriopathy was associated with evidence of vessel occlusion and recanalization, with associated areas of myocardial necrosis in 4 macaques. Two animals had marantic endocarditis, and 1 had a left ventricular mural thrombus on pathological examination. Macaques with cardiac pathology were emaciated to a greater extent than macaques with SIV and similar periods of infection who did not experience cardiac disease.[24]

Left Ventricular Diastolic Dysfunction

Clinical and echocardiographic findings suggest that diastolic dysfunction is relatively common in long-term survivors of HIV infection. Left ventricular diastolic dysfunction may precede systolic dysfunction.[25] One large multicenter echocardiographic study found that asymptomatic HIV-infected patients had 34.6 percent lower E/A ratio (Doppler-derived parameter of diastolic dysfunction: peak early [E] over peak atrial [A] velocity) and 19.7 percent longer isovolumetric relaxation time than healthy adults.[5]

Pericardial Effusion (see Chap. 50)

CLINICAL PRESENTATION.

HIV-infected patients with pericardial effusions generally have a lower CD4 count, marking more advanced disease, than those without effusions.[26] Effusions are generally asymptomatic.

INCIDENCE.

Asymptomatic pericardial effusions are common in HIV-infected patients.[16] [26] [27] The 5-year Prospective Evaluation of Cardiac Involvement in AIDS (PRECIA) study found that 16 of 231 patients (59 subjects with asymptomatic HIV, 62 with AIDS-related complex, and 74 with AIDS) developed pericardial effusions.[26] Three subjects had an effusion on enrollment, and 13 developed effusions during follow-up (12 of them had AIDS). Pericardial effusions were small (maximum pericardial space less than 10 mm at end diastole) in 80 percent and asymptomatic in 87 percent of patients with effusion. The incidence of pericardial effusion among those with AIDS was 11 percent per year.[26] The prevalence of effusion in AIDS patients rises over time, reaching a mean in asymptomatic patients of about 22 percent after 25 months of follow-up.[26]

HIV infection should be suspected whenever young patients have pericardial effusion or tamponade. In a retrospective series of cardiac tamponade cases in a city hospital, 13 of 37 patients (35 percent) had HIV infection.[28]

PATHOGENESIS.

Pericardial effusion may be related to an opportunistic infection or to malignancy (see Table 68-1) , but most often a clear etiology is not found. The effusion is often part of a generalized serous effusive process also involving pleural and peritoneal surfaces. This "capillary leak" syndrome may be related to enhanced cytokine production in the later stages of HIV disease. Other causes may include uremia from HIV-associated nephropathy or drug nephrotoxicity. Fibrinous pericarditis with or without effusion is also well described, comprising 9 percent of cardiac lesions found in AIDS patients in one autopsy series.[26]

COURSE OF DISEASE AND PROGNOSIS.

Effusion markedly increases mortality.[16] [26] [26A] For example, in the PRECIA study, it nearly tripled the risk of death among AIDS patients (Fig. 68-4) .[26] Also 2 of 16 patients with effusions developed pericardial tamponade. Pericardial effusion may, however, resolve spontaneously in up to 42 percent of patients.[16] [26] Mortality was still markedly increased in patients who had developed an effusion.[16] [26]

MONITORING AND THERAPY.

Screening echocardiography is recommended in HIV-infected individuals, regardless of the stage of disease. All HIV-infected patients with evidence of heart failure, Kaposi's sarcoma, tuberculosis, or other pulmonary infections should have baseline

echocardiography, Holter monitoring, and ECG testing.[27] Patients should undergo pericardiocentesis if they have pericardial effusion and clinical signs of tamponade (e.g., elevated jugular venous pressure, dyspnea, hypotension, tachycardia, and pulsus paradoxus) or echocardiographic signs of tamponade (e.g., valvular inflow respiratory variation by continuous wave Doppler, septal bounce, right ventricular diastolic collapse) and a large effusion.

Patients with pericardial effusion without tamponade should be evaluated for treatable opportunistic infections such as tuberculosis and for malignancy. Highly active antiretroviral therapy should be considered if this has not already been instituted. Repeat echocardiography is recommended after 1 month, or sooner if clinical symptoms of tamponade develop in the interim.

Infective Endocarditis (See Chap. 47)

Injection drug users are at greater risk than the general population for infective endocarditis, chiefly of right-sided heart valves. Surprisingly, HIV-infected patients may not

Figure 68-4 Survival of patients with and without pericardial effusions at AIDS diagnosis. (From Heidenreich PA, Eisenberg MJ, Kee LL, et al: Pericardial effusion in AIDS: Incidence and survival. Circulation 92:3229, 1995. Copyright 1995, American Heart Association.)

have a higher incidence of endocarditis than people with similar risk behaviors.[29]

Because the autoimmune response to bacterial endocarditis is often largely responsible for valvular destruction associated with endocarditis, variations in the course of the disease in HIV-infected patients may occur. For example, HIV-infected patients have a higher risk of developing *Salmonella* endocarditis than immunocompetent patients because they are more likely to develop *Salmonella* bacteremia during *Salmonella* infection. However, they respond better to antibiotic therapy and may be less likely to sustain valvular damage because of their impaired immune response.[29] [30] [31]

Common organisms associated with endocarditis in HIV-infected patients include *Staphylococcus aureus* and *Salmonella* species.[29] [31] Fungal endocarditis with organisms such as *Aspergillus fumigatus, Candida* species, and *Cryptococcus neoformans* is more common in intravenous drug users with HIV than in those without it and, again, may be responsive to therapy (see Table 68-1) .[29]

Fulminant courses of infective endocarditis with high mortality may occur in patients with late-stage AIDS with poor nutritional status and severely compromised ability to fight infection, but several cases have been successfully treated with antibiotic therapy.[29]

Operative indications in HIV-infected patients with endocarditis include hemodynamic instability, failure to sterilize cultures after appropriate intravenous antibiotics, and severe valvular destruction in patients with a reasonable life expectancy after recovery from surgery.

Nonbacterial Thrombotic Endocarditis

Nonbacterial thrombotic endocarditis (or marantic endocarditis) involves large friable sterile vegetations that form on the cardiac valves. These lesions have been associated with disseminated intravascular coagulation and systemic embolization. Lesions are rarely diagnosed ante mortem; among patients who do receive the diagnosis, clinically relevant emboli occur in an estimated 42 percent of cases.[29] [32] In the early HIV epidemic, several case series suggested a high incidence of this uncommon disorder; however, very few cases have since been reported, and almost none have been found in prospective series. Marantic endocarditis should be suspected in any patient with systemic embolization; yet it should be considered rare in AIDS patients.

Treatment of nonbacterial thrombotic endocarditis should focus on reducing the underlying disease state causing coagulation abnormalities and/or valvular endothelial damage. Anticoagulation risk/benefit assessment must be made on an individual basis.

Cardiovascular Malignancy (See Chap. 49)

Malignancy affects many AIDS patients, generally in the later stages of disease. Cardiac malignancy is usually metastatic disease.

Kaposi's sarcoma (angiosarcoma) is associated with human herpesvirus-8 and affects up to 35 percent of AIDS patients, particularly homosexuals, with an incidence inversely related to the CD4 count. Autopsy found that 28 percent of HIV-infected patients with widespread Kaposi's sarcoma had cardiac involvement, and rarely described it as a primary cardiac tumor.[33] [34] An endothelial cell neoplasm with a predilection in the heart for subpericardial fat around the coronary arteries, Kaposi's sarcoma has not been found invading the coronary arteries.[33]

Kaposi's sarcoma involving the heart is generally an incidental finding at autopsy, rarely causing cardiac symptoms. Specific symptoms may be related to pericardial effusion associated with the epicardial location of the tumor. Pericardial fluid in patients with cardiac Kaposi's sarcoma is typically serosanguineous without malignant cells or infection.[33] Kaposi's sarcoma is difficult to treat. Most patients die of opportunistic infections related to the advanced stage of immunodeficiency, rather than from the malignancy.

Primary cardiac malignancy associated with HIV infection is generally due to cardiac lymphoma. Non-Hodgkin lymphomas are 25 to 60 times more common in HIV-infected individuals. They are the first manifestation of AIDS in up to 4 percent of new cases.[35] [36] Primary cardiac lymphoma may present as dyspnea, right-sided heart failure, biventricular failure, chest pain, or arrhythmias.[36] Cardiac lymphoma is associated with

rapid progression to cardiac tamponade, symptoms of congestive heart failure, myocardial infarction, tachyarrhythmias, conduction abnormalities, or superior vena cava syndrome.[33] Pericardial fluid typically reveals malignant cells but may be histologically normal. Systemic multiagent chemotherapy with and without concomitant radiation or surgery has been beneficial in some patients, but overall the prognosis is poor.[33] [36]

Leiomyosarcoma, associated with Epstein-Barr virus, is a rare, malignant tumor of smooth muscle origin with an increased incidence in children with AIDS. Leiomyosarcomas are largely noncardiac and often involve the arterial wall.[33] An intracardiac mass in late-stage HIV infection is associated with a uniformly poor prognosis.

Isolated Right Ventricular Disease and Pulmonary Disease (See Chap. 54)

Isolated right ventricular hypertrophy with or without right ventricular dilation is relatively uncommon in HIV-infected individuals and is generally related to pulmonary disease that increases pulmonary vascular resistance. Possible causes include multiple bronchopulmonary infections, pulmonary arteritis from the immunological effects of HIV disease, or microvascular pulmonary emboli caused by thrombus or contaminants in injected drugs.[37]

Primary pulmonary hypertension has been described in a disproportionate number of HIV-infected individuals, primarily in case reports. Primary pulmonary hypertension is estimated to occur in about 0.5 percent of hospitalized AIDS patients.[38] In one series of 6 AIDS patients with pulmonary hypertension associated with right ventricular hypertrophy and failure, clinical findings included dyspnea on exertion, hypoxemia, restrictive lung disease with decreased diffusing lung capacity for carbon monoxide, and right ventricular hypertrophy on ECG.[38]

Plexogenic pulmonary arteriopathy was demonstrated on lung histology from 5 of 12 patients reported as having primary pulmonary hypertension and HIV infection.[39] All of these patients had clear lung fields on examination and chest radiograph and normal perfusion scans.

Pulmonary hypertension is often explained by lung infections, venous thromboembolism, or left ventricular dysfunction. Pulmonary hypertension found on screening echocardiography or right-sided heart catheterization warrants further examination for treatable pulmonary infections.

Primary pulmonary hypertension has been reported in HIV-infected patients without a history of thromboembolic disease, intravenous drug use, or pulmonary infections associated with HIV.[37] [38] [39] [40] One autopsy and one biopsy specimen revealed precapillary muscular pulmonary artery and arteriole medial hypertrophy, fibroelastosis, and eccentric

intimal fibrosis without direct viral infection of pulmonary artery cells.[40] This suggests mediator release from infected cells elsewhere. Primary pulmonary hypertension has also been found in hemophiliacs receiving lipophilized factor VIII, intravenous drug users, and patients with left ventricular dysfunction, obscuring any relationship with HIV.[37] It may be that HIV causes endothelial damage and mediator-related vasoconstriction of the pulmonary arteries.[16] [38] [40] Therapy includes anticoagulation (based on individual risk/benefit analysis) and vasodilator agents as tolerated.

Vasculitis

Vasculitis is being reported more often in HIV-infected patients.[40A] It should be suspected in patients with fever of unknown origin, unexplained multisystem disease, unexplained arthritis or myositis, glomerulonephritis, peripheral neuropathy (especially mononeuritis multiplex), or unexplained gastrointestinal, cardiac, or central nervous system ischemia. Many types of vasculitis have been described in HIV-infected patients (see Table 68-1) .[41] Successful immunomodulatory therapy, chiefly with systemic corticosteroid therapy, has been described.

Accelerated Atherosclerosis (See Chaps. 30 , 31 , and 32)

Accelerated atherosclerosis has been observed in young HIV-infected individuals without traditional coronary risk factors.[42] [43] [44] Significant coronary lesions were discovered at autopsy in 8 HIV-positive subjects aged 23 to 32 who died unexpectedly.[42] Cytomegalovirus was present in 2, and hepatitis B virus was found in 2. None of the 8 patients had evidence of cocaine use.

Premature cerebrovascular disease is common in AIDS patients. An 8 percent stroke prevalence in AIDS patients was estimated in an autopsy study in the 1980s.[45] Of the patients with stroke, 4 of 13 had evidence of cerebral emboli and 3 of those 4 had a clear cardiac source of embolus.

Protease inhibitor therapy significantly alters lipid metabolism and may be associated with premature atherosclerotic disease. Angiographically proven advanced symptomatic coronary artery disease has been reported in three men younger than age 40 treated with protease inhibitors.[46] Chronic inflammatory states have also been associated with premature atherosclerotic vascular disease.

Autonomic Dysfunction

Early clinical signs of autonomic dysfunction in HIV-infected patients include syncope and presyncope, diminished sweating, diarrhea, bladder dysfunction, and impotence. In one study, heart rate variability, Valsalva ratio, cold pressor testing, and hemodynamic responses to isometric exercise, tilt table testing, and standing showed that autonomic dysfunction occurred in patients with AIDS-related complex and was pronounced in

AIDS patients. Patients with HIV-associated nervous system disease had the greatest abnormalities in autonomic function.[47] [47A]

Complications of Therapy for HIV

Potent antiretroviral medications and highly active antiretroviral therapy, which generally combines three or more agents and usually includes a protease inhibitor, have clearly increased the life span and quality of life of HIV-infected patients.[48] [49] [50] [51] However, protease inhibitors, particularly when used in combination therapy or in highly active antiretroviral therapy, are associated with lipodystrophy, fat wasting and redistribution, metabolic abnormalities, hyperlipidemia, insulin resistance, and increased atherosclerotic risk profiles.[52] [53] [54] HIV-infected patients treated with protease inhibitors have reported substantial decreases in total body fat with peripheral lipodystrophy (fat wasting of the face, limbs, and buttocks) and relative conservation or enhancement of central adiposity (truncal obesity, breast enlargement, and "buffalo hump") compared with patients who have not received protease inhibitors.[54] Lipid alterations associated with protease inhibitors include higher triglyceride, total cholesterol, insulin, lipoprotein(a) and C-peptide levels, and lower high-density lipoprotein levels (all promoting an atherogenic profile).[52] [53] [54] [54A] [54B] Flow-dependent vasodilation measured in the brachial artery by venous occlusion plethysmography was impaired in HIV-infected patients taking protease inhibitors.[54A]

Lipid abnormalities vary with different protease inhibitors.[53] Ritonavir had the largest adverse effects on lipids, with a mean increase in total cholesterol of 2.0 mmol/liter and a mean increase in triglyceride level of 1.83 mmol/liter. More modest increases of total cholesterol without significant triglyceride increases were found in patients taking indinavir and nelfinavir. Combination with saquinavir did not further elevate the total cholesterol. Protease inhibitor therapy increased lipoprotein(a) by 48 percent in patients with pretreatment elevated values (>20 mg/dL).[53] In some cases, switching protease inhibitors can reverse both elevations in triglyceride levels and abnormal fat deposition. At this time, increased coronary artery disease secondary to protease inhibitor related dyslipidemia has not been shown.[54C] [54D]

Zidovudine (azidothymidine) has been implicated in skeletal muscle myopathies.[55] [56] In culture, zidovudine causes a dose-dependent destruction of human myotubes.[56] Human-cultured cardiac muscle cells treated with zidovudine develop mitochondrial abnormalities.[56] However, cardiac myopathies have not been evident in clinical data. In a combined retrospective and prospective analysis, both HIV-infected and HIV-negative children born to HIV-infected women and exposed to zidovudine in utero were not more likely to have abnormal left ventricular structure and function than children who were not exposed to zidovudine.[56B] Rare patients with left ventricular dysfunction, however, have improved with cessation of zidovudine therapy and normal troponin T levels have been measured in some of these patients.[56A]

A transgenic versus wild-type mouse model demonstrated cardiomyopathy by HIV infection alone that is enhanced by zidovudine therapy. Zidovudine-treated mice had mitochondrial ultrastructural damage in cardiac myocytes.[57]

Intravenous pentamidine, used to treat *Pneumocystis carinii* pneumonia in patients intolerant of trimethoprim/sulfamethoxazole, has been associated with cases of torsades de pointes and refractory ventricular tachycardia.[21] [58] [59] Recommendations for the use of intravenous pentamidine are outlined in Figure 68-5 (Figure Not Available) .

Multiple medication reactions and interactions have occurred during the treatment of HIV infection and are a significant cause of cardiac emergencies in HIV-infected patients. Common cardiac drug interactions are outlined in Table 68-2 .

Perinatal Transmission and Vertically Transmitted HIV Infection

Most pediatric patients with HIV are infected in the perinatal period, but HIV transmission can be minimized if mothers

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Figure 68-5 (Figure Not Available) Recommendations for HIV-infected patients starting intravenous pentamidine treatment. (From Moorthy LN, Lipshultz SE: Cardiovascular monitoring of HIV-infected patients. *In* Lipshultz SE [ed]: Cardiology in AIDS. New York, Chapman & Hall, 1998, p 345. Data based on Eisenhauer MD, Eliasson AH, Taylor AJ, et al: Incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients. Chest 105:389, 1994.)

are given courses of zidovudine in the second and third trimesters or short courses before parturition.[60] [61] [62] [63] [64] [65] [66] [67]

Rates of congenital cardiovascular malformations in cohorts of HIV-uninfected and HIV-infected children born to HIV-infected mothers ranged from 5.6 to 8.9 percent. These rates were 5 to 10 times higher than reported in population-based epidemiological studies but not higher than in normal populations similarly screened.[68]

In the same cohorts, serial echocardiograms performed at 4- to 6-month intervals found subclinical cardiac abnormalities to be common, persistent, and often progressive.[6] [68A] Some had dilated cardiomyopathy (left ventricular contractility 2 standard deviations or more below the normal mean and left ventricular end-diastolic dimension 2 standard deviations above the mean or more) and inappropriate left ventricular hypertrophy (elevated left ventricular mass in the setting of decreased height and weight). Depressed left ventricular function correlated with immune dysfunction at baseline but not longitudinally, suggesting that the CD4 cell count may not be a useful surrogate marker of HIV-associated left ventricular dysfunction. The development of encephalopathy was highly correlated with a decline in fractional shortening.

In children with vertically transmitted HIV-1 infection, disease may progress rapidly or slowly.[69] Rapid progressors have higher heart rates, higher respiratory rates, and lower fractional shortening on serial examinations than nonrapid progressors and HIV-uninfected children similarly screened. Rapid progressors have higher 5-year

cumulative mortality, higher HIV-1 viral loads, and lower CD8+ (cytotoxic) T cell counts than nonrapid progressors.[69] Knowing the patterns of disease allows more aggressive therapy to be initiated earlier in rapid progressors.

Monitoring Recommendations

Routine, systematic cardiac evaluation including a comprehensive history and thorough cardiac examination is essential for the care of HIV-infected adults and children. Asymptomatic cardiac disease may be fatal, and cardiac symptoms are often confounded by secondary effects of HIV-infection; thus, systematic echocardiographic monitoring is warranted.

HIV-infected individuals without cardiac symptoms should undergo annual echocardiography and should have Holter monitoring and ECG every 2 years.[21] Patients with serious noncardiac illness should undergo echocardiography, ECG, and Holter monitoring followed by echocardiography every 8 months and ECG and Holter monitoring every year.[21] Patients with cardiac symptoms should have a formal cardiac assessment including baseline echocardiography, ECG, and Holter monitoring and should begin directed therapy.[21] Recommendations for Holter monitoring are based on studies illustrating the frequency of high-grade arrhythmias and abnormal conduction patterns. Holter monitoring recommendations have not been tested and are a suggestion based on available data.

In patients with left ventricular dysfunction, serum troponin assays are indicated. Serum troponin elevations warrant consideration of cardiac catheterization and endomyocardial biopsy. Myocarditis proven by biopsy warrants considering therapy with intravenous immunoglobulin. Cytomegalovirus inclusions on the biopsy specimen warrant antiviral therapy, and abnormal mitochondria should encourage consideration of a "drug holiday" from zidovudine. Ultrasound examination should be repeated after 2 weeks of therapy to allow a more aggressive approach if left ventricular dysfunction persists or worsens and to encourage continued therapy if improvement has occurred.[21]

Conclusions

The longer HIV-infected patients live and the more advanced their disease, the higher the risk of cardiac complications.[1] [4] [68] An epidemic number of HIV-infected individuals will present with cardiac complications in the next decade as long-term viral infection, co-infections, drug therapy, and immunosuppression take a toll on the heart. The impact that highly active antiretroviral therapy will have on the incidence and prevalence of cardiac complications in HIV-infected patients is unknown. Early screening and therapy of HIV-infected patients, regardless of the stage of disease, will identify the potentially fatal complications of HIV disease and therapy and allow them to be treated.

TABLE 68-2 -- CARDIOVASCULAR ACTIONS/INTERACTIONS OF DRUGS COMMONLY USED IN HIV THERAPY

CLASS	DRUGS	CARDIAC DRUG INTERACTIONS	CARDIAC SIDE EFFECTS
Antiretroviral			
Nucleoside reverse transcriptase inhibitors	Abacavir (Ziagen) Didanosine (ddl, Videx) Lamivudine (3TC, Epivir) Stavudine (d4T, Zerit) Zalcitabine (ddC, Hivid)		Rare--lactic acidosis Hypotension with abacavir
	Zidovudine (AZT, Retrovir)	Dipyridamole	Skeletal muscle myopathy with Zidovudine
Nonnucleoside reverse transcriptase inhibitors	Delavirdine (Rescriptor) Efavirenz (Sustiva) Nevirapine (Viramune)	Calcium channel blockers, warfarin Warfarin Beta blockers, nifedipine, quinidine, steroids, theophylline. May decrease effects of warfarin.	
Protease inhibitors	Amprenavir (Agenerase) Indinavir (Crixivan) Nelfinavir (Viracept)	All are metabolized by cytochrome P-450 and interact with sildenafil, amiodarone, lidocaine, quinadine, warfarin, and "statins."	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, fat wasting and redistribution
	Ritonavir (Norvir) Saquinavir (Invirase, Fortovase)	Calcium channel blockers, prednisone, quinine; increases beta blocker levels 1.5-3 ×; warfarin may increase levels three times	
Antiinfective			

Antibiotics	Erythromycin	Cytochrome P-450 metabolism and drug interactions	Orthostatic hypotension, ventricular tachycardia, bradycardia, torsades (with drug interactions)
	Trimethoprim-sulfamethoxazole (Bactrim)	Increases warfarin effects	Orthostatic hypotension, anaphylaxis
Antifungal agents	Amphotericin B Ketoconazole Itraconazole (Sporanox)	Digoxin toxicity Cytochrome P-450 metabolism and drug interactions; increases levels of sildenafil, warfarin, "statins," nifedipine, and digoxin	Hypertension, arrhythmia, renal failure, hypokalemia, thrombophlebitis, angioedema
Antiviral agents	Foscarnet		Reversible cardiac failure, electrolyte abnormalities
	Ganciclovir	Zidovudine	Ventricular tachycardia, hypotension
Antiparasitic	Pentamidine (IV)		Hypotension, arrhythmias (torsades), ventricular tachycardia, hyperglycemia, hypoglycemia, sudden death
Chemotherapy agents	Vincristine	Decreases digoxin level	Arrhythmia, myocardial infarction, cardiomyopathy

	Interferon alfa		Orthostatic hypotension (only 1/26 non-HIV, common in HIV patients), myocardial infarction, cardiomyopathy, ventricular and supraventricular arrhythmias, atrioventricular block
	Interleukin-2		Hypotension, arrhythmia, sudden death, myocardial infarction, cardiac failure, capillary leak, thyroid alterations
	Doxorubicin (Adriamycin)	Decreases digoxin level	Myocarditis, cardiomyopathy, cardiac failure
Other			
Systemic corticosteroids	Decreases salicylate levels and increases gastric ulceration in combination with salicylates.		Ventricular hypertrophy, cardiomyopathy, hyperglycemia
Pentoxifylline			Decreased triglyceride levels, arrhythmias, chest pain
Growth hormone			Ventricular hypertrophy, activation of the renal angiotension system (hypertension)
Medroxyprogesterone (Megace)			Edema, thrombophlebitis, hyperglycemia

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Chapter 69 - Hematological-Oncological Disorders and Cardiovascular Disease

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A dialogue between cardiologists and hematologist-oncologists is often required in the care of patients with a variety of disorders encompassing both fields. Intrinsic cardiac disease in patients with neoplastic or benign hematological disorders affects the natural history of the underlying condition as well as the therapeutic possibilities. How primary hematological disorders can affect the cardiovascular system is illustrated by hypercoagulability due to cancer, bleeding, and/or anemia from bone marrow failure and also by hyperviscosity in polycythemia. Tumors that invade or involve the heart are not uncommon. These two disciplines also frequently intersect because of the generally negative effect of antineoplastic drugs on cardiac function. Such agents may have direct effects on the myocardium or act indirectly owing to chemotherapy-induced myelosuppression with associated sepsis.

IRON AND THE HEART

Iron metabolism and its derangements,[1] especially those associated with deficiency or excess, may have profound effects on the cardiovascular system. Iron-deficiency anemia has been the primary hematological problem faced by humans throughout history. In many parts of the world it continues to be a major scourge. Iron overload (Table 69-1) has become a problem only with advances in medical care that have prolonged life and with advances in medical technology that have made feasible repeated blood transfusions. Hereditary hemochromatosis, the best characterized genetic cause of iron overload, generally manifests after about the third decade of life. As late as 1890, the median life expectancy in Europe was only 40 years, meaning that most people with hereditary hemochromatosis died of other causes before developing complications of the disorder. The longer life spans that we currently enjoy have brought this condition to the forefront.

Transfusions are of equally recent advent. Medical researchers discovered blood antigens only at the beginning of the 20th century. Routine blood transfusion was not feasible until the 1940s. Before the 1960s when repeated transfusion therapy became widespread in the industrialized world, patients with chronic severe anemias, such as thalassemia major, succumbed largely to cardiac complications of the anemia.

Iron overload has relatively uniform manifestations, irrespective of cause. Cardiac dysfunction is a primary cause of death in people with iron overload. The heart does not accumulate iron disproportionately to the other organs. The key to the heart's central role in the pathology of iron overload lies in the need for the complex array of cells and structures in the heart to function coordinately. Half of the liver for instance can be lost to fibrosis or cirrhosis, and a person can still survive. Obviously, this is not true of the heart.

ETIOLOGY OF IRON OVERLOAD.

Hereditary hemochromatosis results from a fractional increase in dietary iron absorption. Tissue iron reaches dangerous levels after 30 or 40 years. The gene responsible for hereditary hemochromatosis, *HFE,* resides on chromosome 6. Discovered in 1996, the gene encodes a protein that is homologous to Class I human leukocyte antigens. The alteration in HFE protein that produces hereditary hemochromatosis in 90 percent of those with the disease involves the mutation of a cysteine to tyrosine at position 282 (C282Y).[2] Individuals who have one copy of the mutant *HFE* gene are carriers who only rarely develop iron overload (usually in association with a second defect). People with two copies of the mutant allele

TABLE 69-1 -- CAUSES OF IRON OVERLOAD

I. Primary Hemochromatosis--genetically transmitted (autosomal recessive)
A. Men affected more than women
B. Alcohol increases iron absorption and worsens disease
II. Secondary Hemochromatosis--transfusion related

A. With intestinal hyperabsorption: thalassemias

B. Without intestinal hyperabsorption: bone marrow failure states

1. Aplastic anemia
2. Pure red cell aplasia
3. Myelodysplastic syndromes
4. Agnogenic myeloid metaplasia/myelofibrosis

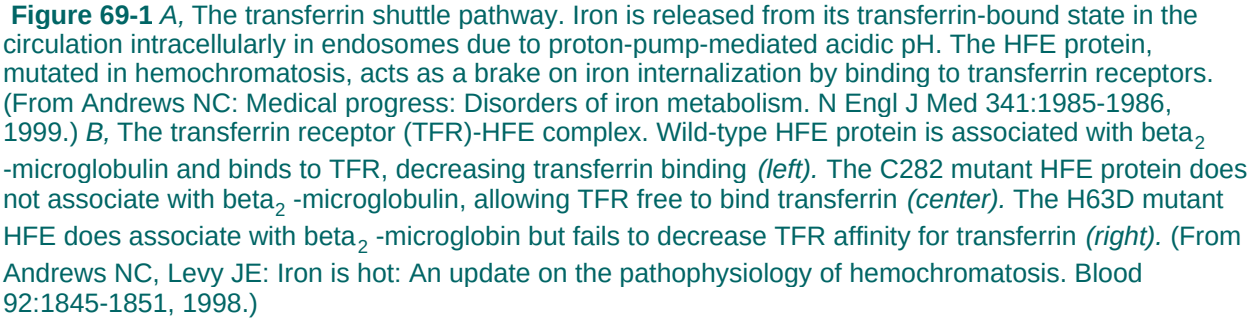

Figure 69-1 *A,* The transferrin shuttle pathway. Iron is released from its transferrin-bound state in the circulation intracellularly in endosomes due to proton-pump-mediated acidic pH. The HFE protein, mutated in hemochromatosis, acts as a brake on iron internalization by binding to transferrin receptors. (From Andrews NC: Medical progress: Disorders of iron metabolism. N Engl J Med 341:1985-1986, 1999.) *B,* The transferrin receptor (TFR)-HFE complex. Wild-type HFE protein is associated with $beta_2$ -microglobulin and binds to TFR, decreasing transferrin binding *(left).* The C282 mutant HFE protein does not associate with $beta_2$ -microglobulin, allowing TFR free to bind transferrin *(center).* The H63D mutant HFE does associate with $beta_2$ -microglobin but fails to decrease TFR affinity for transferrin *(right).* (From Andrews NC, Levy JE: Iron is hot: An update on the pathophysiology of hemochromatosis. Blood 92:1845-1851, 1998.)

can develop iron overload, which engenders a vast array of clinical problems.

Only recently have investigators gained insight into the mechanism by which the mutation in *HFE* alters cellular iron metabolism. Iron in the circulation binds to transferrin, the protein that maintains it in a soluble, nontoxic state. The plasma membrane of cells contains transferrin receptors that mediate cellular iron uptake. Transferrin receptors bind iron-transferrin complexes and mediate their internalization through endosomes. Iron is separated from transferrin in the endosome and is shuttled into the interior of the cell (Fig. 69-1 *A*). The iron-free transferrin (apotransferrin) recycles into the circulation and is free to bind and transport additional iron atoms. The HFE protein associates with transferrin receptors in the plasma membrane, thereby reducing transferrin binding to the receptor and slowing the internalization process.[3]

The cysteine 282 to tyrosine mutation C282Y disrupts the folding of the HFE protein. The mutant HFE protein does not associate with the transferrin receptor and does not act as a brake on iron uptake by cells (see Fig. 69-1 *B*).[4] These insights do not fully explain the increase in gastrointestinal iron absorption, which is the root of hereditary hemochromatosis. They do, however, mechanistically connect HFE and iron metabolism. Improved understanding of the complex process of intestinal iron absorption should provide a better pathophysiological explanation for the clinical manifestations of hereditary hemochromatosis.

Hereditary hemochromatosis is remarkably common. Ten to 12 percent of individuals of European background are heterozygous for the condition.[5] The incidence of homozygosity for the condition approaches 1 in 300,[6] making hereditary hemochromatosis one of the most prevalent genetic conditions in the world.[7] Nonetheless, the clinical incidence of the disorder is less than predicted by the genetic frequency calculations. Variable penetrance, perhaps related to secondary genetic or environmental conditions, must influence clinical manifestations. The C282Y mutation appears to be an uncommon cause of iron overload in people of African[8] or Asian origin.[9]

TRANSFUSIONAL IRON OVERLOAD.

A unit of blood (250 ml) contains about 225 mg of iron. Iron is an integral component of the heme moiety in hemoglobin and cannot be removed from the blood in that state. Reticuloendothelial cells destroy senescent red cells, primarily in the liver and spleen. The iron from the hemoglobin is not excreted but, rather, is used to make new red cells or placed in storage (primarily in hepatocytes).

Those with severe chronic anemias often require regular transfusions to survive. Patients with thalassemia major, a condition in which the genes encoding hemoglobin produce defective protein and consequently defective red cells, require up to 2 units of blood every 3 weeks to avoid the deadly consequences of their severe anemia.[10] Nearly all of

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Figure 69-2 Reactive oxygen species derived from intracellular free iron by Fenton chemistry. (Courtesy of N. C. Andrews.)

the iron from the transfused red cells goes into storage and eventually produces severe iron overload. Therefore, the major problem confronting those patients is not anemia but organ damage from iron.[11] Inherited disorders, such as thalassemia major, or acquired conditions, such as myelodysplastic syndrome, can lead to transfusional iron overload. The redistribution of the excess iron to storage sites means that these patients suffer the same consequences as those with hereditary hemochromatosis.

MECHANISMS OF CARDIAC DAMAGE BY IRON OVERLOAD.

Iron deposition in the cardiac myocytes is the initial event in iron-mediated cardiac injury. Transferrin receptors on the cell surface mediate this process through the well-characterized transferrin cycle just described. Iron-saturated transferrin attaches to these receptors and releases iron to the interior of the cell. The excess iron is stored in

association with the hemosiderin protein.

Iron that is stored in hemosiderin is innocuous.[12] This iron is in equilibrium, however, with a very small pool of so-called free iron in the cell. This pool of iron is so small that its precise size has eluded determination. Better termed loosely bound iron, this material catalyzes the formation of reactive oxygen species through Fenton chemistry (Fig. 69-2) . These reactive oxygen species can mediate cell injury.

Among the several reactive oxygen species promoted by iron overload, the most damaging is the hydroxyl radical.[13] [14] This molecule is extremely short-lived and yet highly active in its interaction with biological molecules.[15] Lipid peroxides, protein disulfide bridges, and DNA cross-linking are some of the consequences of iron-mediated generation of reactive oxygen species.[16]

Cardiac cells are particularly sensitive to oxidant-mediated injury because they must perform a number of complex functions, which include contraction and transmission of electrical impulses. With iron loading, cardiac cells in culture begin to fail, including loss of their characteristic pattern of beating. Desferrioxamine, a powerful iron chelator that binds iron in culture and prevents generation of reactive oxygen species by the Fenton reaction, can restore normal cellular activity.[17]

CLINICAL MANIFESTATIONS OF CARDIAC IRON OVERLOAD (see alsoChap. 40) .

Restrictive cardiomyopathy (Fig. 69-3) is the most common cardiac defect that occurs with iron overload, but other problems have been described, including pericarditis, restrictive cardiomyopathy, and angina without coronary artery disease. A strong correlation exists between the cumulative number of blood transfusions and functional cardiac derangements in patients with thalassemia.[18] Echocardiographic assessment of patients with beta-thalassemia major who receive concurrent chelation therapy with desferrioxamine shows no difference relative to controls in the fractional shortening.[19] A pronounced pattern of integrated backscatter of the interventricular septum and posterior wall is an important echocardiographic finding indicating iron deposition.

The physical examination reveals surprisingly little even in patients with heavy cardiac iron deposition. Once evidence of cardiac failure appears, however, heart function rapidly deteriorates, often resisting medical intervention. Biventricular failure produces pulmonary congestion, peripheral edema, and hepatic engorgement. This potentially lethal cardiac complication has been reversed on occasion by vigorous iron chelation.

Iron deposition in the bundle of His and the Purkinje system impairs signal conduction from the atrial pacemaker to the ventricles. Patients sometimes die suddenly, presumably due to arrhythmias. At one time, patients treated with the chelator desferrioxamine for transfusional iron overload received supplements of ascorbic acid in the range of 15 to 30 mg/kg/d to promote iron mobilization. Reports of sudden death prompted cessation of this practice. At lower doses (2 to 4 mg/kg), ascorbic acid is a safe adjunct to chelation therapy in patients with transfusional iron overload.

Echocardiography in children and radionuclide ventriculography in adults are the most useful noninvasive diagnostic techniques to detect iron-overload-induced cardiomyopathy. The echocardiographic abnormalities correlate roughly with the number of transfusions. Exercise radionuclide ventriculograms are particularly sensitive in the detection of cardiac dysfunction in patients with iron overload.

Treatment of Cardiac Iron Overload

The degree to which aggressive iron chelation therapy can reverse cardiac dysfunction has given rise to vigorous debate. A number of short-term studies suggested that chelation can restore function in patients with significant cardiac compromise.[20] More recently, investigators examined a cohort of patients with beta-thalassemia major who were

Figure 69-3 Consequences of cardiac hemochromatosis. Apical four-chamber views in diastole *(A)* and in systole *(B),* demonstrating moderate biventricular enlargement with markedly reduced systolic performance (ejection fraction, 18 percent). In addition, marked biatrial enlargement is noted. (From Passen EL, Rodriguez ER, Neumann A, et al: Cardiac hemochromatosis. Circulation 94:2302-2303, 1996. Copyright 1996, American Heart Association.)

transfused while receiving chelation therapy.[21] In this series only persistent plasma ferritin values of greater than 2500 ng/ml were associated with cardiac-related death. Another group of investigators recently reviewed the outcome of aggressive treatment of patients who had transfusional iron overload with associated cardiac dysfunction.[22] This group of 19 patients suffered from severe congestive heart failure and/or cardiac arrhythmias. The patients received intravenously administered desferrioxamine on a 24-hour per day regimen. For routine iron chelation, most physicians administer the drug over 12- to 16-hour intervals. In addition to the aggressive iron chelation therapy, the investigators administered current conventional cardiac regimens.

The dramatic results revealed an increase in the mean ejection fraction of the patients with congestive heart failure from 30 to 50 percent. Arrhythmias were controlled, and no patient died suddenly. Sudden death occurs commonly in iron-overloaded patients, presumably resulting from malignant arrhythmias. The iron chelation regimens appeared to facilitate management of arrhythmias in this cohort. The plasma ferritin values exceeded 10,000 ng/ml in many of the patients at the onset of treatment. These values declined but never approached normal values (15-400 ng/ml in men).

Bone marrow transplantation now offers a potential cure for some patients with beta-thalassemia major.[23] [24] The correction of the underlying hemolytic anemia creates a clinical situation analogous to hereditary hemochromatosis: patients are

iron-overloaded with normal hemoglobin values. Some investigators have taken advantage of this situation to use phlebotomy as a means of removing the iron that has accumulated over years of transfusion therapy, even in patients who continue on an iron-chelation regimen.[25] This strategy removes iron and improves cardiac function in most of these patients.[26]

The lessons from these reports are twofold. First, early iron chelation therapy prevents cardiac dysfunction in patients with transfusional iron overload. Second, congestive cardiomyopathy and arrhythmias in these patients are potentially reversible. Unlike the situation with ischemic cardiomyopathy, the cardiac myocytes have not been destroyed by the pathological events that produced the dysfunction. Iron overload injures myocytes by production of free radicals that interfere with their function. Until irreversible damage leading to cell death occurs, the injury can be halted and reversed by chelators that remove the iron, indirectly blocking production of free radicals. Aggressive intervention with cardiac support and chelation therapy is indicated in patients with iron-mediated cardiac dysfunction.

Iron as a Coronary Risk Factor

An important question concerning iron and the heart is whether body iron stores in the normal range increase susceptibility to myocardial infarction. A number of small anecdotal reports lie on either side of the issue and are uninformative. A study published in 1992 examined the relationship between plasma ferritin levels, a reasonable surrogate measure of body iron stores, and coronary artery disease in a cohort of about 2000 men in Finland.[27] The data indicated that elevated plasma ferritin levels increased the risk of acute myocardial infarction by over twofold. However, a variety of common problems including chronic inflammation and smoking can elevate the serum ferritin level. These investigators attempted to compensate for this factor by using a newer test, the plasma transferrin receptor assay, in a small sample of about 200 men.[28] Results of this smaller study agreed with those that the group reported in 1992.

Investigators from the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES) also addressed the question, using a multivariate Cox proportional-hazards model.[29] Using transferrin saturation as an index of body iron stores, the researchers analyzed data on over 4500 people between the years of 1971 and 1987. They found no statistically significant relationship between transferrin saturation and coronary heart disease. Results of an epidemiological study involving about 2000 men in Iceland agreed with those of the NHANES report.[30] The issue of the role of body iron stores in the "normal" range in coronary artery disease remains open. The variable results in epidemiological studies from different countries suggests that iron plays a small role, if any, in this arena.

ANEMIA AND CARDIAC FUNCTION

The heart and blood comprise a single functional unit with two principal purposes: (1) to deliver oxygen and nutrients to peripheral tissues and (2) to remove metabolic waste products. The Fick principle states that cardiac output is proportional to oxygen

consumption and the arteriovenous oxygen difference (Fig. 69-4) (Figure Not Available) . The level of hemoglobin in the blood is the primary determinant of arteriovenous oxygen difference. As the hemoglobin content falls (anemia), cardiac output increases to keep pace with tissue oxygen consumption. Cardiac output depends on the functional capacity of the heart. An important question then, is whether anemia *per se* compromises cardiac function.

One group of investigators examined the question by studying systolic and diastolic left ventricular function in patients with chronic severe anemia (hemoglobin levels of less than 7 gm/dl for more than 3 months). The assessments were done by M-mode, two-dimensional, and Doppler echocardiography.[31] In most instances, the anemia was due to iron deficiency, meaning no primary cardiac insult existed. The cardiac output was elevated as expected, owing to a higher stroke volume and heart rate. Left ventricular contractility was higher than normal, and no evidence existed of diastolic dysfunction. The investigators concluded that, in the absence of primary cardiac disease, anemia does not produce congestive heart failure, at least over the time span studied.

More severe anemia can, however, produce left ventricular dysfunction and circulatory congestion. A group of otherwise healthy children with hemoglobin levels of less than 6 gm/dl due to iron deficiency were also assessed by echocardiography.[32] Left ventricular preload was significantly higher, and left ventricular afterload was significantly lower in the patients relative to controls. Cardiac index was also significantly higher in the severely anemic patients. Iron supplementation eliminated the discrepancy. The interpretation of these results requires consideration that iron deficiency of this severity could impair synthesis of important heme-dependent enzymes, such as the cytochromes.

Figure 69-4 (Figure Not Available) The Fick principle: Cardiac output is proportional to oxygen consumption and the arteriovenous oxygen difference and the hemoglobin concentration. Compensation for hypoxia may be affected by an increase in cardiac output, an increase in erythropoietin production, or shift to the right in the oxygen dissociation curve due to blood pH-mediated increase in red blood cell 2,3-diphosphoglycerate. (From Bunn HF: Pathophysiology of the anemias. *In* Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, 1994, p 1720.)

Cardiac myocytes depend tremendously on these enzymes required for oxidative metabolism. Therefore, the cardiac dysfunction in these severely anemic patients could result in part from compromised myocardial metabolism. Nutritional deficiency that often accompanies very severe iron deficiency can also contribute to cardiac dysfunction.[33]

One way to avoid possible confounding due to secondary contributions of anemia, as might occur with severe iron deficiency, is to examine cardiac function in patients with genetically determined anemia. Investigators have carefully examined cardiac function in patients with thalassemia major. The presentation of these studies is complicated, because most people with thalassemia major have some degree of iron overload due to

repeated transfusion (see earlier). In contrast to thalassemia, people with sickle cell disease usually do not receive chronic transfusions.

Patients with sickle cell disease typically have hemoglobin values in the range of 7 to 9 gm/dl. Cardiomegaly with ventricular dilation develops early in the course of the condition. Early on, patients with sickle cell disease have hyperdynamic hearts with high ejection fractions and a cardiac index that substantially exceed normal values. The heart's ability to maintain this high state of activity declines over time. By early adulthood, many patients begin to exhibit diastolic dysfunction.[34] Volume overload is required to maintain the cardiac index in the face of the low hemoglobin level. Despite the vasoocclusive nature of the disease, definite episodes of typical transmural myocardial infarction are rare. The slow decline in cardiac reserves means that by the fourth or fifth decades these patients begin to have clinically apparent evidence of cardiac dysfunction. Intolerance to the fluid loading used to treat sickle cell vasoocclusive crises is often the harbinger of cardiac involvement in this disease.

HEMATOLOGICAL DISORDERS AND THE CARDIOVASCULAR SYSTEM

Efficient oxygen delivery to cardiac and peripheral tissues requires adequate blood flow, sufficient oxygen-carrying capacity, and a gradient allowing release of oxygen from hemoglobin, In anemia, compensatory responses include increased blood flow owing to increase in cardiac work and a left shift in the oxygen dissociation curve. In contrast, rheological effects of decreased blood flow due to hyperviscosity can be profound, leading to deleterious consequences, including tissue infarction. Hematological/oncological disorders in which hyperviscosity occurs include plasma cell neoplasms (multiple myeloma and Waldenstrom macroglobulinemia), myeloproliferative disorders (polycythemia vera, essential thrombocytosis, and, in rare cases, chronic myeloid leukemia), lymphoma (if associated with cryoglobulinemia), and acute leukemia (hyperleukocytosis in certain subtypes of acute myeloid leukemia). Patients with a variety of neoplasms, particularly those with mucin-producing adenocarcinomas of the gastrointestinal tract, have an increased risk of thrombotic complications. This so-called hypercoagulable state associated with cancer is not due to increased blood viscosity (see Chap. 62) .

Polycythemia

True or absolute polycythemia refers to a condition in which the red cell mass is above normal. Polycythemia must be distinguished from states in which the hematocrit (red cell volume/plasma volume) is increased due to a decrease in plasma volume. An example of a spurious elevation in the hematocrit is Geisboch syndrome, typically seen in middle-aged, overweight hypertensive men.[35] Reducing the red cell mass by phlebotomy or other means does not alter their predisposition to thrombosis, which is likely related to standard atherogenesis rather than to elevated hematocrit.[36] A red cell mass test[37] using chromium-labeled red blood cells is needed to determine if a further work-up for polycythemia is required.

The polycythemias are subclassified into primary disorders and secondary conditions (Table 69-2) [38] in which the increase in red cell mass results from increased production

of erythropoietin, the oxygen-tension regulated protein hormone elaborated by the kidney. Erythropoietin production can be increased in any disorder associated with hypoxemia, such as high-altitude chronic lung disease and cyanotic forms of congenital heart disease[39] ; impaired release of oxygen by certain hemoglobin variants (e.g., hemoglobin Hallamshire), which cause a shift in the oxygen dissociation curve to the left,[40] also leads to an increase in cell mass. The inappropriate production of erythropoietin or erythropoietin-like protein can be the cause of the erythrocytosis associated with certain tumors, such as cerebellar hemangioblastoma,[41] renal cell carcinoma,[42] and hepatocellular carcinomas. [43] An erythropoietin-independent or autonomously driven increase in the red cell mass is the hallmark of polycythemia vera, one of the myeloproliferative disorders.[37]

Whereas there is an increased incidence of symptoms due to thrombosis or impaired blood flow in patients with polycythemia vera,[37] whether the increased red cell mass wholly accounts for these problems is unclear. Supporting the role of erythrocytosis as the major culprit are (1) the known decrease in oxygen transport with increased blood viscosity based on capillary tube experiments (Fig. 69-5) and (Fig. 69-(2) the symptomatic relief achieved by patients when the hematocrit is reduced by phlebotomy.[44] On the other hand, patients with secondary erythrocytosis rarely experience the plethora of nonspecific symptoms (e.g., visual disturbances, dizziness, confusion) typical

TABLE 69-2 -- DIFFERENTIAL DIAGNOSIS OF POLYCYTHEMIA

ERYTHROCYTOSIS ASSOCIATED WITH A NORMAL OR REDUCED RED BLOOD CELL MASS
Acute or chronic hemoconcentration
Spurious polycythemia (stress polycythemia, relative polycythemia, or Gaisbock syndrome)
ERYTHROCYTOSIS ASSOCIATED WITH AN ELEVATED RED BLOOD CELL MASS (ABSOLUTE POLYCYTHEMIA)
Secondary Polycythemia
Increased erythropoietin production (physiologically appropriate)
High altitude
Cardiopulmonary disease
Decreased blood oxygen-carrying capacity due to carboxyhemoglobin
Impaired oxygen delivery, hemoglobin with increased oxygen affinity or congenital decreased red cell 2, 3-diphosphoglycerate
Renal artery stenosis
Familial elevated erythropoietin with appropriate physiological response
Autonomous erythropoietin production
Tumors

- Hypernephroma
- Cerebellar hemangioblastoma
- Hepatoma
- Uterine fibroids
- Pheochromocytoma
- Adrenal cortical adenoma
- Ovarian carcinoma

Renal disorders

- Cysts
- Hydronephrosis
- Bartter syndrome
- Transplantation

Familial polycythemia due to autonomous erythropoietin production

Polycythemia Vera
From Fruchtman SM, Berk PD: Polycythemia vera. In Handin RI, Lux SE, Stossel TP (eds): Blood: Principles and Practice of Hematology. Philadelphia, JB Lippincott, 1995.
Cyclophosphamide >100-140 mg/m^2 (total dose) Congestive heart failure, hemorrhagic myocarditis/pericarditis/necrosis

Figure 69-5 Capillary tube experiment that documents the relationship between blood viscosity and oxygen transport. Blood that is too viscous due to polycythemia does not carry oxygen efficiently. (From Jandl JH: Blood: Textbook of Hematology. 2nd ed. Boston, Little, Brown, 1996, p 159.)

of the patient suffering from polycythemia vera.[37] Second, those with polycythemia vera often have persistent symptoms requiring antineoplastic therapy, which can lead to an amelioration in symptoms when the hematocrit has already been lowered by phlebotomy, perhaps because the platelets in this condition are intrinsically abnormal (e.g., reduced expression of the thrombopoietin receptor c-mpl).[45]

Polycythemia Vera

Polycythemia vera is a clonal chronic myeloproliferative disorder that is characterized by an increase in the red cell mass.[46] Other cell lineages including leukocytes and platelets may also be elevated. Splenomegaly is common. Studies have suggested that the cause of this disorder is an increased sensitivity of hematopoietic progenitor cells to

regulatory factors such as erythropoietin.[47] [48] Patients with polycythemia vera usually have serum erythropoietin levels that are quite low even after phlebotomies have lowered the hemoglobin level. A defect in the cell signaling cascade may cause hypersensitivity to erythropoietin, although some have suggested that red blood cell production in this disease is completely independent of erythropoietin.[49] The *SHP1* gene, which encodes an intracellular phosphatase involved in cell signaling pathways, is potentially dysregulated in polycythemia vera.[50] Mutations in the erythropoietin receptor gene have been reported in a handful of families with familial polycythemia vera.[51]

CLINICAL MANIFESTATIONS.

Patients with polycythemia vera[52] may present with a variety of nonspecific complaints, including headache, weakness, pruritus (especially after showering), dizziness, sweating, abnormal vision, paresthesias, arthralgias, weight loss, or abdominal pain. On physical examination, patients have a ruddy complexion, organomegaly, and hypertension. Both thrombosis and hemorrhage may occur. Thrombosis occurs in up to 30 to 40 percent of patients with the disorder, including deep venous thrombosis of the lower extremities, pulmonary embolism, and coronary, cerebrovascular, or peripheral occlusions.[53] The splanchnic bed is particularly susceptible to thrombosis in patients with polycythemia vera. Cardiac valvular abnormalities also occur in patients with polycythemia vera (usually mitral valve thickening or nonbacterial vegetations). Hepatic or vena caval thrombosis, the Budd-Chiari syndrome, is a serious and not unusual event in patients with polycythemia vera. Of all patients with Budd-Chiari syndrome, up to 10 percent have polycythemia vera.[54] The risk of thrombosis may be related to excessive homocysteine levels.[55] Neurological abnormalities including transient ischemic attacks, cerebral infarction or hemorrhage, fluctuation in mental status, confusional states, and choreic syndromes also have been described. Dizziness, visual disturbances, scalp tenderness, and headache may occur because of increased blood viscosity and reduced cerebral blood flow caused by the erythrocytosis. Basilar artery insufficiency as well as carotid territory strokes may also occur. Peripheral arterial thrombosis, peripheral vascular disease, and erythromelalgia, characterized by burning pain in the digits and potential ulceration, are further manifestations of the circulatory problems typically seen in those with polycythemia vera. Gastrointestinal and cerebral hemorrhage[56] have been described, particularly after the use of antiplatelet agents.

DIAGNOSIS AND TREATMENT.

The polycythemia study group has developed clinical and laboratory criteria for diagnosis[57] that require the presence of an elevated red cell mass and any three of the following criteria: (1) normal arterial oxygen saturation in the presence of erythrocytosis, (2) splenomegaly, (3) thrombocytosis and leukocytosis, (4) bone marrow hypercellularity associated with mature megakaryocytes without myelofibrosis, (5) low serum erythropoietin levels, and (6) abnormal marrow proliferative capacity as manifested by formation of erythroid colonies in the absence of erythropoietin.

Therapy requires individualization; there is no curative therapy other than perhaps bone marrow transplantation[58] in the rare patient with severe clinical manifestations. For most patients it is appropriate to reduce the blood cell count to normal as rapidly as

possible with phlebotomy (1 to 2 units every other day as needed).[59] The hematocrit should be maintained in the 42 to 45 percent range. Pruritus, if present may be treated with cyproheptadine or even interferon alfa.[60] Elective surgery should be delayed until the red cell mass is in the normal range, if possible. Aspirin should be used carefully in a patient with polycythemia vera owing to the risk of hemorrhagic complications.[61] Hydroxyurea, an oral antimetabolite chemotherapy agent, may be helpful in cases where the hematocrit cannot be controlled by phlebotomy alone.[62] The alkylating agent busulfan should be avoided, owing to an increased risk of bone marrow fibrosis and leukemogenesis. Use of phlebotomy alone as a treatment strategy is associated with a higher risk of thrombosis.[59] The risk of leukemogenesis from hydroxyurea is low but real,[63] so this agent must be used carefully as a means of reducing the risk of thrombosis.

THROMBOCYTOSIS

An elevated (>450,000/ml) platelet count can result from physiologically appropriate stimuli, such as those occurring after general surgery, splenectomy, pregnancy, or iron deficiency. Such reactive thrombocytoses are not associated with an increased number of thrombotic events, in contrast to primary or essential thrombocytosis, which is one of the myeloproliferative disorders. In essential thrombocytosis there is a tendency toward increased clotting (as well as to hemorrhage due to intrinsic platelet dysfunction), sometimes with disastrous results, especially in younger patients with this condition.[56] [64] [65] Myocardial infarction is actually less common in those with essential thrombocytosis than with polycythemia vera.[57] [65] The use of hydroxyurea to lower the platelet count (and ameliorate the clonal stem cell defects as well) has been associated with reduction in cardiac risk.[66] The effect of anagrelide, which reproducibly lowers the platelet count, on the natural history of essential thrombocytosis is unclear.[67]

LEUKOCYTOSIS

Leukocytosis in patients with acute leukemia may provoke a host of cardiovascular problems during the course of the disease. Sepsis associated with profoundly myelosuppressive and gut-damaging chemotherapy can be associated with severe, albeit reversible, depression of cardiac function.[68] Two important issues relating leukemia to cardiac physiology are discussed later in this chapter: leukemic cell invasion of the myocardium or pericardium and direct toxic effect of antileukemic drugs, particularly anthracyclines. Occasionally, a very elevated white blood cell count may lead to circulatory compromise. Patients with chronic and acute lymphoid leukemia can tolerate extremely high white blood cell counts (more than several hundred thousand per microliter) without evident problems. However, patients with acute myeloid leukemia, particularly those with the acute monocytic or acute myelomonocytic subtype, may experience so-called leukostatic phenomena.[69] [70] Probably due to adhesion molecules expressed on the leukemia cell surface in those acute myeloid leukemia subtypes, aggregates of such neoplastic cells may cause thrombosis and hemorrhages in microcapillaries of the brain,[71] producing encephalopathy or, in the lung, producing

pulmonary infiltrates and hypoxemia.[72] [73] In instances of cerebral or pulmonary leukostasis, rapid lowering of the white blood cell count is required. Usually, such reduction can be accomplished by institution of hydroxyurea or definitive antileukemic chemotherapy[74] ; occasionally, limited radiation to the brain[74] and/or leukophoresis[75] is required to prevent severe complications. Patients with chronic myeloid leukemia in stable phase who may often have high white blood cell counts, composed of mid-range and mature myeloid cells, occasionally experience leukostatic/thrombotic complications[76] such as priapism or stroke.

HYPERVISCOSITY DUE TO QUANTITATIVE OR QUALITATIVE ABNORMALITIES IN PLASMA PROTEINS

Plasma cell neoplasms are characterized by a clonal proliferation of cells capable of elaborating a single immunoglobulin molecule, either light chains or heavy chains or a structurally complete multimeric protein. The so-called M-component may, depending on its biochemical properties and level, interfere with normal process such as nerve conduction[77] or coagulation[78] owing to effects on clotting factors and/or platelet function. The hyperviscosity syndrome, characterized by circulating immune complexes, is more likely at a given level of IgM excess than in the more common IgG myeloma. Patients with an IgM M-spike and an accumulation of plasmacytoid lymphocytes in the marrow and/or lymph nodes have Waldenstrom macroglobulinemia[79] syndrome. When suspected on clinical grounds, the hyperviscosity syndrome can be confirmed by actual measurements of serum viscosity.[80] Hyperviscosity, a medical emergency, requires a prompt reduction in the M-component,[81] usually through a combination of plasmapheresis plus tumor burden reduction with chemotherapy. Elaboration of proteins that can aggregate at low temperature (cryoglobulins)[82] can result from a host of infections, as well as inflammatory or neoplastic conditions such as lymphoma, and can impose peripheral circulating problems, as discussed later.

PLASMA CELL NEOPLASMS

Multiple myeloma and other plasma cell tumors are neoplasms of plasma cells or plasmacytoid lymphocytes. These disorders may result from dysregulation of normal growth suppression genes. Overproduction of interleukin-6, which serves as an autocrine growth factor for myeloma cells, may also contribute to the development of this disease.[83]

Clinical manifestations of multiple myeloma include bone pain, renal insufficiency, anemia, hypercalcemia, infection, bleeding, and neurological symptoms. Hyperviscosity, especially in patients with IgG subclass myeloma,[84] has been described. Hyperviscosity may also be associated with bleeding. The diagnosis can be made by measuring serum viscosity[80] and by eyeground examination, which discloses the slow blood flow in the retinal blood vessels. Plasmapheresis[81] is the appropriate treatment. The overabundantly elaborated monoclonal protein can be deposited in tissues such as the kidney and heart, producing secondary amyloidosis. Cardiac amyloidosis may lead to cardiomyopathy, characterized by a speckled appearance on echocardiography.

The diagnosis of myeloma[85] rests on finding one major and one minor criteria or at least three minor criteria. The major criteria include plasmacytoma on tissue biopsy,

marrow plasmacytosis greater than 30 percent, monoclonal protein of significant height (IgG greater than 3.5 gm/dl, IgA greater than 2 gm/dl, or light-chain [Bence Jones] protein in the urine greater than 1 gm/24 hr). The minor criteria include marrow plasmacytosis of 10 to 29 percent, monoclonal protein present but less than the levels defined for major criteria, osteolytic bone lesions, or a decrease in uninvolved immunoglobulins.

Waldenstrom macroglobulinemia [79] is characterized by marrow infiltration with lymphoplasmacytoid cells and high levels of IgM in the blood; lymphadenopathy or splenomegaly, rare in and multiple myeloma, is present in at least 40 percent of those with Waldenstrom macroglobulinemia. Complications caused by the macroglobulin production such as hyperviscosity, cold hemolytic anemia, peripheral neuropathy, renal disease, and bleeding are often the presenting manifestations. Although serum viscosity is elevated in most patients with Waldenstrom disease, only 15 to 20 percent have symptoms related to this problem. Congestive heart failure is not unusual, owing to the anemia and expanded plasma volume as well as the increased viscosity.

Patients with asymptomatic multiple myeloma should not be treated until there is clear evidence of disease progression. The aggressive therapeutic approach to multiple myeloma includes up-front high-dose dexamethasone or a vincristine/doxorubicin/dexamethase (VAD) regimen followed by autologous bone marrow transplantation once a reasonable response has been achieved.[86] Patients who are not candidates for high-dose chemotherapy should be treated for at least 12 months with one of the available regimens, including dexamethasone or VAD. Anemia can be corrected in many patients by administration of erythropoietin.[87] Hypercalcemia should be treated. The use of bisphosphonates such as pamidronate to stabilize bone matrix has resulted in a lower incidence of skeletal complications and improved outcome in patients with myeloma.[88] Patients with Waldenstrom macroglobulinemia are usually managed with combination chemotherapy.[79] Thalidomide, which may work by inhibiting angiogenesis, has efficacy in patients with refractory myeloma.[89]

CRYOGLOBULINS

Cryoglobulins are immunoglobulins that produce high-molecular-weight aggregates at temperatures below 37°C (98.6°F). To detect the presence of these proteins, blood should be drawn through a preheated syringe and stored at body temperature.[82] Hepatitis C virus is a particularly important etiological agent.[90] The chief symptoms are peripheral vasculitis. Skin and joint manifestations are most common, but central nervous system dysfunction, renal failure, and even severe hypertension leading to cardiovascular and cerebrovascular accidents have been described in severe cases.[91] Interferon alfa to treat hepatitis C-associated disease[92] and cytotoxic drugs to treat the vascular disease[93] are potentially useful therapeutic modalities.

CARDIAC MANIFESTATIONS OF NEOPLASTIC DISEASE

Based on autopsy series, tumors affecting the heart are much more likely to have originated from a neoplasm elsewhere than to have primarily occurred in the heart.[94] Primary cardiac tumors are discussed in Chapter 49 . Metastatic tumors reach the heart

most commonly by hematogenous dissemination, which cause multiple nodules, occasionally so diffuse as to lead to restrictive cardiomyopathy.[95] Direct extension, especially from mesotheliomas,[96] sarcomas,[97] [98] and mediastinal lymphomas[99] [100] (Hodgkin and non-Hodgkin) also occur (Fig. 69-6) .

Essentially, any tumor may spread to cardiac structures, including the myocardium, pericardium, and valves. The most common tumors to spread to the heart in descending order of frequency are carcinoma of the lung, breast, malignant melanoma, and leukemia. General autopsy series shows cardiac involvement in 1 to 20 percent of patients with malignant diseases; the frequency ranges as high as 60 percent in those with melanoma.[95]

Clinical manifestations of tumors metastatic to the myocardium are generally nonexistent, in distinction to the effects of tumors invading the pericardium, which may produce life-threatening tamponade. Myocardial invasion can occasionally produce tachyarrhythmias, atrioventricular block, or congestive heart failure.[101] [102] The diagnosis of myocardial metastasis ante mortem may be noted on echocardiographic examination, magnetic resonance imaging, gallium scanning, computed tomography, or positron-emission tomography.[103] [104] [105] Such studies may be particularly helpful in cases in which direct extension plays a role.

Pericardial Involvement

(See also Chap. 50)
Hematogenous spread (e.g., breast cancer, melanoma, sarcoma, leukemia)[106] [107] [108] [109] or direct extension of a thoracic tumor (e.g., mesothelioma, lymphoma, or lung cancer)[96] [110] can lead to pericardial involvement. Pericardial involvement[111]

Figure 69-6 Frequency of metastatic tumors to the heart and pericardium. (From English JC, et al: Metastatic tumors of the heart. *In* Goldhaber SZ [ed]: Cardiopulmonary Diseases and Cardiac Tumors. *In* Braunwald E [series ed]: Atlas of Heart Diseases. Vol 3. Philadelphia, Current Medicine, 1995, pp 116.1-116.6. Adapted from McAllister HA, Fenoglio JJ: Tumors of the cardiovascular system. *In* Atlas of Tumor Pathology. 2nd ed. Washington, DC, Armed Forces Institute of Pathology, 1978, pp 111-119.)

can be classified as either primarily infiltrative, with thickening and adherence to or infiltration of the myocardium, or as effusive, where there is significant reactive expansion of pericardial fluid. Although these two categories are not mutually exclusive, the infiltrative form tends to cause constrictive physiology whereas the effusive form results in pericardial tamponade.

Symptoms of pericardial tamponade include dyspnea and tachycardia due to a failure of cardiac output to meet oxygen demand, especially with exercise; cough and chest pain

may also occur, although the key to suspecting the diagnosis is unexplained dyspnea and tachycardia in a cancer patient with normal resting oxygen saturation.

Pulsus paradoxus and paradoxical movement of the jugular venous pulse are important clinical signs of tamponade and should be sought during the physical examination, although their absence does not rule out the syndrome, which may occur only in the setting of relatively advanced pathological findings (see also Chap. 50) . Once the diagnosis of pericardial tamponade is suspected, an echocardiogram should be obtained. Although at cardiac catheterization demonstration of equal diastolic pressure on both sides of the heart is the hemodynamic key to diagnosis, echocardiography also provides critical physiological insight. As intrapericardial pressure rises, the relatively thin right ventricular wall will collapse, particularly in diastole.[112] Such diastolic right ventricular wall collapse is quite sensitive for hemodynamically significant tamponade; sometimes an echocardiogram will also actually delineate the metastasis. Computed tomography or magnetic resonance imaging is more suitable in situations in which pericardial infiltration/constriction is the more prominent physiology.

Not every pericardial effusion in a patient with cancer is due to malignant disease. Prior chest radiation therapy[113] [114] for lung cancer or lymphoma can produce pericardial disease as a late complication. Such radiationinduced effusions do not usually cause tamponade, but extreme care must be taken to exclude this eventuality.

The management of cancer patients with tamponade often requires surgical drainage[115] (e.g., creation of a pericardial window) by thoracotomy, subxiphoid pericardiotomy, or video-assisted thorascopy, [116] which offers a good balance between invasiveness and effectiveness. In patients with lymphoma who present with minimal tamponade early in the course of the disease, chemotherapy can result in rapid amelioration of symptoms.[117]

Figure 69-7 The radiographic appearance of SVC syndrome. Chest venography. (From Roberts JR, et al: Multimodality treatment of malignant superior vena caval syndrome. Chest 116:835-837, 1999.)

Superior Vena Cava Syndrome

Compression of the easily distensible superior vena cava, with or without associated thrombosis, by a thoracic tumor such as carcinoma of the lung or lymphoma can produce significant clinical consequences. The so-called superior vena cava syndrome[118] often presents as facial swelling, headache, and arm edema. A prominent venous pattern can be observed on inspection of the anterior chest wall. The diagnosis can be established by scintigraphy, angiography, or high-resolution contrast medium-enhanced computed tomography (Fig. 69-7) . Although rarely life threatening, the superior vena cava syndrome can lead to considerable morbidity and discomfort.

Emergent radiation treatment is the treatment of choice.[119] In patients with responsive tumors such as Hodgkin disease or non-Hodgkin lymphoma, chemotherapy should be initiated as soon as possible. The likelihood of symptomatic relief with antineoplastic therapy depends on the duration of the obstruction and the intrinsic chemosensitivity of the tumor. Local therapies such as stenting, angioplasty, clot removal, or lysis are currently being developed[120] [121] [122] [123] (see also Chap. 42) . The role of anticoagulation is controversial[124] [125] ; some authorities recommend an angiographic evaluation (e.g., magnetic resonance angiogram) to document thrombosis before initiating such therapy.

Arrhythmias

Arrhythmias, typically due to electrolyte imbalance or decreased oxygen-carrying capacity (hypoxia due to pulmonary involvement with tumor or infection; or anemia) are common in patients with cancer. Tumor involvement of cardiac structures may also lead to nonspecific rhythm disturbances, including low voltage, sinus tachycardia, and ST segment and T wave charges. Atrial fibrillation or flutter can occur due to any of the aforementioned issues or to tumor invasion of the atria or of the coronary arteries that supply this chamber. In rare cases, atrioventricular node involvement will occur, leading to complete heart block.[110] Carotid sinus syncope[126] has been associated, in rare cases, with tumorous involvement of cervical lymph nodes.

Ischemic Heart Disease and Malignancy

In addition to the patient with intrinsic arteriosclerotic coronary disease who also happens to have cancer, there is sometimes a relationship between the malignancy and the ischemic heart disease. For example, tumor emboli can occlude[127] or tumor mass can compress the coronary artery.[128] The hypercoagulable state associated with malignancy, especially mucin-secreting adenocarcinoma, can predispose a patient to develop a coronary thrombosis. Radiation therapy promotes arteriosclerosis[129] (see next section).

Myocardial infarction was suspected as the cause of death in 4 percent of 816 patients with solid tumors undergoing autopsy.[95] In most of the nonarteriosclerotic cases (which account for the majority of such infarctions), extrinsic compression of a coronary artery is the cause of the infarction. Typical angina rarely precedes the coronary event in this setting.

Nonbacterial Thrombotic Endocarditis

(See also Chap. 47)
Although the cardiac valves may be directly involved with metastatic tumor, the most common cause of valvular heart disease in the cancer patient is nonbacterial thrombotic endocarditis (NBTE).[130] [131] [132] [133] NBTE generally involves the aortic and mitral valve and occurs in patients with advanced adenocarcinoma of the gastrointestinal tract and lung. Although the precise pathophysiology of NBTE remains uncertain, associated features include tumor-associated immune complexes and the presence of catheters,

especially in right-sided valvular lesions. The clinical signs of NBTE may be subtle and resemble those of subacute bacterial endocarditis; more dramatic findings such as stroke[133] or myocardial infarction have been noted. Echocardiography can establish the diagnosis; yet treatment is difficult, in great part owing to the generally advanced stage of cancer in these patients.

INFLAMMATORY MEDIATORS ASSOCIATED WITH CARDIAC DISEASE

The carcinoid syndrome (see also Chaps. 46 and 48) is characterized by the elaboration of serotonin and its metabolites from a neoplastic proliferation of neoendocrine cells derived from ectoderm.[134] Clinical findings may include flushing, hypotension, and/or valvular lesions (Fig. 69-8) .[135] [136] The best treatment is reduction of tumor burden by surgery, although cisplatin-based chemotherapy may offer palliation.[134]

In the hypereosinophilic syndrome (see also Chap. 48) , [137] a myeloproliferative disorder, eosinophils infiltrate the bone marrow and circulate in high numbers in the peripheral blood. Cardiac involvement may result from the elaboration of mediators of inflammation as well as from direct invasion by the eosinophils.[138] Because corticosteroids can cause lysis of eosinophils, these drugs have been used successfully to treat cardiac complications such as cardiomegaly with a thickened right ventricular wall (leading to restrictive physiology[139]), mural thrombosis, and right-sided valvular dysfunction.[140] Mast cell neoplasms, including systemic mastocytosis, can also lead to valvular heart disease by a mechanism[141] similar to that described in association with hypereosinophilic syndrome. Massive release of vasodilatory substances during anesthesia has led to cardiovascular collapse in patients with mastocytosis.[142]

Figure 69-8 Carcinoid tumor involving the heart. Echocardiogram demonstrating thickened aortic and mitral valves, a small pericardial effusion and dilated right ventricle. AV=aortic valve; CS=coronary sinus; LA=left atrium; LV=left ventricle; MV=mitral valve; PE=pericardial effusion; RV=right ventricle; VS=ventricular septum. (From Pellikka PA, et al: Carcinoid heart disease: Clinical and echocardiographic spectrum in 74 patients. Circulation 87:1188-1196, 1993. Copyright 1993, American Heart Association.)

CARDIAC EFFECTS OF ANTINEOPLASTIC THERAPY

As understanding of the pathophysiology of neoplasia grows, it is hoped that molecules that specifically target the genetic lesions accounting for a given neoplasm will allow for a markedly improved therapeutic index (likelihood of benefit compared with toxicity). The successful use of all-*trans* retinoic acid in acute promyelocytic leukemia, characterized by a translocation of the retinoic acid receptor alpha gene to the promyelocytic leukemia gene, is one such example of relatively specific therapy, albeit in a rare disease.[143] However, for the most part, chemotherapy or irradiation entails significant side effects that always must be weighed against the goals of treatment, be they palliative or curative. Although many antineoplastic approaches are particularly

toxic to tissues with a high cell turnover rate, such as the bone marrow, hair, and gastrointestinal tract, the heart is frequently adversely affected. In particular, as patients live longer after the diagnosis and therapy of cancer, late cardiac toxicity can lessen the quality of life.

Radiation Therapy

Therapeutic ionizing radiation to the chest is used to prevent local recurrence of breast cancer, to improve disease control in lung cancer and esophageal cancer, as well as to improve the cure rate with Hodgkin and non-Hodgkin lymphoma of the mediastinum. Essentially, all cardiac structures, including the pericardium, myocardium, and coronary arteries may be affected by such efforts.

MECHANISMS OF RADIATION-INDUCED CARDIAC INJURY.

Damage to both normal and neoplastic tissues occurs due to the free electrons, liberated due to the impact of high-energy proton beams, which directly damage DNA or do so indirectly, resulting in the creation of hydroxyl radicals from water.[144] Although the degree of DNA damage induced by radiation is most closely linked with cytotoxicity and therefore generally involves proliferating cells, more long-lived cells can also be affected. Radiation also induces early response genes such as c-*jun, fos,* and *EGR1,* cytokines such as tumor necrosis factor, and fibroblast growth factor, which may also contribute to the toxic effect. Moreover, radiation-induced apoptosis, or programmed cell death, may be a key component of tumor radiosensitivity, as well as cardiac toxicity, owing to endothelial cell damage mediated in this fashion.[145]

The subacute radiation injury to the heart noted clinically may result from a combination of microvascular destruction and apoptosis. The microvascular destruction can lead to coronary artery disease, ischemia, progressive cellular loss, and fibrosis. Late tissue injury to the myocardium, valves, and pericardium[146] [147] [148] [149] may occur. Cardiotoxicity is common at doses over 45 Gy, indicating increased radiosensitivity compared with the brain, esophagus, or bladder.[144]

Radiation-Induced Pericardial Disease

(See also Chap. 50)
Radiation therapy can produce acute or delayed effects on the pericardium. Especially with radiation techniques employed before the 1990s, almost all patients who received over 40 Gy to the anterior mediastinum would develop pericardial effusion or thickening within 9 months of treatment,[150] but symptoms of pericardial disease can be delayed for up to 10 years.[151] [152] Such symptoms occur in a minority of irradiated patients in whom up to 70 percent may have pathological evidence of radiation-related pericardial disease.[153] Late pericardial fibrosis with development of constrictive pericarditis occurred in 3 of 102 Hodgkin patients treated with mediastinal reduction in the 1970s.[154] In the case of pericardial effusions that produce tamponade physiology, a pericardectomy with creation of a window can be a critical therapeutic and diagnostic maneuver, because it is also important to rule out recurrence of the neoplasm. Removal

of the entire pericardium may be alternatively necessary and may be required in patients with constrictive disease. The actual rate of pericardectomy was reported to be 4 percent at 17 years in one study that followed children and adolescents with Hodgkin disease.[154] However, postpericardiectomy mortality is high,[155] presumably because of the problems associated with diffuse damage to the entire heart, such as coronary artery disease, conduction system disturbances (e.g., sinus node disease),[156] and atrioventricular block,[157] and valvular pathology.[153] [158]

Radiation-Induced Myocardial and Ischemic Disease

Although radiation-induced myocardial fibrosis is common,[153] it is more difficult to show that left ventricular dysfunction derives solely from radiation therapy, as opposed to combined modality therapy with anthracycline chemotherapy. Children are certainly at risk for late effects due to chest radiotherapy. The incidence of late electrocardiographic abnormalities in children who received spinal or mediastinal irradiation in childhood is as high as 31 percent; cardiac-limited exercise dysfunction occurs in over 70 percent of children undergoing spinal irradiation, compared with 32 percent who had received flank/mediastinal radiation.[159] However, the most common and arguably the most important late effect is myocardial ischemia/infarction. The distribution of proximal coronary artery narrowing at autopsy[160] may result from the design of radiation ports that tend to primarily encompass the origin of these vessels.

One of the best retrospective series documenting the risk of significant coronary heart disease due to radiation is the Stanford study,[161] which examined the records of 635 individuals younger than the age of 21 treated for Hodgkin disease. Seven of 12 patients who experienced fatal cardiac events had a myocardial infarction (6-22 years post therapy), each of whom received 42 to 45 Gy to the mediastinum between ages 9 and 20 (relative risk was 41.5 percent [95 percent confidence interval was 18.1-82.1 percent]). Chemotherapy did not add risk for myocardial infarction. The actuarial risk of a fatal or nonfatal myocardial infarction was 8 percent at 22 years after therapy. Adults may be at somewhat lower risk, given the case-cohort study of 4665 patients[162] demonstrating an age-adjusted relative risk of death due to myocardial infarction of 2.56 percent after mediastinal irradiation. It has been strongly suggested that patients receiving mediastinal radiation be longitudinally screened for the presence of preclinical cardiac disease.[163]

Given the frequent use of radiation therapy in women with breast cancer after conservative surgery, concerns have been raised about the potentially increased risk of coronary disease in this setting. In 244 patients with stage I or II breast cancer who received breast tangential irradiation (45 Gy with a 16-Gy boost) either before or after doxorubicin-containing chemotherapy regimens, there was no increase in cardiac events in those with either left- or right-sided breast cancer.[164] The trend toward the use of either chemotherapy only or low-dose radiation after chemotherapy for Hodgkin disease will likely result in a markedly decreased incidence of cardiac disease compared with the era when curative intent radiation was primarily employed.[165] [166] Amifostine is a thiol that can salvage the oxygen-derived free radicals that mediate irradiation (and chemotherapy)-induced cytotoxicity and may be selectively taken up by normal, compared with neoplastic, tissues.[167] There are, however, no data at this point

supporting the administration of this agent to protect the heart from the damaging effects of radiation.[168]

There is little prospectively collected data concerning the risk of radiation-induced heart disease. Based largely on retrospective series, the following points are clear: (1) accelerated coronary artery narrowing results from chest irradiation and may lead to serious clinical consequences[160] [162] [169] [170] ; (2) irradiation during childhood or adolescence carries greater impact than similar therapy given later in life[161] [171] [172] ; (3) effects of radiation impairing

function of noncardiac site such as the thyroid, gonads, skeleton, and lungs can have important indirect cardiac effects[163] ; and (4) improvements in radiation techniques such as more focused high-energy beams, careful field design, modified fractionation, and better shielding are lessening the incidence of this problem.[163]

Chemotherapy-Induced Cardiac Disease

Combination chemotherapy leads to cures in patients with germ cell neoplasms, acute leukemias, and lymphomas and performs a critical adjunctive role, along with local tumor control in many other neoplasms, including breast cancer, lung cancer, and colorectal cancer. Toxicities of such regimens that contain cell-cycle or S-phase specific antineoplastic agents generally most markedly impact tissues such as the gastrointestinal tract and bone marrow, characterized by rapid cell tumor. However, chemotherapy-induced myocardial damage is a considerable problem, particularly in patients who are either cured or experience major palliation. Because long-surviving patients may be at risk for a delayed-onset cardiomyopathy, understanding risk factors for and minimizing the likelihood of development of this problem represents a major direction of research in the fields of both oncology and cardiology. The anthracyclines (doxorubicin, daunorubicin, idarubicin, and epirubicin) and the related anthracenedione mitoxantrone are the chemotherapeutic agents most widely recognized for causing cardiotoxicity; however, many other agents, including those in the biological response modifier class, are associated with cardiovascular pathology (Table 69-3) .

PATHOGENESIS OF ANTHRACYCLINE-INDUCED CARDIAC INJURY

Anthracyclines are part of curative therapy for acute leukemias, Hodgkin and non-Hodgkin lymphoma, breast cancer, and sarcomas of the bone. They are employed as palliative therapy in a variety of other neoplasms. These drugs contain an aromatic ring structure that intercalates in-between DNA base pairs; however, the mechanism of cytotoxicity appears to be inhibition of the function of topoisomerase II, an enzyme critical in allowing DNA to undergo efficient repair. Second, these drugs generate free radicals, which can damage cell membranes, in part by lipid peroxidation. The latter effect correlated most closely with cardiac toxicity; members of this class such as amsacrine and mitoxantrone, which produce lower quantities of free radicals, are less

likely to cause cardiomyopathy.[173]

Enzymes such as P450 reductase, xanthine oxidase, and mitochondrial NADH oxidase are plentiful in the energy-dependent and mitochondrial-rich cardiac tissue and are responsible for reducing the anthracyclines to their corresponding semiquinone free radicals. However, the heart may have relatively low ability to detoxify the free radicals because of the presence of only small amounts of catalase, which converts hydrogen peroxide to water.[174] Lack of general free radical scavenging may be less important than the chelation of iron by the anthracyclines. The anthracycline-iron complexes generate tissue-damaging hydroxyl radicals in the immediate vicinity of the target.[173] Consequently, dexrazoxane (Zinacard), a drug that undergoes hydrolysis to a carboxylamine capable of accepting the iron from the anthracycline-iron complex, is the only clinically effective cardioprotectant.[168] [175] General free radical scavengers such as *N*-acetylcysteine are ineffective.[176]

Downstream effects of the free-radical-mediated damage induced by the anthracyclines include defective calcium binding by the sarcoplasmic reticulum; decreased actin, troponin, and myosin light chain 2 gene expression; and release of vasoactive amines and proinflammatory cytokines, such as tumor necrosis factor and interleukin-2.[177] Moreover, the presence of free radicals may activate certain intracellular signaling pathways,[178] [179] which turn on the apoptotic or programmed cell death machinery.[180] The disturbance in sarcoplasmic structures corresponds to ultrastructural damage to these elements and may cause calcium overload leading to deleterious transient activation of contractile proteins.[181] The findings of myofibrillar loss, mitochondrial swelling cisternal disruption, (Fig. 69-9) , and nuclear degeneration are the histopathological consequences of the biochemical changes noted earlier. Second, myocyte loss on the basis of apoptotic cell death has been documented. The degree of pathological changes has been used to establish a grading system to classify the severity of injury.[182] Serial endomyocardial biopsies are seldom used now because of the invasiveness and lack of predictive value of this technique relative to other monitoring strategies.

Clinical Aspects of Anthracycline-Induced Cardiotoxicity

In rare cases, a single dose of anthracycline produces acute or subacute cardiac toxicity. The most common acute toxicities include electrophysiological abnormalities, among them nonspecific ST and T wave abnormalities, decreased QRS voltage, and prolongation of the QT interval.[177] Rhythm disturbances including sinus tachycardia, ventricular and supraventricular arrhythmias, as well as conduction system alterations including atrioventricular block and bundle branch block can occur.[183] [184] Very rare cases of an acute myocarditis-pericarditis syndrome causing sudden death or rapidly progressive heart failure within 2 weeks of administration of the drug have been described.[184]

The common, clinically relevant type and potentially severe anthracycline-induced cardiac toxicity is the chronic cardiomyopathy that results from cumulative exposure to these agents. Although many risk factors, including older age and antecedent heart disease, for the development of anthracycline-induced cardiomyopathy have been

described, the most important is cumulative dose of the drug. There is a nonlinear increase in the incidence of cardiomyopathy from 0.15 percent or lower at 400 mg/m^2 or less cumulative doses, compared with a 7 percent incidence at 550 mg/m^2 (Fig. 69-10) . Although endomyocardial biopsies demonstrate a progressive loss in cardiac myocytes with increasing doses beginning at a low level of total drug administered,

TABLE 69-3 -- CARDIOTOXICITY ANTINEOPLASTIC AGENTS

DRUG	TOXIC DOSE RANGE*	COMMENTS
Doxorubicin	>550 mg/m^2 (total dose) >550 mg/m^2 (total dose)	Congestive heart failure (cumulative toxic effect), arrhythmias Cardiac toxicity with additional risk factors
Daunorubicin	>550 mg/m^2 (total dose)	Same toxicity as doxorubicin
Mitoxantrone	>100-140 mg/m^2 (total dose)	Congestive heart failure, decreases in left ventricular ejection fraction
Cyclophosphamide	>100-120 mg/kg over 2 days	Congestive heart failure, hemorrhagic myocarditis/pericarditis/necrosis
5-Fluorouracil	Conventional dose	Angina/myocardial infarction
Vincristine	Conventional dose	Myocardial infarction
Vinblastine	Conventional dose	Myocardial infarction
Busulfan	Conventional oral daily dose	Endocardial fibrosis
Mitomycin C	Conventional dose	Myocardial damage similar to radiation-induced injury
Cisplatin	Conventional dose	Acute myocardial ischemia
Amsacrine	Conventional dose	Ventricular arrhythmias
Taxol	Conventional dose	Bradycardia
Interferons	Conventional dose	Exacerbates underlying cardiac disease
Interleukin-2	Conventional dose	Acute myocardial injury, ventricular arrhythmias, hypotension

From Holland JF: Cancer Medicine. 4th ed. Baltimore, Williams & Wilkins, 1997, p 897.

*Route of administration is intravenous unless otherwise indicated. Conventional dose is the commonly accepted therapeutic range.

Figure 69-9 Ultrastructural features of an anthracycline-induced cardiac toxicity. *A,* Normal. *B,* Vacuolation. *C,* Myofibrillar dropout. *B* and *C* are after doxorubicin therapy. (From Ali MD, Ewer MS: Cancer and the Cardiopulmonary System. New York, Raven Press, 1984, pp 62-63.)

the clinical expression of the dilated congestive cardiomyopathy generally does not occur until a threshold cumulative dose (which differs for each anthracycline) is reached. Although mortality for anthracycline-induced cardiomyopathy was formerly believed to be as high as 40 percent, recent reports in the current era of afterload reduction suggest a better prognosis. Nonetheless, once heart failure due to long-term exposure to these agents becomes clinically apparent, the disease should be taken very seriously. In a recently published study in which the outcomes of 1230 patients with cardiomyopathies were assessed with a median follow-up of 4.4 years, patients with doxorubicin-associated cardiomyopathy had an inferior survival (hazard ratio 3.46, 95 percent confidence interval 1.67-7.18) compared with patients with idiopathic cardiomyopathy[185] (Fig. 69-11). The timing of the onset of clinical symptoms of congestive heart failure relative to anthracycline exposure can vary substantially. In one small series, heart failure developed at a mean time of 4 weeks (range, 1-17 weeks) from the last dose of chemotherapy. The course was more severe in those patients who had a higher (>300 mg/m^2) dose of doxorubicin.[186]

Standard therapy including inotropic agents, diuresis, and afterload reduction represent the typical medical management of patients with anthracycline-induced cardiomyopathy; some studies have suggested that beta-receptor antagonists might also have a role.[187] [188] [189] Selected patients with severe cardiomyopathy who also have a lower likelihood of responding to medical therapy have undergone successful heart transplantation.[190] [191]

Chronic cardiomyopathy resulting in overt congestive heart failure that might require such a drastic intervention as cardiac transplantation is probably less common than the so-called late-onset anthracycline cardiotoxicity, which can cause a more subtle degree of ventricular dysfunction and/or arrhythmias[177] many years after the anthracyclines have been given.[192] Such delayed-onset effects are a particularly important issue in children who have received moderate to large doses of anthracyclines during therapy for acute lymphoblastic leukemia.[193] [194] [195] Because several studies that have observed patients longitudinally after exposure to anthracyclines during childhood have shown that echocardiographic abnormalities progress over time, there is concern about the potentially widened scope of eventual clinical cardiac dysfunction in such patients. For example, a reduction in intraventricular septum and posterior wall diastolic dimensions is more pronounced 7 years after exposure to anthracyclines than in control subjects.[196] The long-term clinical relevance of such findings is unclear. Moreover, whether the low level of elevation in serum cardiac troponin-T levels, indicating some degree of acute injury, which occurs during acute therapy with doxorubicin, has any clinical impact is unclear, although elevations correlated with abnormal

echocardiograms 9 months after chemotherapy.[197] Some clinical deterioration of cardiac function can be detected more readily with the specialized technique of automatic border detection compared with conventional echocardiography[198] or with indium-111/antimyosin scintigraphy.[199] Echocardiographic abnormalities are more common in girls and those patients exposed at a young age to a high cumulative dose of doxorubicin.[200] Although the eventual clinical impact of the type of systolic and diastolic dysfunction documented as a late effect in children and adults treated with anthracyclines remains unclear, the onset of laboratory evidence of cardiac abnormality has correlated with congestive symptoms in patients with cardiomyopathies due to other causes.[201]

MONITORING OF PATIENTS RECEIVING ANTHRACYCLINES.

The ideal monitoring system for the occurrence of anthracycline-induced cardiotoxicity would be noninvasive, a reliable predictor of eventual clinical dysfunction, and detect disease early enough so that an effective therapeutic strategy could be used. Endomyocardial biopsy, radionuclide angiocardiography, resting echocardiography, and exercise echocardiography have each been used in an effort to predict the development of the so-called early or classic cardiomyopathy. Although endomyocardial biopsy grade can predict the rate of potential clinical progression, sampling errors due to patchy myocardial involvement, invasiveness, and expense have limited the routine use of this technique.[177] [202]

Patients receiving anthracyclines over time are often followed with radionuclide ventriculography, based on an earlier study that suggested that a 15 percent decline in left ventricular ejection fraction (LVEF), or a LVEF of less than 40 percent, occurred in those at high risk for clinical cardiac decompensation.[203] However, concerns have been raised regarding the problem that by the time the LVEF falls a significant amount of myocardium has already been irretrievably lost. Echocardiographic features, such as measurement

Figure 69-10 Anthracycline cardiotoxicity: relationship of dose to the incidence of congestive heart failure. (From Shan K, et al: Anthracycline-induced cardiotoxicity. Ann Intern Med 125:47-58, 1996.)

of the rate of relaxation and fractional shortening of diastolic filling, can also serve as a potentially sensitive means of detecting the early onset anthracycline-induced chronic cardiomyopathy.[204]

The value of very sensitive tests of ventricular function to detect so-called late-onset cardiomyopathy has been discussed earlier with regard to findings on echocardiography or radionuclide angiography in children many years after receiving anthracyclines. Dobutamine/exercise echocardiography and exercise radionuclide angiography have

each been somewhat predictive of this late-onset cardiac dysfunction in patients with normal resting cardiac function.[177] However, the importance of these relatively subtle abnormalities, generally of diastolic dysfunction, is even more unclear in the case of late-onset cardiomyopathy, compared with that of early detection of the chronic dilated cardiomyopathy, which occurs much earlier relative to the chemotherapy treatment.[205]

PREVENTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY.

Strategies for minimizing cardiotoxic effects of anthracyclines include altering the dose and schedule, use of new formulation of anthracyclines (e.g., liposome-encapsulated), calcium channel or beta-adrenergic blocker pharmacological approaches, and "true" cardioprotection using iron-chelating agents and/or free radical scavengers. Each of these strategies has shown some ability to limit cardiotoxicity. However, ensuring antineoplastic efficacy remains a major issue with regard to most of the putative cardioprotective agents. It has been recognized for more than 20 years that administration of a given dose of doxorubicin in smaller fractions or by continuous infusion schedules would produce less cardiac toxicity without any apparent compromise of antineoplastic activity.[206] [207] [208] [209] Examples of changes in dose schedule to produce less cardiotoxicity include weekly dosing of doxorubicin (rather than every 3 weeks) in breast cancer patients, continuous infusion of doxorubicin in patients with multiple myeloma or non-Hodgkin lymphoma (which might also have better activity in drug-resistant cells), or giving the drug over 6 hours.[210]

Liposome-encapsulated anthracyclines may allow administration of a higher total with less cardiotoxicity. Endomyocardial biopsies indicate less marked histopathological changes at a given dose of anthracycline when given by the liposomal route.[211] [212] [213] [214] However, it remains of critical importance to ensure that the use of liposome-encapsulated anthracyclines does not reduce antitumor efficacy. A recent provocative study compared docetaxel, a taxane, versus doxorubicin, in patients with metastatic breast cancer who had received previous

Figure 69-11 Mortality from various causes of cardiomyopathy. (From Felker GM, et al: Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 342:1077-1084, 2000.)

alkylating-agent chemotherapy.[215] Not only was the median time to progression longer in the docetaxel group but there was no cardiotoxicity in this group, compared with four deaths in the patients who received doxorubicin. Therefore, substitution of alternative efficacious agents for the anthracyclines is yet another strategy for reducing cardiotoxicity.

Several compounds have been tested for their ability to protect against

anthracycline-induced cardiomyopathy, including dexrazoxane, amifostine, glutathione, vitamin E, mesna, and ORG 2766.[168] [175] [216] [217] These drugs block toxicity by either reducing free radical generation or increasing free radical scavenging. Dexrazoxane, which has received the most attention, readily penetrates cell membranes and appears to complex with metal cofactors, including iron. Chelation of intracellular iron may decrease doxorubicin-induced free radical formation.[175] The drug should be given within 30 minutes of anthracycline administration. Three randomized, placebo-controlled clinical trials of dexrazoxane in patients with advanced breast cancer have been conducted in which a total of 626 patients were enrolled.[175] [218] [219] [220] The mean decrease in left ventricular injection fraction by radionuclide scanning was lower in women treated with dexrazoxane. However, dexrazoxane was not shown to increase overall or disease-free survival. At higher doses, there was an increase in the incidence of myelosuppression, and concern remains that tumor response rates may be decreased.[168] Moreover, it is not known whether the drug can protect against delayed-onset cardiotoxicity. The vagueness of the American Cancer Society Clinical Practice Guidelines reflects the many unanswered questions regarding the use of the agent. In fact, the only setting in which the agent is recommended even for consideration is in patients who have received 300/mg/m^2 or more of doxorubicin yet who might benefit from further anthracycline.[168]

Other agents with antioxidant effect, such as probucol, coenzyme Q10, and melatonin, may provide cardioprotection without affecting tumor response rates, at least based on animal data.[221] [222] [223] [224] These promising early results await additional confirmatory studies. Pilot data with calcium antagonists[225] and beta-adrenergic blockers,[189] [226] such as metoprolol, have also been developed. Finally, a transgenic mouse overexpressing the human complementary DNA for multiple drug resistance, driven by an alpha-cardiac myosin gene, has been developed.[227] The animals are resistant to doxorubicin-mediated myocyte dropout.

Cardiotoxicity of Other Antineoplastic Agents

5-FLUOROURACIL (5-FU).

This is a fluorinated pyrimidine that undergoes under intracellular metabolism to deoxy-5-fluorouracil monophosphate, an inhibitor of the enzyme thymidylate synthase (as well as interfering with DNA and RNA metabolism). 5-FU is used to treat several important solid tumors, including colorectal cancer, squamous cell carcinoma of the head and neck, and breast cancer. Although it is not a common cause of cardiotoxicity, patients with prior coronary disease and/or those receiving concurrent radiation therapy are at risk for 5-FU-induced heart disease. Vasoocclusive complications, particularly acute myocardial infarction, may be somewhat more likely in patients receiving 5-FU-based chemotherapy. Clinical manifestations of 5-FU cardiotoxicity, which occurs in less than 2 percent of patients receiving this drug, include typical ischemic electrocardiographic changes, chest pain, nausea, and diaphoresis.[228] 5-FU may cause endothelial cell contraction and lysis, perhaps on a vasospastic basis.[229] Vasospastic-type ischemia, arrhythmias, contractile dysfunction, and frank infarction have also been documented in connection with 5-FU.[230] [231] [232] Fortunately, the cardiac effects, including mild depression of contractile function, are usually reversible when the

drug is withdrawn.[233] [234] [235] [236] [237]

CYCLOPHOSPHAMIDE AND IFOSFAMIDE.

The bifunctional alkylating agents cyclophosphamide and ifosfamide are converted in the liver to an active form. In the case of cyclophosphamide, hepatic microsomal mixed function oxidases metabolize the drug to the active moiety, 4-hydroxycyclophosphamide. A severe myocardiopathy may occur in patients receiving high doses of these drugs. Most of the available data comes from patients who have received cyclophosphamide at high doses during preparation for stem cell transplantation who have developed serious heart failure.[238] [239] Cyclophosphamide-induced cardiac failure is manifested by reduction in the electrocardiographic voltage on systolic function and increase in myocardial mass due to edema, with pathology indicating acute myocyte necrosis, hemorrhagic myopericarditis, and endothelial injury. Preexisting heart disease is a predisposing factor,[240] and mortality approaches 33 percent. Six of 19 women undergoing autologous bone marrow transplantation for breast cancer developed transient clinical and chest radiographic evidence of moderate congestive heart failure during the course of recovery from transplantation, with a median time of onset on day 13 after chemotherapy. The median area under the curve of cyclophosphamide concentration was lower in those patients who developed cardiotoxicity, presumably owing to a high rate of conversion of parent compound to the active metabolite.[239] Ifosfamide can cause a similar syndrome of heart failure.[241]

OTHER AGENTS.

Preparative regimens for bone marrow transplantation involving high doses of cyclophosphamide, frequently along with total-body radiation, are not infrequently associated with subacute cardiotoxicity.[242] Life-threatening cardiotoxicity is rare (less than 2 percent) in the posttransplant setting; however, cardiac events seem to be more common in those with a reduced ejection fraction at baseline. Consequently, most transplant protocols eliminate from eligibility patients who have impaired cardiac function at the time of transplant. It is possible that with the advent of so-called miniallogeneic transplant protocols[243] in which the dose of conditioning regimens is decreased in favor of the graft-versus-cancer effect, that such cardiotoxicity will be less common in the future.

Although cisplatin,[244] bleomycin,[245] and *Vinca* alkaloids[246] do not generally cause direct cardiac muscle damage, each of these agents does have potential endothelial and vasospastic[247] effects. As such, it is perhaps not surprising that myocardial infarction has been described. Moreover, because cisplatin causes renal tubular potassium and magnesium wasting, electrocardiographic abnormalities are not uncommon.

The taxanes, relatively new to the clinic, are useful in patients with a host of neoplasms, including breast, lung, and ovarian cancer. Paclitaxel and docetaxel have been associated with the development of brachycardia; it is now recognized that such events are rare (<10 percent), may have been due to the formerly used carrier, and are

generally not clinically significant.[248] These agents do not appear to have any long-term cardiac side effects. Minimal added toxicity from the addition of paclitaxel to doxorubicin for the treatment of breast cancer has been noted.[249] [250] Interferon alfa, which is used in hairy cell leukemia, chronic myelogenous leukemia, and Kaposi sarcoma, can occasionally cause a severe congestive cardiomyopathy with myocardial dysfunction, which is generally reversible with discontinuation of the drug.[251] [252]

High-dose interleukin-2, which may have a role in the treatment of selected patients with renal cancer and melanoma, can cause high fevers and myalgias, as well as, in some cases, life-threatening capillary leak syndromes, including tissue edema, hypotension, noncardiogenic pulmonary edema, renal failure, and an occasional myocardial infarction.[252] [253] [254]

Trastuzamab (Herceptin) is a humanized monoclonal antibody that targets the human epidermal growth factor receptor (HER-2), which is overexpressed in 30 percent of breast carcinomas. This novel agent is associated with clinical responses in HER-2, overexpressing breast cancer when given alone[255] or with other agents such as taxanes or anthracyclines.[256] However, a cardiomyopathy similar to that observed after doxorubicin therapy has been noted. In the context of the known expression of HER-2 or HER-3 receptors in myocardial tissue, this is of concern. The precise mechanism and incidence, if any, of Herceptin-mediated heart problems requires evaluation.[257]

HEMATOLOGICAL EFFECTS OF CARDIAC MEDICATIONS (See also Chap. 62)

Reports exist linking virtually every drug with hematological abnormalities. The focus in this section is primarily on the more common and clinically important hematological effects produced by medications currently employed in the clinical practice of cardiovascular medicine. For a broader discussion of hematological effects of cardiac medications currently less used, the reader can consult previous editions of this text. This discussion considers, in turn, thrombocytopenia, granulocytopenia/aplastic anemia, and anemia.

Thrombocytopenia

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

(see also Chap. 62) . Heparin, a commonly used anticoagulant in cardiovascular diseases, frequently causes thrombocytopenia. Two forms of HIT can occur. In type I HIT, thrombocytopenia occurs within days of initiating therapy. Type I HIT causes modest thrombocytopenia with levels seldom below 75,000 cells/muL. This form of HIT probably results from increased aggregation of platelets that have been cross-linked by the highly negatively charged heparin molecule. Type I HIT is common, occurring in several percent of patients receiving heparin therapy. Type I HIT generally improves

with time, even with continuation of heparin treatment.

In contrast, type II HIT produces more severe thrombocytopenia with levels often below 50,000 cells/cm[3] . Type II HIT occurs later after initiation of therapy, typically between 4 days and 2 weeks of treatment. In type II HIT, thrombosis as well as bleeding can occur. The mechanism of type II HIT involves binding of exogenously administered heparin to a platelet surface protein known as platelet factor 4 (PF4). When an IgG antibody that recognizes this PF4/heparin complex binds, the ternary complex associates with platelet receptors for the Fc portion of the immunoglobulin molecule. Ligation of the Fc receptors causes platelet activation and thrombosis. The second form of HIT requires immediate cessation of heparin therapy. Even heparin flushes of peripheral intravenous catheters should be avoided. Low-molecular-weight heparin is associated with a much lower incidence of HIT.[258] Thrombin inhibitors such as hirudin and argatroban may be very useful as replacement for heparin in type HIT, when even low-molecular-weight heparin must be used with caution.[259]

GLYCOPROTEIN (GP) IIb/IIIa ANTAGONISTS (see also Chap. 62) .

The introduction of IIb/IIIa antagonists represents one of the major advances in cardiology in the past decade. Numerous studies have shown improved outcomes after coronary intervention and the acute coronary syndromes due to administration of these agents.[260] GP IIb/IIIa antagonists currently available for intravenous use include a chimeric antibody (abciximab), small organic molecules (e.g., tirofiban), and a cyclic oligopeptide (eptifibatide). A number of orally active agents exist as well. Each of these drugs can cause thrombocytopenia[261] (Fig. 69-12). Defining clinically significant thrombocytopenia as less than 50,000/muL, the incidence with small molecules is 0.6 to 0.8 percent, with abciximab up to 2 percent.

Administration of these agents requires careful monitoring for thrombocytopenia. A baseline platelet count should be obtained; a basal level of less than 100,000/muL is a relative contraindication to GP IIb/IIIa antagonist use. A platelet count should be obtained 1 to 4 hours after administration of a GP IIb/IIIa antagonist. If the platelet count falls below 50 percent of baseline or less than 100,000/muL,

Figure 69-12 A meta-analysis of rates of thrombocytopenia associated with use of intravenous GP IIb/IIIa antagonists. Data shown compile results from 28 clinical trials. The odds ratio (OR) and 95% confidence intervals (CI) for each agent are depicted on the whisker plots. (After Giugliano RP; from Madan M, Berkowitz SD: Understanding thrombocytopenia and antigenicity with glycoprotein IIb-IIIa inhibitors. Am Heart J 138:317-326, 1999.)

the agent should be discontinued. Because the clinical indications for GP IIb/IIIa and heparin therapy are similar, coadministration of these agents occurs commonly. Hence, the differential diagnosis of thrombocytopenia due to GP IIb/IIIa antagonists versus heparin-induced thrombocytopenia is a common clinical dilemma. Clues to the differential diagnosis include the time course of onset of the thrombocytopenia. The decline in platelet count with GP IIb/IIIa antagonists typically occurs during the first day,

whereas there is a delay of 3 to 4 days in type I HIT. Laboratory evaluation of heparin/PF4/IgG complexes can also aid the differential diagnosis.

Several mechanisms may account for the thrombocytopenia associated with GP IIb/IIIa antagonist administration.[262] One mechanism is analogous to the "innocent bystander" mechanism often responsible for drug-induced hemolytic anemia. In this situation, an antibody binds to the drug, as well as to the platelets. Complement-induced lysis, or enhanced clearance by the spleen due to opsonization, can reduce platelet number. Another potential mechanism involves an antibody response directed against a conformational epitope on the IIb/IIIa complex itself. When a ligand binds to GP IIb/IIIa, it can induce a shape change that uncovers a new antigenic determinant, or epitope, a ligand-induced binding site. The immune response targets a normally concealed part of the GP IIb/IIIa molecule revealed upon binding of the antagonist.

Another potential mechanism is applicable specifically to the chimeric antibody abciximab.[263] In this situation, a portion of the chimeric antibody that retains mouse sequences in the hinge region of the immunoglobulin molecule can engender an antibody response. This mechanism has been called a human anti-chimeric antibody reaction. Because this mechanism requires generation of a antibody response to the foreign epitope (mouse sequences in the chimeric antibody), its onset would be later than most GP IIb/IIIa antagonist-induced thrombocytopenic episodes. Complement-induced lysis of platelet binding the antibody presumably causes the thrombocytopenia. Readministration of abcximab within 2 weeks can lead to profound thrombocytopenia in approximately 12 percent of patients.[264]

The treatment of thrombocytopenia associated with administration of GP IIb/IIIa antagonists involves stopping the drug. Platelet transfusion may prove necessary if the platelet count drops below 20,000/muL3. Although the mechanisms may differ, all three structurally distinct classes of GP IIb/IIIa antagonists can cause thrombocytopenia. Curiously, a number of recent trials with oral GP IIb/IIIa antagonists have shown not only no benefit in terms of event reduction but also a tendency to increase events.[265] The reason for the unexpected lack of efficacy of the oral GP IIb/IIIa antagonists remains uncertain.

THIENOPYRIDINES AND THROMBOTIC THROMBOCYTOPENIC PURPURA.

The introduction of thienopyridine antiplatelet agents has proven a boon in interventional cardiology and for aspirin-allergic patients with atherosclerotic

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disease. These drugs (ticlopidine and clopidogrel) bind to an adenosine diphosphate receptor on the surface of platelets that mediates platelet activation and propagation of platelet aggregation. Before the use of thienopyridine agents, abrupt thrombosis represented a major limitation to the use of coronary stents. Lengthy hospital stays to achieve therapeutic anticoagulation with warfarin were inconvenient for patients,

expensive, fraught with the risk of bleeding with intensive warfarin therapy, and eventually proved less effective than administration of aspirin and thienopyridine after coronary stenting.[266]

Patients with atherosclerosis with indications for aspirin who are unable to take this agent due to allergy have also benefited from thienopyridine therapy.[267] Considerable data establish the utility of agents of this class in reducing unstable coronary events and stroke in patients at risk. However, the possibility of developing thrombotic thrombocytopenic purpura (TTP) requires careful thought when considering use of thienopyridines. First recognized with ticlopidine, and subsequently with clopidogrel, TTP due to thienopyridines presents as the classic findings of thrombocytopenia, microangiopathic hemolytic anemia, central nervous system abnormalities, and renal dysfunction. Because prevention of recurrent strokes is a common indication for this class of drugs, mental status changes due to TTP can present a diagnostic challenge. TTP due to ticlopidine occurs in approximately 1 in 1600 treated patients.[268] The incidence of clopidogrel-induced TTP requires more extensive study but is probably substantially lower.[269]

TTP is life threatening. Death occurs in about a third of patients with ticlopidine-associated TTP. Plasmapheresis should be instituted as soon as the diagnosis is made and appears to strikingly reduce mortality (from 60 percent from patients not undergoing plasmapheresis to 22 percent of those plasmapheresed).[268] The physician should remain vigilant in all patients receiving thienopyridines for early clinical signs of TTP, including rashes or confusion. The finding of schistocytes on a peripheral blood smear supports the diagnosis of TTP. Fortunately, most episodes of TTP due to thienopyridines occur during the first 3 months of therapy, after which point patients require less surveillance.

The precise mechanism of thienopyridine-induced TTP remains elusive. However, it may involve generation of an antibody that inhibits a metalloproteinase important for processing large multimers of von Willebrand factor.[270] [271] Antibody-induced inhibition of this metalloproteinase favors the accumulation of the large von Willebrand factor multimers, which more effectively promote platelet aggregation and cross-linking than lower molecular weight forms.

TTP, although rare, is a serious and frequently lethal complication of thienopyridine therapy. In patients requiring coronary stent placement, the risk/benefit ratio of thienopyridine use, limited to a few weeks, supports the use of these agents to prevent the otherwise common and often disastrous complication of abrupt thrombosis. In candidates for antiplatelet therapy with aspirin allergy, selection of a thienopyridine also likely has a net benefit for the patient. In patients able to tolerate aspirin, individual decisions regarding the use of thienopyridines based on the particular clinical scenario seem warranted.

QUINIDINE.

Quinidine, once a mainstay of antiarrhythmic therapy, has lost popularity in recent years. Hematological side effects, including thrombocytopenia, in addition to a potential

proarrhythmic effect, has contributed to the decline in quinidine's use in the clinic. The mechanism of quinidine-induced thrombocytopenia probably involves a humoral immune response.[272] Cessation of the drug generally leads to a gradual increase in platelet number over a period of days. Alkalization of the urine can help promote the elimination of quinidine, a weak base. Intravenous immunoglobulin may also mitigate quinidine-induced thrombocytopenia. [273]

OTHER CARDIOVASCULAR MEDICATIONS ASSOCIATED WITH THROMBOCYTOPENIA.

Several other cardiac medications cause thrombocytopenia less frequently. However, several of these agents are in very common clinical use, resulting in the number of patients at risk is considerable (Table 69-4) . These agents include the thiazide diuretics, furosemide, digoxin, procainamide, and the phosphodiesterase inhibitor inotropic agents, such as amrinone or milrinone.[274] A comprehensive listing of drugs that induce thrombocytopenia can be found on the Internet at http://moon.ouhsc.edu/jgeorge.

Leukopenia/Aplastic Anemia

Granulocytopenia can occur during treatment with a wide variety of cardiovascular drugs.[275] The sulfhydryl group containing angiotensin-converting enzyme inhibitors (the "prils") represents one class of cardiac medications that with increasing use occasionally causes leukopenia. Procainamide (particularly sustained-release procainamide) can cause severe leukopenia.[276] [277] The granulocytopenia improves after cessation of procainamide treatment. Interestingly, the leukopenia can occur independently of the well-known procainamide-induced lupus syndrome.[278] Granulocyte colony-stimulating factor is one therapeutic option for drug-induced thrombocytopenia.[279] Other cardiovascular drugs that can cause agranulocytosis or aplastic

TABLE 69-4 -- CURRENTLY USED CARDIAC DRUGS IMPLICATED IN DRUG-INDUCED THROMBOCYTOPENIA-

AGENT	FREQUENCY OF USE	INCIDENCE	BLEEDING	THROMBOSIS	CLINICAL IMPORTANCE
Furosemide	++++	+	+	-	+++
Heparin	++++	+++	+	+++	++++
Thiazides	++++	+	+	-	+
Aspirin	+++	+	+++	-	+
Digoxin/digitoxin	+++	+	++	-	+
Glycoprotein IIb/IIIa blockers	+++	++	++	-	+++
Thienopyridines	+++	+	++	++	++
Quinine/quinidine	++	++	+++	-	++

Alpha-methyldopa	+	++	++	-	+
Amrinone, milrinone	+	++	++	-	+
Procainamide	+	+	++	-	+

-Plus (+) and minus (-) signs indicate subjective impressions of the frequency and importance of selected aspects of drug-induced thrombocytopenia, ranging from very low (-) to very high (++++).*Adapted from Giugliano RP: Drug-induced thrombocytopenia: Is it a serious concern for glycoprotein IIb/IIIa receptor inhibitors? J Thromb Thrombolysis 5:191-202, 1998.*

anemia include beta blockers, such as propranolol, dipyridamole, digoxin, and nifedipine.[275] The thienopyridine ticlopidine causes granulocytopenia in about 2.5 percent of recipients. A leukocyte count should be obtained before and at 2-week intervals during the first 3 months. If the drug is omitted during the first 3 months of therapy, a follow-up white blood cell count should be monitored for an additional 2 weeks, because patients are at risk for leukopenia even after stopping ticlopidine. Among the immunosuppressants used in cardiac transplantation recipients, azathioprine can cause a dose-related decrease in white blood cell count. This represents a mechanism-based toxicity related to the drug's primary mode of action as an immunosuppressant.

Anemia

Cardiac medications seem to cause anemia less commonly than thrombocytopenia or leukopenia. Hemolytic anemia due to methyldopa is seen less frequently, because use of this antihypertensive agent has declined. One currently used medication associated with hemolytic anemia is quinidine. Phenytoin, now uncommonly used as an antiarrhythmic agent, and triamterene, a common component of combination diuretic drugs, can cause megaloblastic anemia.

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Chapter 70 - Psychiatric and Behavioral Aspects of Cardiovascular Disease

ARTHUR J. BARSKY

Daily life offers ample empirical evidence of an intimate relationship between the psyche and the heart. Intense emotions such as anxiety, anger, elation, and sexual arousal are accompanied by predictable increases in heart rate and blood pressure. Our everyday speech is filled with cardiac metaphors; the heart "races" with excitement, "pounds" in eager anticipation, "stands still" in dread, "aches" with grief. Many cultures have regarded the heart as the seat of emotion, the origin of love, the source of courage, or the abode of the soul. Generous people have "big hearts," and stingy people are "heartless." When you first met your first love, your heart "skipped a beat," and you were "broken hearted" when you parted ways soon thereafter. We attend funerals with a "heavy heart" and offer our "heartfelt" condolences. The interaction of heart and psyche is bidirectional. Emotions and stressful experiences affect the heart directly through the autonomic nervous system and indirectly through neuroendocrine pathways. Conversely, cardiac activity and function can reach conscious awareness and may be experienced as symptoms.

PSYCHIATRIC AND BEHAVIORAL ASPECTS OF CORONARY HEART DISEASE

Type A Behavior Pattern and Hostility

Clinicians dating back to Sir William Osler have observed that a surprising number of coronary heart disease (CHD) patients seem to be compulsive, driven overachievers who are unable to relax and quick to feel angry and frustrated when things do not proceed as planned. Such observations were reified in the 1960s by Friedman and Rosenman, who advanced the concept of Type A behavior, which was actually a cluster of psychological traits and behavioral patterns. Type A individuals struggled to obtain numerous objectives, as rapidly as possible, from an environment that continually seemed to oppose their efforts. Type A behavior is suffused with ambition, time urgency, and anger and hostility. Type A persons are excessively competitive and aggressive, with an extreme desire for achievement and recognition--impatient people leading fast-paced lives in continual and strenuous pursuit of a goal. This was contrasted to Type B individuals who are relaxed, unhurried, and less aggressive and who do not get as upset when thwarted. Large-scale, prospective studies in the 1970s and 1980s (including the Western Collaborative Group Study) conducted on initially healthy individuals showed that those with Type A behavior pattern, versus Type B individuals, had a significantly elevated rate of developing CHD (two times higher) and myocardial infarction (five times higher) at 5- to 8½-year follow-up and had more extensive CHD at the time of angiography.[1] Some additional longitudinal studies replicated these findings, but a substantial number, including the Multiple Risk Factor Intervention Trial (MRFIT), failed to support this association. In particular, several studies did not find that Type A behavior pattern predicted the subsequent incidence of cardiac events among patients with already established CHD. This suggested that perhaps the association between Type A and the development of CHD might be stronger than the association between Type A and the progression of disease.

These contradictory findings led to a search for more specific features or components of Type A behavior that might be more closely associated with CHD. A body of work emerged suggesting that anger and/or suppressed anger are the pathogenic components of Type A personality,[2] and laboratory studies provided evidence of pathophysiological changes that were associated with anger and hostility. Hostility is thought of as an underlying, enduring personality trait that encompasses a cynical, suspicious, and denigrating attitude toward others. This attitude then results in more frequent, intense, or longer-lasting episodes of anger when the individual is provoked, challenged, or otherwise stressed. Anger, hostility, antagonistic interactions, cynicism, and mistrust have been associated in long-term, prospective studies with the incidence of CHD, coronary events, and total mortality; and this literature suggests that such anger and hostility are independent risk factors for the development of CHD.[2] [3] In a 7-year, follow-up study of 1305 men, for instance, the relative risk for men with the greatest levels of anger was 2.66 for cardiac events (cardiac death, nonfatal myocardial infarction, and angina) as compared

with men with the lowest levels of anger.[4] In the Western Electric study, the baseline hostility scores of 1877 middle-aged men were predictive of CHD events over a 10-year period.[5] Most recently, in a sample of 2890 middle-aged men observed for more than 8 years, suppressed anger was a significant predictor of a major cardiac event (relative odds=1.70; 95 percent confidence interval [CI]=1.26 to 2.29), and this relationship persisted after controlling for physiological, psychosocial, and behavioral risk factors.[6] Several cross-sectional angiographic studies also report an association between the degree of hostility and the extent of CHD.

Other studies, however, have not found an association between anger and CHD, and the evidence linking irritability, anger, and hostility to CHD prognosis and mortality is less conclusive than its association with the incidence of CHD. It has been reported in a 3-year, follow-up study that anger was significantly associated with CHD mortality in men with already established heart disease and with the incidence of restenosis after angioplasty,[7] but in general it appears that hostility and anger may predispose more to the initial cardiac event than they adversely influence the course of already established coronary artery disease. It is unclear to what degree hostility's effect may be mediated through its influence on other risk factors, such as lack of social supports, smoking, diet, and alcohol use. Possible associations between anger and race, socioeconomic status, and gender also represent potential confounds. In sum, although more research is necessary to establish the specifics of the relationship, it appears that anger and hostility do play a role in the development of CHD.

Depression and Anxiety

DEPRESSION.

Recent work has begun to focus on the influence of depression and, to a lesser degree, anxiety on the onset, course, and outcome of CHD. A substantial body of prospective research indicates that major depression and subthreshold depressive symptoms, in both healthy individuals and in patients with CHD, confer an increased risk for subsequent cardiac events. Depression is prevalent in patients with CHD. Clinically significant depressive symptoms are found in 40 to 65 percent of patients after a myocardial infarction, and the prevalence of major depressive disorder is 20 to 25 percent in such patients.[8] [9] In one study, 31.5 percent of post-myocardial infarction patients experienced major depression in the hospital or within 1 year after discharge.[10] The prevalence of depression is also elevated in patients with stable CHD who have not had a recent myocardial infarction or other cardiac event (as high as 20 percent in some studies) and in patients who have undergone coronary artery bypass surgery.[11] Although most subjects in these studies have been male, there is evidence that the risk of depression in women with CHD is twice as high as that of men. Studies also reveal that depression is consistently underdiagnosed by cardiologists and primary care physicians in these patients.

Depression is of course important in and of itself because of the very considerable suffering it imposes. But in addition, depression exacerbates, prolongs, and amplifies cardiac symptoms. CHD patients with depression have more severe cardiac symptoms than nondepressed CHD patients, even after controlling for the severity of cardiac disease. Thus, depressed patients have greater levels of angina during exercise treadmill testing, terminate the treadmill test sooner, and have more persistent angina after myocardial infarction. In addition, depression engenders disability and role impairment, adversely affects compliance with medical therapy, and is detrimental to cardiac rehabilitation. In a 1-year, prospective study of patients who had undergone catheterization for documented CHD, physical functioning and interference with activities were better predicted by baseline depression and anxiety than by the number of stenosed vessels, even after controlling for medical comorbidity and treatment.[12] Although major depression is most powerful in this regard, less severe forms of depression that do not meet diagnostic criteria for major depressive disorder also produce significant functional impairment, after controlling for individual differences in cardiac and medical comorbidity.

Depression also exerts a negative prognostic influence on the course and outcome of CHD. In patients with documented CHD, depression predicts future cardiac events and is associated with significantly elevated rates of cardiac mortality.[8] [13] [14] Major depressive disorder at the time of cardiac catheterization is a significant predictor of subsequent myocardial infarction, angioplasty, coronary artery bypass grafting, and death in patients with evidence of CHD, and this effect is independent of CHD severity, left ventricular ejection fraction, and smoking.[13] After myocardial infarction, depression increases the risk of future coronary events, including reinfarction, cardiac arrest, and death, after taking the severity of CHD into account.[8] [14] [15] In an important longitudinal study of 222 patients, baseline depression was a significant predictor of cardiac mortality 6 and 18 months after myocardial infarction, and this association persisted after taking into account the effects of baseline left ventricular dysfunction, Killip class, previous myocardial infarction, and frequency of premature ventricular contractions.[8] [14] For longer periods, from 6 to 27 years, the relative risk of myocardial infarction or cardiac mortality associated with depression has been reported to be between 1.5 and 6, after controlling for severity of cardiac disease.[14] [16] [17]

The degree of risk associated with depression is as great as that associated with traditional risk factors (e.g., cholesterol, smoking, hypertension) and is largely independent of them. This risk is elevated for women as well as men and not limited to diagnosable, major depressive disorder but also includes depressive symptoms. That is, there is a continuous, linear relationship between the number of depressive symptoms and the risk of subsequent cardiac events. An interaction effect may exist, in which the co-occurrence of both depression and ventricular arrhythmias exerts a particularly poor prognostic influence.[14] Interestingly, optimism seems to have a positive influence on prognosis; optimism at the time of coronary artery bypass surgery is associated with a lower rate of rehospitalization for cardiac events over the subsequent 6 months, after controlling for sociodemographic differences and disease severity.[18]

Depression also appears to be a risk factor for the development of CHD, although the

evidence here is less extensive and somewhat less conclusive, especially since depression tends to co-occur with other risk factors for CHD. Some prospective studies report a modest association between depression and the incidence of CHD, but others fail to find a correlation. In longitudinal studies of initially healthy, community residents without a history of CHD, depression has been associated with a relative risk between 1.5 and 2 for the subsequent development of CHD, myocardial infarction, and cardiac death over periods from 6 to 40 years, and this risk is largely independent of the more traditional risk factors.[16] [17] [19] [20] [21] For example, in a prospective study of 2832 healthy adults, depressed mood was a significant predictor of subsequent fatal and nonfatal CHD.[16] Similar prospective findings have been reported in men and women over a 27-year period and in men over 40 years. Other work, however, has failed to confirm these findings: depression was not associated with an increased risk of CHD over a 15-year period in a study of 2573 adults,[22] nor was it associated with an increased risk of myocardial infarction in a 5-year follow-up of elderly individuals with hypertension.[23]

In sum, the evidence at this point indicates that depression confers an increased cardiovascular risk on healthy individuals and on individuals with already established CHD. Both major depressive disorder and elevated levels of depressive symptoms are significant in this regard. The degree of risk associated with major depression is comparable to that associated with other, established risk factors and is largely independent of them.

This relationship between depression and CHD may be mediated by several different behavioral and physiological mechanisms. Depression may operate through its influence on behavior: Depressed individuals may take poorer care of themselves, pay less attention to diet, drink more alcohol, smoke more, have less motivation and energy to exercise regularly, and be less likely to seek medical care and adhere to the medical regimen. There is, however, only limited empirical evidence bearing on this hypothesis. In addition, depression hinders recovery and causes poorer psychosocial adjustment to, and coping with, disease. Depressed post-myocardial infarction patients are more likely to experience social readjustment problems in the year after myocardial infarction than nondepressed post-myocardial infarction patients, are slower to return to work, and report more associated stress. Depression has an additional adverse consequence: It is associated with poorer adherence to the medical regimen[24] and to cardiac risk factor modification and rehabilitation programs, and depressed patients are more likely to drop out of exercise programs.

At least three separate pathophysiological mechanisms may link depression to CHD.[25] [26] First, depression results in autonomic arousal with hypothalamic-adrenocortical and sympathoadrenal hyperactivity. Depressed patients show hyperactivity of the hypothalamic-pituitary-adrenocortical axis and hypercortisolemia, and corticosteroids have atherogenic effects, including the induction of high blood pressure and increases in cholesterol and free fatty acids. In addition, there is hypersecretion of norepinephrine in depression, and such sympathoadrenal activation can contribute to cardiovascular disease through the direct effects of catecholamines on cardiac function, blood vessels,

and platelets. Second, depressed patients exhibit diminished heart rate variability, and this has been found specifically in depressed cardiac patients as well.[27] This is believed to result from a relative increase in sympathetic tone and/or a relative decrease in parasympathetic tone, and it places depressed cardiac patients at greater risk for fatal arrhythmias. Third, depression may be accompanied by changes in platelet aggregability. Serotonin, which plays a role in depression, influences thrombogenesis and enhances platelet activation and responsiveness to other thrombogenic agents.

ANXIETY.

In addition to depression, chronic anxiety and anxiety disorders such as panic disorder and phobias appear to exert a negative influence on the heart, and several studies suggest a relationship between anxiety disorder and increased cardiac morbidity and mortality. Anxiety has been found to predict CHD mortality and sudden cardiac death in a large, population-based, prospective study, after adjusting for a range of potential confounding variables.[28] In another study, anxiety was an independent predictor of cardiac events after myocardial infarction, after the influence of depression was taken into account.[29] There is also suggestive evidence for anxiety as a risk factor predisposing one to the development of CHD. Thus, initially healthy men who reported phobic anxiety were found to have a strikingly increased likelihood of subsequent death due to CHD, even after taking other CHD risk factors into account.[30] Possible mechanisms explaining this association include a decrease in vagal activity and consequently in heart rate variability in intensely anxious patients, microvascular angina, or idiopathic cardiomyopathy.

Psychosocial Factors

A number of psychosocial, cultural, and environmental factors increase the risk of CHD, either independently or in combination. These include social isolation and lack of social support, life stresses such as job strain, and sociodemographic characteristics. It is important to remember that these psychosocial risk factors tend to be associated with each other and therefore to co-occur within the same individuals. For example, job strain and socioeconomic position may be inversely correlated, and depression may be positively associated with social isolation. These psychosocial factors also tend to be associated with life-style behaviors that are unhealthy. For example, life stress may be correlated with smoking and increased alcohol consumption and body weight, and people with fewer social supports are less likely to stop smoking or to adhere to the medical regimen. This co-occurrence or clustering of psychosocial factors within the same individual is important because they may have a synergistic and not merely an additive effect in elevating risk. This interaction effect also makes studying the role of these variables more difficult.

SOCIAL ISOLATION, LACK OF SOCIAL SUPPORT, AND SOCIAL DISRUPTION.

The literature on social support and cardiac disease emerged from population-based, cross-sectional surveys revealing that measures of social integration (such as being married, having regular contact with friends, and belonging to organizations) were associated with lower levels of CHD. Subsequent work substantiated this, revealing that

social isolation and low social support (living alone, having few friends or family members, and not belonging to organizations, clubs, or churches) are associated with an increased incidence of CHD and a poorer outcome after the first diagnosis of CHD. Thus, those who live alone, are unmarried, or are without a confidante have a higher rate of recurrent myocardial infarction, fatal myocardial infarction, and all-cause cardiac mortality than those who are more socially integrated. Among patients with documented CHD, being unmarried and without a confidante confers a significantly worse 5-year prognosis, even after medical risk factors have been taken into account.[31] Berkman and associates found that elderly men and women who reported less emotional support from others before they sustained a myocardial infarction were almost three times more likely to die in the 6 months after it, after controlling for severity of infarction, comorbidity, coronary artery disease, and socioeconomic status.[32] This effect may be particularly robust in men.

However, many studies of social support and survival after myocardial infarction are retrospective or do not adequately assess and control for comorbid disease. There is suggestive evidence of an interaction effect between low social support and Type A behavior pattern such that low social support is a negative cardiac influence in Type A individuals but not in Type B individuals. Interestingly, animal studies also suggest social support has a protective role against atherogenesis. Thus the fondling by research personnel of laboratory rabbits placed on an atherogenic diet retards the development of coronary artery disease.[33] Crowding and social disruption of animal colonies on the one hand and isolation of individual laboratory animals on the other[34] both result in significantly increased rates of atherogenesis, and this effect is not due to increases in serum lipids.

Acculturation also influences the development of CHD. A classic epidemiological survey compared Japanese men living in Japan, Hawaii, and California. Traditional Japanese culture and lifestyle declined across the three groups, and this was accompanied by an increased incidence of CHD.[35] Similar findings emerged when comparing Japanese-Americans living in California who retained the traditional Japanese culture to varying degrees.[36] Animal work is also

provocative in this regard. Dominant male monkeys fed an atherogenic diet develop coronary atherosclerosis at an accelerated rate when repeatedly moved from one social group to another rather than when left in a single, stable group.

Several mechanisms of action have been proposed to explain the relationship between social integration and CHD. First, concerned and supportive others may encourage healthy behaviors and adherence to the medical regimen and provide a motivation for altering unhealthy, behavioral risk factors. Conversely, loneliness may foster unhealthy behaviors such as smoking and drinking. Second, social support may attenuate and buffer the individual's emotional and/or physiological response to environmental stress. This may occur by virtue of the emotional benefits of comfort, encouragement, and consolation, as well as through practical assistance that mitigates the impact of stressful

life events, for example, lending money, assisting with errands, and providing transportation.

LIFE STRESS AND JOB STRAIN.

There has long been interest in the relationship between life stress and the development and progression of CHD. In animal studies ranging from mice to primates, stressful experimental paradigms that increase aggression and fear, and that decrease social affiliation and disturb stable social hierarchies, are associated with atherosclerosis. Thus, monkeys moved repeatedly from one stable monkey society to another developed more CHD than control monkeys.[37] In humans, two different forms of stress have received particular attention: major life events that tax one's abilities to adapt (such as getting divorced, moving, encountering financial difficulties, or being involved in a lawsuit) and more minor, recurrent irritants and daily frustrations. Some studies of individuals undergoing major, stressful life events have found an association with the incidence of myocardial infarction, the development of CHD, or cardiac mortality, whereas other prospective studies have not found a statistically significant association. At this point, the evidence remains inconclusive.

When turning to daily life stress, job strain and other forms of work-related stress have received considerable attention. Job strain is defined as the combination of high job demands with little autonomy or control over one's working conditions, routine, or schedule. Job strain has been associated with an increased risk of CHD in previously healthy people,[38] but its impact on the prognosis of already developed CHD is less clear. Cross-sectional studies in both the United States and Europe disclose that both male and female workers high in job strain have a higher prevalence of CHD and a higher incidence of myocardial infarction than do those with low job strain.[39] Longitudinal studies also provide some support for this hypothesis. In a large, 1-year prospective study, both men and women in higher-strain jobs had significantly higher rates of myocardial infarction.[40] Johnson and associates[41] conducted a longitudinal study of 12,517 Swedish men over a 14-year period and found that low levels of control over one's work conditions were an independent risk factor for cardiovascular disease mortality. After adjusting the data for the influences of age, smoking, exercise, and social class, workers with low levels of control over their jobs had a relative risk of 1.83 (95 percent CI=1.19 to 2.82) for cardiovascular mortality. Workers with both low control over their work and low levels of social support had a relative risk of 2.62 (95 percent CI=1.27 to 5.61) for cardiovascular mortality.

SOCIODEMOGRAPHIC CHARACTERISTICS.

Health status in general is correlated with socioeconomic position, and persons of lower position have higher rates of CHD and a poorer prognosis after myocardial infarction. Lower socioeconomic status (whether assessed by education, occupation, or income) prospectively predisposes healthy people to an increased risk of CHD and CHD patients to a poorer prognosis. The decline in cardiovascular disease mortality over the past 30 years in the United States has been more pronounced among those of higher socioeconomic status, and the reasons for this are not clear. Because beneficial health habits (including not smoking and weight control) tend to be associated with

socioeconomic status, they may play a role. Poorer nutrition and difficulty obtaining medical care may contribute. In addition, exposure to stressful life events, greater job strain, lack of social support, and diminished sense of self-control may also contribute to the relationship between socioeconomic status and CHD. Finally, hostility and depression may be inversely correlated with social position. There are also complex racial and ethnic differences in cardiovascular disease that remain poorly understood. Because race and ethnicity tend to be confounded with differences in socioeconomic position, it has been difficult to isolate their effects on the incidence, prevalence, course, and outcome of CHD.

Acute Mental Stress

Sudden, acute mental stress has negative cardiovascular consequences. Cardiovascular mortality rises in the month immediately after the death of a loved one,[42] and the incidence of cardiac events also rises immediately after natural disasters and among civilians subjected to military attack. The direct cardiovascular effects of sudden, acute mental stress have been observed during daily life with continuous, ambulatory monitoring and with laboratory paradigms that induce stress experimentally. These laboratory paradigms involve performing tasks that are aversive, challenging, or demanding, such as public speaking or accomplishing difficult intellectual tasks under time pressure or in frustrating circumstances. Such stressors reliably increase heart rate, blood pressure, and myocardial oxygen demands. The effect of acute mental stress on the heart already damaged by preexisting CHD has been studied extensively. Recent work has employed relatively sensitive measures of myocardial ischemia, including regional myocardial perfusion (measured with positron emission tomography) and wall motion abnormalities (assessed with radionuclide ventriculography and echocardiography). Such stress can precipitate myocardial ischemia in 30 to 60 percent of CHD patients.[43]

Mental stress-induced ischemia occurs at lower heart rates and at a lower level of myocardial work than does exercise-induced ischemia, suggesting that decreases in myocardial perfusion may play a role in mental stress-induced ischemia. In a representative study, 59 percent of CHD patients (and 8 percent of controls) exhibited myocardial ischemia during periods of experimentally induced stress using radionuclide ventriculography to detect wall motion abnormalities indicative of ischemia.[44] One third of the CHD patients had a decrease of at least 5 percent in ejection fraction. Clinical characteristics, such as extent of CHD, did not differentiate between those who did and did not develop ischemia when stressed.[44] Such mental stress-induced ischemia is more likely to be "silent" or asymptomatic than is the ischemia induced by exercise. In the study just referred to, 83 percent of mental stress-induced ischemic episodes were asymptomatic.[44]

When patients with preexisting CHD are monitored during daily life, mental challenges, in the absence of strenuous physical exertion, are frequently accompanied by transient myocardial ischemia. Such ischemia has been observed, for example, while driving and during public speaking. Whereas most ischemic episodes during daily life do not appear to be precipitated by psychological or mental stress, a sizable minority (perhaps as

many as one fourth) are.[45] [46] Methodological difficulties however, make it difficult

to establish the relative frequency of such psychological stressor-induced episodes.

CHD patients who exhibit mental stress-induced ischemia during daily life or in the laboratory setting appear to be at increased risk of subsequent fatal and nonfatal cardiac events.[47] [48] This relationship persists after other risk factors (including age, left ventricular function, and prior myocardial infarction) have been taken into account.[47] Acute stress may promote ischemic heart disease in a number of ways. First, stress increases myocardial oxygen demands as a result of its hemodynamic effects. There may also be a decrease in coronary blood flow secondary to vasospasm, especially in more severely diseased vessels.[49] Stress also activates the sympathoadrenal medullary and pituitary-adrenocortical systems, with increases in circulating cortisol and catecholamines, which activate platelets and promote platelet aggregation and which increase cholesterol and decrease high-density lipoproteins. The net result of all these effects is to increase cardiac demand while at the same time decreasing coronary blood supply and to promote plaque rupture and increase thrombus formation.

Sudden Emotion

The work on anger, depression, and anxiety discussed earlier deals with the long-term consequences and sequelae of enduring, persistent emotions. There is also a body of work on the immediate and acute effects of sudden, intense, negative emotion on the cardiovascular system. Because much of this work focuses on its role in triggering arrhythmias and sudden cardiac death, it will be reviewed in the next section. It is important to note here, however, that mental activities leading to intense anger and, to a lesser degree, to anxiety are also potent triggers of myocardial ischemia.[50] [51] Thus, there is a twofold increase in the risk of myocardial infarction in the 2 hours after an episode of intense anger.[52] Because these intense, negative emotional states involve sympathetic arousal, they may act by triggering coronary vasospasm, rupture of atherosclerotic plaques, and increased platelet aggregation. Anger and hostility in particular have been associated with increased platelet adhesion.[53] Hostility is also associated with decreased parasympathetic arousal during ambulatory monitoring.[54] When anger is experimentally induced, patients scoring higher on hostility scales exhibit greater sympathetic nervous system-mediated cardiovascular responses than those who are less hostile.[55]

ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Increasing evidence links mentally stressful and emotionally powerful events with lethal arrhythmias and sudden cardiac death (SCD). Intense emotions such as anxiety and anger, and the events that arouse them, have been associated with both benign and lethal arrhythmias, including ventricular premature contractions, ventricular tachycardia, and ventricular fibrillation. This effect is most evident in hearts that are already

diseased, ischemic, or electrically unstable. There are at least three lines of investigation into the arrhythmogenic potential of stress, emotion, and psychiatric distress: epidemiologic surveys examining the role of life stress or psychiatric distress in predisposing to the subsequent development of lethal arrhythmias or SCD; psychophysiological experiments and anecdotal case reports of sudden, intense emotion or acute stress as immediate precipitants of arrhythmias or SCD; and investigations of the central nervous system's influence over cardiac rate and rhythm.

It has long been suspected that acutely stressful events and sudden, intense emotion can on occasion precipitate fatal arrhythmias and SCD. In 1971, Engel, using reliable, historical anecdotes, compiled a series of cases in which individuals were observed to die suddenly at the peak of intensely stressful and overwhelmingly emotional or traumatic experiences.[56] Reich and colleagues[57] subsequently conducted a careful, retrospective, psychiatric interview of patients hospitalized after a documented episode of ventricular tachycardia or ventricular fibrillation. They found that 21 percent had a major emotional disturbance or psychological trigger in the preceding 24 hours.[57] These included interpersonal conflicts, bereavement, public humiliation, marital separation, and business losses. Other studies produced comparable findings: one fourth to one half of SCD victims were thought to have died within minutes to hours after major psychological stress and acute emotional arousal.[58] [59] Although studies like these tend to suffer from problems of retrospective bias and selective recall, inadequate or absent control groups, and sampling bias, when taken together they nonetheless suggest that acute stress (perhaps in conjunction with other factors such as preexisting ischemic heart disease) can precipitate lethal arrhythmias and contribute to sudden cardiac death in a sizable fraction of cases.

Another line of research has examined the link between emotionally provocative daily stresses and arrhythmias. In healthy subjects, increases in ventricular ectopy occur during driving, public speaking, and stressful interviews. Among cardiac patients undergoing ambulatory monitoring, daily life stresses (but not major life change events) are statistically associated with ectopy. Lown[60] [61] and others have shown that experimentally induced psychological stress lowers the ventricular vulnerable period and the threshold for ventricular fibrillation and increases the frequency of ventricular ectopic beats in patients with preexisting ventricular arrhythmias. The acute, arrhythmogenic effect of stress-induced, sympathetic arousal has been demonstrated in patients with the long QT syndrome. Thus it is clear that stressful experiences and events can produce rhythm changes in both normal subjects and CHD patients. The clinical importance of this remains to be established, but the combination of severe, acute mental distress and a myocardium made vulnerable by virtue of preexisting disease can result in lethal arrhythmias and SCD.

Stressful events and the emotional distress that they evoke also have a less immediate and more prolonged effect in predisposing the individual to lethal arrhythmias and SCD over the long term. Thus, a number of studies report increases in life stress in the months preceding SCD. One prospective study of post-myocardial infarction patients found that a measure of life stress predicted sudden cardiac death in the following 3 years. However, for the most part this research is based on retrospective recall by a spouse or other informant and is subject to systematic reporting bias. In addition, many of these studies lack suitable control groups and/or employ problematic measures of life

stress.[62]

EPIDEMIOLOGICAL SURVEYS.

These suggest that some psychiatric disorders may also predispose to SCD. Anxiety disorders in particular appear to confer an increased risk of cardiac events, cardiac mortality, and SCD.[26] [63] [64] However, these studies are limited in number and generalizability. In one study, psychiatric distress during hospitalization for myocardial infarction predicted ventricular arrhythmias during ambulatory monitoring in the year after the infarct,[61] although a subsequent study by the same investigators failed to confirm these findings.[65] In retrospective work, female SCD victims with no prior history of cardiovascular disease were more likely to have had a psychiatric history than demographically matched, healthy controls.[66] Depression was the most common psychiatric diagnosis in these

studies, and hopelessness may be the most toxic element of depression in this regard.[26] However a number of possible confounds make this work difficult to interpret, and on balance the evidence at this time must be considered equivocal.

Sociocultural and sociodemographic factors may also play a role in SCD. The inverse relationship found between socioeconomic status and cardiac mortality in general is especially robust for SCD, although this may be confounded by an association between socioeconomic status and access to emergency medical care. Other work has disclosed that cardiac mortality is significantly higher immediately after, as compared with immediately before, an important religious holiday. There are also well-recognized, culture-specific syndromes in which sudden death follows ritualized events that have a powerful, culture-specific significance (such as "voodoo death").

The link between stress and arrhythmias has been explored in experimental animal work. When dogs are subject to aversive restraint and electric shock, there is a 49 to 66 percent decrease in the repetitive extrasystole threshold.[67] If a coronary artery occlusion is first produced experimentally, then the same stressful paradigm induces spontaneous ventricular fibrillation.[68] Similarly, when pigs with a coronary artery occlusion are placed in a stressful environment, there is a high incidence of spontaneous ventricular fibrillation.[69] Conditioning and adaptation to the stress reduce its arrhythmogenic effect.

NEURAL CONTROL OF RHYTHM.

A number of pathways mediate neural control of heart rate and rhythm. First, activation of the hypothalamic-adrenomedullary axis, with a resulting increase in circulating catecholamines, increases myocardial irritability and decreases the threshold for inducing ventricular fibrillation. Second, direct sympathetic innervation of the heart exerts a proarrhythmic effect, increasing ventricular ectopy and lowering the threshold

for inducing ventricular arrhythmias, especially in the heart with preexisting ischemic damage or electrical instability. This effect is moderated by an antiarrhythmic, protective effect exerted by the parasympathetic system through the vagus nerve. Animal work has revealed evidence of cortical and brain stem control of cardiac rhythm. Pathways run from the frontal cortex and hypothalamus to the brain stem nuclei controlling cardiovascular function. Stimulation of the lateral and posterior hypothalamus lowers the ventricular fibrillation threshold, and blockade of these corticofrontal pathways can raise the threshold. In humans, electrocardiographic (ECG) changes in rhythm and/or repolarization are seen in many patients suffering cerebrovascular accidents involving the cortex.[70]

Finally, extreme stress and acute psychological trauma can result in myocardial necrosis. In animal models, large quantities of catecholamines, either exogenously administered or stress induced, can result in myofibrillar degeneration and myocardial necrosis. Pathological examination reveals widespread calcification, the result of peroxidation of myocardial lipid membranes and blockage of the calcium channel pump. This same lesion has also been reported in humans who died suddenly at the peak of extreme psychic stress and trauma.[71]

PSYCHIATRIC AND BEHAVIORAL ASPECTS OF HYPERTENSION AND CONGESTIVE HEART FAILURE

Hypertension (see also Chap. 28)

Stress, conditioned learning, and autonomic arousal can all elevate blood pressure. Stimulation of brain sites with connections to the sympathetic nervous system elevates blood pressure, and many of these sites are in turn connected with higher centers involved in the perception of the environment. But the transient elevations of blood pressure that humans manifest in stressful and provocative situations may be unrelated to the persistent, sustained elevation that constitutes the disease of hypertension.

STRESS AND BLOOD PRESSURE.

Stressful environments and situations that are challenging or aversive transiently increase the blood pressure of both normotensive and hypertensive individuals. This has been demonstrated in field studies using ambulatory monitoring of blood pressure during daily life and in laboratory studies assessing blood pressure reactivity to a discrete stimulus or specific experimental stressor. Some individuals exhibit greater reactivity than others, consistently responding to psychological stressors with greater increases in blood pressure and heart rate, more vasoconstriction and catecholamine secretion, and a more prolonged recovery phase. These individual differences in cardiovascular reactivity emerge early in life and appear to be stable and enduring over time. Such physiological hyperreactivity has long been thought to predispose to the eventual development of hypertension and atherosclerosis, but the hypothesis remains unproven and the evidence is still inconclusive. Patients with clinically diagnosed hypertension have been reported to show greater blood pressure responses to behavioral challenge than normotensive individuals,[72] and some prospective studies suggest that greater cardiovascular reactivity to stress is associated with subsequent,

higher systolic and diastolic blood pressure.[73] [74] But the use of laboratory challenges is problematic, and it is not clear that transient blood pressure increases in response to such stressors are precursors of pathological, sustained hypertension.[75] A number of studies have examined whether normotensive individuals with a family history of hypertension show greater cardiovascular reactivity to experimental mental stressors than normotensive individuals without such a family history. The results of this work remain inconclusive and equivocal.[76]

In surveys examining the relationship between naturally occurring stress and blood pressure, major life stress has been associated with the onset or worsening of essential hypertension. Job strain in particular has been associated with an elevated prevalence and incidence of hypertension in men (although this is less clear in women), and the blood pressures of people in more stressful occupations tend to be higher than those in less stressful jobs. However, it appears that such chronic stress requires the simultaneous presence of other etiological factors (e.g., genetic endowment, dietary factors, or renal disease) to cause sustained hypertension. This situation may be analogous to that emerging from animal work. In animals predisposed to hypertension by genetic endowment or salt ingestion, repeated exposure to stress can lead to sustained hypertension.[77] But sustained hypertension does not appear to result in healthy animals without such predisposing factors.

PSYCHOLOGICAL INFLUENCES.

Anger and anxiety are accompanied by increases in peripheral vascular resistance and blood pressure. Anger has been thought to predispose to the development of essential hypertension, but this is controversial, particularly because much of the relevant research is either retrospective or cross-sectional.[78] Hostile individuals respond to provocation, conflict, and disagreement with larger increases in blood pressure than do people who are less hostile.[79] There have been reports of higher levels of anger and suppressed anger among hypertensive patients, but the direction, significance, and certainty of this association remains unclear. In a prospective study, increases in trait anger in women did predict increases in blood pressure over a 3-year period, after controlling for biological and genetic variables.[80] However, it does not appear that the prevalence of essential hypertension

is elevated in hostile, Type A individuals. Studies of minority populations tend to disclose a closer link between anger and hypertension than do studies of nonminorities.

Recent work has focused on the more-difficult-to-measure construct of repressed or*suppressed* emotion (particularly anger), and there are reports of an association between emotional inhibition and essential hypertension. A meta-analysis concluded that there does appear to be an association between*suppressed* anger and resting blood pressure.[81] In one prospective study, men who suppressed their feelings when faced with an interpersonal conflict were more likely to be hypertensive at follow-up.[82]

But, in general, this literature is still inconclusive, in part because of the difficulty in distinguishing transient angry states from anger as a stable, enduring personality trait.

Other studies have examined the role of anxiety. There is some evidence that chronically anxious persons develop greater increases in systolic blood pressure over the ensuing years[80] [83] and may also be at increased risk of developing essential hypertension.[80] [84] It has been suggested that psychological stressors tend to produce more anger in males and more anxiety in females.[79] Both of these affective states are accompanied by arousal of the sympathetic nervous system, and this suggests that chronically increased sympathetic tone is a final common pathway to elevated blood pressure.[80] Finally, the possible etiological role of depression has also been investigated. The prevalence of hypertension is reported to be higher in depressed community residents, depressed medical patients, and depressed psychiatric patients than in nondepressed comparison groups.

Based on this work, therapies such as relaxation training and meditative techniques, blood pressure and heart rate biofeedback, and psychotherapy incorporating relaxation training have all been employed to treat hypertension. Relaxation techniques and meditation apparently decrease blood pressure by lowering total peripheral resistance and vasoconstrictive tone.[85] One potential weakness of such therapies is that the treatment effect may decay upon discontinuation of active treatment. Some studies, however, have found that the beneficial effects of relaxation training (combined with pharmacotherapy) were still evident at long-term follow-up after the behavioral treatment ended.[86] In one study, relaxation training lowered blood pressure while the exercises were being practiced, but ambulatory blood pressure readings during daily life did not decline.[87] In sum, although these behavioral techniques are not very effective when used alone, they may provide some incremental benefit when added to the conventional antihypertensive regimen.[78] They may lead to modest reductions in blood pressure or enable the physician to employ lower doses of antihypertensive medication.[78] The latter outcome is of more than trivial significance because nonadherence to the antihypertensive medication regimen is very common and constitutes a major impediment to effective treatment.

SOCIOCULTURAL FACTORS.

Epidemiological and animal studies suggest a relationship between high blood pressure and sociocultural conditions. Essential hypertension tends to be less prevalent in societies with stronger cultural traditions and more widely held value systems and in those that are safer and more stable, than in societies with more disintegration, higher crime rates, and less stable social orders. In societies undergoing transition, conflict, or disintegration, blood pressures tend to rise over time, but many factors (e.g., changes in diet) may be contributing.[88] Individuals in more crowded and stressful living and working environments tend to show increased levels of catecholamines, increased cardiovascular reactivity, and higher average blood pressures. Animal studies seem to corroborate these findings: Mice subjected to crowding and exposed to threat from cats develop sustained high blood pressure.[89]

Congestive Heart Failure (see also Chap. 17)

The psychiatric and behavioral aspects of congestive heart failure (CHF) have only recently been subjected to scrutiny. It appears that the sorts of psychosocial factors that influence the course and outcome of CHD may also influence CHF. Stress and emotional distress have been linked to the onset or exacerbation of CHF, perhaps by increasing heart rate and blood pressure and/or by provoking myocardial ischemia in patients with preexisting, severe CHD. Emotional factors have been reported to precede admission in 49 percent of hospitalizations for CHF.[90] It has been suggested that left ventricular function is impaired during psychological stress,[91] and stress-induced heart failure has been described. In a study of patients with idiopathic cardiomyopathy, experimental psychological stress (mental arithmetic) was shown to induce changes in left ventricular diastolic function.[92]

Depression has received particular attention in CHF populations because it is chronic and debilitating, and because of its increased prevalence in the elderly. Freedland and coworkers[93] found that 17 percent of elderly patients hospitalized with CHF had current, major depression, and Havranek and colleagues[94] found a significantly higher prevalence of depressive symptoms in outpatients with CHF than in outpatients with hypertension. Others, however, have not found an elevated rate of depression in CHF. This research is complicated by difficulty in differentiating CHF from depressive disorders. The anorexia, fatigue, weakness, and insomnia (resulting from orthopnea and paroxysmal nocturnal dyspnea) accompanying CHF can be confused with the symptoms of depression, and the cardiac cachexia of end-stage CHF may also suggest severe depression. When CHF is severe enough to cause cerebral ischemia, then cognitive dysfunction, confusion, and delirium with psychotic symptoms may result. This may at times be difficult to distinguish from anxiety disorder and panic.

Social support appears to be an important moderator of the clinical course of CHF. Elderly women hospitalized with CHF who have no sources of emotional support have a more than threefold increase in the risk of cardiovascular events in the ensuing year than comparable patients with emotional support.[95] Elderly men without emotional support were not at increased risk. This work also underscored the importance of social ties, because patients without social ties had a more than twofold increase in cardiovascular events, even after taking emotional support into account.[95]

CARDIAC SYMPTOMS: CHEST PAIN AND PALPITATIONS (see also Chap. 3)

Chest Pain

Chest pain, the classic symptom of CHD, is a nonspecific, insensitive, and unreliable indicator of ischemia. Pain does not bear a fixed, one-to-one relationship to demonstrable pathology; many patients with chest pain have no heart disease, and ischemia and infarction are often asymptomatic. Approximately one fourth of myocardial infarctions are "silent," and 70 to 80 percent of out-of-hospital, ischemic episodes in CHD patients are asymptomatic. Conversely, no cardiac cause is found for the vast majority of complaints of chest pain. Even in patients with documented CHD, two thirds

of chest pain episodes occur in the absence of ST segment depression indicative of ischemia.[51]

In one study of primary care patients presenting with chest pain that led to a diagnostic work-up, a definite medical cause could be established in only 5 of 80 patients, at a cost of $4354 per diagnosis.[96] Even among patients undergoing coronary angiography for chest pain, 10 to 30 percent have minimal or no angiographic evidence of CHD.

The absence of demonstrable heart disease, however, does not mean that the patient's chest pain is either inconsequential or self-limited. Follow-up studies of chest pain patients with negative angiography and/or negative exercise stress testing reveal persistent distress and disability. Although rates of myocardial infarction and of cardiac morbidity and mortality remain low in these populations, these patients continue to exhibit elevated levels of symptoms, disability, and medical care utilization. At least half of these patients continue to report recurrent chest pain, the persistent belief that they have serious heart disease, and impaired functioning (at work, socially, and in daily activities) comparable to that of patients with myocardial infarction and angina.[97] [98]

Psychological, psychiatric, and behavioral factors mediate the relationship between CHD on the one hand and the resulting symptoms and disability on the other. Emotional distress is correlated with reports of chest pain in both CHD patients and in those free of cardiac disease.[12] Generalized psychological distress and body awareness is higher in patients with chest pain and normal coronary arteries than in those with CHD.[99] Mood and daily activities may account for as much of the variability in ambulatory patients' reports of chest pain as does ST depression indicative of ischemia.[51] The level of disability in patients with medically unexplained chest pain is strongly associated with the presence of psychiatric morbidity.[98]

Several psychological factors tend to differentiate chest pain patients with and without demonstrable cardiac disease. When those with normal angiography or normal stress tests are compared with those with positive tests, the former group is younger, more likely to be female, and has more psychological distress and a higher prevalence of diagnosable psychiatric disorder.[100] [101] Patients with medically unexplained chest pain have a higher than expected prevalence of depressive and anxiety disorder.[100] When compared with chest pain patients with positive findings on angiography, they have elevated rates of panic disorder (35 to 50 percent vs. 5 percent) and of major depressive disorder (approximately 35 to 40 percent vs. 5 to 8 percent). Of course, cardiac and psychiatric disorders are not mutually exclusive and not infrequently co-occur. Thus, 5 to 23 percent of patients with angiographic evidence of CHD also have panic disorder. These cases of psychiatric and cardiac comorbidity pose especially difficult diagnostic dilemmas, and it is in them that panic disorder is most likely to be overlooked. The chest pain seen in panic disorder is more likely to be atypical in clinical character and to be accompanied by palpitations, dizziness, paresthesias, and multiple

other somatic symptoms.

Palpitations

Palpitations are among the most common symptoms encountered in medical practice, reported by 16 percent of patients in a large survey of a primary care clinic.[102] Yet this subjective sensation corresponds very poorly to demonstrable abnormalities of cardiac rate or rhythm: Most palpitations are not accompanied by arrhythmias, and most arrhythmias are not perceived and reported as palpitations. When patients complaining of palpitations undergo 24-hour, ambulatory ECG monitoring, 39 to 85 percent manifest a rhythm disturbance (the vast majority being benign and clinically insignificant). Approximately three fourths of these patients with arrhythmias report at least one palpitation during 24 hours of monitoring, but in less than 15 percent of them do their symptoms coincide in time with the arrhythmia. Thus, accurate symptom reports occur in less than 10 percent of all patients being monitored.

Because palpitations are rarely accompanied by a clinically significant arrhythmia, it is not surprising that a high proportion of such patients either have a psychiatric cause for their symptom or no etiology can be established. In a careful survey of 190 patients presenting with palpitations, 31 percent were judged to have a psychiatric basis for their presenting symptom and no etiology could be established in an additional 16 percent.[103] The most common psychiatric cause of palpitations is panic disorder, which is found in more than a fourth of ambulatory medical patients complaining of palpitations. In one study, 31 percent of 229 such patients had panic disorder or panic attacks, and in another study, 28 percent of patients referred for 24-hour ambulatory ECG monitoring for palpitations met criteria for lifetime panic disorder and 19 percent met criteria for current panic disorder.[104] In the latter study, a high prevalence of depressive disorder was also reported.

Palpitations that have no demonstrable cardiac basis are nonetheless a persistent and disturbing problem for many patients. In a naturalistic, 1-year follow-up study, 75 percent of palpitation patients were found to have experienced recurrent symptoms, 19 percent reported impairment of their work performance, and 37 percent reported impairment in their role functioning at home.[103] In another study, 84 percent of palpitation patients remained symptomatic 6 months after initially presenting, and they had an elevated rate of medical utilization during the follow-up interval.[105]

Panic attacks and arrhythmias may be difficult to distinguish clinically. Both may present with palpitations, shortness of breath, and lightheadedness, and both not infrequently occur in the young and in those who are otherwise healthy. Frank syncope, however, is unusual in panic disorder and if there have been multiple episodes, panic attacks are more stereotyped and more consistent from episode to episode. Recurrent panic attacks tend to lead to agoraphobia, in which the patient first becomes apprehensive about, and then avoids, situations such as being left alone, trapped in large crowds, and journeying far from home. Conversely, to make matters more difficult, the sympathetic arousal that may accompany an arrhythmia (and other acute cardiac events such as pulmonary emboli, acute valvular dysfunction, and myocardial ischemia as well) may be experienced and reported by the patient as acute anxiety or panic rather than as a

cardiac event.

Delay and Denial of Cardiac Symptoms

Myocardial infarction patients commonly ignore, rationalize, or explicitly deny their symptoms, so that the average interval between the onset of symptoms and arrival in an emergency department is between 3 and 9 hours, depending on the study.[106] Delay before seeking medical attention for acute myocardial infarction is a serious problem, in part because a high proportion of myocardial infarction deaths occur soon after the event and in part because the newer therapies to preserve myocardial tissue (e.g., intravenous thrombolysis) require early intervention (see Chap. 36) . Delay is greater in women and in the elderly[107] [108] and (paradoxically) in those with a history of previous myocardial infarction.[107] From a practical standpoint, a crucial determinant of the length of delay is the interval before the myocardial infarction sufferer informs someone else of his or her symptoms; once the patient informs another person of his or her distress, help is usually rapidly obtained.

PSYCHIATRIC CARE OF THE CARDIAC PATIENT

Acute Care of the Hospitalized Patient

The onset or sudden progression of cardiac disease is a frightening and powerful emotional experience. Pain and physical discomfort, the specter of sudden death or invalidism, and the knowledge that one has a chronic and potentially lethal disease are all profoundly distressing. The initial reaction is almost always one of anxiety. Fears of premature, sudden death loom, and worries about physical, sexual, social, and occupational incapacity materialize and plague patients. They may become terrified of any physical activity or strong emotion, fearing that these can immediately trigger sudden death. As time passes and chronicity sets in, anxiety may be replaced with despondency and a heightened sense of physical vulnerability and of one's mortality. The individual may come to feel damaged or diminished. Patients may feel that their job performance and future livelihood have been irrevocably compromised, that they are old and decrepit, and that they face a restricted and empty future. They may feel guilty and blame themselves for falling ill, ascribing their plight to their failure to exercise enough, diet sufficiently, or maintain other "healthy" habits. All of this may lead to a clinically significant, depressive episode.

Several psychiatric and behavioral problems commonly arise in patients hospitalized for an acute cardiac event. In addition to the illness itself, the experience of hospitalization (and in particular admission to the coronary care or intensive care unit) can be frightening and stressful. Patients suddenly find themselves in an unfamiliar, alien, and terrifying world, surrounded by fearsome machines with blinking lights and beeping alarms, subjected to painful procedures and tests about which they know little and understand less, while their lives seemingly hang in the balance from moment to

moment. The daily routine and the food are alien, and patients feel cut off from family, friends, neighbors, and all that is familiar. Sustained sleep is next to impossible, and many are afraid to fall asleep, believing that the heart is in greater jeopardy during sleep. Their worst fears may seem to come true when they witness a cardiac arrest, or even the death, of another patient.

Hospitalized patients should be kept well informed about what is transpiring, what is being done medically for them, and why. They should be told what to expect before procedures are carried out; the functions of equipment should be explained; and the effects and (especially) side effects of medications should be described in advance. The patient should be reassured that anxiety is a normal and entirely appropriate reaction. Anxiolytics are often prescribed because anxiety is not only uncomfortable but its concomitant sympathetic arousal can be medically dangerous. Benzodiazepines are most commonly used for this purpose and should be prescribed on a regular, round-the-clock (rather than as needed) basis. In the elderly and in those with compromised liver function, the shorter-acting benzodiazepines (e.g., oxazepam or lorazepam) are preferred, because they are cleared primarily by the kidneys. The pharmacology of anxiolytics is discussed in the following section.

DELIRIUM.

This condition is not infrequent in hospitalized cardiac patients, especially after cardiac surgery. Delirium is characterized by an altered level of consciousness and a fluctuating state of confusion. The delirious patient is disoriented to time and place, has impaired memory and attention, develops delusional ideas, and experiences perceptual disturbances such as illusions or hallucinations. The sleep-wake cycle is disrupted, and the level of consciousness and arousal is disturbed, so that the patient may be either stuporous or obtunded, or hyperalert, restless, and agitated. The onset of delirium may be insidious (e.g., insomnia, mild nocturnal confusion, and restlessness) and go unnoticed by the staff, or it may be dramatic and abrupt. The patient begins to misinterpret sensory information (for instance mistaking a shadow for someone lurking in a corner of his or her room) and becomes suspicious and increasingly frightened. As confusion, fear, and excitement mount, frank paranoia sets in and the patient may become agitated, disruptive, belligerent, and out of control. This is a psychiatric emergency, because in their confusion and frenzy, delirious patients may harm themselves accidentally, fall, or pull out therapeutic life lines, catheters, and implanted devices. The incidence of delirium after cardiac surgery is as high as 30 percent in some studies,[109] typically following a lucid interval of 3 to 5 days after surgery. The risk factors for postcardiotomy delirium are advanced age (older than age 70 years); more extensive aortic atherosclerosis (large atheromas may be liberated by surgical manipulation of the aorta); a prior history of neurological disease, particularly preexisting cerebrovascular disease; a history of pulmonary disease, with the concomitant risks of poorer cerebral oxygenation and more hypoxia; and surgery that is more extensive and of longer duration.[110]

Treatment of Delirium.

This rests on rapid identification and correction of the underlying cause of the delirium,

medication for behavioral control if necessary, and supportive measures to provide comfort and safety. The etiological search is paramount. This means checking for cerebral hypoperfusion or hypoxia, acid-base disturbance, inadequate hydration, fluid and electrolyte imbalance, renal or hepatic failure, endocrine dysfunction, infection, and nutritional deficiency. Medications must be carefully reviewed because anticholinergics, narcotics, sedative-hypnotics, and H_2 blockers are common causes of delirium. Common offenders include cimetidine, digoxin, aminophylline, anticonvulsants, and all sedatives and hypnotics. Alcohol or drug withdrawal is a frequent cause, and the history must be searched carefully with this possibility in mind.

If the patient is agitated, combative, or confused enough to require behavioral control, high-potency antipsychotic drugs can be administered. Haloperidol has been widely used for this purpose and is safe and effective in critically ill patients, whether given orally or parenterally (including intravenously in emergency situations).[111] [112] Mild, delirious agitation is treated with 0.5 to 2 mg of haloperidol and moderate delirium with 5 to 10 mg; and the severely delirious patient can be given 10 or more mg of haloperidol. If the agitation persists unabated after 20 to 30 minutes, twice the original dose may be readministered. It has a minimal effect on heart rate, blood pressure, and respiration, and extrapyramidal effects are rare when it is administered intravenously. Parenteral droperidol is sometimes used. If excitement, hyperarousal, and motor agitation are especially prominent, the antipsychotic may be supplemented with a short-acting benzodiazepine such as lorazepam. Antipsychotic agents are discussed in the following section.

Supportive measures should be undertaken to calm, orient, and comfort the delirious patient. He or she should be reoriented frequently by the staff, and a clock and calendar should be prominently displayed to aid in this process. It is helpful to preserve as much of a day-night cycle as is feasible considering the hospital routine and to limit awakenings by staff during the night as much as possible. Family visitation should be encouraged because it is helpful in reassuring and calming the patient and in reducing paranoia. Familiar objects, such as family photographs, should be prominently displayed and plainly visible. Staff need to continually reintroduce themselves, educate the patient about what they are doing, and repeatedly explain the situation.

Physical restraint should be employed whenever necessary to prevent self-harm or harm to the staff.

Convalescence and Recovery

In the weeks after hospital discharge, depression is common, although it varies widely in severity. It is often self-limited, gradually diminishing as the patient resumes his or her old activities and as the specter of the acute episode and the hospitalization recede into the past. Frank discussion of the patient's concerns and educational information about common myths and fears are helpful. Lingering anxiety may have led patients to avoid

activities or situations that they fear will provoke symptoms, cardiac events, or even sudden death. Early, progressive mobilization is the best antidote to anxiety and depression. The patient may be shocked and dismayed at the degree of exhaustion produced by even mild exertion, and although this easy fatigability is actually the result of deconditioning, it is mistakenly interpreted as evidence of permanent cardiac damage. As a result, exercise may be assiduously avoided, which only exacerbates the problem.

Patients are often apprehensive about returning to work because of the stress is engenders. Many believe that strong emotions can be lethal and try to protect themselves by assiduously avoiding all situations or activities that arouse strong feelings, such as sexual activity or watching sports on television. Sexual activity in particular is diminished, and sexual dysfunction is common in both women and men with cardiac disease.[113] Such concerns should be elicited by the physician and then discussed frankly and openly. Recommendations should be as specific as possible about which activities are prescribed and proscribed; simply saying "use your judgment" or "do it in moderation" is not helpful.[114] Group meetings of cardiac patients (such as post-myocardial infarction groups) to share common concerns, provide support, obtain educational information, and guide the progressive resumption of activities can be helpful in recuperation.

If depression lasts more than several weeks and is profound enough to meet diagnostic criteria for major depressive disorder, as happens in one third of patients in the year after myocardial infarction,[10] aggressive therapy is indicated. If left untreated, depression imposes a serious psychosocial burden, medical rehabilitation and recovery are impeded, and the depression itself is likely to become chronic. More than three fourths of post-myocardial infarction patients with major depressive disorder remain depressed 6 to 12 months later.[115] [116] It is thought that successful treatment (psychopharmacological and/or psychosocial) of depression in post-myocardial infarction patients will reduce subsequent cardiac morbidity and mortality, and large-scale, multiinstitutional intervention trials (e.g., Sertraline Antidepressant Heart Attack Randomized Trial [SADHART], Enhancing Recovery in Coronary Heart Disease [ENRICHD]) are now underway to test this hypothesis. The pharmacotherapy of depression is discussed in the following section.

Over the long term, some cardiac patients adopt a persistent coping style that is maladaptive and dysfunctional.[114] They may ignore the episode and deny their illness entirely, maintaining that nothing serious has happened at all. They may refuse to acknowledge any limitations or adhere to a therapeutic regimen, and generally overdo things. Alternatively, they may capitulate completely to their illness and retreat into unwarranted invalidism, becoming "cardiac cripples" who are preoccupied with their health, terrified by every benign twinge or cramp, and living a life of psychological invalidism and disability. Each of these profoundly maladaptive coping patterns deserves psychiatric attention.

Primary Prevention and Rehabilitation

Primary prevention programs attempt to modify behavioral risk factors in individuals who

have not yet manifested significant disease, with the aim of preventing cardiac events from occurring or of delaying their onset. Secondary prevention programs focus on similar factors in patients who already have clinical evidence of disease, with the aim of retarding its progression. These psychosocial, educational, and behavioral programs may include many different components. Most programs assist patients to modify lifestyle behavioral risk factors, including smoking cessation, curtailing alcohol abuse, lowering saturated fat intake, and controlling weight. Almost all emphasize a formal program of graduated, progressive, aerobic exercise. Many programs include educational counseling about CHD, its risk factors and its treatment. Many also attempt to modify hostility or Type A behavior with cognitive/behavioral therapy.

Rehabilitation programs for patients who have sustained a cardiac event often aim to promote psychosocial adjustment and may include psychotherapy (see Chap. 39) . Most programs include stress management and relaxation training, in which patients are taught to identify social and environmental stressors, improve their use of social supports, and develop new skills for managing stressful situations and the disturbing effects that they evoke. Relaxation training generally combines elements of progressive muscle relaxation, diaphragmatic breathing, and focused attention. Patients are taught these techniques and are then encouraged to practice them regularly.

It is difficult to summarize the effectiveness of these heterogeneous psychotherapeutic, psychosocial, and behavioral programs because they vary so widely in quality, content, design, and intensity. Many intervention trials are flawed by small sample size, high dropout rates, insufficient long-term follow-up, and inadequate comparison or control groups. In addition, as standard cardiac care improves so substantially, it becomes more difficult to demonstrate the incremental benefit of these programs in terms of hard cardiac endpoints.[117] Trials reporting positive benefits have generally not been replicated. Nonetheless, it generally appears that when added to standard medical care, many of these programs are more effective than usual care alone in reducing psychiatric distress and morbidity, and in improving quality of life, disability status, and role functioning, and probably in reducing cardiac morbidity and mortality as well.[118] [119] [120] [121] [122]

A careful meta-analysis of 23 randomized, controlled intervention trials involving over 2000 patients, disclosed that when added to standard cardiac care, psychosocial interventions resulted in significant reductions in systolic blood pressure, heart rate, and serum cholesterol, and significantly lower rates of cardiac mortality and cardiac morbidity. These benefits were most evident in the 2 years after the intervention and became less evident thereafter.[118] Two meta-analyses of psychoeducational therapies found favorable effects on cardiac mortality, systolic blood pressure, and on exercise and diet.[123] [124] Finally a recent, thorough meta-analysis of 37 programs with varying components of psychoeducation and stress management found that they resulted in a 34 percent reduction in cardiac mortality and a 29 percent reduction in recurrent myocardial infarction, as well as significant effects on blood pressure and weight.[125]

PSYCHOSOCIAL INTERVENTIONS.

There is a growing interest in supportive, psychosocial interventions designed

particularly to improve social support and lessen social isolation, often in combination with counseling or other treatment for depression and anxiety. In one study of 435 post-myocardial infarction patients randomized to a nursing-based psychosocial intervention or to medical care as usual, 1-year cardiac mortality was half as high in the intervention group[126] and the incidence of recurrent myocardial infarction was significantly lower at 7-year follow-up.[127] On the other hand, three large, randomized trials of multimodal, case management interventions conducted by nurses or health visitors[128] [129] [130] failed to demonstrate a clear reduction in depression or psychological dysphoria. Two of these studies found no effect on cardiac disease outcomes,[128] [129] and one study showed a marginally significant,*negative* impact of the intervention on cardiac outcomes in women.[130]

RELAXATION TRAINING.

Stress management techniques and relaxation therapy have been found to improve cardiac outcomes in some studies. Various combinations of these techniques have been shown to decrease the incidence and frequency of anginal episodes,[131] fatal and nonfatal cardiac events,[126] and disability and role impairment[132] and to improve quality of life. Relaxation training alone has been found to decrease fatal and nonfatal myocardial infarction[133] and to

improve cardiac function.[134] In one large-scale study, a 4-month program of stress management was compared with exercise training and usual care in patients with documented CHD. At follow-up an average of 3 years later, the former group had a lower incidence of cardiac events and fewer ischemic episodes.[135] On the contrary, other studies disclose either a very limited and transient benefit (i.e., seen only in the first month after the intervention) or no benefit at all in terms of anginal frequency, cardiac events, or reduction in blood pressure.[129] [136] Jones and West, for example, randomized over 2000 patients with a recent myocardial infarction to a psychosocial treatment or to care as usual and found no significant differences between the groups in cardiac mortality after 1 year. [128] In summarizing this outcome literature, it appears that these psychosocial and stress reduction programs, when they are focused, well designed, and added to standard cardiac care, do decrease psychiatric distress and improve health-related quality of life and role functioning. They probably also decrease cardiac morbidity and/or mortality, but this has not yet been definitively established.

PSYCHOLOGICAL TREATMENT OF HOSTILITY AND TYPE A BEHAVIOR.

Several intervention trials have specifically assessed psychological treatments to modify hostility and Type A behavior. These treatment programs are manualized and protocol driven. They aim to enhance the awareness and effective management of anger and other negative feelings and thoughts and to improve problem solving and communications skills. A meta-analysis of 18 such controlled trials concluded that treatment had a moderately large effect size in modifying anger, hostility, impatience,

and time urgency.[137] The authors also found a marginally significant effect on cardiac events and mortality in the year after treatment. In a recent, controlled, randomized trial of an eight-session workshop to reduce hostility, the intervention was found to significantly decrease hostility at 2-month follow-up.[140] In the Recurrent Coronary Prevention Project (RCPP), the addition of Type A behavior counseling to a standard psychosocial rehabilitation program of 862 post-myocardial infarction patients produced a significant reduction in Type A behavior and a 44 percent reduction in nonfatal myocardial infarction and cardiac death at 3-year follow-up.[138] The effect on nonfatal myocardial infarction persisted 4½years after the intervention.[139]

Graduated, aerobic exercise training is another keystone of many cardiac rehabilitation programs. Such training improves exercise capacity and lowers blood pressure and body weight, as well as improving subjective, health-related quality of life. It is less clear, however whether these risk factor reductions in turn lead to significant differences in cardiac outcomes.[120] This may be because a sizable fraction of patients do not continue to adhere to the exercise regimen over long periods of time after the program ends.

PSYCHOPHARMACOLOGY IN THE CARDIAC PATIENT

Cardiovascular Aspects of Psychotropic Agents

Antidepressants (Table 70-1)

SEROTONIN REUPTAKE INHIBITORS (SRIs).

The SRIs have superseded the tricyclic antidepressants (TCAs) as the first-line agents for treating the cardiac patient with major depressive disorder. Their efficacy is comparable to that of

TABLE 70-1 -- ANTIDEPRESSANTS

AGENT	STARTING DOSE	MAXIMUM DOSE	SIDE EFFECTS	CARDIOVASCULAR EFFECTS	
Serotonin Reuptake Inhibitors					
Sertraline	12.5-25 mg/d	200 mg/d	Sexual dysfunctionNausea, diarrheaHeadache		Benign bradycardia
Fluoxetine	5-10 mg/d	80 mg/d	Anxiety, agitation, insomniaSomnolence, sedation		
Paroxetine	10 mg/d	50 mg/d	Tremor		
Tricyclics					

Amitriptyline	10-25 mg h.s.	300 mg/d	Sedation, somnolence	Dry mouthBlurry vision	Increase QT, PR, QRS intervals Decrease T wave amplitude
Imipramine	10-25 mg h.s.	300 mg/d		Constipation Urinary retention	Tachycardia Arrhythmias
Nortriptyline	10 mg/d	150 mg/d	Anxiety, insomnia	Postural hypotensionWeight gain	Postural hypotension
Desipramine	25 mg/d	300 mg/d			
Psychostimulants					
Methylphenidate	2.5 mg b.i.d.	20 mg b.i.d.	Anxiety, agitationInsomniaAnorexiaParanoia		Tachycardia (mild)Hypertension (mild)
Other Agents					
Bupropion	75 mg/d	150 mg t.i.d.	Anorexia, nauseaAnxiety, agitationInsomniaSeizures		
Venlafaxine	12.5 mg b.i.d.	125 mg t.i.d.	NauseaHeadacheSexual dysfunctionAnxiety, insomniaSomnolenceDizziness		Hypertension (dose related)
Trazadone	25 mg/d	600 mg/d	SedationNauseaHeadachePriapism (rare)		Postural hypotensionArrhythmias (rare)
Mirtazapine	15 mg q.h.s.	45 mg q.h.s.	Sedation, somnolenceWeight gainDry mouth, anticholinergic effectsDizzinessAgranulocytosis (rare)		

the older TCAs, they are better tolerated and safer in overdose, and they have less pharmacological action on the heart. The serotonergic antidepressants have little anticholinergic, antihistaminic, or noradrenergic activity. However, because they have become available only relatively recently, there has been less systematic study of their efficacy and safety in CHD populations and in the elderly, and few randomized, controlled trials in these populations have been completed. Although more extensive investigation is still necessary, the data thus far suggest that the SRIs have minimal cardiovascular effects and a large margin of safety in treating patients with even very severe heart disease.[141]

In healthy patients, the SRIs have no adverse effects on cardiac contractility or conduction and there is no evidence of cardiotoxicity in overdose. In cardiac populations, they do not appear to cause significant electrocardiographic or blood pressure changes, although they can slow heart rate. Only very rarely do they produce a clinically significant degree of sinus bradycardia. The SRIs have the potential to interact with a number of medications used to treat cardiac disease. They inhibit hepatic cytochrome P450 isoenzymes,[142] a series of isoenzymes involved in the oxidative metabolism of many drugs. These include lipophilic beta blockers (e.g., metoprolol and propranolol), calcium channel blockers, type IC antiarrhythmics, angiotensin-converting enzyme inhibitors, anticonvulsants, antihistamines, benzodiazepines, TCAs, codeine, and warfarin. The SRIs therefore can raise the blood levels of these other agents when co-administered. However, although these interactions can be demonstrated in vitro, their significance in clinical practice is still unclear. Caution should be exercised when giving SRIs to patients on these medications, and in particular the prothrombin time of patients receiving both warfarin and an SRI should be monitored closely. Because the SRIs are highly protein bound, they may displace other protein-bound drugs when co-administered, thereby increasing their bioavailability. This interaction can occur with warfarin and digitoxin, but it does not appear to be clinically significant in magnitude.

TRICYCLIC ANTIDEPRESSANTS (TCAs).

TCAs were previously the mainstay of antidepressant pharmacotherapy and remain effective agents that are still widely employed. However, their multiple cardiovascular side effects and their potential lethality in overdose are disadvantages in patients with cardiac disease. TCAs act on adrenergic neurons in the central nervous system, and in the periphery have anticholinergic properties, have quinidine-like effects, and produce alpha-adrenergic receptor blockade. They affect heart rate, rhythm, conduction, contractility, and blood pressure. Accordingly, these agents are not generally used in the presence of rhythm or conduction disturbances, severe congestive heart failure, or within 4 to 6 weeks of a myocardial infarction. A guiding principle when using them in the elderly and those with cardiac disease is to initiate treatment with low doses and to titrate the dosage upward slowly and carefully. Among the TCAs, the tertiary amines (e.g., imipramine and amitriptyline) are associated with more side effects, and the secondary amines (e.g., nortriptyline) have a preferable side-effect profile in cardiac patients.[143]

The TCAs are type IA antiarrhythmic agents (see Chap. 23) and accordingly depress cardiac conduction, decrease ventricular irritability, and suppress ectopic activity. They slow atrial and ventricular depolarization; increase the QT, PR, and QRS intervals; and decrease T wave amplitude. In the absence of preexisting conduction abnormalities, this action is unlikely to be clinically significant at therapeutic doses. However, second-degree heart block, sick sinus syndrome, bundle branch block, a prolonged QT interval, and the concurrent administration of antiarrhythmic agents are all considered contraindications to their use. In contrast to this antiarrhythmic effect, the TCAs can on occasion be arrhythmogenic. This is probably due to their prolongation of the QT interval and/or an increase in myocardial norepinephrine resulting from their peripheral inhibition of norepinephrine reuptake. Although the most common arrhythmias are atrial

or ventricular premature beats, these may give way to more malignant ventricular arrhythmias. These toxic, proarrhythmic effects are seen primarily in overdose, and at therapeutic levels they are rare and more likely in those with preexisting CHD, a prolonged QT interval, electrical instability, or a recent myocardial infarction.[144] At toxic levels, in overdose, any type of arrhythmia may be seen. These may last for 3 to 4 days after the ingestion. The TCAs also elevate heart rate 5 to 20 beats per minute, as a result of their anticholinergic blockade. Although this does not pose a problem in relatively healthy patients, it may be a consideration in those with heart disease.

TCAs produce postural hypotension in up to 20 percent of patients. In the elderly, in whom orthostatic hypotension can produce cerebral hypoperfusion and lead to falls and fractures, this side effect can be crucial. In these patients, blood pressure should be checked immediately after standing up when treatment is initiated and after increments in dosage. Elderly patients should be advised to stand up slowly after lying or sitting for prolonged periods. The magnitude of this effect is related to the magnitude of pretreatment orthostatic hypotension,[145] and it is more likely to be clinically significant in patients with CHF, impaired left ventricular function, volume depletion, or in patients who are taking antihypertensive medications.[146] Orthostatic hypotension is less likely to be a problem with nortriptyline than with amitriptyline or imipramine. Caution is indicated when treating patients with poor ejection fractions because in animal studies, TCAs exert a depressant effect on myocardial contractility. However, in humans this effect is evident only at toxic doses and only rarely aggravates CHF.[147]

TCAs are generally not prescribed within 4 to 6 weeks after an uncomplicated, acute myocardial infarction. However, the decision of whether or when to initiate treatment with these agents after a myocardial infarction must be made on an individual basis, weighing the particular indications and contraindications (CHF, arrhythmias, and conduction abnormalities) on a case-by-case basis.

OTHER ANTIDEPRESSANTS.

Psychostimulants such as*methylphenidate* and*dextroamphetamine* are used to treat depression in medically compromised and elderly patients.[148] These agents tend to be used when depression is life threatening and immediate treatment response is crucial (because they have a rapid onset of action) and in depressions with very prominent anergia and apathy. Although there is considerable clinical support for their use, there are few rigorously controlled trials demonstrating their sustained efficacy over time. Serious cardiovascular side effects such as tachycardia, hypertension, and arrhythmias are relatively rare, but caution must be exercised when administering these medications to patients with significant hypertension, tachycardia, or ventricular ectopy, and blood pressure and heart rate should be monitored.

Bupropion, a nontricyclic antidepressant that acts on both the dopamine and norepinephrine systems, causes less hypotension than the TCAs; does not affect cardiac rate, conduction, or contractility; and is safely used in patients with cardiac disease.[149] It does not exacerbate ventricular arrhythmias or conduction block in patients with these conditions.[149] An increased incidence of seizures is seen at higher

doses, and bupropion may occasionally elevate blood pressure.

Venlafaxine affects the reuptake of both serotonin and norepinephrine. It appears to have very few cardiovascular actions and no effect on the electrocardiogram.[150] At higher doses, however, venlafaxine has been associated with elevation in blood pressure.[151] Unlike the SRIs, it does not inhibit

P450 cytochrome isoenzymes and may therefore be useful in patients on cardiac medications.

Trazodone, a triazolopyridine antidepressant, is often used in low doses as a hypnotic. Cardiovascular complications from trazodone are very rare. It has few, if any, antiarrhythmic properties, although it has very rarely been associated with heart block and ventricular arrhythmias.[152] Because of its weak alpha-adrenergic blockade, it may also produce orthostatic hypotension.

Mirtazapine is a tetracyclic antidepressant with a complex mechanism of action. It has not been studied in patients with cardiovascular disease, but in noncardiac populations it does not affect blood pressure significantly and does not affect cardiac conduction.[153] It has no anticholinergic activity, but it may increase heart rate slightly.[153]

Neuroleptics (Table 70-2)

Neuroleptic or antipsychotic drugs are used in the treatment of schizophrenia, organic psychoses, and mood disorders with psychotic features. They are also widely used in geriatric patients for agitation, confusion, excitement, and behavioral dyscontrol. In general, neuroleptic drugs affect cardiac conduction and rhythm and produce hypotension. They have alpha-adrenergic blocking and quinidine-like properties, along with anticholinergic activity. They can produce prolongation of the PR and QT intervals, ST segment depression, T wave changes, ventricular arrhythmias, and heart block. Although the quinidine-like effects of the neuroleptics are usually negligible, they can become significant in patients already taking type I antiarrhythmics or in those with hypokalemia or with clinically significant conduction delays.[154] When administering a low-potency neuroleptic along with an antiarrhythmic, the ECG should be monitored for conduction delays. The lower-potency neuroleptics produce more orthostatic hypotension (by means of alpha-adrenergic blockade) and tachycardia (by means of anticholinergic action), and this is of particular concern in the elderly and in the acute myocardial infarction patient.[155] Orthostasis is more likely to be a problem when these agents are combined with antihypertensives.

The higher-potency neuroleptic agents, such as haloperidol and the piperazine phenothiazines, produce less of these effects and are therefore preferred in the presence of significant cardiac disease (especially conduction problems) and after cardiac surgery.[111] Haloperidol in particular has been frequently used with safety and

efficacy in severely ill cardiac patients. Oral haloperidol does not significantly affect the ECG, and intravenous haloperidol is used in acute emergencies such as agitated deliria. Intravenous administration can on rare occasions cause torsades de pointes, and the QT interval should therefore be monitored during aggressive, intravenous haloperidol therapy.[156]

Experience with the newer, "atypical" antipsychotics in cardiac patients is much more limited but suggests a generally similar profile. Clozapine can cause tachycardia and orthostatic hypotension and has significant anticholinergic activity (along with a risk of myelosuppression and agranulocytosis). There are recent reports of an infrequent association of clozapine with ECG changes, arrhythmias, myocarditis, and congestive heart failure.[157] [157A] Olanzapine produces mild orthostatic hypotension but has little effect on the electrocardiogram. Sertindole prolongs the QT interval and may therefore pose a problem in cardiac patients. Risperidone produces hypotension and has a quinidine-like effect, prolonging the QT interval, although this may occur only in overdose.

Mood Stabilizers (Table 70-3)

LITHIUM.

Lithium exerts minimal cardiotoxicity at therapeutic doses in most patients and can be used safely in cardiac disease if initiated at a low dose, increased gradually, and monitored carefully. Benign, reversible T wave changes (including inversion and flattening) are common with lithium administration and are not clinically significant. Clinically significant cardiovascular side effects of lithium are very rare; they may include sinus node dysfunction and increases in ventricular irritability. The major toxic effects of lithium are neural (confusion, sedation), and the primary concern in cardiac patients is lithium toxicity resulting from decreased renal clearance or hypovolemia. This is of concern in patients with congestive heart failure, and it is exacerbated by their restricted sodium intake and the use of diuretics. Sodium depletion decreases renal clearance of lithium. In the kidney, lithium is filtered out at

TABLE 70-2 -- NEUROLEPTIC (ANTIPSYCHOTIC) AGENTS

AGENT	STARTING DOSE	MAXIMUM DOSE	SIDE EFFECTS
Haloperidol	0.5 mg/d	>10 mg q.i.d.	Akathisia
			Dystonia
			Parkinsonism
			Tardive dyskinesiaNeuroleptic malignant syndromeRashAnticholinergic effects
Clozapine	12.5 mg q.h.s. or b.i.d.	200-300 mg t.i.d.	DizzinessSomnolenceWeight gainHypersalivationSeizuresAgranulocytosisAnticholinergic effects

Olanzapine	5 mg/d	20 mg/d	SedationConstipationWeight gainSeizuresAkathisiaExtrapyramidal symptoms
Risperidone	0.25-0.5 mg/d	>6 mg/d	Somnolence Fatigue Nausea, diarrheaWeight gainSexual dysfunctionNasal congestionExtrapyramidal symptoms

TABLE 70-3 -- MOOD STABILIZERS

AGENT	STARTING DOSE	MAXIMUM DOSE	SIDE EFFECTS
Lithium	300 mg b.i.d.	2100 mg/d(titrate against serum concentration)	Drowsiness, sedationConfusionNausea, diarrheaMetallic tastePolyuria/polydipsiaTremorHypothyroidism
Carbamazepine	100 mg b.i.d.	1600 mg/d	DizzinessDrowsiness, sedationAtaxiaDiplopia, blurred visionRashNauseaLeukopeniaHyponatremia
Valproate	250 mg b.i.d.-t.i.d.	3500 mg/d-4500 mg/d	Nausea, vomiting, anorexiaSedationConfusionWeight gainTremor

the glomerulus and then reabsorbed in the proximal tubules. Sodium depletion, such as with diuretics, causes an increased proximal reabsorption of sodium, and lithium is reabsorbed more efficiently at the same time. A given lithium dose thus results in a higher blood lithium level. Lithium may still be administered to the patient on diuretics, but lithium levels must be monitored and lithium dosage may need to be reduced as much as 25 to 50 percent. The elderly also require lower lithium doses because of a decline in the glomerular filtration rate. On rare occasion, lithium may worsen arrhythmias in patients with sinus node dysfunction.[158]

ANTICONVULSANTS.

These drugs are increasingly prescribed to stabilize the mood of patients with bipolar disorder (manic-depressive illness). Their use in cardiac patients has not yet been systematically studied. It is known that carbamazepine has quinidine-like effects and can aggravate heart block,[159] and it may also exacerbate CHF.[160] Carbamazepine can also produce hyponatremia, and this effect is potentiated by other factors that cause hyponatremia, such as diuretics and CHF.[161] Valproate, although not yet studied widely

in cardiac populations, does not appear to have adverse cardiac effects. It can, however, lower the platelet count, decrease fibrinogen levels, and increase the prothrombin time.

Benzodiazepines (Table 70-4)

Benzodiazepines have anxiolytic, sedative, anticonvulsant, and muscle relaxant properties. Anxiety disorders, especially panic disorder and generalized anxiety disorder, are prevalent in patients with cardiac disease. Panic disorder is treated either with a benzodiazepine with antipanic efficacy (such as clonazepam, lorazepam, or alprazolam) or an antidepressant. Generalized anxiety disorder can also be treated with benzodiazepines, buspirone, or SRIs. Hospitalized cardiac patients are acutely anxious; and because anxiety itself can threaten cardiac status, benzodiazepines are widely and almost routinely used in coronary care units. They can decrease respiratory drive in patients with chronic obstructive pulmonary disease and chronic hypercapnia but are free of cardiac side effects and can safely be used in seriously ill cardiac patients, even in the period immediately after myocardial infarction.

Benzodiazepines with longer half-lives (e.g., diazepam, flurazepam, chlordiazepoxide) accumulate in the body with repeated administration. A steady state is reached very slowly, and clearance of the drug after discontinuation is prolonged. Intramuscular absorption of these agents, other than lorazepam and midazolam, is erratic and unpredictable. The most prominent side effects are sedation, fatigue, memory complaints, and psychomotor impairment. In hospitalized patients and in the elderly, these effects can result in oversedation or delirium. Patients with preexisting cognitive impairment or organic brain syndromes often react to benzodiazepines with further confusion, increased memory loss, behavioral disinhibition, and belligerence. Ambulatory patients should be cautioned about driving and participating in activities requiring a high degree of alertness.

TABLE 70-4 -- BENZODIAZEPINES

AGENT	STARTING DOSE	MAXIMUM DOSE	SIDE EFFECTS	CARDIOVASCULAR EFFECTS
Short-Acting Benzodiazepines				
Oxazepam	10 mg b.i.d.	120 mg/d	Sedation, drowsiness	
Lorazepam	0.5 mg b.i.d.	10 mg/d	Slowed psychomotor function	

			Exacerbation of underlying cognitive impairment	
Long-Acting Benzodiazepines				
Ataxia/falls in elderly				
Diazepam	1-2 mg q.d.	60 mg/d	Respiratory depression	
Chlordiazepoxide	5 mg q.d.	100 mg/d	Tolerance/addiction	
Clonazepam	0.25 mg/d	6 mg/d	Amnesia	
Alprazolam	0.25 mg b.i.d.	8 mg/d		

Psychiatric Side Effects of Cardiovascular Drugs

ANTIHYPERTENSIVES.

Many antihypertensive agents have central nervous system side effects.[162] Depression is not uncommon with methyldopa, clonidine, reserpine, and guanethidine. Therefore, calcium channel blockers and angiotensin-converting enzyme inhibitors may be preferable in the hypertensive patient with a history of depression. Abrupt discontinuation of antihypertensive agents can cause anxiety, agitation, and vivid dreams.[163] Clonidine and methyldopa are relatively common causes of insomnia.

BETA-ADRENERGIC RECEPTOR ANTAGONISTS.

There is a long-standing clinical impression that beta blockers can cause depression. Although there are reports that patients maintained on these agents have an elevated rate of concurrent antidepressant pharmacotherapy,[164] other studies have failed to find an association between beta blocker use and depression.[165] Some of the confusion may stem from the fact that these agents cause sedation, lethargy, fatigue, and impotence, side effects that overlap with, and may be confused with, depression. Depression may be more likely in those with a past history or family history of depression, with the more lipophilic agents (e.g., propranolol, metoprolol),[162] and when using higher doses. Beta blockers are also occasionally the cause of vivid dreams and nightmares, hallucinations, and other psychotic symptoms. These tend to occur more often in the elderly.

CALCIUM CHANNEL BLOCKERS.

In general, calcium channel blockers do not have prominent psychiatric side effects. There are isolated case reports of depression associated with their administration, but

this has not yet been demonstrated conclusively.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS.

These agents appear to have relatively few central nervous system side effects, although they may, on rare occasion, induce depression.

ANTIARRHYTHMICS.

Lidocaine is a relatively common cause of anxiety, confusion, disorientation, hallucinations, and central nervous system excitement. Confusion, hallucinations, and delirium have also been reported with high doses of quinidine. Procainamide may cause depression, hallucinations, and other psychotic symptoms.

DIGITALIS.

Anxiety, depression, visual illusions (e.g., yellow halos), and confusion may be the first signs of digitalis toxicity, but psychiatric symptoms may emerge at therapeutic serum levels as well.[166]

DIURETICS.

Diuretics can induce cognitive mental status changes as a result of their producing electrolyte imbalances (e.g., hyponatremia) or hypovolemia, and a secondary mood disorder may also occur, often characterized by anorexia, lethargy, and weakness.

Interactions of Psychotropic and Cardiac Drugs (Table 70-5)

Because many cardiac and psychotropic agents lower blood pressure, additive hypotensive effects are not uncommon, as for example between the TCAs and antihypertensives. Many psychotropic agents slow conduction and prolong the PR, QRS, and QT intervals, and synergistic effects can occur when they are used in conjunction with antiarrhythmic medications, resulting in heart block or the long QT syndrome. There are several interactions between the TCAs and cardiac medications. The TCAs interfere with neuronal reuptake of clonidine and guanethidine and thus antagonize their antihypertensive action. They may potentiate the antihypertensive action of prazosin. And the dry mouth induced by TCAs may hinder the absorption of sublingual nitrates.

Serotonin reuptake inhibitors (e.g., fluoxetine, sertraline,

TABLE 70-5 -- INTERACTIONS OF PSYCHOTROPIC AND CARDIAC DRUGS

MEDICATION	EFFECT ON CARDIAC AGENT
Interactions Involving Tricyclic Antidepressants	

Type IA antiarrhythmics	Potentiate delay in cardiac conduction; heart block
Antihypertensives: guanethidine, clonidine, reserpine	Antagonize antihypertensive effect; potentiate orthostatic hypotension
Sublingual nitrates	Oral absorption hindered by dry mouth
Alpha-adrenergic blocking agents	Potentiate antihypertensive effect

Interactions Involving Serotonergic Antidepressants	
Lipophilic beta blockersCalcium channel blockersType IC antiarrhythmicsAngiotensin-converting enzyme inhibitorsWarfarin	Increase blood levels due to decreased hepatic degradation
DigitoxinWarfarin	Increase bioavailability due to displacement from protein-binding sites

MEDICATION	**EFFECT ON PSYCHOTROPIC AGENT**
Interactions Involving Lithium	
Diuretics that cause sodium loss	Increase blood lithium levels
Calcium channel blockers	Enhance lithium toxicity; bradycardia
Angiotensin-converting enzyme inhibitors	Enhance lithium toxicity
Methyldopa	Enhance lithium toxicity

MEDICATION	**EFFECT ON PSYCHOTROPIC OR CARDIAC AGENT**
Interactions Involving Carbamazepine	
Calcium channel blockers	Enhance carbamazepine toxicity
Antiarrhythmics	Potentiate delay in cardiac conduction

paroxetine, and fluvoxamine) are bound to plasma proteins and can displace other protein-bound drugs, thereby increasing the level of active drug and resulting in possible toxicity. This is particularly salient with warfarin and digitoxin, although the clinical significance of these interactions is not yet clear.[160] As noted earlier, diuretics may raise lithium levels into the toxic range. This can generally be dealt with by reducing the lithium dose, although during acute diuresis the proper adjustment of lithium is difficult because of the massive shifts in sodium and fluid balance.[160]

There are reports of idiosyncratic toxic reactions and of bradycardia when lithium is co-administered with the calcium channel blockers verapamil and diltiazem, and of lithium toxicity precipitated by the use of angiotensin-converting enzyme inhibitors. Methyldopa seems to have a number of interactions with psychotropic agents, including possible toxicity when combined with lithium. The metabolic degradation of carbamazepine may be inhibited by calcium channel blockers, thereby increasing the risk of carbamazepine toxicity.[167] Carbamazepine and antiarrhythmics may have

additive effects in slowing cardiac conduction.

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Chapter 71 - Neurological Disorders and Cardiovascular Disease

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Cardiovascular disease that occurs secondary to an underlying neurological disorder is related either to direct involvement of the heart or due to induced neurohormonal abnormalities that act on the heart. In several neurological disorders, the cardiovascular manifestations can be responsible for a greater risk of morbidity and mortality than the neurological manifestations. This chapter reviews those neurological disorders associated with important cardiovascular sequelae.

THE MUSCULAR DYSTROPHIES

The muscular dystrophies are a diffuse group of heritable disorders in which direct involvement of cardiac muscle is present to a variable degree. The muscular dystrophies can be classified into:

1. Duchenne and Becker muscular dystrophies
2. Myotonic muscular dystrophy

3. Emery-Dreifuss muscular dystrophy
4. Limb girdle muscular dystrophy
5. Facioscapulohumeral muscular dystrophy

Duchenne and Becker Muscular Dystrophies

GENETICS

Both Duchenne and Becker muscular dystrophies are X-linked recessive disorders in which the genetic locus has been identified as an abnormality in the dystrophin gene.[1] [2] This gene is the largest identified in humans to date.[3] [4] Dystrophin messenger RNA is expressed predominantly in skeletal, cardiac, and smooth muscle with lower levels in brain. The dystrophin protein complexes with muscle cytoskeleton, possibly functioning to link contractile proteins to the cell membrane.[5] Its absence can lead to membrane fragility, resulting in myofibril necrosis and eventual loss of muscle fibers with fibrotic replacement. In Duchenne muscular dystrophy, dystrophin is nearly absent; whereas in Becker muscular dystrophy, dystrophin is present but reduced in size or amount.[6] [7] This leads to the characteristic rapidly progressive skeletal muscle disease in Duchenne muscular dystrophy and the more benign course in Becker muscular dystrophy. The heart as a muscle is also involved. Indeed, studies have recognized a distinct clinical syndrome of X-linked dilated cardiomyopathy producing a progressive and severe cardiomyopathy with minimal skeletal muscle weakness that involves a dystrophin mutation.[8] [9] Involvement of the heart with sparing of skeletal muscle occurs secondary to selective abnormalities in certain dystrophin isotype transcripts, allowing functional dystrophin expression in all tissue but cardiac muscle.[10]

CLINICAL PRESENTATION.

Duchenne muscular dystrophy is the most common inherited neuromuscular disorder, with an incidence of 30 per 100,000 live male births. Patients with disease become symptomatic before age 5, presenting with skeletal muscle weakness that progresses such that the boy becomes wheelchair-bound before the age of 13 years (Fig. 71-1). Death occurs commonly by age 20 to 25 years primarily from respiratory failure or cardiac arrest. Becker muscular dystrophy is less common (3 per 100,000 live male births), has a more variable presentation of skeletal muscle weakness (Fig. 71-2) , and has a better prognosis, with most patients surviving to age 40 to 50 years.

CARDIOVASCULAR MANIFESTATIONS.

Virtually all patients with Duchenne muscular dystrophy develop a cardiomyopathy, but clinical recognition may be masked by severe skeletal muscle weakness. Preclinical cardiac involvement is present in one fourth by age 6, with the onset of clinically apparent cardiomyopathy after age 10 being common.[11] Predilection for involvement in the posterobasal and posterolateral left ventricle has been observed (Fig. 71-3) . This has been hypothesized to be related to the increased axial stress that cardiac myocytes encounter in the posterior wall and thus a more important role for dystrophin in limiting sarcolemma damage.[12] As with the skeletal muscle weakness, cardiac involvement in

Becker muscular dystrophy is more variable, ranging from none or subclinical to severe cardiomyopathy requiring transplant.[13] [14] Cardiac involvement in Becker muscular dystrophy is independent of the severity of skeletal muscle involvement, with some investigators observing increased likelihood of cardiovascular disease in older individuals.[14] [15] More than one half of patients with subclinical or benign skeletal muscle disease were noted to have cardiac involvement when carefully evaluated.[16] In follow-up studies, progression in the severity of cardiac involvement is common.[15] Cardiomyopathy can initially only involve the right ventricle.[16]

The cardiovascular examination in Duchenne muscular dystrophy may be altered by thoracic deformities and a high diaphragm. A reduction in the anteroposterior chest dimension is commonly responsible for a systolic impulse displaced to the left sternal border, a grade 1-3/6 short midsystolic murmur in the second left interspace, and a loud pulmonary component of the second heart sound. In both Duchenne and Becker muscular dystrophy, mitral regurgitation is commonly observed. This is believed related to posterior papillary muscle dysfunction in Duchenne muscular dystrophy and to mitral annular dilatation in Becker muscular dystrophy.[17]

Electrocardiography.

In patients with Duchenne muscular

Figure 71-1 *A,* Classic X-linked muscular dystrophy. *Left,* Exaggerated lumbar lordosis. *Right,* Calf pseudohypertrophy and shortening of the Achilles tendons. *B,* Seventeen-year-old boy with Duchenne muscular dystrophy. There is striking enlargement (hypertrophy/pseudohypertrophy) of the deltoid and pectoralis major muscles (upper panel) and of the trapezius (lower panel). There was also striking enlargement of both calves (not shown). (*A* and *B* courtesy of Joseph K. Perloff, M.D.)

dystrophy the electrocardiogram (ECG) is abnormal in 90 percent, demonstrating a distinctive pattern of tall R waves and an increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads related to the characteristic posterolateral left ventricular involvement (Fig. 71-4) . In patients with Becker muscular dystrophy ECG abnormalities are present in up to 75 percent.[14] [15] The ECG abnormalities observed include tall R waves and an increased R/S amplitude in V_1 , similar to that seen in Duchenne muscular dystrophy, but may also show frequent incomplete right bundle branch block. This may be related to early involvement of the right ventricle. In patients with congestive heart failure, left bundle branch block is common (Fig. 71-5) . [15]

In both Duchenne and Becker muscular dystrophies, elevated serum creatinine kinase activity is observed, over 10-fold and 5-fold normal values, respectively.[18]

Arrhythmias.

In Duchenne muscular dystrophy, arrhythmias secondary to disturbances in both rhythm and conduction are observed. Persistent or labile sinus tachycardia is the most recognized abnormality.[19] The pathogenesis of this tachycardia is unknown but does not appear related to abnormal autonomic function.[20] Atrial arrhythmias including atrial fibrillation and atrial flutter occur commonly as a preterminal rhythm.[21] Abnormalities in atrioventricular (AV) conduction have been observed. Up to 10 percent of individuals have PR intervals of less than 120 milliseconds, with an additional 10 percent having prolonged PR intervals.[22] Ventricular arrhythmias occur on monitoring in 30 percent (primarily ventricular premature complexes). More complex ventricular arrhythmias have been reported as well. These are more commonly present in individuals with severe muscle disease.[19] [23] Sudden death occurs in Duchenne muscular dystrophy, primarily in patients with severe skeletal muscle weakness. Whether this is an arrhythmic death is not clear.

Arrhythmic manifestations in Becker muscular dystrophy tend to correspond to the degree of the associated dilated cardiomyopathy but are not well characterized.[24] Distal conduction system disease with complete heart block and bundle branch reentry ventricular tachycardia have been observed.[25] [26]

Female carriers of Duchenne muscular dystrophy are at increased risk of dilated cardiomyopathy.[27] [28] [28A]

TREATMENT AND PROGNOSIS.

Duchenne muscular dystrophy is a progressive disorder with respiratory or cardiac death common by age 20 to 25. A primary cardiac etiology for death occurs in about one fourth of patients with an equal distribution of death from progressive heart failure and sudden death.[19] [21] Intravenous verapamil used for preterminal atrial arrhythmias can lead to acute respiratory failure.[29] A report of the use of an implantable cardioverter-defibrillator for recurrent drug refractory ventricular tachycardia resulted in a periprocedural respiratory death.[30]

In Becker muscular dystrophy or female carriers of Duchenne muscular dystrophy, it is not known whether therapy to decrease myocardial wall stress is beneficial in preventing or delaying progression to cardiac failure. Once heart failure is established, conventional therapy is indicated. Orthotopic cardiac transplantation has been reported.[31]

Myotonic Muscular Dystrophy

GENETICS

Adult myotonic muscular dystrophy (dystrophica myotonia, Steinert disease) is a heredofamilial disease (autosomal dominant) characterized by reflex and percussion

myotonia, weakness, and atrophy of distal skeletal muscles as well as systemic manifestations of early balding, gonadal atrophy, cataracts, mental retardation, and cardiac involvement (Fig. 71-6) .[32] The genetic abnormality responsible for this diffuse systemic disease is an amplified and unstable trinucleotide (cytosine-thymine-guanine [CTG]) repeat found on the long arm of chromosome 19. This repeat sequence is located in the 3
untranslated

Figure 71-2 Late onset, slowly progressive Becker muscular dystrophy in a 22-year-old man. *A,* There is dystrophy of the shoulder girdle, arms, and pelvic girdle (last not shown). *B,* Asymmetric calf pseudohypertrophy is greater on the left than on the right. Dystrophy of proximal leg muscles is not shown. (*A* and *B* courtesy of Joseph K. Perloff, M.D.)

region of a gene encoding a protein homologous to serine/threonine protein kinases, identified as myotonic protein kinase (Mt-PK or DMPK).[33] [34] [35] In individuals without myotonic dystrophy, between 5 and 37 copies of this CTG repeat are present. In individuals with myotonic dystrophy, 50 to several thousand CTG repeats are observed. A direct correlation exists between an increasing number of CTG repeats and earlier age at onset and increasing severity of neuromuscular involvement.[36] [37] [38] Whether increasing CTG expansion correlates with increasing cardiac involvement is debated.[39] [40] [41] [42]

MECHANISM.

The mechanism by which the amplified CTG repeat flanking Mt-PK leads to the characteristic involvement in myotonic dystrophy is not clear but likely involves alterations in tissue phosphorylation related to reduction in Mt-PK activity and possibly a resultant change in ion channel structure or function.[43] [44] Studies using transgenic mice deficient in Mt-PK have shown divergent results regarding the replication of the skeletal muscle disease.[45] [46] Cardiac conduction disease was observed in the transgenic mouse model, similar to what is seen in the human disease, although without characteristic degenerative pathology.[47] Other mechanisms for the cardiac involvement have been hypothesized, including a potential relationship to a second gene adjacent to Mt-PK known to be responsible for progressive familial heart block, impaired glucose utilization possibly related to abnormal protein kinase function, and abnormal coronary reserve.[48] [49] [50]

CLINICAL PRESENTATION.

Myotonic dystrophy is the most common inherited neuromuscular disorder in patients presenting as adults. The global incidence has been estimated to be 1 in 8000, although it is higher in certain populations, such as French Canadians, and lower to nonexistent

in other populations, such as African blacks.[32] The age at onset of symptoms and diagnosis averages 20 to 25 years. Common early manifestations are weakness in the muscles of the face, neck, and distal extremities. On examination, myotonia (delayed muscle relaxation) can be demonstrated

Figure 71-3 *A,* Schematic illustration showing the typical posterobasal myocardial involvement with lateral extension in classic Duchenne muscular dystrophy. The posterolateral papillary muscle is involved (arrow). LA=left atrium; LV=left ventricle; Ao=aorta. *B,* Necropsy section showing posterobasal involvement (arrows) of the left ventricle (LV) in a boy with classic Duchenne muscular dystrophy. The posterolateral papillary muscle was involved, resulting in mitral regurgitation and the jet lesion shown at upper right. (*A* and *B* courtesy of Joseph K. Perloff, M.D.)

Figure 71-4 Electrocardiogram from a 12-year-old boy with classic Duchenne muscular dystrophy. Sinus tachycardia is observed. The QRS complex is typical of Duchenne dystrophy, showing tall R waves in lead V_1 and deep, narrow Q waves in leads I, aVL, and V_4 to V_6 . (Courtesy of Charles Fisch, M.D., Indiana University School of Medicine, Indianapolis, IN.)

in the grip, thenar muscle group, and tongue (Fig. 71-7) (Figure Not Available) . Diagnosis when the individual is asymptomatic is possible using electromyography and genetic testing. Symptomatic myotonic dystrophy tends to present at an earlier age and with increasing severity in successive generations. This property is called anticipation and is related to the increasing amplification of CTG repeat length in successive generations.[38] [51] In general, cardiac symptoms occur after the onset of skeletal muscle weakness but can be the initial manifestation of the disease.

CARDIOVASCULAR MANIFESTATIONS.

Cardiac pathology is commonly seen in myotonic dystrophy and primarily involves degeneration (fibrosis and fatty infiltration) of the specialized conduction tissue, including the sinus node, AV node, and His-Purkinje system. Degenerative changes are observed in working atrial and ventricular tissue but only rarely progress to symptomatic cardiomyopathy (Fig. 71-8) .[52] [53] It is not surprising, based on this preferential degeneration of conduction tissue, that the primary cardiac manifestations of myotonic dystrophy are arrhythmias.

Electrocardiography and Arrhythmias.

The majority of adult patients with myotonic dystrophy have ECG abnormalities. In several large series, atrial fibrillation or atrial flutter was observed in 6 to 11 percent, first-degree AV block was found in 20 to 60 percent, right bundle branch block in 2 to 11 percent, and left bundle branch block in 5 to 13 percent. Q waves not associated with a

known myocardial infarction are common. ECG abnormalities often progress over time (Fig. 71-9) .

Mitral valve prolapse is often observed on echocardiography and is believed to be related to papillary muscle dysfunction. The heart may be involved before myocardial degenerative changes in a manner similar to the myotonia in skeletal muscle. This has been hypothesized to be manifest by echocardiographic evidence of delayed early diastolic relaxation of the left ventricle.[54]

At electrophysiological study, the most common abnormality found is a prolonged His-ventricular (H-V) interval. This was observed in 56 to 90 percent of selected patients and in follow-up studies does appear to progress.[42] [55] Other findings at electrophysiological study include prolongation in the atrial-His (A-H) interval and inducible atrial arrhythmias, primarily atrial fibrillation. In patients without previously known ventricular tachycardia, the likelihood of inducing a sustained ventricular tachycardia is low.

Conduction system disease can progress to symptomatic AV block and necessitate pacemaker implantation. Current prevalence of permanent cardiac pacing in patients with myotonic dystrophy varies between 3 and 22 percent (or higher).[42] [56] Patient selection and indication for pacing is not clear or consistent in these series. Slowed conduction in the ventricles is present, as evidenced by a significant

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Figure 71-5 Gross and microscopic cardiac pathological specimens and the electrocardiogram from a 45-year-old man with late-onset, slowly progressive Becker muscular dystrophy. *A,* Dilated, flabby left ventricle with focal endocardial thickening. *B,* Microscopic section from the left ventricle shows marked confluent scarring with variations in fiber size; there was no significant coronary artery disease. *C,* Electrocardiogram recorded at age 40 years. The 12-lead tracing shows left-axis deviation, a QRS of 0.14 second, small Q waves in leads I and aVL, and loss of R waves in leads V_2 and V_3 . The lower tracings, taken 4 years later (a year before death), show complete heart block with a variable QRS configuration. (From Perloff JK, et al: The cardiomyopathy of progressive muscular dystrophy. Circulation 33:625, 1966. Copyright 1966, The American Heart Association.)

incidence of late potentials on signal-averaged ECGs.[57] [57A] Atrial arrhythmias, primarily atrial fibrillation and atrial flutter, are common in myotonic dystrophy, being seen in approximately 10 percent of a general population, and are more common in those patients with more severe neuromuscular disease.[58] [59] [60] [61] Ventricular tachycardia can occur in patients with myotonic dystrophy.[62] [63] [64] [65] In at least two reports

Figure 71-6 Myotonic muscular dystrophy in three siblings. Note the unaffected mother (front).

Demonstrated is premature balding (left) and characteristic thin facies (rear).

and a series of six patients, the ventricular tachycardia observed was related to reentry in the diseased distal conduction system, as characterized by bundle branch reentry and interfascicular reentry tachycardia (see Chap. 25) .[62] [65] Therapy with right bundle branch and/or fascicular radiofrequency ablation resulted in absence of further inducible ventricular tachycardia.[62] [65]

Sudden Death.

The incidence of sudden death in patients with myotonic dystrophy is substantial and believed to be primarily caused by arrhythmias. In a registry of 180 myotonic dystrophy patients from the Netherlands collected from 1950 to 1997, 29 percent of all deaths were classified as sudden, presumably secondary to arrhythmias.[66] This was secondary only to pneumonia (31 percent) as a cause of death. In a 10-year study of mortality in a cohort of 367 patients from Quebec, 75 (20 percent) patients died.[67] In these 75 deaths, 31 percent were characterized as secondary to cardiovascular causes, with 11 percent sudden. The mechanisms leading to sudden death in myotonic dystrophy are not clear. Both bradyarrhythmias and ventricular tachyarrhythmias may be responsible. Bradyarrhythmias can cause sudden death in that distal conduction disease producing AV block may result in a lack of an appropriate automatic escape rhythm and asystole or bradycardia-mediated ventricular fibrillation. Sudden death can occur in myotonic dystrophy despite previous permanent cardiac pacing, implicating the role of ventricular tachyarrhythmias.

TREATMENT.

Cardiac management in individuals with myotonic dystrophy is not well established. In patients in whom a dilated cardiomyopathy does develop, standard

Figure 71-7 (Figure Not Available) Grip myotonia in myotonic muscular dystrophy. Inability to release (bottom) after exerting grip (top). (Reproduced by permission from Harper PS, et al: Myotonic dystrophy. In Engel AG, Franzini-Armstrong C [eds]: Myology: Basic and Clinical. 2nd ed. vol. II. New York, McGraw-Hill, 1994, p 1195.)

therapy including angiotensin-converting enzyme (ACE) inhibitors and beta-blocking agents has improved symptoms.[68] Patients presenting with symptoms indicative of arrhythmic disease such as syncope and palpitations should undergo an extensive evaluation, including electrophysiological study, to determine an etiology. A low threshold for permanent pacing is warranted. In individuals who are asymptomatic from a cardiac standpoint the degree of appropriate screening is not well established. Most authors recommend ECGs yearly and consideration for 24-hour ambulatory monitoring. Whether significant or progressive ECG abnormalities require intervention (prophylactic pacing, invasive electrophysiological evaluation) is uncertain. In one series, in which 45

individuals with myotonic dystrophy were followed for a mean of 4.6 years, ECG evidence of conduction abnormalities increased from 38 to 62 percent.[60] In this study, baseline or progression of ECG abnormalities did not correlate with the need for pacemaker insertion (5 individuals) or sudden death (1 individual). More recently, a series of 53 patients observed for a mean time period of 6.3 years determined that a PR interval of 240 milliseconds or greater was useful in predicting cardiac events (atrial fibrillation, complete heart block, syncope, and sudden death).[69] The appropriate therapy for this higher risk group was not discussed. Trials encompassing more patients using a multicenter approach have been recommended.[56] Some groups have advocated invasive electrophysiological evaluation and prophylactic permanent pacing in a high proportion of myotonic dystrophy patients.[42] Certain families may be more prone to arrhythmic manifestations of myotonic dystrophy and should be considered for

Figure 71-8 Histopathology of the atrioventricular bundle in myotonic dystrophy. *A,* Fatty infiltration in a 57-year-old man (Masson trichrome stain, ×90). *B,* Focal replacement fibrosis and atrophy in a 48-year-old woman. Arrows demarcate expected size and shape of the branching atrioventricular bundle (Hematoxylin and eosin stain, ×90). LBB=left bundle branch, RBB=right bundle branch. (From Nguyen HH, et al: Pathology of the cardiac conduction system in myotonic dystrophy: A study of 12 cases. J Am Coll Cardiol 11:662, 1988. Copyright 1988, American College of Cardiology.)

more careful evaluation.[70] Anesthesia in individuals with myotonic dystrophy can increase the risk of AV conduction block and other arrhythmias, and therefore these individuals should be carefully monitored and prophylactic temporary pacing considered.

In patients presenting with wide complex tachycardia, invasive electrophysiological testing with careful evaluation for bundle branch reentry tachycardia should be done. The use of class I antiarrhythmic agents in suppressing ventricular tachycardia in myotonic dystrophy has had limited efficacy. Sotalol may be more effective.[63] Whether implantable cardioverter-defibrillators are appropriate or useful has not been described.

PROGNOSIS.

The course of neuromuscular abnormalities in myotonic dystrophy is highly variable. Death from progressive weakness and respiratory difficulty can occur in advanced muscular disease. Other individuals may be only minimally limited by weakness to ages of 60 to 70 years. [32] Sudden death may significantly reduce survival in patients with myotonic dystrophy, including those minimally symptomatic from a neuromuscular status. What evaluation and interventions are appropriate, and the degree of effectiveness to decrease the risk of sudden death, are unclear.

Emery-Dreifuss Muscular Dystrophy

GENETICS

Emery-Dreifuss muscular dystrophy is a rare familial disorder in which skeletal muscle symptoms are often mild but with cardiac involvement common and life threatening.[71]

[72] The disease is primarily inherited in an X-linked recessive fashion, but there is heterogeneity in

Figure 71-9 Electrocardiograms obtained 1 year apart in a 36-year-old man with myotonic dystrophy (top older). Note the abnormal Q waves in the precordial leads. An increasing PR interval and QRS duration are observed consistent with increasing severity of conduction disease.

that families have been reported that fit an autosomal dominant and recessive inheritance pattern.

A gene responsible for the X-linked recessive Emery-Dreifuss muscular dystrophy was identified in 1994.[73] The candidate gene found on chromosome Xq28, *STA,* encodes a nuclear membrane protein called emerin.[74] [75] [76] The lack of emerin in skeletal and cardiac muscle is responsible for the disease phenotype. Recently, the autosomal dominant Emery-Dreifuss muscular dystrophy was linked to chromosome 1 with a candidate gene encoding proteins of the nuclear lamina.[77]

CLINICAL PRESENTATION.

Emery-Dreifuss muscular dystrophy is characterized by a triad of (1) early contractures of the elbow, Achilles tendon, and posterior cervical muscles; (2) slowly progressing muscle weakness and atrophy; and (3) cardiac involvement.[71] [72]

The disorder has been labeled "benign X-linked muscular dystrophy" to differentiate the slowly progressive muscular weakness from that of Duchenne muscular dystrophy. A definitive diagnosis can be made in Emery-Dreifuss muscular dystrophy and in carriers using antiemerin antibodies.[78] [79]

CARDIOVASCULAR MANIFESTATIONS.

Arrhythmias are the primary manifestation of cardiac disease in Emery-Dreifuss muscular dystrophy.[79A] Abnormalities in impulse generation and conduction are exceedingly frequent. ECGs are generally abnormal by age 20 to 30 years, commonly showing first-degree AV block. The atria appear to be involved earlier than the ventricles, with atrial fibrillation and atrial flutter or, more classically, permanent atrial standstill and junctional bradycardia, observed. Abnormalities in impulse generation or conduction are present in virtually all individuals by age 35 to 40 years, and permanent ventricular pacing is often required. Sudden death (presumed cardiac) before age 50 is exceedingly common and is reported to occur in as high as 40 percent of individuals.[80] This may be diminished with prophylactic permanent pacing.

Arrhythmia.

Ventricular tachyarrhythmias including sustained ventricular tachycardia and ventricular fibrillation have been reported. Invasive electrophysiological study data are limited in this rare condition. Mild prolongation of the H-V interval, atrial, AV nodal, and ventricular refractory periods has been observed.[81] Female carriers of Emery-Dreifuss muscular dystrophy do not develop skeletal muscle disease but do develop late cardiac disease, including conduction abnormalities; and sudden death can occur.[82] The characteristic arrhythmic involvement in Emery-Dreifuss muscular dystrophy may be related to the unique localization of emerin in desmosomes and fascia adherens of the intercalated discs.[83] If emerin functions in maintaining cell-to-cell adhesion, then its absence may impair conduction.

Localization of emerin in intercalated discs has not been observed by all investigators.[84] Although arrhythmic disease is the most common presentation of cardiac involvement in Emery-Dreifuss muscular dystrophy, a dilated cardiomyopathy can develop. This may be more common in patients in whom survival has been improved with permanent pacemaker implantation.[85] Both autopsy and endomyocardial biopsy have shown abnormal cardiac fibrosis.[85] [86]

TREATMENT AND PROGNOSIS.

Affected males should be carefully monitored for development of ECG abnormalities

of conduction. Ambulatory electrocardiography may reveal arrhythmic abnormalities during sleep that are not apparent during short-term ECG recording.[80] AV block can occur with anesthesia.[87] Permanent ventricular pacing is recommended once conduction disease is evident and can be life saving. After ventricular pacing, other cardiac manifestations can occur, including ventricular tachyarrhythmias and/or ventricular dysfunction. Female carriers do develop conduction disease, and ECG monitoring on a routine basis is appropriate. Whether prophylactic ventricular pacing is indicated in this group is not clear.

Cardiac disease including sudden death remains responsible for significant mortality in Emery-Dreifuss muscular dystrophy despite early pacing. Whether other therapy (implantable cardioverter-defibrillators) would diminish this mortality has not been tested.

Limb Girdle Muscular Dystrophy

GENETICS

Limb girdle muscular dystrophy constitutes a group of disorders with a limb/pelvic girdle distribution of weakness but with otherwise heterogeneous inheritance and clinical features.[88] Classically, the disorder is inherited in an autosomal recessive fashion, although autosomal dominant and sporadic genetic inheritance has been observed. Positional cloning has improved an understanding of the genetics of limb girdle muscular dystrophy. Abnormalities have been identified in a number of genes most commonly expressed as dystrophin-associated proteins.[89]

CLINICAL PRESENTATION.

The onset of muscle weakness is variable but usually occurs before age 30 years. Patients commonly present with complaints of difficulty with walking or running secondary to pelvic girdle involvement. As the disease progresses, involvement of the shoulder muscles and then more distal muscles occurs, with sparing of facial involvement. Slow progression to severe disability and/or death is common.

CARDIOVASCULAR MANIFESTATIONS.

Historically, cardiac involvement in limb girdle muscular dystrophy has been considered to be rare. However, as more has been understood about the genetic constitution and heterogeneity of this group of disorders, a greater realization of the potential for cardiac involvement is emerging.

An autosomal recessive or sporadic limb girdle muscular dystrophy caused by a deficiency in the sarcoglycan complex associated with dystrophin may be associated with a dilated cardiomyopathy.[90] [91] [92] ECGs from several patients showed abnormalities such as increased R wave in V_1 , consistent with the pattern of dystrophin-related cardiomyopathy, as seen in Duchenne muscular dystrophy. Cardiac abnormalities seen with ECG or echocardiographic evaluation have been detected in up to 80 percent, but with a much smaller proportion of patients being symptomatic.[92] [93]

A recently recognized autosomal dominant limb girdle muscular dystrophy with a high incidence of cardiac arrhythmic involvement has been linked to chromosome 1q11-21.[94] In these families, affected members develop high-degree AV block by age 35 to 45 years. Sudden death believed to be cardiac was reported in eight individuals at a median age of 50 years, including those in whom permanent pacing was previously instituted. A dilated cardiomyopathy was diagnosed in two individuals. In one individual, postmortem examination revealed extensive cardiac fibrosis, including replacement of the specialized conduction tissue. Others have reported families with limb girdle muscular dystrophy in whom AV block, cardiomyopathy, and sudden death were the primary manifestations.[95] [96]

TREATMENT AND PROGNOSIS.

Because of the heterogeneous nature of limb girdle muscular dystrophy, specific recommendations for routine cardiac evaluation are difficult to make. In families in

whom cardiac disease has been shown to be associated with their neuromuscular disorder, cardiac evaluation for arrhythmic disease and ventricular dysfunction should be considered. In individual families, prophylactic permanent pacing can be indicated.[95]

Facioscapulohumeral Muscular Dystrophy

GENETICS

Facioscapulohumeral muscular dystrophy is an autosomal dominant disorder in which the genetic locus has been mapped to chromosome 4q35.[97] Genetic heterogeneity has been reported.[98] Neither the definitive gene nor the gene product responsible for facioscapulohumeral muscular dystrophy has been identified.[99]

CLINICAL PRESENTATION.

Muscle weakness tends to follow a slowly progressive but variable course presenting with facial muscle weakness and progressing to involve the shoulders, foot extensors, and pelvis (Fig. 71-10) .[100]

CARDIOVASCULAR MANIFESTATIONS.

Cardiac involvement in facioscapulohumeral muscular dystrophy has been reported but does not constitute a significant problem in prevalence or severity as it does in many of the other muscular dystrophies. In one series of 31 patients evaluated by physical examination, chest radiograph, ECG, and echocardiogram, no evidence of cardiac abnormalities was found.[101] Other series have reported a propensity toward

Figure 71-10 Facioscapulohumeral muscular dystrophy in a 32-year-old woman. *A,* The face is in repose (myopathic) with dimpling of the corners of the mouth. *B,* Typical winging of the scapulae. (*A* and *B* courtesy of Joseph K. Perloff, M.D.)

arrhythmias.[102] [103] In 30 patients (mean age, 35 years), ECGs were abnormal in 26, primarily with atrial abnormality or minor conduction disease. Ten patients underwent invasive electrophysiological study with findings of abnormal sinus node function in 3, prolonged H-V interval in 1, and inducible sustained or unsustained episodes of atrial fibrillation or atrial flutter with single atrial extrastimuli in 8. In 100 patients with facioscapulohumeral muscular dystrophy genetically linked to chromosome 4q35, 5 percent were found to have arrhythmic disease in the absence of cardiovascular risk factors.[103] Three patients were symptomatic, with one requiring pacemaker implantation for AV block. Clinical correlation and follow-up was not available in either of these studies. Early reports of permanent atrial paralysis in facioscapulohumeral muscular

dystrophy are likely cases of Emery-Dreifuss muscular dystrophy.

TREATMENT AND PROGNOSIS.

Because significant clinical cardiac involvement is rare in facioscapulohumeral muscular dystrophy, specific monitoring or treatment recommendations are not well defined. One group has recommended yearly ECGs.[103]

FRIEDREICH ATAXIA

GENETICS

Friedreich ataxia is a progressive spinocerebellar degenerative disease characterized clinically by ataxia of the limbs and trunk, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities, and cardiac involvement. It is inherited in an autosomal recessive fashion with linkage to chromosome 9.[104] The gene responsible has been identified and has been found to encode a 210-amino acid protein, frataxin.[105] Frataxin is a mitochondrial protein important in iron homeostasis and respiratory function.[106] [107] Abnormalities in frataxin leads to mitochondrial dysfunction, poor cellular response to oxidative stress, and apoptosis.[108] [109]

Messenger RNA for frataxin is highly expressed in the heart. The mutations identified have been primarily an amplified and unstable trinucleotide (guanine-adenine-adenine [GAA]) repeat found in the first intron. Increasing size of this expansion has been found to correlate with the age at onset and severity of neurological symptoms and the degree of left ventricular hypertrophy by echocardiography.[110] [111] [112]

CLINICAL PRESENTATION.

The estimated prevalence of Friedreich ataxia is 1 in 50,000. Neurological symptoms usually manifest around puberty and almost always before age 25. Progressive loss of neuromuscular function, with the individual wheelchair-bound 10 to 20 years after symptom onset, is the norm. Neurological symptoms precede cardiac symptoms in most but not all cases.

CARDIOVASCULAR MANIFESTATIONS.

Friedreich ataxia is frequently associated with a concentric hypertrophic cardiomyopathy (Fig. 71-11) . [112] Asymmetric septal hypertrophy is also observed. A left ventricular outflow gradient has been reported in some cases. Presentation with a dilated cardiomyopathy is more rare but can occur (Fig. 71-12) . Whether the dilated cardiomyopathy occurs as a progressive transition from the hypertrophic cardiomyopathy or is a distinct entity is not known. A recent study would support the former.[113] The prevalence of hypertrophy varies between studies but does increase in likelihood with younger age at diagnosis and with increasing GAA trinucleotide repeat length.[112] [114] As high as 95 percent of neurologically symptomatic patients have cardiac

abnormalities on ECG and echocardiographic evaluation. Findings are consistent with ventricular hypertrophy. On ECGs, left ventricular hypertrophy is not always present despite echocardiographic evidence.[114A] Widespread T wave inversion is common (Fig. 71-13) .

Arrhythmias.

These can occur but are less common then what might be expected considering the high incidence of cardiac muscle involvement and hypertrophy. Atrial arrhythmias including atrial fibrillation and atrial flutter are associated with the dilated cardiomyopathy.[115] Clinically relevant disorders of impulse formation or conduction have not been reported despite histopathological evidence of conduction system involvement.[115] Ventricular tachycardia in the setting of dilated cardiomyopathy has been observed.[116] However, ventricular tachyarrhythmias are not associated with the hypertrophic cardiomyopathy. Sudden death can occur, but the mechanism of this death has not been well characterized.

Endomyocardial Biopsy.

This procedure has demonstrated myocyte hypertrophy and interstitial fibrosis.[117] His

Figure 71-11 *A,* Two-dimensional echocardiogram (parasternal long axis diastolic frames) from a 14-year-old girl with Friedreich ataxia and concentric hypertrophy (arrows) of the left ventricle (LV). *B,* Two-dimensional echocardiogram (parasternal long axis) from a 17-year-old boy with Friedreich ataxia and hypertrophic cardiomyopathy characterized by disproportionate thickness (arrows) of the ventricular septum (VS) compared with the posterior wall (PW). Ao=aorta; LA=left atrium. (From Perloff JK: Cardiac manifestations of neuromuscular disease. *In* Abelmann WH [ed]: Cardiomyopathies, Myocarditis, and Pericardial Disease. vol. 2. *In* Braunwald E [series ed]: Atlas of Heart Diseases. Philadelphia, Current Medicine, 1995, pp 6.1-6.19.)

Figure 71-12 *A,* Gross and histological specimens from a 17-year-old boy with Friedreich ataxia whose echocardiogram progressed from normal at age 13 years to a minimally dilated, hypocontractile left ventricle 3 to 4 years later. The gross specimen shows a mildly dilated left ventricle (LV) with normal wall thickness; the walls were flabby. The microscopic section from the left ventricular free wall shows marked connective tissue replacement. Although specifically sought, small-vessel coronary artery disease was not identified. *B,* Two-dimensional echocardiogram (apical window) showing the mildly dilated, thin-walled left ventricle (LV). LA=left atrium. (From Child JS, et al: Cardiac involvement in Friedreich ataxia. J Am Coll Cardiol 7:1370, 1986. Copyright 1986, American College of Cardiology.)

topathological examination, at the time of autopsy, revealed myocyte hypertrophy and degeneration, interstitial fibrosis, active muscle necrosis, bizarre pleomorphic nuclei, and periodic acid-Schiff-positive deposition in both large and small coronary arteries.

Degeneration and fibrosis in cardiac nerves and ganglia and the conduction system have also been observed.[115] [117] Myocardial fiber disarray, as observed in genetic hypertrophic cardiomyopathy, is rare.[115] Deposition of calcium salts and iron have been reported. How these cardiac pathological findings relate to abnormalities in the protein frataxin is unknown.

TREATMENT AND PROGNOSIS.

No specific therapy for the neurological or cardiac disease is available. Progressive neurological dysfunction is common, with death from respiratory failure or infection occurring in the fourth or fifth decades. Cardiac death can occur, primarily in those developing a dilated cardiomyopathy. These patients tend to do poorly, with rapid progression to end-stage congestive heart failure.

Figure 71-13 Electrocardiogram from a 34-year-old man with Friedreich ataxia. Widespread ST and T changes are observed. (Courtesy of Charles Fisch, M.D., Indiana University School of Medicine, Indianapolis, IN.)

LESS COMMON NEUROMUSCULAR DISEASES ASSOCIATED WITH CARDIAC MANIFESTATIONS

The Periodic Paralyses

GENETICS

The primary periodic paralyses are rare, nondystrophic, autosomal dominant disorders that result from abnormalities in ion channel genes. They can be classified into hypokalemic and hyperkalemic (potassium-sensitive) periodic paralysis with several subclassifications in each. Hypokalemic periodic paralysis is characterized by episodic attacks of weakness in association with decreased serum potassium levels. Penetrance is complete in males and approximately 50 percent in females.[118] Hypokalemic periodic paralysis has been mapped to chromosome 1q31-32 with subsequent identification of mutations in the alpha$_1$ subunit of the dihydropyridine-sensitive calcium channel. [119] [120] The disease may be genetically heterogeneous, as observed with the identification of a family with hypokalemic periodic paralysis and a mutation in the skeletal muscle sodium channel (SCN4A).[118]

Hyperkalemic periodic paralysis also manifests as episodic weakness but with symptoms worsening with potassium supplementation. Complete penetrance is observed. Potassium levels are usually high but may be normal during an attack. Hyperkalemic periodic paralysis is due primarily to mutations in the alpha subunit of

SCN4A found on chromosome 17.[121] Multiple different mutations in this gene have been reported and result in a potassium-sensitive failure of inactivation in the sodium channel.[122] Hyperkalemic periodic paralysis is genetically heterogeneous. Andersen syndrome, a potassium-sensitive periodic paralysis associated with characteristic dysmorphic features and ventricular arrhythmias, is not secondary to SCN4A mutations or known long QT syndrome genetic loci (Fig. 71-14) (Figure Not Available) .[123] The genetic abnormality in this disease remains unknown.

CLINICAL PRESENTATION.

Episodic weakness is usually the presenting symptom in both of the periodic paralyses. Attacks of weakness tend to be more severe and of longer duration with hypokalemic periodic paralysis than with hyperkalemic periodic paralysis. In both diseases, cold and rest after exercise can trigger an attack. Ingestion of carbohydrates can trigger an attack in hypokalemic periodic paralysis but may ameliorate an attack in hyperkalemic periodic paralysis.[124]

CARDIOVASCULAR MANIFESTATIONS.

Patients with the periodic paralyses are at an increased risk of ventricular tachycardias with occurrence more common with hyperkalemic periodic paralysis. In both, bidirectional ventricular tachycardia has been observed independent of digitalis intoxication.[123] [125] The bidirectional ventricular tachycardia occurs independent of attacks of muscle weakness, generally does not correlate with serum potassium levels, and can convert to sinus rhythm with exercise. Ventricular ectopy is common, often seen interspersed with bidirectional ventricular tachycardia (see Chap. 25) .

Prolonged QT interval can be observed. In some reports, this is episodic and associated with weakness, hypokalemia, or antiarrhythmic therapy. In other cases, a prolonged QT interval can be constant. Andersen syndrome is more commonly associated with a prolonged QT interval and ventricular tachycardia. Sudden death has been reported.

TREATMENT AND PROGNOSIS.

The episodes of weakness commonly respond to measures that work to normalize potassium levels.[124] Weakness in hyperkalemic periodic paralysis can respond to mexiletine. Treatment of electrolytes usually does not improve arrhythmias or, if it does, only transiently. Improvement in symptomatic nonsustained ventricular tachycardia associated with a prolonged QT interval has been reported with beta-blocker therapy. Class 1A antiarrhythmic agents can worsen muscle weakness and exacerbate arrhythmia associated with a prolonged QT interval.[125] Bidirectional ventricular tachycardia, not associated with a prolonged QT interval, may not respond to beta-blocker therapy. Imipramine has been observed to decrease the episodes of bidirectional ventricular tachycardia.[125] Whether other antiarrhythmic therapies have a role in the treatment of the periodic paralyses is unknown.

Figure 71-14 (Figure Not Available) Andersen syndrome in a 22-year-old man. Characteristic low-set

ears and hypoplastic mandible. *B,* Electrocardiographic recording revealing ventricular bigeminy. (From Tawil R, et al: Andersen syndrome: Potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol 35:326, 1994. Copyright 1994, American Neurological Association.)

Mitochondrial Encephalomyopathies

GENETICS

The mitochondrial encephalomyopathies are a heterogeneous group of disorders resulting from mutations in mitochondrial DNA.[126] The number of distinct disorders is extensive. Mitochondrial DNA is inherited maternally, and the majority of these disorders are thus transmitted from mother to children of both sexes. Some of the disorders occur sporadically or are inherited in an autosomal fashion. It is not surprising, based on the important metabolic function of mitochondria, that these disorders manifest with systemic pathology involving metabolic, neurological, and cardiac function. Mitochondrial encephalomyopathies, which have cardiac manifestations, present as several clinical phenotypes, including chronic progressive external ophthalmoplegia, which includes the Kearns-Sayre syndrome; myoclonus epilepsy with red ragged fibers [MERRF]; mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes [MELAS]; and Leber hereditary optic neuropathy. Other, more rare mitochondrial disorders present primarily with cardiac manifestations, often a dilated cardiomyopathy.[127] Chronic progressive external ophthalmoplegia is primarily a sporadic disease, whereas the others listed are maternally inherited.

CLINICAL PRESENTATION.

Kearns-Sayre syndrome is characterized by the clinical triad of progressive external ophthalmoplegia, pigmentary retinopathy, and AV block (Fig. 71-15) . Diabetes, deafness, and ataxia can also be associated. Clinical features of MERRF include myoclonus,

Figure 71-15 An 18-year-old girl with Kearns-Sayre syndrome and bilateral asymmetrical ptosis. Within 24 months, her electrocardiogram changed from normal to bifascicular block (complete right bundle branch block and left anterior fascicular block). *A,* Asymmetrical ptosis when the patient looks straight ahead. *B,* Ptosis of the right lid persists when the patient looks up. She also had typical pigmentary retinopathy. (*A* and *B* courtesy of Joseph K. Perloff, M.D.)

seizures, ataxia, dementia, and skeletal muscle weakness. MELAS is the most common of the maternally inherited mitochondrial disorders and is characterized by encephalopathy, subacute strokelike events, migraine-like headaches, recurrent emesis, extremity weakness, and short stature. *Leber hereditary optic neuropathy* manifests as a severe, subacute, painless loss of central vision, predominantly affecting young men.

CARDIOVASCULAR MANIFESTATIONS.

In chronic progressive external ophthalmoplegia, primarily in the *Kearns-Sayre syndrome,* cardiac involvement manifests as conduction abnormalities.[128] [129] A dilated cardiomyopathy has also been reported.[130] In the Kearns-Sayre syndrome, AV block is exceedingly common, usually presenting after eye involvement becomes manifest. In one series reporting 5 cases and reviewing 30 additional cases, Stokes-Adams syncope occurred in 29 percent, 34 percent had permanent pacemakers implanted, and in 7 patients (20 percent) AV block was believed to contribute to death.[128] The H-V interval is prolonged, consistent with distal conduction disease.[131]

Leber hereditary optic neuropathy can be associated with a short PR interval and preexcitation syndromes in a significant proportion.[132] In a review of 55 patients from eight pedigrees, 16 were noted to have a PR interval less than 120 milliseconds, with 5 manifesting preexcitation. Supraventricular tachycardia has been reported.

In MERRF and MELAS, cardiac involvement manifesting as hypertrophic cardiomyopathy (symmetrical or asymmetrical) has been observed.[129] [133] These patients can develop chest pain with ECG abnormalities and myocardial perfusion defects.[134] Progression (or questionably a second entity) to dilated cardiomyopathy can occur with heart failure and death.

Preexcitation has been described with MELAS.[129]

Several mitochondrial DNA mutations can be associated with dilated cardiomyopathy in the absence of other clinical abnormalities.[126]

TREATMENT AND PROGNOSIS.

In *Kearns-Sayre syndrome,* the prophylactic implantation of a pacemaker has been advocated when distal conduction disease is evident. Pacing appears to improve survival.[128] [129] The degree of distal conduction disease that warrants prophylactic pacing is not clear. In *Leber hereditary optic neuropathy,* a baseline ECG may be prudent. In the other mitochondrial disorders, an understanding of the potential for cardiac involvement is necessary. Whether specific evaluation in these disorders without symptoms is necessary is uncertain.

Spinal Muscular Atrophy

GENETICS

Spinal muscular atrophies are a group of lower motor neuron disorders presenting as progressive, symmetrical muscle weakness. In most cases, an autosomal recessive pattern of inheritance is observed but there is genetic heterogeneity.[135] By means of linkage analysis, the spinal muscular atrophies were mapped to chromosome

5q11.2-q13.3.[136] Mutations in a particular gene, *SMN* (survival of motor neuron), are responsible for this disorder.[137] Severity of the disease is correlated with the degree of reduction of the protein product of this gene.[138]

CLINICAL PRESENTATION.

Spinal muscular atrophies are divided into three clinical groups characterized by the age at onset, degree of muscular weakness, and survival.[139] Type I (Werdnig-Hoffmann disease) and type II have early childhood onset with severe limitation of life span. Spinal muscular atrophy type III (Kugelberg-Welander disease) is characterized by childhood or adolescent onset of atrophy and weakness in proximal muscles with slow progression.

CARDIOVASCULAR MANIFESTATIONS.

Cardiac involvement in spinal muscular atrophies include coexisting complex congenital heart disease, cardiomyopathy, and arrhythmias. Congenital heart disease has been associated with type I and III spinal muscular atrophies.[140] The most common abnormality is atrial septal defect, with other abnormalities reported. In spinal muscular atrophy type III, a dilated cardiomyopathy may occur with endomyocardial biopsy specimens demonstrating fibrosis.[141] Progression leading to a fatal outcome has been reported. Arrhythmic abnormalities including atrial standstill, atrial fibrillation, atrial flutter, and AV block may be the most common cardiac manifestation in these diseases.[141] Permanent pacing for atrial standstill and AV block has been reported.

TREATMENT AND PROGNOSIS.

The skeletal muscle involvement in spinal muscular atrophy type I and II limit life span so significantly that treatment of associated cardiac abnormalities is often not indicated. In spinal muscular atrophy type III, awareness of the potential of associated cardiac abnormalities is necessary. Permanent pacing may be required.

Guillain-Barre Syndrome

CLINICAL PRESENTATION.

The Guillain-Barre syndrome is an acute inflammatory demyelinating neuropathy characterized by peripheral, cranial, and autonomic nerve dysfunction.[142] It is the most common acquired demyelinating neuropathy, with an annual incidence of 1.7 per 100,000 population. The syndrome usually occurs 5 days to 3 weeks after a viral respiratory illness, a gastrointestinal infection, an immunization, or surgery. This disorder usually presents as symmetrical limb weakness that can progress to involve cranial and respiratory muscles. Approximately one third of individuals require assisted ventilation.

CARDIOVASCULAR MANIFESTATIONS.

Cardiac involvement in Guillain-Barre syndrome is related to accompanying autonomic nervous system

dysfunction that manifests as hypertension, orthostatic hypotension, resting sinus tachycardia, loss of heart rate variability, ST segment abnormalities, and both bradyarrhythmias and tachyarrhythmias.[143] [144] Significant autonomic nervous system dysfunction occurs primarily in severe cases of Guillain-Barre syndrome. Microneurographic recordings have shown increased sympathetic outflow during an acute phase of the disease that normalized with recovery.[145]

Life-threatening arrhythmias are common in severe cases of Guillain-Barre syndrome, primarily those requiring assisted ventilation. In a prospective study of 100 patients, serious arrhythmias occurred in 11 of 33 patients requiring ventilation.[143] This included asystole in 6, bradycardia of less than 30 beats/min in 1, rapid atrial fibrillation in 2, and ventricular tachycardia/fibrillation in 2. Thirteen deaths occurred, with four due to arrhythmias. All individuals with serious arrhythmias had signs of autonomic dysfunction. In this series and in other reports, asystole was commonly associated with tracheal suction.[143]

TREATMENT AND PROGNOSIS.

In addition to supportive care, early plasmapheresis and intravenous immunoglobulin can improve recovery.[142] In patients requiring ventilation, cardiac rhythm monitoring is mandatory. If serious bradycardia or asystole is observed, temporary or permanent pacing can improve survival. Atropine or isoproterenol during tracheal suction can be of benefit. The mortality rate in individuals hospitalized with Guillain-Barre syndrome is as high as 20 percent. In individuals who recover from Guillain-Barre syndrome, autonomic function also recovers, and no long-term arrhythmia risk has been observed.

Myasthenia Gravis

CLINICAL PRESENTATION.

Myasthenia gravis is a disorder of neuromuscular transmission resulting from production of antibody targeted against the nicotinic acetylcholine receptor.[146] The primary symptom, fluctuating weakness, usually begins with the eye and facial muscles and later can involve the large muscles of the limbs. Patients can present at any age, most commonly at a younger age in women and an older age in men. Myasthenia gravis is usually associated with hyperplasia or a benign or malignant tumor (thymoma) of the

thymus gland. The prevalence in the United States is 1 per 33,000.

CARDIOVASCULAR MANIFESTATIONS.

A myocarditis can be associated with myasthenia gravis, especially that occurring with thymoma.[147] A cardiac muscle antibody may be responsible.[148] Whereas cardiac pathological changes at autopsy are believed to be common, signs and symptoms of cardiac disease have been historically considered to be more rarely observed and nonspecific. This lack of symptomatic involvement may not always be true. In one series of 108 myasthenia gravis patients, 17 (16 percent) had evidence of cardiac abnormalities not explained by another etiology.[147] In 11 (10 percent) of these patients, clinical cardiac manifestations primarily arrhythmic occurred. These included atrial fibrillation, AV block, asystole, and unexplained sudden death. Cardiac abnormalities were more common in thymoma patients (50 percent) than among non-thymoma patients (12 percent). Autopsy findings were consistent with myocarditis.

TREATMENT AND PROGNOSIS.

Myasthenia gravis is treated with anticholinesterase and immunosuppressive agents. Thymectomy is often indicated. Anticholinesterase agents may slow heart rate and lead to hypotension.[149] No specific therapy has been discussed for the cardiac involvement. Whether immunosuppressive agents or thymectomy improves cardiac disease is unknown. Use of quinidine and propranolol in patients with myasthenia gravis may precipitate an acute exacerbation of weakness.[147] [150]

ACUTE CEREBROVASCULAR DISEASE

CARDIOVASCULAR MANIFESTATIONS.

Acute cerebrovascular diseases, including subarachnoid hemorrhage, other stroke syndromes, and head injury, can be associated with severe cardiac manifestations.[151] The mechanism by which this occurs appears to be related to abnormal autonomic nervous system function, primarily a markedly increased sympathetic and parasympathetic output. Hypothalamic stimulation can reproduce the ECG changes observed in acute cerebrovascular disease. ECG changes associated with hypothalamic stimulation or blood in the subarachnoid space can be prevented or diminished with spinal cord transection, stellate ganglion blockade, vagolytics, and adrenergic blockers.

Electrocardiography.

Abnormalities on ECGs are observed in as high as 80 to 90 percent of individuals with subarachnoid hemorrhage.[151] [152] Abnormalities including ST segment elevation and depression, T wave inversion, and pathological Q waves are observed.[151] [153] Peaked inverted T waves and a prolonged QT interval may occur in 25 to 40 percent of patients

(Fig. 71-16) . Hypokalemia is

Figure 71-16 Electrocardiogram from a patient with cerebral hemorrhage. Deep and symmetrical T wave inversions are observed. (Courtesy of Charles Fisch, M.D., Indiana University School of Medicine, Indianapolis, IN.)

Figure 71-17 A 49-year-old patient with cerebral hemorrhage. *A,* Electrocardiogram recorded within 3 hours of admission and 4 hours after onset of symptoms. QT interval prolongation is observed. *B,* Electrocardiographic monitoring at 6 hours after admission. Ventricular bigeminy precedes the onset of polymorphic ventricular tachycardia. Cardioversion was required. The patient was subsequently treated with a beta-adrenergic blocker without further ventricular tachycardia. *C,* Electrocardiogram done 2 weeks after admission. QT interval has normalized.

observed in up to 50 percent of patients with subarachnoid hemorrhage, and this increases the likelihood of QT interval prolongation.[154]

Other stroke syndromes are often associated with abnormal ECGs, but whether these are related to the stroke syndrome or to underlying intrinsic cardiac disease is often difficult to discern.[151] A prolonged QT interval is more common in subarachnoid hemorrhage than other stroke syndromes. Closed-head trauma can cause similar ECG abnormalities as subarachnoid hemorrhage, including a prolonged QT interval. Myocardial damage with liberation of myocardial enzymes and subendocardial hemorrhage or fibrosis at autopsy can occur in the setting of acute cerebrovascular disease. Like the ECG changes, these abnormalities are believed related to local myocardial catecholamine excess.

Neurogenic pulmonary edema may accompany the acute neurological insult.[155] [156] This edema can have both a cardiogenic component, related to systemic hypertension, and a noncardiogenic (pulmonary capillary leak) component.

Arrhythmia.

Life-threatening arrhythmias can occur in the setting of acute cerebrovascular disease. Ventricular tachycardia or fibrillation has been observed in patients with subarachnoid hemorrhage and head trauma.[154] [157] A torsades de pointes type of ventricular

tachycardia can occur (Fig. 71-17) . Often this is observed in the setting of a prolonged QT interval and hypokalemia. Stroke syndromes, other than subarachnoid hemorrhage, appear to be only rarely associated with serious ventricular tachycardias.[151] Atrial tachyarrhythmias including atrial fibrillation and regular supraventricular tachycardia have been observed.[151] [152] [154] Atrial fibrillation is most common in individuals presenting with what is believed to be an acute thromboembolic stroke.[151] Separating an effect from a cause may be difficult. Bradyarrhythmias including sinoatrial block, sinus arrest, and AV block occur in up to 10 percent of individuals with subarachnoid hemorrhage.[154] Bradyarrhythmias are less common in other stroke syndromes.

TREATMENT AND PROGNOSIS.

Beta-adrenergic blockers appear effective in decreasing myocardial damage and in controlling both supraventricular and ventricular tachyarrhythmias associated with subarachnoid hemorrhage and head trauma.[158] Beta-adrenergic blockers can increase the likelihood of bradyarrhythmias.[154] Life-threatening arrhythmias appear to occur in the first day after the neurological event.[154] Continuous ECG monitoring during this period is indicated. Careful monitoring of potassium levels especially in patients with subarachnoid hemorrhage is warranted. Refractory ventricular tachyarrhythmias can be controlled effectively with stellate ganglion blockade.[159]

ECG abnormalities reflect adverse intracranial factors but do not appear to portend a poor cardiovascular outcome.[153] [160] [160A]

Head injury (blunt trauma or gunshot wound) and cerebrovascular accident are the leading causes of brain death in individuals being considered as heart donors. These donors may manifest ECG abnormalities, hemodynamic instability, and myocardial dysfunction related primarily to adrenergic storm and not to intrinsic cardiac disease. Experimental studies on whether contractile performance recovers with transplantation are still controversial.[161] [162] [163] Optimization of volume status and inotropic support with careful echocardiographic evaluation and possibly left-sided heart catheterization may allow the use of some donor hearts that would have otherwise been rejected.

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Chapter 72 - Renal Disorders and Cardiovascular Disease

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CARL V. LEIER

The kidneys can be viewed as components of the circulatory system. Within this integrated system, the function, regulation, and adjustments of the heart and vasculature are closely linked to those of the kidneys. Renal dysfunction and failure adversely affect cardiovascular function, frequently leading to a cardiovascular disorder or failure and, consequently, further impairment of renal performance. Cardiovascular disease, dysfunction, and failure, in turn, can disturb renal function, occasionally to the point of evoking acute or chronic renal failure (CRF), which then causes further deterioration of the cardiovascular condition. Clinicians have for years appreciated the fact that failure of one component of the cardiorenal system (e.g., renal failure) greatly amplifies the difficulty in clinical management of the failure of another component (e.g., heart failure).

The effects of heart failure and cardiogenic shock on renal function are described in Chapters 16 and 35 , respectively. This chapter discusses other cardiovascular disorders that commonly affect renal performance and the primary renal conditions

responsible for altering cardiovascular structure and function.

Cardiovascular Conditions That Affect Renal Function

INFECTIVE ENDOCARDITIS (See also Chap. 47)

In the preantibiotic era, 10 to 15 percent of deaths due to infective endocarditis were attributable to renal failure. Early recognition, precise identification of the infecting organism, and prompt, aggressive antibiotic therapy specifically directed at the offending organism have greatly reduced the renal complications of infective endocarditis, particularly renal failure. Nevertheless, more than 60 percent of patients with documented infective endocarditis have clinical, laboratory, or biopsy evidence of renal involvement.[1] [2] [3] [4] [107A] The manifestations of endocarditic renal disease range from none to hematuria, pyuria, proteinuria, and occasional renal failure. As many as one-third of patients with infective endocarditis present with serum creatinine values of 2.0 mg/dl or higher.[4]

The deposition of immune complex material in glomeruli represents the most common mechanistic link between infective endocarditis and its renal consequences. Circulating immune complexes and their subsequent deposition in kidneys (and elsewhere) account for the common laboratory finding of reduced serum levels of certain complements (e.g., C3, C4, C1q) in affected individuals. The resultant glomerular lesions are generally proliferative in histological type, with demonstrable immune deposits of IgG, IgM, and C3 along the basement membrane and in the mesangium. The distribution of the glomerular lesions ranges from focal/segmental to diffuse, and their clinical behavior from subclinical to rapidly progressive.

FOCAL/SEGMENTAL PROLIFERATIVE GLOMERULONEPHRITIS.

This is the most commonly encountered glomerulopathy in infective endocarditis and represents a wide spectrum of involvement, including focal inflammation of single tufts of glomerull, sporadic glomerular inflammation and fibrosis, and inflammation and fibrosis of most glomerull within a renal segment(s) in the midst of normal-appearing kidney.[1] [2] [3] [107A] The demonstration of immune complex components in the involved glomerull and the observation that similar glomerular lesions can occur in isolated right-sided heart endocarditis, nonendocarditic infections, and noninfectious inflammatory conditions implicate immunological mechanisms as the cause of the focal/segmental glomerulonephritis of infective endocarditis. The focal/segmental glomerulonephritis can be widespread, such that occasionally it is indistinguishable from diffuse proliferative glomerulonephritis. Although the urine of patients with focal/segmental glomerulonephritis may not be unusual. It customarily shows microscopic hematuria, sterile pyuria, or mild proteinuria.

DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS.

This lesion, viewed by many simply to represent a more severe and extensive form of focal/segmental glomerulonephritis, attacks most glomerull with a very proliferative

cellular process, usually involving the entire glomerulus. The clinical consequences of systemic hypertension, nephritic proteinuria, and CRF are considerably more prevalent with the diffuse forms of proliferative glomerulonephritis. Hematuria, sterile pyuria, proteinuria, and heme or red blood cell casts are common features on urinalysis.

Renal biopsy reveals considerable proliferation and swelling of endothelial, epithelial, and mesanglal cells, giving the typically involved glomerulus a packed cellullar, even avascular, appearance. Rapidly progressive glomerulonephritis with widespread glomerular crescent formation can occasionally occur in infective endocarditis and is often the explanation for rapid loss of renal function.

MANAGEMENT.

Prompt identification and aggressive antibiotic treatment of the infecting organism are the principal means of preventing endocarditic renal disease. Antibiotic therapy has lowered the incidence of diffuse proliferative

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glomerulonephritis during infective endocarditis from 55 to 80 percent to less than 15 percent.[1] [2] [3] [107A] [5] [6] Pharmacological control of systemic hypertension and dialysis for renal failure occasionally are necessary supportive measures.

RENAL EMBOLIZATION.

Although evidence of renal embolization is found at necropsy in 60 to 70 percent of patients who die of infective endocarditis, less than 25 percent have clinically recognizable renal emboli[1] [2] [3] [107A] [7] Hematuria is the most common sign of renal emboli. Back or flank pain and renal hemorrhage, rarely fatal, can occur with a large embolus and sizable renal infarction. Larger emboli most often originate from prosthetic valves or from valvular infections caused by*Staphylococcus aureus, Neisseria gonococcus, Streptococcus pneumoniae,* or fungi. On rare occasions, an infected embolus can evolve into a renal abscess. Currently available imaging methods (e.g., echocardiography) do not yet provide the information needed to reliably identify those at risk for systemic or renal embolization.[8] [9] [10]

THROMBOEMBOLIC DISEASE

CAUSES.

Table 72-1 presents the major cardiovascular conditions responsible for renal embolization. Because 14 to 20 percent of cardiac output passes through the kidneys and because of their direct proximity to the commonly diseased aorta, the kidneys represent favorite targets for arterial embolization.[11] [12] [13] [14] [15] [16] [17] [18] [19] The atherosclerotic aorta is a common source of fibrin, plaque, and cholesterol emboli (see

Chap. 40) . Suprarenal aneurysms, aortic surgery, intraaortic balloon counterpulsation, cardiac or aortic catheterization, anticoagulation, and thrombolytic therapy increase the risk

TABLE 72-1 -- MAJOR CARDIOVASCULAR SOURCES, CAUSES, AND PREDISPOSING FACTORS FOR EMBOLIZATION TO KIDNEYS

AORTA
Atherosclerotic disease
Extensive atherosclerotic plaque formation; rupture, thrombus and cholesterol embolization
Suprarenal aortic aneurysm
Cardiac and aortic catheterization
Intraaortic balloon counterpulsation therapy
Anticoagulation
Thrombolytic therapy
Aortic surgery
ATRIA
Atrial fibrillation
Atrial enlargement
Cardiomyopathy
Atrial septal aneurysms
Paradoxical embolization
Myxoma (less commonly located in ventricles and on valves)
States of hypercoagulation (e.g., neoplastic diseases; protein C, protein S, or antithrombin III deficiency)
VENTRICLES
Mural thrombus
Myocardial infarction
Cardiomyopathy
Cardiac tumors
States of hypercoagulation (see Atria, above)
VALVES
Mitral stenosis (via atrial or valvular thrombus calcification)
Prosthetic valves
Endocarditis

Infective
Marantic (noninfective thrombotic)
Mitral annular calcification

of renal embolization from the atherosclerotic aorta. Massive embolization to skeletal muscle can exacerbate or cause renal dysfunction and failure via myoglobinemia-myoglobinuria. The more common cardiac conditions serving as embolic sources are atrial fibrillation, mural thrombi of the left ventricle, mitral stenosis, and prosthetic heart valves (see Table 72-1) .

Renal pathology ranges from isolated occlusion of an arteriole with minimal histological change, to segmental infarction ("white infarcts" and scarring), to complete occlusion of a renal artery with unilateral loss of renal function and mass. Cholesterol clefts and calcified debris are histological features of atherosclerotic emboli. Capsular rupture and retroperitoneal hemorrhage can complicate a large infarction.

Similar to embolization elsewhere, the majority are not likely to be detected clinically. Clinical manifestations include various degrees of hematuria, proteinuria, back or flank pain, systemic hypertension (secondary to elevated plasma renin), and renal dysfunction. Extensive embolization to both kidneys or a large embolus of a sole functioning kidney can result in anuria. Eosinophilia, depressed serum levels of C3 and C4, and rarely, lipid droplets floating in a urine sample can be noted with cholesterol emboli. The renal manifestations of atherosclerotic or cholesterol emboli are commonly part of an embolic multisystem "polyarteritis" presentation. Clinical suspicion of renal emboli is raised in patients with an obvious predisposition (e.g., prosthetic heart valve, atherosclerotic aorta, aortic surgery, recent cardiovascular catheterization). Perfusion defects secondary to large emboli are detectable with renal radionuclide scanning. Renal arteriography generally shows a cutoff sign at the point of occlusion, with few vascular markings distal to the occlusion. The rim sign (subcapsular contrast overlying regions of noncontrast) may be seen with extensive or large embolization.

MANAGEMENT.

This is generally directed at correcting the source of embolization with supportive therapy for accompanying systemic hypertension or renal failure. For large renal emboli, local thrombolytic therapy, angioplasty, retrieval via catheter, and surgical embolectomy are the principal interventional options.[18] [19] The approach to atherosclerotic-cholesterol emboli is somewhat limited; an obvious source (e.g., suprarenal atherosclerotic aortic disease or aneurysm) should be considered for resection, with the understanding that the aorta is usually diffusely involved with atherosclerosis and that further embolization may occur during and after surgery. Options to be considered in long-term medical management include lipid-lowering agents (particularly the statins), anticoagulation, and perhaps antiplatelet agents, although the effectiveness of these therapeutic modalities remains to be proved in this setting.[14] [17]

Other Cardiovascular Conditions

Aortic Aneurysm and Dissection (See also Chap. 40)

Atherosclerotic aneurysms can threaten renal function in a number of ways, including thromboembolism from a suprarenal location (see Thromboembolic disease, earlier), reduction of renal blood flow by local involvement or encroachment, rupture with hypovolemic shock, aortorenal vein fistula, ureteral obstruction, and the consequences of its surgical repair.[11] [20] [21] [22] Ten to 20 percent of atherosclerotic aortic aneurysms are complicated by renal artery stenosis. Clinical suspicion of renal involvement by an atherosclerotic aneurysm is prompted by recent onset or acceleration of systemic hypertension, location near the renal arteries, hematuria, proteinuria, occasional eosinophilla (in cases of atheroemboli), and renal dysfunction and failure. Aneurysmectomy with renal revascularization (when renal arteries are involved) is generally the treatment of choice.

Renal involvement by aortic dissection takes the form of renal artery occlusion or renal dysfunction secondary to compromised hemodynamics from hemorrhagic-hypovolemic shock, cardiac tamponade, or acute heart failure caused by acute aortic valvular insufficiency

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or acute myocardial infarction.[23] [24] Partial or total renal artery occlusion can occur via an ostial flap or displacement of the intima-media into the lumen as the dissecting hematoma moves into the renal artery. Renal manifestations can include proteinuria, hematuria, systemic hypertension (high plasma renin), renal infarction, azotemia, and renal failure. Anuria should bring bilateral renal artery occlusion (unilateral for a sole functioning kidney) into consideration. Operative correction of the dissection with renal revascularization remains the intervention of choice in most instances.[25] [26]

Congenital Heart Disease

CYANOTIC CONGENITAL DISEASE.

The clinical course of cyanotic congenital heart disease is often accompanied by the development of renal dysfunction.[27] [28] [29] Although the mechanism for the renal dysfunction is not known, its severity appears to be related to the level and duration of arterial desaturation, the degree of polycythemia, age, severity of right-sided heart failure, and elevation of systemic venous pressure. Histologically, the glomeruli enlarge ("glomerulomegaly") with mesangial hypercellularity, capillary congestion, focal glomerulosclerosis, and localized thickening of the basement membrane. Functionally, the disorder behaves as a glomerulopathy, with proteinuria occurring in 30 percent and microscopic hematuria in 15 to 20 percent of patients.[27] [29] Five to 10 percent develop considerable proteinuria and occasionally the nephrotic syndrome, usually after the age

of 21 years.[27] [28] Tubular dysfunction can occur. Because of increased uric acid production during polycythemia and the tubular dysfunction, hyperuricemia is a common metabolic complication of cyanotic heart disease. A reduction in renal blood flow, glomerular filtration rate (GFR) and urea clearance also occurs over time. Most of the glomerular lesions, renal dysfunction, and urinary findings are reversible and usually return toward normal after successful surgical correction of the cardiac defect and subsequent improvement in hemodynamics, oxygen delivery, and hematocrit.

COARCTATION OF THE AORTA.

This malformation has a significant impact on renal physiology and function.[30] [31] [32] [33] The lower renal perfusion pressure (distal to the coarctation) evokes sustained release of renin, which contributes to the characteristic hypertension present in the vascular system located above the coarctation. Depending somewhat on the age of the patient and duration of the condition, surgical or angloplasty correction usually does not immediately lower systemic blood pressure (in fact, it may initially increase), and systemic hypertension can persist long term after correction in up to one-third of the patients.[30] [32] [33] Congestive heart failure (CHF), infective endocarditis, and aortic dissection are other complications of coarctation, which, in addition to postrepair systemic hypertension, can adversely affect renal function. Fibromuscular dysplasia and developmental hypoplasia of the renal arteries have been reported in association with coarctation or hypoplasia of the abdominal aorta.[34] [35]

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Effects of Renal Failure on the Cardiovascular System

CARDIAC FAILURE CAUSED BY RENAL FAILURE

Left ventricular (LV) dysfunction and CHF are common complications of CRF.[1] [36] [37] [38] [39] [40] [40A] [40B] [41] [42] [43] [44] [44A] Factors that contribute to myocardial damage and dysfunction in patients with this condition are depicted in Figure 72-1 . Because it is usually difficult to attribute a predominant causative role to any one of these factors or events, the term*uremic cardiomyopathy* is often used to identify the cardiac disorder resulting from the integration of the various disruptive factors of CRF.

Factors Contributing to the Development of Congestive Heart Failure

The conditions contributing to the development of CHF in patients with CRF are presented in Figure 72-2 .

Figure 72-1 Factors contributing to myocardial damage in patients with chronic renal failure. ATPase = adenosine triphosphatase. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

VOLUME OVERLOAD.

Loss of renal function allows salt and fluid retention and the development of volume overload. Other factors that contribute to volume overload are chronic anemia and the arteriovenous (AV) access fistula. Normochromic, normocytic anemia is common in CRF, with nontreated hematocrit values ranging from 20 to 30 percent and hemoglobin

from 7 to 9 gm/dl; the introduction of erythropoietin therapy in CRF has reduced the degree and consequences of anemia. In general, the overall hemodynamic effect of the typical upper-extremity AV access fistula is small; however, the fistula may contribute to the development of CHF in patients with LV dysfunction.

The contribution of volume overload to the development of CHF in CRF is related to the magnitude and time course of volume expansion and to the concomitant status of cardiac function. A sudden rise in plasma volume can increase LV end-diastolic pressure to levels that produce pulmonary edema, even in the presence of normal resting LV systolic function. In contrast, a gradual increase in plasma volume can allow compensatory ventricular dilatation and hypertrophy with less immediate elevations in LV diastolic pressure.

PRESSURE OVERLOAD.

Systemic hypertension, a common finding in patients with CRF, contributes considerably to the generation of acute and chronic CHF by placing an excessive afterload burden on the dysfunctional heart. Increased afterload in CRF is also a result of reduced compliance

Figure 72-2 Factors contributing to the development of congestive heart failure in patients with chronic renal failure. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

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of the aorta and large arteries.[45] Renal artery stenosis with secondary or concomitant CRF can cause episodic, marked systemic hypertension and consequently evoke intermittent acute heart failure and pulmonary edema.[46]

NEGATIVE INOTROPIC EFFECTS.

Several factors in CRF may decrease myocardial contractility. These include hypoxemia (may occur during hemodialysis), subendocardial ischemia, certain buffers (e.g., acetate) added to the hemodialysis fluid, elevated parathormone levels, various metabolic and electrolyte abnormalities, and "uremic toxins."

EFFECTS OF DIALYSIS AND RENAL TRANSPLANTATION ON THE HEART

DIALYSIS.

During dialysis, changes in preload, afterload, arterialPO_2 , adrenergic activity, concentrations of electrolytes, ionized calcium, "uremic toxins," and other metabolites

and the composition of the dialysis solution affect cardiac-ventricular performance (Fig. 72-3) .[1] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [40A] [40B] The baseline status of LV function before the initiation of dialysis therapy is a major determinant of LV performance during dialysis. In general, patients with normal LV function experience little change or a modest decrease in LV performance during dialysis, whereas LV performance in those with baseline systolic dysfunction often improves during the procedure. These observations are due in part to the fact that the preload reduction of dialysis has less effect on LV systolic performance in the dysfunctional (systolic) LV compared with the normal LV, whereas the opposite responses occur during shifts in afterload. Preload reduction during dialysis can adversely affect LV systolic performance and overall hemodynamics in patients with predominant LV diastolic dysfunction.

Changes in preload and afterload during peritoneal dialysis are more gradual and less in magnitude, and thus the effects of peritoneal dialysis on LV performance are not as marked as those of hemodialysis. However, large amounts of intraperitoneal fluid can impair LV systolic performance by reducing venous return and raising afterload.[1] [40]

RENAL TRANSPLANTATION.

LV systolic and diastolic volumes and ventricular mass decrease and ejection fraction generally increases over 3 to 4 months after renal transplantation. These changes are likely related to favorable alterations of LV preload and afterload, an increase in hematocrit value, and correction of the various metabolic/endocrinological abnormalities already discussed.[1] [43] Because commonly

Figure 72-3 Effects of multiple factors and events during dialysis on left ventricular (LV) performance. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

used immunosuppressive agents (e.g., cyclosporine) can evoke systemic hypertension, blood pressure should be checked regularly and treated appropriately in posttransplant patients.

Management of Heart Failure in Patients with Renal Failure

The clinical presentation and evaluation of CHF in patients with CRF are similar to those of patients without this condition (see Chap. 17) . As in patients without CRF, the principles of CHF management in CRF include correcting remedially reversible lesions (e.g., operable occlusive coronary disease), improving contributory conditions (e.g., severe anemia), and optimizing preload, afterload, and cardiac rhythm. Restriction of dietary sodium to 2 gm/day or less is recommended. Angiotensin-converting enzyme inhibitors, digitalis, and vasodilators are often useful in this setting.[1] The duration of dialysis may be lengthened to increase fluid removal or to remove the usual amount of fluid volume more gradually and thus avoid hypotension. Peritoneal dialysis should be considered if problematic hypotension occurs during hemodialysis in patients with both CRF and CHF. Erythropoietin is an effective and safe means of increasing the hematocrit of CRF anemia, and an oversized AV access shunt may have to be modified.

Long-term administration of 1alpha-hydrocholecalciferol may improve LV performance by reducing circulating parathormone and improving cellular calcium, phosphorus, and magnesium metabolism. Renal transplantation usually improves LV performance, hemodynamics, and CHF symptoms. In select patients with end-stage myocardial and kidney disease, combined cardiac and renal transplantation, preferably from the same donor, should be considered.[43] [47]

HYPERTROPHIC CARDIOMYOPATHY (See also Chap. 48)

For yet undetermined reasons, hypertrophic cardiomyopathy and asymmetrical septal hypertrophy are not uncommon complications of CRF.[1] Patients with CRF with hypertrophic cardiomyopathy also invariably have LV diastolic dysfunction, which, when combined with a LV outflow tract gradient, makes them particularly vulnerable to the occurrence of systemic hypotension during hemodialysis. Special care must be taken to avoid volume depletion during hemodialysis in these patients, with consideration for peritoneal dialysis in those who experience problematic hypotension. If symptoms or complications during dialysis appear to be exacerbated by high adrenergic tone, beta-adrenergic blockade is a reasonable option.

ACCELERATED CORONARY ATHEROSCLEROSIS (See also Chap. 31)

Atherogenic Factors in Chronic Renal Failure

Cardiovascular mortality remains high in these patients. This is in large part related to aging of the affected population and to the increased number of diabetic patients undergoing long-term dialysis. Thirty to 35 percent of patients on long-term dialysis management have overt diabetes mellitus. Women with CRF develop coronary artery disease (CAD) as frequently and severely as age-matched men with CRF, perhaps because of earlier menopause and alterations in the pituitary-gonadal axis in these women.[1] [36] [44] For yet unknown reasons,

patients with chronic pyelonephritis or interstitial renal disease develop CAD more frequently than patients with other forms of CRF.

The principal atherogenic factors of CRF are shown in Figure 72-4. Carbohydrate and lipid abnormalities, including lipoprotein (a), occur early in chronic renal insufficiency (serum creatine levels >3 mg/dl) and persist as the patient's condition advances into end-stage renal failure and necessitates long-term dialysis. Glucose intolerance and insulin resistance have been demonstrated in a large proportion of patients who have CRF and who are not overtly diabetic, and patients undergoing long-term dialysis develop carbohydrate and lipid disturbances similar to those of diabetes mellitus (insulin

resistance, glucose intolerance, increased triglycerides). Although the total cholesterol concentration in serum of patients with CRF on maintenance dialysis can be normal, the level of the high-density lipoproteins is usually depressed. Caucasian men with CRF have lower levels of high-density lipoproteins than African American men so affected, which may account for the higher incidence of CAD in the former group.[1] [48] [49] [50] [51] [52] Other abnormalities that likely augment the atherosclerotic process include carnitine deficiency (adversely affects lipoprotein metabolism), secondary hyperparathyroidism, vascular calcification, increased homocystine, various states of hypercoagulation, and enhanced fibrin and platelet deposition.[53] [54] [55] Depressed nitric oxide and elevated local and circulating levels of endothelin in patients with CRF may also have a role.[56] [57]

NEPHROTIC SYNDROME.

Elevation of serum lipid values is a major feature of the nephrotic syndrome. Total cholesterol and low-density lipoprotein cholesterol concentrations are generally elevated, and high-density lipoprotein cholesterol level is normal or low.[1] [58] These lipid derangements can persist for some time after remission of the nephrotic syndrome, particularly in children. Chronic hypertension and corticosteroid therapy further accelerate atherosclerosis in this subgroup of patients.

RENAL TRANSPLANTATION.

Cardiovascular disease contributes heavily to mortality after kidney transplantation. Many patients with CRF have generalized arteriosclerosis-atherosclerosis at the time of transplantation, and thus their pretransplant and posttransplant cardiovascular disease represents a continuum, perpetuated by the persistence, worsening, and accumulation of atherogenic risk factors (e.g., age, hypertension, diabetes, hyperlipidemia, immunosuppressive drugs)[1] [59] [60] (see Fig. 72-4) . The number of acute rejection episodes is also linked as an independent risk factor to the development of cardiovascular disease.[1] Significant proteinuria occurs in 10 to 15 percent of transplant recipients and usually indicates various degrees of graft rejection or failure; urinary protein excretion exceeding 0.5 gm daily in posttransplant patients is associated with a significant rise in low-density and very low-density lipoprotein cholesterol and in total triglyceride values. Immunosuppressive therapy with corticosteroids evokes insulin resistance and hyperlipoproteinemia. Cyclosporine increases total cholesterol by elevating the level of low-density lipoprotein cholesterol.[59] [60] Therefore, the cumulative atherogenic risk factors--long-term dialysis, renal transplantation, and periodic graft rejection--account for the high prevalence of morbid cardiovascular disease in renal transplant recipients.

FACTORS AFFECTING MYOCARDIAL OXYGEN SUPPLY AND DEMAND IN CHRONIC RENAL FAILURE

Although the general determinants of myocardial oxygen supply and demand in these patients are similar to those of patients without renal failure, CRF adds several conditions that can evoke myocardial ischemia, even without occlusive CAD. CRF adversely affects coronary perfusion pressure, diastolic perfusion time, and oxygen-carrying capacity of blood (Fig. 72-5) . Volume and pressure overload increase ventricular diastolic pressure and thus can decrease coronary perfusion pressure

(coronary perfusion pressure during diastole equals coronary artery pressure minus LV diastolic pressure). In the presence of occlusive CAD, coronary artery pressure distal to a high-grade obstruction is not only low but is also not significantly affected by the usual changes in aortic diastolic pressure. Therefore, distal to an obstruction, only changes in LV diastolic pressure can significantly alter coronary perfusion pressure in that region of the heart.[61] An increase in heart rate (as occurs with dialysis, AV shunt, or anemia) reduces myocardial blood flow simply by decreasing diastolic perfusion time.

Because, the majority of coronary blood flow occurs in diastole and the duration of diastole (diastolic perfusion time) has a nonlinear inverse relationship with heart rate, even small increases in heart rate can substantially reduce diastolic perfusion time.[62] Anemia, a common feature of CRF, reduces the oxygen-carrying capacity of blood. Hemodialysis with accompanying hypotension, tachycardia, and leftward shift in the arterial hemoglobin-oxygen dissociation curve can be especially threatening to myocardial oxygenation. Coronary blood flow has been shown to decrease in some patients during hemodialysis.[63]

Chronic Coronary Artery Disease

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION.

CRF modifies the clinical presentation of chronic CAD with a greater prevalence of painless ischemia, partially attributable to a large proportion of patients with CRF with diabetes mellitus, and with chest pain secondary to various nonischemic causes (e.g., uremic pericarditis, neuritis).[1]

Figure 72-4 Factors contributing to the development and acceleration of coronary atherosclerosis in patients with chronic renal failure. HDL = high-density lipoproteins. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

Figure 72-5 Factors affecting myocardial oxygen supply and oxygen requirements in patients with chronic renal failure. AV = arteriovenous; LV = left ventricle. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

Electrocardiographic findings similar to those of myocardial ischemia (e.g., ST segment depression, T wave inversion) are present in many patients with CRF without significant CAD (especially during and after dialysis), thereby limiting the specificity of this diagnostic method. The sensitivity of radionuclide exercise testing for detecting obstructive CAD in CRF is low, perhaps because of generally poor exercise capacity,[1] [64] and data defining the sensitivity and specificity of radionuclide-perfusion imaging after dipyridamole administration are insufficient. Dobutamine-stress echocardiography

has been shown to be a promising means of detecting significant CAD in CRF.[36] [65] Coronary arteriography is often required in patients with suspected or problematic CAD to define their coronary artery anatomy and pathology and to develop the most appropriate management plan.

USE OF CONTRAST RADIOGRAPHY.

To minimize the renal complications of radiocontrast angiography in patients who have serum creatinine concentrations greater than 2 mg/dl and who are not yet undergoing long-term dialysis, preprocedural hydration and postprocedural volume replacement (saline solution for urine volume) are the most effective interventions.[66] [67] Routine administration of 20 percent mannitol solution is no longer advocated in this clinical setting. The smallest possible amount of radiocontrast agent should be used, because the degree of nephrotoxicity is closely related to the quantity injected. Acute renal failure requiring dialysis is extremely unusual in patients who receive less than 100 ml of contrast agent. Patients with renal artery stenosis are especially susceptible to contrast-induced nephropathy. The osmotic and volume load of radiocontrast material can also provoke acute pulmonary edema in patients with CRF and underlying volume overload or LV dysfunction. Nonionic contrast material evokes less intravascular volume expansion and should generally be used in CRF. To further reduce the amount and risk of administered radiocontrast agent, information about ventricular size and function should be obtained via two-dimensional echocardiography or radionuclide angiography. Avoidance of other nephrotoxic drugs, such as nonsteroidal antiinflammatory agents, is prudent. When renal failure requiring dialysis occurs in the days after the procedure, it is associated with a high in-hospital mortality and poor long-term survival.

MANAGEMENT.

The general management approach to CAD in CRF is similar to that for patients without this condition (see Chap. 37) , but certain aspects of management are unique to CRF.[1] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] A diet weighted with polyunsaturated fats and a carbohydrate content of approximately 20 percent of total caloric intake is generally recommended. Lipid-lowering agents are usually effective in this clinical setting, and HMG-CoA reductase inhibitors are generally better tolerated in CRF than most other agents. Because of an increased risk of developing skeletal myopathy and rhabdomyolysis, the HMG-CoA reductase inhibitors must be used with caution in patients receiving cyclosporine. Disturbed calcium-phosphorus metabolism and resultant peripheral and coronary vascular calcification are approached with long-term oral administration of phosphate-binding agents (e.g., calcium carbonate, calcium acetate). For problematic CAD, it is often necessary to administer erythropoietin to keep hemoglobin values at 10 gm/dl or greater. Inadequate hemodialysis is associated with a suboptimal response to erythropoietin therapy. Increasing the intensity of dialysis in patients who have anemia and who are receiving inadequate dialysis results in a significant increase in the hematocrit value.

Oxygen administration at a flow rate of 2 to 3 liters/min may be useful in reducing hypoxemia and ischemic events during hemodialysis. When possible, sodium bicarbonate instead of sodium acetate should be used as the dialysis buffer. This

maneuver improves arterial oxygenation, evokes less hypotension, and reduces the tendency of this procedure to precipitate myocardial ischemia. Certain patients with severe CAD and ventricular dysfunction cannot tolerate hemodialysis because of problematic dialysis-induced reduction in cardiac output or blood pressure; some of these patients require cardioactive drug support (e.g., dopamine, dobutamine) during hemodialysis, and others are best treated with peritoneal dialysis.

Percutaneous coronary intervention can be performed in these patients; however, the restenosis rate is rather high. The high rate of angiographic restenosis in patients with end-stage renal disease seems to be related to the size of the vessel dilated and to an increased prothrombotic risk, as indicated by higher fibrinogen concentrations.[69] [72]

Coronary artery bypass graft surgery (CABG) can be performed with increased but acceptable morbidity and mortality in patients undergoing long-term dialysis. Further, mild renal insufficiency, even in the absence of dialysis, increases the risk of blood transfusion, low-output syndrome, and prolongs the length of intensive care unit and postoperative stay. CABG surgery results in considerable improvement in symptoms and functional status in this group of patients; long-term survival, however, is considerably less than in patients without CRF.[68] [71] [74]

PERIOPERATIVE MANAGEMENT

Table 72-2 lists the major recommendations for perioperative treatment of patients who have CRF and are undergoing cardiac surgery. Intravascular volume, serum potassium level, hematocrit value, and drug administration must be carefully monitored during the perioperative period.[1] [68] Preoperatively, daily dialysis (usually of shorter duration) against a low-potassium bath should be considered to control serum and whole-body potassium content. Hemoglobin and hematocrit values should be raised to 10 gm/dl or greater and 30 percent or greater, respectively, with erythropoietin administration or via red blood cell transfusion during dialysis in more urgent situations.[79] [82]

TABLE 72-2 -- PERIOPERATIVE MANAGEMENT OF CHRONIC RENAL FAILURE IN PATIENTS UNDERGOING CARDIAC SURGERY

PREOPERATIVE
Dental evaluation and correction (in valvular disease)
Decrease intake of sodium, potassium, and fluid volume
Short dialysis daily (low potassium bath)
Beta-blockade therapy throughout perioperative period
Antibiotic prophylaxis (start immediately before surgery and continue for 2 d after surgery)

Raise hemoglobin/hematocrit above 10 gm/dl/30 percent
INTRAOPERATIVE
Keep fluid administration to minimum
Do not administer potassium
Special effort to preserve arm vessels and arteriovenous access fistula
Hemodynamic monitoring (during and after surgery) as needed
POSTOPERATIVE
Determine serum potassium levels and arterial blood gases every 4 hr during first 24 hr
Perform dialysis as indicated
Use regional anticoagulation during dialysis over first 5 to 10 postoperative days

Patients should go to surgery at near "dry weight." Intravenously administered fluids are kept to a minimum, with little or no potassium administration. To prevent excessive hemodilution during cardiopulmonary bypass, both blood and lactated Ringer's solution are used to prime the extracorporeal pump. Beta-adrenergic blockade should be continued throughout the perioperative period to avert the myocardial and dysrhythmic complications of the hyperadrenergic state of cardiac surgery. Intraoperative hemofiltration can be used to treat any excessive intravascular volume accumulated during cardiopulmonary bypass.

Postoperatively, dialysis is used to reverse hyperkalemia, significant azotemia, or volume overload. Regional heparinization or citration should be considered during the first 5 to 10 postoperative days as a means of controlling bleeding complications during hemodialysis. The perioperative management used for patients with CRF on regular dialysis also applies to nondialyzed patients with CRF undergoing cardiac surgery; renal function in the latter patients may have to be supported with dialysis over several postoperative days.[71] [73] [74] [77] [78] Patients with a functioning transplanted kidney can be managed in a near-routine (non-CRF) manner, with special attention directed at providing adequate corticosteroid support, avoiding nephrotoxic drugs, and maintaining adequate urine output.

Pericarditis is a common complication of CRF; total pericardiectomy should be considered as a reasonable elective addition to the cardiac surgical procedure in patients with CRF.

Acute Myocardial Ischemic Syndromes

The clinical presentation, diagnostic steps, and therapeutic measures for patients with CRF and acute ischemic syndromes are generally similar to those directed at patients without CRF. Renal artery stent implantation may improve symptoms in patients with significant renal artery stenosis presenting with acute ischemic syndromes, congestive heart failure, or both; these benefits most likely are related to neurohumoral and hemodynamic improvements. Unfortunately, patients with CRF also frequently exhibit

abnormal electrocardiographic ST segment and T wave abnormalities and elevated serum cardiac enzyme values in the absence of myocardial ischemia-necrosis. Because of impaired renal clearance, total creatine phosphokinase (CK) and lactate dehydrogenase levels are often elevated. However, the total CK usually comprises brain band CK (CK-BB, increased in about 30 percent of patients with CRF) or skeletal muscle band (CK-MM). Therefore, when myocardial ischemia and infarction is suspected, careful monitoring of the myocardial band (CK-MB) over the ensuing 24 to 48 hours becomes important; new or transient elevation of the CK-MB fraction can usually be regarded as an indication of acute myocardial necrosis. Troponins are more likely to be elevated in dialyzed patients than in other patients with renal failure who are not on dialysis. The ability of cardiac troponin T and cardiac troponin I to predict risk for subsequent adverse outcomes in patients presenting with suspected acute coronary syndromes is reduced in the presence of renal disease.[36] [75] [79] [83]

Fluid overload is approached with dialysis in patients who have CRF with acute myocardial infarction and who are nonresponsive to intravenous administration of loop diuretics in moderate to high doses. Hemodynamic monitoring with a flow-directed indwelling pulmonary artery catheter is appropriate when a low perfusion state or heart failure develops. Electrolyte and metabolic abnormalities are controlled with dietary measures and dialysis as needed.

CARDIOVASCULAR CALCIFICATION

Dystrophic (metastatic) calcification commonly occurs in patients who have CRF and who are receiving maintenance dialysis; it can involve all tissues, including heart, vasculature, and kidneys. Hyperphosphatemia with elevation of the calcium-phosphorus product, shifts in plasma and tissue pH during and after dialysis, and secondary hyperparathyroidism are regarded as the most important factors responsible for tissue calcification in CRF (Table 72-3) . [37] [39] [40] [84] The calcification is exacerbated by excessive intake of milk, use of certain antacids, and calcium extraction from calcium polystyrene materials and surfaces (e.g., certain dialysis units).

The mitral annulus and valve and aortic valve are the cardiac sites predisposed to dystrophic calcification in CRF (see Table 72-3) . Consequently, hemodynamically significant valvular stenosis and/or regurgitation, usually manifested clinically as murmurs and occasionally as symptoms and signs of heart failure, are common complications of cardiac calcification in CRF. Myocardial calcification can cause conduction abnormalities (most commonly atrioventricular or bundle branch block), various arrhythmias, ventricular dysfunction, and CHF. Significant annular, valvular, and coronary artery calcification and regions of dense calcification elsewhere in the heart are usually detectable by image-amplified fluoroscopy, echocardiography, or magnetic resonance imaging. Technetium pyrophosphate scintigraphy may demonstrate uptake in areas of myocardial calcification. Pericardial calcification, usually microscopic in degree, contributes to the pathological process of uremic

TABLE 72-3 -- METASTATIC CALCIFICATION OF CHRONIC RENAL FAILURE: CONTRIBUTING FACTORS AND COMMON CARDIOVASCULAR SITES OF INVOLVEMENT

POSSIBLE CONTRIBUTING FACTORS	CARDIOVASCULAR SITES
Hyperphosphatemia	Mitral annulus and valve
Increased ionized calcium	Aortic valve
Increased calcium-phosphorus product	Atrioventricular nodeconduction system
Increased parathormone levels	Myocardium
Acute changes in blood pH	Interventricular septum
Increased calcium ingestion	Coronary arteries
Certain antacids	Pericardium
Extraction from calcium-containing polymers and materials	
Vitamin D preparations	

Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.

pericarditis. Dense pericardial calcification is not a feature of CRF and implicates another disease process.

Prevention of cardiovascular calcification is an important component of the management of CRF. Phosphate-binding agents and dietary measures (restriction of phosphate and avoidance of excessive calcium intake) are used for this purpose. Regression of calcification has been achieved by lowering serum phosphorus levels with oral phosphate-binding agents, parathyroidectomy, and renal transplantation; cardiovascular calcification, however, does not appear to be as readily reversible. Management of the CHF, AV block, and cardiac arrhythmias caused by cardiac calcification is directed at controlling symptoms.

HEART MURMURS AND VALVULAR HEART DISEASE

Heart murmurs and acquired valvular abnormalities are common in CRF. Dystrophic calcification (discussed earlier), infectious and noninfectious endocarditis, and certain renal diseases (e.g., polycystic kidney disease) are associated with structural abnormalities of heart valves.[1] [85] [86] However, heart murmurs are frequently noted in CRF without obvious underlying valvular abnormalities and are probably evoked by anemia, the AV access fistula, hyperadrenergic tone, and volume and pressure overload. Early diastolic murmurs of functional aortic or pulmonic regurgitation, generally related to pressure and volume overload, can appear during advanced stages of renal failure and often disappear after hemodialysis. An occasional murmur audible over the anterior aspect of the chest may be transmitted from an AV access fistula

located in the upper limb. In patients with forearm shunt access, bruits can be heard in the ipsilateral axillary, clavicular, and cervical regions. Cervical venous hums are also common in these patients. Thus, murmurs in CRF can represent valvular disease, functional pulmonic or aortic valvular flow or regurgitation, transmission from an AV fistula, or a venous hum.

As in other conditions, each murmur requires clinical assessment to define the underlying cause and, if associated with valvular or congenital heart disease, evaluation of the severity of the lesion. A precordial systolic murmur secondary to high flow or transmission from the AV fistula can be easily distinguished from other murmurs by observing the response of the murmur to transient obstruction of the fistula. Functional murmurs secondary to pressure or volume overload decrease considerably with control of hypertension, reduction of fluid overload, correction of anemia, and so forth. Venous hums are usually audible throughout the cardiac cycle; are loudest at the base of the neck, in the upright position and during inspiration; and are abolished by compression of the neck veins or by the Valsalva maneuver.

Laboratory evaluation and overall management of valvular heart disease in patients with CRF is similar to that recommended for patients without CRF (see Chap. 46) . Cardiac valve replacement can be done with acceptable operative mortality and reasonably good cardiac rehabilitation in patients undergoing prolonged hemodialysis. Long-term survival for most of these patients is still limited by the clinical course and complications of CRF, but quality of life is generally improved after valve replacement.

Preoperative dental evaluation is mandatory, and dental treatment should be completed several weeks before cardiac surgery. Preparation otherwise is similar to that described for CABG (see Table 72-2) . Patients who have CRF and who are undergoing open-heart surgery--especially placement of prosthetic heart valves--are at high risk for infective endocarditis. In the perioperative period,*S. aureus,* coagulase-negative staphylococci, and diphtheroids are the most common infecting organisms. No single antibiotic agent is effective against all of these organisms, and prolonged use of broad-spectrum antibiotics predisposes patients to superinfection with unusual or resistant organisms. Thus, antibiotic prophylaxis at the time of valvular surgery is primarily directed against staphylococci and should be started immediately before the operative procedure and continued postoperatively for approximately 2 days. The choice of mechanical versus bioprosthetic valve for replacement in CRF remains controversial.[1] [86] [87] When technically feasible, reconstructive valvular repair should be considered for problematic mitral regurgitation.[85] [86]

Figure 72-6 Factors contributing to the development of pericardial disease in patients with chronic renal failure. Ca = calcium; P = phosphorus. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

PERICARDIAL DISEASE

Pericardial disease remains a relatively common complication in these patients. The

contributory factors are depicted in Figure 72-6 , and the evaluation and management of pericardial disorders are presented in Chapter 50 (see also Chap. 72) .

SYSTEMIC HYPERTENSION

HYPERTENSION-ASSOCIATED WITH CHRONIC RENAL FAILURE (see also Chap. 28) .

Systemic hypertension occurs in more than 80 percent of CRF patients before initiation of dialysis. Patients who have CRF and who remain normotensive most often have tubular and interstitial disease or obstructive uropathy as the underlying pathological process. In contrast, arterionephrosclerosis and glomerulopathies are usually associated with hypertension, often marked. The various factors that contribute to the development of systemic hypertension in CRF are presented in Figure 72-7 .[88] [89] [90] [91] [91A]

HYPERTENSION ASSOCIATED WITH RENAL TRANSPLANTATION.

The incidence of systemic hypertension after renal transplantation varies widely (25 to 80 percent) and is highest during the early months after transplantation. The incidence 5 years after transplantation is about 40 to 50 percent. Renal graft failure is increased considerably in the setting of poorly controlled systemic hypertension.[92] Renal artery stenosis (of the transplanted kidney or native kidneys), chronic rejection, native kidney disease, therapy with corticosteroids or cyclosporine, and essential hypertension before transplantation are the leading causes of systemic hypertension in posttransplant patient. Recipients of cadaveric kidneys from donors with a family history of essential hypertension are also more likely to experience posttransplant hypertension. On the other hand, essential hypertension can undergo remission for up to 8 to 10 years after successful transplantation of a kidney from a normotensive donor.

MANAGEMENT.

Diagnostic studies should be undertaken in patients with renal failure and hypertension to preclude a reversible renovascular cause (see Chap. 28) and determine the nature of the underlying renal disease. Distinguishing hypertension secondary to renal parenchymal disease from essential hypertension with resultant hypertensive renal disease is often difficult at this stage. The medical history may identify patients who have had longstanding essential hypertension and a familial tendency for

Figure 72-7 Pathophysiological mechanisms contributing to the development of systemic hypertension in patients with parenchymal renal disease and failure. ANP = atrial natriuretic peptide; SLE = systemic lupus erythematosus. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases.

Armonk, NY, Futura, 1992.)

such, diabetes mellitus, or an episode of glomerulonephritis before developing renal failure.

The treatment of systemic hypertension in patients with active glomerulonephritis and/or CRF is similar to that of essential hypertension (see Chap. 29) . However, in patients with CRF, the dosage schedule of drugs cleared by the kidneys has to be modified to match renal function to avoid the deleterious effects of accumulated drug or metabolite. Dialysis should be considered for patients with a substantial reduction of renal function and hypertension refractory to medical management (Fig. 72-8) [1] [93] Early initiation of dialysis decreases the consequences of uremia, allows easier control of hypertension, and reduces the complications of chronic hypertension.

Bilateral nephrectomy is reserved for severely hypertensive CRF patients whose hypertension is refractory to aggressive hemodialysis and optimal drug therapy. The results of nephrectomy are best in patients with markedly elevated plasma renin activity. The major but correctable disadvantages of nephrectomy are a further drop in the hemoglobin and hematocrit values (reduced erythropoietin) and exacerbation

Figure 72-8 General management of arterial hypertension caused by renal parenchymal disease. AV = arteriovenous. (Modified from Leier CV, Boudoulas H: Cardiorenal Disorders and Diseases. Armonk, NY, Futura, 1992.)

of renal osteodystrophy (depressed generation of certain forms of vitamin D). The availability of potent oral antihypertensive agents, such as central sympatholytic drugs (e.g., clonidine), high-dose anglotensin-converting enzyme inhibitors, and minoxidil, has now made bilateral nephrectomy an uncommon procedure in CRF.

The management of systemic hypertension is often complicated by drug therapy needed for the management of the renal disease. This is particularly relevant to posttransplant patients.[1] [94] Corticosteroids adversely affect hypertension control by increasing blood volume and insulin resistance and blunting responsiveness to antihypertensive drugs. Cyclosporine commonly provokes or exacerbates systemic hypertension, occasionally to extremely high levels of blood pressure; calcium channel blocking drugs are usually effective in controlling cyclosporine-induced hypertension. A marked and often refractory increase in systemic blood pressure and occasionally renal interstitial disease can follow administration of nonsteroidal antiinflammatory agents.

Because spontaneous improvement of systemic hypertension in posttransplant patients with obstructing renal artery lesions (usually at the site of vascular anastomosis) is not uncommon, conservative management is generally recommended for transplant recipients who have stable, adequate renal function and whose hypertension is amenable to medications. When stenosis-induced hypertension becomes difficult to control or renal function falls, percutaneous transluminal angioplasty of the arterial lesion becomes a therapeutic option. Surgical intervention may become necessary if

angioplasty is not feasible or is unsuccessful. Effective treatment of posttransplant hypertension is very important for the long-term health and survival of both graft and patient.[88] [92]

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias constitute a major clinical problem in CRF because of their increased prevalence and potentially serious complications; their episodic nature also makes identification and characterization difficult. A multicenter study of longstanding hemodialyzed patients showed that ventricular arrhythmias, as assessed by 48-hour ambulatory monitoring, were present in 76 percent of patients[95] ; 39 percent had two or more events of two or more sequential ventricular ectopic beats (i.e., couplets or nonsustained ventricular tachycardia) per hour. The frequency of ventricular arrhythmias rose significantly after the second hour of hemodialysis and lasted up to 5 hours following dialysis. The independent risk factors for the presence of ventricular arrhythmias were age over 55 years and LV dysfunction. The frequency of ventricular ectopic beats also appeared to vary directly with resting heart rate. Sixty-nine percent of the patients who had CRF and who were undergoing long-term dialysis had supraventricular arrhythmias, mostly nonsustained. Table 72-4 lists the major factors in CRF

TABLE 72-4 -- FACTORS CONTRIBUTING TO DEVELOPMENT OF CARDIAC ARRHYTHMIAS IN PATIENTS WITH CHRONIC RENAL FAILURE

Underlying Cardiac Disease
Myocardial disease (left ventricular hypertrophy, left ventricular dysfunction)
Coronary artery disease--myocardial ischemia
Pericardial disease--myocardial inflammation
Cardiac calcification
Hemodialysis
Rapid changes in serum electrolytes
Rapid changes in blood pH
Hypoxemia
Autonomic Dysfunction
High Calcium-Phosphorus Product
High Parathormone Levels(?)

From Leier CV, Boudoulas H: Cardiovascular Disorders and Diseases. Armonk, NY, Futura, 1992.

likely to contribute to the development of cardiac arrhythmias.[96] [97] [98]

MANAGEMENT.

As in other patients, the initial approach is directed at treating remediable cardiac disease and at reversing contributory factors (see Table 72-4) . Caffeine and other cardiac stimulants should be avoided by patients with CRF and tachyarrhythmias. If arrhythmias are related to hemodialysis, attention should be directed to the potassium concentration of the dialysis bath. A low potassium concentration of the dialysate can lead to hypokalemia and serious rhythm disturbances, particularly in patients who are receiving digitalis or are afflicted with CAD, LV hypertrophy, or LV dysfunction. A dialysate potassium concentration of 3.5 mEq/liter usually abolishes dialysis-related ventricular arrhythmias. If the dialysate potassium concentration exceeds 3.5 mEq/liter, dietary potassium restriction is usually necessary between hemodialysis runs to prevent life-threatening hyperkalemia. Arrhythmias secondary to pericarditis tend to respond to treatment of the inflammatory component, when present. Increased sympathetic activity contributes to cardiac arrhythmias in patients with chronic renal disease. Physical training in patients undergoing hemodialysis augments cardiac vagal activity and may decrease vulnerability to arrhythmia. Angiotensin-converting enzyme inhibition also decreases sympathetic hyperactivity.[96] [97] [98]
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PREDISPOSITION FOR CARDIOVASCULAR INFECTIONS

Infections are common in patients with end-stage renal disease. Because these patients undergo dialysis 100 to 180 times a year, it is not surprising that infections often involve the AV access site or the abdominal catheter in patients receiving peritoneal dialysis. It is estimated that up to 6 percent of hemodialyzed patients will develop infective endocarditis sometime during the course of their disease; the most common culprit organism is*S. aureus,* followed by*Streptococcus viridans* and enterococci; the aortic valve is the usual target, followed by the mitral valve.[1]

Proper sterile technique during the entire dialysis procedure is mandatory to prevent infectious disease in this very susceptible patient population. Patients should maintain good oral health and personal hygiene to reduce other potential sources for bacteremia and infective endocarditis. Skin flora of dialyzed patients and the dialysis staff should be controlled with bactericidal soap. The staff (via nasal discharge, skin, and other sites) is not an uncommon source for culprit organisms.[99] [100] Patients who are undergoing long-term hemodialysis and who have prosthetic valves and those who have had renal transplantation should receive antibiotics prophylactically.

Recurrent or prolonged bacteremia and septicemia in patients who have CRF and are receiving dialysis implicates persistent infection of the access shunt or catheter or infective endocarditis. Appropriate antibiotic therapy, based on blood culture and antibiotic sensitivity data, should be initiated as soon as possible in these patients. Surgical consultation is indicated when access shunts show abscess or aneurysm formation, thrombosis, or bleeding. Clinical recognition of infective endocarditis in the

setting of CRF is often difficult, because many features (e.g., recurrent bacteremia, anemia, and encephalopathy) can occur in patients with end-stage renal failure without infective endocarditis. It is prudent to suspect infective endocarditis in any such patient with fever, leukocytosis, or bacteremia, particularly if associated with an infected access site. The appearance of new murmurs or changes in murmurs increases the likelihood of infective endocarditis. Demonstration of valvular vegetations by echocardiography is most informative and can be diagnostic in the presence of other clinical manifestations of infective endocarditis.

AUTONOMIC DYSFUNCTION

Derangements of the autonomic nervous system in CRF most commonly manifested as postural or dialysis-induced hypotension, abnormal hemodynamic responses to Valsalva and other maneuvers, decreased heart rate variability,[96] [97] impairment of perspiration, and alterations in gastric motility, can evoke major symptoms and disability. The cause of autonomic dysfunction in these patients is multifactorial and attributable in some cases to the underlying cause of CRF (e.g., diabetes mellitus, amyloidosis), antihypertensive drugs (e.g., sympatholytic agents), aluminum intoxication from certain antacids, and the uremic syndrome itself.[101] [102] [103] Determination of the specific type of autonomic dysfunction can be difficult and may require additional diagnostic testing (e.g., nerve conduction, bladder and sphincter function, tilt studies). Informative yet simple and inexpensive clinical maneuvers include blood pressure and heart rate responses to upright posture or the Valsalva maneuver, heart rate response to normal and deep inspiration, and determination of heart rate variability.[96] [97] In general, specific therapy for the autonomic dysfunction of renal disease is rather limited, and symptomatic therapy is used in most instances.

CARDIOVASCULAR DRUG THERAPY IN PATIENTS WITH RENAL DISEASE

Patients with acute or chronic renal failure are often treated with drugs primarily cleared or metabolized by the kidneys. In comparison with patients with normal renal function, any dose or dosage schedule of such agents in patients with renal failure usually produces higher plasma concentrations for longer duration. In addition, patients with renal failure can react unpredictably and atypically to pharmacological agents; thus, the adverse effects of a drug in this clinical setting are often related to factors other than plasma drug concentration. For example, nausea and vomiting after ingestion of certain agents (e.g., analgesics, potassium elixirs) occur more frequently in patients with CRF because of preexisting chronic inflammation of the gastrointestinal mucosa, and the adverse effects of digitalis and antiarrhythmic agents are exacerbated by abnormalities in serum potassium, magnesium, and calcium levels; hypoxemia; and the hyperadrenergic state of renal disease and dialysis. Side effects of a drug must always be considered when a patient with CRF experiences unexpected or unusual symptoms.

Renal failure often modifies the pharmacokinetics and pharmacodynamics of a drug[1] [93] [104] [105] [106] [107] [107A] ; many of these variations, however, are not directly linked to the simple reduction in renal function and GFR. The pharmacokinetic pharmacodynamic modifications of CRF are also related to greater variability in drug absorption, protein binding, metabolism, and receptor affinity, sensitivity, and responsiveness. Lower

protein binding for many agents is related to hypoproteinemia or hypoalbuminemia, an alteration of the protein molecule, or competition for protein-binding sites by endogenous substances and other types of CRF therapy. Nonesterified fatty acids, increased in CRF and with heparin administration, can displace certain drugs from their binding sites. Anemia with reduced red blood cell binding increases the plasma concentration of certain drugs. Patients with renal failure are commonly treated with several agents; drug-drug interactions can affect gastrointestinal absorption, protein binding, tissue distribution, drug metabolism and clearance, and pharmacodynamic properties.

For drugs cleared by the kidneys, dosing is adjusted for renal function. Three dosing modifications can be used: the dosing interval can be lengthened without altering the dose amount, the dose amount can be lowered without changing the dosing schedule, or a combination of both. The second approach is preferable in most patients because it averts wide swings in plasma drug concentration. Precise adjustment of dosing is usually not necessary for drugs with few

TABLE 72-5 -- CARDIOVASCULAR DRUG TH

DRUG	THERAPEUTIC RANGE/ml (PLASMA LEVELS)	ELIMINATION AND METABOLISM	HALF-LIFE--hr	
			Normal	Renal Failure
CARDIAC GLYCOSIDES				
Digoxin	0.8-2.0 ng	75% renal	45	72-96
Digitoxin	20-35 ng	95% hepatic	145	Unchanged
Quabain		40-50% excreted unchanged	21	60-70
ANTIARRHYTHMIC AGENTS				
Procainamide	4.0-10.0 mug	50% renal 50% hepatic	3-4	11-20

N-Acetylprocainamide	10-20 mug	Renal	6-8	35-70
Quinidine	2.0-5.0 mug	85% hepatic 15% renal	6	5-14
Disopyramide	0.5-2.0 mug	60% renal 40% hepatic	5-7	10-18
Lidocaine	1.5-5.0 mug	90% hepatic	1.2-2.2	1.3-3
Tocainide	4-10 mug	40% renal	15	--
Mexiletine	2-7 mug	Hepatic Renal	7-11	
Phenytoin	10.0-18.0 mug	Hepatic	24	May be shorter
Encainide	250 mug	Hepatic (93% population)	2.3	--
		Hepatic-renal (7% population)	11.3	--
a. O-desmethylencainide	30 mug	Hepatic (90%) Renal	3.5	--
b. 3-Methoxy-O-desemethylencainide	100 ng	Hepatic Renal	6.4	--
Flecainide	0.4-0.8 mug	Hepatic Renal (40%)	8-14	
Propafenone	--	Hepatic	2-10	--
Moricizine	--	Hepatic	--	--
Amiodarone	0.5-3.0 mug	Hepatic	53 days	--
Brethlium	--	80% renal 20% nonrenal	6.0	13.6
Adenocine		<5% excreted unchanged	<10	Unchanged
Cibenzoline		50-60% excreted unchanged	7	22
BETA-ADRENERGIC BLOCKERS				
Acebutolol	--	Hepatic	8	22
Alprenolol	--	Hepatic	1-3	2-3
Atonolol	--	Ronal	6-9	15-35

Metoprolol	--		Hepatic	2.5	4.5
Nadolol	--		Renal	14-24	45
Oxprenolol		--	Hepatic	2ndash;3	2ndash;3
Pindolol		--	Hepatic Renal	3-4	3-4
Propranolol		--	Hepatic	2-4	2-4
Sotalol		--	Renal (60%) Hepatic	8	15-50
Timolol		--	Hepatic	4-6	4-6
Estnolol		--	Hepatic	.06-2	--
Labetolol		--	Mostly hepatic	6-8	--
Cartelol		--	60-70% renal	6	-
Penbutolol		--	Hepatic	5	5
Betaxolol		--	Primarily hepatic, renal	14-22	30-40
Bisoprolol			50% excreted unchanged	9-13	8-24
Bobindolol			<10% excreted unchanged	4-10	Unchanged
Carvedilol			<2% excreted unchanged	5-8	Unchanged
Celiprolol			<10% excreted unchanged	4-5	5
Dievalol			<5% excreted unchanged	8-12	19-30
Amlodipine			<10% excreted unchanged	30-50	50
Nisoldipine			<10% excreted unchanged unchanged	6.6-7.9	6.8--9.7
CALCIUM CHANNEL BLOCKERS					
Verapamil		--	Hepatic	3	?7

Diltiazem	--	Hepatic	2	?8
Nifedipine	--	Hepatic	4	?5.5
Nicardipine	--	Hepatic	1-1.6	--
Nimodipine	--	Hepatic	8-9	--
Bepridil hydrochloride	--	Liver 70% urine excretion of metabolites		--
Isradipine	--	Hepatic	Early 1.5-2 Terminal 8	95
Felodipine	--	Hepatic	11-16	--
ANTIHYPERTENSIVES				
Methyldopa	--	Mostly renal	5-8	7-16
Clonidine	--	Renal	6-23	39-42
Guanfacine	--	Hepatic, renal	12-24	--
Guanabenz	--	Hepatic	4-6	--
Trimethaphan	--	--	--	--
Mecamylamine	--	Renal	--	--
Guanethidine	--	Mostly renal, less nonrenal	48-72	96-196
Reserpine	--	Hepatic, nonrenal	50-170	87-320
Minoxidil	--	Hepatic	2.8-4.2	--

Hydralazine	--	Hepatic, nonrenal	2.5-5	7-16
Diazoxide	--	Mostly renal	17-31	>30
Guanadril		30-40% excreted unchanged	4-10	19
Ketanserin		<2% excreted unchanged	14-19	25-35
Prazosin	--	Mostly hepatic, some renal	2-3	--
Doxazosin	--	Liver	22	--
Terazosin	--	10% urine	12	--
Nitroglycerin (sublingual)	--	Hepatic	2-4 (min)	2-4 (min)
Isosorbide-2-mononitrate	--	Hepatic	1.5-2.4	
Isosorbide-5-mononitrate	--	Hepatic	4.0-5.0	
Nitroprusside	--	Nonrenal	<10 min	<10 min
CONVERTING ENZYME INHIBITORS				
Captopril	--	Mostly renal, some hepatic	1.9	Prolonged
Enalapril	--	Mostly renal	11	--
Lisinopril	--	Renal	12	--
Enalaprilat	--	Renal	11	--

Benazopril	--	--	10--11	96.7
Fosinopril sodium	--	50% Urine	12	(95
Ramipril	--	60% Urine	13--17	--
Cilarapril		80--90% excreted unchanged	40--50	>50
Pentopril		80--90%excreted unchanged	2--3	10--40
Perintopril		<10% excreted unchanged	5	27
Quinapril		30% excreted unchanged	1--2	6--15
ANGIOTENSIN RECEPTOR BLOCKERS				
Losartan		10--15% excreted unchanged	3--10	4--6
				DIURETICS
Thiazides	--	Renal1	1--2	4--6
Metolazono	--	--	--	--
Furosemide	--	Mostly renal	1	3
Ethacrynic acid	--	Renal, hepatic	3	--
Bumetanido	--	Renal,hepatic	1	--
Acetazolamide	--	Renal	8	Prolonged
Amiloride	--	Renal	7.5	Prolonged

Triamterene	--	Hepatic, renal	2--12	10
Spironolactone	--	Hepatic	10--35	10--35
Indapamide	--	Mostly renal, some hepatic	14	--
Chlorthalidone		50% excreted unchanged	44--80	Unknown
Piretanide		30--40% excreted unchanged	1.4	1.6--3.4
Torasemide		25% excreted unchanged	2--4	4--5
ANTICOAGULANTS				
Heparin	--	Nonrenal	0.3-2.0	0.5-3.0
Warfarin	--	Hepatic	40	40
THROMBOLYTICS				
Streptokinase	--	--	0.38	--
Anistreplase	--	--	1-2	--
Urokinase	--	Hepatic	0.33	--
Tissue plasminogen activators (t-PA)	--	Hepatic	0.05	--
Alteplase		Unknown	0.5	Unknown
LIPID-LOWERING AGENTS				

Cholestyramine	--	Not absorbed	--	--
Colestipol	--	Not absorbed	--	--
Clofibrate	--	Renal (40-60%), hepatic	17	46-110
Gemfibrozil	--	Renal, fecal	1.5	--
Nicotinic acid	--	Hepatic, renal	0.5-1.0	--
Lovastatin	--	Hepatic, renal	--	--
Fluvostatin		<1% excreted unchanged	0.5-1.0	Unknown
Pravastatin		<10% excreted unchanged	0.8-3.2	Unchanged
Simvastatin		<0.5% excreted unchanged	2.0	Unknown
Probucol	--	Hepatic	--	--
MISCELLANEOUS				
Dobutamine		<10% excreted unchanged	2-3 min	Unknown
Amrinone		10-40% excreted unchanged	2.6-8.3	Unknown
Milrinone		80-85% excreted unchanged	1-2	1.5-3
Midoldrine		75-80% excreted unchanged	0.5	Unknown

CAPD=continuous ambulatory peritoneal dialysis; ESRD=end-stage renal disease; GFR=glomerular f

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adverse effects and a large therapeutic index (safety margin). Pharmacokinetic and dose-adjustment information about the more commonly used cardiovascular drugs in renal disease is presented in Table 72-5 . [1] [93] In most instances, the application and monitoring of drug therapy in CRF are based on pharmacodynamic and clinical

responses, occasionally supplemented by determination of the drug's plasma concentration (e.g., digitalis) or another laboratory endpoint (e.g., prothrombin time for warfarin).

The therapeutic objectives are fairly well defined for most cardiovascular drugs. For example, for drugs used to control systemic hypertension or edema, the therapeutic endpoints are clear (decrease arterial pressure, reduce edema) and are best followed by clinical observations (blood pressure, physical examination, body weight) for proper drug and dose selection. Angiotensin-converting enzyme inhibitors, most vasodilators, and calcium channel blockers have reasonably well-defined clinical endpoints (e.g., decrease arterial pressure, improve symptoms of heart failure, control angina pectoris). The therapeutic objectives of beta-adrenergic blocking drugs can be followed clinically in most patients (e.g., reduce arterial pressure, myocardial ischemia, and angina; control cardiac rhythms). For digitalis and antiarrhythmic drugs, the clinical endpoints are more elusive and are threatened by potentially serious adverse effects; determination of plasma drug concentrations for such agents often becomes an important component of optimally effective, safe dosing.

CARDIOVASCULAR COMPLICATIONS DURING DIALYSIS

SYSTEMIC HYPOTENSION.

Removal of fluid volume, redistribution of plasma volume, baroreceptor disturbances, dysfunction of the autonomic nervous system, depressed responsiveness to alpha-adrenergic receptor stimulation, concomitant drug therapy (e.g., antihypertensive agents), and LV diastolic dysfunction contribute to the propensity of patients with CRF to develop hypotension during hemodialysis. Interestingly, some patients who have renal disease with dialysis-induced hypotension have higher plasma concentrations of atrial natriuretic peptide and lower norepinephrine levels compared with patients with CRF without hypotension.[37] [39] [108]

Symptomatic depletion of fluid volume during dialysis can be averted by allowing a modest amount of weight gain between dialysis treatments. When feasible, antihypertensive therapy and other potential hypotension-inducing drugs (e.g., nitrates) can be withheld 4 to 6 hours before dialysis to minimize their contribution to the problem. Of the antihypertensive agents, minoxidil is least likely to cause unpredictable changes in blood pressure during hemodialysis; however, drug-induced hirsutism and occasional pericarditis make this drug unacceptable to some patients, particularly women. Small doses of noncardioselective beta-adrenergic blocking drugs can be effective in maintaining acceptable arterial pressure; the $beta_1$ - and $beta_2$ -receptor blockade allows circulating norepinephrine to evoke unopposed alpha-adrenergic receptor stimulation and vasoconstriction. Either peritoneal dialysis or renal transplantation is the best option for patients who have CRF and who poorly tolerate hemodialysis because of hypotension.

HYPOXEMIA.

The mechanisms for hemodialysis-induced hypoxemia have not been definitively established; leading explanations include nonbicarbonate buffers (e.g., acetate) used in the dialysis bath, Cupraphane membranes, and pulmonic ventilation-perfusion mismatch elicited by systemic hypotension. Acetate buffer evokes a significant leftward shift in the hemoglobin-oxygen dissociation curve and can disturb ventilation-perfusion of the lungs through its vasodilatory properties. Activation of complement along Cupraphane exchange membranes can result in sequestration of leukocytes within pulmonary vessels, ventilation and perfusion abnormalities, and hypoxemia; this complication has been reduced considerably with the use of biocompatible dialyzers.[1]

ELECTROLYTE AND OTHER METABOLIC ABNORMALITIES.

Electrolyte disturbances, metabolic acidosis, and other metabolic abnormalities likely contribute to the development of various cardiovascular derangements in CRF (e.g., cardiac arrhythmias, depression of myocardial contractility). The rate of change in pH, electrolyte concentrations, and other metabolic factors during dialysis is probably as important as the actual degree of change with respect to the clinical consequences of these disturbances. The most common and crucial electrolyte disturbances in patients undergoing hemodialysis involve potassium. Hyperkalemia is a common problem in these patients, and plasma and whole-body potassium levels can be dramatically altered by hemodialysis. The dialysis buffer, acetate, transiently decreases serum bicarbonate level, and with repeated dialysis patients with CRF can become depleted of bicarbonate; bicarbonate has now largely replaced acetate as the dialysis buffer at most modern facilities.[1] [37] [39]

COMPLICATIONS OF THE ARTERIOVENOUS ACCESS FISTULA DURING HEMODIALYSIS.

The external access vascular shunt is used when a patient is expected to require only short-term dialysis (days to a few weeks). Because of fewer complications (e.g., lower infection rate and less thrombogenic) over time, the surgically constructed subcutaneous AV fistula is used for long-term dialysis management. In certain patients, particularly the elderly and those with peripheral vascular disease or diabetes mellitus, reduction of blood flow distal to the fistula can lead to local ischemia and infarction, occasionally requiring amputation of a digit or distal extremity.[1] [37] [39] An infrequent complication during hemodialysis involves a "steal syndrome," which may occur when the radial artery distal to a forearm fistula has not been ligated; this vascular arrangement can allow blood to flow from the ulnar artery through the palmar arch (as nonnutritive flow), retrograde into the radial artery and access fistula.

OTHER DIALYSIS-INDUCED COMPLICATIONS.

Air embolization and hemolysis, although rare, are serious complications. Hemolysis can occur from improper composition or chemical contamination of the dialysate. Severe illness and death have resulted from dialysate contaminated with excessive aluminum, calcium, or fluoride.[1] [37] [39] [109] Other substances, such as polyvinylchloride, have been leached from membranes, dialyzer shells, and tubing to cause systemic and

cardiovascular toxicity.[110] With the use of high-flux polyacryionitrile AN 69 exchange membranes, patients who have CRF and are receiving angiotensin-converting enzyme inhibitors appear to be somewhat more susceptible to anaphylactoid reactions during hemodialysis.[1] [37] [39] [110]

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file:///c%3a/documents%20and%20settings/administrator/desktop/braunwald/pages/3/40.html#C0178561
file:///c%3a/documents%20and%20settings/administrator/desktop/braunwald/pages/3/10.html#C0038561

file:///c%3a/documents%20and%20settings/administrator/desktop/braunwald/pages/3/61.html#C0238561
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file:///das/book/29208265/view/924/182.html/top
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http://home.mdconsult.com/agreement.html